Novartis Clinical Trial Results

Sponsor:

Novartis

Generic Drug Name:

Osilodrostat

Trial Indication(s)

Hepatic impairment

Protocol Number

CLCI699C2103

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 impaired hepatic function compared to subjects with normal hepatic function

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase III

Study Start/End Dates

First patient enrolled: 21-Apr-2015 (first subject first visit)

Last patient completed: 19-May-2016 (last subject last visit)

Reason for Termination (If applicable)

Not Applicable

Study Design/Methodology

This was an open-label, multi-center, single dose, parallel group study to evaluate the pharmacokinetics and safety of a single dose of osilodrostat 30 mg in subjects with varying degrees of hepatic impairment according to the Child-Pugh classification (mild, moderate, severe), and a matching control cohort of subjects with normal liver function.

Centers

This study was conducted at three centers in the United States

Objectives:

Primary: To assess the pharmacokinetics of a single dose of osilodrostat in subjects with impaired hepatic function (Child-Pugh; mild, moderate and severe) compared to subjects with normal hepatic function.

Secondary

- To evaluate the relationship between hepatic function parameters and pharmacokinetics
- To evaluate the safety of osilodrostat in subjects with varying degrees of hepatic impairment

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

Study drug	Pharmaceutical form and route of administration
Osilodrostat	Film coated tablets (10 mg strength) for oral use

Statistical Methods

Three analysis sets were defined for the evaluation of data from this study:

Full analysis set (FAS): The Full Analysis Set (FAS) comprised all subjects who received study medication (osilodrostat).

Safety set: The safety set included all subjects who received study medication (osilodrostat).

Pharmacokinetic analysis set (PAS):

The Pharmacokinetic Analysis Set (PAS) included all subjects who received the planned amount of study drug (osilodrostat), did not vomit within 4 hours of study drug administration and provided sufficient PK data to determine at least one primary PK parameter (Cmax, AUClast, AUCinf).

PK evaluations – Analysis of PK:

No formal statistical hypothesis was tested as the main purpose of the statistical analysis was to estimate the effects of hepatic impairment on the PK of osilodrostat.

Following log-transformation, the osilodrostat PK parameters (Cmax, AUClast, and AUCinf) were analyzed by means of an analysis of variance (ANOVA) model including impairment cohort (normal, mild, moderate, and severe) as fixed effect. The mild, moderate and severe hepatic cohorts were the test treatments and the normal cohort was the reference treatment. Point estimates and the corresponding 90% confidence intervals for the mean difference between each test and the reference cohort were calculated. The geometric mean ratio and their 90% CI were derived by anti-logged transformation of point estimates and the corresponding 90% confidence intervals for the mean difference between each test and the reference cohort.

The effect of baseline covariates (such as sex, age and weight) on PK parameters (Cmax, AUClast, and AUCinf) of osilodrostat was investigated.

A sensitivity analysis was performed on the primary PK parameters (Cmax, AUClast, and AUCinf) excluding subjects with the protocol deviation ID G05 (i.e., subjects that received drug from a bottle open for >3 months).

All pharmacokinetic parameters and concentrations were summarized in descriptive statistics presenting n, geometric and arithmetic means, SD, CV% and CV% geo-mean, median, min and max (for Tmax only median, minimum and maximum) by hepatic function group and by time point where applicable. All plasma PK parameters and concentrations were listed.

All analyses were conducted using the PAS unless otherwise specified. All data was listed by hepatic cohort using the FAS.

Analysis of safety

For all safety analyses, the safety set was used. All listings were presented by hepatic cohort.

Adverse events (AEs)

Adverse events were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE, version 4.03). Only treatment-emergent adverse events (TEAEs) recorded during the study were summarized. TEAEs are defined as those that started on or after the day study drug was administered but not after the end of study or after 30 days from the study drug administration date (whichever is longer), or those that started before study drug administration but worsened afterwards. The incidence (number and percentage) of TEAEs (new or worsening from Baseline) was summarized by system organ class (SOC), preferred term (PT), and maximum severity (based on CTCAE grades) by hepatic impairment group. Additional summary tables were provided for the TEAEs which were suspected to be related to the study drug and for serious adverse events. Treatment-emergent serious AEs (SAEs), deaths, and TEAEs that caused study drug discontinuation, required dose adjustment or interruption, as well as TEAEs of special interest were listed separately. All adverse events (regardless whether defined as treatment emergent or not) recorded during the study were listed. Non treatment-emergent AEs were flagged in listings.

