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Novartis Clinical Trial Results

Sponsor

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Generic Drug Name

BYL719 (alpelisib)

Trial Indication(s)

Not applicable.

Protocol Number

CBYL719A2103

Protocol Title

A single-center, open-label, randomized, five-period, ten-sequence crossover study to investigate the singular and joint effect of food and the histamine H2 -receptor antagonist (H2RA) ranitidine on the pharmacokinetics (PK) of oral alpelisib (BYL719) in healthy volunteers

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase I

Study Start/End Dates

18-Nov-2015 to 04-March-2016

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Reason for Termination

Not applicable.

Study Design/Methodology

This was a single center, open-label, randomized study to investigate the impact of food and acid reducing agents (ARA) (alone or in combination) on the PK of oral alpelisib. The study employed a five period, ten sequence, Williams square crossover design, as it limited the influence of confounding covariates by allowing intra-subject comparison.
Each subject received alpelisib administered in each of the five following conditions:

- Treatment A: alpelisib in fasted condition (reference)
- Treatment B: alpelisib with HFHC meal
- Treatment C: alpelisib with LFLC meal
- Treatment D: alpelisib co-administered with ranitidine in fasted condition
- Treatment E: alpelisib co-administered with ranitidine with LFLC meal

The period between each alpelisib administration was at least eight days (+ 14 days time window) to avoid any drug carryover effect.
Twenty subjects were planned to be recruited and each subject was to be randomly assigned to one of the ten treatment sequences.

Centers

1 center in 1 country: Germany (1)

Objectives:

Primary objective(s)

- To assess the impact of low fat low calorie (LFLC) meal and high fat high calorie (HFHC) meal on the rate and extent of absorption of alpelisib.
- To assess the impact of co-administration of ranitidine and its effect on the rate and extent of absorption of alpelisib either fasted, or with LFLC meal

Secondary objective(s)

- To describe the PK of alpelisib either fasted or with LFLC or HFHC meal
- To describe the PK of alpelisib with co-administration of ranitidine either fasted or with LFLC meal
- To describe the PK of ranitidine when co-administered with alpelisib either fasted, or with LFLC meal

- To assess the safety and tolerability of alpelisib:
  - when administered either fasted or with LFLC or HFHC meal
  - when administered with or without ranitidine when fasted or with LFLC meal

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

The investigational drug consisted of alpelisib tablets at dose strengths of 50 mg and 200 mg.

Statistical Methods

Three analysis sets were defined for the evaluation of data from this study:
Full Analysis Set
The Full Analysis Set (FAS) comprised of all randomized subjects
Safety Set
The Safety Set included all subjects who received at least one dose of study drug (alpelisib or ranitidine) and had at least one post-baseline safety assessment.
Pharmacokinetic analysis set
The Pharmacokinetic analysis set (PAS) was used for all PK analyses and comprised of all subjects who received at least one scheduled dose of alpelisib and for the respective dose:

- received all assigned doses of ranitidine in the applicable periods (treatments D and E)
- have not vomited within four hours after dosing of alpelisib or ranitidine
- have consumed >75% of the assigned meal in the applicable period (treatment B, C and E)
- provided sufficient concentration data to support the calculation of at least one primary alpelisib PK parameter (Cmax or AUCinf)

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

- Subject has signed the Informed Consent Form prior to any screening procedures being performed.
- Subjects should be in good health as determined by no clinically significant findings from past medical history, physical e examination, vital signs, electrocardiogram.
- Laboratory values (if not otherwise specified) within the reference range at the local laboratory, unless deemed not clinically significant by the Investigator or designee.

- Subject should not have significant illness, including infections, or hospitalization within the two weeks prior to dosing. Invasive systemic infections including fungal need to be fully resolved prior to screening.
- Subjects willing to avoid or have consumed, grapefruit, grapefruit juices, grapefruit hybrids, Seville oranges, pummelos, pomegranates, cranberries and star fruits from two weeks prior to first dosing and until the end of the study.
- Subject has not 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.
- Has not used any other investigational drugs (i.e. participation in any clinical investigation) within 30 days prior to dosing or longer if required by local regulation, or within five-half-lives of the investigational agent taken previously (whichever is longer).

