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Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Ribociclib/LEE011

Trial Indication(s)

Renal Impairment

Protocol Number

CLEE011A2116

Protocol Title

A phase I, open label, multicenter, parallel-group, single dose two-staged study to evaluate the pharmacokinetics and safety of a single 400 mg oral dose of LEE011 in subjects with varying degrees of impaired renal function compared to matched healthy volunteers with normal renal function

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase IV

Study Start/End Dates

Study Start Date: October 2015 (Actual)
Primary Completion Date: September 2017 (Actual)
Study Completion Date: May 2018 (Actual)

Reason for Termination (If applicable)

Not Applicable

Study Design/Methodology

This was a Phase I, open label, multicenter, parallel-group, single dose two-staged study following a single oral dose (400 mg) of ribociclib in adult subjects with various degrees of renal impairment compared to matched healthy subjects with normal renal function. The study was divided in two parts:
Part I: The effects of impaired renal function on the PK of ribociclib were first evaluated in subjects with normal renal function (Cohort 1, seven subjects), severe renal impairment (Cohort 2, seven subjects) and End stage renal disease (ESRD) but not yet on dialysis (Cohort 3, three subjects). An interim PK analysis was performed after subjects in the severe renal impairment cohort along with the matching normal renal function subjects completed the study. Part II of the study was planned if the results from Part I showed a significant clinical effect (>50% increase in AUCinf of ribociclib).
Part II: This part started after the interim analysis results from Part I showed a significant clinical effect in subjects with severe renal impairment compared to subjects with normal renal function.

In Part II, subjects with mild (Cohort 4, eight subjects) and moderate renal impairment (Cohort 5, six subjects) were enrolled along with additional matched subjects with normal renal function (Cohort 1, 14 subjects total).

Centers

4 centers in 4 countries: Germany(1), Bulgaria(1), Czech Republic(1), United States(1)

Objectives:

Primary

• To determine the impact of various degrees of renal impairment on primary PK parameters of ribociclib following a single 400 mg oral dose of ribociclib

Secondary

- To determine the impact of various degrees of renal impairment on secondary PK parameters of ribociclib following a single 400 mg oral dose of ribociclib
- To evaluate the PK of LEQ803, an active metabolite, in subjects with various degrees of renal impairment following a single 400 mg oral dose of ribociclib
- To evaluate the safety and tolerability of a single 400 mg oral dose of ribociclib in subjects with renal impairment

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

Ribociclib was prepared and supplied by Novartis to investigators as 200 mg capsules. Each subject received a single oral dose of 400 mg ribociclib (2 x 200 mg capsules) on Day 1. No control or reference drug was used in the study.

Statistical Methods

Full Analysis Set (FAS) consisted of all subjects who received the study drug (ribociclib). Subjects were analyzed according to their renal cohort decided by absolute GFR at Screening visit. Safety set was the same as FAS. Pharmacokinetics Analysis Set (PAS) consisted of all subjects who received the study drug and had blood samples collected after drug administration that yielded an evaluable PK profile. A profile was considered non-evaluable if any of the following conditions were met: the subject did not receive the planned amount of ribociclib dose or the subject had vomited within 4 hours after administration of ribociclib or the subject had insufficient PK concentration data. A subject was considered having insufficient PK concentration data when there was not enough data to determine at least one primary or secondary PK parameter.

In Part I of the study, ribociclib exposure in the severe renal impairment cohort was compared to the exposure in the normal renal function cohort. Pharmacokinetic data from the ESRD subjects (Cohort 3) was also evaluated. A formal comparison was conducted using primary PK parameters (i.e., Cmax, AUClast, AUCinf, and CL/F) except Tmax for ribociclib. A linear model including cohort as a fixed effect was fit to log-transformed PK parameters for ribociclib using data from the control (normal cohort) and severe renal impairment cohorts. The severe renal impairment cohort was the test treatment and the normal cohort was the reference treatment. The ESRD cohort was not included in the model, since

there were < 4 subjects in this cohort. Point estimates and the corresponding 90% confidence intervals (CIs) for the difference in mean values between each test and the reference treatment were calculated. This was anti-logged to obtain the point estimates and 90% CIs for the ratio of the geometric means on the original scale.

