

A Phase-I, Open-Label, Single-Dose Study of the Pharmacokinetics of Buparlisib in Subjects With Mild to Severe Hepatic Impairment

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Abstract

The pharmacokinetics (PK) and safety of single-dose buparlisib (30 mg) were assessed in subjects with mild to severe hepatic impairment ($n = 6$ each) relative to healthy controls ($n = 13$). Blood samples were collected until 336 hours postdose and evaluated by liquid chromatography tandem mass spectrometry. PK parameters (including area under the curve [AUC_{∞}] and C_{max}) were derived using noncompartmental analysis. Buparlisib was rapidly absorbed in all groups (median T_{max} 1.0–1.3 h). Buparlisib exposure (AUC_{∞}) was moderately increased in subjects with mild (geometric mean ratio [GMR] 1.16; 90%CI 0.81, 1.65), moderate (GMR 1.14; 90%CI 0.80, 1.63), or severe (GMR 1.20; 90%CI 0.84, 1.72) hepatic impairment, relative to healthy controls. Apparent oral clearance was similar across groups. Due to a higher unbound fraction in the severe group (0.21) than all other groups (0.17), subjects with severe hepatic impairment had greater exposure to unbound buparlisib (GMR relative to healthy controls: AUC_{∞} 1.52; 90%CI 1.09, 2.13; C_{max} 1.83; 90%CI 1.42, 2.36). The results indicate that a buparlisib dose adjustment may not be necessary for patients with mild to moderate hepatic impairment. The safety and therapeutic indices should be considered before determining if a dose adjustment is appropriate for patients with severe hepatic impairment.

Keywords

buparlisib, hepatic impairment, pharmacokinetics, PI3K inhibitor

The phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) signaling pathway regulates cellular processes key for cancer growth and progression, including cell survival, proliferation, cellular resilience and repair, cell migration, and angiogenesis.¹ Constitutive PI3K/AKT/mTOR pathway activation—for example, through direct mutation of the gene encoding the class I PI3K catalytic subunit p110 α (*PIK3CA*) or through alteration of upstream activators or the downstream repressor phosphatase and tensin homolog (PTEN)—contributes to the onset and growth of many tumor types.^{2–12}

Buparlisib (BKM120; Novartis Pharma AG, Basel, Switzerland) is an oral pan-PI3K inhibitor that targets all 4 isoforms (α , β , γ , δ) of class I PI3K.¹³ Buparlisib has a molecular mass of 446.86 g/mol and is highly permeable and soluble, with increased solubility at low pH; buparlisib is administered orally in capsules or tablets.^{14,15} The antitumor activity of buparlisib has been demonstrated in a range of preclinical models, both as a single agent^{13,16–18} and in combination with other therapies such as chemotherapy and endocrine therapy.^{19–21} Preliminary signs of clinical antitumor activity have also been observed with single-agent buparlisib in patients with advanced solid tumors^{22,23}

and as a combination therapy in patients with ovarian or breast cancer.^{24–26}

Early preclinical and clinical investigations have shown that buparlisib undergoes both phase-1 and phase-2 metabolism.¹⁵ Phase-1 oxidative metabolism of buparlisib is primarily mediated by CYP3A (estimated fraction metabolized >0.9).¹⁵ Coadministration of buparlisib with the CYP3A inhibitor ritonavir in a healthy volunteer study resulted in increased buparlisib

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exposure (area under the curve [AUC_∞]), a 73% increase; increased maximum plasma concentration [C_{max}] geometric mean ratio [GMR], a 19% increase; increased elimination half-life (T_{1/2}, 53.3 to 71.6 hours); and decreased apparent clearance (5.37 L/h to 3.27 L/h).¹⁵ Phase-2 metabolism of buparlisib consists of direct glucuronidation.¹⁵ In rats, buparlisib is eliminated primarily by biliary excretion, with 20–30% of the dose eliminated renally.¹⁵ In a human absorption, distribution, metabolism, and excretion study, a greater fraction of the total dose (total radioactivity) of [¹⁴C]buparlisib was recovered in the urine (51%) compared with the feces (42%); however, a greater fraction of parent buparlisib was recovered in the feces (7–23%) than the urine (1%).¹⁵ Plasma protein binding of buparlisib is moderate (79–85% across species) and independent of drug concentration.¹⁵ In patients with advanced solid tumors, maximum plasma concentrations of buparlisib are observed 1–4 hours postdose, and buparlisib exhibits approximately dose-proportional increases in C_{max} and AUC_{0–24} following multiple doses.^{23,27}

