Protocol

A Phase 1 Study to Investigate the Absorption, Metabolism, and Excretion of [^{14}C]-Pamiparib following Single Oral Dose Administration in Patients with Advanced and/or Metastatic Solid Tumors

Protocol Version 1.0 Date: 25 June 2018
Protocol Amendment Version 3.0 Date: 12 December 2018

Investigational Medicinal Product: [^{14}C]-Pamiparib and Pamiparib

Protocol Reference Number: BGB-290-106
Covance Study Number: 8381180
EudraCT Number: 2018-001156-36

Sponsor:
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Principal Investigator:

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SPONSOR APPROVAL

Protocol Number: BGB-290-106

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[redacted] Date

Sponsor Medical Monitor

INVESTIGATOR AGREEMENT

Protocol Identifier: BGB-290-106

Protocol Title: A Phase 1 Study to Investigate the Absorption, Metabolism, and Excretion of [^{14}C]-Pamiparib following Single Oral Dose Administration in Patients with Advanced and/or Metastatic Solid Tumors

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. 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 Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd or one of its subsidiaries.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 or its designee.

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

[redacted] _____

Date

Principal Investigator

PROTOCOL AMENDMENT VERSION 3.0 (12 DECEMBER 2018)

The Protocol Amendment Version 2.0 (Covance Study 8381180), dated 31 October 2018, is revised as Protocol Amendment Version 3.0, dated 12 December 2018 based on Health Authority. Additions are in **bold text**. Key changes are summarized by protocol section as shown below:

Section	Key Change
Appendix 8	Added text to Appendix 8: **All male patients with partners of childbearing potential who take part in this study, must use condoms during sexual intercourse in addition to one of the highly effective methods of contraception listed below, from the time of taking the first dose of pamiparib until 6 months after taking the last dose of pamiparib. If a female partner of a male patient is already pregnant, the male patient must use condoms during sexual intercourse for the duration of the study and for at least 6 months after the last dose of pamiparib.** **Female patients of childbearing potential must use one of the highly effective forms of birth control below (preferably those with low user dependency) for the duration of the study and for at least 6 months after the last dose of pamiparib.**
Appendix 8	Added asterisks to birth control methods intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, and vasectomized male partner to indicate that: ***Contraception methods that in the context of this protocol are considered to have low user dependency.**

STUDY IDENTIFICATION

Sponsor	BeiGene, Ltd. c/o BeiGene USA, Inc. 2929 Campus Drive, Suite 300 San Mateo, CA, 94403, USA
Sponsor's Study Contact	[redacted]
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Bioanalytical Analysis	Covance Inc. 1121 East 3900 South Building C, Suite 210 Salt Lake City, UT 84124, USA
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Statistician	[redacted]

SYNOPSIS

Title of study: A Phase 1 Study to Investigate the Absorption, Metabolism, and Excretion of [^{14}C]-Pamiparib following Single Oral Dose Administration in Patients with Advanced and/or Metastatic Solid Tumors

Objectives:

The primary objectives of the study are:

- To assess the disposition of [^{14}C]-pamiparib following oral administration of a single 60 mg (~100 μCi) dose in patients with advanced and/or metastatic solid tumors
- To assess the plasma pharmacokinetics (PK) of total radioactivity and pamiparib following a single oral dose of [^{14}C]-pamiparib
- To determine the whole blood and plasma concentrations of total radioactivity
- To determine the urinary and fecal recovery of total radioactivity

The secondary objectives of this study are:

- To characterize and identify metabolites of [^{14}C]-pamiparib in plasma, urine, and feces
- To determine plasma and urine concentrations of pamiparib and/or its major metabolites
- To assess the safety and tolerability of pamiparib during the treatment phase

Study design:

This is an open-label study, in patients with advanced and/or metastatic solid tumors, which consists of 2 parts: a research phase (inpatient) and a treatment phase.

Part 1 - Research Phase

The research phase of the study will assess the disposition of [^{14}C]-pamiparib following oral administration of a single dose of 60 mg. Patients will be resident at the Clinical Research Unit (CRU) from Day -1 until completion of all assessments on Day 7 but may be discharged earlier at the Principal Investigator's (PI's) discretion if they meet the following discharge criteria:

- Approximately 90% of the radioactive dose is recovered

or

- < 1% of the radioactive dose is recovered in urine and feces for 2 consecutive 24-hour collection intervals.

If the discharge criteria have not been met on Day 7, patients may be asked to collect 24-hour excreta samples for up to 7 days on a non-residential basis. Patients may remain resident at the CRU if deemed necessary by the PI for safety reasons. A Follow-up visit will occur within 7 days of discharge from the CRU (if discharged on Day 7 or before), or within 7 days of the patients' final non-residential visit (if additional non-residential visits are required). At the Follow-up visit, patients' ability to continue into the treatment phase will be determined by the PI.

Part 2 - Treatment Phase

The treatment phase of the study will allow patients to have continued access to pamiparib. Safety assessments will be conducted ≤ 7 days prior to the start of pamiparib treatment at either the Follow-up visit for Part 1 or at a separate visit. Patients will undergo 28-day cycles of pamiparib 60 mg twice daily dosing. Pamiparib treatment will be continued unless any of the following occur: 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. There will be a Follow-up visit approximately 30 days following the final administration of pamiparib.

Number of patients:
Approximately 10 patients will be enrolled so that 4 patients complete Part 1 of the study.

Diagnosis and main criteria for inclusion:
Patients will be male or female, ≥ 18 years of age, who have histologically or cytologically confirmed malignancy that has progressed to the advanced or metastatic stage. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1.

Investigational products, dose, and mode of administration:
Part 1: A single oral dose of [^{14}C]-pamiparib 60 mg containing approximately 100 μCi (3.7 MBq).
Part 2: Oral doses of pamiparib 60 mg twice daily.

Duration of patient participation in the study:
Planned Screening duration: approximately 27 days.
Planned study duration: Part 1 – up to 22 days (Day -1 to Day 21); Part 2 - variable based on time required for study drug discontinuation to occur (see previous section).

Endpoints:
Pharmacokinetics:
Part 1
Plasma, urine, and feces will be collected for the analysis of pamiparib concentrations and total radioactivity. The PK parameters of pamiparib and total radioactivity will be calculated using standard noncompartmental methods. The following PK parameter endpoints for pamiparib in plasma and total radioactivity in whole blood and plasma will be calculated whenever possible: area under the concentration-time curve (AUC) from time zero to infinity ($AUC_{0-\infty}$), AUC from time zero to the last quantifiable concentration (AUC_{0-t}), maximum observed concentration (C_{max}), time of C_{max} (t_{max}), and apparent terminal elimination half-life ($t_{1/2}$). The apparent total clearance (CL/F) and apparent volume of distribution (V_z/F) will also be determined.
The $AUC_{0-\infty}$ of plasma pamiparib relative to $AUC_{0-\infty}$ of plasma total radioactivity ($AUC_{0-\infty}$ Plasma pamiparib/Total Radioactivity Ratio) and $AUC_{0-\infty}$ of whole blood total radioactivity to $AUC_{0-\infty}$ of plasma total radioactivity ($AUC_{0-\infty}$ Blood/Plasma Ratio) will be calculated.
The following PK parameter endpoints for pamiparib and total radioactivity in urine will be calculated whenever possible: amount excreted in urine (A_{eu}), cumulative A_{eu}, percentage excreted in urine (f_{eu}), and cumulative f_{eu}. The renal clearance (CL_R) will also be determined for pamiparib.
The following PK parameter endpoints for total radioactivity in feces will be calculated whenever possible: amount excreted in feces (A_{ef}), cumulative A_{ef}, percentage excreted in feces (f_{ef}), and cumulative f_{ef}.
Plasma, urine, and fecal samples will also be used to establish the metabolic profile of pamiparib and to identify its metabolites.
Part 2
No analysis of pamiparib PK will be conducted during the treatment phase.
Safety:
Safety endpoints for this study include AEs, vital sign measurements, 12-lead electrocardiograms, clinical laboratory evaluations, and physical examinations. Tumor assessments will be conducted using a computerized tomography or magnetic resonance imaging scan at Screening and every 12 weeks following the baseline scan. The ECOG performance status will be assessed during Part 1 and Part 2.

