NOVARTIS

Clinical Trial Results Database

Sponsor

Novartis

Generic Drug Name

LEE011 / Ribociclib

Trial Indication(s)

Hepatic Impairment

Protocol Number

CLEE011A2109

Protocol Title

A Phase I, open label, multi-center, parallel cohort, single dose study to evaluate the pharmacokinetics (PK) of LEE011 in healthy subjects with normal hepatic function and subjects with impaired hepatic function.

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase IV

Study Start/End Dates

17-Mar-2015 to 09-Jan-2017

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was a Phase I, open-label, multi-center, parallel cohort, single oral dose study to assess the PK and safety of 400 mg of ribociclib in subjects with impaired hepatic function and healthy subjects with normal hepatic function. Subjects were assigned by

hepatic function: normal, mild, moderate, and severe impairment (according to the Child-Pugh classification) as determined at the Screening visit.

Centers

Three study centers in the United States of America

Objectives:

Primary objective

- To evaluate the PK of a single oral dose of ribociclib in subjects with impaired hepatic function as compared to healthy subjects with normal hepatic function.

Secondary objective

- To evaluate the safety and tolerability of a single oral dose of ribociclib in healthy subjects and subjects with varying degrees of hepatic function (mild to severe)

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

Single oral dose of ribociclib 400mg (2 X 200mg capsules)

Statistical Methods

The pharmacokinetic analysis set (PAS), included all subjects who received the study drug (ribociclib) and had blood samples collected following drug administration that yielded an evaluable PK profile. The full analysis set (FAS) included all subjects who received the study drug (ribociclib). Subjects were analyzed according to their hepatic cohort. The safety set was the same as the FAS.

The analysis on primary objective was performed on the PAS. A formal statistical comparison was conducted on the following PK parameters for both ribociclib and LEQ803: Cmax, AUClast, and AUCinf. A linear model including hepatic function cohort (i.e. normal, mild, moderate, or severe) as a fixed effect was fitted to the log-transformed PK parameters. The impaired cohorts were the test treatments and the control cohort (normal hepatic function) was the reference treatment. Point estimates and the corresponding 90% confidence intervals (CIs) for the mean difference between each test and reference 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. For Tmax, difference of medians was provided for comparisons across cohorts.

The effect of baseline covariates (sex, age group (< 65 years, ≥ 65 years), and weight) on PK parameters (Cmax, AUClast, and AUCinf) of ribociclib was also investigated by repeating the aforementioned linear model including sex and age group as categorical variables and weight as a continuous variable. The 90% CIs for the ratio of the geometric means for the covariate adjusted analysis were presented.

The assessment of safety on the secondary objective was based mainly on the frequency of AEs and on the number of laboratory values that fell outside of pre-determined ranges. Other safety data (e.g., ECG, vital signs, and any other safety data) were summarized as appropriate.

Study Population: Key Inclusion/Exclusion Criteria

Diagnosis and main criteria for inclusion

The Child-Pugh classification was used to categorize the degree of hepatic impairment.

Key inclusion criteria

- Male or female (sterile or postmenopausal) subjects between 18 - 75 years of age (both inclusive).
- Subjects with body mass index (BMI) between 18 kg/m2 and 36 kg/m2 and weigh at least 50 kg and no more than 120 kg.
- Subjects with normal hepatic function: Healthy subjects as determined by the absence of clinically significant deviation from normal and adequate end organ function as defined by levels of bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (AP), serum creatinine, serum amylase and lipase ≤ ULN.

Subjects in Child-Pugh A, B and C cohorts:

- Subjects with confirmed hepatic disease by at least one of the following criteria: histologically by prior liver biopsy showing cirrhosis, clinically by physical examination, laboratory data, liver imaging or endoscopic findings.
- Subjects with Child-Pugh Clinical Assessment Score consistent with degree of hepatic impairment
- Subjects with other stable medical disorders such as diabetes, hypertension, hyperlipidemia, hypothyroidism as long as they were considered healthy in general as determined by past medical history, physical examination, vital signs, electrocardiogram (ECG) and laboratory tests at Screening.
- Subjects with no change in hepatic status for at least one month prior to dosing.

Key exclusion criteria

- Participation in any clinical study within 4 weeks prior to dosing.
- Subjects with medical history of allergy or known hypersensitivity to ribociclib.
- History or presence of impaired cardiac function.

