PROTOCOL

A Phase 1, Open-label, Parallel-group, Fixed-sequence Study to Investigate the Effect of the CYP3A Inducer Rifampin and the CYP3A Inhibitor Itraconazole on the Pharmacokinetics of Pamiparib (BGB-290) in Cancer Patients

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Study Drug: Pamiparib (BGB-290)

Sponsor Reference Number: BGB-290-105

EudraCT Number: 2019-000112-28

SPONSOR AGREEMENT

I have read the following protocol and approve it as described herein:

[redacted]

17 June 2019
Date

STUDY IDENTIFICATION

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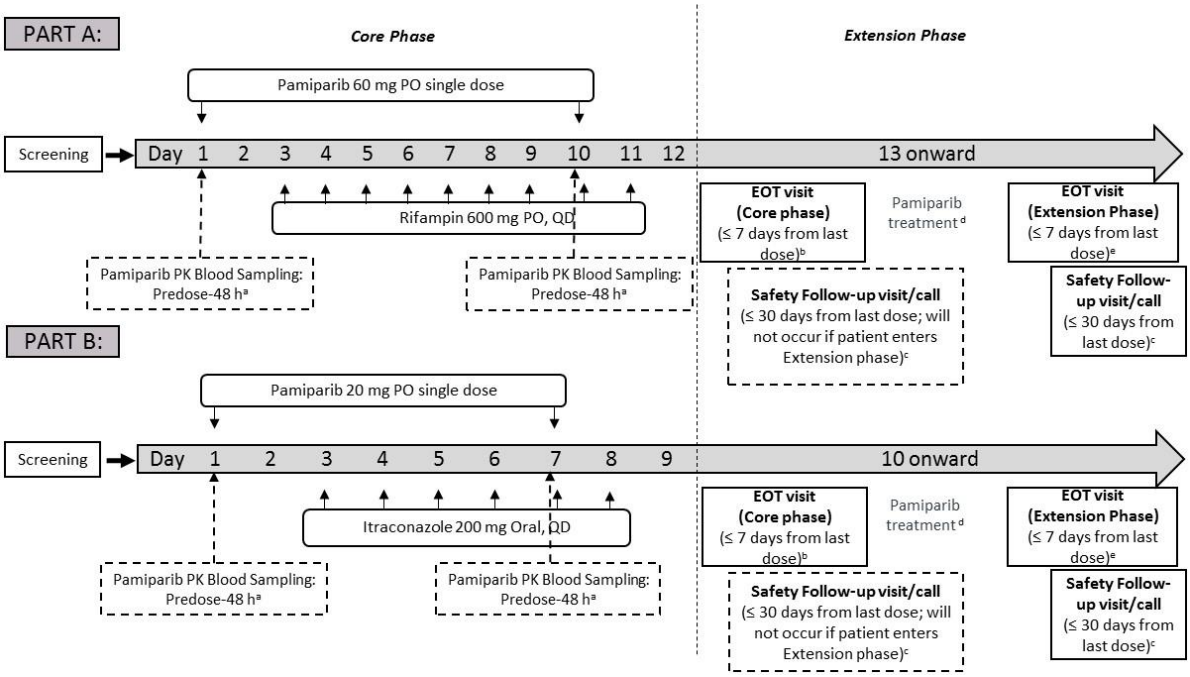
SYNOPSIS

Title of study: A Phase 1, Open-label, Parallel-group, Fixed-sequence Study to Investigate the Effect of the CYP3A Inducer Rifampin and the CYP3A Inhibitor Itraconazole on the Pharmacokinetics of Pamiparib (BGB-290) in Cancer Patients
Objectives: The primary objectives of the study are: • To determine the effect of the strong cytochrome P450 (CYP)3A inducer rifampin on the pharmacokinetics (PK) of pamiparib in patients with advanced solid tumors • To determine the effect of the strong CYP3A inhibitor itraconazole on the PK of pamiparib in patients with advanced solid tumors The secondary objectives of the study are: • To evaluate the safety and tolerability of pamiparib when coadministered with rifampin or itraconazole in patients with advanced solid tumors • To further investigate the safety of oral pamiparib in patients with advanced solid tumors (Extension Phase)

Study design:

This is an open-label, parallel-group, fixed-sequence study in patients with advanced solid tumors. The study consists of a Core Phase and an Extension Phase. The Core Phase is comprised of Part A and Part B, which will run in parallel (Figure 1). Part A will investigate the effect of CYP3A induction by rifampin on the pharmacokinetics (PK) of a single dose of pamiparib. Part B will investigate the effect of CYP3A inhibition by itraconazole on the PK of a single dose of pamiparib (Figure S-1).

Figure S-1. Study Design



Abbreviations: EOT = End-of-Treatment; PK = pharmacokinetic; PO = orally; QD = once a day.

[a] PK Samples at: Predose; 0.5, 1, 2, 4, 6, 9, 12, 24, and 48 hours postdose.

[b] End of Treatment (EOT) Visit (Core Phase, outpatient) to occur within 7 days of last dose of rifampin or itraconazole; assessments performed at this visit can be used as the assessments of the predose visit of the Extension Phase provided that they are performed within 7 days of the start of pamiparib dosing in the Extension Phase.

[c] Safety Follow-up Visit (outpatient)/call to occur at the end of Core Phase only if patient does not continue into the Extension Phase; Safety Follow-up Visit (outpatient)/call to occur at the end of the Extension Phase.

[d] Pamiparib will be given at 60 mg orally twice a day in 28-day cycles until progression of disease, unacceptable toxicity, withdrawal of consent, or any other reason for discontinuation.

[e] End-of-Treatment Visit (Extension Phase) to occur within 7 days of last dose of pamiparib.

In Part A, all patients will receive the following treatments:

- Day 1 and Day 10: A single dose of 60 mg pamiparib orally in the fasted state (at least 8 hours predose). On Day 10, 600 mg rifampin will be administered concomitantly. Fasting will continue for 4h postdose

- Day 3 to 9 and Day 11: 600 mg rifampin once a day in the fasted state (at least 2 hours predose). Fasting will continue for 1h postdose

In Part B, all patients will receive the following treatments:

- Day 1 and Day 7: A single dose of 20 mg pamiparib orally in the fasted state (at least 8 hours predose). On Day 7, itraconazole will be administered concomitantly. Fasting will continue for 4h postdose

- Days 3 to 6 and Day 8: 200 mg itraconazole once a day approximately 30 minutes after completing a meal

Patients enrolled in either part of the study will be admitted to the Clinical Research Unit (CRU) on Day -1 and will remain in the CRU for the duration of treatment until their discharge on Day 12 (patients enrolled on Part A) or Day 9 (patients enrolled on Part B). Patients will return to the CRU for an End of Treatment Visit within 7 days from the last dose of study drug. Patients who are discontinued early in the Core Phase or who will not participate in the Extension Phase will return 30 days (±7 days) after the last dose of study drug or before initiation of new anticancer therapy, whichever occurs first, for the Safety Follow-up Visit. If new anticancer therapy is inadvertently initiated before the Safety Follow-up Visit, (eg, without the knowledge of the study center team), a Safety Follow-up Visit should be scheduled as soon as possible. For patients who do not want to or cannot return to the clinic for the Safety Follow-up Visit, the patient should be contacted by telephone for a review of AEs. If these attempts of contact are unsuccessful, the additional attempts detailed in Section 9.1.4 should be made. Patients who complete the Core Phase of the study or who discontinue treatment during the Core Phase may enter the Extension Phase and receive pamiparib twice a day (BID) until disease progression, unacceptable toxicity, withdrawal of consent, or any other reason for discontinuation. Patients will have an End-of-Treatment visit within 7 days of the last dose of pamiparib. Thirty days (±7 days) after the last dose of pamiparib or before initiation of new anticancer therapy, whichever occurs first, the Safety Follow-up Visit will occur with the outlined safety assessments. If new anticancer therapy is inadvertently initiated before the Safety Follow-up Visit, (eg, without the knowledge of the study center team), a Safety Follow-up Visit should be scheduled as soon as possible. Clinical Study Reports (CSR) will be compiled based on data from the Core Phase (CSR A) and from the Extension Phase (CSR B). The two reports will then be combined as a final CSR. During the Extension Phase, scheduled assessments will be performed as shown in Appendix 1.

Number of patients:

A total of approximately 24 patients will be enrolled (approximately 12 in each part) to ensure that at least 20 patients (10 in each part) complete the study.

Inclusion criteria:

Patients must meet all of the following criteria to be eligible for the study:

1. Voluntarily agreed to participate by signing an informed consent form (ICF)
2. Age ≥ 18 years
3. Histologically or cytologically confirmed advanced or metastatic solid tumors that are refractory or resistant to standard therapy or for which no suitable effective standard therapy exists.
4. Disease that is evaluable per RECIST Version 1.1 or PCWG-3
5. ECOG performance status ≤ 1 (Appendix 2)
6. Life expectancy ≥ 12 weeks
7. Ability to swallow whole capsules
8. Adequate hematologic and end-organ function, as defined by the following laboratory results (obtained ≤ 14 days before day 1):
    a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
    b. Platelet count ≥ 100 x 10^9/L
    c. Hemoglobin ≥ 9 g/dL (≥ 14 days after growth factor support or transfusion)
    d. Estimated glomerular filtration rate ≥ 50 mL/min/1.73 m^2 by the Modification of Diet in Renal Disease study equation (MDRD STUDY EQ; www.mdrd.com)
    e. Total serum bilirubin ≤ 1.5 x upper limit of normal (ULN)
        a. ≤ 4 × ULN, if Gilbert's syndrome or if indirect bilirubin concentrations suggestive of extrahepatic source of elevation
    f. Aspartate and alanine aminotransferase (AST and ALT) ≤ 3 x ULN or ≤ 5 x ULN for patients with liver metastases
9. Females of childbearing potential and nonsterile males must use a highly effective method of birth control (see Appendix 4) while in the Core Phase of the study and for at least 6 months after the Core Phase is completed. In the Extension Phase, females of childbearing potential and nonsterile males must use a highly effective method of birth control (see Appendix 4) for the duration of the study and for at least 6 months after the last dose of study drug. Females of childbearing potential and non-sterile males must also agree to not freeze/donate oocytes or sperm respectively.
10. Willingness and ability to comply with the protocol for the duration of the study
11. Body weight ≥ 60 Kg at screening

Exclusion criteria:

Patients will be excluded from the study for any of the following reasons:

1. History of hypersensitivity to rifampin, any rifamycin or any of the components of the rifampin capsule (Part A).
2. History of hypersensitivity to itraconazole or any of the components of the itraconazole capsule (Part B).

3. Unresolved acute effects from prior medications of ≥ Grade 2 (CTCAE v5.0)
    a. Except for adverse effects not considered a likely safety risk (eg, alopecia, neuropathy and specific laboratory abnormalities)
4. Prior treatment with a PARP inhibitor at therapeutic doses is allowed, provided that such treatment was not the most recent therapy (PARP inhibitor must have been discontinued ≥ 3 months prior to the first dose of pamiparib)
    a. Patients who experienced prior severe toxicity to PARP inhibitors that in the opinion of the investigator precludes further treatment with PARP inhibitors should be excluded
5. Major surgical procedure, open biopsy, or significant traumatic injury ≤ 4 weeks prior to Day 1 of pamiparib administration, or anticipation of need for major surgical procedure during the course of the study
    a. Placement of vascular access device is not considered major surgery
6. Diagnosis of Myelodysplastic syndrome (MDS)
7. Other diagnosis of malignancy
    a. Except for surgically excised non-melanoma skin cancer, adequately treated carcinoma in situ of the cervix, localized prostate cancer treated with curative intent, adequately treated low-stage bladder cancer, ductal carcinoma in situ treated surgically with curative intent, or a malignancy diagnosed > 2 years ago with no current evidence of disease and no therapy ≤ 2 years prior to Day 1
8. Untreated leptomeningeal disease or brain metastasis. Patients with previously treated brain metastases are eligible if the metastases have shown no progression on brain computed tomography (CT) or magnetic resonance imaging (MRI) over at least 4 weeks prior to Day 1 of pamiparib administration, the patient has no symptoms due to the brain metastases, and the patient has been off corticosteroids for ≥ 2 weeks
9. Active infection requiring systemic treatment
10. Have known human immunodeficiency virus (HIV) infection or serologic status reflecting active viral hepatitis infection as follows:
    a. Patients with untreated chronic hepatitis B or chronic hepatitis B virus (HBV) carriers whose HBV DNA is > 500 IU/mL should be excluded. Patients positive for anti HCV and positive for HCV PCR test are to be excluded. Note: Inactive HBsAg carriers, treated and stable hepatitis B (HBV DNA ≤ 500 IU/mL) can be enrolled.
11. Any of the following cardiovascular criteria:
    a. Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living, ≤ 28 days before Day 1 of pamiparib administration
    b. Symptomatic pulmonary embolism ≤ 28 days before Day 1 of pamiparib administration
    c. Any history of acute myocardial infarction ≤ 6 months before Day 1 of pamiparib administration

d. Any history of heart failure meeting New York Heart Association Classification III or IV (Appendix 5) ≤ 6 months before Day 1 of pamiparib
   - Patients with congestive heart failure or history of heart failure should be excluded from Part B (itraconazole)

e. Any event of ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before Day 1 of pamiparib administration

f. Any history of cerebral vascular accident ≤ 6 months before Day 1 of pamiparib administration

12. Previous complete gastric resection or lap-band surgery, chronic diarrhea, active inflammatory gastrointestinal disease, known diverticular disease or any other disease-causing malabsorption syndrome
    a. Gastroesophageal reflux disease under treatment with proton pump inhibitors is allowed.
13. Active bleeding disorder, including gastrointestinal bleeding, as evidenced by hematemesis, significant hemoptysis, or melena ≤ 6 months before Day 1 of pamiparib administration
14. Use or anticipated need for food or drugs known to be strong or moderate CYP3A inhibitors or strong CYP3A inducers ≤ 14 days (or ≤ 5 half-lives, if half- life is known) prior to Day 1 of pamiparib administration (Appendix 6)
15. Pregnant or nursing females
    a. Females of childbearing potential require a negative serum pregnancy test ≤ 7 days before Day 1 of pamiparib administration
16. Known history of intolerance to the excipients of the pamiparib capsule
17. Have known hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption

Test products, dose, and mode of administration:

Core Phase: All doses will be administered in the morning with approximately 240 mL of water. On the days of PK sampling (Days 1 and 10 in Part A and Days 1 and 7 in Part B), patients are required to fast for at least 8 hours before and 4 hours after study drug administration. Water is allowed during the fasting period, except 1h predose and 1 h postdose. Rifampin (Part A) or itraconazole (Part B) will be administered first, followed within 5 minutes by pamiparib.

Patients enrolled in Part A will receive rifampin in the fasted state (at least 2 hours predose) on Days 3 to 9 and Day 11. Patients will continue to fast for 1h postdose on those days.

Patients enrolled in Part B will received itraconazole approximately 30 minutes after completing a meal on Days 3 to 6 and Day 8.

Extension Phase:

Patients may receive 60 mg pamiparib orally twice a day; doses should be taken 10 to 12 hours apart with approximately 240 mL of water. Predose or postdose fasting is not required.

Duration of treatment:

Planned screening duration: Up to 28 days

Length of clinic confinement: Days -1 to 12 for Part A and Days -1 to 9 for Part B

Outpatient visits: Every month after discharge from the clinic until progression of disease, unacceptable toxicity, or other reason for discontinuation (eg, withdraw consent).

Criteria for evaluation:

Pharmacokinetics:

Blood samples will be collected for the analysis of pamiparib plasma concentrations at the following timepoints: 30 minutes predose and 0.5, 1, 2, 4, 6, 9, 12, 24, and 48 hours postdose. Pamiparib PK parameters following dosing on Days 1 and 10 (Part A) and on Days 1 and 7 (Part B) will be calculated using standard non-compartmental methods. The following PK parameter endpoints will be calculated: area under the concentration-time curve (AUC) from time zero to time of last quantifiable concentration postdose (AUC_{0-t}), from zero to 12 hour (AUC_{0-12}) and from zero to infinity ($AUC_{0-\infty}$), maximum observed concentration (C_{max}), time of the maximum observed concentration (t_{max}), apparent terminal elimination half-life ($t_{1/2}$), apparent oral clearance (CL/F), and apparent volume of distribution (V_z/F). Additional PK parameters may also be reported.

Safety:

Safety endpoints for this study include assessment of adverse events (AEs) graded by CTCAE v5.0, and physical examinations, vital signs, clinical laboratory results, and 12-lead electrocardiograms (ECGs).