Statistical methods:
Pharmacokinetic parameters will be summarized using descriptive methodology. Efficacy and safety assessments will be summarized using descriptive methodology and/or listed. No formal statistical analysis will be performed.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
A_{ef}	amount excreted in feces
A_{eu}	amount excreted in urine
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{0-\infty}$	area under the concentration-time curve from time zero to infinity
$AUC_{0-\infty}$ Blood/ Plasma Ratio	area under the concentration-time curve from time zero to infinity of whole blood total radioactivity to area under the concentration-time curve from time zero to infinity of plasma total radioactivity
$AUC_{0-\infty}$ Plasma pamiparib /Total Radioactivity Ratio	area under the concentration-time curve from time zero to infinity of plasma pamiparib relative to area under the concentration-time curve from time zero to infinity of plasma total radioactivity
AUC_{0-t}	area under the concentration-time curve from time zero to the last quantifiable concentration
BID	twice daily
BRCA	breast cancer susceptibility gene
^{14}C	carbon-14
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL/F	apparent total clearance
CL_R	renal clearance
C_{max}	maximum observed concentration
CNS	central nervous system
CR	complete response
CRO	Contract Research Organization
CRU	Clinical Research Unit
CSR	Clinical Study Report
CT	computed tomography
CYP	cytochrome P450
DLT	dose-limiting toxicity
ECOG	Eastern Cooperative Oncology Group

EDC	electronic data capture
E/C	etoposide and carboplatin
EC	Ethics Committee
EC_{50}	half-maximal effective concentration
ECG	electrocardiogram
eCRF	electronic Case Report Form
EOT	end-of-treatment
FDG-PET	fluorodeoxyglucose-positron emission tomography
f_{ef}	percentage excreted in feces
f_{eu}	percentage excreted in urine
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
hERG	human ether-à-go-go related gene
IB	Investigator's Brochure
IC_{50}	half-maximal inhibition concentration
ICF	Informed Consent Form
ICH	International Council for/Conference on Harmonisation
ICRP	International Commission on Radiological Protection
IMP	investigational medicinal product
MDRD	Modification of Diet in Renal Disease
MDS	myelodysplastic syndrome
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
PAR	poly (ADP-ribose)
PARP	poly (ADP-ribose) polymerase
PD	progressive disease
PI	principal investigator
PK	pharmacokinetic(s)
PR	partial response
QWBA	quantitative whole-body autoradiography
QTc(F)	QT interval corrected for heart rate using Fridericia's formula
SAE	serious adverse event
SCLC	small cell lung cancer
SD	stable disease
SEM	standard error of the mean
SOP	standard operating procedure

SSBs	single-strand DNA breaks
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	apparent terminal elimination half-life
TEAE	treatment-emergent adverse event
t_{max}	time of maximum observed concentration
ULN	upper limit of normal
V_Z/F	apparent volume of distribution

1. INTRODUCTION

1.1. Poly (ADP-ribose) Polymerase 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 (SSBs) 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 breast cancer susceptibility gene (BRCA)-deficient cells and, more broadly, cells with homologous recombination deficiency, accumulation of unrepaired SSBs 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 SSBs.[1–3]

In the clinic, PARP inhibitors, including olaparib, rucaparib, niraparib, and talazoparib, have demonstrated sustained antitumor responses as a single agent in patients with BRCA1- or BRCA2-mutated tumors, while achieving a favorable safety profile. Olaparib has been approved in the US as a single agent for advanced ovarian cancer patients with a deleterious germline BRCA mutation whereas rucaparib has been approved for patients with a deleterious germline or somatic BRCA mutation.[4,5] Niraparib was approved by the US Food and Drug Administration in 2017 for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete response (CR) or partial response (PR) to platinum-based chemotherapy.

1.2. PARP Inhibitor Pamiparib

1.2.1. Nonclinical Data for Pamiparib

[redacted]

1.2.2. Nonclinical Safety Data

[redacted]

[redacted]

1.2.3. Nonclinical Activity Data

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

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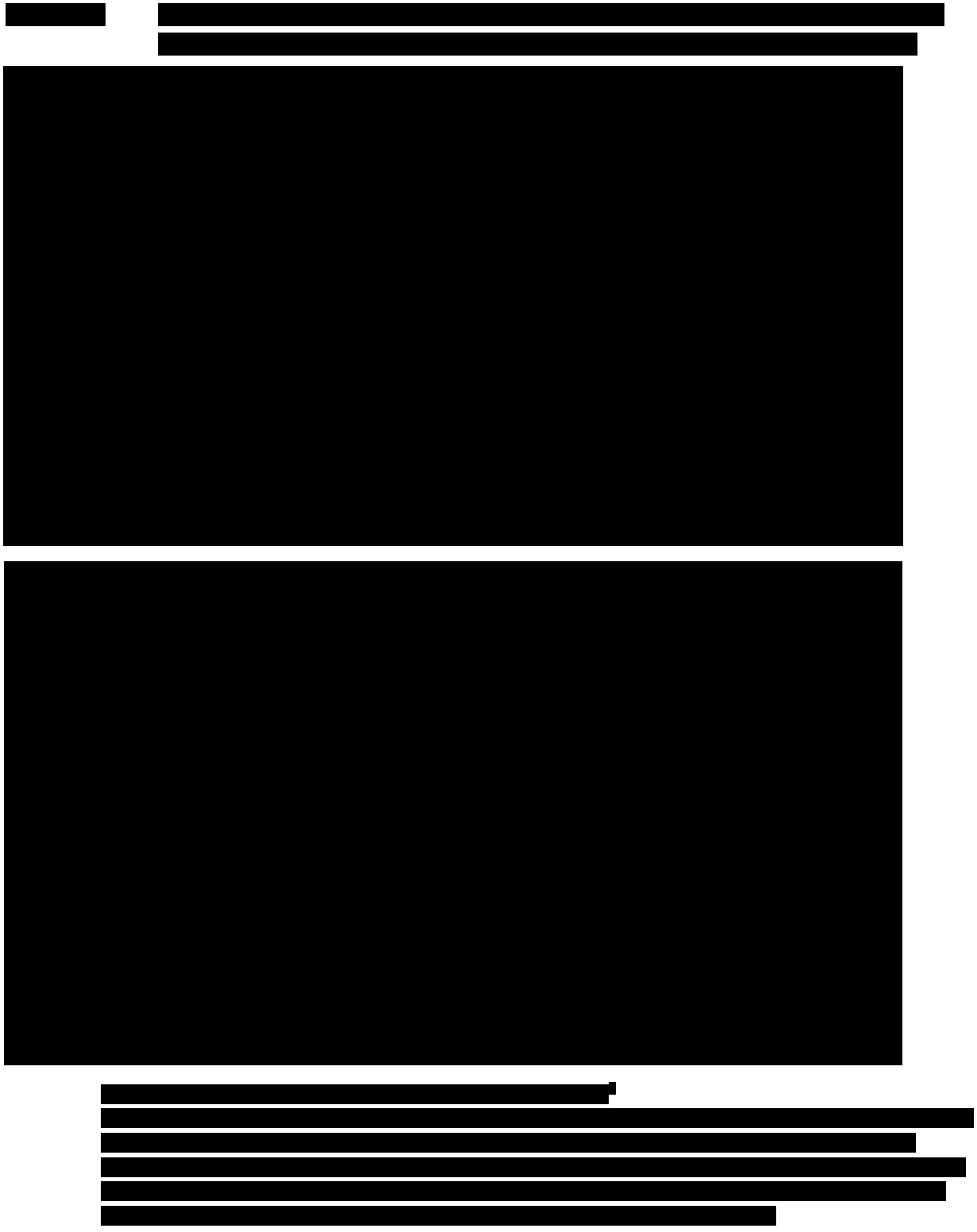
[redacted]

[redacted]

[redacted]

Figure 1: Pamiparib Activity with Etoposide and Carboplatin and as Maintenance Monotherapy in BCLU-053 Small Cell Lung Cancer Xenograft Model



1.3. Clinical Data for Pamiparib

Pamiparib monotherapy has been administered in 2 Phase 1 studies. This includes 81 patients across Phase 1A and Phase 1B in Study BGB-290-AU-002 (01 Dec 2017), and 15 patients in Study BGB-290-102 (25 Sept 2017). Data are also available for pamiparib in combination regimens. This includes 10 patients in Study BGB-290-103 (combination with temozolomide; 01 Dec 2017), 4 patients in Study BGB-290-104 (combination with radiation therapy and/or temozolomide; 01 Dec 2017) and 82 patients in BGB-A317/BGB-290_Study_ 001(combination with the antibody tislelizumab [also known as BGB-A317, an immune checkpoint inhibitor targeting programmed cell death-1];05 February 2018).

Three additional studies are in study start-up: monotherapy study BGB-290-201 and placebo-controlled studies BGB-290-302 and BGB-290-303.

The study data from BGB-290-AU-002 are the most mature and key interim results are summarized below.

1.3.1. Clinical Safety and Preliminary Efficacy for Pamiparib

BGB-290-AU-002 is a first-in-human study evaluating pamiparib to characterize the safety, the 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 to 120 mg orally twice daily.

Dose-limiting toxicities (DLTs) were observed in 4 patients during Cycle 1 at the following dose levels: 40 mg PO twice daily (n = 1); 80 mg PO twice daily (n = 1); and 120 mg PO twice daily (n = 2). Two patients, one treated with 40 mg PO twice daily and one treated with 80 mg PO twice daily, had two separate events of Grade 2 nausea lasting between 2 and 9 days that resulted in dose interruption. One patient treated with 120 mg PO twice daily had two separate Grade 2 events of nausea and anorexia events each that resulted in dose interruption and dose reduction. A second patient treated with 120 mg PO twice daily experienced Grade 2 nausea starting on Day 3 lasting for 13 days, Grade 3 fatigue and Grade 2 paresthesia starting on Day 4 and lasting for 12 and 6 days respectively, followed by Grade 3 paresthesia starting on Day 11 and lasting for 17 days, all resulting in dose interruption. Dose-limiting toxicities were not reported beyond Cycle 1 or in any additional patients.

The MTD was determined to be 80 mg PO twice daily based on 2 of 5 patients (40%) who experienced a DLT at 120 mg PO twice daily.

In Phase 1A, Part 1 of the study (twice daily dosing), 100.0% of patients experienced a treatment-emergent adverse event (TEAE), while 75.6% of patients experienced a drug-related TEAE. A total of 10 patients (22.2%) experienced a severe (≥ Grade 3) pamiparib-related TEAE. Serious TEAEs were reported in 25 patients (55.6%), while 6.7% experienced a serious pamiparib-related TEAE. Four patients (8.9%) died as a result of a TEAE in Phase 1A, Part 1 of Study BGB-290-AU-002 (1 adverse event [AE] of pleural effusion in a breast cancer patient who died of disease progression complicated by respiratory failure; 1 AE of intestinal obstruction in

an ovarian cancer patient; 1 AE of intestinal perforation in an ovarian cancer patient; and 1 AE of gastric obstruction in a fallopian tube cancer patient). All 4 fatal events were assessed by the investigator as not related to the study treatment.

