STATISTICAL ANALYSIS PLAN

Study Protocol Number:	BGB-290-102
Study Protocol Title:	An Open Label, Multi-Center Phase I/II Study to Evaluate Efficacy and Safety of BGB-290 in Chinese Subjects with Advanced Ovarian Cancer, Fallopian Cancer, and Primary Peritoneal Cancer, or Advanced Triple Negative Breast Cancer
Date:	February 28, 2020
Version:	1.1

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TABLE OF CONTENTS

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ATC	Anatomical Therapeutic Chemical
AUC	area under the plasma concentration-time curve
BID	twice daily
BOR	best overall response
BP	blood pressure
BRCA	breast cancer susceptibility gene
CBR	clinical benefit rate
CI	confidence interval
CR	complete response
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
GCIG	Gynecological Cancer Intergroup
HGOC	high grade ovarian cancer
IRC	independent review committee
MedDRA®	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
ORR	objective response rate
OS	overall survival
PA	protocol amendment
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
PROC	platinum-resistant ovarian cancer
PSOC	platinum-sensitive ovarian cancer
PT	preferred term
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse events
SAP	statistical analysis plan

SD	stable disease
SOC	system organ class
TEAE	treatment-emergent adverse event
TNBC	triple negative breast cancer
TTR	time to response

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for Protocol BGB-290-102, An Open Label, Multi-Center Phase I/II Study to Evaluate Efficacy and Safety of BGB-290 in Chinese Subjects with Advanced Ovarian Cancer, Fallopian Cancer, and Primary Peritoneal Cancer, or Advanced Triple Negative Breast Cancer.

Reference materials for this statistical plan include the protocol BGB-290-102 (version 5.0, 2018-09-21 and version 1.1, 2016-08-15). This study contains 2 phases. Since majority of patients of Phase 1 were end of study before the protocol version 2.0 released, protocol version 1.1 will be referred to for the study operation of Phase 1 portion. For the final analysis, the latest version of the protocol will be referred to for both Phase 1 and Phase 2. If the protocol or case report forms are amended or updated, then appropriate adjustments to the SAP may be made if they are related to the planned analyses.

The SAP described hereafter is an *a priori* plan. This is an open label study and the SAP will be finalized and approved before database lock. Statistical programming may occur as study data accumulate in order to have analysis programs ready at the time the study finishes.

2 STUDY OVERVIEW

This is a Phase 1/2, open-label, multicenter study of pamiparib administered orally twice daily (BID) to adult Chinese patients with advanced solid tumors which have progressed despite standard therapy or for which no standard therapy exists.

The Phase 1 portion of this study is designed to evaluate the safety, tolerability and PK profile of pamiparib in Chinese patients with advanced solid tumors and to determine RP2D of pamiparib for Chinese patients. In this study, three dose levels, 20 mg, 40 mg, and 60 mg BID, were evaluated. The purpose of this study is to determine the RP2D and MTD, if any, of pamiparib in Chinese cancer patients. Dose escalation will follow a modified 3+3 dose escalation design.

In the Phase 2 portion, approximately 100 evaluable patients (80 previously treated platinum-sensitive and 20 previously treated platinum-resistant) with advanced high grade (Grade 2 or Grade 3 endometrioid epithelial cancer is acceptable too), non-mucinous, epithelial ovarian cancer (including fallopian cancer, or primary peritoneal cancer) of either known deleterious or suspected deleterious *BRCA1/2* mutations who have received at least two lines of prior therapies will be enrolled.

3 STUDY OBJECTIVES

3.1 PHASE 1 PORTION

3.1.1 Primary Objectives

- To evaluate the safety and tolerability of pamiparib in Chinese patients with advanced solid

tumors

- To determine the recommended Phase 2 dose of pamiparib

3.1.2 Secondary Objectives

- To characterize the pharmacokinetics of pamiparib in Chinese patients
- To evaluate the clinical antitumor activity of pamiparib in Chinese patients with TNBC or high-grade epithelial, non-mucinous ovarian cancer (including fallopian cancer, or primary peritoneal cancer)
- To evaluate the relationship between pamiparib PK and clinical endpoints

3.1.3 Exploratory Objectives

- [redacted]

3.2 PHASE 2 PORTION

3.2.1 Primary Objectives

- To evaluate the efficacy of pamiparib as measured by objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (RECIST v1.1), by independent review committee (IRC) in patients with advanced platinum-sensitive or platinum-resistant high grade, non-mucinous, epithelial ovarian cancer (including fallopian cancer or primary peritoneal cancer) harboring germline breast cancer susceptibility gene 1/gene 2 (BRCA1/2) mutation