It is anticipated that buparlisib will be used in patients with coexisting morbidities including hepatic impairment. Hepatic dysfunction results in pathophysiological changes that can alter drug pharmacokinetics (PK).²⁸ For example, plasma protein binding, plasma clearance, biliary excretion, and/or oxidative metabolism of drugs can be compromised in patients with hepatic impairment, potentially resulting in drug accumulation.²⁸ It is therefore important to determine the impact of hepatic impairment on the PK of buparlisib. The primary objective of this phase-1 multicenter, open-label, two-stage, parallel-group study (NCT01727128) was to assess the effect of hepatic impairment on the systemic exposure to a single dose of buparlisib in noncancer subjects with hepatic impairment as per the criteria in the Child–Pugh categories defining mild, moderate, and severe hepatic impairment, relative to healthy controls with normal liver function.^{29,30}

Methods

Study Design

The study protocol and all amendments were reviewed by the Independent Ethics Committee or Institutional Review Board for each center (Umhat “Sv. Ivan Rilski” Ltd, Sofia 1431, Bulgaria; Landesamt für Gesundheit und Soziales, Berlin 10707, Germany; Council of Ethics, Moscow 127994, Russia). All participating subjects provided written informed consent before screening. The study was conducted in accordance with the Declaration of Helsinki.

The study consisted of a screening period (days –14 to –2), baseline evaluations (day –1), single-dose treatment period (day 1; buparlisib 30 mg administered orally after

an overnight fast of ≥10 hours), on-site observation period (days 1–7; standardized meals were provided), discharge (day 7), scheduled study center visits on days 9, 11, 13, and 15 (end of study), and a safety follow-up on day 31. A buparlisib dose of 30 mg was expected to be well tolerated in subjects with hepatic impairment, and the data derived from this dose will be predictive of results at higher doses given that the PK of buparlisib is linear up to and beyond the maximum tolerated dose (100 mg/day).^{22,27}

The study was conducted in 2 stages to mitigate difficulties in the prediction of buparlisib safety and PK in subjects with hepatic impairment. Three subjects with mild hepatic impairment were initially dosed, and safety data (to day 15) were reviewed in stage 1; if the safety profile of buparlisib was acceptable, a further 3 subjects with mild, and 6 subjects with moderate, hepatic impairment would be enrolled to complete stage 1. Subjects with severe hepatic impairment were enrolled in stage 2 following a review of the safety and PK profiles of buparlisib in stage 1. Healthy subjects were enrolled only after the subject with hepatic impairment to whom they would be matched (by sex, age, body weight, and body mass index [BMI]) had completed the study. A healthy subject could be matched to more than 1 subject with hepatic impairment.

Study Population

The study population consisted of subjects (ages 18–75; BMI 18.5–35.0 kg/m²) with mild, moderate, or severe hepatic impairment (n=6 per group), as defined by Child–Pugh score (Table 1), who were otherwise healthy (exhibited physical signs consistent with stable hepatic impairment and were free of significant medical disorders unrelated to their hepatic disorder), and matched healthy control subjects (matched by sex, age [±10 years], body weight [±20%], and BMI [±5%]; n=6–18). Female subjects were clinically confirmed as postmenopausal; male subjects agreed to use highly effective contraception for the duration of the study and to continue using contraception and refrain from fathering a child for 16 weeks postdose.

