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Clinical Trial Results Database

Sponsor

Novartis

Generic Drug Name

Osilodrostat

Trial Indication(s)

Impaired renal function

Protocol Number

CLCI699C2104

Protocol Title

A Phase I, open-label, multi-center, single dose, parallel group study to evaluate the pharmacokinetics and safety of LCI699 in subjects with varying degrees of impaired renal function compared to subjects with normal renal function

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase III

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Study Start/End Dates

06-Nov-2015 to 21-Mar-2016

Reason for Termination (If applicable)

NA.

Study Design/Methodology

This was a Phase I, open-label, multi-center, single dose, parallel group study which evaluated the PK and safety of LCI699 in subjects with varying degrees of impaired renal function compared to subjects with normal renal function.

Subjects were staged by their respective degree of renal function (normal, severe and end stage renal disease (ESRD)) according to the Classification of Renal Function from Food and Drug Administration (2010) and European Medicines Agency (2014), as well as in control cohort (subjects with normal renal function), based on eGFR (modification of diet in renal disease equation) and calculated absolute GFR (not adjusted by body surface area) determined at the Baseline visit using serum creatinine levels measured with a standardized assay (i.e., kinetic alkaline picrate).

If the interim PK analysis results showed a change in LCI699 exposure in subjects with severe renal impairment compared to subjects with normal renal function (≥50% change in AUCinf and safety assessments consideration), Part II of the study was supposed to start; otherwise, Part II did not need to be undertaken, which was the case for this study.

Centers

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

Publication

None

Objectives:

Primary objective:

- To assess the effect of varying degrees of impaired renal function on the primary PK of osilodrostat compared to a matched control group of healthy volunteers with normal renal function.

Secondary objectives:

- To assess the effect of varying degrees of impaired renal function on secondary PK parameters of osilodrostat
- To assess the safety and tolerability of a single oral dose of osilodrostat in subjects with varying degrees of impaired renal function.

Test Product, Dose, and Mode of Administration

Osilodrostat film-coated tablets were supplied at dose strengths of 10 mg. Treatment consisted of a single 30 mg osilodrostat dose.

Statistical Methods

A linear model including renal function cohort (normal, severe, and ESRD) as a fixed effect was fit to the log-transformed primary PK parameters (Cmax, AUCinf, AUClast, CL/F, and CLR). The severe, and ESRD were the test cohorts and the normal cohort was the reference cohort. Point estimates and corresponding 90% confidence intervals for the least square mean difference between each test and the reference cohort (test - reference) were calculated. The geometric mean ratio and their 90% confidence intervals were derived by anti-logged transformation of point estimates and the corresponding 90% confidence intervals for the least square mean difference between each test and the reference cohort. No formal statistical hypothesis was tested.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

- Male or female aged 18 to 75 years.
- Weight $\geq$ 50 kg.
- Body mass index 18 to 35 kg/m^2.

- Stable renal disease without evidence of progressive decline in renal function (stable renal disease was defined as no significant change, such as, stable estimated glomerular filtration rate (eGFR) <90 mL/min, for 12 weeks prior to study entry)
- Other than renal impairment, subjects were stable and appropriately managed relative to chronic diseases (such as diabetes and hypertension).

Exclusion criteria

- History of any surgical or medical condition other than renal impairment which might significantly alter the absorption, distribution, metabolism or excretion of drugs.
- Ongoing alcohol or drug abuse within 1 month prior to dosing or evidence of such abuse as indicated by the laboratory assays conducted during the screening or baseline evaluations.
- Screening 12-lead electrocardiogram QTcF of >450 ms for males or >460 ms for female.

Participant Flow Table

Subject disposition, by renal function cohort (Full analysis set)

Disposition	Normal N=6	Severe N=6	ESRD N=3	All subjects N=15
Completed, n (%)	6 (100)	6 (100)	3 (100)	15 (100)

ESRD: end stage renal disease.

Baseline Characteristics

Demographics and other Baseline characteristics by renal function cohort (Full analysis set)

Demographic variable, n (%)	Normal (N=6)	Severe (N=6)	ESRD (N=3)	All subjects (N=15)
Age (years)				
n	6	6	3	15
Mean (SD)	55.2 (14.51)	55.0 (10.35)	51.3 (15.50)	54.3 (12.26)