In Phase 1A, Part 2 (once daily dosing), 2 patients (66.7%) experienced a TEAE; both were assessed as pamiparib-related TEAEs. One patient (33.3%) experienced a severe (≥ Grade 3) TEAE, which was assessed as related to pamiparib. No serious AEs (SAEs) were reported and no patients discontinued treatment due to a TEAE in Phase 1A, Part 2 of Study BGB-290-AU-002.

In Phase 1B of the study (dose expansion), 100.0% of patients experienced a TEAE, while 87.9% of patients experienced a drug-related TEAE. A total of 10 patients (30.3%) experienced a severe (≥ Grade 3) pamiparib-related TEAE. Serious TEAEs were reported in 9 patients (27.3%), while 1 patient (3.0%) experienced a serious pamiparib-related TEAE. No patients discontinued treatment due to a TEAE or died in Phase 1B of Study BGB-290-AU-002.

Ten patients achieved either CR (n = 2) or PR (n = 8); all responses were observed in patients with gynecological cancers.

Please refer to the Investigator's Brochure (IB) for additional information regarding clinical studies being conducted with pamiparib.[6]

1.3.2. Pharmacokinetics and Pharmacodynamics

[redacted]

1.4. Study Rationale

The purpose of this study is to determine the absorption, metabolism, and excretion of [^{14}C]-pamiparib and to characterize and identify metabolites present in plasma, urine, and, where possible, feces, in male and female patients with advanced and/or metastatic solid tumors following a single oral administration.

Pamiparib was not mutagenic in the in vitro Ames (bacterial reverse mutation) assay, but, consistent with its mechanism of action, was clastogenic in the in vitro chromosomal aberration assay in mammalian CHO cells and in the in vivo rat bone marrow micronucleus assay. Consequently, pamiparib cannot be given to healthy volunteers and will be administered to cancer patients in this study. The results from this study may guide future study designs evaluating the potential for drug-drug interactions.

1.5. Benefit-Risk Assessment

Pamiparib has been studied in nonclinical toxicity and Phase 1 clinical studies. Pamiparib toxicities are largely consistent with the safety profile shared by other PARP inhibitors with the possible exception that pamiparib may cause less myelosuppression.

The radiation dose is an acceptable dose to give to both male and female patients with advanced cancer (Section 3.3).

More information about the known and expected benefits, risks, and reasonably anticipated AEs associated with pamiparib may be found in the IB.[6] For the most comprehensive nonclinical and clinical information regarding pamiparib background, safety, efficacy, and in vitro and in vivo nonclinical activity and toxicology of pamiparib, refer to the latest version of the pamiparib IB.[6]

Based on the nonclinical and clinical data to date, pamiparib warrants further exploration in patients with advanced solid tumors and the overall risk-benefit ratio appears favorable.

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objectives

The primary objectives of the study are:

- To assess the disposition of [^{14}C]-pamiparib following oral administration of a single 60 mg (~100 µCi) dose in patients with advanced and/or metastatic solid tumors
- To assess the plasma PK of total radioactivity and pamiparib following a single oral dose of [^{14}C]-pamiparib
- To determine the whole blood and plasma concentrations of total radioactivity
- To determine the urinary and fecal recovery of total radioactivity

2.1.2. Secondary Objectives

The secondary objectives of the study are:

- To characterize and identify metabolites of [^{14}C]-pamiparib in plasma, urine, and feces

- To determine plasma and urine concentrations of pamiparib and/or its major metabolites
- To assess the safety and tolerability of pamiparib during the treatment phase

2.2. Endpoints

2.2.1. Primary Endpoints

The following PK outcome endpoints of pamiparib (plasma), and total radioactivity (whole blood and plasma) derived from the concentration-time profiles following a single oral dose of [^{14}C]-pamiparib are as follows:

- AUC from time zero to infinity ($AUC_{0-\infty}$)
- AUC from time zero to the last quantifiable concentration (AUC_{0-t})
- C_{max}
- Time of C_{max} (t_{max})
- $t_{1/2}$
- Apparent total clearance (CL/F)
- Apparent volume of distribution (V_z/F)
- $AUC_{0-\infty}$ of plasma pamiparib relative to $AUC_{0-\infty}$ of plasma total radioactivity ($AUC_{0-\infty}$ Plasma Pamiparib Total Radioactivity Ratio)
- $AUC_{0-\infty}$ of whole blood total radioactivity to $AUC_{0-\infty}$ of plasma total radioactivity ($AUC_{0-\infty}$ Blood/Plasma Ratio).

The primary PK outcome endpoints of pamiparib and total radioactivity derived from urine collections are as follows:

- Amount excreted in urine (A_{eu})
- Cumulative A_{eu}
- Percentage excreted in urine (f_{eu})
- Cumulative f_{eu}
- Renal clearance (CL_R; pamiparib only).

The primary PK outcome endpoints of total radioactivity derived from fecal collections are as follows:

- Amount excreted in feces (A_{ef})
- Cumulative A_{ef}
- Percentage excreted in feces (f_{ef})

- Cumulative f_{ef}.

2.2.2. Secondary Endpoints

The metabolite outcome endpoints will be derived:

- Metabolic profile of pamiparib
- Identification of pamiparib metabolites.

The secondary safety outcome measures are as follows:

- Incidence and severity of AEs
- Incidence of laboratory abnormalities, based on hematology and clinical chemistry test results
- 12-lead ECG parameters
- Vital sign measurements
- Physical examinations.

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

This is an open-label, inpatient study in patients with advanced and/or metastatic solid tumors, which consists of 2 parts: a research phase and a treatment phase.

An overview of the study design for Part 1 and Part 2 is shown in Figure 3 and Figure 4, respectively.

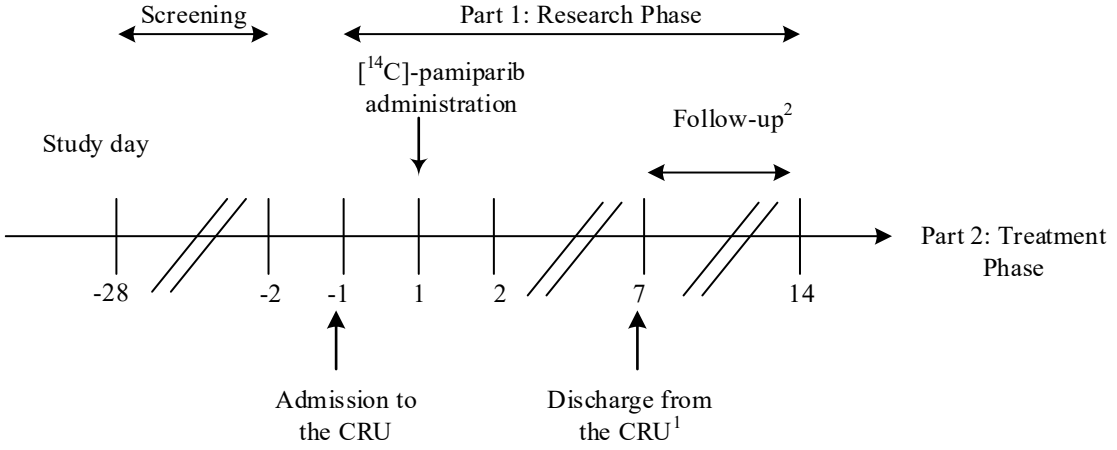
Potential patients will be screened to assess their eligibility to enter the study within 28 days prior to the first dose administration. Re-screening of patients will be allowed per the Principal Investigator's (PI's) discretion. Up to approximately 10 patients will be enrolled to ensure 4 patients complete Part 1 of the study.

The start of the study is defined as the date the first enrolled patient signs an Informed Consent Form (ICF). The point of enrollment occurs at the time of patient number allocation. The end of the study is defined as the date of the last patient's last assessment (scheduled or unscheduled) or follow-up.

A Schedule of Assessments is presented in Appendix 4.

3.1.1. Study Part 1 (Research Phase)

Figure 3: Study Schematic: Part 1



Abbreviation: CRU = Clinical Research Unit.
[1] Discharge may occur earlier than Day 7 if discharge criteria have been met (approximately 90% mass balance recovery, or < 1% of total dose recovered in urine and feces for 2 consecutive 24-hour collection intervals).
[2] Patients will attend a Follow-up visit within 7 days of Discharge (if discharged on Day 7 or before), or within 7 days of their final non-residential visit (if additional non-residential visits are required).

Patients will be admitted into the Clinical Research Unit (CRU) on Day -1. On the morning of Day 1, patients will receive a single oral dose of 60 mg containing approximately 100 µCi (3.7 MBq) of [^{14}C]-pamiparib.

Patients will be resident at the CRU until completion of all assessments on Day 7, but may be discharged earlier at the PI's discretion if they meet the following discharge criteria:

- Approximately 90% of the radioactive dose is recovered

or

- < 1% of the radioactive dose is recovered in urine and feces for 2 consecutive 24-hour collection intervals.

If the discharge criteria have not been met on Day 7, patients may be asked to collect 24-hour excreta samples for up to a further 7 days (up to Day 14) on a non-residential basis. Patients may be required to remain resident at the CRU for longer than 7 days if deemed necessary by the PI to ensure patient safety. If the discharge criteria have not been met by Day 14, the need for additional sample collection will be at the discretion of the PI.

