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Sponsor

Novartis

Generic Drug Name

Buparlisib

Trial Indications

Renal impairment

Protocol Number

CBKM120C2113

Protocol Title

An open-label, single dose, multicenter study to evaluate the pharmacokinetics and safety of 50 mg oral buparlisib in subjects with moderate and severe renal impairment compared to matched control healthy volunteers.

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase III

Study Start/End Dates

Study initiation date: 21-Mar-2014 (first subject first visit)

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Study completion date: 18-Mar-2015 (last subject last visit)

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was an open label, single dose, multi-center study with sequential design to assess the safety in subjects with varying renal impairment (moderate and severe renal impairment) compared to matching healthy (control) subjects. Subjects enrolled in this study were allocated to three groups by their respective degree of renal function at the time of screening.

Enrollment in this study started with subjects who had moderate renal impairment (Group 2) and their matching controls (Group 1). The enrollment of subjects with severe impairment (Group 3) began only after a preliminary safety and preliminary PK assessment of buparlisib in first 3 subjects with moderate impairment had been performed. Based on these results, the same dose of 50 mg was also selected for administration to subjects in the severe group. Matching was based on gender, race, age (±10 years), and weight (±20%). Each subject received a single, oral 50 mg dose of buparlisib.

Centers

Four sites enrolled subjects: Germany (1 site), Czech Republic (1 site), Romania (1 site), Bulgaria (1 site).

Publication

None

Objectives:

Primary objective:

- To determine the impact of renal impairment on the pharmacokinetics (PK) of buparlisib based on primary PK parameters following one 50 mg buparlisib dose.

Key secondary objectives:

- To determine the impact of renal impairment on secondary PK parameters and plasma protein binding of buparlisib following one 50 mg buparlisib dose.
- To determine the relationship between renal function measures and PK parameters.

Other secondary objectives:

- To evaluate safety and tolerability of 50 mg buparlisib in subjects with moderate and severe renal impairment compared to healthy subjects with normal renal function.

Test Product, Dose, and Mode of Administration

Single oral dose of buparlisib 50 mg capsule.

Statistical Methods

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

- Primary PK parameters (Cmax, AUCinf, AUC0-t, CL/F and urine PK parameter CLR) were analyzed separately on the log scale by means of an ANOVA model including the renal function group (control, moderate, severe) as a fixed effect. The geometric mean of each PK parameter was derived from the model for each renal function group; the ratio of the PK parameter geometric means between the control group and each one of the other renal function groups and their 90% CI were also derived from the model.
- The same analysis was performed for the secondary PK parameters and unbound PK parameters.
- For Tmax the medians of each renal function group and difference of medians between each of the impairment groups and the control group were presented.
- All PK parameters, concentrations and fraction unbound 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 renal function group and by time point where applicable. For plasma and urine concentrations both n (number of non-missing values) and m (number of non-zero values) were presented.

- The relationship between the primary PK variables and renal functions parameter eGFR were explored by means of regression analysis between log-transformed PK parameters and log-transformed renal function parameters considering age and weight as covariates. The regression coefficients representing the relationship between the PK parameters and the renal function parameters were estimated together with its 90% CI from the model. The relationship between primary PK parameters and eGFR were repeated using PK parameters expressed in terms of unbound concentration.
- The incidence (number and percentage) of all the treatment emergent adverse events (TEAEs) were summarized by system organ class (SOC), preferred term (PT), maximum CTCAE grade and by the renal function group and additionally by PT and the renal function group. Additional summary tables were provided for the TEAEs which were suspected to be related to the study drug and for SAEs. The severity of AEs was assessed using appropriate Common Terminology Criteria for Adverse Events (CTCAE version 4.03).

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion criteria:

- Other than renal impairment, subjects in good health as determined by past medical history, physical examination, vital signs, electrocardiogram, (except for additional inclusion criteria for renal impaired patients).
- Subjects with a BMI between 18 kg/m2 and 34 kg/m2, weight at least 50 kg and no more than 120 kg.

