STATISTICAL ANALYSIS PLAN

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

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Clinical Phase 1

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1 STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURES

By signing this page when the Statistical Analysis Plan (SAP) is considered final, the signatories agree to the statistical and pharmacokinetic (PK) analyses to be performed for this study, and to the basic format of the tables, figures, and listings (TFLs). Once the SAP has been signed, programming of the TFLs based upon this document can proceed. Any modifications to the SAP and TFLs made after signing may result in a work-scope change.

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3 ABBREVIATIONS

Abbreviations pertain to the SAP only (not the TFLs).

ADaM	analysis data model
AE	adverse event
A_{ef}	Amount excreted in the feces per sampling interval
A_{eu}	Amount excreted in urine per sampling interval
AUC	area under the concentration-time curve
AUC_{0-t}	AUC from time 0 to the time of last quantifiable concentration, calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations
$AUC_{0-\infty}$	AUC from time zero to infinity
$AUC_{0-\infty}$ Blood/Plasma Ratio	Ratio of $AUC_{0-\infty}$ of whole blood total radioactivity relative to $AUC_{0-\infty}$ of plasma total radioactivity
$AUC_{0-\infty}$ Plasma Pamiparib / Total Radioactivity Ratio	Ratio of $AUC_{0-\infty}$ of plasma pamiparib relative to $AUC_{0-\infty}$ of plasma total radioactivity
BLQ	below the limit of quantification
CDISC	Clinical Data Interchange Standards Consortium
BID	twice daily
CL/F	Apparent total plasma clearance (pamiparib only)
CL_R	Renal clearance (pamiparib only)
C_{max}	maximum observed concentration
CSR	Clinical Study Report
CRU	Clinical Research Unit
CT	computed tomography
Cum A_{ef}	Cumulative amount excreted in feces
Cum A_{eu}	Cumulative amount excreted in urine
Cum $\%f_{ef}$	Cumulative percentage of radioactive dose excreted in feces
Cum $\%f_{eu}$	Cumulative percentage of drug or radioactive dose excreted in urine
CV%	coefficient of variation
EC	Early Clinical
ECG	electrocardiogram

ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOT	End-of-treatment
$\%f_{ef}$	Percentage of radioactive dose excreted in feces per sampling interval
$\%f_{eu}$	Percentage of drug or radioactive dose excreted in urine per sampling interval
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
λz	Apparent terminal elimination rate constant
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NR	no result
NC	not calculated
NDA	New Drug Application
PI	Principal Investigator
PK	pharmacokinetic
QTc	QT correction; QT interval corrected for heart rate
QTcF	QTc calculated using the Fridericia correction
SAP	Statistical Analysis Plan
$t_{1/2}$	Apparent terminal elimination half-life
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
t_{max}	Time of C_{max}
V_z/F	Apparent volume of distribution during the terminal elimination phase (pamiparib only)
WHO	World Health Organization

4 INTRODUCTION

This SAP has been developed after review of the clinical study protocol (Final Version 1.0 dated 25 June 2018) and protocol amendment Version 3 dated 12 December 2018.

This SAP describes the planned analysis of the safety, tolerability and PK data from this study. A detailed description of the planned TFLs to be presented in the Clinical Study Report (CSR) is provided in the accompanying TFL shell document.

The intent of this document is to provide guidance for the statistical analyses of PK data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement between BeiGene, Ltd. and Covance Early Clinical (EC) Biometrics. A limited amount of information concerning this study (eg, objectives, study design) is given to help the reader's interpretation. This SAP must be finalized prior to the lock of the clinical database for this study. When the SAP and TFL shells are agreed upon and finalized, they will serve as the template for this study's CSR.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon between BeiGene, Ltd. and Covance EC Biometrics and identified in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 guideline entitled, "Guidance for Industry: Statistical Principles for Clinical Trials" and the ICH E3 guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports."[1,2]

5 STUDY OBJECTIVES

5.1 Primary Objectives

- 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 faecal recovery of total radioactivity

5.2 Secondary Objectives

- 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

6 STUDY DESIGN

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.