Since the results from subjects with severe renal impairment (Cohort 2) showed a significant clinical effect (> 50% increase in AUCinf of ribociclib), the study expanded into Part II and the statistical analysis as mentioned above for Part I was conducted for the purpose of this CSR. The mild, moderate, and severe renal impairment cohorts were the test treatments and the normal renal function cohort was the reference treatment. Point estimates and the corresponding 90% CIs for the difference in mean values between each test and the reference treatment, i.e., mild - normal, moderate - normal and severe - normal were calculated.

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria (All Subjects):
- Male or female (sterile or postmenopausal) subjects between 18-75 (both inclusive) years of age and healthy as determined by absence of clinically significant deviation from normal in medical history, physical examination, vital signs, electrocardiograms, and clinical laboratory determinations (except for renal impaired subjects).
- Subjects must have a BMI between 18 kg/m2 and 38 kg/m2 and weight at least 50 kg and no more than 120 kg.
- Additional inclusion criteria for subjects with normal renal function:
. An absolute GFR as determined by MDRD equation and conversion within normal range as determined by GFR > 90 mL/min

Key Inclusion Criteria (for subjects with impaired renal function):
- Subjects must have documented stable renal disease without evidence of renal progressive disease (stable renal disease is defined as no significant change, such as a stable absolute GFR, for 4 weeks prior to study entry.

Key Exclusion Criteria (All Subjects):
- Subject has received a renal transplant at any time in the past and is on immunosuppressant therapy
- History or presence of impaired cardiac function
- Any surgical or medical condition that may significantly alter the absorption, distribution, metabolism, or excretion of drugs
- Administration of CYP3A4/5 inhibitors or inducers or CYP3A4 substrates with narrow therapeutic windows
- Administration of medications that prolong the QT interval
- Subject has a history of immunodeficiency diseases, including HIV, as confirmed by (HIV-1, HIV-2) test
- Receipt of investigational product in another clinical trial within 4 weeks of dosing

Key Exclusion Criteria (for subjects with impaired renal function):

- Severe albuminuria > 300 mg/day
- Subjects undergoing any method of dialysis
- Subjects with renal impairment due to hepatic disease (hepatorenal syndrome)

Participant Flow Table

Overall Study

	Normal renal function	Mild renal impairment	Moderate renal impairment	Severe renal impairment	End stage renal disease	Total
Arm/Group Description	Cohort 1: absolute Glomerular Filtration Rate (GFR) (>= 90 ml/min)	Cohort 4: absolute GFR (60-89 ml/min)	Cohort 5: absolute GFR (30-59 ml/min)	Cohort 2: absolute GFR (15-29 ml/min)	Cohort 3: absolute GFR (<15 ml/min, not on dialysis)	
Started	14	8	6	7	3	38
Completed	13	8	6	7	3	37
Not Completed	1	0	0	0	0	1
Withdrawal by Subject	1	0	0	0	0	1

Baseline Characteristics

	Normal renal function	Mild renal impairment	Moderate renal impairment	Severe renal impairment	End stage renal disease	Total
Arm/Group Description	Cohort 1: absolute Glomerular Filtration Rate	Cohort 2: absolute GFR (60-89 ml/min)	Cohort 3: absolute GFR absolute GFR (30-59 ml/min)	Cohort 4: absolute GFR (15-29 ml/min)	Cohort 5: absolute (<15 ml/min, not on dialysis)	

	(GFR) (>= 90 ml/min)					
Number of Participants [units: participants]	14	8	6	7	3	38
Age Continuous (units: years) Mean ± Standard Deviation						
	57.9±9.38	65.8±5.65	65.0±7.04	53.1±9.74	63.0±4.36	
Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)						
Female	6	4	5	2	2	19
Male	8	4	1	5	1	19
Age, Customized (units: Participants) Count of Participants (Not Applicable)						
Adults (18-64 years)	9	2	2	6	1	20
From 65-84 years	5	6	4	1	2	18
Race/Ethnicity, Customized (units: Participants) Count of Participants (Not Applicable)						
White	13	7	6	7	3	36
Black or African American	1	1	0	0	0	2