Key exclusion criteria included any surgical or medical condition or medical history that could affect the PK of buparlisib, use of any medication or food supplement 14 days prior to dosing or during the study that could affect the PK of buparlisib, medical history of relevant psychiatric disorders or immunodeficiency diseases, donation or loss of ≥400 mL blood or plasma <4 weeks prior to screening, participation in another study with an investigational drug ≤30 days predose, history of significant drug-induced skin rash, use of tobacco products ≤2 weeks predose or during the study, consumption of alcohol ≤2 days predose or during the study, and ongoing alcohol and/or drug abuse ≤1 month

Table 1. Child–Pugh Classification and Liver Parameters

Hepatic Impairment Classification	Score	Mild* (total score 5-6; n = 6), n (%)	Moderate* (total score 7-9; n = 6), n (%)	Severe* (total score 10-15; n = 6), n (%)
Encephalopathy[†]				
None	1	3 (50)	0	0
Grade 1-2	2	3 (50)	6 (100)	6 (100)
Grade 3-4	3	0	0	0
Ascites				
Absent	1	6 (100)	2 (33)	0
Slight	2	0	4 (67)	0
Moderate or large	3	0	0	6 (100)
Total bilirubin (mg/dL)				
<2	1	6 (100)	3 (50)	1 (17)
2-3	2	0	2 (33)	1 (17)
>3	3	0	1 (17)	4 (67)
Serum albumin (g/dL)				
>3.5	1	6 (100)	5 (83)	1 (17)
2.8-3.5	2	0	1 (17)	4 (67)
<2.8	3	0	0	1 (17)
INR				
<1.7	1	6 (100)	5 (83)	3 (50)
1.7-2.3	2	0	1 (17)	3 (50)
>2.3	3	0	0	0
Score				
5		3	0	0
6		3	0	0
7		0	3	0
8		0	2	0
9		0	1	0
10		0	0	2
11		0	0	2
12		0	0	2

INR, international normalized ratio.

*Mild = Child–Pugh class A; moderate = Child–Pugh class B; severe = Child–Pugh class C.

[†]Encephalopathy clinical features:

Grade 0: Subclinical; normal mental status but minimal changes in memory, concentration, intellectual function, and coordination.

Grade 1: Mild confusion, euphoria or depression, decreased attention, slowing of ability to perform mental tasks, irritability, disorder of sleep pattern (eg, inverted sleep cycle).

Grade 2: Drowsiness, lethargy, gross deficits in ability to perform mental tasks, obvious personality changes, inappropriate behavior, intermittent disorientation (usually for time).

Grade 3: Somnolent but arousable, unable to perform mental tasks, disorientation to time and place, marked confusion, amnesia, occasional fits of rage, speech is present but incomprehensible.

predose. Additional exclusion criteria for subjects with hepatic impairment included prior surgical portosystemic shunting, ascites requiring intervention, or evidence of progressive liver disease within the last 4 weeks prior to screening, as indicated by liver transaminases, alkaline phosphatase, and γ -glutamyltransferase or a $\geq 50\%$ worsening of serum bilirubin or prothrombin time.

Subjects could withdraw or be removed from the study at any time, including for reasons of vomiting within 4 hours after dose administration, or missed, off-schedule, incomplete, or incorrect assessments. Subjects who withdrew were replaced.

Study Assessments

Pharmacokinetic Sample Collection. Blood samples for plasma concentration-time profiles of buparlisib were collected from all subjects predose and then at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 144, 192, 240, 288, and 336 hours postdose; additional samples for protein binding were collected predose and 1 and 8 hours postdose. Blood samples were collected into K₃EDTA- (for plasma concentration) or sodium heparin-containing tubes (for protein binding) and immediately stored at 4 °C for ≤ 30 minutes before plasma separation via centrifugation (~ 1500 g for 10 minutes at 3–5 °C); plasma samples were stored at –70 °C until analyzed.

