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Clinical Trial Results Database

Sponsor

Novartis

Generic Drug Name

Sonidegib

Trial Indication

Pharmacokinetic study in healthy subjects with normal hepatic function and subjects with impaired hepatic function.

Protocol Number

CLDE225A2113

Protocol Title

A Phase I, open label, multi-center, single dose study to evaluate the pharmacokinetics of sonidegib (LDE225) in healthy subjects with normal hepatic function and subjects with impaired hepatic function.

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase IV

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Study Start/End Dates

20-Mar-2013 (first subject first visit) to 24-Mar-2015 (last subject last visit).

Reason for Termination (If applicable)

Not applicable.

Study Design/Methodology

A Phase I, multi-center, open-label, single oral dose, parallel group study to assess the PK and safety of 800 mg of sonidegib in subjects with impaired hepatic function and healthy subjects with normal hepatic function. Subjects were assigned to a hepatic group based on hepatic function (according to the Child-Pugh classification) as determined at the Screening visit: group 1, normal hepatic function; group 2, mild hepatic impairment; group 3, moderate hepatic impairment; and group 4, severe hepatic impairment.

Centers

5 centers in 5 countries: Belgium (1), Bulgaria (1), Germany (1), Israel (1) and USA (1)

Publication

None.

Objectives:

Primary objective

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

Secondary objectives

Key Secondary: To evaluate the safety and tolerability of a single oral dose of sonidegib in subjects with varying degrees of hepatic function.

Other Secondary: To evaluate the plasma protein binding of sonidegib and PK expressed as unbound drug in subjects with impaired hepatic function as compared to healthy subjects.

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

Sonidegib 800 mg single oral dose.

Statistical Methods

A formal statistical comparison was conducted for the following PK parameters: AUCinf, AUClast, and Cmax using all groups. A linear model including group (i.e. normal, mild, moderate, or severe) as a fixed effect was fitted to the log-transformed PK parameters. The mild, moderate, and severe hepatic groups were the test groups and the normal group was the reference group. Point estimates and the corresponding 90% confidence interval for the mean difference between each test and reference group were calculated. This was anti-logged to obtain the point estimate and 90% confidence interval for the ratio of the geometric means on the untransformed scale.

The effect of baseline covariates on AUCinf, AUClast, and Cmax such as sex, age group (<65 years, ≥ 65 years), and weight were investigated. A covariate adjusted analysis was done by repeating the aforementioned linear model including sex and age group as categorical covariates and weight as a continuous covariate. The 90% confidence interval for the ratio of the geometric means for the covariate adjusted analysis was presented.

Summary statistics for continuous variables included n, mean, standard deviation (SD), median, minimum, and maximum, unless otherwise specified. For PK concentration and PK parameters, coefficient of variation percentage (CV%) for mean, geometric mean, and CV% for geometric mean were presented in addition to the above mentioned summary statistics. For categorical variables, frequency count and percent were presented.

Summary statistics for all PK parameters for sonidegib and LGE899 were provided by hepatic group using pharmacokinetic analysis set (PAS). Only median values and ranges were given for Tmax. Summary statistics for sonidegib and LGE899 plasma concentration were presented at each scheduled time point by hepatic group using PAS.

Geometric mean together with arithmetic mean (SD) concentration-time profiles were plotted for sonidegib and LGE899 by hepatic group using PAS. Individual concentration-time profiles for sonidegib and LGE899 plasma concentrations with median by hepatic group were plotted using full analysis set (FAS). For AUCinf, AUClast, and Cmax of sonidegib, individual subject values and geometric mean were plotted by hepatic group using PAS.

The assessment of safety was based mainly on the frequency of AEs and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g. ECG, vital signs) was also summarized.

Study Population: Key Inclusion/Exclusion Criteria

Key criteria for inclusion of subjects in all groups: Male and sterile or postmenopausal female age ≥ 18 to ≤ 75 years old. Body mass index (BMI) of 18-35 kg/m2, with body weight ≥ 50 kg.

Key criteria for inclusion of subjects in normal group (control group): Healthy subjects with no clinically significant abnormalities as determined by past medical history, physical examination, vital signs, ECG and clinical laboratory tests; adequate end organ function and laboratory values.

