Sponsor

Novartis

Generic Drug Name

Buparlisib/ BKM120

Trial Indications

Healthy subjects and hepatic impaired subjects

Protocol Number

CBKM120C2104

Protocol Title

A Phase I, multicenter, open-label, single-dose, parallel group study to assess the pharmacokinetics (PK) of BKM120 in subjects with mild, moderate and severe hepatic impairment.

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase III

Study Start/End Dates

25-Oct-2011 to 17-Aug-2013

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was an open label, multicenter, parallel group design to assess the PK of BKM120 in subjects with impaired hepatic function compared to healthy subjects. Subjects were categorized using the three Child-Pugh categories measured at the time of the screening visit; these three categories were compared to a control group (healthy subjects with normal hepatic function). Group 1 consisted of healthy subjects (with apparent normal hepatic function) matched to Group 2 (subjects with impaired hepatic function) by gender, age (± 10 years), body weight (weight ± 20%) and Body Mass Index (BMI ± 5%). Each subject in all groups received a single oral dose of 30 mg BKM120.

Centers

Three study centers enrolled the subjects: Russia (1 site), Germany (1 site) and Bulgaria (1 site).

Publication

Not applicable

Objectives:

Primary objective

To evaluate the PK of a single oral dose of BKM120 in subjects with mild, moderate and severe hepatic impairment (Child-Pugh A, B and C) relative to healthy control subjects (with apparently normal liver function).

Secondary objectives

- To assess the tolerability and safety of a single dose of BKM120 in subjects with mild, moderate and severe hepatic impairment.
- To explore the relationship between PK and hepatic function parameters.
- To determine the plasma protein binding (free fraction) of BKM120.

Test Product, Dose, and Mode of Administration

Single oral dose of buparlisib 30 mg gelatin capsule

Statistical Methods

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 BKM120.

- Following log-transformation, the PK parameters (Cmax, AUClast, AUC0-t, and AUCinf) were analyzed separately by means of an analysis of variance (ANOVA) model including hepatic function group (mild, moderate, severe, and control) as fixed effect. Appropriate contrasts were estimated for each hepatic function group (mild, moderate and severe) versus control. The geometric mean ratio and their 90% confidence interval (CI) were derived by anti-logged transformation of estimates of the differences and their confidence intervals.
- A supportive analysis was done by repeating the analysis mentioned above, by including sex as a factor and age at screening, weight (instead of BMI) at baseline as continuous covariates.

- Primary and secondary PK parameters of BKM120 were summarized in descriptive statistics by hepatic function group (normal hepatic function (control group), mild, moderate, and severe hepatic function group). Descriptive statistics of PK parameters included number of observations, range given as minimum and maximum, median, geometric and arithmetic means, standard deviation (SD), Coefficient of variation% (CV) and CV% geo-mean. For Tmax only median, minimum and maximum values was provided.
- These analyses were repeated for the PK parameters (Cmax, AUClast, AUC0-t, and AUCinf) expressed in term of unbound concentration.
- The difference of Tmax was compared between each hepatic function group (mild, moderate and severe) and control group by its median, minimum and maximum. Median difference was estimated by means of the Hodges-Lehmann estimator and its respective two-sided 90% Moses confidence intervals.
- Concentrations of BKM120 were summarized by hepatic impairment group and scheduled time point reporting n (number of non-missing values), m (number of non-zero values), mean, SD, CV, geometric mean, CV% of geometric mean, median, minimum and maximum.
- The relationship between the primary PK variables (AUClast, AUCinf, and AUC0-t and Cmax, but not Tmax) and hepatic functions (total bilirubin, international normalized ratio (INR), and albumin levels) was investigated with linear regression models predicting log-transformed PK parameter by log-transformed liver function at Day −1.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