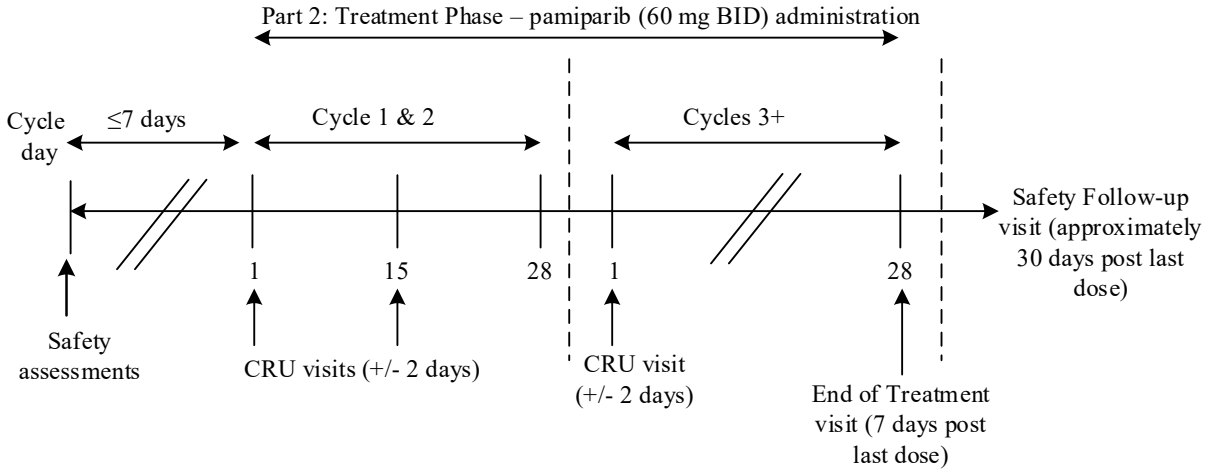
Patients experiencing emesis during the first 4 hours postdose may not be evaluable and therefore may be discharged on the same day from the clinical site, provided there are no safety concerns, and after discharge study procedures are performed. These patients will attend a

Follow-up visit within 7 days of Discharge and may be enrolled to Part 2 of the study at the discretion of the PI. Patients may be prescribed anti-emetics if required.

A Follow-up visit will occur within 7 days of Discharge from the CRU (if discharged on Day 7 or before), or within 7 days of the patients' final non-residential visit (if additional non-residential visits are required). During the Follow-up visit, the patients may be entered into Part 2 of the study if deemed appropriate by the PI.

3.1.2. Study Part 2 (Treatment Phase)

Figure 4: Study Schematic: Part 2



Abbreviations: BID = twice daily; CRU = Clinical Research Unit.

Patients will undergo safety assessments ≤ 7 days prior to the start of pamiparib treatment in Part 2. These assessments may be conducted at the Follow-up visit for Part 1 if it occurs within this time window, or at a separate site visit. If there are greater than 8 weeks between tumor assessments at study Screening and the planned start of pamiparib treatment in Part 2, patients should undergo a computed tomography (CT) scan prior to the start of treatment in Part 2.

During Part 2, patients will attend 2 site visits per cycle during Cycles 1 and 2, and 1 site visit per cycle during each subsequent cycle. Patients will continue receiving treatment 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. Patients will attend an End-of-treatment (EOT) visit within 7 days following their last dose and a safety Follow-up visit approximately 30 days after the last dose of pamiparib.

The reason for treatment discontinuation will be recorded on the electronic Case Report Form (eCRF). An EOT visit should occur within 7 days after the final pamiparib dose. The 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. Every effort must be made to encourage the patient to complete their EOT visit and appropriate safety follow-ups.

3.2. Discussion of Study Design

This study is an open-label study with the objectives and endpoints described in Section 2. The study will be conducted in patients with advanced and/or metastatic solid tumors. The dose, patient population, study duration, and sample collection timing are considered adequate to achieve the study objectives.

Oral administration was chosen since this is the intended clinical route of administration. Based on the nonclinical data and the known PK of pamiparib, the sample collection timing and duration of this study are considered adequate to achieve the study objectives.

Part 2 of the study is to allow patients participating in Part 1 of the study continued access to pamiparib. Patients will be allowed to continue on the study as detailed in Section 3.1.2.

3.3. Selection of Doses in the Study

A dose of oral pamiparib 60 mg twice daily was chosen based upon the overall safety, efficacy, and PK profile of pamiparib using available clinical data from Study BGB-290-AU-002 (Section 1.3.1). Study BGB-290-AU-002 determined the MTD of pamiparib to be 80 mg administered orally twice daily (160 mg/day). The dose of 60 mg twice daily was selected for further evaluation based on the following findings (refer to the pamiparib IB[6]):

- A linear PK profile observed up to 80 mg twice daily
- Similar toxicity profiles at 60 mg and 80 mg twice daily with the following exceptions:
    - Fewer patients at 60 mg twice daily experienced treatment-related TEAEs of anemia and neutropenia than those receiving higher doses
    - There was a slightly higher rate of dose interruptions at 80 mg versus 60 mg twice daily for anemia and nausea
- Responses were observed across the dose range evaluated.

In Part 1, the radioactive dose of approximately 3.7 MBq (~100 µCi) of [^{14}C]-pamiparib was chosen to provide sufficient radioactive signal for total radioactivity counting and quantitative radio-profiling of [^{14}C]-pamiparib in blood, plasma, and excreta (primary objectives of the study), with minimal radiation risk to patients.

Dosimetry calculations were based on QWBA studies in male and female Long Evans rats receiving an oral dose of [^{14}C]-pamiparib. An administration of approximately 3.7 MBq will result in an overall human effective dose of 0.98 to 1.08 mSv. This falls well within the International Commission on Radiological Protection (ICRP) 62[9,10] risk category IIb (1 to 10 mSv, minor to intermediate risk) and World Health Organization[11] category IIb (0.5 to 5 mSv, within dose limits for members of the public).

The effective radiation dose is defined as being within dose limits for members of the public (Category II study, World Health Organization) with a minor associated risk (risk Category IIb, ICRP).[10]

4. SELECTION OF STUDY POPULATION

4.1. Inclusion Criteria

Patients must satisfy all of the following criteria at the Screening visit unless otherwise stated:

1. Able to comprehend and willing to sign an ICF and to abide by the study restrictions
2. Male or female of any race, ≥ 18 years of age at Screening
3. A total body weight between 50 and 100 kg, inclusive, at Screening
4. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1 (see Appendix 3)
5. Ability to swallow whole capsules
6. Histologically and/or cytologically confirmed advanced or metastatic solid tumor that has progressed after treatment with approved therapies or for which there are no standard therapies available
7. Adequate organ functions as indicated by the following Screening laboratory values (obtained ≤ 2 weeks prior to Day 1):
   - Absolute neutrophil count ≥ 1.5 x 10^9/L
   - Platelets ≥ 100 x 10^9/L
   - Hemoglobin ≥ 9 g/dL (≥ 14 days after growth factor support or transfusion)
   - Estimated glomerular filtration rate ≥ 30 mL/min/1.73 m^2 by the Modification of Diet in Renal Disease study equation
   - Total serum bilirubin ≤ 1.5 x ULN (total bilirubin must be ≤ 4 x ULN for patients with Gilbert's syndrome)
   - Aspartate and alanine aminotransferase ≤ 3 x ULN OR ≤ 5 x ULN for patients with liver metastases
   - Serum albumin ≥ 3 g/dL
8. Patients must agree to use contraception as detailed in Section 6.4. Nonsterile males must avoid sperm donation for the duration of the study and for at least 6 months after the last dose of study drug.
9. Have regular bowel movements (minimum of 1 bowel movement per day or every other day; no more than 3 bowel movements per day) for 2 weeks without diarrhea prior to Screening (laxatives will be allowed in the study per the PI's discretion)
10. Have the ability to provide regular urine samples.

4.2. Exclusion Criteria

Patients will be excluded from the study if they satisfy any of the following criteria at the Screening visit unless otherwise stated:

1. Chemotherapy, biologic therapy, immunotherapy, investigational agents, or herbal remedies ≤ 14 days (or ≤ 5 half-lives, whichever is shorter) prior to Day 1
   - Bisphosphonate and denosumab use is allowed on study as appropriate, if administered at a stable dose > 28 days before enrollment
   - Patients who have participated in any clinical trial involving a radiolabeled investigational product within 12 months prior to Check-in are excluded
2. Patients who have received local radiotherapy of non-target lesions for local symptom control within the last 4 weeks must have recovered from any adverse effects of radiotherapy before commencing this study
3. Unresolved acute effects of any prior therapy of Grade 2 or higher, except for AEs not constituting a safety risk (eg, alopecia, neuropathy, and specific laboratory abnormalities)
4. Major surgical procedure, open biopsy, or significant traumatic injury ≤ 2 weeks prior to Day 1, or anticipation of need for major surgical procedure during the course of the study
   - Placement of a vascular access device is not considered major surgery
5. Leptomeningeal disease or uncontrolled, untreated brain metastases. Patients with a history of treated and, at the time of screening, asymptomatic brain metastases are eligible, provided they meet all of the following:
   - Only supratentorial metastases
   - Brain imaging at Screening without evidence of interim progression
   - No ongoing requirement for corticosteroids as therapy for brain metastases
     - Anticonvulsants at a stable dose allowed
   - No stereotactic radiation or whole-brain radiation ≤ 14 days prior to Day 1
6. Active infection requiring systemic treatment, active viral hepatitis, or active tuberculosis
7. Any of the following cardiovascular criteria:
   - Cardiac chest pain, defined as moderate pain that limits instrumental activities of daily living, ≤ 28 days before first dose
   - Symptomatic pulmonary embolism ≤ 28 days before first dose
   - Any history of acute myocardial infarction ≤ 6 months before first dose
   - Any history of heart failure meeting New York Heart Association Classification III or IV ≤ 6 months before first dose (see Appendix 5)

- Any event of ventricular arrhythmia ≥ Grade 2 in severity ≤ 6 months before enrollment
- Any history of cerebral vascular accident ≤ 6 months before enrollment.