Statistical methods:

The sample size chosen for this study was based on precedent set by other PK studies of similar nature and was not based on power calculations.

PK Analysis:

The PK population will include all patients who received at least 1 dose of pamiparib and have evaluable PK data. A patient will be excluded from the PK summary statistics if the patient has an AE of vomiting that occurs at or before 2 x median t_{max}.

The primary PK parameters are $AUC_{0-\infty}$, AUC_{0-12}, AUC_{0-t}, C_{max}, t_{max}, $t_{1/2}$, CL/F, and V_z/F for pamiparib following pamiparib dosing on Days 1 and 10 in Part A and Days 1 and 7 in Part B. Other PK parameters may be reported but will be regarded as secondary and will not be subjected to inferential statistical analysis. A linear mixed-model analysis will be applied to analyze the log-transformed primary PK parameters ($AUC_{0-\infty}$, AUC_{0-t} and C_{max}) for each part of the study. The model assumes a fixed effect for treatment and a random effect for patient. Estimates of geometric mean ratios together with the corresponding 90% confidence intervals will be derived for the comparisons of the PK parameters as follows:

- Part A: Pamiparib plus rifampin (test) versus pamiparib alone (reference)
- Part B: Pamiparib plus itraconazole (test) versus pamiparib alone (reference)

Safety Analysis:

The safety population will include all patients who received at least 1 dose of pamiparib. Safety will be assessed by monitoring and recording all AEs graded by the CTCAE v5.0. Laboratory values (CBC, clinical chemistry, coagulation, and urinalysis), vital signs, physical examinations, and ECG findings will also be used in determining safety. Descriptive statistics will be used to analyze all safety data in the Safety Population.

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LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
AML	acute myeloid leukemia
AUC	area under the concentration-time curve
CL/F	apparent oral clearance
C_{max}	maximum observed concentration
CRU	Clinical Research Unit
CSR	clinical study report
CYP	cytochrome P450
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EOT	End-of-Treatment
HRD	homologous recombination deficiency
IB	Investigator's Brochure
ICF	Informed Consent Form
IRB	Institutional Review Board
MDS	myelodysplastic syndrome
PARP	poly (ADP-ribose) polymerase
PBMC	peripheral blood mononuclear cells
PD	disease progression
PFS	progression-free survival
PI	principal investigator
PK	pharmacokinetic(s)
SAE	serious adverse event
$t_{1/2}$	apparent terminal elimination half-life
t_{max}	time of the maximum observed concentration
ULN	upper limit of normal
V_z/F	apparent volume of distribution

1 INTRODUCTION

Pamiparib is a potent and selective inhibitor of poly (ADP-ribose) polymerase (PARP) proteins being developed by BeiGene USA Inc. (BeiGene) for the treatment of patients with various malignancies. Please refer to the Investigator's Brochure for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event (AE) profile of pamiparib as well as a list of ongoing studies.

1.1 PARP Inhibitors

Poly (ADP-ribose) polymerase (PARP) proteins are involved in DNA replication, transcriptional regulation, and DNA damage repair. DNA-bound PARP1/2 catalyzes the synthesis of poly (ADP-ribose) (PAR) onto a range of DNA-associated proteins that mediate DNA repair. PARP1 also undergoes auto-PARylation, a molecular change that ultimately leads to its release from DNA. Inhibition of PARP converts common single-strand DNA breaks into double-strand breaks during DNA replication. Small-molecule inhibitors of PARP1/2 represent a class of anticancer agents that exert their cytotoxic effects by interfering with DNA repair mechanisms. Since the discovery of synthetic lethality of PARP inhibitors in *BRCA*-deficient cells and, more broadly, cells with homologous recombination deficiency (HRD), accumulation of unrepaired single-strand DNA breaks resulting from catalytic PARP inhibition has been considered central to the mechanism of action of PARP inhibitors. More recently, it has been demonstrated that PARP inhibitors also trap PARP1- and PARP2-DNA complexes at DNA damage sites and that PARP trapping can be more cytotoxic than unrepaired single-strand DNA breaks (Pommier et al, 2016; O'Connor, 2015; Lord and Ashworth, 2017).

In the clinic, PARP inhibitors, including olaparib, rucaparib, niraparib, and talazoparib, have demonstrated sustained antitumor responses as a single agent in subjects with *BRCA1*- or *BRCA2*-mutant tumors, while achieving a favorable safety profile. Olaparib and rucaparib have been approved for the treatment of patients with advanced ovarian cancer that harbors germline or somatic/germline mutations in the *BRCA* gene (g*BRCA*m), respectively. Olaparib, rucaparib and niraparib have been approved as maintenance therapy for ovarian cancer. In addition, Olaparib was approved for the treatment of patients with human epidermal growth factor receptor-2 negative (HER2-) and g*BRCA*m breast cancer (Approved product package insert available online).

Aside from *BRCA1* or *BRCA2* mutations, other alterations can also result in HRD, which is characterized by '*BRCA*-like" genomic scarring. HRD does not only make cancer cells sensitive to PARP inhibitors but also to platinum agents, and shared mechanisms of resistance suggest that both classes of drugs have similar antitumor effects in cancers with HRD (Edwards et al, 2008; Sakai et al, 2008; Sakai et al, 2009). This concept is supported by clinical data for the PARP inhibitor olaparib in patients with *BRCA*-mutated ovarian cancer demonstrating that platinum sensitivity correlated with response and platinum refractoriness with an almost complete lack of response to olaparib (Fong et al, 2010; Gelmon et al, 2011). In addition, rucaparib has been shown to be effective in platinum-sensitive ovarian cancer with *BRCA*-mutated patients deriving most benefit, followed by non-*BRCA* HRD and non-HRD patients (Swisher et al, 2017).

The strongest evidence that platinum sensitivity can predict clinical benefit from PARP inhibition is provided by 2 studies conducted in ovarian cancer patients. The NOVA study for the PARP inhibitor niraparib in patients with platinum-sensitive ovarian cancer demonstrated that patients had significantly improved median progression-free survival (PFS) with niraparib compared with placebo, regardless of *BRCA* mutation or HRD status (Mirza et al, 2016). Median PFS for niraparib in patients with germline *BRCA*-mutations was 21.0 versus 5.5 months for placebo (Hazard Ratio [HR] 0.27; $P < 0.001$). An exploratory analysis for patients who were biomarker negative (germline *BRCA*-wild-type and HRD negative) showed a median PFS of 6.9 versus 3.8 months (HR 0.58, $P = 0.02$). This led to the approval of niraparib for the maintenance treatment of patients who are in a complete response or partial response to platinum-based chemotherapy (Zejula [niraparib] prescribing information 2017). Similar results were recently reported for rucaparib in the ARIEL3 study. Median PFS for rucaparib in patients with *BRCA*-mutant (germline or somatic) ovarian cancers was 16.6 versus 5.4 months for placebo (HR 0.23; $P < 0.0001$). In an exploratory analysis for patients who were biomarker negative (*BRCA*-wild-type and HRD negative), median PFS was 6.7 versus 5.4 months (HR 0.58, $P = 0.0049$) (Coleman et al, 2017).

1.2 PARP Inhibitor Pamiparib

Pamiparib is a potent and selective inhibitor of PARP1 and PARP2 with potent PARP-trapping activity and significant brain penetration in preclinical models.

1.2.1 Clinical Data for Pamiparib

There are 5 ongoing studies with pamiparib with available preliminary data: ongoing monotherapy studies BGB-290-AU-002 and BGB-290-102; and combination therapy studies BGB-290-103 (pamiparib in combination with temozolomide in solid tumors), BGB-290-104 (pamiparib in combination with radiation and/or temozolomide in glioblastoma), and BGB-A317/BGB-290_Study_001 (pamiparib in combination with the anti-PD-1 antibody tislelizumab [also known as BGB-A317]). The study data from BGB-290-AU-002 are the most mature and interim results are summarized below.

1.2.1.1 Pharmacokinetics Data for BGB-290-AU-002

In the first-in-human Phase 1 study, interim pharmacokinetics (PK) data of pamiparib showed that pamiparib is rapidly absorbed and eliminated after oral administration. The maximum serum concentration and the drug exposure area under the concentration-time curve (AUC) increased in a nearly dose proportional manner from 2.5 to 120 mg twice a day both after the single-dose administration and at steady-state. The terminal half-life was determined to be approximately 13 hours, with a range of 5.5 to 34 hours. At steady-state, from 2.5 to 120 mg twice a day, drug exposure was increased in a dose-dependent manner.

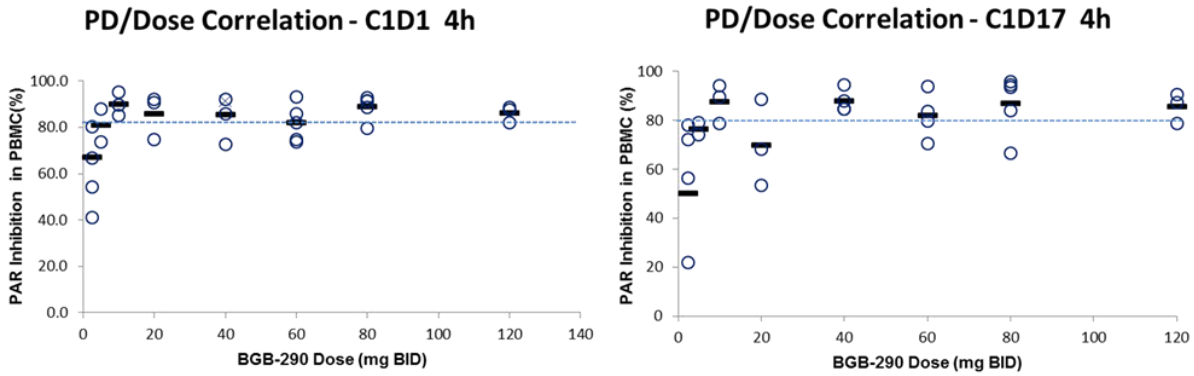
A total of 13 patients in Study BGB-290-AU-002 contributed to serial plasma samples at predose, 0.5, 1, 2, 4, 7, 24 and 48 hours after a single 60 mg dose of pamiparib, either fasted or with high-fat breakfast, each followed by a 5-day washout for food-effect PK investigation.

When pamiparib was administered with food, a reduction of 15% in AUC and 41% in C_{max} was observed, along with a delay of T_{max} from 2 to 7 hours.
The 15% reduction in AUC is not considered to be clinically relevant and falls well within the variability of pamiparib exposure of approximately 50% coefficient of variation. Therefore, food restrictions are not required with pamiparib administration.

1.2.1.2 Exploratory Biomarker Data

The PAR formation from peripheral blood mononuclear cells (PBMCs) was detected by enzyme-linked immunosorbent assay to explore the pharmacodynamic activity in the Phase 1 study BGB-290-AU-002. Blood samples for PK and isolation of PBMCs were obtained at baseline on Day 1 (predose) and 4 hours postdose on Days 1 and 17 of Cycle 1. The pharmacodynamic activity at 4 hours postdose on Days 1 and 17 was reported as percentage of predose PAR inhibition. PK/pharmacodynamic correlation analyses were conducted in 30 patients who received doses of 2.5, 5, 10, 20, 40, 60, 80, and 120 mg twice a day. Robust PAR inhibition in PBMCs was observed at the first dose level of 2.5 mg twice a day. The pharmacodynamic activity increased in a dose-dependent manner from 2.5 to 10 mg twice a day. Sustained PAR inhibition in PBMCs was observed at steady-state for patients treated at 10 mg twice a day or higher dose levels (Figure 1).

Figure 1: Correlation of PAR Inhibition in Peripheral Blood Mononuclear Cells with BGB-290 Dose



Abbreviations: BID = twice a day; h = hours.

1.2.1.3 Clinical Safety and Preliminary Efficacy for BGB-290-AU-002

BGB-290-AU-002 is a first-in-human study evaluating pamiparib to characterize the safety, maximum tolerated dose (MTD), preliminary antitumor activity, and the PK of pamiparib given as a monotherapy in a 3+3 dose escalation scheme. Pamiparib was administered in doses ranging from 2.5 mg up to 120 mg orally twice a day.

The study is being conducted in 5 Australian study centers and preliminary data for 81 patients are available (cut-off date of 01 December 2017).

The Dose Limiting Toxicity was Grade 2 nausea, which persisted despite optimal standard medical therapy and was observed in the 120 mg twice daily cohort (n = 2) and in the 40 mg and 80 mg twice daily cohorts (1 patient each). The MTD of pamiparib was 80 mg orally twice a day.

The most frequent treatment-emergent AEs occurring in ≥ 2 patients included nausea (64.4%), vomiting (35.6%), fatigue (33.3%), and diarrhea (28.9%). Anemia was the most frequent hematologic AE (33%), followed by neutropenia (11%).

Twenty-six percent of the patients experienced a ≥ Grade 3 AE deemed related to pamiparib. The most frequent Grade 3 pamiparib related AEs were anemia (11.5%); neutropenia (7.7%); nausea, fatigue and diarrhea (2.6% each); and oral paresthesia, paresthesia, vomiting, hypophosphatemia, AT elevated, abdominal pain, and platelet counts decreased (1.3% each). Serious AEs reported as related to pamiparib included anemia (n = 2) and nausea (n = 2).

Four patients experienced AEs with fatal outcome, which included worsening of pleural effusion, intestinal obstruction, gastric obstruction, and intestinal perforation.

Three patients experienced AEs leading to discontinuation of pamiparib; 2 of those AEs were deemed related to pamiparib (Grade 1 paresthesia of hands and mouth, and Grade 2 vomiting). The third, not related AE was a serious event of Grade 3 traumatic hematoma due to fall.

No fatal AE was deemed related to pamiparib.

Fifty-four patients with gynecological cancers have been enrolled in the BGB-290-AU-002 study as of 01 December 2017. Seventeen patients achieved either complete (n = 5) or partial (n = 12) responses; and responses were observed across all dose levels including a partial response (PR) at 2.5 mg twice a day.

Based upon the overall safety, efficacy, and PK profile of pamiparib, a dose of 60 mg orally twice a day was selected as the recommended phase 2 dose (RP2D) for further investigation.

1.3 Study Rationale

Available human in-vitro metabolism data suggest that pamiparib is metabolized mainly by CYP3A; therefore, inducers and inhibitors of CYP3A have the potential to lower and raise pamiparib plasma concentrations, respectively. Given the theoretical potential for CYP3A inducers and inhibitors to alter the PK of pamiparib, a clinical drug interaction study is warranted to determine the extent of any interaction. This study is designed to determine the effect of CYP3A induction by rifampin and CYP3A inhibition by itraconazole on the PK of pamiparib. Rifampin and itraconazole are commonly used in drug interaction studies as a prototypical CYP3A inducer and inhibitor, respectively, (CDER Guidance; European Medicines Agency, CHMP).

1.4 Benefit-Risk Assessment

Patients carrying HRD tumors may receive health benefit from participating in the Extension Phase of the study. Pamiparib has been studied in nonclinical toxicity and Phase 1 clinical studies and its toxicities are largely consistent with the safety profile shared by other PARP inhibitors, with the potential exception that pamiparib may cause less myelosuppression. Myelodysplastic

syndrome (MDS) and acute myeloid leukemia (AML) have been reported in a small number (< 1%) of patients treated with PARP inhibitors, especially in patients harboring a germline *BRCA* mutation (Ricks et al 2015). Typically, patients who develop MDS and AML while on PARPi therapy had a history of extensive previous chemotherapy and some had a history of previous cancer or bone marrow abnormalities. To date, there have been no reports of MDS or AML in patients treated with pamiparib and no fatal drug reactions. Patients in this study will be monitored monthly for hematological toxicities, and events of MDS and AML will be reported as serious AEs (SAEs). The doses of rifampicin and itraconazole are the same as those previously used in other PARP inhibitor drug-drug interaction (DDI) studies.

Based on the nonclinical and clinical collected data to date, pamiparib warrants further exploration in patients with advanced solid tumors and the overall risk-benefit ratio appears to be favorable. More information about the known and expected benefits, risks, and reasonably anticipated AEs associated with pamiparib may be found in the Investigator's Brochure (IB) (Pamiparib [BGB-290] Investigator's Brochure). More information about the known and expected benefits and risks of rifampin and itraconazole may be found in their respective prescribing information.