- Subjects with good health as determined by past medical history, physical examination, vital signs, electrocardiogram.
- Laboratory values including blood cell count, electrolytes, blood lipids) within the normal range or ≤ grade 1 severity if judged clinically not significant by the Investigator. Except for those specific to hepatic dysfunction for the hepatic impaired subjects or for those specific to the control group.
- Subjects who weighed at least 45 kg and had a body mass index (BMI) in the range 18.5-35.0 kg/m^2.
- Vital signs (after three minutes resting measured in sitting position), at screening, and baseline within the following ranges:
  - Body temperature: ≥ 35.0 and ≤ 37.5°C
  - Systolic blood pressure: ≥ 90 and ≤ 160 mm Hg
  - Diastolic blood pressure: ≥ 50 and ≤ 95 mm Hg
  - Pulse rate: ≥ 40 and ≤ 100 beats per minute (BPM)

- Female subjects who were postmenopausal or not of child bearing potential. (All females were postmenopausal or were surgically sterilized at least six months prior to screening and were to have negative pregnancy test results at screening and baseline. Women were considered post-menopausal if they had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum follicular stimulating hormone (FSH) levels >40 mIU/mL.)
- Sexually active male subjects were required to use a condom during intercourse for the entire duration of the study and continuing for 16 weeks after the last BKM120 administration.
- Additional inclusion criteria for Group 1 - control healthy subjects
  - Subjects who matched to the hepatic impaired subjects of group 2 in gender, age (±10 years), weight (±20%), and BMI (±5%).
  - Hemoglobin > lower limit of normal (LLN)
  - Total bilirubin ≤ upper limit of normal (ULN)
  - Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma glutamyl transferase (GGT) ≤ ULN
  - Albumin within normal range
  - Creatinine ≤ ULN
  - Amylase ≤ ULN
  - Lipase ≤ ULN.
- Additional inclusion criteria for Group 2 - hepatic impaired subjects
  - Subjects with physical signs consistent with stable hepatic impairment.
  - Child-Pugh Clinical Assessment Score consistent with degree of hepatic impairment.
  - Subjects who were free of significant medical disorders unrelated to the subject's hepatic disorder as judged by the Investigator.
  - White Blood cells (WBCs) ≥ 3.0×10^9 /L.
  - Absolute neutrophil count (ANC) ≥ 1.5×10^9 /L.
  - Hemoglobin ≥ 9 g/dl.
  - Lymphocytes ≥ 0.8×10^9 /L.
  - Platelet count ≥ 50×10^9 /L.
  - Serum creatinine ≤ 1.5×ULN.
  - Amylase ≤ ULN.
  - Lipase ≤ ULN.

Exclusion Criteria

- Fertile males subjects, defined as all males physiologically capable of conceiving offspring UNLESS the study participant and his partner agreed to comply with acceptable contraception, for 16 weeks following the study drug administration.

- Significant illness, including infections, or hospitalization within the two weeks prior to dosing.
- Use of tobacco products, alcohol consumption, prescription drugs, herbal medications/ supplements, over-the-counter (OTC) medication, dietary supplements within the defined time periods prior to dosing or during the study.
- Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the subject in case of participation in the study.
- Medical history of any clinically significant hematologic, renal, endocrinologic, pulmonary, cardiovascular, hepatic, or allergic disease.
- Subjects at risk, with symptoms or with family history of: diabetes mellitus, cardiac disease, relevant psychiatric disorder, immunodeficiency disease.
- For the normal group; subject with history of liver disease or liver injury or with positive hepatitis C test or hepatitis B surface Antigen.
- For hepatic impaired subjects:
  - Any evidence of progressive liver disease (within the last 4 weeks prior to the screening visit) as indicated by liver transaminases, alkaline phosphatase and gamma glutamyl transferase (GGT) or a ≥ 50% worsening of serum bilirubin or prothrombin time.
  - Total bilirubin >6 mg/dl.