8. Have a previous complete gastric resection, chronic diarrhea, active inflammatory gastrointestinal disease, or any other disease causing malabsorption syndrome. Gastro-esophageal reflux disease under treatment with proton pump inhibitors is allowed
9. Use or have anticipated need for food or drugs known to be strong or moderate CYP3A inhibitors or strong CYP3A inducers ≤ 10 days or ≤ 5 half-lives, whichever is shorter, prior to Day 1 (see Appendix 6)
10. Are pregnant or nursing (females of childbearing potential require a negative serum pregnancy test at Screening and a negative urine pregnancy test on Day -1)
11. Significant intercurrent illness that may result in the patient's death before death from cancer
12. History of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, including known history of intolerance to the excipients of the pamiparib capsule
13. Poor peripheral venous access. Venous access via a port will be permitted.

4.3. Patient Number and Identification

At Screening, all patients will be assigned a unique screening identification number. If enrolled into the study, patients will be assigned a patient number prior to the first dosing occasion. Assignment of patient numbers will be in ascending order based on time of enrollment, and no numbers will be omitted (eg, Patients 101, 102, 103).

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

4.4. 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:

- PD
- AEs
- Pregnancy
- Major protocol violation
- Patient withdrew consent for study treatment
    - Patients may voluntarily withdraw consent from study treatment at any time

  - Patients should be requested to participate in the follow-up phase, if patient withdraws consent from the treatment phase only

- Investigator's discretion
- 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 4). Other procedures may be performed at the 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 return 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 withdrawn prior to first investigational medicinal product (IMP) administration and/or during Part 1 of the study may be replaced following discussion between the PI and Sponsor.

4.5. 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, all patients have completed and all obligations have been fulfilled).

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.

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. STUDY TREATMENTS

5.1. Description, Storage, Packaging, and Labelling

[redacted]

5.2. Study Treatment Administration

5.2.1. Part 1

Patients should be fasted 1 hour before and 2 hours after the dose. [^{14}C]-pamiparib will be administered orally with approximately 240 mL of room temperature water. [redacted] At all times during the study, patients may consume water ad libitum.

Patients will be dosed while seated and will not be permitted to lie supine for 2 hours after administration of [^{14}C]-pamiparib except as necessitated by the occurrence of an AE(s) and/or study procedures.

5.2.2. Part 2

Pamiparib capsules will be dispensed to patients by qualified site personnel at scheduled site visits throughout Part 2 to ensure that patients have an adequate drug supply for administration at home. The patient will be instructed to take the study drug exactly as prescribed, once in the morning and once in the evening at approximately the same time each day.

Patients will be requested to bring their unused medication to the CRU at each visit. All dosages prescribed and dispensed to the patient and all dose changes including reason for dose changes during the study must be recorded in the eCRF.

5.3. Treatment Compliance

The following measures will be employed to ensure treatment compliance in Part 1:

- The dose will be administered under the supervision of suitably qualified study site staff.
- Immediately after oral administration, visual inspection of the mouth will be performed on each patient.

In Part 2, patients will self-administer all doses of pamiparib at home. Patients will be asked to record daily timing and dose in a dosing diary, and the dosing diary will be reviewed at site visits to check treatment compliance.

5.4. Drug Accountability

The PI (or designee) will maintain an accurate record of the receipt of the study supplies received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each patient and the date of dispensing. 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.

In Part 1, empty, used unit dose containers will undergo radioanalysis to determine the amount of any residual radioactivity remaining after dose administration and will be discarded upon satisfactory completion of the compliance and accountability procedures. Any unused assembled unit doses will be retained until completion of Part 1 of the study before being returned to the Sponsor or disposed of by the study site, per the Sponsor's written instructions or site standard operating procedures (SOPs).

In Part 2, all unused pamiparib will be returned to the study site.

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

5.5. Dose Hold and Modification

The relationship between AEs and pamiparib will be assessed by the PI (or designee). Dosing of pamiparib in Part 2 can be withheld for up to 28 days consecutively.

Criteria for treatment modifications and suggested guidelines for the management of some toxicity related to pamiparib are summarized below. These general guidelines may be modified at the discretion of the PI based on discussions with the Medical Monitor and the best clinical judgment at that time; any decisions should be documented. Any toxicity related to pamiparib 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 2. Pamiparib should be dose-modified as outlined in Table 3.

Table 2: Dose Levels for Pamiparib

Dose Level	Pamiparib
1	60 mg orally, twice daily
-1	40 mg orally, twice daily
-2	20 mg orally, twice daily

Pamiparib may be dose-reduced for a maximum of 2 dose reductions.

Table 3: Criteria for Modification of Pamiparib Dosing for Related Adverse Events

Toxicity	Recommended Dose Modification[a]
Hematologic	
Anemia (hemoglobin, Hgb)	
Grade 2 (Hgb < 10 - 8 g/dL)	First occurrence: continue dosing at current dose level Second and subsequent occurrences: hold pamiparib until resolved to ≤ Grade 1 or baseline • If resolved ≤ 14 days, then maintain dose levels • If resolved > 14 days, then ↓ pamiparib by 1 dose level
Grade 3 (Hgb < 8 g/dL)	Hold pamiparib until resolved to ≤ Grade 1 or baseline • If resolved ≤ 14 days, then maintain dose levels • If resolved > 14 days, then ↓ pamiparib by 1 dose level
Grade 4 (life-threatening consequences; urgent intervention indicated)	Hold pamiparib until resolved to ≤ Grade 1 or baseline and ↓ pamiparib by 1 dose level
Neutropenia (absolute neutrophil count, 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

Toxicity	Recommended Dose Modification[a]
Thrombocytopenia (platelet count, PLT)	
Grade 3 (PLT < 50 - 25 × 10^9/L)	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 (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 7)	
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
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 ≤ 5 × ULN within 14 days, then ↓ pamiparib by 1 dose level • If second episode, permanently discontinue pamiparib • If persistent for > 14 days, permanently discontinue pamiparib
Grade 4 (> 20 × ULN)	Permanently discontinue pamiparib
Pancreatic	
Pancreatitis	
Grade 3 or 4	Permanently discontinue pamiparib

Toxicity	Recommended Dose Modification[a]
Cardiac	
Cardiac - Prolonged QTc interval	
QTcF > 500 ms or > 60 ms from the higher of the baseline or predose value	• Obtain triplicate ECGs (2 to 3 minutes apart) ~ 1 hour after initial ECG • If mean QTcF > 500 ms, or > 60 ms from baseline value, hold pamiparib until evaluation of ECGs by cardiologist o Cardiology evaluation as soon as practical but within 7 days of initial abnormal ECG • If mean QTcF > 500 ms 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
Grade 4	Permanently discontinue pamiparib
Other adverse events	
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: ECG = electrocardiogram; MDRD = Modification of Diet in Renal Disease; 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.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapies

The PI will instruct the patient to notify the study site about any new medical treatment that she/he takes during the study period. All concomitant medications, both permitted and non-permitted, and significant non-drug therapies (eg, surgery, blood transfusions, and physical therapy) administered/conducted after the patient is enrolled in this study will be recorded in the source documents and eCRF. 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 as well.

6.1.1. Permitted Concomitant Treatment

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.

6.1.2. Prohibited Concomitant Treatment

Patients are not allowed to receive other anticancer therapy, including surgery; chemotherapy; radiation therapy; immunotherapy; investigational agents; cytotoxic, biologic, or hormone therapy; anticancer Chinese medicine; or herbal remedies ≤ 14 days (or ≤ 5 half-lives, if applicable, whichever is shorter) prior to first dose and during the study. Hormone replacement therapy is allowed. Bisphosphonate and denosumab use is permitted if the patient had already been receiving it at a stable dose > 28 days before enrollment.

The primary metabolic pathway for pamiparib involves the CYP3A isoform. Administration of strong/moderate inhibitors of CYP3A or strong CYP3A inducers is not allowed ≤ 10 days or ≤ 5 half-lives, whichever is shorter, prior to Day 1 until the EOT visit. Refer to the drugs/substances listed in Appendix 6 for a more complete list of medications that are not allowed or that need to be taken with caution.

6.2. 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. [redacted]

Caffeine-containing foods and beverages will not be allowed from 36 hours before Check-in until discharge from the CRU (Part 1).

Consumption of alcohol will not be permitted from 36 hours prior to Check-in until the end of Part 1.

6.3. Smoking

Patients will not be permitted to use tobacco-containing products while admitted to the CRU. Nicotine replacement therapy will be available on request to be used per the package insert.

6.4. Contraception

Females of childbearing potential, nonsterile males, and female partners of nonsterile male study patients must agree to practice highly effective methods of birth control for the duration of the study and for at least 6 months after the last dose of study drug. Nonsterile males must avoid sperm donation for the duration of the study and for at least 6 months after the last dose of study drug. See Appendix 8 for contraception guidelines.