Laboratory abnormalities:

All laboratory values were converted into SI units and classified in severity grades using appropriate CTCAE version 4.03. Laboratory data for hematology and chemistry were summarized by presenting summary statistics and change from baseline values (means, medians, standard deviations, ranges). Subject listings were provided with abnormal values flagged.

Other safety data

Data from other tests (e.g., electrocardiogram (ECG) and vital signs) were listed, notable values were flagged, and any other information collected was listed as appropriate.

ECG

ECG data was summarized by presenting summary statistics of raw data and change from Baseline by hepatic function group and Visit and time of measurement. Individual listings were provided for the ECG parameters by hepatic function group with out-of-range and notable abnormal values flagged.

Vital signs

For vital signs, summary statistics for baseline values, actual assessments values, and change from baseline values were presented by visit and hepatic cohort using the Safety Set. All vital signs and weights for all subjects were listed by subject and hepatic cohort using the FAS and notably abnormal values were flagged.

Study Population: Key Inclusion/Exclusion Criteria

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 years and 75 years of age.
- Body mass index (BMI) between 18 kg/m2 and 38 kg/m2 and a weight of at least 50 kg

Subjects in Child-Pugh Class A, B and C (Cohorts 2 - 4)

- Subjects with evidence of hepatic impairment, consistent with the Child-Pugh Clinical Assessment Score A, B or C.
- Subjects with stable hepatic cirrhosis confirmed by imaging or histopathology.
- Subjects with physical signs consistent with a clinical diagnosis of stable liver cirrhosis (e.g., liver firmness to palpation, splenic enlargement, ascites, jaundice, spider angiomata, palmar erythema, parotid hypertrophy, testicular atrophy, gynecomastia).

Subjects with normal hepatic function (Cohort 1):

- Healthy subjects as determined by the Investigator on the basis of past medical history, physical examination, vital signs, electrocardiogram, and clinical laboratory tests at screening.

- Laboratory values (hematology, blood chemistry and Urinary tests) within normal range, unless deemed not clinically significant by the Investigator and approved by the Sponsor.

Key exclusion criteria

- A known hypersensitivity or history of intolerance to osilodrostat or drugs related to investigational drug class
- History of exposure to systemic glucocorticoid therapy during the 3 months prior to study entry.
- Any surgical or medical condition that may significantly alter the absorption, distribution, metabolism or excretion of drugs (e.g. surgical portosystemic shunt)
- Subjects receiving any concomitant medication that is a strong inducer of CYP3A4/5

Subjects with normal hepatic function (Cohort 1):

- Clinical evidence of hepatic disease or hepatic injury as indicated by abnormal hepatic function tests and/or a positive Hepatitis B surface antigen or Hepatitis C test result.
- History of cardiovascular disease (e.g. ischemic heart disease, heart failure).
- Use of prescription drug or over the counter medication within 14 days prior to dosing.

Subjects in Child-Pugh Class A, B and C (Cohorts 2 - 4):

- Symptoms or history of grade 2 or above encephalopathy within 3 months prior to dosing, clinical evidence of severe ascites, (INR) >3, or total bilirubin >6 mg/dL.
- History or presence of impaired renal function; or in the absence of intrinsic renal disease, creatinine clearance <50 mL/min and/or blood urea nitrogen (BUN) values and/or abnormal urinary constituents (e.g., albuminuria) and/or serum creatinine >1.5 mg/dL.
- Subjects with history of heart failure.