Exclusion criteria

- Fertile male subjects, unless the study participant and his female partner agree to comply with highly effective contraception. Male subjects and their female partner should comply with highly effective contraception for the duration of the study and up to one week following the last study drug administration.
- Subject had significant illness, including infections, or hospitalization within the two weeks prior to dosing. Invasive systemic infections including fungal were to be fully resolved prior to screening.
- Subject had a contraindication or hypersensitivity to alpelisib or ranitidine or any of its excipients, derivatives, or metabolites from a similar class of study drug.
- Subject used tobacco products (including e-cigarettes) within three months prior to first dosing. Urine cotinine levels were measured during screening for all subjects. Smokers were defined as any subject who reported use of tobacco products (smoker or nonsmoker) or had a positive urine cotinine test (>500 ng/ml).
- Subject consumed alcohol within 48 hours prior to first dosing.

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Participant Flow Table

Subject disposition (Full analysis set)

Disposition	All subjects N=21 n (%)
Completed study	20 (95.2)
Discontinued prior to completion	1 (4.8)
Primary reason for discontinuation	
Physicians decision	1 (4.8)

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Baseline Characteristics

Demographics summary (Full analysis set)

Demographic Variable	All Subjects N=21 n (%)
Age (years)	
N	21
Mean (SD)	43.7 (8.20)
Median (Range)	47.0 (28-54)
Sex – n (%)	
Female	4 (19.0)
Male	17 (81.0)
Race – n (%)	
Caucasian	21 (100)
Ethnicity – n (%)	
Other	21 (100)
Child bearing potential – n (%)	
Post-menopausal	2 (9.5)
Sterile of child bearing age	2 (9.5)
Weight (Kg)	
N	21
Mean (SD)	75.99 (11.56)
Median (Range)	74.2 (55.2 – 98)
Height (cm)	
N	21
Mean (SD)	178.3 (6.93)
Median (Range)	180 (165 - 188)
BMI (kg/m2)	
N	21
Mean (SD)	23.82 (2.71)
Median (Range)	23.74 (19.47 – 29.26)

BMI = body mass index

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Primary Outcome Result(s)

Summary of primary PK parameters for alpelisib by treatment (Pharmacokinetic analysis set)

Parameter	Statistics	A	B	C
Cmax (ng/mL)	N	20	20	21
	Mean (SD)	1230 (610)	2040 (494)	2680 (563)
	CV%	49.8	24.2	21.0
	Geo-mean	1080	1980	2620
	geo-CV%	58.8	25.8	22.0
	Median	1070	2120	2700
	[Min; Max]	[341; 2390]	[1160; 2830]	[1690; 3930]
Tmax (hr)	n	20	20	21
	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	1.98	3.00	2.45
	[Min; Max]	[1.00; 2.50]	[1.00; 4.07]	[0.967; 4.00]
AUCinf (ng*hr/mL)	n	20	20	21
	Mean (SD)	10400 (4440)	17500 (5530)	17600 (5110)
	CV%	42.7	31.7	29.0
	Geo-mean	9630	16600	17000
	geo-CV%	41.7	32.6	26.6
	Median	10600	16000	15100
	[Min; Max]	[4190; 25200]	[7710; 28200]	[12300; 30200]

CV% = coefficient of variation (%) = SD/mean*100, Geo-CV% = sqrt (exp (variance for log transformed data)-1)*100
A: fasted; B: with HFHC meal; C: with LFLC meal

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Summary of statistical analysis of primary PK parameters for alpelisib (Pharmacokinetic analysis set)

					Treatment comparison		
						90% CI	
PK parameter (unit)	Treatment	n*	Adjusted geo-mean	Comparison(s)	Geo-mean ratio	Lower	Upper
Cmax (ng/mL)	A	20	1070				
	B	20	1970	B/A	1.84	1.56	2.17
	C	21	2620	B/C	0.753	0.638	0.888
				C/A	2.45	2.08	2.89
Tmax (hr)	A	20	1.98				
	B	20	3.00	B-A	1.50	-0.48	3.00
	C	21	2.45	B-C	0.47	-0.53	3.03
				C-A	0.45	-1.03	2.47
AUCinf (ng*hr/mL)	A	20	9590				
	B	20	16600	B/A	1.73	1.55	1.93
	C	21	16900	B/C	0.978	0.876	1.09
				C/A	1.77	1.58	1.97

A: fasted; B: with HFHC meal; C: with LFLC meal
Model is a linear mixed effects model of the log-transformed PK parameters. Included in the model were period, sequence, and treatment as fixed effects and subject within sequence as a random effect. 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', median difference under 'Geo-mean ratio', and minimum and maximum differences under 90% CI