Summary of Efficacy

Primary Outcome Result(s)

Primary pharmacokinetics (PK) parameter for ribociclib: Cmax

(Time Frame: Pre-dose/0h to 312h post dose)

	Normal renal function	Mild renal impairment	Moderate renal impairment	Severe renal impairment	End stage renal disease
Arm/Group Description	Cohort 1: absolute Glomerular Filtration Rate (GFR) (>= 90 ml/min)	Cohort 4: absolute GFR (60-89 ml/min)	Cohort 5: absolute GFR (30-59 ml/min)	Cohort 2: absolute GFR (15-29 ml/min)	Cohort 3: absolute GFR (<15 ml/min, not on dialysis)
Number of Participants Analyzed [units: participants]	14	8	6	7	3
Primary pharmacokinetics (PK) parameter for ribociclib: Cmax (units: ng/mL) Mean ± Standard Deviation					
	262 ± 115	439 ± 137	435 ± 125	579 ± 241	596 ± 65.0

Statistical Analysis

Groups	Normal renal function, Mild renal impairment
Other Geo-mean ratio	1.80
90 % Confidence Interval 2-Sided	1.30 to 2.51

Statistical Analysis

Groups	Normal renal function, Moderate renal impairment
Other Geo-mean ratio	1.79

90 % Confidence Interval 2-Sided	1.25 to 2.58

Statistical Analysis

Groups	Normal renal function, Severe renal impairment
Other Geo-mean ratio	2.30
90 % Confidence Interval 2-Sided	1.63 to 3.25

Primary pharmacokinetics (PK) parameter for ribociclib: AUClast, AUCinf

(Time Frame: Pre-dose/0h to 312h post dose)

	Normal renal function	**Mild renal impairment**	**Moderate renal impairment**	**Severe renal impairment**	**End stage renal disease**
Arm/Group Description	Cohort 1: absolute Glomerular Filtration Rate (GFR) (>= 90 ml/min)	Cohort 4: absolute GFR (60-89 ml/min)	Cohort 5: absolute GFR (30-59 ml/min)	Cohort 2: absolute GFR (15-29 ml/min)	Cohort 3: absolute GFR (<15 ml/min, not on dialysis)
Number of Participants Analyzed [units: participants]	14	8	6	7	3
Primary pharmacokinetics (PK) parameter for ribociclib: AUClast, AUCinf (units: ng*hr/mL) Mean ± Standard Deviation					
AUClast	4450 ± 1770	6950 ± 2570	8560 ± 4170	11400 ± 4360	13700 ± 2880
AUCinf	4510 ± 1780	7030 ± 2560	8660 ± 4210	11600 ± 4390	13800 ± 2920

Statistical Analysis

Groups	Normal renal function, Mild renal impairment
Other Geo-mean ratio	1.63
90 % Confidence Interval 2-Sided	1.17 to 2.26

Statistical Analysis

Groups	Normal renal function, Moderate renal impairment
Other Geo-mean ratio	1.95
90 % Confidence Interval 2-Sided	1.35 to 2.80

Statistical Analysis

Groups	Normal renal function, Severe renal impairment
Other Geo-mean ratio	2.68
90 % Confidence Interval 2-Sided	1.89 to 3.78

Statistical Analysis

Groups	Normal renal function, Mild renal impairment
Other Geo-mean ratio	1.62
90 % Confidence Interval 2-Sided	1.17 to 2.25

Statistical Analysis

Groups	Normal renal function, Moderate renal impairment
Other Geo-mean ratio	1.94
90 % Confidence Interval 2-Sided	1.35 to 2.78

Statistical Analysis

Groups	Normal renal function, Severe renal impairment
Other Geo-mean ratio	2.67
90 % Confidence Interval 2-Sided	1.89 to 3.75

Primary pharmacokinetics (PK) parameter for ribociclib: CL/F

(Time Frame: Pre-dose/0h to 312h post dose)