Participant Flow Table

Disposition reason	Normal	Mild	Moderate	Severe	All Subjects
	N=10	N=8	N=8	N=7	N=33
	n (%)	n (%)	n (%)	n (%)	n (%)
Completed	9 (90.0)	8 (100)	8 (100)	7 (100)	32 (97.0)
Discontinued	1 (10.0)	0	0	0	1 (3.0)
Subject withdrew consent	1 (10.0)	0	0	0	1 (3.0)

Baseline Characteristics

Demographic Variable	Normal N=10	Mild N=8	Moderate N=8	Severe N=7	All Subjects N=33
Age (years)					
n	10	8	8	7	33
Mean	55.1	55.8	59.9	54.7	56.3
SD	5.45	6.71	7.45	7.78	6.78
Median	54.5	55.5	62.5	53.0	56.0
Minimum	48	46	43	44	43
Maximum	64	65	66	64	66
Sex -n (%)					
Male	7 (70.0)	6 (75.0)	7 (87.5)	4 (57.1)	24 (72.7)
Female	3 (30.0)	2 (25.0)	1 (12.5)	3 (42.9)	9 (27.3)
Race -n (%)					
Caucasian	9 (90.0)	6 (75.0)	8 (100)	5 (71.4)	28 (84.8)
Black	1 (10.0)	1 (12.5)	0	0	2 (6.1)
Asian	0	1 (12.5)	0	0	1 (3.0)
Native American	0	0	0	1 (14.3)	1 (3.0)
Other	0	0	0	1 (14.3)	1 (3.0)
Ethnicity -n (%)					
Hispanic/Latino	3 (30.0)	4 (50.0)	3 (37.5)	3 (42.9)	13 (39.4)
Other	7 (70.0)	4 (50.0)	5 (62.5)	4 (57.1)	20 (60.6)
Weight (kg)					
Mean	85.15	79.09	85.71	87.53	84.32
SD	11.447	14.876	18.805	18.888	15.470
Median	85.60	75.65	83.85	83.20	83.20
Minimum	67.0	60.7	66.0	61.3	60.7

Demographic Variable	Normal N=10	Mild N=8	Moderate N=8	Severe N=7	All Subjects N=33
Maximum	105.0	103.9	124.1	122.1	124.1
Height (cm)					
Mean	171.96	168.19	172.25	168.29	170.34
SD	8.910	8.319	7.904	10.992	8.809
Median	171.25	167.15	172.50	170.00	170.00
Minimum	157.0	158.2	162.0	152.0	152.0
Maximum	187.0	180.0	184.0	182.0	187.0
BMI (kg/m^2)					
Mean	28.812	28.151	28.754	30.743	29.047
SD	3.2986	6.0935	5.0258	4.6724	4.6551
Median	28.585	26.920	27.870	31.510	28.030
Minimum	21.88	21.00	21.71	23.95	21.00
Maximum	33.20	37.34	38.43	36.86	38.43

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/m**2) = weight (kg) / height (m)**2. BMI is calculated using the Baseline weight and Screening height.

Summary of Pharmacokinetics

Primary Outcome Result(s)

Summary of primary PK parameters for LCI699 by hepatic impairment group (Pharmacokinetic analysis set)

Hepatic impairment group	Statistics	Cmax (ng/mL)	AUClast (ng.h/mL)	AUCinf (ng.h/mL)
Normal (N=9)	**n**	**9**	**9**	**9**
	Mean (SD)	209 (38.1)	1520 (422)	1570 (435)
	CV% mean	18.2	27.7	27.7
	Geo-mean	206	1470	1520
	CV% geo-mean	18.9	28.0	27.9
	Median	213	1660	1740
	[Min; Max]	[156; 266]	[1060; 2310]	[1080; 2400]
Mild (N=8)	**n**	**8**	**8**	**8**
	Mean (SD)	220 (102)	1600 (880)	1610 (880)
	CV% mean	46.3	55.2	54.7
	Geo-mean	188	1280	1300
	CV% geo-mean	81.8	103.6	98.5
	Median	202	1430	1450
	[Min; Max]	[36.9; 346]	[187; 3080]	[207; 3090]
Moderate (N=8)	**n**	**8**	**8**	**8**
	Mean (SD)	180 (44.7)	2290 (847)	2330 (864)
	CV% mean	24.9	36.9	37.0
	Geo-mean	174	2140	2180
	CV% geo-mean	28.7	42.9	42.9
	Median	193	2570	2610
	[Min; Max]	[102; 231]	[1260; 3260]	[1280; 3290]
Severe (N=7)	**n**	**7**	**7**	**7**
	Mean (SD)	170 (49.5)	4010 (1060)	4180 (1190)

Hepatic impairment group	Statistics	Cmax (ng/mL)	AUClast (ng.h/mL)	AUCinf (ng.h/mL)
	CV% mean	29.1	26.4	28.4
	Geo-mean	164	3880	4040
	CV% geo-mean	29.7	28.0	29.6
	Median	170	4360	4540
	[Min; Max]	[106; 259]	[2730; 5400]	[2770; 5980]

n: number of subjects with non-missing values.