2 OBJECTIVES

2.1 Primary Objectives

The primary objectives of the study are:

- to determine the effect of the strong CYP3A inducer rifampin on the PK of pamiparib in cancer patients
- to determine the effect of the strong CYP3A inhibitor itraconazole on the PK of pamiparib in cancer patients

2.2 Secondary Objectives

The secondary objectives of the study are:

- to evaluate the safety and tolerability of pamiparib when coadministered with rifampin or itraconazole/fluconazole in cancer patients
- to further investigate the tolerability of oral pamiparib in patients with advanced solid tumors (Extension Phase).

3 ENDPOINTS

3.1 Primary Endpoints

The PK outcome endpoints of pamiparib derived from the plasma concentration-time profiles following oral administration of pamiparib on Days 1 and 10 in Part A (rifampin interaction) and Days 1 and 7 in Part B (itraconazole interaction) are as follows:

- maximum observed concentration (C_{max})
- AUC from time zero to time of last quantifiable concentration postdose (AUC_{0-t})
- AUC from zero to infinity ($AUC_{0-\infty}$)
- AUC from zero to 12 hours (AUC_{0-12})
- time of the maximum observed concentration (t_{max})
- apparent terminal elimination half-life ($t_{1/2}$)
- apparent oral clearance (CL/F)
- apparent volume of distribution (V_z/F)

3.2 Secondary Endpoints

- incidence and severity of AEs
- incidence of laboratory abnormalities, based on hematology, clinical chemistry, and urinalysis test results
- vital sign assessments
- 12-lead electrocardiogram (ECG) parameters
- physical examinations

4 INVESTIGATIONAL PLAN

4.1 Study Design

This is an open-label, parallel-group, fixed-sequence study in male and female cancer patients. Part A will investigate the effect of CYP3A induction by rifampin on the single-dose PK of pamiparib, and Part B will investigate the effect of CYP3A inhibition by itraconazole on the single-dose PK of pamiparib.

The study consists of two phases: the Core Phase, which is divided into Part A and Part B, and the Extension Phase. A total of approximately 24 patients will be enrolled (approximately 12 in each part) to ensure that at least 20 patients (10 in each part) complete the study.

In Part A, all patients will receive the following treatments:

- Day 1 and Day 10: single oral doses of 60 mg pamiparib
- Days 3 to 11: oral doses of 600 mg rifampin once a day

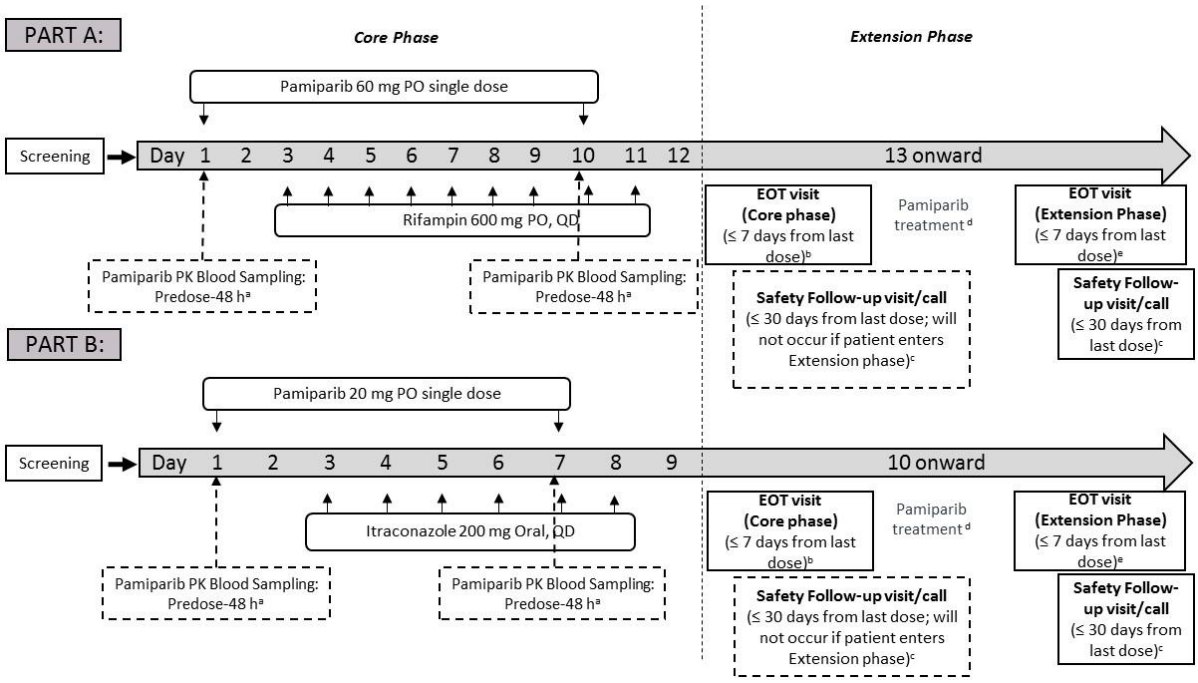
In Part B, all patients will receive the following treatments:

- Day 1 and Day 7: single oral doses of 20 mg pamiparib
- Days 3 to 8: oral doses of 200 mg itraconazole once a day

An overview of the study design is shown in Figure 2.

For both parts of the study, potential patients will be screened to assess their eligibility within 28 days prior to the first dose administration. Patients enrolled in either part of the study will be admitted to the Clinical Research Unit (CRU) on Day -1 and will remain in the CRU for the duration of treatment until their discharge on Day 12 (patients enrolled on Part A) or Day 9 (patients enrolled on Part B). Patients will return to the CRU for an EOT Visit within 7 days from the last dose of study drug. Patients who are discontinued early during the Core Phase or who will not participate in the Extension Phase will return for a Safety Follow-up Visit 30 days (±7 days) after the last dose of study drug or before initiation of new anticancer therapy, whichever occurs first. If new anticancer therapy is inadvertently initiated before the Safety Follow-up Visit, (eg, without the knowledge of the study center team), a Safety Follow-up Visit should be scheduled as soon as possible. For patients who do not want to or cannot return to the clinic for the Safety Follow-up Visit, the patient should be contacted by telephone for a review of AEs. If these attempts of contact are unsuccessful, the additional attempts detailed in Section 9.1.4 should be made.

Figure 2: Study Schematic



Abbreviations: EOT = End-of-Treatment; PK = pharmacokinetic; PO = orally; QD = once a day.

[a] PK Samples at: Predose; 0.5, 1, 2, 4, 6, 9, 12, 24, and 48 hours postdose.

[b] End of Treatment Visit (Core Phase, outpatient) to occur within 7 days of last dose of study drug; assessments performed at this visit can be used as the assessments of the predose visit of the Extension Phase provided that they are performed within 7 days of the start of pamiparib dosing in the Extension Phase.

[c] Safety Follow-up Visit (outpatient)/call to occur at the end of Core Phase only if patient does not continue into the Extension Phase; Safety Follow-up Visit (outpatient)/call to occur at the end of the Extension Phase.

[d] Pamiparib will be given at 60 mg orally twice a day in 28-day cycles until progression of disease, unacceptable toxicity, withdrawal of consent, or any other reason for discontinuation.

[e] End-of-Treatment (Extension Phase) visit to occur within 7 days of last dose of pamiparib

After completing the Core Phase, patients may participate in the Extension Phase, in which they will receive pamiparib twice a day in 28-day cycles until progression of disease, unacceptable toxicity, withdraw consent, or any other reason for discontinuation. Patients will have a Predose visit within 7 days of the first planned dose of pamiparib in the Extension Phase. Assessments performed at the EOT Visit of the Core Phase (performed within 7 days from last dose) can be used for the Predose visit and need not to be repeated provided they are performed within 7 days of the first planned dose of pamiparib on the Extension Phase. During the Extension Phase, patients will undergo assessments as delineated in Appendix 1. Patients will have an End-of-Treatment visit within 7 days of the last dose of pamiparib and a Safety Follow-up Visit approximately 30 days after the last dose if they experienced clinical laboratory abnormalities in their last visit. Patients who did not experience such abnormalities, will be contacted by phone to collect any AEs or SAEs. Clinical Study Reports (CSR) will be compiled based on data from the Core Phase (CSR A) and from the Extension Phase (CSR B). The two reports will then be combined as a final CSR.

The Schedule of Assessments is presented in Appendix 1.

4.2 Discussion of Study Design

This is an open label, non-randomized study designed to evaluate the effect of rifampin (a strong CYP3A inducer) and itraconazole (a strong CYP3A inhibitor) on the PK of pamiparib in cancer patients.

A parallel-group design has been selected due to the potential for carryover of CYP induction following rifampin dosing, which can remain for several weeks following cessation of dosing (Reitman, et al) and would prolong the study duration to a significant degree if a crossover design were utilized.

For the Core Phase, the total duration of study participation for each patient (from Screening through the EOT Visit) is anticipated to be approximately 48 days.

Patients may participate in the Extension Phase during which they will receive pamiparib monotherapy until disease progression, unacceptable toxicity, withdrawal of consent, or any other reason for discontinuation.

Rationale for selection of the pamiparib dose:

A dose of 60 mg pamiparib has been chosen for the induction portion of the study (Part A), as 60 mg twice daily was administered to patients in Phase 1 study BGB-290-AU-002 and was well tolerated.

A dose of 20 mg pamiparib has been chosen for the inhibition portion of the study (Part B), as it is one-sixth of 120 mg, where 120 mg BID is the highest dose administered in the phase I trial. With an observed rate of accumulation of approximately 2-fold, this gives an approximate of 12-fold margin, which should be sufficient to cover the plasma exposure increase due to complete blockade of CYP3A by itraconazole after a single-dose administration of 20 mg pamiparib. In addition, 20 mg is the lowest dose strength of pamiparib.

Given the objective of determining whether a CYP3A inducer or inhibitor has an effect on the BGB-290 PK, these doses are considered to be adequate to achieve study objectives with minimal risk to subjects.

Rationale for selection of the rifampin and itraconazole doses:

A dose of 600 mg rifampin once a day has been selected for Part A, as this is the recommended daily dose for adults weighing 60 kg or above (10 mg/kg/day, to a maximum of 600 mg/day). It is also the most commonly selected rifampin dose in drug interaction studies (Xu, et al). In this study, to achieve induction of CYP3A, 600 mg rifampin once a day will be administered for 7 days to reach steady state, coadministered with pamiparib on Day 10, and given for an additional day following pamiparib dosing to maintain steady state.

A dose of 200 mg itraconazole once a day has been selected for Part B, as this dose is standard in clinical practice and has been demonstrated to inhibit CYP3A (Liu, et al). In this study, to achieve sufficient inhibition of CYP3A, 200 mg itraconazole once a day will be administered for a 4-day run-in period (Days 3 to 6) to reach steady state, coadministered with pamiparib on Day 7, and given for an additional day following pamiparib dosing to maintain CYP3A inhibition during the elimination phase of pamiparib.

Doses of 600 mg rifampin once a day and 200 mg itraconazole once a day are considered to be safe and anticipated to provide sufficient CYP3A induction and inhibition, respectively, to fulfill the primary study objectives.

5 STUDY POPULATION

5.1 Inclusion Criteria

Patients must meet all of the following criteria to be eligible for the study:

1. Voluntarily agreed to participate by signing an informed consent form (ICF)
2. Age ≥ 18 years
3. Histologically or cytologically confirmed advanced or metastatic solid tumors that are refractory or resistant to standard therapy or for which no suitable effective standard therapy exists.
4. Disease that is evaluable per RECIST Version 1.1 or PCWG-3
5. ECOG performance status ≤ 1 (Appendix 2)
6. Life expectancy ≥ 12 weeks
7. Ability to swallow whole capsules
8. Adequate hematologic and end-organ function, as defined by the following laboratory results (obtained ≤ 14 days before day 1):
    a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
    b. Platelet count ≥ 100 x 10^9/L
    c. Hemoglobin ≥ 9 g/dL (≥ 14 days after growth factor support or transfusion)
    d. Estimated glomerular filtration rate ≥ 50 mL/min/1.73 m^2 by the Modification of Diet in Renal Disease study equation (MDRD STUDY EQ; www.mdrd.com)
    e. Total serum bilirubin ≤ 1.5 x upper limit of normal (ULN)
        - ≤ 4 x ULN, if Gilbert's syndrome or if indirect bilirubin concentrations suggestive of extrahepatic source of elevation
    f. Aspartate and alanine aminotransferase (AST and ALT) ≤ 3 x ULN or ≤ 5 x ULN for patients with liver metastases
9. Females of childbearing potential and nonsterile males must use a highly effective method of birth control (see Appendix 4) while in the Core Phase of the study and for at least 6 months after the Core Phase is completed. In the Extension Phase, females of childbearing potential and nonsterile males must use a highly effective method of birth control (see Appendix 4) for the duration of the study and for at least 6 months after the last dose of study drug. Females of childbearing potential and non-sterile males must also

agree to not freeze/donate oocytes or sperm respectively.

10. Willingness and ability to comply with the protocol for the duration of the study

11. Body weight ≥ 60 Kg at screening

5.2 Exclusion Criteria

Patients will be excluded from the study for any of the following reasons:

1. History of hypersensitivity to rifampin, any rifamycin or any of the components of the rifampin capsule (Part A).
2. History of hypersensitivity to itraconazole or any of the components of the itraconazole capsule (Part B).
3. Unresolved acute effects from prior medications of ≥ Grade 2 (CTCAE v5.0)
    a. Except for adverse effects not considered a likely safety risk (eg, alopecia, neuropathy and specific laboratory abnormalities)
4. Prior treatment with a PARP inhibitor at therapeutic doses is allowed, provided that such treatment was not the most recent therapy (PARP inhibitor must have been discontinued ≥ 3 months prior to the first dose of pamiparib)
    a. Patients who experienced prior severe toxicity to PARP inhibitors that in the opinion of the investigator precludes further treatment with PARP inhibitors should be excluded
5. Major surgical procedure, open biopsy, or significant traumatic injury ≤ 4 weeks prior to Day 1 of pamiparib administration, or anticipation of need for major surgical procedure during the course of the study
    a. Placement of vascular access device is not considered major surgery
6. Diagnosis of Myelodysplastic syndrome (MDS)
7. Other diagnosis of malignancy
    a. Except for surgically excised non-melanoma skin cancer, adequately treated carcinoma in situ of the cervix, localized prostate cancer treated with curative intent, adequately treated low-stage bladder cancer, ductal carcinoma in situ treated surgically with curative intent, or a malignancy diagnosed > 2 years ago with no current evidence of disease and no therapy ≤ 2 years prior to Day 1
8. Untreated leptomeningeal disease or brain metastasis. Patients with previously treated brain metastases are eligible if the metastases have shown no progression on brain computed tomography (CT) or magnetic resonance imaging (MRI) over at least 4 weeks

prior to Day 1 of pamiparib administration, the patient has no symptoms due to the brain metastases, and the patient has been off corticosteroids for ≥ 2 weeks

9. Active infection requiring systemic treatment

10. Have known human immunodeficiency virus (HIV) infection or serologic status reflecting active viral hepatitis infection as follows:

    a. Patients with untreated chronic hepatitis B or chronic hepatitis B virus (HBV) carriers whose HBV DNA is > 500 IU/mL should be excluded. Patients positive for anti HCV and positive for HCV PCR test are to be excluded. Note: Inactive HBsAg carriers, treated and stable hepatitis B (HBV DNA ≤500 IU/mL) can be enrolled

11. Any of the following cardiovascular criteria:

    a. Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living, ≤ 28 days before Day 1 of pamiparib administration

    b. Symptomatic pulmonary embolism ≤ 28 days before Day 1 of pamiparib administration

    c. Any history of acute myocardial infarction ≤ 6 months before Day 1 of pamiparib administration

    d. Any history of heart failure meeting New York Heart Association Classification III or IV (Appendix 5) ≤ 6 months before Day 1 of pamiparib

        - Patients with congestive heart failure or history of heart failure should be excluded from Part B (itraconazole)

    e. Any event of ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before Day 1 of pamiparib administration

    f. Any history of cerebral vascular accident ≤ 6 months before Day 1 of pamiparib administration

12. Previous complete gastric resection or lap-band surgery, chronic diarrhea, active inflammatory gastrointestinal disease, known diverticular disease or any other disease-causing malabsorption syndrome

    a. Gastroesophageal reflux disease under treatment with proton pump inhibitors is allowed

13. Active bleeding disorder, including gastrointestinal bleeding, as evidenced by hematemesis, significant hemoptysis, or melena ≤ 6 months before Day 1 of pamiparib administration

14. Use or anticipated need for food or drugs known to be strong or moderate CYP3A inhibitors or strong CYP3A inducers ≤ 14 days (or ≤ 5 half-lives if half-life is known) prior to Day 1 of pamiparib administration (Appendix 6)

15. Pregnant or nursing females

    a. Females of childbearing potential require a negative serum pregnancy test ≤ 7 days before Day 1 of pamiparib administration

16. Known history of intolerance to the excipients of the pamiparib capsule

17. Have known hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption

5.3 Patient Number and Identification

After signing the ICF, patients will be assigned a unique screening number by the study site. Patients will be assigned a patient number at the time of the first dosing occasion. Assignment of numbers will be in ascending order and no numbers will be omitted (eg, Subjects 101, 102, 103).