Main additional inclusion criteria renal impairment subjects:

- Subjects with stable renal disease without evidence of renal progressive disease defined as moderate renal impairment (eGFR 30-59 mL/min/1.73m2) or severe renal impairment (eGFR 15-29 mL/min/1.73m2).

Main additional inclusion criteria matched control subjects:

- Matched to at least one renal impaired subject by gender, race, age (± 10 years), and weight (± 20%).
- An estimated GFR as determined by modification of diet in renal disease (MDRD) equation within normal range as determined by eGFR ≥ 90 mL/min/1.73m2

Key exclusion criteria:

- Significant illness, including infections, or hospitalization within the 2 weeks prior to dosing, except for the renal impaired subjects who due to their renal disease were affected by significant medical problems which require frequent hospitalizations.
- Any surgical or medical condition that may significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the subject in case of participation in the study
- Subject with a medical history of cardiac disease and/or clinically significant ECG abnormalities within 6 months prior to screening.
- Subject with an active or a history within 6 months prior to screening of clinically significant hematologic, endocrinologic, pulmonary, cardiovascular, hepatic, or allergic disease, medically documented (other than clinical conditions associated with renal impairment for the renal impaired subjects only).

Main additional exclusion criteria renal impairment subjects:

- Severe albuminuria > 300 mg/day.
- Subjects undergoing any method of dialysis.
- Subjects with renal impairment due to hepatic disease (hepatorenal syndrome).
- Subjects with clinically significant abnormal findings, not consistent with clinical disease, upon physical examination, ECG or laboratory evaluation.
- Use of any prescription or non-prescription medication that had the potential to interact with buparlisib within two weeks prior to dosing or during the study.

Main additional exclusion criteria matched control subjects:

- Use of any prescription or non-prescription medication or vitamins during 14 days prior to dosing.

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Participant Flow Table

Subject disposition, by renal function group (Full Analysis Set [FAS])

Disposition	Control (N=7) n (%)	Moderate (N=6) n (%)	Severe (N=6) n (%)	All subjects (N=19) n (%)
Completed	7 (100)	6 (100)	6 (100)	19 (100)

Baseline Characteristics

Demographics and other baseline characteristics by renal function group (FAS)

Demographic variable	Control (N=7)	Moderate (N=6)	Severe (N=6)	All subjects (N=19)
Age (Years)				
n	7	6	6	19
Mean (SD)	55.6 (14.60)	56.8 (15.55)	62.2 (7.47)	58.1 (12.74)
Median	54.0	58.0	59.5	57.0
Min- Max	28-73	37-75	55-74	28-75
Sex - n (%)				
Male	5 (71.4)	4 (66.7)	3 (50.0)	12 (63.2)
Female	2 (28.6)	2 (33.3)	3 (50.0)	7 (36.8)
Race - n (%)				
Caucasian	7 (100)	6 (100)	6 (100)	19 (100)
Ethnicity - n (%)				
Other	7 (100)	6 (100)	6 (100)	19 (100)
Weight (kg)				
n	7	6	6	19
Mean (SD)	79.00 (18.245)	79.58 (21.394)	79.82 (13.918)	79.44 (17.089)

Demographic variable	Control (N=7)	Moderate (N=6)	Severe (N=6)	All subjects (N=19)
Median	85.00	79.50	80.00	80.00
Min - Max	53.4 -107.5	55.0-108.0	62.0-100.9	53.4-108.0
Height (cm)				
n	7	6	6	19
Mean (SD)	173.29 (8.976)	167.75 (11.583)	168.00 (7.642)	169.87 (9.357)
Median	178.00	169.00	168.00	169.00
Min - Max	161.0-182.0	151.5-180.0	159.0-177.0	151.5-182.0
Body mass index (kg/m^2)				
n	7	6	6	19
Mean (SD)	26.008 (3.8912)	28.012 (5.6139)	28.211 (3.9004)	27.337 (4.3727)
Median	26.235	28.419	28.387	26.827
Min- Max	19.85-32.45	20.20-33.71	21.71-32.57	19.85-33.71
Body surface area (m^2)				
n	7	6	6	19
Mean (SD)	1.941 (0.2674)	1.916 (0.3073)	1.933 (0.1951)	1.930 (0.2465)
Median	2.049	1.931	1.906	1.930
Min- Max	1.57-2.33	1.55-2.32	1.72-2.23	1.55-2.33

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.
BSA (m^2) = $((\text{weight (kg)} \times \text{height (m)})^{0.5})/6$. BSA is calculated using the screening weight and screening height.