	Normal renal function	Mild renal impairment	Moderate renal impairment	Severe renal impairment	End stage renal disease
Arm/Group Description	Cohort 1: absolute Glomerular Filtration Rate (GFR) (>= 90 ml/min)	Cohort 4: absolute GFR (60-89 ml/min)	Cohort 5: absolute GFR (30-59 ml/min)	Cohort 2: absolute GFR (15-29 ml/min)	Cohort 3: absolute GFR (<15 ml/min, not on dialysis)
Number of Participants Analyzed [units: participants]	14	8	6	7	3
Primary pharmacokinetics (PK) parameter for ribociclib: CL/F (units: Litre/hour (L/hr))					

Mean ± Standard Deviation					
	112 ± 79.0	63.4 ± 21.0	54.1 ± 21.7	38.7 ± 13.4	29.8 ± 5.91

Statistical Analysis

Groups	Normal renal function, Mild renal impairment
Other Geo-mean ratio	0.616
90 % Confidence Interval 2-Sided	0.444 to 0.855

Statistical Analysis

Groups	Normal renal function, Moderate renal impairment
Other Geo-mean ratio	0.515
90 % Confidence Interval 2-Sided	0.359 to 0.738

Statistical Analysis

Groups	Normal renal function, Severe renal impairment
Other Geo-mean ratio	0.375
90 % Confidence Interval 2-Sided	0.266 to 0.528

Primary pharmacokinetics (PK) parameter for ribociclib: Tmax

(Time Frame: Pre-dose/0h to 312h post dose)

	Normal renal function	Mild renal impairment	Moderate renal impairment	Severe renal impairment	End stage renal disease
Arm/Group Description	Cohort 1: absolute Glomerular Filtration Rate (GFR) (>= 90 ml/min)	Cohort 4: absolute GFR (60-89 ml/min)	Cohort 5: absolute GFR (30-59 ml/min)	Cohort 2: absolute GFR (15-29 ml/min)	Cohort 3: absolute GFR (<15 ml/min, not on dialysis)
Number of Participants Analyzed [units: participants]	14	8	6	7	3
Primary pharmacokinetics (PK) parameter for ribociclib: Tmax (units: Hour (hr)) Median (Full Range)					
	2.00 (0.917 to 6.05)	2.00 (1.00 to 3.93)	2.48 (0.983 to 6.02)	2.00 (0.967 to 3.00)	2.98 (2.00 to 4.03)

Statistical Analysis

Groups	Normal renal function, Mild renal impairment
Other Adjusted geo-mean	0.00
90 % Confidence Interval 2-Sided	0.00 to 0.00

Statistical Analysis

Groups	Normal renal function, Moderate renal impairment

Other Adjusted geo-mean	0.475
90 % Confidence Interval 2-Sided	0.00 to 0.475

Statistical Analysis

Groups	Normal renal function, Severe renal impairment
Other Adjusted geo-mean	0.00
90 % Confidence Interval 2-Sided	0.00 to 0.00

Primary pharmacokinetics (PK) parameter for LEQ803: Cmax

(Time Frame: Pre-dose/0h to 312h post dose)

	Normal renal function	**Mild renal impairment**	**Moderate renal impairment**	**Severe renal impairment**	**End stage renal disease**
Arm/Group Description	Cohort 1: absolute Glomerular Filtration Rate (GFR) (>= 90 ml/min)	Cohort 4: absolute GFR (60-89 ml/min)	Cohort 5: absolute GFR (30-59 ml/min)	Cohort 2: absolute GFR (15-29 ml/min)	Cohort 3: absolute GFR (<15 ml/min, not on dialysis)
Number of Participants Analyzed [units: participants]	14	8	6	7	3
Primary pharmacokinetics (PK) parameter for LEQ803: Cmax (units: ng/mL) Mean ± Standard Deviation					
	41.4 ± 17.7	49.5 ± 17.0	49.0 ± 18.4	39.4 ± 15.9	46.4 ± 22.7

Statistical Analysis

Groups	Normal renal function, Mild renal impairment
Other Adjusted geo-mean	1.23
90 % Confidence Interval 2-Sided	0.945 to 1.60

Statistical Analysis

Groups	Normal renal function, Moderate renal impairment
Other Adjusted geo-mean	1.20
90 % Confidence Interval 2-Sided	0.901 to 1.61