Demographic variable, n (%)	Normal (N=6)	Severe (N=6)	ESRD (N=3)	All subjects (N=15)
Median	56.0	59.5	51.0	56.0
Min-Max	32 - 72	38 - 64	36 - 67	32 - 72
Sex				
Male	3 (50.0)	5 (83.3)	0	8 (53.3)
Female	3 (50.0)	1 (16.7)	3 (100)	7 (46.7)
Race				
Caucasian	6 (100)	6 (100)	3 (100)	15 (100)
Ethnicity				
Other	6 (100)	6 (100)	3 (100)	15 (100)
Weight (kg)				
n	6	6	3	15
Mean (SD)	75.92 (12.815)	78.33 (15.462)	70.33 (17.502)	75.77 (14.034)
Median	77.20	79.00	70.00	79.00
Min-Max	54.8 - 94.4	58.0 - 105.0	53.0 - 88.0	53.0 - 105.0
Height (cm)				
n	6	6	3	15
Mean (SD)	172.8 (8.40)	174.5 (8.80)	163.3 (4.16)	171.6 (8.62)
Median	173.0	176.5	162.0	172.0
Min-Max	159 - 184	160 - 186	160 - 168	159 - 186
BMI (kg/m^2)				
n	6	6	3	15
Mean (SD)	25.228 (2.2219)	25.733 (4.8484)	26.460 (7.2343)	25.677 (4.2254)
Median	25.510	24.930	24.800	24.930
Min-Max	21.68 - 27.88	20.07 - 34.29	20.20 - 34.38	20.07 - 34.38
BSA (m^2)				
n	6	6	3	15
Mean (SD)	1.906 (0.2075)	1.942 (0.2113)	1.776 (0.2183)	1.894 (0.2053)

Demographic variable, n (%)	Normal (N=6)	Severe (N=6)	ESRD (N=3)	All subjects (N=15)
Median	1.917	1.976	1.807	1.948
Min-Max	1.56 - 2.20	1.65 - 2.26	1.54 - 1.98	1.54 - 2.26

BMI: body mass index; BSA: body surface area; ESRD: end stage renal disease.
The Baseline weight (kg) and Baseline height (cm) were defined as the last non-missing assessment of weight and height before the first study drug administration.
BMI (kg/m2) = weight (kg) / height (m)2. BSA (m2) = sqrt (weight(kg) x height(cm))/60. BMI and BSA are calculated using the Baseline weight and Screening height.

Summary of Efficacy

Primary Outcome Results

Summary of primary PK parameters for osilodrostat by renal function cohort (Pharmacokinetic analysis set)

Parameter	Statistics	Normal (N=6)	Severe (N=6)	ESRD (N=3)
Cmax (ng/mL)	n	6	6	3
	Mean (SD)	214 (65.0)	187 (22.0)	171 (15.4)
	CV% mean	30.4	11.8	9.0
	Geo-mean	207	186	171
	CV% geo-mean	28.6	11.7	9.2
	Median	202	188	175
	Min-Max	153 - 332	161 - 222	154 - 184
AUCinf (ng•hr/mL)	n	6	6	3
	Mean (SD)	1820 (555)	1720 (282)	1780 (465)
	CV% mean	30.4	16.5	26.1
	Geo-mean	1760	1700	1740
	CV% geo-mean	29.7	17.6	26.0

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Parameter	Statistics	Normal (N=6)	Severe (N=6)	ESRD (N=3)
	Median	1810	1770	1680
	Min-Max	1270 - 2790	1250 - 2100	1380 - 2290
AUClast (ng•hr/mL)	n	6	6	3
	Mean (SD)	1800 (556)	1690 (280)	1760 (446)
	CV% mean	30.8	16.6	25.4
	Geo-mean	1740	1670	1720
	CV% geo-mean	30.3	17.5	25.6
	Median	1790	1720	1680
	Min-Max	1250 - 2760	1240 - 2090	1350 - 2240
CL/F (L/hr)	n	6	6	3
	Mean (SD)	17.6 (4.86)	17.9 (3.32)	17.6 (4.34)
	CV% mean	27.6	18.5	24.7
	Geo-mean	17.1	17.7	17.2
	CV% geo-mean	29.7	17.6	26.0
	Median	16.7	16.9	17.8
	Min-Max	10.8 - 23.6	14.3 - 24.0	13.1 - 21.8
CLR (L/hr)	n	6	6	3
	Mean (SD)	1.18 (0.501)	0.746 (0.485)	0.582 (0.546)
	CV% mean	42.5	65.0	93.8
	Geo-mean	1.10	0.613	0.416
	CV% geo-mean	42.5	81.3	138.7
	Median	1.07	0.667	0.399
	Min-Max	0.644 - 2.05	0.240 - 1.52	0.151 - 1.20

CV: coefficient of variation; ESRD: end stage renal disease; SD: standard deviation.
n: number of subjects with corresponding evaluable PK parameters.
CV% = coefficient of variation (%) = sd/mean*100, CV% geometric-mean = sqrt (exp (variance for log transformed data)-1)*100.

