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Sponsor

Novartis

Generic Drug Name

Alpelisib

Trial Indication(s)

Hepatic impairment

Protocol Number

CBYL719A2105

Protocol Title

A phase 1, open-label, single-dose, multicenter, parallel group study to assess the pharmacokinetics and safety of alpelisib (BYL719) in subjects with hepatic impairment compared to matched healthy control subjects

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase III

Study Start/End Dates

21-Dec-2015 to 01-Oct-2017

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was a multicenter, open-label, parallel group study with sequential enrollment of moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic-impaired subjects to assess the PK of alpelisib in subjects with impaired hepatic function compared to healthy subjects (with apparent normal liver function). Matching will be based on sex, race, age (± 10 years), and weight (± 10%). Enrollment commenced with 3 subjects from the moderate hepatic impairment group. The enrollment of healthy matching controls did not start before his/her matching hepatic impaired subject had completed the end of study (EOS) visit. While enrollment in the moderate hepatic impairment group continued, an evaluation for safety and preliminary PK was made after the first

3 moderate impaired subjects and their 3 matching healthy controls have completed the study evaluations up to and including the EOS visit. Based on the outcome of this preliminary evaluation, a lower dose of alpelisib, which may have been proposed to be used in the severe hepatic impairment group, was not required and the severe hepatic impairment group was enrolled with the same dose.

Centers

4 centers in 1 country: USA (4)

Objectives:

Primary objective

- To determine the impact of hepatic impairment (moderate and severe) on the PK of alpelisib relative to healthy control subjects (with apparently normal liver function) based on primary PK parameters. The study was completed as planned.

Secondary objectives

- To evaluate the PK of a single oral dose of alpelisib in subjects with moderate and severe hepatic impairment and healthy control subjects (with apparently normal liver function)
- To evaluate the tolerability and safety of a single dose of alpelisib in all subjects
- To evaluate the relationship between PK of alpelisib and hepatic function parameters

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

This was a non-randomized study. All subjects were assigned to the same treatment: a single dose of alpelisib 300 mg administered orally in tablets.

Statistical Methods

No formal statistical hypothesis was tested as the main purpose of the statistical analysis was to determine the impact of hepatic impairment on the PK of alpelisib relative to healthy control subjects. After log transformation, each primary PK parameter (Cmax, AUClast and AUCinf) was analyzed separately by means of an ANCOVA with group as fixed effect and age, weight, sex, and race (if applicable) as covariates. The differences between the control group and each one of the hepatic function groups and the two-sided 90% CIs were derived from the model. These were back−transformed to obtain the point estimates and the 90% confidence intervals (CIs) for the ratios of the geometric means on the original scale. All subjects received 300 mg alpelisib and there was no dose normalization for analysis of PK parameters. No imputation of missing data was performed. Cross-tabulations were

provided to show the shift between results of the Child-Pugh classification at Screening, Baseline and EOS using the full analysis set.

Study Population: Key Inclusion/Exclusion Criteria

The main inclusion criteria for all subjects included:

- Subject must provide written Informed Consent prior to any Screening procedures being performed.
- Women must be of non-childbearing potential.
- Sexually active male subjects must use a condom during intercourse while taking drug and for 1 week after stopping study medication and should not father a child in this period.
- Subjects must weigh at least 50 kg and no more than 120 kg to participate in this study and have a body mass index (BMI) in the range 18.0 to 36.0 kg/m2.

The additional inclusion criteria for Group 1 (matched control subjects) included:

- Subjects in good health as determined by no clinically significant findings from medical history, physical examination, vital signs, and electrocardiogram (ECG).
- Laboratory values (if not otherwise specified) within the reference range at the local laboratory, unless deemed not clinically significant by the Investigator or Designee.
- At Screening and Baseline, subject has vital signs (after 5 minutes resting measured in sitting position) which are within the following ranges:
    - Body temperature: ≥ 35.0 and ≤ 37.5°C
    - Systolic blood pressure: ≥ 90 and ≤ 140 mmHg
    - Diastolic blood pressure: ≥ 50 and ≤ 90 mmHg
    - Pulse rate: ≥ 50 and ≤ 90 beats per minute (bpm)

The additional inclusion criteria for Group 2 and 3 (hepatic impaired subjects) included:

- Subjects must have a score clinically determined and calculated as per the Child-Pugh classification and consistent with the degree of hepatic impairment in which study is currently enrolling.
- Stable Child-Pugh status within 28 days prior to dosing.
- Subjects with stable hepatic impairment with other stable medical disorders such as hypertension, hyperlipidemia, hypothyroidism etc., are eligible, as long as they are considered appropriate for enrollment as determined by past medical history, physical examination, vital signs, ECG, and laboratory tests at Screening and Baseline.
- Absence of moderate to severe impaired renal function as indicated by any or all of the following criteria:
    - Creatinine clearance ≥ 45 mL/min as calculated using Cockcroft-Gault formula
    - Serum creatinine ≤ 1.5 × Upper Limit of Normal (ULN)
    - Fasting serum lipase ≤ 3 × ULN

- At Screening and Baseline, vital signs (after 5 minutes resting measured in sitting position) which are within the following ranges:
    - Body temperature: ≥ 35.0 and ≤ 37.5°C
    - Systolic blood pressure: ≥ 90 and ≤ 150 mm Hg
    - Diastolic blood pressure: ≥ 50 and ≤ 100 mm Hg
    - Pulse rate: ≥ 50 and ≤ 100 bpm

The main exclusion criteria for all subjects included:

- Women of childbearing potential.
- Fertile male subjects UNLESS the study participant and his female partner agree to comply with highly effective contraception for the duration of the study and up to 1 week following study drug administration and should not father a child in this period.
- Subject has received a liver transplant at any time in the past and is on immunosuppressant therapy.
- Any condition which, in the opinion of the Investigator, is likely to interfere with the study conduct, such as uncontrolled infection, uncontrolled blood pressure variation (hypo- or hypertension), active gastrointestinal bleeding, or hospitalization within 14 days prior to dosing.
- Smokers not willing to limit the use of tobacco or products containing nicotine to approximately 10 cigarettes per day (or equivalent) starting 1 week prior to dosing until the last day of confinement in study center.
- Subject has had any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the subject's safety in case of participation in the study. History of acute pancreatitis within 1 year of study entry.
- Subjects with fasting plasma glucose levels > 160 mg/dL or > 8.88 mmol/L.
- Subjects with medical history judged by the Investigator as clinically significant for the risk of developing diabetes mellitus during the study.
- Dosing in any clinical investigation within 30 days of dosing or five half-lives of the investigational product, whichever is longer, or longer if required by local regulations.
- Contraindication or hypersensitivity to any drug or metabolites from similar class as study drug or to any excipients of alpelisib drug formulation
- Subject has used any herbal medications/supplements within 14 days prior to dosing. Herbal preparations are not allowed throughout the study.

The additional exclusion criteria for Group 1 (matching control subjects) included:

- Use of any prescription or non-prescription medication, dietary supplements, or vitamins during 14 days prior to dosing.
- A positive Hepatitis B surface antigen or Hepatitis C test result.
- History of drug or alcohol abuse within 1 month prior to dosing or evidence of such abuse as indicated by laboratory values at Screening or Baseline.
- Screening or baseline ECG: QTcF > 450 msec for males; QTcF > 460 msec for females; PR > 200 msec; QRS complex > 110 msec, or other morphological changes other than repolarization, nonspecific S-T or T-wave changes.

The additional exclusion criteria for Group 2 and 3 (hepatic impaired subjects) included:

- Use of any prescription or non-prescription medication, dietary supplements, or vitamins that has the potential to interact with alpelisib, within 14 days prior to dosing or during the study. Concomitant medications without potential to interact with alpelisib must be stable in dose and dosing regimen within 14 days prior to dosing (diuretics given to treat ascites must be stable in dose and dosing regimen within 28 days) and must be discussed with and approved by the Sponsor prior to subject enrollment.
- Subjects requiring tapping (more frequently then every three months) for the management of ascites are excluded.
- Encephalopathy grade 3 or worse within 28 days prior to dosing.
- International normalized ratio (INR) > 2.5 indicating impact of liver disease on coagulation.
- Total bilirubin (TBIL) > 6 mg/dL.
- Corrected serum calcium < 7.0 mg/dL.
- History of drug or alcohol abuse within 1 month prior to dosing or evidence of such abuse as indicated by laboratory values at Screening or Baseline. However, subjects may participate in the trial if the positive drug screen is due to prescription drug use for a specific symptom such as insomnia or pain.
- Screening or baseline ECG: QTcF > 480 msec for both genders.