Key criteria for inclusion of subjects in mild, moderate and severe groups:

- Subjects with confirmed cirrhosis by at least one of the following criteria:
- Histologically by prior liver biopsy showing cirrhosis.
- Clinically by physical examination (e.g., liver firmness to palpation, splenic enlargement, spider angioma, palmar erythema, parotid hypertrophy, testicular atrophy, ascites, presence of asterixis or gynecomastia), and/or laboratory data, and/or liver imaging (CT, and/or US and/or Magnetic Resonance Imaging (MRI) scans), and/or endoscopic findings.
- Child-Pugh Clinical Assessment Score consistent with degree of hepatic impairment.

Exclusion criteria:

Key criteria for exclusion of subjects in normal group (control group):

- Clinical evidence of liver disease or liver injury as indicated by abnormal liver function tests such as alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase, or serum bilirubin. ALT and AST beyond the normal range before inclusion, GGT>2 X ULN, alkaline phosphatase >2 X ULN, and serum bilirubin >27 μmol/L (1.6 mg/dL).
- Presence of impaired renal function as indicated by abnormal creatinine (creatinine clearance <80 mL/min) values or abnormal urinary constituents (e.g., albuminuria) and/or serum creatinine ≥ 1.8 mg/dL.
- A positive Hepatitis B surface antigen (HBsAg) or Hepatitis C test result (antibody positive subjects were allowed if non-viremic)
- Administration of CYP3A4 inhibitors or inducers (including St John's wort) within 4 weeks prior to study initiation.
- Use of any prescription drug or over-the-counter (OTC) medication within 4 weeks or 10-times the estimated half-lives of the prescription or OTC medication prior to dosing (whichever was longer).

Key criteria for exclusion of subjects in mild, moderate and severe groups:

- Symptoms or history of encephalopathy (grade III or worse) within 3 months prior to dosing.
- Clinical evidence of severe ascites.
- International normalized ratio (INR) >2.5.
- For Child-Pugh Groups A, B, and for first two subjects who were enrolled in Child-Pugh Group C before amendment 2: any evidence of progressive liver disease (within the last 4 weeks) as indicated by liver transaminases (>3.0 X ULN), alkaline phosphatase (>2.5 X ULN), and GGT (>2.5 X ULN), or a ≥ 50% worsening of serum bilirubin or prothrombin time. For Child-Pugh Group C only after amendment 2: any evidence of progressive liver disease (within the last 4 weeks) as indicated by liver transaminases (>6.0 X ULN). There are no restrictions for alkaline phosphatase, GGT, serum bilirubin or prothrombin time.

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Participant Flow Table

Subject disposition, by hepatic group (Full analysis set)

Disposition reason	Normal (N=8) n (%)	Mild (N=8) n (%)	Moderate (N=8) n (%)	Severe (N=9) n (%)	All subjects (N=33) n (%)
Completed study	8 (100.0)	8 (100.0)	8 (100.0)	7 (77.8)	31 (93.9)
Discontinued	0	0	0	2 (22.2)	2 (6.1)
Administrative problems	0	0	0	1 (11.1)	1 (3.0)
Protocol deviation	0	0	0	1 (11.1)	1 (3.0)

Baseline Characteristics

Demographics, by hepatic group (Full analysis set)

Demographic variable	Normal (N=8)	Mild (N=8)	Moderate (N=8)	Severe (N=9)	All subjects (N=33)
Age (Years)					
n	8	8	8	9	33
Mean	56.8	56.4	57.3	53.1	55.8
SD	6.92	4.60	5.06	8.88	6.58
Median	55.0	55.5	58.0	56.0	56.0
Minimum	48	50	49	40	40
Maximum	69	63	65	63	69
Age category (years)-n (%)					
<65	7 (87.5)	8 (100.0)	7 (87.5)	9 (100.0)	31 (93.9)
>=65	1 (12.5)	0	1 (12.5)	0	2 (6.1)
Sex - n (%)					
Female	3 (37.5)	3 (37.5)	1 (12.5)	2 (22.2)	9 (27.3)