7. STUDY ASSESSMENTS AND PROCEDURES

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

In Part 1, the recommended order of priority for scheduling procedures around a timepoint is (in descending order of priority):

- Physical examinations
- ECOG
- Vital sign measurements
- ECGs
- Blood and urine samples for clinical laboratory evaluations
- Dosing
- Blood samples for PK assessments of pamiparib, total radioactivity, and metabolites
- Start and end of urine and fecal collections for PK assessments.

In Part 2, assessments will be conducted at study visits as in the Schedule of Assessments in Appendix 4.

7.1. Pharmacokinetic Assessments (Part 1 Only)

7.1.1. Pharmacokinetic and Metabolite Blood Sample Collection and Processing

Blood samples will be collected by venipuncture or cannulation at the times indicated in the Schedule of Assessments in Appendix 4 for determination of pamiparib concentration, total

radioactivity, and metabolite profiling and identification. Procedures for collection, processing, and shipping of blood samples will be detailed in a separate document.

Approximately 1 × 2 mL blood sample will be collected for total radioactivity in whole blood and approximately 1 × 6 mL blood sample will be collected for total radioactivity in plasma. Approximately 1 × 4 mL blood sample will be collected for pamiparib concentration in plasma. Approximately 1 × 10 mL blood sample will be collected for metabolite profiling and identification in plasma.

7.1.2. Pharmacokinetic, Total Radioactivity, and Metabolite Urine and Fecal Collection and Processing

Urine will be collected over the time intervals indicated in the Schedule of Assessments in Appendix 4 for determination of pamiparib concentration, total radioactivity, and metabolite profiling and identification. Procedures for collection, processing, and shipping of urine collections will be detailed in a separate document.

Feces will be collected over the time intervals indicated in the Schedule of Assessments in Appendix 4 for determination of total radioactivity, and, where possible, metabolite profiling and identification. If possible, a single baseline fecal sample will be collected between Check-in on Day -1 and dose administration on Day 1. Procedures for collection, processing, and shipping of fecal collections will be detailed in a separate document.

7.1.3. Emesis Sample Collection

For patients experiencing emesis within 4 hours following oral dosing, vomitus will be collected. If possible, vomitus from patients experiencing emesis after 4 hours postdose will be collected. All vomitus collected will be stored for possible analysis as deemed appropriate.

7.1.4. Analytical Methodology

Plasma and urine concentrations of pamiparib will be determined using a validated analytical procedure. Whole blood, plasma, urine, and feces total radioactivity will be determined with liquid scintillation counting. Profiling and identification of metabolites in plasma, urine, and, where possible, feces will be conducted using standard laboratory procedures. Specifics of the analytical methods will be provided in separate documents.

7.2. Safety and Tolerability Assessments (Parts 1 and 2)

7.2.1. Adverse Events

Adverse event definitions, assignment of severity and causality, and procedures for reporting SAEs are detailed in Section 8.

The condition of each patient will be monitored from the time of signing the ICF to final discharge from 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 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 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.

7.2.2. Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations (including clinical chemistry, hematology, serology, and urinalysis) at the times indicated in the Schedule of Assessments in Appendix 4. Clinical laboratory evaluations are listed in Appendix 1.

For all female patients of childbearing potential, a pregnancy test will be performed at the times indicated in the Schedule of Assessments (Part 1 and Part 2) in Appendix 4. An FSH test will be performed at Screening to confirm postmenopausal status.

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

7.2.3. Vital Signs

Supine blood pressure, supine heart rate, and oral body temperature will be assessed at the times indicated in the Schedule of Assessments in Appendix 4. Vital signs will be performed at other times if judged to be clinically appropriate, if the ongoing review of the data suggests a more detailed assessment of vital signs is required. These data will be captured in the eCRF. In line with local CRU policies, vital signs will also be assessed at other timepoints but will not be documented unless determined to be of clinical relevance.

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 in Part 1, blood pressure, heart rate, and temperature measurements should be conducted in the morning.

7.2.4. 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 4.

Single 12-lead ECGs will be repeated once if outside the clinical reference range.

In the case of an abnormality such as prolonged QT interval corrected for heart rate using Fridericia's formula > 500 msec or > 60 msec from the highest baseline or predose value, new arrhythmia, or other clinically significant finding, ECGs will be recorded in triplicate at least 2 minutes apart.

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 that a more detailed assessment of ECGs is required. The PI (or designee) will perform a clinical assessment of each 12-lead ECG.

7.2.5. Physical Examination

Complete and limited physical examinations will be performed at the timepoints specified in the Schedule of Assessments in Appendix 4. 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.

7.2.6. Eastern Cooperative Oncology Group

The ECOG performance status will be evaluated at the times indicated in the Schedule of Assessments in Appendix 4.

7.2.7. Tumor Assessments

Tumor imaging (CT or magnetic resonance imaging [MRI], with preference for CT) will be performed at Screening or Part 2 Pre-dose Visit and every 12 weeks (± 7 days) from the time of the Part 2 C1D1. At the PI's discretion, CT or MRI scans may be repeated at any time if PD is suspected.

A CT scan or MRI of the thorax, abdomen, and pelvis plus other relevant evaluations as appropriate will be performed to assess all known disease.

The same imaging technique should be used for each patient throughout the study.

7.3. End-of-Treatment Visit

The EOT visit should occur within 7 days after pamiparib has been permanently discontinued. Required assessments are listed in Appendix 4. 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. The visit at which tumor assessments showed PD may be used as the EOT visit provided that 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.

7.4. Follow-up Assessments

7.4.1. Safety Follow-up

All patients who discontinue pamiparib will have a safety follow-up approximately 30 days after the last day of study drug or before initiation of new anticancer therapy, whichever comes first. The purpose of this visit is to collect AEs and SAEs that may have occurred after the patient discontinued from the study drug, as well as to record any additional concomitant medications and to conduct a limited physical examination. For patients who complete Part 2, clinical laboratory evaluations are only required if the patient had an ongoing clinical laboratory abnormality at the previous visit that the PI considered to be related to study drug.

8. SAFETY MONITORING AND REPORTING

The PI 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.

8.1. Adverse Events

8.1.1. 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 pamiparib or not.

Examples of an AE 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 PI to review all documentation (eg, hospital progress notes, laboratory results, and diagnostics reports) relative to the AE or SAE.

The PI 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 before submission to the Sponsor.

8.1.2. Assessment of Severity

The PI will make an assessment of severity for each AE and SAE reported during the study. Adverse events and SAEs should be assessed and graded based upon the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 or higher.

Toxicities that are not specified in the National Cancer Institute Common Terminology Criteria for Adverse Events 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 (eg, 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 below in Section 8.8.

8.1.3. Assessment of Causality

The PI is obligated to assess the relationship between the study drug and the occurrence of each AE or SAE. The PI will use clinical judgment to determine the relationship. 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 the study drug will be considered and investigated. The PI will also consult the IB[6] in the determination of his assessment.

There may be situations when an SAE has occurred and the PI has minimal information to include in the initial report to the Sponsor. However, it is very important that the PI always make an assessment of causality for every SAE before transmission of the SAE report/eCRF to the Sponsor since the causality assessment is one of the criteria used when determining regulatory reporting requirements. The PI may change his opinion of causality in light of follow up information, amending the SAE report accordingly.

The causality of each AE should be assessed and classified by the PI as “related” or “not related.” An AE is considered related if there is “a reasonable possibility” that the AE may have

been caused by the study drug (ie, there are facts, evidence, or arguments to suggest possible causation). A number of factors should be considered in making this assessment, including:

- Temporal relationship of the AE to the administration of study drug/study procedure
- Whether an alternative etiology has been identified
- Mechanism of action of the study drug
- Biological plausibility.

An AE should be considered "related" to study drug if any of the following criteria are met, otherwise the event should be recorded 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 the study drug). However, the influence of other factors may have contributed to the AE (eg, the patient's clinical condition or other concomitant AEs).

8.1.4. Follow-up of Adverse Events

After the initial AE or SAE report, the PI 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 PI 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, histopathological examinations, or consultation with other health care professionals.

The Sponsor may request that the PI 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 PI 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.

New or updated information will be recorded on the originally completed SAE report, with all changes signed and dated by the PI. The updated SAE report should be re-sent to the Sponsor within the timeframes outlined in Table 4.

8.2. Laboratory Test Abnormalities

Abnormal laboratory findings (eg, hematology or chemistry) or other abnormal assessments (eg, ECGs or vital signs) that are judged by the PI as clinically significant will be recorded as AEs or SAEs. This includes clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study. The definition of clinically significant is left to the judgment of the PI. In general, these are the laboratory test abnormalities that are associated with clinical signs or symptoms, require active medical intervention, or lead to dose interruption, discontinuation, or further diagnostic investigation.

8.3. Definition of a Serious Adverse Event

An SAE is defined as 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 which 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.

- 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 PI 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 is not considered an SAE

- Hospitalization for social/convenience considerations is not considered an SAE
- Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience, is not considered an SAE.

8.4. Timing, Frequency, and Method of Capturing Adverse Events and Serious Adverse Events

8.4.1. Adverse Event Reporting Period

After the ICF has been signed, but prior to administration of study drug, only SAEs should be reported. After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, 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 PI should report any SAEs that are believed to be related to study drug.

8.4.2. Eliciting Adverse Events

The PI or designee will inquire 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?

8.5. Disease Progression

Disease progression (including fatal disease progression), which is expected in this study population, should not be reported as an AE term. Instead, the symptoms, signs, or clinical sequelae that result from disease progression should be reported as the AE term(s).