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Participant Flow Table

Subject disposition by hepatic function group (Full analysis set)

Disposition Reason	Control N=11 n (%)	Moderate N=6 n (%)	Severe N=6 n (%)	All subjects N=23 n (%)
Completed study	11 (100)	6 (100)	6 (100)	23 (100)

Percentage is based on N

Baseline Characteristics

Demographics by hepatic function group (Full analysis set)

Demographic Variable	Control N=11	Moderate N=6	Severe N=6	All subjects N=23
Age (years)				
Mean (SD)	56.8 (6.71)	57.0 (3.69)	58.8 (7.76)	57.4 (6.16)
Median	57.0	57.0	62.5	58.0
Minimum – Maximum	47 - 68	53 - 62	48 - 66	47 - 68
Sex-n (%)				
Female	5 (45.5)	3 (50.0)	2 (33.3)	10 (43.5)
Male	6 (54.5)	3 (50.0)	4 (66.7)	13 (56.5)
Race-n (%)				
Caucasian	10 (90.9)	5 (83.3)	6 (100)	21 (91.3)
Black	1 (9.1)	1 (16.7)	0	2 (8.7)
Ethnicity-n (%)				
Hispanic/Latino	5 (45.5)	4 (66.7)	3 (50.0)	12 (52.2)
Mixed Ethnicity	2 (18.2)	0	0	2 (8.7)
Other	4 (36.4)	2 (33.3)	3 (50.0)	9 (39.1)
Creatinine clearance (mL/min)				
Mean (SD)	122.824 (38.0853)	130.172 (10.9189)	136.052 (56.7164)	128.191 (38.0765)
Median	112.290	131.160	137.725	127.280
Minimum – Maximum	81.03 - 201.61	111.27 - 140.97	56.81 - 231.53	56.81 - 231.53

The baseline weight (kg), baseline height (cm) and baseline creatinine clearance (mL/min) are defined as the last non missing assessment of weight, height and creatinine clearance prior to the first study drug administration.

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Child-Pugh classification and liver parameters at screening by hepatic function group (Full analysis set)

Assessment	Moderate N=6 n (%)	Severe N=6 n (%)
Encephalopathy		
Grade 1-2	6 (100)	6 (100)
Ascites		
Slight	6 (100)	0
Moderate	0	6 (100)
Total Bilirubin (mg/dL)		
< 2	6 (100)	0
2 - 3	0	2 (33.3)
> 3	0	4 (66.7)
Serum Albumin (g/dL)		
> 3.5	6 (100)	1 (16.7)
2.8 - 3.5	0	3 (50.0)
< 2.8	0	2 (33.3)
INR		
< 1.7	5 (83.3)	3 (50.0)
Prothrombin time (seconds over control)		
< 4	1 (16.7)	2 (33.3)
4 to 6	0	1 (16.7)
Score		
7	6 (100)	0
10	0	3 (50.0)
11	0	1 (16.7)
12	0	1 (16.7)
13	0	1 (16.7)

Moderate = Child-Pugh B; Severe = Child-Pugh C

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Summary of Efficacy

Primary Outcome Result(s)

Summary of primary PK parameters for alpelisib by hepatic function group (Pharmacokinetic analysis set)

Parameter	Statistics	Control N=11	Moderate N=6	Severe N=6
Cmax (ng/mL)	Mean (SD)	1350 (805)	1300 (861)	1130 (566)
	CV%	59.5	66.3	49.9
	Geo-mean	1140	986	1020
	Geo-CV%	70.7	112.4	53.6
	Median	1320	1390	1040
	[Min; Max]	[432; 2700]	[248; 2280]	[468; 2140]
AUClast (ng*hr/mL)	Mean (SD)	14500 (7060)	13900 (10100)	15900 (6020)
	CV%	48.6	72.5	37.8
	Geo-mean	12600	10300	14300
	Geo-CV%	65.8	117.1	63.6
	Median	15900	10900	18100
	[Min; Max]	[4000; 23600]	[2250; 26200]	[4490; 20500]
AUCinf (ng*hr/mL)	Mean (SD)	14900 (6990)	14200 (10100)	16300 (5940)
	CV%	47.0	71.2	36.5
	Geo-mean	13100	10700	14800
	Geo-CV%	62.8	111.4	58.2
	Median	16000	11200	18600
	[Min; Max]	[4360; 23800]	[2470; 26400]	[5080; 20800]

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

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Summary of statistical analysis of primary PK parameters for alpelisib by hepatic function group (Pharmacokinetic analysis set)