Demographic variable	Normal (N=8)	Mild (N=8)	Moderate (N=8)	Severe (N=9)	All subjects (N=33)
Male	5 (62.5)	5 (62.5)	7 (87.5)	7 (77.8)	24 (72.7)
Female with child bearing potential - n (%)					
Postmenopausal	3 (37.5)	3 (37.5)	1 (12.5)	2 (22.2)	9 (27.3)
Race - n (%)					
Caucasian	8 (100.0)	8 (100.0)	8 (100.0)	9 (100.0)	33 (100.0)
Ethnicity - n (%)					
Hispanic/Latino	4 (50.0)	0	4 (50.0)	5 (55.6)	13 (39.4)
Other	4 (50.0)	8 (100.0)	4 (50.0)	4 (44.4)	20 (60.6)
Body mass index (kg/m^2)					
n	8	8	8	9	33
Mean	25.873	25.423	29.963	29.082	27.630
SD	2.7518	4.1636	5.0688	5.0301	4.6193
Median	25.150	25.285	31.235	28.700	26.540
Minimum	23.18	19.72	20.28	20.96	19.72
Maximum	30.38	33.02	34.57	35.79	35.79
Body surface area (m^2)					
n	8	8	8	9	33
Mean	1.921	1.949	2.068	1.979	1.979
SD	0.1964	0.2472	0.2329	0.3009	0.2436
Median	1.887	1.934	2.047	1.963	1.973
Minimum	1.62	1.65	1.70	1.54	1.54
Maximum	2.17	2.43	2.42	2.42	2.43

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.
BSA (Gehan and George): BSA(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.

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Child-Pugh classification and liver parameters at Screening/Baseline visit, by hepatic group (Full analysis set)

Hepatic Impairment Classification	Mild (N=8) n (%)	Moderate (N=8) n (%)	Severe (N=9) n (%)
Encephalopathy			
None	8 (100.0)	3 (37.5)	2 (22.2)
Grade 1-2	0	5 (62.5)	4 (44.4)
Grade 3-4	0	0	3 (33.3)
Ascites			
Absent	6 (75.0)	1 (12.5)	0
Slight	2 (25.0)	4 (50.0)	2 (22.2)
Moderate	0	3 (37.5)	7 (77.8)
Total bilirubin (mg/dL)			
< 2.0	8 (100.0)	7 (87.5)	3 (33.3)
2-3	0	1 (12.5)	2 (22.2)
> 3.0	0	0	4 (44.4)
Serum albumin (g/dL)			
> 3.5	8 (100.0)	5 (62.5)	0
2.8-3.5	0	3 (37.5)	7 (77.8)
< 2.8	0	0	2 (22.2)
INR			
< 1.7	8 (100.0)	4 (50.0)	1 (11.1)
1.7-2.3	0	0	2 (22.2)
Prothrombin time (seconds over control)			
< 4	2 (25.0)	4 (50.0)	5 (55.6)
4-6	0	0	1 (11.1)
Score			
5	6 (75.0)	0	0
6	2 (25.0)	0	0

Hepatic Impairment Classification	Mild (N=8) n (%)	Moderate (N=8) n (%)	Severe (N=9) n (%)
7	0	6 (75.0)	0
8	0	1 (12.5)	0
9	0	1 (12.5)	0
10	0	0	5 (55.6)
11	0	0	3 (33.3)
12	0	0	1 (11.1)

Mild = Child-Pugh A; Moderate = Child-Pugh B; Severe = Child-Pugh C.

Summary of Pharmacokinetics

Primary Outcome Results

Summary of PK parameters for sonidegib by hepatic group (Pharmacokinetic analysis set)

Hepatic group	Statistics	AUCinf (ng*hr/mL)	AUClast (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)	CL/F (L/hr)	Vss/F (L)
Normal (N=8)	n	8	8	8	8	8	8	8
	Mean (SD)	13300 (9180)	12500 (8200)	299 (195)	N/A	293 (95.5)	86.8 (48.3)	27800 (13600)
	CV% mean	69.0	65.4	65.0	N/A	32.6	55.6	48.8
	Geo-mean	10900	10400	256	N/A	280	73.2	24900
	CV% geo-mean	73.9	71.7	61.9	N/A	33.9	73.9	54.8

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Clinical Trial Results Database