3.2.2 Secondary Objectives

- To evaluate the efficacy of pamiparib as measured by progression free survival (PFS), duration of response (DOR) by both IRC and investigator review, and overall survival (OS) by investigator review
- To evaluate the efficacy of pamiparib as measured by the ORR by investigator review
- To evaluate the safety and tolerability of pamiparib
- To evaluate the efficacy of pamiparib as measured by disease control rate (DCR), best overall response (BOR) and clinical benefit rate (CBR) by both IRC and investigator review
- To evaluate the carcinoma antigen-125 (CA-125) response rate per Gynecological Cancer Intergroup (GCIG) for CA-125 changes
- To further characterize the PK of pamiparib

3.2.3 Exploratory Objectives

- [redacted]

4 STUDY ENDPOINTS

4.1 PHASE 1 PORTION

4.1.1 Primary Endpoint

- Incidence of adverse events, overall and by severity, and incidence of SAEs according to National Cancer Institute Common Toxicity Criteria for Adverse Events, version 4.03 (NCI-CTCAE); laboratory abnormalities; changes in laboratory assessments, ECGs, and assessment of physical examinations.

4.1.2 Secondary Endpoints

- PK parameters of pamiparib and possible its major metabolite(s): area under the plasma concentration-time curve (AUC), maximum observed plasma concentration (C_{max}), and time to reach C_{max} (T_{max}); elimination half-life ($t_{1/2}$), apparent clearance (CL/F), and apparent volume of distribution during terminal phase (V_z/F) and other applicable parameters.
- Efficacy assessment by the investigator based on the RECIST, v1.1:
  - ORR is defined as the proportion of patients who had confirmed CR or PR
  - DOR is defined as the time from the first determination of a confirmed overall response until the first documentation of progression or death, whichever comes first
  - DCR is defined as a BOR of CR, PR and stable disease (SD)
  - CBR is defined as a BOR of CR, PR and SD lasting ≥24 weeks
  - PFS is defined as the time from first dose of study medication to the first documented disease progression or death due to any cause, whichever occurs first

4.1.3 Exploratory Endpoint

- [redacted]

4.2 PHASE 2 PORTION

4.2.1 Primary Endpoint

- ORR as defined above in advanced HGOC patients by IRC

4.2.2 Secondary Endpoints

- DOR is defined as the time from the first determination of a confirmed overall response until the first documentation of progression or death, whichever comes first
- PFS is defined as the time from first dose of study medication to the first documented disease progression or death due to any cause, whichever occurs first
- OS is defined as the time from the first dose of study medication to the date of death due to any cause

- ORR as defined above in advanced HGOC patients by investigator review
- CA-125 response rate per GCIG criteria for CA-125 changes
- Incidence of AEs, overall and by severity, and incidence of SAEs; laboratory abnormalities; changes in laboratory assessments, ECGs, and assessment of physical examinations such as vital signs
- For patients participating intensive PK sample collection: AUC, C_{max}, and T_{max}; $t_{1/2}$, CL/F, V_Z/F
- DCR and CBR as defined above

4.2.3 Exploratory Endpoints

- [redacted]

5 SAMPLE SIZE CONSIDERATIONS

Approximately 14-18 evaluable patients will be enrolled in Phase 1 portion of the trial. In the Phase 2 portion of the trial, approximately 100 evaluable patients will be enrolled.

In recurrent HGOC patients, it is assumed that ORR is 52% with pamiparib in previously treated platinum-sensitive patients with BRCA mutation. A total of 80 evaluable patients will give 98% power to demonstrate a statistical difference versus a historical response rate of 30% using a binomial exact test at an alpha of 0.025. The 2-sided exact 95% CI is (40.5%, 63.3%) when the observed ORR is 52%. Approximately 20 patients will be enrolled to the platinum-resistant HGOC patients.

Hence, approximately 118 patients will be enrolled to obtain 14-18 evaluable patients in Phase 1 and 100 evaluable patients in Phase 2.

6 STATISTICAL METHODS

6.1 ANALYSIS SETS

The Safety Analysis Set includes all patients who received at least one dose of pamiparib.

The Efficacy Evaluable Analysis Set includes all patients in the safety analysis set who had measurable disease at baseline per RECIST, v1.1 (based on investigator assessment for phase 1 and IRC assessment for phase 2) and had at least one post baseline tumor assessment unless discontinued treatment due to clinical progression or death prior to tumor assessment.