				Group comparison		
					90% CI	
PK parameter (unit)	Group	Adjusted geo-mean	Comparison(s)	Geo-mean ratio	Lower	Upper
Cmax (ng/mL)	Control	1180				
	Moderate	986	Moderate/Control	0.833	0.530	1.31
	Severe	1190	Severe/Control	1.00	0.636	1.58
AUClast (ng*hr/mL)	Control	13300				
	Moderate	9630	Moderate/Control	0.726	0.487	1.08
	Severe	16700	Severe/Control	1.26	0.845	1.87
AUCinf (ng*hr/mL)	Control	13700				
	Moderate	9990	Moderate/Control	0.730	0.499	1.07
	Severe	17100	Severe/Control	1.25	0.859	1.83
Tmax (hr)	Control	2.02				
	Moderate	1.75	Moderate-Control	-0.267		
	Severe	2.75	Severe-Control	0.733		

Model is an ANCOVA model of the log-transformed PK parameters which was used to estimate the geometric mean ratio of the healthy control subject group and each one of the hepatic function groups. Included in the model were hepatic function group as a fixed effect and weight and sex as significant covariates. The results were back transformed to get adjusted geometric 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 medians under 'Geo-mean ratio'.

Secondary Outcome Result(s)

Summary of secondary PK parameters for alpelisib by hepatic function group (Pharmacokinetic analysis set)

Parameter	Statistics	Control N=11	Moderate N=6	Severe N=6
AUC0-24 (ng*hr/mL)	Mean (SD)	11300 (5620)	11600 (8140)	12900 (5100)
	CV%	49.9	70.0	39.6
	Geo-mean	9830	8920	11700
	Geo-CV%	62.3	105.3	55.0
	Median	13500	9460	12900
	[Min; Max]	[4000; 19500]	[2250; 22500]	[4490; 18800]
AUC0-144 (ng*hr/mL)	Mean (SD)	14800 (7020)	14100 (10100)	16300 (5900)
	CV%	47.5	71.3	36.3
	Geo-mean	13000	10700	14800
	Geo-CV%	62.6	110.4	57.6
	Median	16000	11100	18500
	[Min; Max]	[4520; 23800]	[2520; 26300]	[5140; 20800]
T1/2 (hr)	Mean (SD)	12.6 (5.03)	11.4 (4.84)	9.93 (6.34)
	CV%	40.1	42.6	63.8
	Geo-mean	11.7	10.6	8.80
	Geo-CV%	40.8	43.5	52.4

Parameter	Statistics	Control N=11	Moderate N=6	Severe N=6
	Median	11.1	11.3	7.52
	[Min; Max]	[5.78; 22.2]	[6.54; 19.8]	[5.81; 22.6]
Tmax (hr)	Mean (SD)	N/A	N/A	N/A
	CV%	N/A	N/A	N/A
	Geo-mean	N/A	N/A	N/A
	Geo-CV%	N/A	N/A	N/A
	Median	2.02	1.75	2.75
	[Min; Max]	[1.50; 6.00]	[1.00; 2.00]	[1.00; 6.00]
CL/F (L/hr)	Mean (SD)	27.1 (18.0)	40.3 (41.6)	23.6 (17.5)
	CV%	66.5	103.3	74.3
	Geo-mean	23.0	28.0	20.2
	Geo-CV%	62.8	111.4	58.2
	Median	18.7	29.1	16.2
	[Min; Max]	[12.6; 68.8]	[11.4; 122]	[14.4; 59.0]
Vz/F (L)	Mean (SD)	465 (307)	512 (363)	309 (211)
	CV%	66.0	70.9	68.3
	Geo-mean	388	427	257
	Geo-CV%	68.1	71.4	72.8
	Median	263	355	217
	[Min; Max]	[185; 1040]	[187; 1180]	[125; 645]

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

Summary of statistical analysis of the relationship between primary PK parameters for alpelisib and hepatic function parameters (Pharmacokinetic analysis set)

Cmax vs Total bilirubin

Effect	Estimate [90%]	Standard error	Degrees of freedom	t value	Pr > |t|
Intercept	6.63 [5.98; 7.29]	0.382	20	17.4	<.0001
Total bilirubin	-0.0150 [-0.234; 0.204]	0.127	20	-0.119	0.9068
Sex	0.869 [0.498; 1.24]	0.215	20	4.04	0.0006

Cmax vs INR

Effect	Estimate [90%]	Standard error	Degrees of freedom	t value	Pr > |t|
Intercept	6.61 [6.34; 6.89]	0.158	20	41.8	<.0001
INR	-0.234 [-1.63; 1.16]	0.810	20	-0.289	0.7753
Sex	0.889 [0.506; 1.27]	0.222	20	4.00	0.0007

Cmax vs Serum albumin

Effect	Estimate [90%]	Standard error	Degrees of freedom	t value	Pr > |t|
Intercept	6.06 [2.77; 9.35]	1.91	20	3.18	0.0047
Serum albumin	0.144 [-0.748; 1.04]	0.517	20	0.279	0.7834
Sex	0.880 [0.507; 1.25]	0.216	20	4.07	0.0006