Participant Flow Table

Subject disposition (FAS)

Disposition	Normal (N = 13) n (%)	Mild (N=6) n (%)	Moderate (N=6) n (%)	Severe (N=6) n (%)	All Subjects (N=31) n (%)
Completed	13 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	31 (100.0)
Discontinued	0	0	0	0	0

Normal group corresponds to healthy subjects with normal hepatic function (control group).
Mild = Child-Pugh class A, Moderate = Child-Pugh class B, Severe = Child-Pugh class C

Baseline Characteristics

Demographics and other baseline characteristics (FAS)

Demographic variable	Normal (N = 13)	Mild (N = 6)	Moderate (N = 6)	Severe (N = 6)	All Subjects (N = 31)
Age (years)					
n	13	6	6	6	31
Mean (SD)	53.8 (10.73)	55.3 (5.32)	52.0 (5.55)	51.2 (9.58)	53.2 (8.56)
Median	55.0	54.5	54.5	50.0	55.0
Min - Max	29 - 71	49 - 62	42 - 56	38 - 66	29 - 71
Sex – n (%)					

Demographic variable	Normal (N = 13)	Mild (N = 6)	Moderate (N = 6)	Severe (N = 6)	All Subjects (N = 31)
Male	6 (46.2)	2 (33.3)	2 (33.3)	3 (50.0)	13 (41.9)
Female	7 (53.8)	4 (66.7)	4 (66.7)	3 (50.0)	18 (58.1)
Race – n (%)					
Caucasian	13 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	31 (100.0)
Ethnicity – n (%)					
Other	13 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	31 (100.0)
Weight (Kg)					
n	13	6	6	6	31
Mean (SD)	79.22 (17.835)	77.27 (6.694)	75.30 (19.759)	79.30 (19.257)	78.10 (16.251)
Median	74.00	78.20	71.05	76.05	76.40
Min - Max	51.4 - 110.7	69.3 - 87.0	56.2 - 103.8	58.2 - 101.8	51.4 - 110.7
Height (cm)					
n	13	6	6	6	31
Mean (SD)	172.2 (9.66)	165.3 (8.73)	168.3 (13.66)	169.3 (9.03)	169.6 (10.09)
Median	174.0	165.0	164.5	172.0	170.0
Min - Max	159 - 185	156 - 178	156 - 192	158 - 181	156 - 192
BMI (kg/m^2)					
n	13	6	6	6	31
Mean (SD)	26.62 (5.272)	28.53 (4.529)	26.52 (6.043)	27.63 (6.062)	27.17 (5.232)
Median	24.70	28.10	24.15	27.85	25.20
Min - Max	20.3 - 34.2	23.7 - 33.6	21.0 - 34.6	19.2 - 34.3	19.2 - 34.6

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/m2) = weight (kg) / height (m)2. BMI is calculated using the baseline weight and baseline height.
Normal group corresponds to healthy subjects with normal hepatic function (control group).
Mild = Child-Pugh class A, Moderate = Child-Pugh class B, Severe = Child-Pugh class C

Summary of Efficacy

No efficacy was evaluated in this study.

Summary of pharmacokinetics

Primary Outcome Results

Summary of primary PK parameters for BKM120 (PAS)

Hepatic function Group	Statistics	AUClast (ng*h/mL)	AUC0-144 (ng*h/mL)	AUCinf (ng*h/mL)	Cmax (ng/mL)	Tmax (h)
Normal	n	13	13	13	13	13
	Mean (SD)	6197.48 (2331.651)	5115.67 (1303.355)	6401.79 (2546.495)	225.08 (45.619)	N/A
	CV% mean	37.62	25.48	39.78	20.27	N/A
	Geo-mean	5848.32	4966.98	6010.77	220.96	N/A