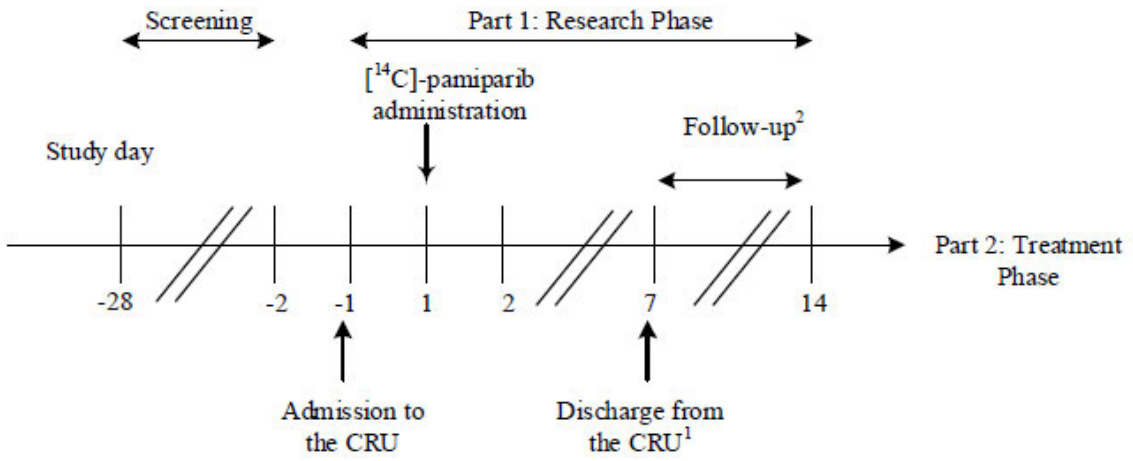
An overview of the study design for Part 1 and Part 2 is shown in Figure 1 and Figure 2, respectively.

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.

6.1 Study Part 1 (Research Phase)

Figure 1: 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

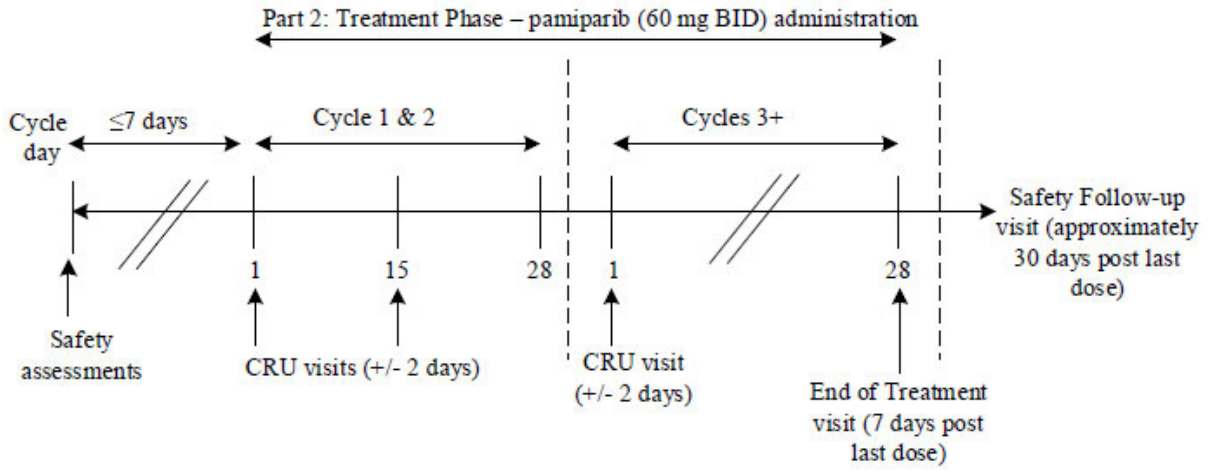
If the discharge criteria have not been met on Day 7, patients may be asked to collect 24-hour excreta samples for up to a further 7 days (up to Day 14) on a non-residential basis. Patients may be required to remain resident at the CRU for longer than 7 days if deemed necessary by the PI to ensure patient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

6.2 Study Part 2 (Treatment Phase)

Figure 2: Study Schematic: Part 2



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, 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.

7 TREATMENTS

The following is a list of the study treatment abbreviations and ordering that will be used in the TFLs.

Part	Study Treatment Name
1	60 mg [^{14}C]-pamiparib
2	60 mg pamiparib BID

8 SAMPLE SIZE JUSTIFICATION

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 DEFINITION OF ANALYSIS POPULATIONS

The **Safety Population for part 1** will consist of all patients who received at least 1 dose of study drug, 60 mg [^{14}C]-pamiparib in Part 1.