Summary of Efficacy

No efficacy was evaluated in this study.

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Summary of Pharmacokinetics

Summary of primary PK parameters for plasma buparlisib by renal function group based on screening eGFR (FDA guidance) (Pharmacokinetic Analysis Set [PAS])

Renal function group	Statistics	Cmax (ng/mL)	AUCinf (ng.h/mL)	AUC0-192 (ng.h/mL)	CL/F (L/hr)	CLR (L/hr)
Control (N=7)	n	7	7	7	7	7
	Mean (SD)	352 (115)	9230 (2750)	8450 (2460)	6.10 (2.82)	0.0246 (0.00587)
	CV% mean	32.7	29.8	29.1	46.2	23.9
	Geo-mean	335	8780	8070	5.70	0.0240
	CV% geo-mean	36.1	38.5	36.5	38.5	24.8
	Median	393	10100	9370	4.94	0.0251
	[Min; Max]	[205; 504]	[4090; 12600]	[3930; 11800]	[3.97; 12.2]	[0.0174; 0.0329]
Moderate (N=6)	n	6	5	6	5	6
	Mean (SD)	384 (111)	10900 (3070)	10600 (2780)	4.88 (1.42)	0.0310 (0.0213)
	CV% mean	29.0	28.1	26.3	29.1	68.6
	Geo-mean	371	10600	10300	4.72	0.0265
	CV% geo-mean	29.3	29.7	26.3	29.7	63.6
	Median	355	11000	10600	4.54	0.0222
	[Min; Max]	[268; 542]	[7570; 14200]	[7520; 15100]	[3.51; 6.60]	[0.0141; 0.0712]
Severe (N=6)	n	6	4	6	4	6
	Mean (SD)	331 (97.5)	15100 (4910)	12800 (3110)	3.59 (1.18)	0.0297 (0.00921)
	CV% mean	29.4	32.5	24.3	32.8	31.0
	Geo-mean	318	14500	12400	3.44	0.0284
	CV% geo-mean	32.7	33.9	27.2	33.9	35.4

Renal function group	Statistics	Cmax (ng/mL)	AUCinf (ng.h/mL)	AUC0-192 (ng.h/mL)	CL/F (L/hr)	CLR (L/hr)
	Median	351	14700	12900	3.45	0.0322
	[Min; Max]	[194; 463]	[9790; 21400]	[7780; 16800]	[2.34; 5.11]	[0.0168; 0.0384]

Classification based on screening eGFR (FDA guidance)
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 plasma buparlisib without covariates - classification based on screening eGFR (PAS)

					Renal function group comparison		
						90% CI	
PK parameter (unit)	Group	n[1]	Adjusted Geo-mean	Comparison(s)	Geo-mean Ratio	Lower	Upper
Cmax (ng/mL)	Control	7	335				
	Moderate	6	371	Moderate / Control	1.106	0.809	1.512
	Severe	6	318	Severe / Control	0.950	0.695	1.298
AUCinf (ng.hr/mL)	Control	7	8780				
	Moderate	5	10590	Moderate / Control	1.206	0.849	1.714
	Severe	4	14520	Severe / Control	1.655	1.136	2.410
AUC0-192 (ng.hr/mL)	Control	7	8070				
	Moderate	6	10300	Moderate / Control	1.276	0.953	1.708
	Severe	6	12420	Severe / Control	1.539	1.150	2.060
CL/F (L/hr)	Control	7	5.70				
	Moderate	5	4.72	Moderate / Control	0.829	0.583	1.178
	Severe	4	3.44	Severe / Control	0.604	0.415	0.880

PK parameter (unit)	Group	n[1]	Adjusted Geo-mean	Comparison(s)	Renal function group comparison Geo-mean Ratio	90% CI Lower	90% CI Upper
CLR (L/hr)	Control	7	0.0240				
	Moderate	6	0.0265	Moderate / Control	1.104	0.744	1.638
	Severe	6	0.0284	Severe / Control	1.183	0.797	1.756

Classification based on eGFR (FDA guidance).
Model is a linear model of the log-transformed PK parameters, including renal function status group as fixed effect.
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.
n[1] = number of subjects with non-missing values.