Pharmacokinetic Sample Analyses. Plasma concentrations of buparlisib were determined by a previously validated liquid chromatography tandem mass spectrometry (LC-MS/MS) assay by Novartis Pharma AG, Basel. Briefly, buparlisib and stable labeled internal buparlisib standard were extracted from plasma by solid-phase extraction using Oasis HLB 96-well plates (10 mg, 30 μ m; Waters Corporation, Milford, Massachusetts). After evaporation to dryness under a nitrogen stream and reconstitution in methanol/water (30/70, v/v), the extracts were analyzed by reversed-phase LC-MS/MS using a gradient from 75% of 0.2% formic acid to 95% of 0.1% formic acid in methanol on a Supelco Ascentis Express C18 (5 cm \times 2.1 mm, 2.7 μ m; Sigma-Aldrich, St. Louis, Missouri) chromatography column. The Applied Biosystems API 4000 mass analyzer (Life Technologies, Grand Island, New York) was operated in the positive polarity mode with mass transitions of m/z 411.20 (parent ion) and 367.20 (daughter ion); the limits of detection were 1.0–1000 ng/mL.

Protein binding was determined by the addition of a [¹⁴C]buparlisib internal standard to plasma samples (to a final concentration of 100 or 1000 ng/mL), ultracentrifugation ($\sim 356,160$ g for 3 hours at 37 °C), and liquid scintillation counting. All protein-binding samples were analyzed at the same time to minimize variability in results. The unbound fraction of buparlisib was calculated by the ratio of buparlisib in the supernatant of ultracentrifuged samples to the concentration in the sample prior to ultracentrifugation.

Safety Assessments. The safety of single-dose oral buparlisib 30 mg was assessed throughout the study by the recording of adverse events (AEs), clinical laboratory parameters, electrocardiograms (ECGs), and physical examinations; event severity (according to National Cancer Institute Common Terminology Criteria for

Adverse Events [NCI-CTCAE] version 4.03) and relationship to study drug were also recorded.

Statistical Analysis

Population Size. The sample size (6 subjects per hepatic impairment group with a within-study control population) was based on practical considerations and guidance from the US Food and Drug Administration and European Medicines Agency.^{31,32}

Pharmacokinetic Analyses. The primary PK parameters (AUC_{∞} , C_{max} , and time of maximum observed concentration [T_{max}]) and secondary PK parameters (apparent total body clearance [CL/F], apparent volume of distribution [Vz/F], and half-life [$T_{1/2}$]) of oral buparlisib 30 mg were determined from individual plasma concentration-time profiles using noncompartmental analysis (Phoenix 6.3; Pharsight, Mountain View, California) and were summarized by hepatic function using descriptive statistics. AUC_{∞} and C_{max} were also expressed in terms of unbound drug concentrations (by multiplying the PK parameter by the fraction unbound at predose).

Log-transformed parameters (C_{max} and AUC_{∞}) for both total and unbound buparlisib were analyzed by means of an analysis of variance (ANOVA) model with hepatic function as the fixed effect; supportive analyses were performed with sex as a factor and with age and weight as continuous covariates. The differences on the log-transformed scale and the corresponding 90% confidence intervals between each hepatic impairment group and the controls were antilogged to obtain the GMR and corresponding 90%CI. The relationship between AUC_{∞} and C_{max} with hepatic function was investigated with 3 separate linear regression analyses predicting log-transformed PK parameters by log-transformed liver function (total bilirubin, international normalized ratio [INR], and albumin levels) at day -1.

Safety Analyses. All recorded AEs, vital signs, and clinical laboratory test results were listed, tabulated, and summarized by hepatic function.

Results

Subject Demographics

A total of 31 subjects (6 subjects in each hepatic impairment group and 13 healthy controls) were enrolled into this study; all subjects completed the study without major protocol deviations postdose and were included in the PK and safety analysis sets. All subjects were white, and the majority (58%) were female; other baseline characteristics were similar across treatment groups (Table 2). The Child-Pugh scores by treatment group are presented in Table 1. No subjects had a change in Child-Pugh score during the study.