Hepatic group	Statistics	AUCinf (ng*hr/mL)	AUClast (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)	CL/F (L/hr)	Vss/F (L)
Mild (N=8)	Median	9860	9670	221	2.49	278	86.0	26300
	[Min; Max]	[5340; 29600]	[5030; 26000]	[152; 639]	[2.00; 5.03]	[155; 476]	[27.0; 150]	[12200; 49800]
	n	7	8	8	8	7	7	7
	Mean (SD)	7680 (5380)	8060 (5320)	263 (207)	N/A	306 (70.2)	138 (64.9)	48800 (21900)
	CV% mean	70.0	66.1	79.0	N/A	22.9	47.0	44.9
	Geo-mean	6540	6770	204	N/A	299	122	43300
	CV% geo-mean	62.9	68.4	89.9	N/A	24.7	62.9	62.9
Moderate (N=8)	Median	6590	6300	193	2.00	339	121	56500
	[Min; Max]	[3590; 19100]	[3350; 18100]	[55.9; 686]	[1.00; 3.98]	[204; 391]	[42.0; 223]	[16200; 73800]
	n	4	8	8	8	4	4	4
	Mean (SD)	10800 (7450)	15100 (9580)	246 (152)	N/A	309 (149)	130 (128)	40300 (29000)
	CV% mean	68.8	63.4	61.7	N/A	48.3	98.7	71.9
	Geo-mean	8480	11900	202	N/A	277	94.4	34500
	CV% geo-mean	109.9	99.1	80.4	N/A	62.0	109.9	66.1

Hepatic group	Statistics	AUCinf (ng*hr/mL)	AUClast (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)	T1/2 (hr)	CL/F (L/hr)	Vss/F (L)
Severe (N=9)	Median	10200	14400	221	2.00	315	80.6	27400
	[Min; Max]	[2500; 20300]	[2310; 32000]	[66.6; 508]	[0.500; 5.00]	[128; 479]	[39.4; 320]	[22900; 83400]
	n	4	8	9	9	4	4	4
	Mean (SD)	10700 (4150)	9950 (6630)	115 (69.3)	N/A	408 (176)	85.7 (38.7)	55700 (38300)
	CV% mean	38.9	66.6	60.0	N/A	43.2	45.1	68.9
	Geo-mean	10000	8050	102	N/A	383	79.9	45800
	CV% geo-mean	44.5	83.1	51.6	N/A	42.5	44.5	86.9
	Median	10700	9340	86.2	3.00	365	75.8	48200
	[Min; Max]	[5700; 15700]	[2530; 22600]	[58.1; 284]	[2.00; 10.0]	[245; 659]	[51.0; 140]	[17500; 109000]

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 PK parameters (AUCinf, AUClast, Cmax) for sonidegib (Pharmacokinetic analysis set)

					Hepatic group comparison		
						_90% CI_	
PK parameter (unit)	Hepatic group	n*	Adjusted geo-mean	Comparison(s)	Geo-mean ratio	Lower	Upper
AUCinf (ng*hr/mL)	Normal	8	10900				
	Mild	7	6540	Mild/Normal	0.599	0.335	1.07

PK parameter (unit)	Hepatic group	n*	Adjusted geo-mean	Comparison(s)	Hepatic group comparison Geo-mean ratio	90% CI Lower	Upper
	Moderate	4	8480	Moderate/Normal	0.776	0.391	1.54
	Severe	4	10000	Severe/Normal	0.916	0.462	1.82
AUClast (ng*hr/mL)	Normal	8	10400				
	Mild	8	6770	Mild/Normal	0.649	0.355	1.19
	Moderate	8	11900	Moderate/Normal	1.14	0.624	2.08
	Severe	8	8050	Severe/Normal	0.771	0.422	1.41
Cmax (ng/mL)	Normal	8	256				
	Mild	8	204	Mild/Normal	0.796	0.463	1.37
	Moderate	8	202	Moderate/Normal	0.790	0.460	1.36
	Severe	9	102	Severe/Normal	0.400	0.236	0.677

Model is a linear model of the log-transformed PK parameters. Included in the model is hepatic group 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.

Secondary Outcome Results

Summary of statistical analysis of LDE225 PK parameters (AUCinf, AUClast, Cmax) expressed as unbound drug (Pharmacokinetic analysis set)

PK parameter (unit)	Hepatic group	n*	Adjusted geo-mean	Comparison(s)	Hepatic group comparison Geo-mean ratio	90% CI Lower	Upper

PK parameter (unit)	Hepatic group	n*	Adjusted geo-mean	Comparison(s)	Hepatic group comparison Geo-mean ratio	90% CI Lower	90% CI Upper
AUCinf, u (ng*hr/mL)	Normal	8	**18.2**				
	Mild	7	**14.0**	Mild/Normal	**0.768**	**0.409**	**1.44**
	Moderate	4	**13.3**	Moderate/Normal	**0.730**	**0.346**	1.54
	Severe	4	**17.6**	Severe/Normal	**0.966**	**0.458**	**2.04**
AUClast, u (ng*hr/mL)	Normal	8	**17.4**				
	Mild	8	**13.8**	Mild/Normal	**0.792**	**0.421**	**1.49**
	Moderate	8	**19.2**	Moderate/Normal	**1.10**	**0.586**	2.08
	Severe	8	**13.8**	Severe/Normal	0.793	**0.421**	1.49
Cmax, u (ng/mL)	Normal	8	**0.427**				
	Mild	8	**0.415**	Mild/Normal	**0.972**	**0.557**	**1.70**
	Moderate	8	**0.327**	Moderate/Normal	**0.765**	**0.438**	1.34
	Severe	9	**0.182**	Severe/Normal	**0.425**	0.247	**0.731**

