Statistical Analysis Plan

Sponsor:	BeiGene, Ltd
Protocol No:	BGB-290-105
PRA Project ID:	BEI001PC-170016
Protocol Title:	Phase 1, Open-label, Parallel-group, Fixed-sequence Study to Investigate the Effect of the CYP3A Inducer Rifampin and the CYP3A Inhibitor Itraconazole on the Pharmacokinetics of Pamiparib (BGB-290) in Cancer Patients
Version Date:	19 Dec 2019

1.0 Approvals

The undersigned have approved this Statistical Analysis Plan for use in this study.

Name of Sponsor Representative / Title:	[redacted] / Biostatistics, Director
Signature of Sponsor Representative / Date:	[redacted] 19 Dec 2019
Name of Author / Title:	[redacted] / Associate Director of Data Services – Patient Pharmacology Services
Signature of Author / Date:	[redacted] Signed by: [redacted] Associate Director of Data Services Reason: I am approving this document. Date & Time: 19 Dec 2019 01:34 PM +01:00 DocuSign

2.0 Table of Contents

3.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical methods that will be used during the analysis and reporting of data collected under BeiGene, Ltd, Protocol BGB-290-105.

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the plan has been developed using the protocol amendment 1 dated 14 Jun 2019 and the final CRF(s) dated 19 Aug 2019.

An approved and signed SAP is a requirement for database lock. This SAP only covers the results that will be processed by the PRA Early Development Services (EDS) Biostatistics Department.

PRA EDS will perform the Pharmacokinetic (PK) and Safety evaluations.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. Any post-hoc or unplanned analyses, or significant changes from the planned analysis in this SAP performed to provide results for inclusion in the clinical study report (CSR) but not included in this SAP, will be clearly identified in the CSR. Changes to planned analyses do not require an updated SAP but should be included in the CSR if significant.

4.0 Changes from Previous Version of Approved SAP

This is the first version of the SAP.

5.0 Study Objectives and Endpoints

5.1 Objectives

5.1.1 Primary Objectives

- To determine the effect of the strong cytochrome P450 (CYP)3A inducer rifampin on the pharmacokinetics (PK) of pamiparib in patients with advanced solid tumors
- To determine the effect of the strong CYP3A inhibitor itraconazole on the PK of pamiparib in patients with advanced solid tumors

5.1.2 Secondary Objectives

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

5.2 Endpoints

5.2.1 Primary Endpoints

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

- maximum observed concentration (C_{max})
- AUC from time zero to time of last quantifiable concentration postdose (AUC_{0-t})
- AUC from zero to infinity ($AUC_{0-\infty}$)
- AUC from zero to 12 hours (AUC_{0-12})
- AUC from zero to 9 hours (AUC_{0-9})

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- time of the maximum observed concentration (t_{max})
- apparent terminal elimination half-life ($t_{1/2}$)
- apparent oral clearance (CL/F)
- apparent volume of distribution (V_z/F)

5.2.2 Secondary Endpoints

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

6.0 Study Design

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

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

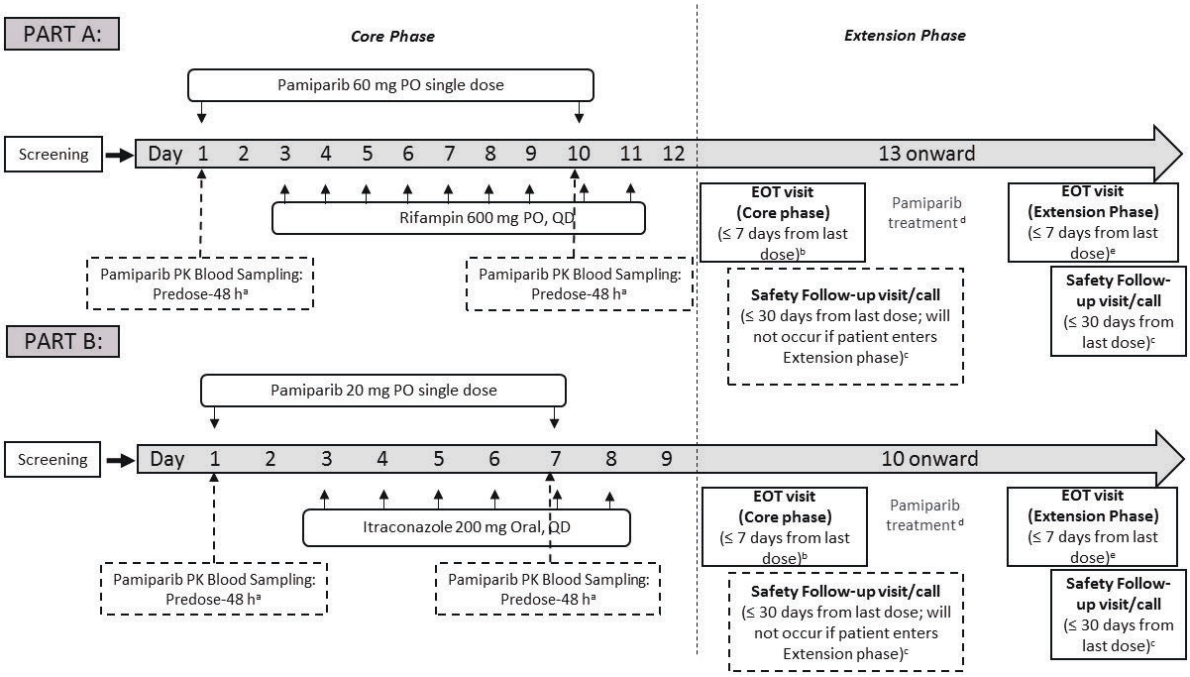
In Part A, all patients will receive the following treatments:

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

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

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

After completing the Core Phase, patients may participate in the Extension Phase, in which they will receive pamiparib twice a day in 28-day cycles until progression of disease, unacceptable toxicity, withdraw consent, or any other reason for discontinuation.



6.1 Sample Size Considerations

Approximately 24 patients (approximately 12 in each part) will be enrolled to ensure that 20 patients (10 in each part) complete the study.
The sample size chosen for this study was based on precedent set by other PK studies of similar nature and was not based on power calculations.

6.2 Randomization

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

7.0 Overview of Planned Analysis

7.1 Changes from Protocol

There are no changes from protocol.

7.2 Interim Analysis

Primary and secondary endpoints from the core phase (part A and B) will be analyzed taking into consideration all data from all available patients for this phase.

7.3 Final Analysis

The final analysis will be performed once the extension phase of the study is complete, i.e. once all patients have completed all study procedures.

Final analysis will include safety data collected in the extension phase. For continuity reasons, core phase safety data will be listed and summarized again for final analysis.

8.0 Data Review

8.1 Data Management

Data handling and transfer will take place under the Data Management Plan for the study.

8.2 Acceptance of Data for Summarization

Programming of analysis datasets and TFLs may be ongoing during the data management of the study. However, programming of analysis datasets and TFLs will be completed and quality controlled (QC'd) after clean data extraction for the core phase and after database lock for the extension phase. Only quality assured (QA'd) results released by the Bioanalytical Laboratories, or other external data source will be used for the programming of analysis datasets and TFLs for the final report. Any data values requiring investigation or corrections that are identified while programming the analysis datasets and TFLs will be sent to the project Data Manager. Database will not be locked until the identified issues are resolved.

9.0 Definitions and General Analysis Methods

9.1 Analysis Data Presentation

9.1.1 Rounding

In listings, data will be presented with the same precision as the original data. Derived data will be rounded for presentation purposes.

PK parameters will be as calculated in the datasets. For presentation purpose, PK parameters will be rounded to 3 significant digits for $t_{1/2}$ and T_{max}, and 4 significant digits for everything else for listings and tables.

Summary statistics will be calculated using individual parameter values before rounding.

For all safety summaries, the mean and median will be presented to one decimal place greater than the data, standard deviation to two greater than the data, and the minimum and maximum will be presented to the same number of decimal places as the data.

Frequency percentages will be presented with one decimal.

9.1.2 Imputation

Unless otherwise noted data will not be imputed.

9.1.3 Descriptive Statistics

Unless otherwise indicated, continuous variables will be summarized with the following descriptive statistics: n (number of observations), (arithmetic) mean, standard deviation (SD), minimum (min) value, median, and maximum (max) value.

Where calculated, Geometric CV (%) = sqrt(exp(S^2) - 1) x 100, where S^2 is the sample variance of PK parameters in the logarithmic scale.

Categorical data will be summarized with frequencies and percentages. Percentages by categories will be based on the number of patients exposed within a category of interest.

For categorical data the categories will be presented in the tables exactly as they appear in the CRF / Database. No data manipulation will be done for presentation purposes.

9.1.4 Pooling

No data pooling will be performed.