Secondary Outcome Results

Summary of secondary PK parameters for plasma buparlisib by renal function group based on screening eGFR (PAS)

Renal function group	Statistics	Tmax (h)	T1/2 (h)	Vz/F (L)	Ae0-144 (ng)
Control (N=7)	n	7	7	7	7
	Mean (SD)	N/A	52.7 (12.6)	444 (161)	0.189 (0.0606)
	CV% mean	N/A	23.9	36.2	32.1
	Geo-mean	N/A	51.3	421	0.181
	CV% geo-mean	N/A	27.0	35.7	33.1
	Median	1.00	52.8	433	0.189
	[Min; Max]	[0.983; 2.00]	[31.8; 64.8]	[279; 735]	[0.112; 0.294]
Moderate (N=6)	n	6	6	5	6

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Renal function group	Statistics	Tmax (h)	T1/2 (h)	Vz/F (L)	Ae0-144 (ng)
	Mean (SD)	N/A	62.7 (31.2)	338 (79.1)	0.296 (0.186)
	CV% mean	N/A	49.8	23.4	62.9
	Geo-mean	N/A	55.4	330	0.249
	CV% geo-mean	N/A	62.4	25.2	72.0
	Median	1.00	67.5	378	0.228
	[Min; Max]	[0.983; 1.50]	[25.5; 108]	[242; 411]	[0.104; 0.561]
Severe (N=6)	n	6	6	4	6
	Mean (SD)	N/A	115 (51.0)	422 (132)	0.323 (0.126)
	CV% mean	N/A	44.5	31.3	38.9
	Geo-mean	N/A	106	408	0.306
	CV% geo-mean	N/A	43.5	30.4	36.2
	Median	1.02	90.0	391	0.288
	[Min; Max]	[0.483; 2.00]	[68.2; 191]	[298; 608]	[0.204; 0.555]

Classification based on screening eGFR (FDA guidance)
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

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Summary of statistical analysis of secondary PK parameters for plasma buparlisib without covariates based on total drug concentration – classification based on screening eGFR (PAS)

					Renal function group comparison		
						90% CI	
PK parameter (unit)	**Group**	**n[1]**	**Adjusted Geo-mean**	**Comparison(s)**	**Geo-mean Ratio**	**Lower**	**Upper**
Tmax (hr)	Control	7	1.00				
	Moderate	6	1.00	Moderate - Control	0		
	Severe	6	1.02	Severe - Control	0.016		
T1/2 (hr)	Control	7	51.3				
	Moderate	6	55.4	Moderate / Control	1.080	0.712	1.637
	Severe	6	106.4	Severe / Control	2.076	1.369	3.147
Vz/F (L)	Control	7	421				
	Moderate	5	330	Moderate / Control	0.784	0.570	1.079
	Severe	4	408	Severe / Control	0.968	0.688	1.363
Ae0-144 (ng)	Control	7	0.181				
	Moderate	6	0.249	Moderate / Control	1.382	0.887	2.152
	Severe	6	0.306	Severe / Control	1.695	1.088	2.640

Classification based on eGFR (FDA guidance)
Model is a linear model of the log-transformed PK parameters, including renal function group as fixed effect.
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.
For Tmax, the median is presented under 'Adjusted geo-mean' and median difference between the control group and each of the other renal function groups under "Geo-Mean ratio"
n^1 = number of subjects with non-missing values.