Model is a linear model of the log-transformed PK parameters. Included in the model is hepatic group 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.

Summary of Safety

Safety Results

Adverse Events by System Organ Class

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

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	Normal		Mild		Moderate		Severe		All subjects	
	N=8		N=8		N=8		N=9		N=33	
Primary system organ class Preferred term	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
Any primary system organ class	1 (12.5)	0	3 (37.5)	1 (12.5)	2 (25.0)	0	1 (11.1)	1 (11.1)	7 (21.2)	2 (6.1)
Blood and lymphatic system disorders	0	0	1 (12.5)	1 (12.5)	0	0	0	0	1 (3.0)	1 (3.0)
Cardiac disorders	0	0	1 (12.5)	0	0	0	0	0	1 (3.0)	0
Infections and infestations	0	0	0	0	0	0	1 (11.1)	1 (11.1)	1 (3.0)	1 (3.0)
Injury, poisoning and procedural complications	1 (12.5)	0	0	0	0	0	0	0	1 (3.0)	0
Investigations	0	0	0	0	1 (12.5)	0	0	0	1 (3.0)	0
Metabolism and nutrition disorders	0	0	0	0	1 (12.5)	0	0	0	1 (3.0)	0
Nervous system disorders	1 (12.5)	0	0	0	0	0	0	0	1 (3.0)	0
Reproductive system and breast disorders	0	0	1 (12.5)	0	0	0	0	0	1 (3.0)	0

Primary system organ classes are presented alphabetically; preferred terms are sorted within
primary system organ class in descending frequency of all grades column, as reported in 'All subjects'.
A subject with multiple occurrences of an AE under one hepatic group is counted only once in the AE category for that group.

Most Frequently Reported AEs Overall by Preferred Term n (%)

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

	Normal		Mild		Moderate		Severe		All subjects	
	N=8		N=8		N=8		N=9		N=33	
Preferred term	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
Neutropenia	0	0	1 (12.5)	1 (12.5)	0	0	0	0	1 (3.0)	1 (3.0)
Sinus tachycardia	0	0	1 (12.5)	0	0	0	0	0	1 (3.0)	0

	Normal		Mild		Moderate		Severe		All subjects	
	N=8		N=8		N=8		N=9		N=33	
Preferred term	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Peritonitis bacterial	0	0	0	0	0	0	1 (11.1)	1 (11.1)	1 (3.0)	1 (3.0)
Arthropod sting	1 (12.5)	0	0	0	0	0	0	0	1 (3.0)	0
Gamma-glutamyltransferase increased	0	0	0	0	1 (12.5)	0	0	0	1 (3.0)	0
Hyperuricaemia	0	0	0	0	1 (12.5)	0	0	0	1 (3.0)	0
Headache	1 (12.5)	0	0	0	0	0	0	0	1 (3.0)	0
Erectile dysfunction	0	0	1 (12.5)	0	0	0	0	0	1 (3.0)	0

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency of all grades column, as reported in 'All subjects'.
A subject with multiple occurrences of an AE under one hepatic group is counted only once in the AE category for that group.

Serious Adverse Events and Deaths

There were no deaths reported in this study. One subject in the severe group was diagnosed with spontaneous bacterial peritonitis infection of grade 3 severity, which was reported as an SAE.

Other Relevant Findings

None.

Conclusion:

Conclusion:

- After a single 800 mg dose, sonidegib pharmacokinetics was modestly affected by hepatic impairment. The study results showed similar total sonidegib exposure (AUClast) in all groups, and dose adjustment is not considered necessary for mild, moderate, or severe hepatic impaired subjects.
- No significant safety concerns were identified. A single 800 mg dose of sonidegib was generally safe and well tolerated in normal and hepatic impaired subjects.

Date of Clinical Trial Report

CSR: 30-Oct-2015

CSR amendment 1: 09-Feb-2017