9.1.5 Unscheduled Measurements

Unscheduled measurements will be included in the listings. With the exception of unscheduled measurements used to define baseline or to define the largest change of CTCAE grade in shift table, unscheduled measurements will be excluded from the descriptive statistics and statistical analysis.

9.2 Analysis Data Definitions

9.2.1 Baseline Definition

Unless otherwise stated, baseline for post-dose evaluations is defined as the last observation recorded before the first study drug administration. The last observation can be an unscheduled / repeated measurement.

For PK, vital signs and ECG in the core phase a second baseline is defined as the last non-missing measurement taken before dosing on Day 10 for treatment part A and on Day 7 for treatment part B, i.e. the first coadministration.

9.2.2 Treatment/Patient Grouping

Treatment emergent Adverse events (TEAEs) will be summarized by the last treatment received, i.e. "Treatment at onset"
The following treatment labels will be used for the core phase:

Part/Treatment Arm	Treatment Label	Dosing	Used for assessments done at
A	'Pamiparib only'	60 mg single dose	Day 1 - 2
A	'Rifampin'	600 mg QD	Day 3 - 9
A	'Pamiparib with Rifampin'	60 mg and 600 mg	Day 10 - 12
B	'Pamiparib only'	20 mg single dose	Day 1 - 2
B	'Itraconazole'	200 mg QD	Day 3 - 6
B	'Pamiparib with Itraconazole'	20 mg and 200 mg	Day 7 - 9

9.2.3 Other Definitions

General definitions for variables as used in the text.

Change from baseline will be calculated for safety measures, see below.

Variable	Dataset	Definition/Calculation
Change from Baseline	All	Post-dose Observation minus Baseline Observation
Study Day (Prior to first dose day)	All	Date of Measurement minus Dose Date
Study Day (Predose on first dose day and post first dose)	All	Date of Measurement minus Dose Date +1
TEAE	AE	AE is a TEAE if the AE with an onset date on or after the date of first dose of study medication until the date of last study medication dose plus 30 days.

9.2.4 ADaM Datasets

The analysis datasets will be generated in accordance with Clinical Data Interchange Standard Consortium (CDISC) Analysis Data Model (ADaM) Version 2.1.

ADaM compliant datasets will be delivered to the sponsor. A define.xml file version 2 with the corresponding metadata will be included. Analysis results metadata are excluded.

9.3 Software

The statistical analysis and reporting will be done using SAS® for Windows™ version 9.4 or higher (SAS Institute, Inc.).

PK parameter calculations will primarily be done using Phoenix® WinNonlin® version 8.1 or higher (Certara, Inc.).

PK computations or summaries may also be performed in SAS®.

9.4 Statistical Methods

9.4.1 Statistical Outlier Determination

No statistical outlier analysis is planned.

9.4.2 Predetermined Covariates and Prognostic Factors

There are no predetermined covariates or prognostic factors.

9.4.3 Hypothesis Testing

No formal hypothesis testing will be done.

9.5 TFL Layout

Report layout will be according to the PRA EDS – ICH E3 compliant – CSR Template. The layout of Tables, Figures and Listings (TFLs) will be according to the PRA EDS standards.

10.0 Analysis Sets

10.1 Safety Population

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

10.2 Pharmacokinetic Population

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

Analyses	Safety Population	Pharmacokinetic Population
Disposition Summaries	✓	
Safety Assessments	✓	
Baseline Characteristics	✓	
Primary Endpoint		✓
Secondary Endpoint	✓	

11.0 Patient Disposition

Patient disposition will be summarized by part using frequency counts and the corresponding percentages. The number of patients in each analysis population, number of patients discontinued, the primary reason for treatment discontinuation, and the primary reason for study discontinuation will be summarized.

Disposition data including date of informed consent and end of treatment will be listed.

12.0 Protocol Deviations and Violations

Protocol deviations/violations will be listed.

13.0 Demographic and Baseline Characteristics

13.1 Demographics

Patient demographics will be summarized descriptively for all patients by part. The summary will include the patients' age at informed consent (in years), gender, race, ethnicity, weight (in kg) at baseline, height (in cm), and BMI (in kg/m^2) at baseline. Demographics will be summarized for the safety analysis set.

Associated person's demographics will be listed.

13.2 Medical History

Medical history will be listed by part.

Disease history will be listed by part.