Concomitant Medications

Most subjects (5/6; 83%) in the mild group and all subjects (6/6; 100%) in the moderate and severe groups took at least 1 concomitant medication or significant nondrug therapy prior to or after administration of study drug, compared with only 1 subject (1/13; 8%) in the normal group. Fourteen subjects (45%) received spironolactone, 10 subjects (32%) received propranolol, 5 subjects (16%) received furosemide, 4 subjects (13%) received lactulose, and 3 subjects (10%) each received ornithine/ornithine aspartate and paracetamol prior to or after administration of buparlisib (Table 3). The administration of these concomitant medications is common in this population of hepatically impaired subjects. Based on the current knowledge of the PK and metabolic characteristics of buparlisib, none of the concomitant medications received by any of the study subjects was expected to have any interaction with buparlisib.

Pharmacokinetics

Complete PK sampling was achieved in 29 of the 31 study subjects; 2 subjects (in the normal [$n = 1$] and mild [$n = 1$] hepatic function groups) each had 1 missing PK sample (at 288 and 192 hours postdose, respectively). In subjects with or without hepatic impairment, buparlisib was rapidly absorbed (median T_{max} 1.0–1.3 hours), and a secondary absorption peak was observed at approximately 24 hours

Table 2. Subject Characteristics at Baseline

Characteristic	Hepatic Function Group				All (N = 31)
	Normal* (n = 13)	Mild* (n = 6)	Moderate* (n = 6)	Severe* (n = 6)	
Median age, years (range)	55 (29–71)	55 (49–62)	55 (42–56)	50 (38–66)	55 (29–71)
Male, n (%)	6 (46)	2 (33)	2 (33)	3 (50)	13 (42)
Female, n (%)	7 (54)	4 (67)	4 (67)	3 (50)	18 (58)
Median BMI, kg/m ² (range) [†]	25 (20–34)	28 (24–34)	24 (21–35)	28 (19–34)	25 (19–35)

BMI, body mass index.

*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.

[†]BMI (kg/m²) = weight (kg) / height (m)². BMI is calculated using the baseline weight and baseline height.

Table 3. Concomitant Medications or Significant Nondrug Therapies Taken Prior to or After Administration of Study Drug

Concomitant Medication or Significant Nondrug Therapy*	Hepatic Function Group				All (N = 31)
	Normal [†] (n = 13)	Mild [†] (n = 6)	Moderate [†] (n = 6)	Severe [†] (n = 6)	
Spirolactone	0	2 (33)	6 (100)	6 (100)	14 (45)
Propranolol	0	2 (33)	3 (50)	5 (83)	10 (32)
Furosemide	0	0	1 (17)	4 (67)	5 (16)
Lactulose	0	0	1 (17)	3 (50)	4 (13)
Ornithine/ornithine aspartate	0	1 (17)	0	2 (33)	3 (10)
Paracetamol [‡]	1 (8)	1 (17)	0	1 (17)	3 (10)
Ursodeoxycholic acid	0	0	2 (33)	0	2 (6)
Ademetionine	0	1 (17)	0	0	1 (3)
Ceftriaxone	1 (8)	0	0	0	1 (3)
Ibuprofen	1 (8)	0	0	0	1 (3)
Levothyroxine	0	1 (17)	0	0	1 (3)
Milgamma	0	1 (17)	0	0	1 (3)
Norfloxacin	0	0	1 (17)	0	1 (3)

*Concomitant medications are defined as medications that started after the first dose of buparlisib and medications that started prior to the first dose of buparlisib and continued after the first dose.

[†]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.

[‡]Also known as acetaminophen.

postdose (Figure 1 and Table 4); between-group differences in T_{max} were not substantial.

Compared with subjects with normal hepatic function, buparlisib exposure (AUC_{∞}) was moderately increased in subjects with mild (16%), moderate (14%), and severe (20%) hepatic impairment. More than 85% of the AUC was characterized for each hepatic impairment group with the PK sampling. C_{max} was also moderately increased in subjects with mild (26%) or moderate (8%) hepatic impairment but was increased to a greater degree in subjects with severe hepatic impairment (45%). Differences in the parameters of drug elimination ($T_{1/2}$ and CL/F) between subjects with and without hepatic impairment were considered to be inconsequential given the degree of change and inherent variability in measurements. Results similar to those reported for the primary analysis were observed when sex was included as a factor, and age and

weight at screening/baseline were considered as continuous covariates, in the supportive analysis of PK parameters.