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Summary of PK parameters for plasma buparlisib based on unbound drug concentration by renal function group based on screening eGFR (PAS)

Renal function group	Statistics	Cmax,u (ng/mL)	AUCinf,u (ng.h/mL)	AUC0-192,u (ng.h/mL)	CLu/F (L/hr)	Vu/F (L)
Control (N=7)	n	7	7	7	7	7
	Mean (SD)	51.6 (19.4)	1380 (554)	1260 (474)	0.888 (0.410)	66.3 (27.3)
	CV% mean	37.5	40.1	37.7	46.1	41.2
	Geo-mean	48.7	1280	1170	0.828	61.3
	CV% geo-mean	37.9	47.2	43.5	39.5	46.4
	Median	45.3	1230	1110	0.708	65.9
	[Min; Max]	[31.2; 78.2]	[589; 2150]	[566; 1860]	[0.583; 1.76]	[31.8; 106]
Moderate (N=6)	n	6	5	6	5	5
	Mean (SD)	50.5 (19.1)	1480 (742)	1420 (587)	0.620 (0.221)	44.5 (18.6)
	CV% mean	37.8	50.3	41.4	35.6	41.7
	Geo-mean	46.9	1320	1300	0.590	41.3
	CV% geo-mean	47.2	57.0	49.7	36.6	47.0
	Median	50.3	1290	1550	0.579	41.7
	[Min; Max]	[21.1; 76.2]	[715; 2320]	[710; 2040]	[0.357; 0.969]	[22.9; 65.4]
Severe (N=6)	n	6	4	6	4	4
	Mean (SD)	57.3 (18.4)	2690 (724)	2170 (425)	0.656 (0.255)	77.1 (28.8)
	CV% mean	32.2	26.9	19.6	38.9	37.4
	Geo-mean	54.7	2610	2140	0.620	73.5

Renal function group	Statistics	Cmax,u (ng/mL)	AUCinf,u (ng.h/mL)	AUC0-192,u (ng.h/mL)	CLu/F (L/hr)	Vu/F (L)
	CV% geo-mean	35.0	27.5	20.6	40.4	36.4
	Median	58.8	2620	2160	0.618	70.0
	[Min; Max]	[35.5; 81.0]	[1900; 3610]	[1510; 2830]	[0.396; 0.991]	[50.4; 118]

Classification based on screening eGFR (FDA guidance)
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 PK parameters for plasma buparlisib without covariates based on unbound drug concentration – classification based on screening eGFR (PAS)

					Renal function group comparison		
						90% CI	
PK parameter (unit)	Group	n[1]	Adjusted Geo-mean	Comparison(s)	Geo-mean Ratio	Lower	Upper
Cmax,u (ng/mL)	Control	7	48.7				
	Moderate	6	46.9	Moderate / Control	0.963	0.662	1.402
	Severe	6	54.7	Severe / Control	1.124	0.772	1.636
AUCinf,u (ng.hr/mL)	Control	7	1280				
	Moderate	5	1320	Moderate / Control	1.037	0.655	1.641
	Severe	4	2610	Severe / Control	2.049	1.253	3.349
AUC0-192,u (ng.hr/mL)	Control	7	1170				
	Moderate	6	1300	Moderate / Control	1.111	0.766	1.612
	Severe	6	2140	Severe / Control	1.821	1.255	2.642

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PK parameter (unit)	Group	n[1]	Adjusted Geo-mean	Comparison(s)	Renal function group comparison Geo-mean Ratio	90% CI Lower	90% CI Upper
CLu/F (L/hr)	Control	7	0.828				
	Moderate	5	0.590	Moderate / Control	0.712	0.483	1.051
	Severe	4	0.620	Severe / Control	0.748	0.494	1.135
Vu/F (L)	Control	7	61.3				
	Moderate	5	41.3	Moderate / Control	0.674	0.434	1.046
	Severe	4	73.5	Severe / Control	1.199	0.749	1.921

Classification based on eGFR (FDA guidance)
Model is a linear model of the log-transformed PK parameters, including renal function status as fixed effect.
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.
n^1 = number of subjects with non-missing values

Summary of linear regression that describes relationship between log-transformed PK parameters (dependent) and log-transformed baseline eGFR (PAS)