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Summary of primary PK parameters of alpelisib following co-administration with ranitidine including reference treatment

Parameter	Statistics	A	C	D	E
Cmax (ng/mL)	n	20	21	20	20
	Mean (SD)	1230 (610)	2680 (563)	579 (252)	1770 (547)
	CV%	49.8	21.0	43.4	31.0
	Geo-mean	1080	2620	532	1680
	geo-CV%	58.8	22.0	44.7	33.1
	Median	1070	2700	523	1680
	[Min; Max]	[341; 2390]	[1690; 3930]	[230; 1240]	[821; 2830]
Tmax (hr)	n	20	21	20	20
	Mean (SD)	N/A	N/A	N/A	N/A
	CV%	N/A	N/A	N/A	N/A
	Geo-mean	N/A	N/A	N/A	N/A
	geo-CV%	N/A	N/A	N/A	N/A
	Median	1.98	2.45	2.03	2.52
	[Min; Max]	[1.00; 2.50]	[0.967; 4.00]	[1.45; 4.12]	[1.48; 4.05]
AUCinf (ng*hr/mL)	n	20	21	19	20
	Mean (SD)	10400 (4440)	17600 (5110)	7110 (2830)	14500 (5750)
	CV%	42.7	29.0	39.8	39.8
	Geo-mean	9630	17000	6580	13500
	geo-CV%	41.7	26.6	43.0	39.4
	Median	10600	15100	5990	11400
	[Min; Max]	(4190; 25200)	[12300; 30200]	(3370; 11700)	(8110; 25200)

A: fasted; C: with LFLC meal; D: with ranitidine and fasted; E: with ranitidine and LFLC meal

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Summary of statistical analysis of primary PK parameters for alpelisib following co-administration with ranitidine including reference treatment (Pharmacokinetic analysis set)

PK parameter (unit)	Treatment	n*	Adjusted geo-mean	Comparison(s)	Treatment comparison Geo-mean ratio	90% CI Lower	90% CI Upper
Cmax (ng/mL)	A	20	1070				
	C	21	2620	C/A	2.45	2.08	2.89
	D	20	528	D/A	0.494	0.418	0.583
	E	20	1670	E/A	1.56	1.32	1.85
				E/C	0.639	0.542	0.754
Tmax (hr)	A	20	1.98				
	C	21	2.45	C-A	0.45	-1.03	2.47
	D	20	2.03	D-A	0.48	-1.00	2.52
	E	20	2.52	E-A	1.00	-0.47	2.47
				E-C	0.47	-1.02	2.05
AUCinf (ng*hr/mL)	A	20	9590				
	C	21	16900	C/A	1.77	1.58	1.97
	D	19	6700	D/A	0.699	0.624	0.782
	E	20	13400	E/A	1.40	1.25	1.56
				E/C	0.791	0.708	0.884

Model is a linear mixed effects model of the log-transformed PK parameters. Included in the model were period, sequence, and treatment as fixed effects and subject within sequence as a random effect. The results were back transformed to get adjusted geometric mean, geometric mean ratio, and 90% CI.
A: fasted; C: with LFLC meal; D: with ranitidine and fasted; E: with ranitidine and LFLC meal
n* = number of subjects with non-missing values
For Tmax, median is presented under 'Adjusted geo-mean', median difference under 'Geo-mean ratio', and minimum and maximum differences under 90% CI

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Secondary Outcome Result(s)

Summary of secondary PK parameters for alpelisib by treatment (Pharmacokinetic analysis set)