13.3 Anti-Cancer Treatments and Procedures

The following listings will be provided:

- listing of previous anti-cancer therapy
- listing of previous anti-cancer radiotherapy
- listing of post treatment discontinuation anti-cancer therapy

These will include all collected data from the corresponding CRF pages.

13.4 Other Baseline Characteristics

The following baseline characteristics will be listed:

- Non-compliance to inclusion or exclusion criteria (if any)
- The results of alcohol screen
- The results of urine drug screen
- The results of HBV/HCV tests
- Viral load assessments

14.0 Prior and Concomitant Medications/Procedures

Prior and concomitant medication and procedures will be listed by part. Medications with an end date prior to the first dose of study drug will be considered prior medications. If a partial date allows a medication to be considered concomitant it will be categorized as such.

15.0 Treatment Compliance and Exposure

Exposure data will be listed.

The number of patients receiving doses of pamiparib, rifampin or itraconazole will be summarized separately for the core phase.

The following variables will be summarized using extension phase data only:

- The number of cycles initiated
- Duration of treatment

- Dose intensity (see below)
- Number of patients with exactly one planned dose reduction and the number of patients with 2 or more planned dose reductions.

The duration of treatment will be calculated as the number of days from the first dose of study drug to the day of the last dose of study drug +1. If a patient is ongoing, then the date of the data cutoff will be used.

Dose intensity will be calculated for each patient by adding the actual total dose received divided by the duration of treatment. Relative dose intensity is defined as total actual dose received divided by total planned dose. Both will be shown.

16.0 Pharmacokinetic Analyses

16.1 Pharmacokinetic Variables

- Plasma concentration of pamiparib with and without rifampin and itraconazole, respectively.
- PK Parameters for pamiparib with and without rifampin and itraconazole, respectively

16.2 Estimation of Pharmacokinetic Parameters

Patients who experience events that may affect their PK profile (e.g. lack of compliance with dosing) may be excluded from the PK analysis. At the discretion of the pharmacokineticist, a concentration value may also be excluded if the deviation of sampling time from the nominal time is of sufficient concern or if the concentration is anomalous for any other reason.

The following PK parameters will be calculated as data allows for pamiparib concentrations in plasma:

Primary:

Parameter	Description	SAS Programming Notes
C_{max}	Maximum plasma concentration. Observed peak analyte concentration obtained directly from the experimental data without interpolation, expressed in concentration units	Cmax from WNL
AUC_{last}	Area under the concentration-time curve (time 0 to time of last quantifiable concentration).	AUClast from WNL
$AUC_{0\text{-}12h}$	Area under the concentration-time curve (time 0 to time 12h) as observed.	AUC at tpt=12 h from WNL
$AUC_{0\text{-}9h}$	Area under the concentration-time curve (time 0 to time 9h) as observed.	AUC at tpt=9 h from WNL
AUC_{inf}	Area under the plasma concentration-time curve (time 0 to infinity). Percent extrapolation less than or equal to 20% and an r^2 greater than 0.90 are required to retain AUC_{inf}.	AUCINF_obs from WNL If AUC_%Extrap_obs >20% or Rsq ≤ .90 then parameter is deleted
T_{max}	Time to maximum plasma concentration. First observed time to reach peak analyte concentration obtained directly from the experimental data without interpolation, expressed in time units.	Tmax from WNL

Parameter	Description	SAS Programming Notes
$T_{1/2}$	Terminal phase half-life expressed in time units. Percent extrapolation less than or equal to 20% and r^2 greater than 0.90 is required to retain $T_{1/2}$.	HL_Lambda_z from WNL If AUC_%Extrap_obs >20% or Rsq ≤ .90 then parameter is deleted
CL/F	Apparent clearance Percent extrapolation less than or equal to 20% and r^2 greater than 0.90 is required to retain $T_{1/2}$.	CL_F_obs from WNL If AUC_%Extrap_obs >20% or Rsq ≤ .90 then parameter is deleted
V_z/F	Apparent volume of distribution during terminal phase Percent extrapolation less than or equal to 20% and r^2 greater than 0.90 is required to retain $T_{1/2}$.	Vz_F_obs from WNL If AUC_%Extrap_obs >20% or Rsq ≤ .90 then parameter is deleted

Note: AUCs are calculated using linear up / log down, expressed in units of concentration x time.