Statistical Analysis

Groups	Normal renal function, Severe renal impairment
Other Adjusted geo-mean	0.959
90 % Confidence Interval 2-Sided	0.728 to 1.26

Primary pharmacokinetics (PK) parameter for LEQ803: AUClast, AUCinf

(Time Frame: Pre-dose/0h to 312h post dose)

	Normal renal function	Mild renal impairment	Moderate renal impairment	Severe renal impairment	End stage renal disease

Arm/Group Description	Cohort 1: absolute Glomerular Filtration Rate (GFR) (>= 90 ml/min)	Cohort 4: absolute GFR (60-89 ml/min)	Cohort 5: absolute GFR (30-59 ml/min)	Cohort 2: absolute GFR (15-29 ml/min)	Cohort 3: absolute GFR (<15 ml/min, not on dialysis)
Number of Participants Analyzed [units: participants]	14	8	6	7	3
Primary pharmacokinetics (PK) parameter for LEQ803: AUClast, AUCinf (units: ng*hr/mL) Mean ± Standard Deviation					
AUClast	1210 ± 464	1600 ± 732	1740 ± 582	2080 ± 572	2410 ± 1330
AUCinf	1300 ± 483	1710 ± 750	1870 ± 612	2250 ± 570	2620 ± 1430

Statistical Analysis

Groups	Normal renal function, Mild renal impairment
Other Adjusted geo-mean	1.32
90 % Confidence Interval 2-Sided	1.02 to 1.73

Statistical Analysis

Groups	Normal renal function, Moderate renal impairment
Other Adjusted geo-mean	1.47
90 % Confidence Interval 2-Sided	1.10 to 1.97

Statistical Analysis

Groups	Normal renal function, Severe renal impairment
Other Adjusted geo-mean	1.79
90 % Confidence Interval 2-Sided	1.36 to 2.36

Statistical Analysis

Groups	Normal renal function, Mild renal impairment
Other Adjusted geo-mean	1.32
90 % Confidence Interval 2-Sided	1.02 to 1.70

Statistical Analysis

Groups	Normal renal function, Moderate renal impairment
Other Adjusted geo-mean	1.47
90 % Confidence Interval 2-Sided	1.11 to 1.94

Statistical Analysis

Groups	Normal renal function, Severe renal impairment
Other Adjusted geo-mean	1.80
90 % Confidence Interval 2-Sided	1.38 to 2.34

Primary pharmacokinetics (PK) parameter for LEQ803: Tmax

(Time Frame: Pre-dose/0h to 312h post dose)

	Normal renal function	Mild renal impairment	Moderate renal impairment	Severe renal impairment	End stage renal disease
Arm/Group Description	Cohort 1: absolute Glomerular Filtration Rate (GFR) (>= 90 ml/min)	Cohort 4: absolute GFR (60-89 ml/min)	Cohort 5: absolute GFR (30-59 ml/min)	Cohort 2: absolute GFR (15-29 ml/min)	Cohort 3: absolute GFR (<15 ml/min, not on dialysis)
Number of Participants Analyzed [units: participants]	14	8	6	7	3
Primary pharmacokinetics (PK) parameter for LEQ803: Tmax (units: Hour (hr)) Median (Full Range)					
	3.49 (0.917 to 6.00)	2.50 (1.95 to 3.93)	3.00 (1.95 to 6.02)	3.05 (2.00 to 6.02)	6.03 (3.97 to 8.02)

Statistical Analysis

Groups	Normal renal function, Mild renal impairment
Other Adjusted geo-mean	-0.992
90 % Confidence Interval 2-Sided	-0.992 to 0.00

Statistical Analysis

Groups	Normal renal function, Moderate renal impairment

Other Adjusted geo-mean	-0.492
90 % Confidence Interval 2-Sided	-0.492 to 0.00

Statistical Analysis

Groups	Normal renal function, Severe renal impairment
Other Adjusted geo-mean	-0.442
90 % Confidence Interval 2-Sided	-0.442 to 0.0

Secondary Outcome Result(s)

Secondary PK parameter of ribociclib: T1/2

(Time Frame: Pre-dose/0h to 312h post dose)