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 LCI699 (Pharmacokinetic analysis set)

					Hepatic impairment group comparison		
						90% CI	
PK Parameter (unit)	Group	n*	Adjusted geo-mean	Comparison(s)	Geo-mean Ratio	Lower	Upper
Cmax (ng/mL)	Normal	9	206				
	Mild	8	188	Mild/Normal	0.912	0.645	1.29
	Moderate	8	174	Moderate/Normal	0.846	0.598	1.20
	Severe	7	164	Severe/Normal	0.798	0.557	1.14
AUCinf (ng.h/mL)	Normal	9	1520				
	Mild	8	1300	Mild/Normal	0.860	0.569	1.30
	Moderate	8	2180	Moderate/Normal	1.44	0.950	2.18
	Severe	7	4040	Severe/Normal	2.66	1.73	4.09
AUClast (ng.h/mL)	Normal	9	1470				
	Mild	8	1280	Mild/Normal	0.869	0.569	1.33
	Moderate	8	2140	Moderate/Normal	1.45	0.953	2.22
	Severe	7	3880	Severe/Normal	2.64	1.70	4.09

					Hepatic impairment group comparison		
						90% CI	
PK Parameter (unit)	Group	n*	Adjusted geo-mean	Comparison(s)	Geo-mean Ratio	Lower	Upper

Model is a linear model of the log-transformed PK parameters, including hepatic impairment status as fixed effect.

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

The analysis is conducted on log-transformed PK parameters. Then the results are back- transformed to get adjusted geo-mean, GM ratio and 90% CI.

Summary of statistical analysis of primary PK parameters for LCI699 with weight as covariate (Pharmacokinetic analysis set)

						Hepatic impairment group comparison		
							90% CI	
PK Parameter (unit)	Group	n *	Adjusted Geo-mean	Comparison	Arithmetic mean Weight(kg)	Geo-mean Ratio	Lower	Upper
AUCinf (h*ng/mL)	Normal	9	1520		84.1			
	Mild	8	1190	Mild/Normal	84.1	0.782	0.554	1.11
	Moderate	8	2250	Moderate/Normal	84.1	1.47	1.05	2.08
	Severe	7	4300	Severe/Normal	84.1	2.82	1.98	4.03
AUClast (h*ng/mL)	Normal	9	1480		84.1			
	Mild	8	1170	Mild/Normal	84.1	0.790	0.553	1.13
	Moderate	8	2210	Moderate/Normal	84.1	1.49	1.05	2.13
	Severe	7	4140	Severe/Normal	84.1	2.80	1.93	4.04
Cmax (ng/mL)	Normal	9	206		84.1			
	Mild	8	176	Mild/Normal	84.1	0.851	0.626	1.16
	Moderate	8	178	Moderate/Normal	84.1	0.861	0.636	1.17
	Severe	7	172	Severe/Normal	84.1	0.832	0.607	1.14

						Hepatic impairment group comparison		
							90% CI	
PK Parameter (unit)	Group	n *	Adjusted Geo-mean	Comparison	Arithmetic mean Weight(kg)	Geo-mean Ratio	Lower	Upper

Model is a linear model of the log-transformed PK parameters, including hepatic impairment status group as fixed effect and age, gender, race and weight as covariates with a modified step-wise backward selection of the covariates that eliminates the least statistically significant covariate until all remaining covariates, if any, have p-value <0.05. Only weight was kept in the final model for each primary PK parameter and results are presented in the table.

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

The analysis is conducted on log-transformed PK parameters. Then the results are back-transformed to get adjusted geo-mean, GM ratio and 90% CI.