Enrolled patients will be identified by patient number only on all study documentation. A list identifying the patients by patient number and screening number will be kept in the Site Master File.

5.4 Patient Withdrawal and Replacement

A patient is free to withdraw from the study at any time. A patient may be withdrawn for any of the following reasons:

a. Disease progression (PD)
b. AEs
c. Major protocol violation
d. Patient withdrew consent for study treatment either during the Core Phase or during the Extension Phase
    - Patients may voluntarily withdraw consent from study treatment at any time
e. Investigator's discretion
f. Start of new anticancer therapy

If a patient is withdrawn from dosing, the Sponsor will be notified and the date and reason(s) for the withdrawal will be documented in the patient's eCRF. If a patient is withdrawn, efforts will be made to perform all discharge assessments, if possible (Appendix 1). Other procedures may be performed at the principal investigator's (PI's) (or designee's) and/or sponsor's discretion. If the patient is in-house, these procedures should be performed before the patient is discharged from the clinic. The PI (or designee) may also request that the patient returns for an additional

Follow-up Visit. All withdrawn patients will be followed until resolution of all their AEs or until the unresolved AEs are judged by the PI (or designee) to have stabilized.

Patients who withdraw during the Core Phase may be replaced following discussion between the PI and sponsor.

5.5 Study Termination

The sponsor has the right to terminate this study at any time. Reasons for terminating the study early may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients
- Overall patient enrollment is unsatisfactory
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Good Clinical Practice (GCP) noncompliance
- Study activity is completed (ie, the last patient accrued in the Extension Phase has been discontinued from the study due to intolerable toxicity, disease progression or voluntary withdrawal)

The sponsor will notify the PI if a decision is made to terminate the study. Should this be necessary, prematurely discontinued patients should be seen as soon as possible for an EOT Visit and Safety Follow-up Visit (Core and Extension Phase).

The PI may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The PI will be responsible for informing the EC of the early termination of the study.

5.6 Data Entry in the eCRF

Data collection on the eCRF must follow the instructions described in the eCRF completion guidelines.

6 STUDY TREATMENTS

6.1 Description, Storage, Packaging, and Labeling

Pamiparib is provided in 20-mg or 60-mg capsules, based upon availability and approval status. Pamiparib capsules will be provided in 30-[redacted].

Itraconazole will be provided as 100 mg capsules in 60-count packs.

Rifampin will be provided as 300 mg capsules in 60-count packs.

Excipients contained in the pamiparib capsule are listed in the Investigator's Brochure. Excipients contained in the rifampin and itraconazole capsules are listed in their respective product inserts.

The contents of the labels will be in accordance with all applicable local regulatory requirements. Labels will include at a minimum: drug name, dose strength, contents, sponsor, protocol number, bottle number, directions for use, storage conditions, caution statements, retest or expiration date, and space to enter the patient number and name of investigator

6.1.1 Handling and Storage

The instructions for drug ordering are in the pharmacy binder. Pamiparib will be dispatched to a study center only after receipt of the required documents in accordance with applicable regulatory requirements and the sponsor's procedures. The investigator or pharmacist/designated personnel are responsible for maintaining the drug supply inventory and acknowledging receipt of all pamiparib shipments. Pamiparib must be stored in a secure area with access limited to the investigator and authorized study center personnel and under physical conditions that are consistent with pamiparib specific requirements.

Pamiparib must be kept at the condition as specified on the labels. [redacted].

Itraconazole should be stored below 25°C and rifampin should be stored below 30°C.

6.2 Study Treatment Administration

Core Phase

All doses should be administered in the morning.

On the days of PK sampling (Days 1 and 10 in Part A and Days 1 and 7 in Part B), patients are required to fast for at least 8 hours before and 4 hours after study drug administration. Water is allowed during the fasting period, except 1h predose and 1h postdose. Rifampin (Part A) or itraconazole (Part B) will be administered first, followed within 5 minutes by pamiparib. Both study drugs should be taken with approximately 240 mL of water.

Patients enrolled in Part A will receive rifampin once a day on Day 3 to 9 and on Day 11 in the fasted state (at least 2 hours predose) and will continue to fast for 1h postdose. Water is allowed during the fasting period.

Patients enrolled in Part B will receive itraconazole once a day on Days 3 to 6 and on Day 8 approximately 30 minutes after completing a meal.

Extension Phase

During the Extension Phase, pamiparib capsules will be administered orally at 60 mg, twice a day 10 to 12 hours apart on Days 1 to 28 of a 28-day cycle.

6.3 Randomization

This is a nonrandomized study. The study has a fixed treatment sequence.

6.4 Blinding

This is an open-label study.

6.5 Study Treatment Compliance

During the Core Phase of the study, the following measures will be employed to ensure treatment compliance:

- All doses will be administered under the supervision of suitably qualified study site staff.
- Immediately after dose administration, visual inspection of the mouth and hands will be performed for each patient.
- At each dosing occasion, a predose and postdose inventory of pamiparib (Parts A and B), rifampin (Part A) and itraconazole (Part B) will be performed.

6.6 Drug Accountability

The investigator (or designee) will maintain an accurate record of the receipt of pamiparib capsules received, including the date in which they were received. One copy of this receipt will be returned to the Sponsor when the contents of the shipment have been verified. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject; subject identification number; date of dispensing; and lot number(s) pamiparib, rifampin, and itraconazole. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures. Any unused assembled unit doses will be retained until completion of the study. A record of quantities destroyed or returned to BeiGene shall also be documented.

At the completion of the study, all unused pamiparib capsules will be returned to the Sponsor or disposed of by the study site, per the Sponsor's written instructions.

Rifampin and itraconazole will also be subject to accountability procedures, and the CRU staff will not destroy unused supplies of rifampin and itraconazole until drug accountability and reconciliation has been performed by the Study Monitor.

6.7 Dose Holds and Modifications

AEs should be assessed as best as possible regarding their relatedness to study drug. Investigators should make every effort to maintain dose intensity in patients.

Core Phase

Patients who experience AEs that require dose holds should be discontinued from the Core Phase. Patients who experience AEs deemed related to rifampin or itraconazole are eligible to enter the Extension Phase.

Extension Phase

Dosing of pamiparib can be withheld for up to 28 days consecutively (up to 56 days consecutively for investigational drug-related anemia). If drug is planned to be held > 28 days (> 56 days for investigational drug-related anemia), the medical monitor should be contacted before permanent patient discontinuation from the study drug.

Criteria for treatment modifications and suggested guidelines for the management of some toxicities related to pamiparib are summarized below. These general guidelines may be modified at the discretion of the investigator based on discussions with the medical monitor and the best clinical judgment at that time; any decisions should be documented. Any toxicities related to pamiparib or placebo should be managed according to standard medical practice.

A maximum of 2 dose reductions is allowed before the patient must be permanently withdrawn from study drug. Dose levels for pamiparib are summarized in Table 1. Pamiparib will be dose modified as outlined in Table 2.

Table 1: Dose Levels for Pamiparib

Dose Level	Pamiparib
1	60 mg PO BID
-1	40 mg PO BID
-2	20 mg PO BID

Abbreviations: PO = oral; BID = twice daily.
Pamiparib may be dose-reduced for a maximum of 2 dose reductions.

Table 2: Criteria for Modification of Pamiparib Dosing for Related Adverse Events

Toxicity		Recommended Dose Modification [a]
Hematologic		
Anemia (hemoglobin, Hgb)		
Hgb < 9.0 g/dL		• **First occurrence of Hgb < 9.0 g/dL:** Hold pamiparib and treat as medically indicated to get Hgb to ≥ 9 g/dL, and then ↓ pamiparib by 1 dose level to 40 mg BID
Grade 2 (Hgb < 10-8 g/dL)	Hgb < 10-9 g/dL	• Continue dosing at current dose level and treat with appropriate supportive care as medically indicated
	Hgb < 9-8 g/dL	• **Subsequent occurrence following dose reduction for anemia:** o Continue pamiparib without interruption with appropriate supportive care based on clinical assessment OR o Hold pamiparib and treat as medically indicated to get Hgb to ≥ 9 g/dL, then restart at reduced dose level OR o Hold pamiparib and treat as medically indicated to get Hgb to ≥ 9 g/dL, then ↓ pamiparib by 1 additional dose level to 20 mg BID
Grade 3 (Hgb < 8 g/dL)		• **Subsequent occurrence following dose reduction for anemia:** o Continue pamiparib without interruption with appropriate supportive care based on clinical assessment OR o Hold pamiparib and treat as medically indicated to get Hgb to ≥ 9 g/dL, then restart at reduced dose level OR o Hold pamiparib and treat as medically indicated to get Hgb to ≥ 9 g/dL, then ↓ pamiparib by 1 additional dose level to 20 mg BID
Grade 4 (life-threatening consequences; urgent intervention indicated)		• **Second occurrence following dose reduction for anemia:** o Hold pamiparib and treat as medically indicated to get Hgb to ≥ 9 g/dL, then ↓ pamiparib by 1 additional dose level to 20 mg BID • **Third occurrence following 2 dose reductions for anemia:** o Discontinue pamiparib if anemia is not caused by any other confounding event, eg, GI hemorrhage. o Hold pamiparib and treat as medically indicated to get Hgb to ≥ 9 g/dL, then restart at reduced dose level.

Toxicity	Recommended Dose Modification [a]
Note: 1) Weekly hematology test should be done for the first 3 cycles during the study. For all Grade 2 or higher anemia, hematology test should be done weekly thereafter until adequate recovery. 2) For any patients showing Hgb dropping > 2 g/dL especially within a short time without alternative explanation such as gastrointestinal bleeding, ↓ pamiparib by 1 dose level should be considered. 3) Dose increase can be considered in certain cases, depending on approval from the medical monitor, provided Hgb has been maintained above 9 g/dL for at least 3 months.	
Neutropenia (ANC)	
Grade 3 (ANC < 1.0 - 0.5 × 10^9/L)	Hold pamiparib until resolved to Grade ⩽ 2 or baseline • If resolved ≤ 7 days, then maintain dose levels • If resolved > 7 days, then ↓ pamiparib by 1 dose level
Grade 4 (ANC <0.5 × 10^9/L)	Hold pamiparib until resolved to Grade ⩽ 1 or baseline and ↓ pamiparib by 1 dose level
Febrile neutropenia (ANC < 1.0 × 10^9/L with single temperature of > 38.3°C or sustained temperature of ⩾ 38°C for > 1 hour)	Hold pamiparib until resolved and ↓ pamiparib by 1 dose level
Thrombocytopenia (PLT)	
Grade 3 (PLT < 50 - 25 × 10^9/L)	Hold pamiparib until resolved to Grade ⩽ 1 or baseline and ↓ pamiparib by 1 dose level
Grade 4 (PLT < 25 × 10^9/L)	Hold pamiparib until resolved to Grade ⩽ 1 or baseline and ↓ pamiparib by 1 dose level
Renal	
Estimated glomerular filtration rate (MDRD STUDY EQ; www.mdrd.com or Appendix 9)	
If ≥ 60 mL/min/1.73 m^2 at baseline: < 30 to 15 mL/min/1.73 m^2 or If < 60 mL/min/1.73 m^2 at baseline: ⩾ 50% reduction from baseline	Hold pamiparib until resolved to ⩾ 60 mL/min/1.73 m^2 • If resolved ≤ 7 days, then maintain dose levels • If resolved > 7 days, then ↓ pamiparib by 1 dose level
Regardless of baseline: < 15 mL/min/1.73 m^2	Permanently discontinue pamiparib
Hepatic	
Bilirubin	
Grade 2 (> 1.5 - 3.0 × ULN) *Only applies to patients with normal bilirubin at baseline*	Hold pamiparib until resolved to Grade ⩽ 1 or baseline • If resolved ≤ 7 days, then maintain dose levels • If resolved > 7 days, then ↓ pamiparib by 1 dose level

Toxicity	Recommended Dose Modification [a]
Grade 3 (> 3.0 - 10.0 × ULN)	Hold pamiparib until resolved to Grade ⩽ 1 or baseline • If resolved ≤ 7 days, then maintain dose levels If resolved > 7 days, then ↓ pamiparib by 1 dose level
Grade 4 (> 10.0 × ULN)	Permanently discontinue pamiparib Note: If Grade 3 or 4 hyperbilirubinemia is due to the indirect (unconjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (eg, review of peripheral blood smear and haptoglobin determination), then ↓ pamiparib by 1 dose level and continue treatment at the discretion of the investigator in discussion with the medical monitor
Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT)	
Grade 3 (> 5 and ⩽ 20 × ULN)	Hold pamiparib until AST and/or ALT resolved to ⩽ 5 × ULN or baseline • If not resolved within 7 days to ≤ 5 × ULN*, then pamiparib should be decreased by 1 dose level • If second episode, permanently discontinue pamiparib *if other etiologies have been reasonably excluded and not solely based on abnormality/increase of AST/ALT laboratory results
Grade 4 (> 20 × ULN)	Permanently discontinue pamiparib
Pancreatic	
Pancreatitis	
Grade 3 or 4	Permanently discontinue pamiparib
Cardiac	
Cardiac - Prolonged QTc interval	
QTcF > 500 msec or Change in QTc interval > 60 msec from the highest value at baseline or predose	• Obtain triplicate electrocardiograms (2 to 3 minutes apart) ~1 hour after initial electrocardiogram • If mean QTcF > 500 ms or mean change in QTc interval > 60 msec, hold pamiparib until evaluation of electrocardiograms by cardiologist o Cardiology evaluation as soon as practical but within 7 days of initial abnormal electrocardiogram If mean QTcF > 500 ms or mean change in QTc interval > 60 msec is confirmed by cardiologist, permanently discontinue pamiparib
Cardiac – General	
Grade 3	Hold pamiparib until resolved to Grade ⩽1 or baseline and ↓ pamiparib by 1 dose level • In the event of acute coronary syndrome, congestive heart failure and myocardial infarction, treatment should be permanently discontinued
Grade 4	Permanently discontinue pamiparib

Toxicity	Recommended Dose Modification [a]
Other AEs	
Grade 3	Hold pamiparib until resolved to Grade ⩽1 or baseline and ↓ pamiparib by 1 dose level No dose reduction required for asymptomatic laboratory abnormalities
Grade 4	Permanently discontinue pamiparib

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BID = twice daily; Hgb = hemoglobin; MDRD = Modification of Diet in Renal Disease; PLT = platelet (count); QTc = QT interval corrected for heart rate; QTcF = QT interval corrected for heart rate using Fridericia's formula; ULN = upper limit of normal.

a. Dosing of pamiparib can be withheld for up to 28 days consecutively (up to 56 days consecutively for investigational drug-related anemia).

7 CONCOMITANT MEDICATIONS AND OTHER RESTRICTIONS

7.1 Concomitant Medications

All concomitant medications, including all prescription and over-the-counter drugs, supplements, and intravenous medications and fluids, taken by or administered to the patient within 28 days before Day 1 should be recorded in the source documents and eCRF.

The PI will instruct the patient to notify the study site about any new medical treatment taken during the Extension Phase.

7.1.1 Core Phase

Patients will refrain from use of any prescription or nonprescription medications/products during the study through the EOT Visit, unless the investigator and/or sponsor have given their prior consent.

Acetaminophen (2 g/day for up to 3 consecutive days) is an acceptable concomitant medication. Acetaminophen can be taken as specified above at any time relative to the administration of study drug. The administration of any other concomitant medications during the study is prohibited without prior approval of the investigator, unless its use is deemed necessary in a medical emergency. Any medication taken by a subject during the course of the study and the reason for its use will be documented in the source data.

7.1.1.1 Diet

While confined at the study site, patients will receive a standardized diet at scheduled times that do not conflict with other study-related activities.

Foods and beverages containing poppy seeds, grapefruit, or Seville oranges will not be allowed from 72 hours prior to Check-in (Day -1) until discharge on Day 12 (Part A) and Day 9 (Part B).