Hepatic function Group	Statistics	AUClast (ng*h/mL)	AUC0-144 (ng*h/mL)	AUCinf (ng*h/mL)	Cmax (ng/mL)	Tmax (h)
	CV% geo-mean	35.57	25.60	36.93	20.09	N/A
	Median	5476.76	4760.34	5547.39	204.00	1.02
	[Min; Max]	[3832.2; 11565.4]	[3305.6; 7165.3]	[3917.5; 12513.8]	[166.0; 314.0]	[1.0; 3.0]
Mild	n	6	6	6	6	6
	Mean (SD)	7093.16 (3006.633)	5838.59 (1751.073)	7579.39 (3748.125)	280.83 (43.204)	N/A
	CV% mean	42.39	29.99	49.45	15.38	N/A
	Geo-mean	6623.18	5630.29	6958.00	278.30	N/A
	CV% geo-mean	41.57	30.01	45.74	14.51	N/A
	Median	6470.76	5764.31	6578.72	269.50	1.00
	[Min; Max]	[3923.9; 12464.6]	[3925.3; 8717.3]	[4190.1; 14642.0]	[241.0; 361.0]	[0.5; 1.0]
Moderate	n	6	6	6	6	6
	Mean (SD)	7203.08 (4298.556)	5777.95 (2184.788)	8077.96 (6145.600)	246.00 (57.827)	N/A
	CV% mean	59.68	37.81	76.08	23.51	N/A
	Geo-mean	6461.93	5495.16	6857.99	239.68	N/A
	CV% geo-mean	50.01	34.38	61.47	26.31	N/A
	Median	5655.44	5394.28	5733.80	258.50	1.25
	[Min; Max]	[3898.2; 15777.9]	[3578.3; 9990.6]	[3960.4; 20468.6]	[151.0; 327.0]	[0.5; 2.0]
Severe	n	6	6	6	6	6
	Mean (SD)	7386.15 (2454.948)	6394.92 (2178.355)	7651.44 (2533.265)	350.67 (182.136)	N/A
	CV% mean	33.24	34.06	33.11	51.94	N/A
	Geo-mean	6982.01	6080.16	7223.89	319.55	N/A
	CV% geo-mean	40.37	36.64	41.09	48.05	N/A
	Median	7864.20	5851.63	8369.51	311.50	1.25
	[Min; Max]	[3523.6; 10614.3]	[3402.4; 9922.7]	[3595.4; 10688.6]	[170.0; 704.0]	[0.5; 3.0]

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
Normal group corresponds to healthy subjects with normal hepatic function (control group).
Mild = Child-Pugh class A, Moderate = Child-Pugh class B, Severe = Child-Pugh class C

Secondary Outcome Results

Summary of secondary PK parameters for BKM120 (PAS)

Hepatic function Group	Statistics	T1/2 (h)	CL/F (L/h)	Vz/F (L)
Normal	n	13	13	13
	Mean (SD)	56.09 (21.759)	5.27 (1.673)	387.79 (76.934)

Hepatic function Group	Statistics	T1/2 (h)	CL/F (L/h)	Vz/F (L)
	CV% mean	38.80	31.74	19.84
	Geo-mean	52.94	4.99	381.21
	CV% geo-mean	35.21	36.93	19.22
	Median	50.03	5.41	363.78
	[Min; Max]	[30.6; 115.1]	[2.4; 7.7]	[277.9; 573.5]
Mild	n	6	6	6
	Mean (SD)	63.04 (35.575)	4.63 (1.773)	359.44 (61.430)
	CV% mean	56.43	38.26	17.09
	Geo-mean	57.10	4.31	355.19
	CV% geo-mean	47.70	45.74	16.90
	Median	52.20	4.62	349.08
	[Min; Max]	[36.6; 133.6]	[2.0; 7.2]	[290.1; 455.4]
Moderate	n	6	6	6
	Mean (SD)	63.04 (42.186)	4.86 (1.986)	354.09 (85.319)
	CV% mean	66.92	40.86	24.10
	Geo-mean	54.71	4.37	345.30
	CV% geo-mean	58.71	61.47	25.17
	Median	47.40	5.23	359.77
	[Min; Max]	[33.3; 145.1]	[1.5; 7.6]	[252.0; 452.8]
Severe	n	6	6	6
	Mean (SD)	55.68 (32.677)	4.46 (2.054)	324.87 (156.060)
	CV% mean	58.69	46.02	48.04
	Geo-mean	48.36	4.15	289.71
	CV% geo-mean	63.27	41.09	59.10
	Median	44.35	3.59	342.37
	[Min; Max]	[23.5; 108.3]	[2.8; 8.3]	[135.3; 519.8]