Secondary Outcome Result(s)

Summary of other PK parameters for LCI699 by hepatic impairment group (Pharmacokinetic analysis set)

Hepatic impairment group	Statistics	Tmax (h)	T1/2 (h)	Vz/F (L)	CL/F (L/h)
Normal (N=9)	n	9	9	9	9
	Mean (SD)	N/A	5.31 (1.12)	151 (27.3)	20.4 (5.45)
	CV% mean	N/A	21.0	18.1	26.7
	Geo-mean	N/A	5.21	149	19.8
	CV% geo-mean	N/A	20.5	17.8	27.9
	Median	1.00	5.17	147	17.2
	[Min; Max]	[0.500; 1.50]	[3.66; 7.70]	[114; 193]	[12.5; 27.9]
Mild (N=8)	n	8	8	8	8
	Mean (SD)	N/A	4.67 (1.17)	197 (209)	34.5 (45.1)
	CV% mean	N/A	25.0	106.0	130.4
	Geo-mean	N/A	4.54	151	23.0
	CV% geo-mean	N/A	25.7	75.3	98.5
	Median	1.00	4.93	126	20.7

Hepatic impairment group	Statistics	Tmax (h)	T1/2 (h)	Vz/F (L)	CL/F (L/h)
	[Min; Max]	[0.50; 2.00]	[3.21; 6.69]	[76.1; 711]	[9.70; 145]
Moderate (N=8)	n	8	8	8	8
	Mean (SD)	N/A	9.33 (4.75)	185 (99.3)	14.9 (6.28)
	CV% mean	N/A	50.9	53.8	42.3
	Geo-mean	N/A	8.45	168	13.8
	CV% geo-mean	N/A	49.3	45.9	42.9
	Median	1.25	7.77	140	11.5
	[Min; Max]	[0.500; 6.00]	[4.33; 19.4]	[110; 404]	[9.11; 23.4]
Severe (N=7)	n	7	7	7	7
	Mean (SD)	N/A	19.5 (5.76)	212 (75.6)	7.70 (2.22)
	CV% mean	N/A	29.6	35.6	28.8
	Geo-mean	N/A	18.8	202	7.43
	CV% geo-mean	N/A	28.0	33.6	29.6
	Median	2.00	16.4	194	6.61
	[Min; Max]	[0.500; 3.00]	[14.9; 29.4]	[130; 363]	[5.01; 10.8]

n: number of subjects with non-missing values.

CV% = coefficient of variation (%) = sd/mean*100, CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100.

Summary of Safety

Safety Results

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

Primary System Organ Class Preferred Term Maximum grade	Normal (N=10) n (%)	Mild (N=8) n (%)	Moderate (N=8) n (%)	Severe (N=7) n (%)	All Subjects (N=33) n (%)
Any primary system organ class					
Total	2 (20.0)	1 (12.5)	2 (25.0)	4 (57.1)	9 (27.3)
Grade 1	1 (10.0)	1 (12.5)	1 (12.5)	1 (14.3)	4 (12.1)
Grade 2	1 (10.0)	0	0	2 (28.6)	3 (9.1)
Grade 3	0	0	1 (12.5)	1 (14.3)	2 (6.1)
Gastrointestinal disorders					
Total	1 (10.0)	0	2 (25.0)	2 (28.6)	5 (15.2)
Nausea	1 (10.0)	0	0	0	1 (3.0)
Grade 1	1 (10.0)	0	0	0	1 (3.0)
Vomiting	1 (10.0)	0	0	0	1 (3.0)
Grade 1	1 (10.0)	0	0	0	1 (3.0)
Diarrhoea	0	0	1 (12.5)	0	1 (3.0)
Grade 1	0	0	1 (12.5)	0	1 (3.0)
Gastrooesophageal reflux disease	0	0	0	1 (14.3)	1 (3.0)
Grade 1	0	0	0	1 (14.3)	1 (3.0)
Oesophageal varices haemorrhage	0	0	1 (12.5)	0	1 (3.0)
Grade 3	0	0	1 (12.5)	0	1 (3.0)
Rectal haemorrhage	0	0	0	1 (14.3)	1 (3.0)
Grade 3	0	0	0	1 (14.3)	1 (3.0)
Investigations					