Caffeine-containing foods and beverages will not be allowed from 72 hours prior to Check-in (Day -1) until discharge on Day 12 in Part A and Day 9 in Part B.

Consumption of alcohol will not be permitted from 72 hours prior to Check-in (Day -1) until discharge on Day 12 (Part A) and Day 9 (Part B), and alcohol intake will be limited to a maximum of 2 units/day on all other days while patients are not in the CRU, from Screening through the EOT Visit (end of Core Phase).

On days 3 to 9 and 11, patients should be given rifampin in the fasted state (at least 2 hours); patients should continue to fast for 1h postdose.

On Days 3 to 6 and 8, patients should be given itraconazole 30 minutes after a meal.

7.1.1.2 Smoking

Use of tobacco- or nicotine-containing products will not be permitted from Screening until the EOT Visit (end of Core Phase).

7.1.1.3 Exercise

Patients are required to refrain from strenuous exercise from 72 hours before Check-in (Day -1) until the EOT Visit (end of Core Phase) and will otherwise maintain their normal level of physical activity during this time (ie, will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

7.1.1.4 Blood Donation

Patients are required to refrain from donation of blood from 56 days prior to Screening, plasma from 30 days prior to Screening, or platelets from 6 weeks prior to Screening until 3 months after the EOT Visit (end of Core Phase).

7.1.2 Extension Phase

Supportive therapy considered necessary for the patients' welfare may be given at the discretion of the PI. This includes, but is not limited to analgesics, anticonvulsants, anti-emetics, antidiarrheal treatment, laxatives, opiates, and transfusion of blood products.

7.1.2.1 Prohibited Medications

Patients are not allowed to receive other anticancer therapy, including surgery; radiation therapy; immunotherapy; investigational agents; cytotoxic, biologic, or hormone therapy; anticancer Chinese medicine; or herbal remedies ≤ 14 days (or ≤ 5 half-lives, if applicable) before Day 1 of the Core Phase and during the study, including the Extension Phase. Hormone replacement therapy use is allowed during the Extension Phase.

Use of bisphosphonate and denosumab is permitted if the patient had already been receiving it at a stable dose > 28 days before Day 1.

The primary metabolic pathway for pamiparib involves the CYP3A isoform. Administration of strong/moderate inhibitors of CYP3A or strong CYP3A inducers is not allowed during the Core and Extension Phase.

Please refer to the drugs/substances listed in Appendix 6 and to http://medicine.iupui.edu/clinpharm/ddis/main-table/ for a more complete list of medications that are not allowed. Consumption of grapefruit and Seville oranges or their juices are not allowed throughout the study. No other dietary restrictions will apply.

7.1.2.2 Medications to Be Used with Caution (Core and Extension Phases)

Based on preliminary in vitro screening assays, pamiparib is not a strong inhibitor of other human CYP isoenzymes tested. It is a moderate inhibitor of CYP2C9 (IC_{50} = 6.48 μM). Investigators need to be aware that pamiparib has the potential to interfere with the appropriate metabolism of medications that rely on CYP2C9 and follow the prescribing information recommendations for use with CYP2C9 inhibitors. Therefore, careful monitoring should be used when co-prescribing CYP2C9 substrates with a narrow therapeutic index, such as phenytoin and warfarin.

Examples of these medications are listed in Appendix 6 and these should be used cautiously with drug concentration monitoring where appropriate.

In addition to CYP3A, pamiparib can also be metabolized by [redacted] in human liver microsomes, but to a lesser extent. See Appendix 6 for medications that should be used with caution for that reason.

7.2 Contraception

Please refer to Appendix 4.

8 STUDY ASSESSMENTS AND PROCEDURES

Every effort will be made to schedule and perform the procedures as closely as possible to the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same timepoint.

The order of priority for scheduling procedures around a timepoint is (in descending order of priority):

- dosing
- blood samples
- any other procedures (ECGs will be scheduled before vital sign measurements)

8.1 Pharmacokinetic Assessments (Core Phase ONLY)

8.1.1 Pharmacokinetic Blood Sample Collection and Processing

Blood samples (approximately 1 x 2 mL for pamiparib) will be collected by venipuncture or cannulation at the times indicated in the Schedule of Assessments in Appendix 1. Procedures for collection, processing, and shipping of PK blood samples will be detailed in the laboratory manual. Plasma samples remaining after bioanalysis of pamiparib may be used to qualitatively or quantitatively characterize any metabolites of pamiparib.

8.1.2 Analytical Methodology

Plasma concentrations of pamiparib will be determined using a validated analytical procedure. Specifics of the analytical method will be provided in a separate document.

8.2 Safety and Tolerability Assessments (Core and Extension Phases)

8.2.1 Adverse Events

Adverse event definitions, assignment of severity and causality, and procedures for reporting SAEs are detailed in Section 9. The condition of each patient will be monitored from the time of signing the Informed Consent Form (ICF) to the end of the study. Patients will be observed for any signs or symptoms and asked about their condition by open questioning, such as “How have you been feeling since you were last asked?” at least once each day while a resident at the study site and at each study visit. Patients will also be encouraged to spontaneously report AEs occurring at any other time during the study. Any AEs, SAEs, and remedial action required will be recorded in the patient’s source data. The nature, time of onset, duration, and severity will be documented, together with a PI’s (or designee’s) opinion of the relationship to study drug. Adverse events recorded during the course of the study will be followed-up, where possible, until resolution. This will be completed at the PI’s (or designee’s) discretion.

8.2.2 Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations (including clinical chemistry, hematology, urinalysis, and serology) at the times indicated in the Schedule of Assessments in Appendix 1. Clinical laboratory evaluations are listed in Appendix 7. Blood volume required is listed in Appendix 8.

Patients will be asked to provide urine samples for a drugs of abuse screen and undergo an alcohol breath test at the times indicated in the Schedule of Assessments in Appendix 1. For all female subjects, a pregnancy test will be performed at the times indicated in the Schedule of Assessments in Appendix 1.

The Investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

8.2.3 Vital Signs

Supine blood pressure, supine pulse rate, respiratory rate, and body temperature will be assessed at the times indicated in the Schedule of Assessments in Appendix 1. Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

All measurements will be performed singly and repeated once if outside the relevant clinical reference range.

Patients must be supine for at least 5 minutes before blood pressure, heart rate, and temperature measurements. During the in-house period of the Core Phase, blood pressure, heart rate, and temperature measurements should be conducted in the morning. When scheduled at the same time, vital sign assessments are to be performed prior to PK blood draws, with blood draws to occur as close to the nominal times as possible except for Screening and Day -1.

8.2.4 12-Lead Electrocardiogram

Resting 12-lead ECGs will be recorded after the patient has been supine and at rest for at least 5 minutes at the times indicated in the Schedule of Assessments in Appendix 1.

Single 12-lead ECGs will be repeated once if either of the following criteria apply postdose:

- QTcF > 500 msec
- QTcF change from the baseline (predose) is > 60 msec

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required. The investigator (or designee) will perform a clinical assessment of each 12-lead ECG. When numerous assessments are scheduled at the same time, ECGs are to be performed prior to vital sign assessments and PK blood draws, with PK blood draws to occur as close to the nominal times as possible except for Screening and Day -1.

8.2.5 Physical Examination

Complete and limited physical examinations will be performed at the timepoints specified in the Schedule of Assessments in Appendix 1. A complete physical examination includes a review of the following systems: head/neck/thyroid; eyes/ears/nose/throat; respiratory; cardiovascular; lymph nodes; abdomen; skin; musculoskeletal; and neurological. A limited physical examination includes an assessment of the patient's general appearance, skin, thorax/lungs, cardiovascular, and abdomen.

8.2.6 Tumor Assessments

Tumor imaging (CT or magnetic resonance imaging [MRI], with preference for CT) will be performed at Screening and every 8 weeks (± 7 days) or as per standard of care. At the PI's discretion, CT or MRI scans may be repeated at any time if disease progression (PD) is suspected. The same imaging technique should be used for each patient throughout the study.

8.3 End-of-Treatment Visit

EOT Visit should occur within 7 days after the last dose of rifampin/itraconazole (Core Phase) or pamiparib (Extension Phase). Required assessments are listed in Appendix 1. A visit should be scheduled as soon as possible, but the EOT Visit may occur later after discussion with the medical monitor for specific circumstances, such as prolonged hospitalization. During the Extension Phase, the visit at which tumor assessments showed PD may be used as the EOT visit providing all required assessments were performed. Tumor assessments do not have to be repeated if they were performed within 14 days of the EOT visit, or at a prior response evaluation that documented PD. An ECG does not have to be repeated if it was performed within 14 days of the EOT visit.

8.4 Safety Follow-up Visit/Call

The Safety Follow-Up visit will occur 30 days (±7 days) after the last dose of study drug or before initiation of new anticancer therapy, whichever occurs first. The Safety Follow-up in the Core Phase is only to be conducted if the patient does not continue to the Extension Phase. If new anticancer therapy is inadvertently initiated before the Safety Follow-up Visit, (eg, without the knowledge of the study center team), a Safety Follow-up Visit should be scheduled as soon as possible. For patients who do not want to or cannot return to the clinic for the Safety Follow-up Visit, the patient should be contacted by telephone for a review of AEs. If these attempts of contact are unsuccessful, the additional attempts detailed in Section 9.1.4 should be made.

9 SAFETY MONITORING AND REPORTING

The investigator is responsible for the monitoring and documentation of events that meet the criteria and definition of an AE or SAE as provided in this protocol.

9.1 Adverse Events

9.1.1 Definition and Reporting of an Adverse Event

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study drug, whether considered related to study drug or not.

Examples of AEs include:

- Worsening of a chronic or intermittent pre-existing condition including an increase in severity, frequency, duration, and/or has an association with a significantly worse outcome
- New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concurrent medication (overdose per se should not be reported as an AE or SAE)

When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory results, and diagnostics reports) relative to the AE or SAE. The investigator will then record all relevant information regarding an AE or SAE in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by the sponsor. In this instance, all patient identifiers will be blinded on the copies of the medical records prior to submission to the sponsor.

9.1.2 Assessment of Severity

The investigator will assess the severity for each AE and SAE reported during the study. AEs and SAEs should be assessed and graded based upon the NCI-CTCAE v5.0.

Toxicities that are not specified in the NCI-CTCAE will be defined as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living

- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Note: The terms "severe" and "serious" are not synonymous. Severity is a measure of intensity (for example, grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life-threatening [Grade 4]), whereas seriousness is classified by the criteria based on the regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities as described in Section 9.2.

9.1.3 Assessment of Causality

The investigator is obligated to assess the relationship between pamiparib and the occurrence of each AE or SAE using best clinical judgment. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, and other risk factors, and the temporal relationship of the AE or SAE to pamiparib will be considered and investigated. The investigator should consult the Pamiparib Investigator's Brochure in the determination of his/her assessment. There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always provides an assessment of causality for every SAE before transmission of the SAE report/eCRF to the sponsor because the causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator may change his/her opinion of causality based on follow-up information, amending the SAE report/eCRF accordingly.

The causality of each AE should be assessed and classified by the investigator as "related" or "not related." An AE is considered related if there is at least "a reasonable possibility" that the AE may have been caused by pamiparib (ie, there are facts, evidence, or arguments to suggest possible causation, or a causal relationship between the AE and the drug cannot be ruled out). A number of factors should be considered in making this assessment, including:

- Temporal relationship of the AE to the administration of pamiparib/study procedure
- Whether an alternative etiology has been identified
- Mechanism of action of pamiparib
- Biologic plausibility
- An AE should be considered "related" to pamiparib if any of the following are met, otherwise the event should be assessed as "not related":
    - There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out
    - There is evidence to suggest a causal relationship, and the influence of other factors is unlikely
    - There is some evidence to suggest a causal relationship (eg, the AE occurred within a reasonable time after administration of pamiparib). However, the

influence of other factors may have contributed to the AE (eg, the patient's clinical condition or other concomitant AEs).

- A causal relationship between the AE and the study drug cannot be ruled out

9.1.4 Follow-Up of Adverse Events

After the initial AE or SAE report, the investigator is required to proactively follow each patient and provide further information to the sponsor on the patient's condition.

All AEs and SAEs documented at a previous visit/contact and designated as ongoing will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution, the condition stabilizes or is considered chronic, the AE or SAE is otherwise explained, the patient is lost to follow-up, or the patient withdraws consent. Once resolved, the appropriate AE or SAE eCRF page(s) will be updated. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathologic examinations, or consultation with other health care professionals.

The sponsor may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. If a patient dies during participation in the study or during a recognized follow-up period, the sponsor will be provided with a copy of any postmortem findings, including histopathology, if conducted.

New or updated information will be recorded on the originally completed SAE report/eCRF, with all changes SAE form changes signed and dated by the investigator. The updated SAE follow-up report/eCRF should be re-sent to the sponsor within the time frames outlined in Section 9.5.1.

If a patient is lost to follow-up, study center personnel must do their utmost to re-establish contact with the patient. All measures taken to follow up with the patient should be recorded.

Should attempts to contact the patient by telephone be unsuccessful, the following additional attempts should be made to obtain protocol-required follow-up information. The patient should be contacted by mail in a manner that provides proof of receipt by the patient. If unsuccessful, other contacts should be explored, such as referring physicians or relatives. Attempts of contact should be documented in the patient's source documents. If a patient cannot be contacted despite all attempts, the patient will be considered lost to follow-up, and death information should be obtained through a public record search if local agencies permit.

9.1.5 Laboratory Test Abnormalities

Abnormal laboratory findings (eg, chemistry, hematology, or coagulation) or other abnormal assessments (eg, ECGs, x-rays, or vital signs) that are judged by the investigator as clinically

significant will be recorded as AEs or SAEs. This includes clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen during the study. The definition of clinically significant is entrusted to the judgment of the investigator. In general, these are the abnormalities that:

- Are associated with clinical signs or symptoms, or
- Require active medical intervention, or
- Lead to dose interruption or discontinuation, or
- Require close observation, more frequent follow-up assessments, or
- Further diagnostic investigation

9.2 Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

  Note: The term "life-threatening" in the definition of "serious" refers to an AE in which the patient was at risk of death at the time of the AE. It does not refer to an AE that hypothetically might have caused death if it were more severe.
- Requires hospitalization or prolongation of existing hospitalization

Note: In general, hospitalization signifies that the patient was admitted (usually involving at least an overnight stay) to the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the AE is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

- Results in disability/incapacity

Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect
- Is considered a significant medical AE by the investigator based on medical judgment (eg, may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

  The following are NOT considered SAEs:

  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from

baseline

- Hospitalization for social/convenience considerations
- Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience

9.3 Timing, Frequency, and Method of Capturing Adverse Events and Serious Adverse Events

9.3.1 Adverse Event Reporting Period

After the ICF has been signed but prior to the administration of the study drug, only SAEs should be reported to the sponsor.

After initiation of study drug, all AEs and SAEs, regardless of relationship to pamiparib or placebo, will be reported until 30 days after the last dose of study drug or initiation of new anticancer therapy, whichever occurs first. After this period, the investigator should report any SAEs that are believed to be related to prior study treatment.

After a patient is discontinued from the study, investigators are not obligated to actively seek AEs or SAEs from the former patient. However, if the investigator learns of any SAE, including a death, at any time, and considers the SAE related to pamiparib, the investigator will notify the sponsor.

9.3.2 Eliciting Adverse Events

The investigator or designee will ask patients about AEs by asking the following standard questions:

- How are you feeling?
- Have you had any medical problems since your last visit?
- Have you taken any new medicines since your last visit?

9.4 Study-Specific Adverse Event and Serious Adverse Event Reporting Instructions

9.4.1 Disease Progression

"Disease progression" (including fatal disease progression), which is expected in this study population and measured as an efficacy endpoint, should not be reported as an event term. Instead, the symptoms, signs, or clinical sequelae that result from disease progression should be reported as the event terms.

For example, a patient presents with pleural effusion resulting from disease progression of metastasis to lungs. The event term should be reported as "pleural effusion" instead of disease progression. If a patient experienced a fatal multiorgan failure due to disease progression, the term "multiorgan failure" should be reported as the SAE with death as outcome instead of reporting "fatal disease progression" or "death due to disease progression".