Additional PK parameters (only in listings):

Parameter	Description	SAS Programming Notes
AUC_{extrap}%	Percentage of AUC_{inf} obtained by forward extrapolation.	AUC_%Extrap_obs from WNL
r^2	Goodness of fit statistic for the terminal phase rate constant (kel)	Rsq from WNL
k_{el}	Rate constant for terminal phase	Lambda_z from WNL If AUC_%Extrap_obs >20% or Rsq ≤ .90 then parameter is deleted
$k_{el, t(lo)}$	First time point value used in the calculation of k_{el}	Lambda_z_lower from WNL If AUC_%Extrap_obs >20% or Rsq ≤ .90 then parameter is deleted
$k_{el, t(hi)}$	Last time point value used in the calculation of k_{el}	Lambda_z_upper from WNL If AUC_%Extrap_obs >20% or Rsq ≤ .90 then parameter is deleted
$k_{el, t(n)}$	Number of time points used in the calculation of k_{el}	No_points_lambda_z from WNL If AUC_%Extrap_obs >20% or Rsq ≤ .90 then parameter is deleted

The plasma PK parameters of pamiparib following pamiparib dosing on Days 1 and 10 in Part A and Days 1 and 7 in Part B will be calculated from pamiparib concentration-time profiles using standard noncompartmental methods. with WinNonlin®.

In estimating the PK parameters, BQL values at the beginning of the profile will be set to zero. BQL values that occur after the first quantifiable point will be set to missing. Values that are embedded between BQLs, or quantifiable values occurring after two or more BQLs, may be set to missing at the discretion of the pharmacokineticist. Actual sampling times, rather than scheduled sampling times, will be used in all computations involving sampling times. If the actual time or dose time is missing, the scheduled time may be substituted in order to calculate the PK parameter. In the event the PK draw occurs during the start or end of daylight savings time, the time will be adjusted to reflect the actual time from when the study drug was taken rather than the time on the clock.

As appropriate, additional PK parameters may be calculated and reported.

16.3 Pharmacokinetic Concentrations

Plasma concentrations below the quantifiable limit (BQL) will be set to 0 in the computation of concentration summary statistics.

Descriptive statistics, including number (N), number for higher or equal values of Lower Limit of quantification (N>=LLOQ), arithmetic mean, standard deviation (SD), coefficient of variation (%CV), standard error of the mean (SEM), minimum, median, maximum, and geometric mean will be used to summarize the plasma concentrations at each scheduled time point. As BQL results are set to 0, statistics will be calculated with 0 for BQL results, i.e. minimum will be displayed as 0, and the respective patient will be included in counting the number of patients with results, but excluded in counting the number of patients with higher or equal values of LLOQ. Zero concentrations will be considered as missing in geometric mean calculations. If more than half of the patients have values BQL, the summary descriptive statistics will not be performed for that time point.

Linear and semi-logarithmic plots of the arithmetic mean (+/-SD) plasma concentration by scheduled sampling time will be provided. These plots will show time in hours. The plots will match the summary table results and will not have an observation at a given time point if more than half of the patients have values BQL.

Linear and semi-logarithmic plots of the individual plasma concentration by actual sampling time will be provided by patient (one patient per page). These plots will show time in hours. In individual plots concentrations BQL will not be shown.

All individual patient plasma concentration data will be listed.

16.4 Statistics of Pharmacokinetic Parameters

Statistical analyses will be performed to assess the effect of steady-state itraconazole and rifampin on the PK of pamiparib using the treatment in combination with pamiparib as test and the treatment with pamiparib only as reference.

Summary statistics will include number (N), arithmetic mean, standard deviation (SD), %CV, standard error of the mean (SEM), minimum, median, maximum, and geometric mean. For Tmax, only n, median, min and max will be presented.

Data for each treatment part will be analyzed separately.

A linear mixed model with a fixed effect for treatment and a random effect for patient will be used on the natural log-transformed parameters C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$. A point estimate and the corresponding 90% CI for the difference between least squares means of Test and Reference treatment (Test – Reference) will be calculated. The antilogarithm of this value will be calculated to obtain the point estimate and the 90% CI for the ratio (Test/Reference) of the geometric means on the untransformed scale. For each

parameter selected for analysis, patients who do not have valid parameters in both periods will not be included for analysis.

The SAS PROC MIXED code is as follows:

```
proc mixed data = adpp;
   by parameter;
   class treatment patient;
   model ln(aval) = treatment;
   random patient;
   lsmeans treatment / alpha = 0.1;
   estimate "Pamiparib only vs Pamiparib with Itraconazole/Rifampin"
   treatment -1 1 / e cl alpha=0.1;
run;
```

For parameters C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ a listing of the individual patient ratios (Test/Reference) will be provided.