	Normal renal function	**Mild renal impairment**	**Moderate renal impairment**	**Severe renal impairment**	**End stage renal disease**
Arm/Group Description	Cohort 1: absolute Glomerular Filtration Rate (GFR) (>= 90 ml/min)	Cohort 4: absolute GFR (60-89 ml/min)	Cohort 5: absolute GFR (30-59 ml/min)	Cohort 2: absolute GFR (15-29 ml/min)	Cohort 3: absolute GFR (<15 ml/min, not on dialysis)
Number of Participants Analyzed [units: participants]	14	8	6	7	3
Secondary PK parameter of ribociclib: T1/2 (units: Hour (hr)) Mean ± Standard Deviation					

	36.9 ± 8.48	41.6 ± 8.41	51.2 ± 11.3	58.3 ± 17.0	55.1 ± 11.9

Secondary PK parameter of ribociclib: Lambda_z

(Time Frame: Pre-dose/0h to 312h post dose)

	Normal renal function	Mild renal impairment	Moderate renal impairment	Severe renal impairment	End stage renal disease
Arm/Group Description	Cohort 1: absolute Glomerular Filtration Rate (GFR) (>= 90 ml/min)	Cohort 4: absolute GFR (60-89 ml/min)	Cohort 5: absolute GFR (30-59 ml/min)	Cohort 2: absolute GFR (15-29 ml/min)	Cohort 3: absolute GFR (<15 ml/min, not on dialysis)
Number of Participants Analyzed [units: participants]	14	8	6	7	3
Secondary PK parameter of ribociclib: Lambda_z (units: 1/Hour (1/hr)) Mean ± Standard Deviation					
	0.0197 ± 0.00430	0.0172 ± 0.00344	0.0141 ± 0.00315	0.0128 ± 0.00369	0.0130 ± 0.00321

Secondary PK parameter of ribociclib: CLr

(Time Frame: Pre-dose/0h to 312h post dose)

	Normal renal function	Mild renal impairment	Moderate renal impairment	Severe renal impairment	End stage renal disease
Arm/Group Description	Cohort 1: absolute Glomerular Filtration Rate (GFR) (>= 90 ml/min)	Cohort 4: absolute GFR (60-89 ml/min)	Cohort 5: absolute GFR (30-59 ml/min)	Cohort 2: absolute GFR (15-29 ml/min)	Cohort 3: absolute GFR (<15 ml/min, not on dialysis)

Number of Participants Analyzed [units: participants]	14	8	6	7	3
Secondary PK parameter of ribociclib: CLr (units: Litre/hour (L/hr)) Mean ± Standard Deviation					
	5.40 ± 2.00	3.28 ± 0.965	2.83 ± 1.18	1.17 ± 0.347	0.652 ± 0.197

Secondary PK parameter of ribociclib: Vz/F

(Time Frame: Pre-dose/0h to 312h post dose)

	Normal renal function	Mild renal impairment	Moderate renal impairment	Severe renal impairment	End stage renal disease
Arm/Group Description	Cohort 1: absolute Glomerular Filtration Rate (GFR) (>= 90 ml/min)	Cohort 4: absolute GFR (60-89 ml/min)	Cohort 5: absolute GFR (30-59 ml/min)	Cohort 2: absolute GFR (15-29 ml/min)	Cohort 3: absolute GFR (<15 ml/min, not on dialysis)
Number of Participants Analyzed [units: participants]	14	8	6	7	3
Secondary PK parameter of ribociclib: Vz/F (units: Litre (L)) Mean ± Standard Deviation					
	5470 ± 2550	3730 ± 1230	3840 ± 1410	3090 ± 854	2320 ± 339

Secondary PK parameter of LEQ803: T1/2

(Time Frame: Pre-dose/0h to 312h post dose)

	Normal renal function	Mild renal impairment	Moderate renal impairment	Severe renal impairment	End stage renal disease
Arm/Group Description	Cohort 1: absolute Glomerular Filtration Rate (GFR) (>= 90 ml/min)	Cohort 4: absolute GFR (60-89 ml/min)	Cohort 5: absolute GFR (30-59 ml/min)	Cohort 2: absolute GFR (15-29 ml/min)	Cohort 3: absolute GFR (<15 ml/min, not on dialysis)
Number of Participants Analyzed [units: participants]	14	8	6	7	3
Secondary PK parameter of LEQ803: T1/2 (units: Hour (hr)) Mean ± Standard Deviation					
	52.0 ± 12.5	60.9 ± 12.7	67.9 ± 13.4	81.5 ± 27.9	87.1 ± 10.1