Parameter	Statistics	A	B	C
AUClast (ng*hr/mL)	n	20	20	21
	Mean (SD)	10000 (4370)	17300 (5590)	17400 (5140)
	CV%	43.6	32.4	29.5
	Geo-mean	9260	16400	16800
	geo-CV%	41.9	33.5	27.1
	Median	10400	15900	15000
	[Min; Max]	[4100; 25000]	[7530; 28000]	[12000; 29900]
AUC0-72 (ng*hr/mL)	n	20	20	21
	Mean (SD)	10200 (4360)	17500 (5440)	17700 (5020)
	CV%	42.8	31.0	28.4
	Geo-mean	9440	16800	17100
	geo-CV%	41.5	32.1	26.0
	Median	10500	16100	15300
	[Min; Max]	[4100; 25000]	[7670; 28000]	[12500; 30200]
T1/2 (hr)	n	20	20	21
	Mean (SD)	12.4 (6.52)	6.52 (1.92)	6.36 (2.40)
	CV%	52.4	29.5	37.7
	Geo-mean	10.9	6.27	6.03
	geo-CV%	57.8	29.8	32.8
	Median	12.0	6.40	6.43
	[Min; Max]	[4.17; 30.7]	[3.95; 10.6]	[3.73; 15.2]
CL/F (L/hr)	n	20	20	21
	Mean (SD)	33.6 (14.2)	18.9 (6.41)	18.2 (4.24)
	CV%	42.1	33.9	23.3
	Geo-mean	31.1	18.0	17.6
	geo-CV%	41.7	32.6	26.6
	Median	28.4	18.7	19.8
	[Min; Max]	[11.9; 71.6]	[10.7; 38.9]	[9.93; 24.5]
Vz/F	n	20	20	21
	Mean (SD)	606 (391)	177 (103)	159 (45.4)
	CV%	64.4	58.2	28.5
	Geo-mean	491	163	153
	geo-CV%	78.2	37.6	29.0
	Median	561	155	150
	[Min; Max]	[163; 1520]	[105; 597]	[101; 266]

A: fasted; B: with HFHC meal; C: with LFLC meal
CV% = coefficient of variation (%) = SD/mean*100, Geo-CV% = sqrt (exp (variance for log transformed data)-1)*100

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Summary of secondary PK parameters for alpelisib following co-administration with ranitidine including reference treatment (Pharmacokinetic analysis set)

Parameter	Statistics	A	C	D	E
AUClast (ng*hr/mL)	n	20	21	20	20
	Mean (SD)	10000 (4370)	17400 (5140)	7090 (3000)	14200 (5720)
	CV%	43.6	29.5	42.3	40.3
	Geo-mean	9260	16800	6500	13200
	geo-CV%	41.9	27.1	45.8	40.2
	Median	10400	15000	6010	11000
	[Min; Max]	[4100; 25000]	[12000; 29900]	[3220; 13400]	[7730; 25000]
AUC0-72 (ng*hr/mL)	n	20	21	20	20
	Mean (SD)	10200 (4360)	17700 (5020)	7190 (2960)	14400 (5630)
	CV%	42.8	28.4	41.2	39.0
	Geo-mean	9440	17100	6620	13500
	geo-CV%	41.5	26.0	44.4	38.7
	Median	10500	15300	6080	11700
	[Min; Max]	[4100; 25000]	[12500; 30200]	[3350; 13400]	[8360; 25000]
T1/2 (hr)	n	20	21	20	20
	Mean (SD)	12.4 (6.52)	6.36 (2.40)	14.7 (6.45)	8.30 (3.01)
	CV%	52.4	37.7	43.9	36.2
	Geo-mean	10.9	6.03	13.7	7.81
	geo-CV%	57.8	32.8	39.2	36.9
	Median	12.0	6.43	12.9	7.93
	[Min; Max]	[4.17; 30.7]	[3.73; 15.2]	[7.20; 34.9]	[4.02; 14.6]
CL/F (L/hr)	n	20	21	19	20
	Mean (SD)	33.6 (14.2)	18.2 (4.24)	49.4 (20.6)	23.8 (8.28)
	CV%	42.1	23.3	41.7	34.8
	Geo-mean	31.1	17.6	45.6	22.3
	geo-CV%	41.7	26.6	43.0	39.4
	Median	28.4	19.8	50.1	26.3
	[Min; Max]	[11.9; 71.6]	[9.93; 24.5]	[25.7; 89.0]	[11.9; 37.0]
Vz/F	n	20	21	19	20
	Mean (SD)	606 (391)	159 (45.4)	923 (359)	271 (120)
	CV%	64.4	28.5	38.9	44.3
	Geo-mean	491	153	856	251
	geo-CV%	78.2	29.0	42.5	40.8
	Median	561	150	925	232
	[Min; Max]	[163; 1520]	[101; 266]	[434; 1680]	[142; 625]

A: fasted; C: with LFLC meal; D: with ranitidine and fasted; E: with ranitidine and LFLC meal

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Summary of PK parameters intra- and inter-subject variability for alpelisib (Pharmacokinetic analysis set)

Parameter (unit)	n	Intra subject variance	Intra subject CV%	Inter subject variance	Inter subject CV%
Cmax (ng/mL)	21	0.1	32.3	0.04	20.7
AUCinf (ng*hr/mL)	21	0.04	21.3	0.09	29.9
AUClast (ng*hr/mL)	21	0.05	22	0.09	30.9