A forest plot of the geometric LS mean ratios of C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ will be provided for a visual representation of the data.

All plasma PK parameters will be listed by patient.

17.0 Tumor Assessment

Tumor identification and assessment will be listed..

18.0 Safety Analyses

18.1 Safety Variables

The following safety variables will be summarized:

- Adverse Events (AEs)
- Vital Signs, including weight
- Electrocardiograms (ECG)
- Clinical Laboratory Evaluations

All summaries will be by treatment within a part/treatment arm.

18.1.1 Adverse Events

Adverse events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system.

All adverse events (including non-treatment-emergent events) recorded on the CRF will be listed.

All AE summaries will include only treatment-emergent adverse events. Treatment-emergent adverse events are those AEs with an onset date on or after the date of first dose of study medication until the date of last study medication dose plus 30 days.

AEs will be categorized according to the following:

- Prior to Day 1 (thus not summarized, just listed)
- From Day 1 to the day prior to start rifampin or itraconazole dosing (category = pamiparib only)
- Part A: The day of start of rifampin dosing to the day prior to combined pamiparib and rifampin dosing (category = rifampin)
- Part A: At or after the day of coadministration until date of last dosing in core phase plus 30 days and before the administration of pamiparib in the Extension Phase (category = pamiparib with rifampin)

- Part B: The day of start of itraconazole dosing to the day prior to combined pamiparib and itraconazole dosing (category = itraconazole)
- Part B: At or after the day of coadministration until date of last dosing in core phase plus 30 days and before the administration of pamiparib in the Extension Phase (category = pamiparib with itraconazole)
- Extension Phase AEs

An overview of all AE will present the following frequencies by treatment and part:

- All treatment-emergent AEs
- Grade 3 or greater treatment-emergent AEs
- Treatment-related, treatment-emergent AEs
- Serious treatment-emergent AEs
- Serious, treatment-related treatment-emergent AEs
- Treatment-emergent AEs with an outcome of death
- Treatment-emergent AEs leading to discontinuation of study treatment

A breakdown of the number and percentage of patients reporting each adverse event, categorized by body system and preferred term, will be presented. Counting will be done by patient only, not by event; patients will only be counted once within each body system or preferred term.

A summary of drug related events reported, categorized by relationship to either study drug, will be provided. Patients with multiple events within a particular body system or preferred term will be counted once for a relation to study drug within that body system or preferred term.

A summary of events reported, categorized by toxicity grade (CTCAE version 5.0), will be provided. If a patient experiences multiple occurrence of the same AE with different intensity toxicity grades, the patient will be counted once for the maximum (most severe) toxicity grade. AEs with a missing intensity will be presented in the summary table with a toxicity grade of “Missing”. For each toxicity grade, the number and percentage of patients with at least 1 treatment emergent AE of the given grade will be summarized.

A listing of adverse events leading to treatment discontinuation will be provided.

The following missing data will be imputed as defined (for calculations only / will not be presented):

- Missing AE start times for the determination of treatment emergence will be assumed to occur after treatment unless partial date documents the AE as happening prior to treatment
- Missing or partial AE start date will be assumed to be after treatment for the determination of TEAE unless the start or end date is prior to treatment

18.1.2 Deaths and Serious Adverse Events

A listing of deaths and other serious adverse events will be provided.

18.1.3 Laboratory Data

All laboratory data will be listed. A separate listing, including results with CTCAE (version 5.0) grade 3 or higher will also be provided. For listings, normal ranges will be used directly from the clinical laboratory.

For summaries, clinical laboratory data will be presented using Système International (SI) units (also used in the SDTM Controlled Terminology). Data will be standardized for units while site specific reference ranges for normal results will be maintained (in the standardized unit).

Hematology (including coagulation) and serum chemistry values at baseline, post-baseline and changes from baseline for each scheduled timepoint will be summarized.

For parameters with CTCAE grading, for all post-baseline results (scheduled and unscheduled) the shift to worst CTCAE grade after baseline grade will be identified per parameter and patient. This worst post baseline grade will be used in shift tables to summarize shifts from baseline using patient counts and percentages by treatment.

Pregnancy tests will be listed.

18.1.4 Vital Signs

Descriptive statistics will be provided to summarize vital signs and changes from baseline at each scheduled time and presented separately for each treatment group. All Vital Signs, including repeats in response to abnormalities, will be listed.