Secondary PK parameter of LEQ803: Lambda_z

(Time Frame: Pre-dose/0h to 312h post dose)

	Normal renal function	Mild renal impairment	Moderate renal impairment	Severe renal impairment	End stage renal disease
Arm/Group Description	Cohort 1: absolute Glomerular Filtration Rate (GFR) (>= 90 ml/min)	Cohort 4: absolute GFR (60-89 ml/min)	Cohort 5: absolute GFR (30-59 ml/min)	Cohort 2: absolute GFR (15-29 ml/min)	Cohort 3: absolute GFR (<15 ml/min, not on dialysis)
Number of Participants Analyzed [units: participants]	14	8	6	7	3
Secondary PK parameter of LEQ803: Lambda_z (units: 1/Hour (1/hr))					

Mean ± Standard Deviation					
	0.0141 ± 0.00324	0.0118 ± 0.00249	0.0106 ± 0.00238	0.00923 ± 0.00262	0.00803 ± 0.000969

Secondary PK parameter of LEQ803: CLr

(Time Frame: Pre-dose/0h to 312h post dose)

	Normal renal function	Mild renal impairment	Moderate renal impairment	Severe renal impairment	End stage renal disease
Arm/Group Description	Cohort 1: absolute Glomerular Filtration Rate (GFR) (>= 90 ml/min)	Cohort 4: absolute GFR (60-89 ml/min)	Cohort 5: absolute GFR (30-59 ml/min)	Cohort 2: absolute GFR (15-29 ml/min)	Cohort 3: absolute GFR (<15 ml/min, not on dialysis)
Number of Participants Analyzed [units: participants]	14	8	6	7	3
Secondary PK parameter of LEQ803: CLr (units: Litre/hour (L/hr)) Mean ± Standard Deviation					
	8.38 ± 2.86	5.91 ± 1.83	5.24 ± 2.02	2.06 ± 0.624	1.20 ± 0.231

Secondary PK parameter of ribociclib: MR

(Time Frame: Pre-dose/0h to 312h post dose)

	Normal renal function	Mild renal impairment	Moderate renal impairment	Severe renal impairment	End stage renal disease
Arm/Group Description	Cohort 1: absolute Glomerular Filtration Rate	Cohort 4: absolute GFR (60-89 ml/min)	Cohort 5: absolute GFR (30-59 ml/min)	Cohort 2: absolute GFR (15-29 ml/min)	Cohort 3: absolute GFR (<15 ml/min,

	(GFR) (>= 90 ml/min)				not on dialysis)
Number of Participants Analyzed [units: participants]	14	8	6	7	3
Secondary PK parameter of ribociclib: MR (units: ratio) Mean ± Standard Deviation					
	0.338 ± 0.147	0.262 ± 0.0734	0.245 ± 0.0899	0.221 ± 0.0983	0.208 ± 0.125

Secondary PK parameter of ribociclib: Ae0-144h

(Time Frame: Pre-dose/0h to 144h post dose)

	Normal renal function	**Mild renal impairment**	**Moderate renal impairment**	**Severe renal impairment**	**End stage renal disease**
Arm/Group Description	Cohort 1: absolute Glomerular Filtration Rate (GFR) (>= 90 ml/min)	Cohort 4: absolute GFR (60-89 ml/min)	Cohort 5: absolute GFR (30-59 ml/min)	Cohort 2: absolute GFR (15-29 ml/min)	Cohort 3: absolute GFR (<15 ml/min, not on dialysis)
Number of Participants Analyzed [units: participants]	14	8	6	7	3
Secondary PK parameter of ribociclib: Ae0-144h (units: mg) Mean ± Standard Deviation					
	22.6 ± 9.10	20.6 ± 5.63	20.3 ± 6.74	11.8 ± 3.33	8.21 ± 1.50