The **Safety Population for part 2** will consist of all patients who received at least 1 dose of 60 mg pamiparib in Part 2.

The **PK Population** will consist of all patients who received at least 1 dose of study drug (60 mg [^{14}C]-pamiparib, and have evaluable PK data. A patient will be excluded from the PK summary statistics and statistical analysis if the patient has an adverse event (AE) of vomiting that occurs at or before 2 times median time to maximum concentration (t_{max}).

All protocol deviations that occur during the study will be considered prior to database lock for their severity/impact and will be taken into consideration when patients are assigned to analysis populations. Details of patient assignment to the analysis populations will be listed.

10 STATISTICAL METHODOLOGY

10.1 General

Data listings will be provided for the Safety Population. Summary statistics and statistical analyses will be performed for patients included in the relevant analysis populations (Safety/PK).

For continuous data, summary statistics will include the arithmetic mean, arithmetic standard deviation, median, minimum, maximum, and number. For log-normal data (eg, the PK parameters: areas under the concentration-time curve [AUCs] and maximum observed concentration [C_{max}]), the geometric mean and geometric coefficient of variation (CV%) will also be presented. For categorical data, frequency counts and percentages will be presented. Data listings will be provided for all patients up to the point of withdrawal, with any patients excluded from the relevant population highlighted. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Missing values will not be imputed.

Data analysis will be performed using SAS® Version 9.4 or higher.

Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) ADaM Version 2.1, and CDISC ADaM Implementation Guide Version 1.1. Pinnacle 21 Community Validator Version 2.2.0 will be utilized to ensure compliance with CDISC standards.

10.1.1 Definition of Baseline and Change from Baseline

Baseline for each parameter is in each part defined as the last value measured prior to dosing for that part i.e. Baseline for Part 1 is to be the last value prior to dosing for Part 1 and for Part 2, last value prior to the 1st dose in Part 2, including repeat (vital signs and electrocardiograms [ECGs]) and unscheduled (clinical laboratory parameters) readings (see Section 10.1.2 for definitions of repeat and unscheduled readings). For ECGs taken in triplicate, baseline will be the mean of the last 3 values taken prior to dosing.

Mean change from baseline is the mean of all individual patient's change from baseline values. Each individual change from baseline will be calculated by subtracting the individual patient's baseline value from the value at the timepoint. The individual patient's change from baseline

values will be used to calculate the mean change from baseline using a SAS procedure such as Proc Univariate.

10.1.2 Repeat and Unscheduled Readings

Repeat readings occur when the original vital signs or ECG result requires confirmation. Repeat readings are labelled as 'Repeat' in the listings and replace the original readings in all summaries and changes from baseline presentations and calculations. Prior to dosing, all readings taken in addition to the original reading are defined as predose repeats. Postdose repeat readings are defined as readings collected within 15 minutes of the actual time of the original reading. Where results are taken in triplicate and repeated, the last 3 readings are used in all subsequent calculations**.**

With the exception of predose results described above, unscheduled readings for vital signs or ECGs are defined as readings collected >15 minutes from the actual time of the original reading. Where results are taken in triplicate, the original reading is defined as the first reading of the triplicate. All results not taken at a scheduled timepoint for other data types (eg, clinical laboratory parameters) are unscheduled. Unscheduled readings are labelled as 'Unscheduled' in the listings. Because unscheduled readings are not associated with any scheduled timepoint, they are excluded from all summaries (with the exception that they may be used as baseline, as stated in Section 10.1.1).

10.2 Demographics and Patient Disposition

The demographic variables age, sex, race, ethnicity, body weight, height, and body mass index will be summarized and listed. If only a subset of patient's progress from part 1 to part 2 then demographics will be also presented by part. Patient disposition will be summarized and listed.

Disease-specific characteristics and surgical history, including previous cancer treatment will be summarized and listed. Medical history data will be listed.