- Subject who had a medically documented history of clinically significant hematological, endocrinological, pulmonary, cardiovascular, hepatic, or allergic disease.
- Any surgical or medical condition that may significantly alter the absorption, distribution, metabolism or excretion of drugs.
- Subject who used any herbal medications/supplements, over-the-counter (OTC) medication, or dietary supplements (vitamins excluded) within 1 week or 5 half-lives prior to dosing (whichever is longer).
- Subjects with normal hepatic function: Clinical evidence of hepatic disease or hepatic injury as indicated by abnormal hepatic function tests and a positive Hepatitis B surface antigen or Hepatitis C test result.
- Subjects in Child-Pugh A, B and C cohorts: Symptoms or history of grade 3 or worse encephalopathy within 4 weeks prior to dosing, clinical evidence of severe ascites, INR >2.5, any evidence of progressive hepatic disease (within the last 4 weeks), history of surgical portosystemic shunt and bilirubin >6 mg/dL.

Participant Flow Table

Subject disposition, by hepatic cohort (FAS)

Disposition Reason	Normal N=12 n (%)	Mild N=6 n (%)	Moderate N=6 n (%)	Severe N=6 n (%)	All Subjects N=30 n (%)
Completed study	12 (100)	6 (100)	6 (100)	6 (100)	30 (100)

Baseline Characteristics

Demographics, by hepatic cohort (FAS)

Demographic Variable	Normal N=12	Mild N=6	Moderate N=6	Severe N=6	All Subjects N=30
Age (years)					
n	12	6	6	6	30
Mean	54.9	53.8	59.0	55.2	55.6
SD	6.63	6.43	2.83	8.47	6.39
Median	54.5	55.5	58.0	56.5	56.5
Minimum	47	45	56	44	44
Maximum	69	60	63	64	69
Age category (years) -n (%)					
<65	11 (91.7)	6 (100)	6 (100)	6 (100)	29 (96.7)
≥ 65	1 (8.3)	0	0	0	1 (3.3)
Sex -n (%)					
Male	7 (58.3)	6 (100)	4 (66.7)	3 (50.0)	20 (66.7)
Female	5 (41.7)	0	2 (33.3)	3 (50.0)	10 (33.3)
Race -n (%)					
Caucasian	11 (91.7)	6 (100)	5 (83.3)	6 (100)	28 (93.3)
Black	1 (8.3)	0	1 (16.7)	0	2 (6.7)
Ethnicity -n (%)					
Hispanic/Latino	7 (58.3)	5 (83.3)	3 (50.0)	3 (50.0)	18 (60.0)
Other	5 (41.7)	1 (16.7)	3 (50.0)	3 (50.0)	12 (40.0)
Weight (kg)					
n	12	6	6	6	30
Mean	88.142	90.367	83.617	87.817	87.617
SD	16.0959	10.1277	21.7179	17.9719	16.0612
Median	89.450	89.800	80.500	84.900	87.700
Minimum	65.20	74.40	59.80	64.00	59.80
Maximum	113.50	101.80	115.40	115.60	115.60
Height (cm)					
n	12	6	6	6	30
Mean	170.575	173.167	166.550	165.850	169.343
SD	8.1413	11.1400	9.4454	8.7621	9.1075
Median	172.500	173.450	165.150	166.750	169.900
Minimum	153.00	160.00	156.00	152.00	152.00
Maximum	180.00	192.60	182.00	178.60	192.60
Body surface area (m^2)					
n	12	6	6	6	30
Mean	2.058	2.100	1.977	2.030	2.045
SD	0.2283	0.1410	0.3090	0.2472	0.2278

Demographic Variable	Normal N=12	Mild N=6	Moderate N=6	Severe N=6	All Subjects N=30
Median	2.105	2.115	1.940	2.000	2.070
Minimum	1.69	1.86	1.66	1.73	1.66
Maximum	2.40	2.24	2.44	2.42	2.44
Body mass index (BMI) (kg/m^2)					
n	12	6	6	6	30
Mean	30.081	30.378	29.760	31.783	30.417
SD	3.5801	4.5619	5.0391	4.7896	4.1600
Median	29.250	31.515	29.230	33.210	30.190
Minimum	24.90	23.13	22.37	23.37	22.37
Maximum	35.55	35.35	35.69	36.24	36.24

- 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 $(m)^2$.
- Body surface area (BSA: Gehan and George) (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.

Summary of Efficacy

No efficacy was evaluated in this study.