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.
Normal group corresponds to healthy subjects with normal hepatic function (control group).
Mild = Child-Pugh class A, Moderate = Child-Pugh class B, Severe = Child-Pugh class C

Summary of statistical analysis of primary PK parameters of BKM120 (PAS)

					Hepatic function group comparison		
					90% CI		
PK parameter (unit)	Hepatic function Group	n*	Adjusted geo-mean	Comparison(s)	Geo-mean ratio	Lower	Upper
AUClast (hr*ng/mL)	Normal	13	5848.32				
	Mild	6	6623.18	Mild / Normal	1.13	0.82	1.57
	Moderate	6	6461.93	Moderate / Normal	1.10	0.80	1.53

PK parameter (unit)	Hepatic function Group	n*	Adjusted geo-mean	Comparison(s)	Hepatic function group comparison Geo-mean ratio	90% CI Lower	90% CI Upper
	Severe	6	6982.01	Severe / Normal	1.19	0.86	1.66
AUC0-144 (hr*ng/mL)	Normal	13	4966.98				
	Mild	6	5630.29	Mild / Normal	1.13	0.88	1.46
	Moderate	6	5495.16	Moderate / Normal	1.11	0.86	1.42
	Severe	6	6080.16	Severe / Normal	1.22	0.95	1.57
AUCinf (hr*ng/mL)	Normal	13	6010.77				
	Mild	6	6958.00	Mild / Normal	1.16	0.81	1.65
	Moderate	6	6857.99	Moderate / Normal	1.14	0.80	1.63
	Severe	6	7223.89	Severe / Normal	1.20	0.84	1.72
Cmax (ng/mL)	Normal	13	220.96				
	Mild	6	278.30	Mild / Normal	1.26	1.00	1.58
	Moderate	6	239.68	Moderate / Normal	1.08	0.87	1.36
	Severe	6	319.55	Severe / Normal	1.45	1.15	1.81
Tmax (hr)	Normal	13	1.02				
	Mild	6	1.00	Mild - Normal	-0.03	-0.50	0.00
	Moderate	6	1.25	Moderate - Normal	0.00	-0.50	0.50
	Severe	6	1.25	Severe - Normal	0.00	-0.50	0.50

Model is a linear model of the log-transformed PK parameters, including hepatic function group as fixed effect.
Ratio of geometric means and their CI are back-transformed from the group differences and their CIs of the log-transformed data.
n* = number of subjects with non-missing values.
For Tmax, median is presented under 'Adjusted Geo-mean', Hodges-Lehmann estimate under 'Geo-mean Ratio', and asymptotic CI under 90% CI.
Normal group corresponds to healthy subjects with normal hepatic function (control group).
Mild = Child-Pugh class A, Moderate = Child-Pugh class B, Severe = Child-Pugh class C.

Summary of statistical analysis of primary PK parameters for unbound concentration of BKM120 (PAS)

PK parameter (unit)	Hepatic function Group	n*	Adjusted geo-mean	Comparison(s)	Hepatic function group comparison Geo-mean ratio	90% CI Lower	90% CI Upper
AUClast (hr*ng/mL)	Normal	13	979.79				
	Mild	6	1124.92	Mild / Normal	1.15	0.84	1.57
	Moderate	6	1119.70	Moderate / Normal	1.14	0.84	1.56
	Severe	6	1481.33	Severe / Normal	1.51	1.11	2.06
AUC0-144 (hr*ng/mL)	Normal	13	832.14				
	Mild	6	956.28	Mild / Normal	1.15	0.90	1.47