Primary System Organ Class Preferred Term Maximum grade	Normal (N=10) n (%)	Mild (N=8) n (%)	Moderate (N=8) n (%)	Severe (N=7) n (%)	All Subjects (N=33) n (%)
Total	0	0	0	1 (14.3)	1 (3.0)
Blood potassium decreased	0	0	0	1 (14.3)	1 (3.0)
Grade 2	0	0	0	1 (14.3)	1 (3.0)
Metabolism and nutrition disorders					
Total	0	0	0	1 (14.3)	1 (3.0)
Type 2 diabetes mellitus	0	0	0	1 (14.3)	1 (3.0)
Grade 2	0	0	0	1 (14.3)	1 (3.0)
Nervous system disorders					
Total	1 (10.0)	1 (12.5)	0	0	2 (6.1)
Headache	1 (10.0)	0	0	0	1 (3.0)
Grade 2	1 (10.0)	0	0	0	1 (3.0)
Dizziness	0	1 (12.5)	0	0	1 (3.0)
Grade 1	0	1 (12.5)	0	0	1 (3.0)

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 Normal column.

A subject with multiple occurrences of an AE under one hepatic impairment group is counted only once in the AE category for that hepatic impairment group.

A subject with multiple adverse events within a primary system organ class is counted only once in the total row.

Adverse events, regardless of study drug relationship, by preferred term, and hepatic impairment group (Safety set)

Preferred term	Normal (N=10) n (%)	Mild (N=8) n (%)	Moderate (N=8) n (%)	Severe (N=7) n (%)	All Subjects (N=33) n (%)
Total	2 (20.0)	1 (12.5)	2 (25.0)	4 (57.1)	9 (27.3)
Headache	1 (10.0)	0	0	0	1 (3.0)
Nausea	1 (10.0)	0	0	0	1 (3.0)
Vomiting	1 (10.0)	0	0	0	1 (3.0)
Blood potassium decreased	0	0	0	1 (14.3)	1 (3.0)
Diarrhoea	0	0	1 (12.5)	0	1 (3.0)
Dizziness	0	1 (12.5)	0	0	1 (3.0)
Gastrooesophageal reflux disease	0	0	0	1 (14.3)	1 (3.0)
Oesophageal varices haemorrhage	0	0	1 (12.5)	0	1 (3.0)
Rectal haemorrhage	0	0	0	1 (14.3)	1 (3.0)
Type 2 diabetes mellitus	0	0	0	1 (14.3)	1 (3.0)

Preferred terms are sorted by descending order of frequencies, as reported in the Normal column.

A subject with multiple occurrences of an AE under one hepatic impairment group is counted only once in the AE category for that hepatic impairment group.

A subject with multiple adverse events is counted only once in the total row

Serious adverse events, regardless of study drug relationship, by primary system organ class, preferred term, maximum CTCAE grade and hepatic impairment group (Safety set)

Primary System Organ Class Preferred Term Maximum Grade	Normal (N=10) n (%)	Mild (N=8) n (%)	Moderate (N=8) n (%)	Severe (N=7) n (%)	All Subjects (N=33) n (%)
Any primary system organ class					
Total	0	0	1 (12.5)	1 (14.3)	2 (6.1)
Grade 3	0	0	1 (12.5)	1 (14.3)	2 (6.1)
Gastrointestinal disorders					
Total	0	0	1 (12.5)	1 (14.3)	2 (6.1)
Oesophageal varices haemorrhage	0	0	1 (12.5)	0	1 (3.0)
Grade 3	0	0	1 (12.5)	0	1 (3.0)
Rectal haemorrhage	0	0	0	1 (14.3)	1 (3.0)
Grade 3	0	0	0	1 (14.3)	1 (3.0)

A subject with multiple occurrences of an AE under one hepatic impairment group is counted only once in the AE category for that hepatic impairment group.
A subject with multiple adverse events within a primary system organ class is counted only once in the total row.

Other Relevant Findings

Not Applicable

Conclusion:

- Increased exposure (AUClast and AUCinf) was observed in the moderate and severe impairment cohort when compared to the normal cohort. No significant change in Cmax across cohorts was observed. Exposures (Cmax and AUC) in the mild impairment cohort were similar to those in the normal cohort.

- There was a decrease in the apparent clearance of osilodrostat associated with increase in the severity of hepatic impairment in the moderate and severe cohorts as compared to the normal cohorts.

- For hepatic impaired subjects whether a dose adjustment recommendation is needed would require further evaluation and need to take into consideration the therapeutic index of osilodrostat based on the ongoing patient clinical studies.

Date of Clinical Trial Report:

17 Feb 2017