Relationship Between PK and Hepatic Function Parameters

Based on linear regression analyses, higher AUC_{∞} and C_{max} values were associated with lower albumin levels and higher levels of INR and total bilirubin; however, these trends were not statistically significant. The lower (34%) baseline albumin level in the severe hepatic impairment group relative to the control group (29.7 g/L vs 45.2 g/L) was associated with increases in C_{max} and AUC_{∞} of 15% and 26%, respectively. The higher (52%) INR in the severe hepatic impairment group, relative to the control group (1.6 vs 1.0), was associated with increases in C_{max} and AUC_{∞} of 11% and 15%, respectively. The higher (8.6-fold) baseline total bilirubin level in the severe hepatic impairment group relative to the control group (65.0 $\mu\text{mol/L}$ vs 7.6 $\mu\text{mol/L}$) was associated with increases in C_{max} and AUC_{∞} of 23% and 16%, respectively.

Plasma Protein Binding of Buparlisib

Hepatic dysfunction can result in reduced plasma albumin and α_1 -acid glycoprotein, leading to less plasma protein binding and altered drug disposition.²⁸ Therefore, the plasma protein binding of buparlisib was assessed in the different hepatic function groups. Plasma protein binding was similar across normal (as assessed by the geometric mean of the unbound fraction [GMf_u] 0.17; percentage coefficient of variation [CV%] 17.2), mild (GMf_u 0.17; CV% 14.1), and moderate groups (GMf_u 0.17; CV% 15.6), whereas it was reduced in the severe hepatic

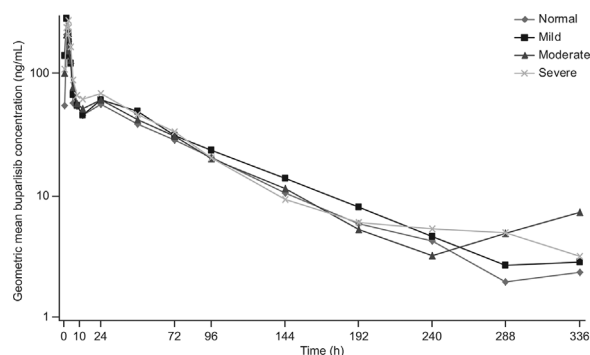


Figure 1. Geometric mean concentration-time profiles for buparlisib (semilogarithmic view).

Table 4. Pharmacokinetics of Buparlisib

Pharmacokinetic Parameter	Hepatic Function Group			
	Normal* (n = 13) [‡]	Mild* (n = 6) [‡]	Moderate* (n = 6) [‡]	Severe* (n = 6) [‡]
<i>C</i> _{max} (ng/mL)				
Geometric mean (CV%) [‡]	221 (20)	278 (15)	240 (26)	320 (48)
Total buparlisib GMR (90%CI) [#]	N/A	1.26 (1.00, 1.58)	1.08 (0.87, 1.36)	1.45 (1.15, 1.81)
Unbound buparlisib GMR (90%CI) [#]	N/A	1.28 (0.99, 1.64)	1.12 (0.87, 1.44)	1.83 (1.42, 2.36)
AUC _∞ (ng • h/mL)				
Geometric mean (CV%) [‡]	6011 (37)	6958 (46)	6858 (62)	7224 (41)
Total buparlisib GMR (90%CI) [#]	N/A	1.16 (0.81, 1.65)	1.14 (0.80, 1.63)	1.20 (0.84, 1.72)
Unbound buparlisib GMR (90%CI) [#]	N/A	1.17 (0.84, 1.64)	1.18 (0.84, 1.65)	1.52 (1.09, 2.13)
<i>T</i> _{max} (h)				
Median (range)	1.0 (1.0-3.0)	1.0 (0.5-1.0)	1.3 (0.5-2.0)	1.3 (0.5-3.0)
<i>T</i> _{1/2} (h)				
Geometric mean (CV%) [‡]	53 (35)	57 (48)	55 (59)	48 (63)
CL/F (L/h)				
Geometric mean (CV%) [‡]	5.0 (37)	4.3 (46)	4.4 (62)	4.2 (41)
Vz/F (L)				
Geometric mean (CV%) [‡]	381 (19)	355 (17)	345 (25)	290 (59)