For instance, a patient with pleural effusion presents with shortness of breath. The cause of the shortness of breath is a pleural effusion resulting from disease progression. The AE term should be reported as “pleural effusion” instead of disease progression. If a patient has a seizure that is determined to be associated with a brain metastasis, the term “seizure” should be recorded as the AE instead of disease progression or brain metastasis. If a patient experienced multi-organ failure due to disease progression, the term “multi-organ failure” should be reported as the SAE with death as the outcome instead of reporting “fatal disease progression” or “death due to disease progression.”

8.6. Death

Death is an outcome and usually not 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”).

8.7. Myelodysplastic Syndrome and Acute Myeloid Leukemia

Events of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) should be treated as medically serious, even if the patient is not admitted to a hospital. These events should be reported to the Sponsor irrespective of the time elapsed since the end of study treatment.

8.8. Reporting Serious Adverse Events

8.8.1. Prompt Reporting of Serious Adverse Events

As soon as the PI determines that an AE meets the protocol definition of an SAE, the event must be reported promptly (within 24 hours) to the Sponsor or designee as described in Table 4.

Table 4: Timeframes for Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

Type of SAE	Timeframe for Making Initial Report	Documentation Method	Timeframe for Making Follow-up Report	Documentation Method	Reporting Method
All SAEs	Within 24 hours of first knowledge of the AE	SAE form	As expeditiously as possible	Updated SAE form	Email or fax SAE form or Pregnancy form

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

8.8.2. Completion and Transmission of the Serious Adverse Event Report

Once the PI becomes aware that an SAE has occurred in a patient, he will report the information to the Sponsor within 24 hours as detailed above in Table 4. 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.

If the PI does not have all information regarding an SAE, he will not 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 PI must always provide an assessment of causality for each SAE as described in Section 8.1.3.

8.9. Regulatory Reporting Requirements for Serious Adverse Events

The PI will promptly report all SAEs to the Sponsor in accordance with the procedures detailed above. 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 PI, 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 Ethics Committee (EC).

All suspected unexpected serious adverse reactions (SUSARs; as defined in Section 8.10) will be submitted to all applicable regulatory authorities and Investigators for pamiparib studies.

When a study site receives an initial or follow-up report or other safety information (eg, revised IB) from the Sponsor, the PI or designate responsible is required to promptly notify his/her EC. The PI should place copies of Safety Reports from the Sponsor in the Investigator Site File.

8.10. Suspected Unexpected Serious Adverse Reactions

A SUSAR is a serious adverse reaction that is both unexpected (ie, not present in the product's Reference Safety Information) and meets the definition of a serious adverse drug reaction, the specificity or severity of which is not consistent with those noted in the IB.

8.11. Pregnancy Reporting

If a female patient or the partner of a male patient becomes pregnant while receiving study drug or within 6 months after the completion of the last dose of study drug, a pregnancy report form should 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.

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 always be reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a patient exposed to the study drug should be recorded and reported as an SAE.

8.12. Post Study Adverse Events

A post study AE or SAE is defined as any AE that occurs outside of the AE/SAE reporting period.

The PI should follow up patients for post study period cases of MDS and AML. If the PI learns of any study drug-related SAE, including a death, at any time after a patient has been discharged from the study, he/she should notify the Sponsor using the SAE procedure.

8.13. Expedited Reporting to Health Authorities, Ethics Committees, and the Principal Investigator

The Sponsor will promptly assess all SAEs against cumulative study drug experience to identify and expeditiously communicate new safety findings to regulatory authorities, the PI, and ECs based on applicable legislation. To determine the reporting requirements for individual SAEs, the

Sponsor will assess the expectedness of the SAEs using the following reference safety information document:

- Pamiparib (BGB-290) IB[6].

8.14. Regulatory, Ethical, and Study Oversight Considerations

8.14.1. Regulatory and Ethical Considerations

This study will be conducted 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 ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, and other relevant documents must be submitted to an 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 nonsubstantial 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.

8.14.2. Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

8.14.3. 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.

8.14.4. 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.

8.14.5. 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.

8.14.6. 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.
- Covance 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 from 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 5 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.

8.14.7. 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 electronically to the Sponsor or designee, 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.

8.14.8. Publications and Data Sharing

A Clinical Study Report (CSR) will be prepared and provided to the regulatory agency(ies). BeiGene Ltd. (the Sponsor) 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 the 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. 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.[12]

After conclusion of the study and without prior written approval from the Sponsor, the PI 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 the Sponsor in an abstract, manuscript, or presentation form; or
- The study has been completed for at least 2 years.

No such communication, presentation, or publication will include the Sponsor's confidential information.

The PI agrees to submit all manuscripts or congress abstracts and posters/presentations to the Sponsor prior to submission. This allows the Sponsors to protect proprietary information, provide comments based on information from other studies that may not yet be available to the PI, 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 PI's clinical study agreement.

9. SAMPLE SIZE AND DATA ANALYSIS

9.1. Determination of Sample Size

No formal statistical assessment of sample size has been conducted. The sample size chosen for this study is common in human radiolabeled studies and is considered sufficient to achieve the objectives of the study. Up to approximately 10 patients will be enrolled and studied in order that 4 patients complete Part 1 of the study.

9.2. Analysis Populations

9.2.1. Pharmacokinetic Population

The PK population will include all patients who received [^{14}C]-pamiparib and have evaluable PK data. Patients will be excluded from the PK summary statistics and statistical analysis if a patient has an AE of vomiting that occurs at or before 2 times median t_{max}.

9.2.2. Safety Population

The safety population will include all patients who received [^{14}C]-pamiparib.

9.3. Pharmacokinetic Analyses

Plasma and urine PK parameters of pamiparib and whole blood and plasma parameters of total radioactivity will be calculated using standard noncompartmental methods.

Additional noncompartmental PK parameters may be determined where appropriate.

Pharmacokinetic parameters will be summarized using descriptive methodology. No formal statistical analysis will be performed.

Descriptive statistics (mean, median, minimum, maximum, standard deviation, geometric mean, and geometric coefficient of variation) will be calculated for all PK parameters and PK concentration data where applicable.

Specification of PK parameters to be presented in the CSR; procedures for accounting for missing, unused, or spurious data; procedures for reporting deviations from the original statistical plan; and selection of patients to be included in the analyses population(s) will be presented in the CSR and/or the Statistical Analysis Plan as appropriate.

All statistical summary calculations will be performed using SAS® Version 9.4 or greater.

9.4. Safety Analysis

All AEs will be listed and summarized using descriptive methodology. No formal statistical analysis will be performed. The incidence of AEs will be presented by severity and by relationship with the study drug as determined by the PI (or designee). Each AE will be coded using the Medical Dictionary for Regulatory Activities.

Patient ECOG performance will be reported for the Safety population and will be listed.

9.5. Interim Analysis

No interim analyses are planned for this study.

10. REFERENCES

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11. APPENDICES

Appendix 1: Clinical Laboratory Evaluations

Clinical Chemistry:	Hematology:	Urinalysis:	Serology[a]:
Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Albumin Total bilirubin Direct bilirubin Blood urea nitrogen or urea Potassium Sodium Corrected calcium Creatinine Glucose Lactate dehydrogenase Total protein	Hematocrit Hemoglobin Platelet count Red blood cell (RBC) count White blood cell (WBC) count WBC differential: Lymphocytes Neutrophils	Blood Glucose Ketones pH Protein Specific gravity Urobilinogen Microscopic examination	Hepatitis B surface antigen Hepatitis C antibody **Hormone Panel – females only** Follicle-stimulating hormone (FSH)[b] Serum pregnancy test (human chorionic gonadotropin)[c] Urine pregnancy test[d]

a. Only analyzed at Screening.
b. Performed at Screening on postmenopausal females only.
c. Performed at Screening on female patients of childbearing potential.
d. Performed on females of childbearing potential at Day -1 (Part 1) and on Day 1 of each treatment cycle (Part 2). A positive urine pregnancy test will be confirmed with a serum pregnancy test.

Appendix 2: Total Blood Volume

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

Part 1:

	Volume per blood sample (mL)	Maximum estimated number of blood samples	Total amount of blood (mL)
Clinical chemistry	4.7	4	18.8
Hematology	2.7	4	10.8
Serology	7.5	1	7.5
Glucose	2.7	4	10.8
Plasma for pamiparib concentration	4	16	64
Whole blood for total radioactivity	2	16	32
Plasma for total radioactivity	6	16	96
Plasma for metabolite profiling and identification	10	11	110
Total:			349.9

Part 2:

	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 Follow-up visits			
Clinical chemistry	4.7	1	4.7
Hematology	2.7	1	2.7
Glucose	2.7	1	2.7
	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

If extra blood samples are required in Part 1, the maximum blood volume to be withdrawn per patient will not exceed 400 mL. If extra blood samples are required in Part 2, the maximum blood volume to be withdrawn per patient will not exceed 40 mL per cycle.