Summary of pharmacokinetics

Summary of primary PK parameters for plasma ribociclib by hepatic cohort (PAS)

Cohort	Statistics	Cmax (ng/mL)	AUClast (ng*hr/mL)	AUCinf (ng*hr/mL)	Tmax (hr)
Normal (N=12)	n	12	12	12	12
	Mean (SD)	374 (228)	6430 (2270)	6510 (2270)	N/A
	CV% mean	61.1	35.4	34.8	N/A
	Geo-mean	317	6080	6170	N/A
	CV% geo-mean	65.6	35.8	35.2	N/A
	Median	310	6300	6390	4.00
	[Min; Max]	[140; 792]	[3710; 11500]	[3770; 11500]	[1.00; 6.00]
Mild (N=6)	n	6	6	6	6
	Mean (SD)	347 (78.5)	6610 (2370)	6700 (2370)	N/A
	CV% mean	22.6	35.9	35.4	N/A
	Geo-mean	339	6230	6330	N/A
	CV% geo-mean	24.2	40.3	39.5	N/A
	Median	351	6700	6800	3.00
	[Min; Max]	[234; 439]	[3340; 10200]	[3440; 10300]	[1.00; 4.00]
Moderate (N=6)	n	6	6	6	6
	Mean (SD)	461 (75.5)	8150 (2630)	8240 (2650)	N/A
	CV% mean	16.4	32.2	32.2	N/A
	Geo-mean	455	7840	7920	N/A
	CV% geo-mean	18.2	30.4	30.4	N/A
	Median	488	7710	7790	2.00
	[Min; Max]	[326; 530]	[5210; 13100]	[5260; 13200]	[2.00; 6.00]
Severe (N=6)	n	6	6	6	6
	Mean (SD)	446 (158)	8110 (2290)	8240 (2290)	N/A
	CV% mean	35.6	28.2	27.8	N/A
	Geo-mean	419	7830	7960	N/A
	CV% geo-mean	41.4	30.7	30.0	N/A
	Median	468	8130	8260	1.00
	[Min; Max]	[218; 674]	[4750; 11500]	[4900; 11700]	[0.500; 2.03]

- n = number of subjects with evaluable PK data.
- CV% = coefficient of variation (%) = SD/mean*100,CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100.

Summary of statistical analysis of primary PK parameters for plasma ribociclib (PAS)

PK Parameter (unit)	Hepatic cohort	n*	Adjusted Geo-mean	Cohort Comparison			
				Comparison	Geo-mean Ratio	90% CI Lower	90% CI Upper
Cmax (ng/mL)	Normal	12	317				
	Mild	6	339	Mild/Normal	1.07	0.733	1.57
	Moderate	6	455	Moderate/Normal	1.44	0.981	2.10
	Severe	6	419	Severe/Normal	1.32	0.905	1.94
AUClast (ng*hr/mL)	Normal	12	6080				
	Mild	6	6230	Mild/Normal	1.02	0.768	1.37
	Moderate	6	7840	Moderate/Normal	1.29	0.967	1.72
	Severe	6	7830	Severe/Normal	1.29	0.965	1.72
AUCinf (ng*hr/mL)	Normal	12	6170				
	Mild	6	6330	Mild/Normal	1.03	0.772	1.36
	Moderate	6	7920	Moderate/Normal	1.28	0.966	1.71
	Severe	6	7960	Severe/Normal	1.29	0.971	1.71
Tmax (hr)	Normal	12	4.00				
	Mild	6	3.00	Mild-Normal	-1.00		
	Moderate	6	2.00	Moderate-Normal	-2.00		
	Severe	6	1.00	Severe-Normal	-3.00		

- Model is a linear representation of the log-transformed PK parameters. Included in the model was hepatic cohort 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 median under 'Geo-mean Ratio'

Summary of secondary PK parameters for ribociclib by hepatic cohort (PAS)

Cohort	Statistics	T1/2 (hr)	CL/F (L/hr)	Vz/F (L)
Normal (N=12)	n	12	12	12
	Mean (SD)	40.9 (8.70)	68.3 (22.9)	4040 (1650)
	Geo-mean (CV%)	40.1 (20.8)	64.8 (35.2)	3750 (42.4)
Mild (N=6)	n	6	6	6
	Mean (SD)	45.0 (9.58)	67.3 (27.5)	4280 (1570)
	Geo-mean (CV%)	44.2 (20.3)	63.2 (39.5)	4030 (39.8)
Moderate (N=6)	n	6	6	6
	Mean (SD)	37.5 (8.33)	52.3 (14.7)	2740 (661)
	Geo-mean (CV%)	36.8 (21.1)	50.5 (30.4)	2680 (22.5)
Severe (N=6)	n	6	6	6
	Mean (SD)	57.4 (23.1)	52.2 (16.3)	4550 (3040)
	Geo-mean (CV%)	53.5 (43.0)	50.3 (30.0)	3880 (65.2)

- n = number of subjects with evaluable PK data.
- CV% = coefficient of variation (%) = SDmean*100, CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100.