AUC_∞, area under the curve from time zero to infinity; CI, confidence interval; CL/F, total body clearance; *C*_{max}, maximum blood concentration; CV%, coefficient of variation (%); GMR, geometric mean ratio; N/A, not applicable; *T*_{1/2}, elimination half-life; *T*_{max}, time at which *C*_{max} is reached; Vz/F, apparent volume of distribution.

*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.

[‡]Number of subjects with nonmissing values.

[‡]CV% = standard deviation/mean × 100; CV% geometric mean = sqrt[exp (variance for log-transformed data) – 1] × 100.

[#]GMRs are versus the normal hepatic function group. Model is a linear model of the log-transformed pharmacokinetic parameters, including hepatic function group as the fixed effect. Ratio of geometric means and their CI are back-transformed from the group differences and their CIs of the log-transformed data.

impairment group (GMf_u 0.21; CV% 14.35). When adjusted for unbound fraction, the increases in buparlisib exposure (*C*_{max} and AUC_∞) in subjects with mild to moderate hepatic impairment, compared with healthy subjects with normal hepatic function, were generally similar to those calculated for total buparlisib; adjustment for protein binding in subjects with severe hepatic impairment led to greater increases in AUC_∞ (52%) and *C*_{max} (83%), respectively (Table 4).

Safety

There were no deaths during the study. One subject in the normal hepatic function group experienced a serious AE (grade-2 febrile bacterial infection) that was not considered to be related to treatment. Ten subjects (32%) in total experienced at least 1 AE regardless of relationship to study drug; all AEs were grade-1 to -2 in severity except for one case of grade-4 hypercalcemia unrelated to treatment in a subject with moderate hepatic impairment (Table 5). Treatment-related AEs were reported by 2 subjects with normal hepatic function (grade-1 dizziness [n = 1], grade-1 dermatitis acneiform [n = 1]), 2 subjects with moderate hepatic impairment (grade-1 prolonged corrected QT interval using the Fridericia formula [QTcF] [n = 1], grade-1 hypertension [n = 1]), and 1 subject with

severe hepatic impairment (grade-2 thrombocytopenia); there was no correlation between the incidence of AEs and the severity of hepatic impairment. In addition to the grade-2 thrombocytopenia, a grade-4 increase in serum calcium (not suspected to be study-drug related; moderate-hepatic-function group) was a newly occurring or worsening clinically significant laboratory value reported as an AE in 1 subject. There were no clinically significant changes from baseline in vital signs.

Notable changes in QTcF intervals occurred mainly in subjects with hepatic dysfunction. Six subjects experienced a QTcF increase of >30 milliseconds from baseline (2 in each of the normal-, mild-, and moderate-hepatic-function groups). Eight subjects had QTcF >450 milliseconds (4 in each of the moderate- and severe-hepatic-function groups), of whom 2 subjects experienced an increase of >30 milliseconds compared with the respective baseline. All of the ECG abnormalities were reported as not clinically significant except for 1 grade-1 QTcF prolongation >500 milliseconds.