Appendix 3: Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	Description
0	Fully active, able to carry on all pre-diseases 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: Schedule of Assessment

Schedule of Assessments – Part 1

Study Procedures	Screening[a]	Days				Part 1 Follow-up Visit[c]
		-1	1	2-7	7-14[b]	
Informed consent	X					
Inclusion/exclusion criteria	X	X				
Demographic data[d]	X					
Medical history/current medical conditions[e]	X					
Alcohol breath test	X	X				
Serology	X					
Follicle-stimulating hormone[f]	X					
Pregnancy test[g]	X	X				
Height	X					
Body weight	X	X				X
ECOG performance status	X	X	X			
Tumor assessments: CT or MRI scan	X					
Study residency:						
Check-in		X				
Check-out				X[b]		
Non-residential visit	X				X	X
Study drug administration:						
[^{14}C]-pamiparib (60 mg)			X			
Pharmacokinetics[h]:						
Blood sampling for pamiparib concentration (plasma)[h 1]			X	X	X	
Blood sampling for total radioactivity (whole blood and plasma)[h 2]			X	X	X	

Schedule of Assessments – Part 1

Study Procedures	Screening[a]	Days				Part 1 Follow-up Visit[c]
		-1	1	2-7	7-14[b]	
Blood sampling for metabolite profiling and identification (plasma)[h 3]			X	X		
Urine collection for pamiparib concentration, total radioactivity, and metabolite profiling and identification[h 4]			X	X	X	
Fecal collection for total radioactivity and metabolite profiling and identification[h 5]			X	X	X	
Safety and tolerability:						
Adverse event recording	X	X	X	X	X	X
Prior/concomitant medication monitoring	X	X	X	X	X	X
Clinical chemistry, hematology, and urinalysis	X	X		X (Day 5)		X
Vital signs[i]	X	X	X	X (Day 5)	X	X
12-lead electrocardiogram[j]	X	X	X	X (Day 5)		X
Complete physical examination[k]	X	X				
Limited physical examination[l]			X	X (Day 5)	X	X

Abbreviations: CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; MRI = magnetic resonance imaging; QTc(F) = QT interval corrected for heart rate using Fridericia's formula.

a. **Screening:** Screening period extends from Day -28 to Day -2. The Screening assessments must be performed within 28 days before dosing.
b. **Discharge:** Patients can be discharged on Day 7, or before at the discretion of the PI if the discharge criteria are met: approximately 90% mass balance recovery, or < 1% of total dose recovered in urine and feces for 2 consecutive 24-hour collection intervals. If the discharge criteria have not been met on Day 7, patients may be asked to collect 24-hour excreta samples for up to 7 days on a non-residential basis.
c. **Follow-up visit**: to occur within 7 days of Discharge (if on Day 7 or before), or final non-residential visit (if discharge criteria have not been met by Day 7). If the patient is discontinued from the study, a Follow-up visit should occur within 7 days after dosing, and subjects will attend a Safety Follow-up visit approximately 30 days after the last day of study drug administration or before initiation of new anticancer therapy, whichever occurs first. This visit may occur later than 7 days

after discussion with the Medical Monitor for specific circumstances, such as prolonged hospitalization. An ECG does not need to occur at the End-of-Treatment visit if one was performed within 14 days prior to the visit. This visit will count as the patient's End-of-Treatment visit.

d. **Demographics:** Date of birth, gender, ethnicity, and race must be recorded.
e. **Medical History/Current Medical Conditions:** General and disease-specific medical history including a history of past and current medical conditions must be recorded at Screening.
f. **Follicle-stimulating hormone:** conduced in postmenopausal females only.
g. **Pregnancy test (in female patients of childbearing potential):** Performed in serum at Screening and in urine at all other times. A positive urine pregnancy test will be confirmed with a serum pregnancy test.
h. **PK sample timepoints:**
    1. **Blood sampling for pamiparib concentration (plasma)**: Predose and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 6, 12, 24, 48, 72, 96, 120, and 144 hours postdose. If patient does not meet discharge criteria by Day 7, additional samples may be collected every 24 hours after Day 7.
    2. **Blood sampling for total radioactivity (plasma and whole blood)**: Predose and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 6, 12, 24, 48, 72, 96, 120, and 144 hours postdose. If patient does not meet discharge criteria by Day 7, additional samples may be collected every 24 hours after Day 7.
    3. **Blood sampling for metabolite analysis (plasma):** 0.5, 1, 2, 6, 12, 24, 48, 72, 96, 120, and 144 hours postdose.
    4. **Urine collection:** Predose (within 1 hour prior to dosing [patients will be asked to empty their bladder immediately prior to administration of [^{14}C]-pamiparib on Day 1]) and 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, and 120 to144 hours postdose. Complete daily urine output may be collected at home if ≥ 90% of the radioactivity dose is not recovered while the patient is in the CRU.
    5. **Fecal collection:** Predose (-12 to 0 hours) and 0 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, and 120 to 144 hours postdose. Complete daily fecal output may be collected at home if ≥ 90% of the radioactivity dose is not recovered while the patient is in the Clinical Research Unit.

    For subjects who meet Discharge criteria and are discharged from the CRU prior to Day 7, blood, urine, and feces sampling for PK will cease.

i. **Vital signs:** Blood pressure, heart rate, and temperature must be measured after the patient has been supine for at least 5 minutes at Screening and in the morning during the in-house period
j. **ECG:** Single 12-lead ECGs will be repeated once if outside the clinical reference range. A single ECG will be recorded unless there is an abnormality such as prolonged QTc(F) > 500 msec or > 60 msec from the highest baseline or predose value, new arrhythmia, or other clinically significant finding, then ECGs will be recorded in triplicate at least 2 minutes apart. ECGs will be recorded after the patient has been supine for at least 5 minutes.
k. **Complete physical examination:** 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.
l. **Limited physical examination:** A limited physical examination includes assessment of general appearance and additional examination of symptomatic systems or those affected by the patient's disease.

Schedule of Assessments – Part 2

Study Procedures		Cycles 1 and 2		Cycles 3+[b]		
Day of Cycle	Predose Visit[a]	D1[c]	D15	D1	End-of-treatment Visit[d]	Follow-up Visit[e]
Allowed time window (days)	≤ 7 days prior to Cycle 1 D1	±2	±2	±2		
Body weight	X	X		X	X	
Pregnancy test[f]		X		X	X	
Study drug administration:						
Pamiparib (60 mg twice daily)[g]		X		X		
Assessments:						
ECOG performance status		X		X	X	
Tumor assessments: CT or MRI scan[h]	X (12 week intervals ± 7 days)					
Safety and tolerability:						
Adverse event recording	X	X	X	X	X	X
Prior/concomitant medication	X	X	X	X	X	X
Clinical chemistry and hematology	X	X	X	X	X	X[i]
Urinalysis	X	X			X	
Vital signs[i]	X	X	X	X	X	
12-lead electrocardiogram[j]	X				X	
Limited physical examination[k]	X	X		X	X	X

Abbreviations: CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; MRI – magnetic resonance imaging; QTc(F) = QT interval corrected for heart rate using Fridericia's formula.

a. **Predose visit:** The Follow-up visit for Part 1 may be used as the predose visit for Part 2 if it occurs ≤ 7 days prior to the start of pamiparib treatment in Part 2. In this event, assessments only need to be conducted once.
b. **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.
c. **Cycle 1, Day 1:** Assessments will be conducted prior to first dosing in Part 2.
d. **End-of-treatment 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 End-of-Treatment visit if one was performed within 14 days prior to the visit.

e. **Safety Follow-up visit:** Approximately 30 days after the last day of study drug administration or before initiation of new anticancer therapy, whichever occurs first; a safety follow-up will occur with the outlined safety assessments. 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.
f. **Pregnancy test (in female patients of childbearing potential):** Urine pregnancy test conducted as indicated. A positive urine pregnancy test will be confirmed with a serum pregnancy test.
g. **Dosing:** Pamiparib capsules should be administered continuously from Cycle 1 Day 1 (60 mg twice daily), until patients are discontinued from treatment.
h. **CT or MRI scan:** Scan to be done every 12 weeks ± 7 days from the time of Part 2 C1D1.
i. **Vital Signs:** Blood pressure, heart rate, and temperature must be measured after the patient has been supine for 5 minutes at Screening.
j. **ECG** 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.
k. **Limited physical examination:** A 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 whilst the patient is attending the clinic.
l. **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 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 and Medications to Be Used with Caution

Strong and Moderate Cytochrome P450 (CYP)3A 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

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: Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 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. Read more about creatinine standardization. This CKD-EPI equation calculator should be used when Scr 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 × min (Scr /κ, 1)α × max(Scr /κ, 1)-1.209 × 0.993Age × 1.018 [if female] × 1.159 [if black]

where:

Scr 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 Scr /κ or 1, and

max indicates the maximum of Scr /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/healthinformation/health-communication-programs/nkdep/lab-evaluation/gfr-calculators/Pages/gfrcalculators.aspx.

Appendix 8: Contraception Guidelines and Definitions of "Women of Childbearing Potential", "No Childbearing Potential"

Contraception Guidelines

All male patients with partners of childbearing potential who take part in this study, must use condoms during sexual intercourse in addition to one of the highly effective methods of contraception listed below, from the time of taking the first dose of pamiparib until 6 months after taking the last dose of pamiparib. If a female partner of a male patient is already pregnant, the male patient must use condoms during sexual intercourse for the duration of the study and for at least 6 months after the last dose of pamiparib.

Female patients of childbearing potential must use one of the highly effective forms of birth control below (preferably those with low user dependency) for the duration of the study and for at least 6 months after the last dose of pamiparib.

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, or 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*, provided that the vasectomized partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of surgical success
- 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 not considered a highly effective method of contraception and if used, this method must be combined with another acceptable method listed above.

*Contraception methods that in the context of this protocol 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 females who are physiologically capable of becoming pregnant.

Conversely, "women of no childbearing potential" are defined as females meeting any 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 and all alternative medical causes for the lack of spontaneous menses for ≥ 12 months have been ruled out, such as polycystic ovarian syndrome, hyperprolactinemia, etc.

If an FSH measurement is required to confirm postmenopausal state, concomitant use of hormonal contraception or hormonal replacement therapy should be excluded.

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

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