10.3 Pharmacokinetic Assessment

10.3.1 Pharmacokinetic Analysis

The following PK parameters will be determined where possible from the plasma concentrations of pamiparib and the whole blood and plasma concentrations of total radioactivity using non-compartmental methods performed using Phoenix WinNonlin (Version 8.1 or higher):

Parameter	Definition
AUC_{0-t}	AUC from time 0 to the time of last quantifiable concentration, calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations
$AUC_{0-\infty}$	AUC from time zero to infinity
AUC_{0-9}	AUC from time zero to 9 hours postdose
AUC_{0-12}	AUC from time zero to 12 hours postdose
C_{max}	Maximum observed concentration
t_{max}	Time of C_{max}
λ_z	Apparent terminal elimination rate constant
$t_{1/2}$	Apparent terminal elimination half-life
CL/F	Apparent total plasma clearance (pamiparib only)
V_z/F	Apparent volume of distribution during the terminal elimination phase (pamiparib only)
$AUC_{0-\infty}$ Blood/Plasma Ratio	Ratio of $AUC_{0-\infty}$ of whole blood total radioactivity relative to $AUC_{0-\infty}$ of plasma total radioactivity
$AUC_{0-\infty}$ Plasma pamiparib / Total Radioactivity Ratio	Ratio of $AUC_{0-\infty}$ of plasma pamiparib relative to $AUC_{0-\infty}$ of plasma total radioactivity

Additional PK parameters may be determined where appropriate.

The ratio of AUC total radioactivity in whole blood to AUC total radioactivity in plasma and the ratio of AUC of plasma pamiparib to AUC total radioactivity in plasma will be based on $AUC_{0-\infty}$. Where $AUC_{0-\infty}$ cannot be reliably calculated an alternative AUC measure, such as AUC to a common time point or AUC_{0-t}, may be used.

Additionally, blood-to-plasma ratios at each sampling time point will be calculated to determine partitioning of total radioactivity into red blood cells. Plasma pamiparib-to-total radioactivity ratios at each sampling time point will be calculated to determine the fraction of total radioactivity attributed to pamiparib. These ratios will be calculated by the radioanalysis laboratory and reported in the radioanalysis report

The PK analysis will, where possible, be carried out using actual postdose times recorded in the raw data.

Concentrations are used as supplied by the analytical laboratory for PK analysis. The units of concentration and resulting PK parameters, with amount or concentration in the unit, will be presented as they are received from the analytical laboratory.

The C_{max} and t_{max} will be obtained directly from the plasma concentration-time profiles. For multiple peaks, the highest postdose concentration will be reported as C_{max}. In the case that multiple peaks are of equal magnitude, the earliest t_{max} will be reported.

The following excretion parameters will be calculated, whenever possible, based on the urine concentrations of pamiparib using Phoenix WinNonlin (Version 8.1 or higher):

Parameter	Definition
A_{eu}	Amount excreted in urine per sampling interval
Cum A_{eu}	Cumulative amount excreted in urine
CL_R	Renal clearance, where: CL_R = Cum A_{eu} / AUC $AUC_{0-\infty}$ may be used, if appropriate (pamiparib only)
$\%f_{eu}$	Percentage of drug or radioactive dose excreted in urine per sampling interval
Cum $\%f_{eu}$	Cumulative percentage of drug or radioactive dose excreted in urine

The amount excreted in urine (A_{eu}) for each collection interval will be calculated as the product of urine concentration and urine sample weight (assuming a specific gravity of 1 g/mL); Cum A_{eu} will be calculated by summing the A_{eu} values for each collection interval over the entire collection period.

The percent of the dose excreted ($\%f_{eu}$) will be calculated for each urine collection interval (i) according to the following formula: $\%f_{eu}(i) = [f_{eu}(i) / dose] \times 100$

Cum $\%f_{eu}$ will be calculated by summing the $\%f_{eu}$ values for each collection interval over the entire collection period.

The following PK parameters will be calculated, whenever possible, based on the fecal total radioactivity concentrations:

Parameter	Definition
A_{ef}	Amount excreted in the feces per sampling interval
Cum A_{ef}	Cumulative amount excreted in feces
$\%f_{ef}$	Percentage of radioactive dose excreted in feces per sampling interval
Cum $\%f_{ef}$	Cumulative percentage of radioactive dose excreted in feces

Excretion parameters for total radioactivity (A_{eu}, Cum A_{eu}, $\%f_{eu}$, Cum $\%f_{eu}$, A_{ef}, Cum A_{ef}, $\%F_{ef}$, and Cum $\%f_{ef}$) will be calculated by the radioanalysis laboratory and reported in the radioanalysis report and therefore not presented within the TFLs.