Summary of primary PK parameters for LEQ803 by hepatic cohort (PAS)

Cohort	Statistics	Cmax (ng/mL)	AUClast (ng*hr/mL)	AUCinf (ng*hr/mL)	Tmax (hr)
Normal (N=12)	n	12	12	12	12
	Mean (SD)	36.6 (20.7)	1280 (503)	1380 (518)	N/A
	CV% mean	56.4	39.4	37.6	N/A
	Geo-mean	31.9	1190	1290	N/A
	CV% geo-mean	59.1	40.8	38.9	N/A
	Median	29.9	1140	1250	4.00
	[Min; Max]	[12.9; 77.8]	[652; 2230]	[747; 2340]	[1.00; 6.00]
Mild (N=6)	n	6	6	6	6
	Mean (SD)	27.9 (11.6)	829 (286)	906 (293)	N/A
	CV% mean	41.6	34.5	32.3	N/A
	Geo-mean	25.8	791	870	N/A
	CV% geo-mean	46.4	33.9	31.7	N/A
	Median	28.3	710	772	5.00
	[Min; Max]	[14.4; 45.4]	[538; 1250]	[608; 1330]	[3.00; 6.00]
Moderate (N=6)	n	6	6	6	6
	Mean (SD)	33.7 (16.4)	1130 (319)	1230 (327)	N/A
	CV% mean	48.6	28.1	26.6	N/A
	Geo-mean	30.5	1100	1200	N/A
	CV% geo-mean	51.9	27.4	25.9	N/A
	Median	29.6	1080	1160	5.00
	[Min; Max]	[14.7; 61.7]	[772; 1690]	[851; 1800]	[2.00; 6.00]
Severe (N=6)	n	6	6	5	6
	Mean (SD)	11.5 (3.01)	569 (243)	712 (260)	N/A
	CV% mean	26.3	42.8	36.4	N/A
	Geo-mean	11.1	529	678	N/A
	CV% geo-mean	27.1	42.9	35.5	N/A
	Median	11.4	468	576	3.50
	[Min; Max]	[8.13; 15.7]	[316; 949]	[498; 1100]	[1.00; 7.98]

- n = number of subjects with evaluable PK data.
- CV% = coefficient of variation (%) = SD/mean*100,
CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100.

Summary of statistical analysis of primary PK parameters for plasma LEQ803 (PAS)

PK Parameter (unit)	Hepatic cohort	n*	Adjusted Geo-mean	Comparison	Cohort Comparison Geo-mean Ratio	90% CI Lower	90% CI Upper
Cmax (ng/mL)	Normal	12	31.9				
	Mild	6	25.8	Mild/Normal	0.811	0.542	1.21
	Moderate	6	30.5	Moderate/Normal	0.958	0.640	1.43
	Severe	6	11.1	Severe/Normal	0.349	0.233	0.523
AUClast (ng*hr/mL)	Normal	12	1190				
	Mild	6	791	Mild/Normal	0.666	0.488	0.908
	Moderate	6	1100	Moderate/Normal	0.925	0.678	1.26
	Severe	6	529	Severe/Normal	0.445	0.326	0.607
AUCinf (ng*hr/mL)	Normal	12	1290				
	Mild	6	870	Mild/Normal	0.673	0.505	0.897
	Moderate	6	1200	Moderate/Normal	0.925	0.694	1.23
	Severe	5	678	Severe/Normal	0.525	0.386	0.712
Tmax (hr)	Normal	12	4.00				
	Mild	6	5.00	Mild-Normal	1.00		
	Moderate	6	5.00	Moderate-Normal	1.00		
	Severe	6	3.50	Severe-Normal	-0.500		

- Model is a linear model of the log-transformed PK parameters. Included in the model was hepatic cohort as a fixed effect. Results were back transformed to get adjusted geo-mean, geometric-mean ratio, and 90% CI.