PK parameter (unit)	Hepatic function Group	n*	Adjusted geo-mean	Comparison(s)	Hepatic function group comparison Geo-mean ratio	90% CI Lower	90% CI Upper
	Moderate	6	952.18	Moderate / Normal	1.14	0.90	1.46
	Severe	6	1289.99	Severe / Normal	1.55	1.21	1.98
AUCinf (hr*ng/mL)	Normal	13	1007.01				
	Mild	6	1181.79	Mild / Normal	1.17	0.84	1.64
	Moderate	6	1188.33	Moderate / Normal	1.18	0.84	1.65
	Severe	6	1532.65	Severe / Normal	1.52	1.09	2.13
Cmax (ng/mL)	Normal	13	37.02				
	Mild	6	47.27	Mild / Normal	1.28	0.99	1.64
	Moderate	6	41.53	Moderate / Normal	1.12	0.87	1.44
	Severe	6	67.80	Severe / Normal	1.83	1.42	2.36

Model is a linear model of the log-transformed PK parameters, including hepatic function group as fixed effect.
Ratio of geometric means and their CI are back-transformed from the group differences and their CIs of the log-transformed data.
n* = number of subjects with non-missing values.
Normal group corresponds to healthy subjects with normal hepatic function (control group).
Mild = Child-Pugh class A, Moderate = Child-Pugh class B, Severe = Child-Pugh class C

Summary of Safety

Safety Results

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

	Normal (N=13)		Mild (N= 6)		Moderate (N= 6)		Severe (N= 6)		All subjects (N=31)	
Primary System Organ Class Preferred Term	**Grade 1/2 n (%)**	**Grade 4 n (%)**	**Grade 1/2 n (%)**	**Grade 4 n (%)**	**Grade 1/2 n (%)**	**Grade 4 n (%)**	**Grade 1/2 n (%)**	**Grade 4 n (%)**	**Grade 1/2 n (%)**	**Grade 4 n (%)**
Any primary system organ class										
Total	4 (30.8)	0	1 (16.7)	0	2 (33.3)	1 (16.7)	2 (33.3)	0	9 (29.0)	1 (3.2)
Blood and lymphatic system disorders	0	0	0	0	0	0	1 (16.7)	0	1 (3.2)	0
Thrombocytopenia	0	0	0	0	0	0	1 (16.7)	0	1 (3.2)	0
Infections and infestations	1 (7.7)	0	0	0	1 (16.7)	0	1 (16.7)	0	3 (9.7)	0
Nasopharyngitis	1 (7.7)	0	0	0	0	0	1 (16.7)	0	2 (6.5)	0
Bacterial infection	1 (7.7)	0	0	0	0	0	0	0	1 (3.2)	0
Urinary tract infection	0	0	0	0	1 (16.7)	0	0	0	1 (3.2)	0
Investigations	0	0	0	0	1 (16.7)	0	0	0	1 (3.2)	0
Electrocardiogram QT prolonged	0	0	0	0	1 (16.7)	0	0	0	1 (3.2)	0

	Normal (N=13)		Mild (N= 6)		Moderate (N= 6)		Severe (N= 6)		All subjects (N=31)	
Primary System Organ Class Preferred Term	**Grade 1/2 n (%)**	**Grade 4 n (%)**	**Grade 1/2 n (%)**	**Grade 4 n (%)**	**Grade 1/2 n (%)**	**Grade 4 n (%)**	**Grade 1/2 n (%)**	**Grade 4 n (%)**	**Grade 1/2 n (%)**	**Grade 4 n (%)**
Metabolism and nutrition disorders	0	0	0	0	0	1 (16.7)	0	0	0	1 (3.2)
Hypercalcaemia	0	0	0	0	0	1 (16.7)	0	0	0	1 (3.2)
Musculoskeletal and connective tissue disorders	1 (7.7)	0	0	0	0	0	0	0	1 (3.2)	0
Myalgia	1 (7.7)	0	0	0	0	0	0	0	1 (3.2)	0
Nervous system disorders	1 (7.7)	0	0	0	0	0	0	0	1 (3.2)	0
Dizziness	1 (7.7)	0	0	0	0	0	0	0	1 (3.2)	0
Psychiatric disorders	0	0	1 (16.7)	0	0	0	0	0	1 (3.2)	0
Insomnia	0	0	1 (16.7)	0	0	0	0	0	1 (3.2)	0
Skin and subcutaneous tissue disorders	1 (7.7)	0	0	0	0	0	0	0	1 (3.2)	0
Dermatitis acneiform	1 (7.7)	0	0	0	0	0	0	0	1 (3.2)	0
Vascular disorders	0	0	0	0	1 (16.7)	0	0	0	1 (3.2)	0
Hypertension	0	0	0	0	1 (16.7)	0	0	0	1 (3.2)	0