10.3.2 Criteria for handling concentrations below the limit of quantification in Pharmacokinetic analysis

Concentration values that are below the level of quantification (BLQ) will be set to zero, with defined exceptions as follows;

- Any embedded BLQ value (between 2 quantifiable concentrations) and BLQ values following the last quantifiable concentration in a profile will be set to missing for the purposes of PK analysis.
- If there are late positive concentration values following 2 BLQ concentration values in the apparent terminal phase, these values will be evaluated. If these values are considered to be anomalous, they will be set to missing.
- If an entire concentration-time profile is BLQ, the profile will be excluded from the PK analysis.
- If a predose concentration is missing, it will be set to zero by default within Phoenix WinNonlin.

10.3.3 Criteria for the Calculation of an Apparent Terminal Elimination Half-Life

10.3.3.1 Number of Data Points

At least three data points will be included in the regression analysis and preferably should not include C_{max}.

10.3.3.2 Goodness of Fit

When assessing terminal elimination phases, the R^2 adjusted value will be used as a measure of the goodness of fit of the data points to the determined line.

Regression-based parameters ($AUC_{0-\infty}$, λ_z, $t_{1/2}$, CL/F, and V_z/F) will only be calculated if the R^2 adjusted value of the regression line is greater than or equal to 0.7.

10.3.3.3 Period of Estimation

Time period used for the estimation of apparent terminal elimination half-lives, where possible, will be over at least two half-lives.

Where an elimination half-life is estimated over a time period of less than two half-lives, it will be flagged in the data listings at the discretion of the pharmacokineticist, and the robustness of the value should be discussed in the study report.

10.3.4 Calculation of AUC

- The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive concentrations above the lower limit of quantification (LLOQ), with at least one of these concentrations following C_{max}.

- For any partial AUC determination (eg, AUC from time zero to 24 hours postdose), nominal time will generally be used for the end of the interval. Actual times for partial AUC intervals may be used at the discretion of the Pharmacokineticist.

- $AUC_{0-\infty}$ values where the percentage extrapolation is greater than 30% will be listed but excluded from descriptive statistics.

10.3.5 Anomalous Values

If a value is considered to be anomalous due to being inconsistent with the expected PK profile, it may be appropriate to exclude this point from the PK analysis. However, the exclusion of data must have strong justification and will be documented in the raw data and study report.

Embedded BLQ values may be considered anomalous depending on the route of administration and the characteristics of the drug.

Positive predose value(s) greater than 5% of C_{max} may be excluded from the summary statistics of PK tables and statistical analysis at the discretion of the Pharmacokineticist.

10.4 Presentation of Pharmacokinetic Data

10.4.1 Presentation of Pharmacokinetic Plasma Drug Concentrations and Total Radioactivity in Whole Blood and Plasma Data

The following rules will be applied if there are values that are BLQ or if there are missing values (eg, no result [NR]) in a concentration data series to be summarized.

- For the calculation of summary statistics, BLQ values will be set to zero.

- If an embedded BLQ value is considered anomalous within the concentration-time profile, this value will be excluded from the summary statistics.

- Where there is NR, these will be set to missing.

- If there are less than three values in the data series, only the min, max and N will be presented. The other summary statistics will be denoted as not calculated (NC). BLQ is considered a value.

- If all the values are BLQ, then the arithmetic mean, arithmetic standard deviation, median, min and max will be presented as zero, and the geometric mean and geometric CV% will be denoted as NC.

- If the value of the arithmetic mean or median is below the LLOQ, these values will be presented as zero and the geometric mean and geometric CV% will be denoted as NC.

10.4.2 Presentation of Pharmacokinetic Parameters

For the calculation of summary statistics of PK parameters, all NR and NC values in a data series will be set to missing.

The AUC values will be set to NC if they have been calculated using fewer than three concentrations, and/or three concentrations if the last is C_{max}.

10.4.3 Pharmacokinetic Statistical Methodology

No formal statistical analysis will be performed.

Assessment of pamiparib is only occurring in Part 1 of the study.