18.1.5 Electrocardiograms

Descriptive statistics will be provided to summarize ECG parameters and changes from baseline at scheduled time and presented separately for each treatment group, and overall.

ECG parameters will be listed.

18.1.6 Other Observations Related to Safety

ECOG Performance Status will be listed and summarized descriptively .

Physical examination data will be listed by patient

19.0 References

Clinical Study Protocol. A Phase 1, Open-label, Parallel-group, Fixed-sequence Study to Investigate the Effect of the CYP3A Inducer Rifampin and the CYP3A Inhibitor Itraconazole on the Pharmacokinetics of Pamiparib (BGB-290) in Cancer Patients. Version 1.0, Final, 14 Jun 2019.

Appendix 1: Glossary of Abbreviations

Glossary of Abbreviations:	
ADaM	Analysis Data Model
AE	Adverse Event
AUC	Area under the curve
BMI	Body Mass Index
BQL	Below the Quantifiable Limit
CL	Clearance
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDS	Early Development Services
ICH	The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
LLOQ	Lower Limit of quantification
LS	Least Square
PK	Pharmacokinetic
QA	Quality Assured
QC	Quality Controlled
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Standard Data Tabulation Model
SEM	Standard Error of Mean
TEAE	Treatment-emergent Adverse Event
TFL	Tables, Figures and Listings
WNL	WinNonlin

Appendix 2: Schedule of Assessments

Schedule of Assessments: Part A

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

Prior/concomitant medication recording	X	X	X	X	X	X	X

Schedule of Assessments: Part A (Continued)

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

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

a. Confirmation of eligibility: all laboratory values obtained on Day -1 must meet eligibility criteria.
b. Demographic data: Date of birth, gender, ethnicity, and race must be recorded.
c. Medical History/Current Medical Conditions: General and disease specific medical history including a history of past and current medical conditions.
d. For females of childbearing potential, a highly sensitive serum pregnancy test must be performed at a central or local laboratory within 7 days before Day 1. For subsequent pregnancy testing, highly sensitive urine pregnancy tests, performed at a central or local laboratory, are allowed. If a urine pregnancy test is positive, a confirmatory serum pregnancy test is required.
e. Height will be measured at Screening only for BMI calculation.
f. Serology: hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B Core antibody, and hepatitis C antibody
g. On Day 1 and Day 10, patients are required to fast for at least 8 hours before and 4 hours after pamiparib and rifampin administration. Water is allowed during the fasting period. On Day 10, rifampin will be administered first, followed within 5 minutes by pamiparib. On Days 3-9 and Day patients are required to fast for 2 hours before and 1 hour after rifampin administration.
h. Blood samples for clinical laboratory evaluations (clinical chemistry, hematology, and urinalysis) will be collected after at least an 8-hour fast. If Screening urinalysis and chemistry and hematology laboratory evaluations were performed within 3 days of Day-1, they do not need to be repeated on Day-1.
i. Vital signs include supine blood pressure, supine pulse rate, respiratory rate, and body temperature. Patients are to remain supine for at least 5 minutes prior to blood pressure and pulse rate measurements. When scheduled at the same time, vital sign assessments are to be performed prior to PK blood draws, with blood draws to occur as close to the nominal times as possible except for Screening and Day -1.

j. Patients are to remain supine for at least 5 minutes prior to ECG assessments. When numerous assessments are scheduled at the same time, ECGs are to be performed prior to vital sign assessments and PK blood draws, with PK blood draws to occur as close to the nominal times as possible except for Screening and Day -1.
k. Complete physical examination at Screening and Day -1.
l. Limited physical examination to occur on Days 1, 10 and 12, EOT and Safety Follow-up includes assessment of general appearance and additional examination of symptomatic systems or those affected by the patient's disease.
m. A computed tomography (CT) or MRI scan of the thorax, abdomen, and pelvis plus other relevant evaluations as appropriate will be performed at Screening.
n. All assessments obtained within 3 days of Day -1 do not have to be repeated on Day -1.
o. Check-out takes place on Day 12 after all procedures have been completed.
p. All patients, including those who withdraw early from the study, will have an EOT visit within 7 days after the last dose of rifampicin. Safety Follow-up in the Core Phase is only to be conducted if the patient does not continue to the Extension Phase. All patients who permanently discontinue study drug will have a Safety follow-up approximately 30 days after the last day of study drug or before initiation of new anticancer therapy, whichever occurs first. AEs and SAEs will be collected; clinical laboratory assessment should only be conducted if the patient had an ongoing clinical laboratory abnormality in the previous visit, which the PI considers to be related to study drug. If no laboratory assessments are required, the patient should be contacted by telephone for a review of AEs/concomitant medications and the limited physical exam will not be performed.