Discussion

This phase-1 study evaluated the PK and safety of buparlisib in subjects with different degrees of hepatic

Table 5. Adverse Events Regardless of Study Drug Relationship

Primary System Organ Class Preferred Term, n (%) [*]	Hepatic Function Group									
	Normal [†] (n = 13)		Mild [†] (n = 6)		Moderate [†] (n = 6)		Severe [†] (n = 6)		All (N = 31)	
	G 1/2	G 3/4	G 1/2	G 3/4	G 1/2	G 3/4	G 1/2	G 3/4	G 1/2	G 3/4
Nasopharyngitis	1 (8)	0	0	0	0	0	1 (17)	0	2 (6.5)	0
Bacterial infection	1 (8)	0	0	0	0	0	0	0	1 (3)	0
Electrocardiogram QT prolonged	0	0	0	0	1 (17)	0	0	0	1 (3)	0
Dermatitis acneiform	1 (8)	0	0	0	0	0	0	0	1 (3)	0
Dizziness	1 (8)	0	0	0	0	0	0	0	1 (3)	0
Hypertension	0	0	0	0	1 (17)	0	0	0	1 (3)	0
Insomnia	0	0	1 (17)	0	0	0	0	0	1 (3)	0
Myalgia	1 (8)	0	0	0	0	0	0	0	1 (3)	0
Thrombocytopenia	0	0	0	0	0	0	1 (17)	0	1 (3)	0
Urinary tract infection	0	0	0	0	1 (17)	0	0	0	1 (3)	0
Hypercalcemia	0	0	0	0	0	1 (17)	0	0	0	1 (3)

AE, adverse event; G, Grade.

^{*}Preferred term in descending frequency of Grade 1/2 AEs in all subjects. A subject with multiple occurrences of an AE is counted only once in that AE category. 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.

impairment compared with healthy subjects. The PK characteristics reported here in subjects with normal hepatic function are consistent with data reported previously using similar volunteer profiles and the same dose of buparlisib (Novartis Oncology, unpublished data, 2013). Secondary peaks in the concentration-time profiles at 24 hours postdose were also observed in both studies (Novartis Oncology, unpublished data, 2013). The mechanism responsible for these peaks is currently not clear, although enterohepatic circulation could be a potential explanation. Glucuronide metabolites are known to undergo enterohepatic circulation, and enterohepatic circulation is often associated with multiple peaks.³³

Exposure to buparlisib was modestly increased in subjects with mild or moderate hepatic impairment, and there was a slightly larger increase in the severe group, especially in C_{max} (45% for total buparlisib). Subjects with moderate hepatic impairment had slightly lower exposure to buparlisib than subjects with mild hepatic impairment, suggesting that there is no trend between increases in PK parameters and increasing severity of hepatic dysfunction up to Child–Pugh class B. The larger increases in PK parameters in the severe group could indicate a threshold of hepatic impairment that results in greater increases in buparlisib exposure.

Similar plasma protein binding of buparlisib was observed for the normal-, mild-, and moderate-hepatic-impairment groups. A slightly higher unbound fraction was measured in the severe group, which is most likely due to lower plasma protein formation and possible competition in binding with endogenous substances due to the compromised hepatic function. Taking into account

the change in the plasma protein binding of buparlisib and the observed increase in C_{max} and AUC_{∞} in the severe group, the changes in the unbound primary PK parameters were more pronounced in the severe group compared with the normal group (C_{max} 83%; AUC_{∞} 52%). The linear regression analyses suggested that a general worsening of hepatic function, rather than any one particular hepatic laboratory parameter, may lead to increased exposures to buparlisib in individuals with severe hepatic impairment.

Buparlisib was well tolerated in subjects with and without hepatic impairment, and no new safety signals were noted. AEs were infrequent and mainly grade 1–2 in severity. The tolerability and safety profile of buparlisib did not appear to be affected by the degree of hepatic impairment.

Conclusion

A single oral 30-mg dose of buparlisib was well tolerated in healthy subjects with and without hepatic impairment, and no new safety signals were reported. The PK results indicate that a buparlisib dose adjustment may not be required in patients with mild to moderate hepatic impairment. The safety and therapeutic indices of buparlisib should be considered before determining if a dose adjustment is appropriate for patients with severe hepatic impairment.

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Declaration of Conflicting Interests

DC, KH, EW, SL, VD, and LT are full-time employees of Novartis Pharmaceuticals. DC, SL, and VD own shares in Novartis Pharmaceuticals.

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