Secondary PK parameter of LEQ803: Ae0-144h

(Time Frame: Pre-dose/0h to 144h post dose)

	Normal renal function	Mild renal impairment	Moderate renal impairment	Severe renal impairment	End stage renal disease
Arm/Group Description	Cohort 1: absolute Glomerular Filtration Rate (GFR) (>= 90 ml/min)	Cohort 4: absolute GFR (60-89 ml/min)	Cohort 5: absolute GFR (30-59 ml/min)	Cohort 2: absolute GFR (15-29 ml/min)	Cohort 3: absolute GFR (<15 ml/min, not on dialysis)
Number of Participants Analyzed [units: participants]	14	8	6	7	3
Secondary PK parameter of LEQ803: Ae0-144h (units: mg) Mean ± Standard Deviation					
	9.36 ± 3.77	8.25 ± 3.27	7.76 ± 4.06	3.43 ± 0.958	2.37 ± 1.16

Summary of Safety

Safety Results

All-Cause Mortality

	Normal renal function N = 14	Mild renal impairment N = 8	Moderate renal impairment N = 6	Severe renal impairment N = 7	End stage renal disease N = 3	All subjects N = 38

Arm/Group Description	Cohort 1: absolute Glomerular Filtration Rate (GFR) (>= 90 ml/min)	Cohort 4: absolute GFR (60-89 ml/min)	Cohort 5: absolute GFR (30-59 ml/min)	Cohort 2: absolute GFR (15-29 ml/min)	Cohort 3: absolute GFR (<15 ml/min, not on dialysis)	Cohort 1 to 5
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

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 reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.
Source Vocabulary for Table Default	MedDRA 20.1
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	Normal renal function N = 14	**Mild renal impairment N = 8**	**Moderate renal impairment N = 6**	**Severe renal impairment N = 7**	**End stage renal disease N = 3**	**All subjects N = 38**
Arm/Group Description	Cohort 1: absolute Glomerular Filtration Rate (GFR) (>= 90 ml/min)	Cohort 4: absolute GFR (60-89 ml/min)	Cohort 5: absolute GFR (30-59 ml/min)	Cohort 2: absolute GFR (15-29 ml/min)	Cohort 3: absolute GFR (<15 ml/min, not on dialysis)	Cohort 1 to 5
Total participants affected	3 (21.43%)	2 (25.00%)	2 (33.33%)	4 (57.14%)	1 (33.33%)	12 (31.58%)

Cardiac disorders						
Tachycardia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	1 (2.63%)
Gastrointestinal disorders						
Abdominal pain	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)
Constipation	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	1 (2.63%)
Diarrhoea	1 (7.14%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (5.26%)
General disorders and administration site conditions						
Catheter site haematoma	1 (7.14%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)
Chest discomfort	0 (0.00%)	1 (12.50%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)
Infections and infestations						
Influenza	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	1 (2.63%)
Investigations						
Blood creatinine increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (14.29%)	0 (0.00%)	1 (2.63%)
Musculoskeletal and connective tissue disorders						
Arthralgia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)	1 (2.63%)
Back pain	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (2.63%)
Nervous system disorders						
Head discomfort	1 (7.14%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.63%)
Headache	1 (7.14%)	0 (0.00%)	1 (16.67%)	1 (14.29%)	0 (0.00%)	3 (7.89%)

Skin and subcutaneous tissue disorders						
Dry skin	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)	0 (0.00%)	1 (2.63%)

Other Relevant Findings

Not Applicable

Conclusion:

Results from this study demonstrated that ribociclib exposure was higher in subjects with renal impairment compared to subjects with normal renal function. AUCinf and Cmax increased 1.62 and 1.80-fold in mild, 1.94 and 1.79-fold in moderate, and 2.67 and 2.30-fold in severe renal impairment subjects compared to subjects with normal renal function. Median Tmax values were similar in the renal impairment cohorts compared to the normal renal function cohort. A single oral dose of 400 mg ribociclib was generally safe and well tolerated in healthy subjects with normal renal function and in subjects with varying degrees of impaired renal function.

Date of Clinical Trial Report

19 Dec 2018