PK parameter	Effect	Estimate (90%CI)	Standard error	Degrees of freedom	t value	Pr > |t|
Cmax	Intercept	6.79 [5.88;7.7]	0.518	15	13.1	<.0001
	Age	-0.000797 [-0.008629;0.007034]	0.004	15	-0.18	0.8608
	Weight	-0.0128 [-0.0186;-0.007]	0.003	15	-3.89	0.0015
	Log EGFR	0.0266 [-0.1231;0.1763]	0.085	15	0.31	0.7597
AUCinf	Intercept	10.8 [9.3;12.2]	0.834	12	12.9	<.0001
	Age	0.000988 [-0.011311;0.013287]	0.007	12	0.14	0.8885
	Weight	-0.0045 [-0.01341;0.0044]	0.005	12	-0.9	0.3852

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PK parameter	Effect	Estimate (90%CI)	Standard error	Degrees of freedom	t value	Pr > |t|
	Log EGFR	-0.304 [-0.554;-0.055]	0.14	12	-2.17	0.0505
AUC0-144	Intercept	10.4 [9.3;11.5]	0.606	15	17.16	<.0001
	Age	0.0000599 [-0.0090974;0.0092172]	0.005	15	0.01	0.991
	Weight	-0.00456 [-0.0113;0.00218]	0.004	15	-1.19	0.2538
	Log EGFR	-0.243 [-0.418;-0.068]	0.1	15	-2.43	0.0281
AUC0-192	Intercept	10.5 [9.4;11.7]	0.659	15	16	<.0001
	Age	0.000915 [-0.009043;0.010874]	0.006	15	0.16	0.8741
	Weight	-0.00372 [-0.01105;0.00362]	0.004	15	-0.89	0.3883
	Log EGFR	-0.285 [-0.475;-0.095]	0.109	15	-2.63	0.0191
CL/F	Intercept	0.0594 [-1.4275;1.5464]	0.834	12	0.07	0.9444
	Age	-0.000988 [-0.013287;0.011311]	0.007	12	-0.14	0.8885
	Weight	0.0045 [-0.0044;0.01341]	0.005	12	0.9	0.3852
	Log EGFR	0.304 [0.055;0.554]	0.14	12	2.17	0.0505
CLR	Intercept	-4.2 [-5.69;-2.72]	0.849	15	-4.95	0.0002
	Age	0.0127 [-0.0001;0.0256]	0.007	15	1.74	0.1026
	weight	-0.00105 [-0.0105;0.00839]	0.005	15	-0.20	0.8479
	Log EGFR	-0.0253 [-0.2705;0.22]	0.14	15	-0.18	0.8592
CMAX,u	Intercept	4.74 [3.64;5.85]	0.632	15	7.5	<.0001
	Age	0.00677 [-0.00279;0.01633]	0.005	15	1.24	0.2335

PK parameter	Effect	Estimate (90%CI)	Standard error	Degrees of freedom	t value	Pr > |t|
	Weight	-0.015 [-0.022;-0.008]	0.004	15	-3.74	0.002
	Log EGFR	-0.00921 [-0.19189;0.17348]	0.104	15	-0.09	0.9308
AUCINF,u	Intercept	8.57 [6.51;10.63]	1.157	12	7.41	<.0001
	Age	0.0098 [-0.00726;0.02685]	0.01	12	1.02	0.3261
	Weight	-0.00602 [-0.01836;0.00633]	0.007	12	-0.87	0.4023
	Log EGFR	-0.335 [-0.68;0.011]	0.194	12	-1.72	0.1104
AUC0-144,u	Intercept	8.35 [6.91;9.8]	0.824	15	10.14	<.0001
	Age	0.00763 [-0.00482;0.02007]	0.007	15	1.07	0.2999
	Weight	-0.00677 [-0.01593;0.00239]	0.005	15	-1.3	0.2149
	Log EGFR	-0.278 [-0.516;-0.041]	0.136	15	-2.05	0.0581
AUC0-192,u	Intercept	8.5 [6.96;10.03]	0.874	15	9.72	<.0001
	Age	0.00848 [-0.00473;0.0217]	0.008	15	1.13	0.2782
	Weight	-0.00592 [-0.01565;0.00381]	0.006	15	-1.07	0.3028
	Log EGFR	-0.321 [-0.573;-0.068]	0.144	15	-2.23	0.0417
CL/F,u	Intercept	-2.13 [-3.71;-0.55]	0.887	12	-2.4	0.0335
	Age	0.00782 [-0.00525;0.02089]	0.007	12	1.07	0.3072
	Weight	0.00299 [-0.00648;0.01246]	0.005	12	0.56	0.5838
	Log EGFR	0.274 [0.009;0.539]	0.149	12	1.84	0.0905