Secondary Outcome Results

Summary of secondary PK parameters for osilodrostat by renal function cohort (Pharmacokinetic analysis set)

Parameter	Statistics	Normal (N=6)	Severe (N=6)	ESRD (N=3)
Tmax (hr)	n	6	6	3
	Median	1.00	1.46	3.00
	Min-Max	0.500 - 1.50	0.500 - 2.00	0.500 - 3.00
T1/2 (hr)	n	6	6	3
	Mean (SD)	4.72 (0.588)	4.64 (1.59)	5.46 (2.30)
	CV% mean	12.4	34.2	42.1
	Geo-mean	4.69	4.46	5.17
	CV% geo-mean	12.3	30.5	40.6
	Median	4.60	4.16	4.27
	Min-Max	4.12 - 5.45	3.44 - 7.69	4.01 - 8.11
Vz/F (L)	n	6	6	3
	Mean (SD)	117 (20.9)	120 (46.1)	130 (22.0)
	CV% mean	17.8	38.5	16.9
	Geo-mean	116	114	128
	CV% geo-mean	19.1	34.0	16.9
	Median	119	109	126
	Min-Max	84.1 - 142	83.5 - 209	110 - 153
Ae0-72 (ng)	n	6	6	3
	Mean (SD)	2060000 (952000)	1230000 (772000)	1180000 (1360000)
	CV% mean	46.2	62.7	115.0
	Geo-mean	1930000	1040000	726000
	CV% geo-mean	37.3	72.3	183.4
	Median	1730000	1030000	550000
	Min-Max	1520000 - 3990000	504000 - 2400000	254000 - 2740000

CV: coefficient of variation; ESRD: end stage renal disease; SD: standard deviation.
n: number of subjects with corresponding evaluable PK parameters.
CV% = coefficient of variation (%) = sd/mean*100, CV% geometric-mean = sqrt (exp (variance for log transformed data)-1)*100.

Summary of Safety

Safety Results

AEs regardless of study drug relationship by preferred term and renal function cohort (Safety set)

Preferred term, n (%)	Normal N=6	Severe N=6	ESRD N=3	All Subjects N=15
Total	0	2 (33.3)	2 (66.7)	4 (26.7)
Blood creatinine increased	0	1 (16.7)	1 (33.3)	2 (13.3)
Blood creatine increased	0	0	1 (33.3)	1 (6.7)
Blood creatine phosphokinase increased	0	0	1 (33.3)	1 (6.7)
Blood uric acid increased	0	0	1 (33.3)	1 (6.7)
Hypoglycaemia	0	1 (16.7)	0	1 (6.7)
Hypotension	0	1 (16.7)	0	1 (6.7)

Preferred terms are sorted by descending order of frequencies, as reported in the All subjects column.
A subject with multiple occurrences of an AE under one renal function cohort is counted only once in the AE category for that renal function cohort.
A subject with multiple adverse events is counted only once in the total row.

Adverse events, suspected to be study drug related, by primary system organ classes, preferred term, maximum CTCAE grade and renal function cohort (Safety set)

Primary system organ class Preferred term Maximum grade	Normal N=6 n (%)	Severe N=6 n (%)	ESRD N=3 n (%)	All Subjects N=15 n (%)
-Any primary system organ class				
-Total	0	0	1 (33.3)	1 (6.7)
Grade 1	0	0	1 (33.3)	1 (6.7)

Primary system organ class Preferred term Maximum grade	Normal N=6 n (%)	Severe N=6 n (%)	ESRD N=3 n (%)	All Subjects N=15 n (%)
Investigations				
-Total	0	0	1 (33.3)	1 (6.7)
Grade 1	0	0	1 (33.3)	1 (6.7)
Blood creatine increased	0	0	1 (33.3)	1 (6.7)
Grade 1	0	0	1 (33.3)	1 (6.7)
Blood creatine phosphokinase increased	0	0	1 (33.3)	1 (6.7)
Grade 1	0	0	1 (33.3)	1 (6.7)

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class by descending order of frequencies, as reported in the All subjects column.
A subject with multiple occurrences of an AE under one renal function cohort is counted only once in the AE category for that renal function cohort.
A subject with multiple adverse events within a primary system organ class is counted only once in the total row.

Other Relevant Findings

NA

Conclusion:

The study results indicate that there is no significant change between the degree of renal impairment and change of PK exposure. Calculated geometric mean ratio (GMR), between severe and normal cohorts of PK parameters (AUClast, AUCinf), is not greater than 1.5. In addition, the safety findings in subjects with renal impairment were consistent with the known safety profile of osilodrostat for a single 30 mg dose. This indicated that the study will not be continued for Part II for additional renal impairment.

Date of Clinical Trial Report

3 October 2016