9.4.2 Death

Death is an outcome and not usually considered an event. If the only information available is death and the cause of death is unknown, then the death **is reported as an event, eg, "death," "death of unknown cause," or "death unexplained."**

9.5 Prompt Reporting of Serious Adverse Events

9.5.1 Timeframes for Submitting Serious Adverse Events

If serious adverse events are identified by or reported to the investigator or study team, the SAEs will be reported within 24 hours of first knowledge of the SAEs to the sponsor or designee as described in Table 3 once the investigator determines that the AE meets the protocol definition of an SAE.

Table 3: Timeframes and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

Type of SAE	Initial SAE Report	Document	Follow-up SAE and AE of Special Interest Report	Reporting Method
All SAEs	Within 24 hours of first knowledge of the SAE	SAE report	As expeditiously as possible	Email or fax SAE form or Pregnancy form

Abbreviations: AE = adverse event; SAE = serious adverse event.

9.5.2 Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a patient, he/she will report the information to the sponsor within 24 hours as outlined in Section 9.5.1. The SAE report will always be completed as thoroughly as possible with all available details of the SAE and forwarded to the sponsor or designee within the designated timeframes. The paper SAE form, signed by the investigator, should be scanned and faxed and/or e-mailed to IQVIA. The original SAE form should then be filed appropriately, along with proof of reporting.

If the investigator does not have all information regarding an SAE, he/she is not to wait to receive additional information before notifying the sponsor or designee of the SAE and completing the form. The form will be updated when additional information is received.

The investigator will always provide an assessment of causality at the time of the initial report as described in Section 9.1.3.

The sponsor will provide contact information for SAE receipt.

9.5.3 Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all SAEs to the sponsor in accordance with the procedures detailed in Section 9.5.2. The sponsor has a legal responsibility to notify, as appropriate, both the

local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the IRB/IEC.

All suspected unexpected serious adverse reactions (as defined in Section 9.6) will be submitted to all applicable regulatory authorities and investigators for pamiparib studies.

When a study center receives an initial or follow-up safety report or other safety information (eg, revised IB) from the sponsor, the investigator or designated responsible person is required to promptly notify his/her IRB or IEC. The investigator should place copies of safety reports from the sponsor in the Investigator Site File.

9.6 Suspected Unexpected Serious Adverse Reactions and Expedited Reporting

A suspected unexpected serious adverse reaction is a serious adverse reaction that is both unexpected (ie, not present in the product's Reference Safety Information in the IB) and assessed as related to pamiparib either by the investigator or the sponsor. The sponsor will promptly assess the expectedness for all SAEs against the list of expected serious adverse reactions in the Reference Safety Information and expeditiously submit suspected unexpected serious adverse reactions to regulatory authorities, investigators, IRBs, and IECs based on applicable legislation.

9.7 Pregnancy Reporting

If a female patient or the partner of a male patient becomes pregnant while receiving study drug or within 6 months after completion of the last dose of study drug, a pregnancy report form is required to be completed and expeditiously submitted to the sponsor to facilitate outcome follow-up. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

An abortion, whether accidental, therapeutic, or spontaneous, should be always reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a patient exposed to study drug should be recorded and reported as an SAE.

10 DATA HANDLING AND QUALITY ASSURANCE

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures, working practice documents, and applicable regulations and guidelines. Study center audits may be made periodically by the sponsor's or the contract research organization's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

10.1 Data Collection

Data will be entered into the eCRFs in an electronic data capture (EDC) system.

Data collection on the eCRF must follow the instructions described in the eCRF completion guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee must sign the completed casebooks to attest to its accuracy, authenticity, and completeness.

Data contained in the eCRFs are the sole property of BeiGene and should not be made available in any form to third parties without written permission from BeiGene, except for authorized representatives of BeiGene or appropriate regulatory authorities.

10.2 Data Management/Coding

All final patient data, both eCRF and external data (eg, laboratory data), collected according to the protocol, will be stored at BeiGene at the end of the study.

Standard procedures (including following data review guidelines, computerized validation to produce queries, and maintenance of an audit file, which includes all database modifications) will be followed to support accurate data collection. Data will be reviewed for outliers, logic, data inconsistencies, and completeness.

During the course of the study, a study monitor will make study center visits to review protocol compliance, compare eCRFs against individual patient's medical records, and ensure that the study is being conducted according to pertinent regulatory requirements.

eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained. Checking the eCRFs for completeness, clarity, and cross checking with source documents is required to monitor the progress of the study. Direct access to source data is also required for inspections and audits, and will be carried out giving due consideration to data protection and medical confidentiality.

The monitor will review the eCRFs and evaluate them for completeness and consistency. The eCRF will be compared with the source documents to ensure that there are no discrepancies between critical data. All entries, corrections, and alterations are to be made by the responsible investigator or his/her designee. The monitor cannot enter data in the eCRFs. Once clinical data have been entered into the eCRF, any corrections or alterations to the data fields will be traceable

via an audit trail, meaning that the reason for change, the name of the person who performed the change, together with time and date will be logged. Roles and rights of the study center personnel responsible for entering the clinical data into the eCRF will be determined in advance. If additional corrections are needed, the responsible monitor or data manager will raise a query in the EDC application. The appropriate study center personnel will respond to any queries raised.

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the investigator or hospital that relate to the subject's medical history, that verify the existence of the subject, the inclusion and exclusion criteria, and all records covering the subject's participation in the study. They include laboratory notes, ECG results, memoranda, pharmacy dispensing records, subject files, etc.

The investigator is responsible for maintaining source documents. These will be made available for inspection by the study monitor at each monitoring visit. The investigator must submit a completed eCRF for each subject who receives the study drug, regardless of the duration. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and subject number. Any personal information, including subject name, should be removed or rendered illegible to preserve individual confidentiality.

The eCRF records will be automatically appended with the identification of the creator by means of their unique User ID. Specified records will be electronically signed by the investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the investigators unique User ID and password; date and time stamps will be added automatically at the time of the electronic signature. If an entry on an eCRF requires change, the correction should be made in accordance with the relevant software procedures. All changes will be fully recorded in a protected audit trail, and a reason for the change will be required.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) Version 20.10 or higher. Concomitant medications will be coded using the World Health Organization Drug Dictionary. Concomitant diseases/medical history will be coded using the MedDRA Version 20.10 or higher.

10.3 Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the sponsor may conduct a quality assurance audit. Regulatory agencies may also conduct a regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to the facilities used for this trial and all relevant documents and to allocate his/her time and the time of his/her personnel to the auditor/inspector to discuss findings and any relevant issues.

11 SAMPLE SIZE AND DATA ANALYSES

11.1 Determination of Sample Size

Approximately 24 patients (approximately 12 in each part) will be enrolled to ensure that 20 patients (10 in each part) complete the study.

The sample size chosen for this study was based on precedent set by other PK studies of similar nature and was not based on power calculations.

11.2 Analysis Populations

11.2.1 Pharmacokinetic Population

The PK population will include all patients who received at least 1 dose of pamiparib and have evaluable PK data. A patient will be excluded from the PK summary statistics and statistical analysis if the patient has an AE of vomiting that occurs at or before 2 x median t_{max}.

11.2.2 Safety Population

The safety population will include all patients who received at least 1 dose of pamiparib.

11.3 Pharmacokinetic Analyses

The plasma PK parameters of pamiparib following pamiparib dosing on Days 1 and 10 in Part A and Days 1 and 7 in Part B will be calculated from pamiparib concentration-time profiles using standard noncompartmental methods. Leftover plasma samples may be analyzed for metabolite(s) of interest.

The primary PK parameters are $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}12}$, C_{max}, t_{max}, $t_{1/2}$, CL/F, and V_z/F for pamiparib. Other PK parameters may be reported but will be regarded as secondary and will not be subject to inferential statistical analysis.

A linear mixed-model analysis will be applied to analyze the log-transformed primary PK parameters ($AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and C_{max}) for each part of the study. The model assumes a fixed effect for treatment and a random effect for patient.

Estimates of geometric mean ratios together with the corresponding 90% confidence intervals will be derived for the comparisons of the PK parameters as follows:

- Part A: pamiparib plus rifampin (test) versus pamiparib alone (reference)
- Part B: pamiparib plus itraconazole (test) versus pamiparib alone (reference)

11.4 Safety Analysis

All AEs will be listed and summarized using descriptive methodology. The incidence of AEs for each treatment will be presented by severity and by association with the study drugs, as determined by the investigator. Each AE will be coded using MedDRA. Observed values for clinical laboratory evaluations data, 12-lead ECGs, and vital signs will be listed and summarized descriptively.

12 REGULATORY, ETHICAL AND STUDY OVERSIGHT CONSIDERATIONS

12.1 Regulatory Authority Approval

The sponsor will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements or file the protocol to appropriate regulatory agency before the study is initiated at a study center in that country.

12.2 Investigator Responsibilities

12.2.1 Regulatory and Ethical Considerations

This study will be conducted by the principal investigator and the study center in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable International Conference on Harmonisation (ICH) GCP Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, and other relevant documents must be submitted to an Ethics Committee (EC) by the PI and reviewed and approved by the EC, and also approved by the regulatory authority (as applicable by local law and regulation), before the study is initiated.

Any substantial protocol amendments, likely to affect the safety of the patients or the conduct of the study, will require EC and regulatory authority (as locally required) approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients or any non-substantial changes, as defined by regulatory requirements.

The PI will be responsible for the following:

- Providing written summaries of the status of the study to the EC annually or more frequently in accordance with the requirements, policies, and procedures established by the EC
- Notifying the EC of SAEs or other significant safety findings as required by EC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

The study will additionally be approved by the Administration of Radioactive Substances Advisory Committee.

12.3 Informed Consent

Prior to starting participation in the study, each patient will be provided with a study-specific ICF giving details of the study drugs, procedures, and potential risks of the study. Patients will be instructed that they are free to obtain further information from the PI (or designee) and that their participation is voluntary, and they are free to withdraw from the study at any time. Patients will be given an opportunity to ask questions about the study prior to providing consent for participation.

Following discussion of the study with CRU personnel, patients will sign 3 copies of the ICF in the presence of a suitably trained member of staff to indicate that they are freely giving their informed consent. One copy will be given to the patient, one placed in the site file, and the other will be maintained in the patient's records.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

12.4 Confidentiality

Information on maintaining patient confidentiality in accordance to individual local and national patient privacy regulations must be provided to each patient as part of the informed consent process, either as part of the ICF or as a separate signed document (for example, in the US, a study-center specific HIPAA consent may be used). The investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only patient initials, date of birth, and an identification code (ie, not names) should be recorded on any form or biological sample submitted to the sponsor, IRB, or laboratory. The investigator must keep a screening log showing codes, names, and addresses for all patients screened and for all patients enrolled in the study.

The investigator agrees that all information received from BeiGene, including but not limited to the IB, this protocol, eCRFs, the Investigational New Drug (IND), and any other study information, remain the sole and exclusive property of BeiGene during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from BeiGene. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

If a written contract for the conduct of the study includes confidentiality provisions inconsistent with this section is executed, that contract's provisions shall apply to the extent they are inconsistent with this section.

12.5 Inspections

The investigator should understand that the facilities used for this trial and all source documents for this study should be made available to appropriately qualified personnel from BeiGene or its representatives, to IRBs/IECs, or to regulatory authority or health authority inspectors.

12.6 Protocol Adherence

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol. Investigators assert they will apply due diligence to avoid protocol deviations and shall report all protocol deviations to sponsor.

12.7 Patient Data Protection

Patients will be assigned a unique identifier and will not be identified by name in eCRFs, study-related forms, study reports, or any related publications. Patient and PI personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a public registry, all identifiable information from individual patients or PI will be redacted according to applicable laws and regulations.

The patient must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient. The patient must also be informed that their study-related data may be examined by sponsor or Contract Research Organization (CRO) auditors or other authorized personnel appointed by the sponsor, by appropriate EC members, and by inspectors from regulatory authorities.

12.8 Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential. The PI (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor.

12.9 Data Quality Assurance

The following data quality steps will be implemented:

- All patient data relating to the study will be recorded on eCRFs unless directly transmitted to the Sponsor or designee electronically (eg, laboratory data). The PI is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The PI must maintain accurate documentation (source data) that supports the information entered in the eCRF.

- The PI must permit study-related monitoring, audits, EC review, and regulatory agency inspections and provide direct access to source data documents.
- CRO is responsible for the data management of this study including quality checking of the data. Predefined, agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in a Data Management Plan.
- A study monitor will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable rom source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the PI in the study site archive for at least 25 years after the end of the study unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

12.10 Principal Investigator Documentation Responsibilities

All individual, patient-specific study data will also be entered into a 21 CFR Part 11-compliant electronic data capture (EDC) system on an eCRF in a timely fashion.

All data generated from external sources (eg, laboratory and bioanalytical data), and transmitted to the sponsor or designee electronically, will be integrated with the patient's eCRF data in accordance with the Data Management Plan. EDC data will be transmitted to the sponsor at the end of the study as well.

An eCRF must be completed for each patient who signs an ICF, undergoes screening procedures, and is not a screen failure in accordance with the eCRF completion instructions. The Sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data.

The PI will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff. The PI will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the PI reviewed and approved the data on the eCRF, data queries, and site notifications.

12.11 Sponsor Responsibilities

12.11.1 Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study patients, may be initiated only by BeiGene. All protocol modifications must be submitted to regulatory authorities and the IRB/IEC together with, if applicable, a revised model ICF in accordance with local requirements. As applicable by local requirements, written documentation of regulatory authorities, IRB/IEC and required study center approval must be obtained by the sponsor before changes can be implemented.

Information on any change in risk and /or change in scope must be provided to patients already actively participating in the study, and they must read, understand and sign each revised ICF confirming his/her willingness to remain in the study.

12.11.2 Use of Information and Publication

A CSR will be prepared and provided to the regulatory agency(ies) of participating countries. BeiGene will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

The results of this study will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry and regulatory guidance, and the need to protect the intellectual property of BeiGene (sponsor), regardless of the outcome of the study. The data generated in this clinical study are the exclusive property of the sponsor and are confidential. For multicenter studies, the first publication or disclosure of study results shall be a complete, joint multicenter publication or disclosure coordinated by the sponsor. Thereafter, any secondary publications will reference the original publication(s). Authorship will be determined by mutual agreement and all authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors Uniform Requirements for Manuscripts or stricter local criteria (International Committee of Medical Journal Editors 2016).

After conclusion of the study and without prior written approval from BeiGene, investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- The results of the study in their entirety have been publicly disclosed by or with the consent of BeiGene in an abstract, manuscript, or presentation form; or
- The study has been completed at all study sites for the earlier of: at least 2 years or the period indicated in the clinical study agreement.
- No such communication, presentation, or publication will include BeiGene's confidential information.

  Each investigator agrees to submit all manuscripts or congress abstracts and

posters/presentations to the sponsor prior to submission in accordance with the clinical study agreement. This allows the sponsors to protect proprietary information, provide comments based on information from other studies that may not yet be available to the investigator, and ensure scientific and clinical accuracy. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this trial will be presented in the investigator's clinical study agreement. Each investigator agrees that, in accordance with the terms of clinical study agreement, a further delay of the publication/presentation may be requested by the sponsor to allow for patent filings and/or protection in advance of the publication/presentation.

12.11.3 Study and Study Center Closure

Upon completion of the study, the monitor will conduct the following activities in conjunction with the investigator or study center personnel, as appropriate:

- Return of all study data to the sponsor
- Data queries
- Accountability, reconciliation, and arrangements for unused study drug(s)
- Review of study records for completeness
- Return of treatment codes to the sponsor
- Shipment of PK samples to assay laboratories

In addition, the sponsor reserves the right to temporarily suspend or prematurely discontinue this study either at a single study center or at all study centers at any time for reasons including, but not limited to, safety or ethical issues or severe noncompliance with this protocol, GCP, the clinical study agreement, or applicable laws and regulations. If the sponsor determines such action is needed, the sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. When feasible, the sponsor will provide advance notification to the investigator of the impending action before it takes effect.

The sponsor will promptly inform all other investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must still be provided to the sponsor. In addition, arrangements will be made for all unused study drug(s) in accordance with the applicable sponsor procedures for the study.

Financial compensation to investigators and/or institutions will be in accordance with the agreement established between the investigator and the sponsor.

12.12 Records Retention and Study Files

12.12.1 Study Files and Retention of Records

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) investigator's study file, and (2) patient clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRF and query forms, IRB/IEC, and governmental approval with correspondence, ICF, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs) would include (although not be limited to) the following: patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, electroencephalogram, X-ray, pathology and special assessment reports, consultant letters, screening and enrollment log, etc.

Following closure of the study, the investigator must maintain all study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (eg, audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and personnel.