The PK parameters of pamiparib (plasma) and total radioactivity (plasma and whole blood) will be listed and summarized. The concentrations of plasma pamiparib will be listed and summarized. Ratios of plasma pamiparib to plasma total radioactivity concentrations and ratios of whole blood total radioactivity to plasma total radioactivity will be summarized and listed.

Concentrations of pamiparib (plasma) and total radioactivity (plasma and whole blood) will be presented graphically on linear and semi-logarithmic scales; this will include individual patient profiles, arithmetic mean (± standard deviation) profiles, and individual profiles for all patients over time.

10.5 Safety and Tolerability Assessments

10.5.1 Adverse Events

A baseline signs and symptom is defined as an AE that starts after the patient has provided written informed consent and that resolves prior to the first dosing occasion, or an AE that starts prior to the first dosing occasion and does not increase in toxicity grade after dosing. A treatment emergent AE (TEAE) is defined as an AE that occurs postdose or that is present predose and becomes more severe postdose. A Part 1 TEAE is defined as an AE that occurs or becomes more severe post Part 1 dosing and prior to Part 2 dosing. A Part 2 TEAE is defined as an AE that occurs or becomes more severe after dosing in Part 2.

All TEAEs will be listed. The TEAEs will be summarized by part, toxicity grade, and relationship to the study drug. The frequency (the number of TEAEs, the number of patients experiencing a TEAE, and the percentage of patients experiencing a TEAE) of TEAEs will be

summarized by part and by Medical Dictionary for Regulatory Activities (MedDRA version 21.1 or higher) system organ class, preferred term and Lowest Level Terms. A frequency summary will be presented by day of onset across the multiple-dosing period for Part 2. The summary and frequency TEAE tables will be presented for all causalities and for those TEAEs considered related to the study drug (those that have a relationship of related). Any severe (CTCAE grade 3, 4 or 5) or serious TEAEs will be tabulated. For any AEs that change toxicity grade or severity the AE within the same Part will be included only once under the maximum toxicity grade in the summaries. A TEAE which occurs in Part 1 and becomes more severe in Part 2 will be presented in both Parts with the corresponding severity.

Onset times postdose are calculated from the time of the last dose administered.

10.5.2 Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (Version September 2018 Dictionary Global B3 format [or higher if version is updated during the study]). Prior and concomitant medications will be listed separately.

10.5.3 Clinical Laboratory Parameters

Clinical chemistry and hematology data will be summarized by part and parameter. In addition, all clinical chemistry, hematology, and urinalysis data outside the clinical reference ranges will be listed by part and parameter.

Values for any clinical chemistry, hematology, and urinalysis values outside the clinical reference ranges will be flagged on the individual patient data listings.

10.5.4 Vital Signs

The vital signs data (including supine blood pressure, supine pulse rate, and body temperature) will be summarized together with changes from baseline by part. Figures of mean change from baseline profiles will be presented by part. Vital signs values outside the clinical reference ranges will be flagged on the individual patient data listings. Repeat and unscheduled readings will be handled as defined in Section 10.1.2.

10.5.5 Electrocardiogram

The ECG data will be obtained directly from the 12-lead ECG traces. These data include the QT interval calculated using the Fridericia correction (QTcF), the PR and QT intervals, the QRS duration, and heart rate.

Where ECGs are measured in triplicate (at approximately 2-minute intervals), the mean value will be used in all subsequent calculations. Changes from baseline will be calculated.

Values for ECG parameters outside the clinical reference ranges will be flagged on the individual patient data listings.

The ECG data will be summarized by part. Change from baseline will also be summarized for Part 1.

10.5.6 Eastern Cooperative Oncology Group (ECOG) Performance Status

The frequency of patients with each grade will be presented for ECOG performance status data by part and listed for individual patients.

10.5.7 Tumor Assessment

Tumor imaging (CT or magnetic resonance imaging [MRI], with preference for CT) will be performed.

Data will be listed for individual patients and overall tumor assessment data for each tumor assessment (response rates) will be presented in a frequency table.

10.5.8 Other Assessments

All other safety assessments not detailed in this section will be listed but not summarized or statistically analyzed.

10.5.9 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

11 INTERIM ANALYSES

No formal interim statistical analyses are planned.

12 CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol-specified statistical analyses.

13 DATA PRESENTATION

13.1 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of patients or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, “No serious adverse events occurred for this study.”

14 REFERENCES

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.