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ Class in descending frequency of Grade 1/2 column, as reported in the Severe hepatic function.
A subject with multiple occurrences of an AE under one 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.
A subject with multiple grade ratings for an AE while on a treatment is only counted under the maximum rating.
Normal group corresponds to healthy subjects with normal hepatic function (control group).
Mild = Child-Pugh class A, Moderate = Child-Pugh class B, Severe = Child-Pugh class C

Most Frequently Reported AEs Overall by Preferred Term regardless of study drug relationship n (%)

Preferred term	**Normal (N=13) n%**	**Mild (N=6) n%**	**Moderate (N=6) n%**	**Severe (N=6) n%**	**All subjects (N=31) n%**
Any Preferred term Total	4 (30.8)	1 (16.7)	3 (50.0)	2 (33.3)	10 (32.3)
Bacterial infection	1 (7.7)	0	0	0	1 (3.2)
Dermatitis acneiform	1 (7.7)	0	0	0	1 (3.2)
Dizziness	1 (7.7)	0	0	0	1 (3.2)
Myalgia	1 (7.7)	0	0	0	1 (3.2)
Nasopharyngitis	1 (7.7)	0	0	1 (16.7)	2 (6.5)
Electrocardiogram QT prolonged	0	0	1 (16.7)	0	1 (3.2)
Hypercalcaemia	0	0	1 (16.7)	0	1 (3.2)

Preferred term	Normal (N=13) n%	Mild (N=6) n%	Moderate (N=6) n%	Severe (N=6) n%	All subjects (N=31) n%
Hypertension	0	0	1 (16.7)	0	1 (3.2)
Insomnia	0	1 (16.7)	0	0	1 (3.2)
Thrombocytopenia	0	0	0	1 (16.7)	1 (3.2)
Urinary tract infection	0	0	1 (16.7)	0	1 (3.2)

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 group is counted only once in the AE category for that group.
Normal group corresponds to healthy subjects with normal hepatic function (control group).

Three subjects had AEs (nasopharyngitis, febrile bacterial infection and urinary tract infection) not suspected to be study drug related that required additional therapy.

None of the subjects discontinued from the study due to AEs (not study drug related).

Serious Adverse Events and Deaths

There were no deaths during the study.

One subject reported one serious adverse event which was grade 2 bacterial infection.

Other Relevant Findings

Not applicable

Conclusion:

- Increases in Cmax compared to healthy group were 26%, 8% and 45% in the mildly, moderately and severely hepatic impairment groups, respectively.
- Tmax was consistent between normal and all hepatic impairment groups.
- The exposure of BKM120 as described by AUCinf, showed increases in the geometric means compared to normal group was 16%, 14% and 20% in the mild, moderate and severe hepatic impairment groups, respectively.
- A single oral dose of BKM120 30 mg was well tolerated in healthy volunteers and subjects with hepatic impairment with no new safety signals reported among subjects with hepatic impairment.
- Plasma protein binding measures were was similar in across the normal, mild and moderate groups; a higher unbound fraction was measured in the severe group.
- Pharmacokinetic results indicate a dose adjustment is not required for mild and moderate hepatic impaired subjects.
- For severely impaired subjects, the safety and therapeutic indices will need to be considered before determining if a dose adjustment is appropriate.

Date of Clinical Trial Report

30-Apr-2014

Date of Initial Inclusion on Novartis Clinical Trial Results website

8-Jul-2014

Date of Latest Update

Reason for Update