The sponsor will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that study center for the study, as dictated by any institutional requirements or local laws or regulations, or the sponsor's standards/procedures; otherwise, the retention period will default to 25 years.

The investigator must notify the sponsor of any changes in the archival arrangements, including, but not limited to, the following: archiving at an off-site facility and transfer of ownership of or responsibility for the records in the event the investigator leaves the study center.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, arrangements must be made between the investigator and BeiGene to store these in secure containers outside of the study center so that they can be returned to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the study center.

Biological samples at the conclusion of this study may be retained as outlined in the agreement with the CRO managing the biological samples, for the shorter of: a period of up to 10 years or as allowed by the site's IRB/IEC.

12.12.2 Provision of Study Results and Information to Investigator

When the CSR is completed, the sponsor will provide the major findings of the study to the investigator.

The sponsor will not routinely inform the investigator or patient of any exploratory biomarker tests results, because the information generated from this study will be preliminary in nature, and the significance and scientific validity of the results will be undetermined at such an early stage of research.

12.13 Information Disclosure and Inventions

All information provided by the sponsor and all data and information generated by the study center as part of the study (other than a patient's medical records) is the sole property of the sponsor.

All rights, title, and interests in any inventions, know-how or other intellectual or industrial property rights that are conceived or reduced to practice by the study center personnel during the course of or as a result of the study are the sole property of the sponsor, and are hereby assigned to the sponsor.

If a written contract for the conduct of the study that includes ownership provisions inconsistent with this statement is executed between the sponsor and the study center, that contract's ownership provisions shall apply rather than this statement.

All information provided by the sponsor and all data and information generated by the study center as part of the study (other than a patient's medical records) will be kept confidential by the investigator and other study center personnel. This information and data will not be used by the investigator or other study center personnel for any purpose other than conducting the study without the prior written consent of the sponsor.

These restrictions do not apply to:

- Information which becomes publicly available through no fault of the investigator or study center personnel
- Information which is necessary to disclose in confidence to an IEC/IRB solely for the evaluation of the study
- Information which is necessary to disclose in order to provide appropriate medical care to a patient
- Study results that may be published as described in Section 12.11.2

If a written contract for the conduct of the study which includes provisions inconsistent with this statement is executed, that contract's provisions shall apply rather than this statement.

12.14 Joint Investigator/Sponsor Responsibilities

12.14.1 Access to Information for Monitoring

In accordance with ICH GCP guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the eCRFs for consistency.

The monitor is responsible for routine review of the CRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries on the eCRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

12.14.2 Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of BeiGene may conduct inspections or audits any time during or after completion of this clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the sponsor or its designee immediately. The investigator agrees to provide to representatives of a regulatory agency or BeiGene access to records, facilities, and personnel for the effective conduct of any inspection or audit.

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14 APPENDICES

Appendix 1: Schedule of Assessments

Schedule of Assessments: Part A

Study Procedures	**Screening**	**Core Phase**					**Safety Follow-up Visit (≤30 days after last dose)** [p]
Day of Phase	**Days -28 to -1**[n]	**Day -1**	**Day 1**	**Days 2 to 11**	**Day 12**	**Core Phase EOT Visit (≤7 days after last dose)**	
Informed consent	X						
Inclusion/exclusion criteria	X						
Confirm eligibility (laboratory values) [a]		X					
Demographic data [b]	X						
Medical history [c]	X						
ECOG Performance Status	X						
Urine drug screen	X	X					
Alcohol breath test	X	X					
Serum pregnancy test/FSH [d]	X (Days -7 to -1)						
Height, BMI [e]	X						
Weight	X	X			X		
Serology (HBV, HCV) [f]	X						
Study residence							
Check-in		X					
Check-out					X [o]		
Non-residential visit						X	
Study drug administration [g]							
Pamiparib Dosing			X	Day 10			
Rifampicin Dosing				Days 3 to 11			
Pharmacokinetics							
Blood samples for pamiparib concentration			X (30 min predose, 0.5, 1, 2, 4, 6, 9, 12, 24, and 48 hours postdose)	Day 10: 30 min predose, 0.5, 1, 2, 4, 6, 9, 12, 24, and 48 hours postdose			

Schedule of Assessments: Part A (Continued)

Study Procedures	Screening	Core Phase					Safety Follow-Up Visit (≤30 days after last dose) [p]
Day of Phase	**Days -28 to -1[n]**	**Day -1**	**Day 1**	**Days 2 to 11**	**Day 12**	**Core Phase EOT Visit (≤7 days after last dose)**	
Safety and tolerability							
Adverse event recording	X	X	X	X	X	X	X
Prior/concomitant medication recording	X	X	X	X	X	X	X
Clinical chemistry, hematology and urinalysis [h]	X	X			X	X	X
Vital signs [i]	X	X	X (30 min predose and 1, 2, 4, and 24 hours postdose	Day 10: 30 min predose and 1, 2, 4, and 24 hours postdose	X	X	X
12-lead ECG [j]	X		X (30 min predose and 2 hours postdose)	Day 10: 30 min predose and 2 hours postdose	X	X	
Complete physical examination [k]	X	X					
Limited physical examination [l]			X	X (Day 10)	X	X	X
CT or MRI [m]	X						

Abbreviations: BMI = body mass index; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; ECG = electrocardiogram; EOT: end of treatment; FSH = follicle-stimulating hormone; MRI = magnetic resonance imaging; PK = pharmacokinetic; SAE = serious adverse event.

a. Confirmation of eligibility: all laboratory values obtained on Day -1 must meet eligibility criteria.
b. Demographic data: Date of birth, gender, ethnicity, and race must be recorded.
c. Medical History/Current Medical Conditions: General and disease specific medical history including a history of past and current medical conditions.

d. For females of childbearing potential, a highly sensitive serum pregnancy test must be performed at a central or local laboratory within 7 days before Day 1. For subsequent pregnancy testing, highly sensitive urine pregnancy tests, performed at a central or local laboratory, are allowed. If a urine pregnancy test is positive, a confirmatory serum pregnancy test is required.
e. Height will be measured at Screening only for BMI calculation.
f. Serology: hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B Core antibody, and hepatitis C antibody
g. On Day 1 and Day 10, patients are required to fast for at least 8 hours before and 4 hours after pamiparib and rifampin administration. Water is allowed during the fasting period. On Day 10, rifampin will be administered first, followed within 5 minutes by pamiparib. On Days 3-9 and Day patients are required to fast for 2 hours before and 1 hour after rifampin administration.
h. Blood samples for clinical laboratory evaluations (clinical chemistry, hematology, and urinalysis) will be collected after at least an 8-hour fast. If Screening urinalysis and chemistry and hematology laboratory evaluations were performed within 3 days of Day-1, they do not need to be repeated on Day-1.
i. Vital signs include supine blood pressure, supine pulse rate, respiratory rate, and body temperature. Patients are to remain supine for at least 5 minutes prior to blood pressure and pulse rate measurements. When scheduled at the same time, vital sign assessments are to be performed prior to PK blood draws, with blood draws to occur as close to the nominal times as possible except for Screening and Day -1.
j. Patients are to remain supine for at least 5 minutes prior to ECG assessments. When numerous assessments are scheduled at the same time, ECGs are to be performed prior to vital sign assessments and PK blood draws, with PK blood draws to occur as close to the nominal times as possible except for Screening and Day -1.
k. Complete physical examination at Screening and Day -1.
l. Limited physical examination to occur on Days 1, 10 and 12, EOT and Safety Follow-up includes assessment of general appearance and additional examination of symptomatic systems or those affected by the patient's disease.
m. A computed tomography (CT) or MRI scan of the thorax, abdomen, and pelvis plus other relevant evaluations as appropriate will be performed at Screening.
n. All assessments obtained within 3 days of Day -1 do not have to be repeated on Day -1.
o. Check-out takes place on Day 12 after all procedures have been completed.
p. All patients, including those who withdraw early from the study, will have an EOT visit within 7 days after the last dose of rifampicin. Safety Follow-up in the Core Phase is only to be conducted if the patient does not continue to the Extension Phase. All patients who permanently discontinue study drug will have a Safety follow-up approximately 30 days after the last day of study drug or before initiation of new anticancer therapy, whichever occurs first. AEs and SAEs will be collected; clinical laboratory assessment should only be conducted if the patient had an ongoing clinical laboratory abnormality in the previous visit, which the PI considers to be related to study drug. If no laboratory assessments are required, the patient should be contacted by telephone for a review of AEs/concomitant medications and the limited physical exam will not be performed.

Schedule of Assessments: Part B

Study Procedures	**Screening**	**Core Phase**					**Safety Follow-Up Visit (≤30 days after last dose)** [p]
Day of Phase	**Days -28 to -1** [n]	**Day -1**	**Day 1**	**Days 2 to 8**	**Day 9**	**Core Phase EOT Visit (≤7 days after last dose)**	
Informed consent	X						
Inclusion/exclusion criteria	X						
Confirm eligibility (laboratory values) [a]		X					
Demographic data [b]	X						
Medical history [c]	X						
ECOG Performance Status	X						
Urine drug screen	X	X					
Alcohol breath test	X	X					
Serum pregnancy test/ FSH [d]	X (Days -7 to -1)						
Height, BMI [e]	X						
Weight	X	X			X		
Serology (HBV, HCV) [f]	X						
Study residence							
Check-in		X					
Check-out					X[o]		
Non-residential visit						X	
Study drug administration [g]							
Pamiparib Dosing			X	Day 7			
Itraconazole Dosing				Days 3 to 8			
Pharmacokinetics							
Blood samples for pamiparib concentration			X (30 min predose, 0.5, 1, 2, 4, 6, 9, 12, 24, and 48 hours postdose)	Day 7:30 min predose, 0.5, 1, 2, 4, 6, 9, 12, 24, and 48 hours postdose			

Schedule of Assessments: Part B (Continued)

Study Phase	Screening	Core Phase					Safety Follow-Up Visit (≤30 days after last dose) [p]
Day of Phase	Days -28 to -1[n]	Day -1	Day 1	Days 2 to 8	Day 9	Core Phase EOT Visit (≤7 days after last dose)	
Safety and tolerability							
Adverse event recording	X	X	X	X	X	X	X
Prior/concomitant medication recording	X	X	X	X	X	X	X
Clinical chemistry, hematology and urinalysis [h]	X	X			X	X	X
Vital signs [i]	X	X	X (30 min predose and 1, 2, 4, and 24 hours postdose	Day 7: 30 min predose and 1, 2, 4, and 24 hours postdose	X	X	X
12-lead ECG [j]	X		X (30 min predose and 2 hours postdose)	Day 7: 30 min predose and 2 hours postdose	X	X	
Complete physical examination [k]	X	X					
Limited physical examination [l]			X	X (Day 7)	X	X	X
CT or MRI [m]	X						

Abbreviations: BMI = body mass index; CT = computed tomography ECG = electrocardiogram; EOT: end of treatment; FSH = follicle-stimulating hormone; MRI = magnetic resonance imaging; PK = pharmacokinetic; SAE = serious adverse event.

a. Confirmation of eligibility: all laboratory values obtained on Day -1 must meet eligibility criteria.
b. Demographic data: Date of birth, gender, ethnicity, and race must be recorded.
c. Medical History/Current Medical Conditions: General and disease specific medical history including a history of past and current medical conditions.
d. For females of childbearing potential, a highly sensitive serum pregnancy test must be performed at a central or local laboratory within 7 days before Day 1. For subsequent pregnancy testing, highly sensitive urine pregnancy tests, performed at a central or local laboratory, are allowed. If a urine pregnancy test is positive, a confirmatory serum pregnancy test is required.
e. Height will be measured at Screening only for BMI calculation.
f. Serology: hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B Core antibody, and hepatitis C antibody

g. On Day 1 and Day 7, patients are required to fast for at least 8 hours before and 4 hours after pamiparib and itraconazole administration. Water is allowed during the fasting period. Itraconazole will be administered approximately 30 minutes after completing a meal on Days 3 to 6 and 8. On Day 7, itraconazole will be administered first, followed within 5 minutes by pamiparib.
h. Blood samples for clinical laboratory evaluations (clinical chemistry, hematology, and urinalysis) will be collected after at least an 8-hour fast. If Screening urinalysis and chemistry and hematology laboratory evaluations were performed within 3 days of Day-1, they do not need to be repeated on Day-1.
i. Vital signs include supine blood pressure, supine pulse rate, respiratory rate, and body temperature. Patients are to remain supine for at least 5 minutes prior to blood pressure and pulse rate measurements. When scheduled at the same time, vital sign assessments are to be performed prior to PK blood draws, with blood draws to occur as close to the nominal times as possible except for Screening and Day -1.
j. Patients are to remain supine for at least 5 minutes prior to ECG assessments. When numerous assessments are scheduled at the same time, ECGs are to be performed prior to vital sign assessments and PK blood draws, with PK blood draws to occur as close to the nominal times as possible except for Screening and Day -1.
k. Complete physical examination at Screening and Day -1.
l. Limited physical examination to occur on Days 1, 7 and 9, EOT and Safety Follow-up includes assessment of general appearance and additional examination of symptomatic systems or those affected by the patient's disease.
m. A computed tomography (CT) or MRI scan of the thorax, abdomen, and pelvis plus other relevant evaluations as appropriate will be performed at screening
n. All assessments obtained within 3 days of Day -1 do not have to be repeated on Day- 1.
o. Check-out takes place on Day 9 after all procedures have been completed.
p. All patients, including those who withdraw early from the study, will have an EOT visit within 7 days after the last dose of itraconazole. Safety Follow-up visit in the Core Phase is only to be conducted if the patient does not continue to the Extension Phase. All patients who permanently discontinue study drug will have a Safety follow-up approximately 30 days after the last day of study drug or before initiation of new anticancer therapy, whichever occurs first. AEs and SAEs will be collected; clinical laboratory assessment should only be conducted if the patient had an ongoing clinical laboratory abnormality in the previous visit, which the PI considers to be related to study drug. If no laboratory assessments are required, the patient should be contacted by telephone for a review of AEs/concomitant medications and the limited physical exam will not be performed.

Schedule of Assessments Extension Phase

Study Procedures	Predose Visit (≤ 7 days prior to Cycle 1 Day 1) [e]	Cycles 1 and 2		Cycle ≥ 3 [f]	EOT visit [g]	Safety Follow-up Visit (≤30 days after last dose) [h]
		Day 1 [i]	Day 15	Day 1		
Allowed time window (days)		± 2	± 2	± 2		
Body Weight	X	X		X	X	
ECOG performance status		X		X	X	
Urinalysis	X				X	
Vital Signs [a]	X				X	
12-Lead ECG [b]	X				X	
Limited Physical examination [c]	X	X		X	X	X
Clinical chemistry and hematology	X	X	X	X	X	X [j]
Pregnancy test	X	X		X	X	
Pamiparib administration [d]		X (60 mg PO twice daily)				
Tumor assessments (CT or MRI scan)	X (every 8 weeks ± 7 days)					
Adverse event recording	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X

Abbreviations: CT = computed tomography ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT: end of treatment; MRI = magnetic resonance imaging; PO = orally.

a. Vital Signs: Blood pressure, heart rate, and temperature must be measured after the patient has been supine for 5 minutes at Screening and EOT.
b. Single 12-lead ECGs will be repeated once if outside the clinical reference range, or there is other clinically significant finding. Repeat ECGs will be recorded in triplicate at least 2 minutes apart. ECGs will be recorded after the patient has been supine for 5 minutes.
c. Limited physical examination: includes assessment of general appearance and additional examination of symptomatic systems or those affected by the patient's disease. For the follow-up visit, the limited physical examination is only to be done if this visit is conducted while the patient is attending the clinic.
d. Dosing: Pamiparib capsules should be administered continuously from Cycle 1 Day 1 (60 mg twice daily), until patients are discontinued from treatment.
e. Predose visit: Assessments performed in the Core Phase Follow-up visit for Part 1 may be used as the predose visit for the Extension Phase if it occurs ≤ 7days prior to the start of pamiparib treatment in Extension Phase.

f. Cycle 3+:Cycles will continue as long as the patient is experiencing clinical benefit, or until occurrence of progressive disease (PD), unacceptable toxicity, pregnancy, death, withdrawal of consent, lost to follow-up, major protocol violation which in the opinion of the sponsor would have significant impact on the study or its outcome, start of new anticancer therapy, withdrawal by the PI, or study termination by sponsor.
g. End-of-Treatment (EOT) Visit: To occur within 7 days after the last day of study drug administration. A visit should be scheduled as soon as possible, but may occur later after discussion with the medical monitor for specific circumstances, such as prolonged hospitalization. An ECG does not need to occur at the EOT Visit if one was performed within 14 days prior to the visit.
h. Safety Follow-up Visit: To occur approximately 30 days after the last day of study drug administration or before initiation of new anticancer therapy, whichever occurs first. If new anticancer therapy is initiated before this safety follow-up, a safety follow-up should be scheduled as soon as possible. Clinical laboratory evaluations are only required if the patient had an ongoing clinical laboratory abnormality at the previous visit that the principal investigator considered to be related to study drug. For patients who do not want to or cannot return to the clinic for the safety follow-up, the patient should be contacted by telephone for a review of adverse events.
i. Cycle 1 Day 1: Assessments will be conducted prior to first dosing in the Extension Phase.
j. Follow-up assessments: only to be conducted if the patient has an ongoing laboratory abnormality at the previous visit that the PI considers to be related to the study drug.