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AUClast vs Total bilirubin

Effect	Estimate [90%]	Standard error	Degrees of freedom	t value	Pr > |t|
Intercept	8.60 [7.95; 9.25]	0.377	20	22.8	<.0001
Total bilirubin	0.155 [-0.0610; 0.371]	0.125	20	1.24	0.2303
Sex	0.915 [0.548; 1.28]	0.213	20	4.30	0.0003

AUClast vs INR

Effect	Estimate [90%]	Standard error	Degrees of freedom	t value	Pr > |t|
Intercept	8.96 [8.69; 9.24]	0.158	20	56.6	<.0001
INR	0.842 [-0.554; 2.24]	0.810	20	1.04	0.3107
Sex	0.829 [0.446; 1.21]	0.222	20	3.73	0.0013

AUClast vs Serum albumin

Effect	Estimate [90%]	Standard error	Degrees of freedom	t value	Pr > |t|
Intercept	12.9 [9.37; 16.5]	2.07	19	6.26	<.0001
Serum albumin	-0.646 [-1.49; 0.201]	0.490	19	-1.32	0.2027
Weight (kg)	-0.0178 [-0.0312; -0.00445]	0.00775	19	-2.30	0.0327
Sex	0.589 [0.186; 0.992]	0.233	19	2.53	0.0205

AUCinf vs Total bilirubin

Effect	Estimate [90%]	Standard error	Degrees of freedom	t value	Pr > |t|
Intercept	9.95 [8.74; 11.2]	0.699	19	14.2	<.0001
Total bilirubin	0.154 [-0.0377; 0.345]	0.111	19	1.39	0.1810
Weight (kg)	-0.0151 [-0.0275; -0.00271]	0.00716	19	-2.11	0.0486
Sex	0.652 [0.279; 1.03]	0.216	19	3.02	0.0071

AUCinf vs INR

Effect	Estimate [90%]	Standard error	Degrees of freedom	t value	Pr > |t|
Intercept	9.01 [8.75; 9.27]	0.152	20	59.5	<.0001
INR	0.850 [-0.488; 2.19]	0.775	20	1.10	0.2861
Sex	0.790 [0.423; 1.16]	0.213	20	3.71	0.0014

AUCinf vs Serum albumin

Effect	Estimate [90%]	Standard error	Degrees of freedom	t value	Pr > |t|
Intercept	13.0 [9.55; 16.4]	1.97	19	6.57	<.0001
Serum albumin	-0.643 [-1.45; 0.164]	0.467	19	-1.38	0.1843
Weight (kg)	-0.0175 [-0.0303; -0.00472]	0.00738	19	-2.37	0.0286
Sex	0.556 [0.172; 0.940]	0.222	19	2.51	0.0215

Model is a linear regression model of the log-transformed PK parameter as dependent variable and the log-transformed hepatic function parameter total bilirubin, INR, or serum albumin and weight and sex as significant covariates.

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Summary of Safety

Safety Results

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

Preferred Term Maximum Grade	Control N=11 n (%)	Moderate N=6 n (%)	Severe N=6 n (%)	All subjects N=23 n (%)
-Any preferred term	1 (9.1)	2 (33.3)	0	3 (13.0)
Grade 1	1 (9.1)	1 (16.7)	0	2 (8.7)
Grade 2	0	1 (16.7)	0	1 (4.3)
Nausea	0	2 (33.3)	0	2 (8.7)
Blood pressure increased	0	1 (16.7)	0	1 (4.3)
Dizziness	1 (9.1)	0	0	1 (4.3)

A subject with multiple occurrences of an AE under a hepatic function group is counted only once in the AE category for that group.
A subject with multiple adverse events within a primary system organ class is counted only once in the total row at maximum severity grade.
All adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA) versions 18.0 and 20.0 and Novartis WHODrug dictionaries from Sept 2014 (NVR092014V) and March 2017 (NVR032017V).
The severity is assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version v4.03.

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No Serious Adverse Events

No Death

Other Relevant Findings

None

Conclusion:

Alpelisib was well tolerated in the study population. There was no impact of moderate or severe hepatic impairment on the clearance, elimination, or distribution of alpelisib. Therefore, it is reasonable to conclude that mild hepatic impairment also has no impact. In conclusion, this analysis supports that no dose adjustment of alpelisib is required in subjects with mild, moderate, or severe hepatic impairment.

Date of Clinical Trial Report

27-Mar-2018