Regression model defined as: log(PK parameter)= Intercept + Slope*log(eGFR) + age + weight.

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Clinical Trial Results Database

Summary of Safety

Safety Results

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

Primary system organ class Preferred term Maximum grade	Control (N=7) n (%)	Moderate (N=6) n (%)	Severe (N=6) n (%)	All subjects (N=19) n (%)
Any primary system organ class - Total	1 (14.3)	3 (50.0)	2 (33.3)	6 (31.6)
Grade 1	1 (14.3)	2 (33.3)	1 (16.7)	4 (21.1)
Grade 3	0	1 (16.7)	1 (16.7)	2 (10.5)
Infections And Infestations -Total	1 (14.3)	0	0	1 (5.3)
Grade 1	1 (14.3)	0	0	1 (5.3)
Nasopharyngitis	1 (14.3)	0	0	1 (5.3)
Grade 1	1 (14.3)	0	0	1 (5.3)
Injury, Poisoning And Procedural Complications - Total	0	0	1 (16.7)	1 (5.3)
Grade 1	0	0	1 (16.7)	1 (5.3)
Contusion	0	0	1 (16.7)	1 (5.3)
Grade 1	0	0	1 (16.7)	1 (5.3)
Investigations - Total	0	1 (16.7)	1 (16.7)	2 (10.5)
Grade 3	0	1 (16.7)	1 (16.7)	2 (10.5)
Amylase Increased	0	1 (16.7)	0	1 (5.3)
Grade 3	0	1 (16.7)	0	1 (5.3)
International Normalised Ratio Increased	0	0	1 (16.7)	1 (5.3)
Grade 3	0	0	1 (16.7)	1 (5.3)
Prothrombin Time Prolonged	0	0	1 (16.7)	1 (5.3)

Primary system organ class Preferred term Maximum grade	Control (N=7) n (%)	Moderate (N=6) n (%)	Severe (N=6) n (%)	All subjects (N=19) n (%)
Grade 2	0	0	1 (16.7)	1 (5.3)
Musculoskeletal And Connective Tissue Disorders - Total	0	1 (16.7)	0	1 (5.3)
Grade 1	0	1 (16.7)	0	1 (5.3)
Back Pain	0	1 (16.7)	0	1 (5.3)
Grade 1	0	1 (16.7)	0	1 (5.3)
Renal And Urinary Disorders - Total	0	1 (16.7)	0	1 (5.3)
Grade 1	0	1 (16.7)	0	1 (5.3)
Polyuria	0	1 (16.7)	0	1 (5.3)
Grade 1	0	1 (16.7)	0	1 (5.3)

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

Serious Adverse Events and Deaths

There were no serious adverse events or deaths reported during the study.

Other Relevant Findings

Not applicable.

Conclusion:

- Despite the renal clearance contributing to a small fraction of the total clearance, renal impaired subjects had lower total clearance compared to control the group.

- The AUC0-192 was increased by 28% in the moderate and 54% in the severe renal impairment groups. The AUCinf was increased by 21% and 66% in the moderate and the severe renal impairment groups, respectively. The Cmax was comparable across the groups.
- The unbound fraction was comparable across the groups.
- A single oral dose of 50 mg buparlisib was generally safe and well tolerated in healthy subjects with normal renal function and in the subjects with moderate or severe renal impairment.

Date of Clinical Trial Report

31-Jul-2015