Appendix 2: The Response Evaluation Criteria In Solid Tumors (RECIST) Guidelines, Version 1.1

The text below was obtained from the following reference: Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228-247 (Eisenhauer et al, 2009).

DEFINITIONS

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (Version 1.1). Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or nonmeasurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Measurable Disease

Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm).
- 10 mm caliper measurement by clinical exam (when superficial).
- 20 mm by chest x-ray (if clearly defined and surrounded by aerated lung).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by computed tomography (CT) scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Nonmeasurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter ≥10 to <15 mm with conventional techniques or <10 mm using spiral CT scan), are considered nonmeasurable disease. Leptomeningeal disease, ascites, pleural, or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques are all nonmeasurable.

Bone lesions:

- Bone scan, positron-emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or magnetic

resonance imaging (MRI) can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are nonmeasurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Trial protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organ, but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. Pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered nontarget lesions. Nodes that have a short axis <10 mm are considered nonpathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline

sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Nontarget Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as nontarget lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present", "absent", or in rare cases "unequivocal progression" (more details to follow). In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the electronic case report form (eCRF) (eg, "multiple enlarged pelvic lymph node" or "multiple liver metastases").

GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and P10 mm diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the trial.

Chest x-ray: Chest CT is preferred over chest x-ray, particularly when progression is an important endpoint, since CT is more sensitive than x-ray, particularly in identifying new lesions. However, lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in CR. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and prostate-specific antigen response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria that are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between partial response (PR) and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease (SD) in order to differentiate between response (or SD) and progressive disease (PD).

RESPONSE CRITERIA

Evaluation of Target Lesions

CR: Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm.

PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

PD: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become "too small to measure": While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure". When this occurs it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially nonreproducible; therefore, providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment: When non-nodal lesions "fragment", the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion".

Evaluation of Nontarget Lesions

While some nontarget lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

CR: Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits.

PD: Unequivocal progression (see comments below) of existing nontarget lesions.

When the patient also has measurable disease: In this setting, to achieve "unequivocal progression" on the basis of the nontarget disease, there must be an overall level of substantial worsening in nontarget disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more nontarget lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in nontarget disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only nonmeasurable disease: This circumstance arises in some Phase 3 trials when it is not a criterion of trial entry to have measurable disease. The same general

concept applies here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in nonmeasurable disease burden. Because worsening in nontarget disease cannot be easily quantified (by definition: if all lesions are truly nonmeasurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in nonmeasurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large", an increase in lymphangitic disease from localized to widespread, or may be described in protocols as "sufficient to require a change in therapy". If "unequivocal progression" is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to nonmeasurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified on a follow-up trial in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on trial has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET (PET scanning with the tracer fluorine-18 [F-18]fluorodeoxyglucose [FDG]) response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible "new" disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of

disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a preexisting site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study drug treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the trial and the protocol requirements, it may also require confirmatory measurement. Specifically, in nonrandomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "best overall response".

The best overall response is determined once all the data for the patient is known. Best response determination in trials where confirmation of CR or PR IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered unevaluable.

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

Note: When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the eCRF.

In trials where confirmation of response is required, repeated 'not evaluable (NE)' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping trial therapy.

Conditions that define "early progression, early death, and inevaluability" are trial specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of CR. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/ sensitivity.

For equivocal findings of progression (eg, very small and uncertain new lesions, cystic changes, or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

Confirmation

In nonrandomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, ie, in randomized trials (Phase 2 or 3) or trials where stable disease or PD are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial

results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in trials which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after trial entry at a minimum interval (in general not less than 6 weeks).

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity, and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

Appendix 3: ECOG Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction. (Karnofsky 90-100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work). (Karnofsky 70-80)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. (Karnofsky 50-60)
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. (Karnofsky 30-40)
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. (Karnofsky 10-20)
5	Dead

As published by (Oken et al, 1982). Eastern Cooperative Oncology Group, Robert Comis MD, Group Chair.

Appendix 4: Contraception Guidelines and Definitions Of "Women Of Childbearing Potential" and "No Childbearing Potential"

Females of childbearing potential and nonsterile males must use a highly effective method of birth control while in either Phase of the study (Core Phase/Extension Phase) and for at least 6 months after the last dose of pamiparib. In addition to a highly effective method of birth control, nonsterile males must also use a condom during intercourse while in either Phase of the study and for an additional 6 months after the last dose of pamiparib, even if the female partner of the male patient is already pregnant.

Contraception Guidelines

This study includes the use of the strong cytochrome P450 CYP3A inducer rifampin and the strong CYP3A inhibitor itraconazole, which may interact with hormonal contraceptives. Patients are not allowed to use hormonal contraceptives during the Core Phase of this study and for an additional 30 days after the last dose of either strong CYP3A inhibitor/inducer.
The following highly effective methods of contraception are accepted during the Core Phase and for the additional 30 days following the end of Core Phase:

- Non-hormonal intrauterine device (IUD)
- Bilateral tubal occlusion
- Vasectomized male partner
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of exposure associated with the study treatment)

  NOTE: Total sexual abstinence should only be used as a contraceptive method if it is in line with the patient's usual and preferred lifestyle.
  Periodic abstinence (eg, calendar, ovulation, symptothermal, or postovulation methods), declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception.

After the 30 days following the last dose of either strong CYP3A inhibitor/inducer, patients are allowed to use hormonal contraceptives as listed below. Patients should be educated on how to transition from one birth control method to another, especially when initiating hormonal contraceptives while in the study.

The Clinical Trials Facilitation Group's recommendations related to contraception and pregnancy testing in clinical trials include the use of highly effective forms of birth control. These methods include the following:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with the inhibition of ovulation
    - oral
    - intravaginal
    - transdermal
- Progestogen-only hormonal contraception associated with the inhibition of ovulation
    - oral
    - injectable
    - implantable*
- Intrauterine device (IUD)*
- Intrauterine hormone-releasing system (IUS)*
- Bilateral tubal occlusion*
- Vasectomized male partner*
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of exposure associated with the study treatment)

  NOTE: Total sexual abstinence should only be used as a contraceptive method if it is in line with the patient's usual and preferred lifestyle. Periodic abstinence (eg, calendar, ovulation, symptothermal, or postovulation methods), declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable methods of contraception.

Of note, barrier contraception (including male and female condoms with or without spermicide) is <u>not</u> considered a highly effective method of contraception and if used, this method must be combined with another acceptable method listed above.

*For this study, it is recommended the use of one of the contraception methods described above marked with an asterisk (*) as they are considered to have low user dependency.

Definitions of "Women of Childbearing Potential", "Women of No Childbearing Potential"

As defined in this protocol, "women of childbearing potential" are female patients who are physiologically capable of becoming pregnant.
Conversely, "women of no childbearing potential" are defined as female patients meeting > 1 of the following criteria:

- Surgically sterile (ie, through bilateral salpingectomy, bilateral oophorectomy, or hysterectomy)
- Postmenopausal, defined as:
    - ≥ 55 years of age with no spontaneous menses for ≥ 12 months OR
    - < 55 years of age with no spontaneous menses for ≥ 12 months AND with a postmenopausal follicle-stimulating hormone concentration > 30 IU/mL

Adapted from Clinical Trials Facilitation Group (CTFG). Recommendations related to contraception and pregnancy testing in clinical trials. September 15, 2014. http://www hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

Appendix 5: New York Heart Association Functional Classification

Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, eg, no shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, eg, walking short distances (20-100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

Adapted from Dolgin M, Association NYH, Fox AC, Gorlin R, Levin RI, New York Heart Association. Criteria Committee. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. 9th ed. Boston, MA: Lippincott Williams and Wilkins; March 1, 1994.
Original source: Criteria Committee, New York Heart Association, Inc. Diseases of the Heart and Blood Vessels. Nomenclature and Criteria for diagnosis, 6th edition Boston, Little, Brown and Co. 1964, p 114.

Appendix 6: Prohibited Medications

Strong and Moderate CYP3A Inhibitors and Strong CYP3A Inducers

Strong CYP3A Inhibitors
Antibiotics: clarithromycin, telithromycin, troleandomycin
Antifungals: itraconazole, ketoconazole, posaconazole, voriconazole
Antivirals: boceprevir, telaprevir
Other: cobicistat, conivaptan, elvitegravir, mibefradil, nefazodone
Protease inhibitors: indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir
Strong CYP3A Inducers
Avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (*Hypericum perforatum*)
Moderate CYP3A Inhibitors
Antibiotics: ciprofloxacin, erythromycin
Antifungals: fluconazole
Protease inhibitors: amprenavir, atazanavir, darunavir, fosamprenavir
Calcium channel blockers: diltiazem, verapamil
Tyrosine kinase inhibitors (anticancer): imatinib
Food products: grapefruit and juice (*Citrus paradisi*), Seville orange and juice (*Citrus aurantium*)
Herbal medications: *Schisandra sphenanthera*
Others: aprepitant, casopitant, cimetidine, cyclosporine, dronedarone, tofisopam

Data compiled from the FDA's "Guidance for Industry, Drug Interaction Studies;" http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664 htm from the Indiana University School of Medicine's "Clinically Relevant" Table http://medicine.iupui.edu/flockhart/table htm; from the University of Washington's Drug Interaction Database www.druginteractioninfo.org

Medications to be Used with Caution

Sensitive CYP2C9 Substrates or CYP2C9 Substrates with Narrow Therapeutic Index
Celecoxib[a]
Phenytoin[b]
Warfarin[b]

a. Sensitive substrates: Drugs that exhibit an area under the concentration-time curve (AUC)ratio (AUCi/AUC) of 5-fold or more when coadministered with a known potent inhibitor, where AUCi is the AUC of the substrate when coadministered with a known potent inhibitor and AUC is the AUC of substrate alone.

b. Substrates with narrow therapeutic index: Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (eg, Torsade de Pointes).

Strong CYP2C8 Inhibitors:

- Gemfibrozil

Data compiled from the FDA's "Guidance for Industry, Drug Interaction Studies" (http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664 htm);from the Indiana University School of Medicine's "Clinically Relevant" Table (http://medicine.iupui.edu/flockhart/table.htm); from the University of Washington's Drug Interaction Database (www.druginteractioninfo.org)

Appendix 7: Clinical Laboratory Evaluations

Clinical Chemistry:	**Hematology:**	**Urinalysis:**
Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Albumin Total bilirubin Direct bilirubin Blood urea nitrogen or urea Potassium Phosphorus Sodium Corrected calcium [a] Calcium Creatinine Glucose Lactate dehydrogenase Total protein	Hematocrit Hemoglobin Platelet count Red blood cell (RBC) count White blood cell (WBC) count WBC differential: Basophils Eosinophils Lymphocytes Monocytes Neutrophils	Blood Glucose Ketones pH Protein Specific gravity Urobilinogen Microscopic examination
Viral Serology: [b]	**Urinary drug screen: [c]**	**Hormone panel (females only):**
Hepatitis B surface antigen Hepatitis B surface antibody Hepatitis B Core antibody Hepatitis C antibody	Including but not limited to: Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine (metabolite) Methadone Phencyclidine Opiates Tetrahydrocannabinol/cannabinoids Alcohol breath test [d]	Follicle-stimulating hormone [b,e] Serum pregnancy test (human chorionic gonadotropin) [f]

a. Corrected calcium= calcium corrected for hypoalbuminemia (Serum calcium (mg/dL) + 0.8* (4-serum albumin [g/dL]).

b. Analyzed at Screening only; for patients with known chronic but controlled hepatitis B or C, or with panel results unclear or suggestive of infection, a PCR test for viral DNA should be conducted to evaluate DNA levels.

c. Analyzed at Screening and Day 1.

d. Performed at Screening and Day 1.

e. Postmenopausal females only as per Appendix 4.

f. Performed at Screening and Check-in for all females.

Appendix 8: Total Blood Volume

The following blood volume are the maximum planned to be withdrawn for each patient.

Core Phase

	Volume per blood sample (mL)	Maximum estimated number of blood samples	Total amount of blood (mL)
Clinical chemistry	4.7	5	23.5
Hematology	2.7	5	13.5
Serology	7.5	1	7.5
Glucose	2.7	5	13.5
Plasma for pamiparib concentration	4	20	80.0
Total:			138.0

Extension Phase

	Volume per blood sample (mL)	Maximum estimated number of blood samples per visit	Total amount of blood (mL) per visit
Predose, End of treatment, and Safety Follow-up visits			
Clinical chemistry	4.7	1	4.7
Hematology	2.7	1	2.7
Glucose	2.7	1	2.7
Total:			10.1

	Volume per blood sample (mL)	Maximum estimated number of blood samples per cycle	Total amount of blood (mL) per cycle
Cycle 1 and Cycle 2			
Clinical chemistry	4.7	2	9.4
Hematology	2.7	2	5.4
Glucose	2.7	2	5.4
Cycles 3+			
Clinical chemistry	4.7	1	4.7
Hematology	2.7	1	2.7
Glucose	2.7	1	2.7
Total:			30.3

Appendix 9: Chronic Kidney Disease Epidemiology Collaboration Equation

In adults, the most widely-used equations for estimating glomerular filtration rate (GFR) from serum creatinine are the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and the Modification of Diet in Renal Disease Study equation. The National Kidney Disease Education Program calculators rely on creatinine determinations, which are isotope dilution mass spectrometry traceable. All laboratories should be using creatinine methods calibrated to be isotope dilution mass spectrometry traceable.

This CKD-EPI equation calculator should be used when S_{cr} is reported in mg/dL. This equation is recommended when estimated GFR values above 60 mL/min/1.73 m^2 are desired.

GFR = 141 x min (S_{cr} /κ, 1)α x max(S_{cr} /κ, 1)-1.209 x 0.993Age x 1.018 [if female] x 1.159 [if black]

where:

S_{cr} is serum creatinine in mg/dL,

κ is 0.7 for females and 0.9 for males,

α is -0.329 for females and -0.411 for males,

min indicates the minimum of S_{cr} /κ or 1, and

max indicates the maximum of S_{cr} /κ or 1.

The equation does not require weight because the results are reported normalized to 1.73 m^2 body surface area, which is an accepted average adult surface area. The online calculator for CKD-EPI can be found here: https://www.niddk.nih.gov/health-information/communication-programs/nkdep/laboratory-evaluation/glomerular-filtration-rate-calculators/ckd-epi-adults-conventional-units

MDRD

This IDMS-traceable MDRD study equation calculator should be used when S_{cr} is reported in µmol/L. This equation should ***not*** be used when eGFR values above 60 mL/min/1.73 m^2 are desired.

GFR (mL/min/1.73 m^2) = 175 x $(S_{cr}/88.4)^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.212 if African American) (SI units)

Online calculator: https://www.niddk.nih.gov/health-information/communication-programs/nkdep/laboratory-evaluation/glomerular-filtration-rate-calculators/mdrd-adults-si-units

Appendix 10: Signature of Investigator

Protocol Title:	A Phase 1, Open-label, Parallel-group, Fixed-sequence Study to Investigate the Effect of the CYP3A Inducer Rifampin and the CYP3A Inhibitor Itraconazole on the Pharmacokinetics of Pamiparib (BGB-290) in Cancer Patients
Protocol Identifier:	BGB-290-105

This protocol is a confidential communication of BeiGene, Ltd., and its subsidiaries. I confirm that I have read this protocol, I understand it, and I will work according to this protocol and the terms of the clinical study agreement governing the study. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd., or one of its subsidiaries.

Instructions for Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the center in which the study will be conducted. Return the signed copy to BeiGene, Ltd. or its designee.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date:_____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

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