Schedule of Assessments: Part B

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

Schedule of Assessments: Part B (Continued)

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

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

a. Confirmation of eligibility: all laboratory values obtained on Day -1 must meet eligibility criteria.
b. Demographic data: Date of birth, gender, ethnicity, and race must be recorded.
c. Medical History/Current Medical Conditions: General and disease specific medical history including a history of past and current medical conditions.
d. For females of childbearing potential, a highly sensitive serum pregnancy test must be performed at a central or local laboratory within 7 days before Day 1. For subsequent pregnancy testing, highly sensitive urine pregnancy tests, performed at a central or local laboratory, are allowed. If a urine pregnancy test is positive, a confirmatory serum pregnancy test is required.
e. Height will be measured at Screening only for BMI calculation.
f. Serology: hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B Core antibody, and hepatitis C antibody
g. On Day 1 and Day 7, patients are required to fast for at least 8 hours before and 4 hours after pamiparib and itraconazole administration. Water is allowed during the fasting period. Itraconazole will be administered approximately 30 minutes after completing a meal on Days 3 to 6 and 8. On Day 7, itraconazole will be administered first, followed within 5 minutes by pamiparib.
h. Blood samples for clinical laboratory evaluations (clinical chemistry, hematology, and urinalysis) will be collected after at least an 8-hour fast. If Screening urinalysis and chemistry and hematology laboratory evaluations were performed within 3 days of Day-1, they do not need to be repeated on Day-1.

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

Schedule of Assessments Extension Phase

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

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

a. Vital Signs: Blood pressure, heart rate, and temperature must be measured after the patient has been supine for 5 minutes at Screening and EOT.
b. Single 12-lead ECGs will be repeated once if outside the clinical reference range, or there is other clinically significant finding. Repeat ECGs will be recorded in triplicate at least 2 minutes apart. ECGs will be recorded after the patient has been supine for 5 minutes.
c. Limited physical examination: includes assessment of general appearance and additional examination of symptomatic systems or those affected by the patient's disease. For the follow-up visit, the limited physical examination is only to be done if this visit is conducted while the patient is attending the clinic.
d. Dosing: Pamiparib capsules should be administered continuously from Cycle 1 Day 1 (60 mg twice daily), until patients are discontinued from treatment.
e. Predose visit: Assessments performed in the Core Phase Follow-up visit for Part 1 may be used as the predose visit for the Extension Phase if it occurs ≤ 7days prior to the start of pamiparib treatment in Extension Phase.
f. Cycle 3+:Cycles will continue as long as the patient is experiencing clinical benefit, or until occurrence of progressive disease (PD), unacceptable toxicity, pregnancy, death, withdrawal of consent, lost to follow-up, major protocol violation which in the opinion of the sponsor would have significant impact on the study or its outcome, start of new anticancer therapy, withdrawal by the PI, or study termination by sponsor.

g. End-of-Treatment (EOT) Visit: To occur within 7 days after the last day of study drug administration. A visit should be scheduled as soon as possible, but may occur later after discussion with the medical monitor for specific circumstances, such as prolonged hospitalization. An ECG does not need to occur at the EOT Visit if one was performed within 14 days prior to the visit.
h. Safety Follow-up Visit: To occur approximately 30 days after the last day of study drug administration or before initiation of new anticancer therapy, whichever occurs first. If new anticancer therapy is initiated before this safety follow-up, a safety follow-up should be scheduled as soon as possible. Clinical laboratory evaluations are only required if the patient had an ongoing clinical laboratory abnormality at the previous visit that the principal investigator considered to be related to study drug. For patients who do not want to or cannot return to the clinic for the safety follow-up, the patient should be contacted by telephone for a review of adverse events.
i. Cycle 1 Day 1: Assessments will be conducted prior to first dosing in the Extension Phase.
j. Follow-up assessments: only to be conducted if the patient has an ongoing laboratory abnormality at the previous visit that the PI considers to be related to the study drug.

Document History

Version Date	Modified/Reviewed By	Brief Summary of Changes (if created from a template, include template code)
06 Nov 2019	[redacted]	Created from template EDSREP 009 T 01 E
21 Nov 2019	[redacted]	Modified based on sponsor comments
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