Summary of PK parameters for ranitidine by treatment (Pharmacokinetic analysis set)

Parameter	Statistics	D	E
Cmax (ng/mL)	N	20	20
	Mean (SD)	460 (157)	458 (128)
	CV%	34.2	27.9
	Geo-mean	436	443
	geo-CV%	33.9	25.9
	Median	470	426
	[Min; Max]	[241; 903]	[283; 846]
Tmax (hr)	N	20	20
	Mean (SD)	N/A	N/A
	CV%	N/A	N/A
	Geo-mean	N/A	N/A
	geo-CV%	N/A	N/A
	Median	3.74	2.51
	[Min; Max]	[0.500; 6.00]	[1.00; 4.00]
AUCinf(ng*hr/mL)	N	20	20
	Mean (SD)	2760 (737)	2560 (419)
	CV%	26.7	16.3

Parameter	Statistics	D	E
	Geo-mean	2640	2530
	geo-CV%	32.4	16.8
	Median	2880	2530
	[Min; Max]	[1030; 4170]	[1920; 3330]
AUClast (ng*hr/mL)	N	20	20
	Mean (SD)	2720 (738)	2530 (410)
	CV%	27.1	16.2
	Geo-mean	2610	2500
	geo-CV%	33.2	16.6
	Median	2870	2500
	[Min; Max]	[996; 4100]	[1900; 3320]
AUC0-26 (ng*hr/mL)	N	20	20
	Mean (SD)	2740 (716)	2540 (416)
	CV%	26.1	16.4
	Geo-mean	2640	2500
	geo-CV%	31.5	16.8
	Median	2870	2530
	[Min; Max]	[1050; 4090]	[1900; 3320]

D: with ranitidine and fasted; E: with ranitidine and LFLC meal

Safety Results

Adverse events, regardless of study drug relationship, by primary system organ class (all grades) (Safety set)

Primary system organ class (all grades)	All Subjects N=21 n (%)
Subjects with at least one AE	**13 (61.9)**
Gastrointestinal disorders	6 (28.6)
Infections and infestations	6 (28.6)
Nervous system disorders	2 (9.5)
Musculoskeletal & connective tissue disorders	1 (4.8)
Skin & subcutaneous tissue disorders	1 (4.8)
Cardiac disorders	1 (4.8)
Injury, poisoning and procedural complications	1 (4.8)

Adverse events, regardless of study drug relationship, by preferred term (all grades) (Safety set)

Preferred term (all grades)	All Subjects N=21 n (%)
Subjects with at least one AE	**13 (61.9)**
Nausea	4 (19.0)
Nasopharyngitis	3 (14.3)
Oral herpes	2 (9.5)
Toothache	2 (9.5)
Back pain	1 (4.8)
Dizziness postural	1 (4.8)
Extrasystoles	1 (4.8)
Fungal skin infection	1 (4.8)
Headache	1 (4.8)
Rash	1 (4.8)
Skin abrasion	1 (4.8)

Serious Adverse Events and Deaths

No deaths, SAEs, AEs leading to discontinuation or any other AEs of special interest were reported in the study.

Conclusion:

Alpelisib has been administered in most human cancer studies (including the first-in-man study) with a light meal. Data from the current study confirms that both Cmax and AUCinf increased in the presence of food compared to fasted condition. This conclusion is also strengthened by the result of the ARA part of the study, showing that ranitidine did not lead to a significant decrease in exposure when administered with a meal. In the absence of food, the decrease under ranitidine was more pronounced.

Date of Clinical Trial Report

04-Aug-2016

Swiss Authorization date and authorization number

Swissmedic Approval Number: 67359

Swissmedic Approval Date 24.03.2020

Novartis Study Code

CBYL719A2103

EudraCT Number

Not Applicable

Planned and Actual Number of Patients

Planned: 20
Actual: 21

Batch Numbers

Study drug and strength	Formulation	Batch numbers
BYL719 50 mg	Film-coated tablet	X260KK
BYL719 200 mg	Film-coated tablet	X261HK
Ranitidine 150 mg	Tablet	P47664
BYL719 = alpelisib		

Information on comparators drug dosage, route of administration, batch numbers

Not applicable

Publication(s)

Not applicable

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Investigators & Information on Study Centers

Investigator	**Facility Name** **Address** **Country**
Dr. med. Georg Golor	PAREXEL International GmbH Early Phase Clinical Unit Berlin Berlin 14050 Germany