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

- For Tmax, median is presented under 'Adjusted Geo-mean', difference of median under 'Geo-mean Ratio'

Summary of Safety

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

Primary system organ class Preferred term	Normal N=12 n (%)	Mild N=6 n (%)	Moderate N=6 n (%)	Severe N=6 n (%)	All Subjects N=30 n (%)
-Any primary system organ class					
-Total	0	2 (33.3)	1 (16.7)	3 (50.0)	6 (20.0)
Grade 1	0	2 (33.3)	0	3 (50.0)	5 (16.7)
Grade 3	0	0	1 (16.7)	0	1 (3.3)
Grade 3/4	0	0	1 (16.7)	0	1 (3.3)
Gastrointestinal disorders					
-Total	0	0	1 (16.7)	2 (33.3)	3 (10.0)
Grade 1	0	0	1 (16.7)	2 (33.3)	3 (10.0)
Abdominal pain					
-Total	0	0	1 (16.7)	0	1 (3.3)
Grade 1	0	0	1 (16.7)	0	1 (3.3)
Diarrhoea					
-Total	0	0	0	1 (16.7)	1 (3.3)
Grade 1	0	0	0	1 (16.7)	1 (3.3)
Nausea					
-Total	0	0	0	1 (16.7)	1 (3.3)
Grade 1	0	0	0	1 (16.7)	1 (3.3)
General disorders and administration site conditions					
-Total	0	0	0	1 (16.7)	1 (3.3)
Grade 1	0	0	0	1 (16.7)	1 (3.3)
Chills					
-Total	0	0	0	1 (16.7)	1 (3.3)
Grade 1	0	0	0	1 (16.7)	1 (3.3)
Infections and infestations					

Primary system organ class Preferred term	Normal N=12 n (%)	Mild N=6 n (%)	Moderate N=6 n (%)	Severe N=6 n (%)	All Subjects N=30 n (%)
-Total	0	1 (16.7)	0	0	1 (3.3)
Grade 1	0	1 (16.7)	0	0	1 (3.3)
Tooth abscess					
-Total	0	1 (16.7)	0	0	1 (3.3)
Grade 1	0	1 (16.7)	0	0	1 (3.3)
Upper respiratory tract infection					
-Total	0	1 (16.7)	0	0	1 (3.3)
Grade 1	0	1 (16.7)	0	0	1 (3.3)
Injury, poisoning and procedural complications					
-Total	0	0	1 (16.7)	0	1 (3.3)
Grade 1	0	0	1 (16.7)	0	1 (3.3)
Contusion					
-Total	0	0	1 (16.7)	0	1 (3.3)
Grade 1	0	0	1 (16.7)	0	1 (3.3)
Nervous system disorders					
-Total	0	1 (16.7)	1 (16.7)	2 (33.3)	4 (13.3)
Grade 1	0	1 (16.7)	0	2 (33.3)	3 (10.0)
Grade 3	0	0	1 (16.7)	0	1 (3.3)
Grade 3/4	0	0	1 (16.7)	0	1 (3.3)
Headache					
-Total	0	1 (16.7)	0	1 (16.7)	2 (6.7)
Grade 1	0	1 (16.7)	0	1 (16.7)	2 (6.7)
Hepatic encephalopathy					
-Total	0	0	0	1 (16.7)	1 (3.3)
Grade 1	0	0	0	1 (16.7)	1 (3.3)
Syncope					
-Total	0	0	1 (16.7)	0	1 (3.3)
Grade 3	0	0	1 (16.7)	0	1 (3.3)
Grade 3/4	0	0	1 (16.7)	0	1 (3.3)

- Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency as reported in 'All subjects'.
- A subject with multiple occurrences of an AE under one hepatic cohort is counted only once in the AE category for that cohort.
- A subject with multiple severity ratings for an AE while on treatment is only counted under the maximum rating.
A subject with multiple AEs within a primary system organ class is counted only once in the total row at

Deaths, serious adverse events, and other significant AEs

None were reported during the study. None of the subjects discontinued study treatment due to AEs.

Conclusion:

- Ribociclib exposure was similar in subjects with mild hepatic impairment compared to subjects with normal hepatic function. Ribociclib AUClast and AUCinf were approximately 30% higher in subjects with moderate and severe hepatic impairment compared to subjects with normal hepatic function.
- Ribociclib at a dose of 400 mg was generally well tolerated in subjects with varying degrees of hepatic impairment.
- The results from this study indicate no ribociclib dose adjustment is warranted for patients with mild hepatic impairment (Child-Pugh A), while a dose reduction to 400 mg in patients with moderate (Child-Pugh B) and severe hepatic impairment (Child-Pugh C) is recommended.

Date of Clinical Trial Report

10 July 2017