The DLT Analysis Set includes all patients who received at least 75% of pamiparib or who experienced a DLT event during the DLT observation period (Cycle 1).

The PK Analysis Set includes all patients for whom valid pamiparib PK parameters can be estimated.

The CA-125 Evaluable Analysis Set is defined as the subset of patients in the Safety Analysis Set with baseline CA-125 ≥ 2 x ULN. This will be the primary analysis set for the analysis of CA-125 response rate.

6.2 DATA ANALYSIS GENERAL CONSIDERATIONS

6.2.1 Definitions and Computations

Study day: Study day will be calculated in reference to the date of the first dose of study drug. For assessments conducted on or after the date of the first dose of study drug, study day will be calculated as (assessment date – date of first dose of study drug + 1). For assessments conducted before the date of the first dose of study drug, study day is calculated as (assessment date – date of first dose of study drug). There is no study day 0.

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings. Study day and any corresponding durations will be presented based on the imputations specified in Appendix 10.1.

Treatment duration: The treatment duration will be calculated as (date of the last non-zero dose of study drug – date of first dose of study drug + 1).

Baseline: the non-missing value most recently collected before the first dose.

All calculations and analyses will be conducted using SAS version 9.4 or higher.

6.2.2 Conventions

Unless otherwise specified, the following conventions will be applied to all analyses:

- 1 year = 365.25 days. Number of years is calculated as (days/365.25) rounded up to 1 significant digit.
- 1 month = 30.4375 days. Number of months is calculated as (days/30.4375) rounded up to 1 significant digit.
- Age will be calculated as the integer part of (date of informed consent – date of birth + 1)/365.25
- P-values will be rounded to 4 decimal places. P-values that round to 0.0000 will be presented as '< 0.0001' and p-values that round to 1.000 will be presented as '> 0.9999'.
- Time-to-event or duration of event endpoints will be based on the actual date the radiograph was obtained rather than the associated visit date.
- Missing efficacy or safety data will not be imputed unless otherwise specified.
- For laboratory results collected as < or >, a numeric value, 0.0000000001 will be subtracted or added, respectively, to the value.
- For by-visit observed data analyses, percentages will be calculated based on the number of patients with non-missing data as the denominator, unless otherwise specified.

- For continuous endpoints, summary statistics will include n, mean, standard deviation, median, Q1, Q3 and range (minimum and maximum).

6.2.3 Handling of Missing Data

Missing data will not be imputed unless otherwise specified elsewhere in the SAP. Missing dates or partially missing dates will be imputed conservatively for adverse events and prior/concomitant medications/procedures. Specific rules for handling of missing or partially missing dates for adverse events and prior/concomitant medications/procedures are provided in Appendix 10.1.

By-visit endpoints will be analyzed using observed data, unless otherwise specified. For observed data analyses, missing data will not be imputed and only the observed records will be included.

At the time of primary analysis, if death or disease progression is not observed from a patient, corresponding censoring rules for OS, DOR and PFS will be followed.

6.2.4 Adjustment for Covariates

No adjustments for covariates are planned for primary, secondary and exploratory analyses in the study.

6.2.5 Multiplicity Adjustment

No multiplicity adjustments will be made in this study. Two-sided 95% confidence interval (CI) will be used to describe the precision of the rate estimate whenever appropriate.

6.3 SUBJECT CHARACTERISTICS

6.3.1 Subject Disposition

The number (percentage) of patients treated, discontinued from study treatment, entered survival follow-up visit (only for Phase 2), discontinued from study (including those who discontinued study treatment and did not enter survival follow-up, and those discontinued from the survival follow-up) and duration of follow-up will be summarized. The primary reason for study drug discontinued will be summarized according to the categories in the eCRF. The survival end of study status (alive, death, withdrew consent or lost to follow-up) at the data cutoff date will be listed using the data from the eCRF.

6.3.2 Protocol Deviations

Major protocol deviation criteria will be established and patients with major protocol deviations will be identified and documented before the database lock.

Major protocol deviations will be summarized for all patients in the safety analysis set. They will also be listed by each category.

6.3.3 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized in the safety analysis set, using descriptive statistics.

Continuous demographic and baseline variables include age, BMI, body weight, and height; categorical variables include age group (<65 years, ≥65 years), race, ECOG performance status and germline BRCA mutation type at study entry. In addition, disease characteristics include types of cancer, tumor staging, tumor diagnosis, target lesion diameter at study entry (for phase 2 only), CA-125 value at study entry (for phase 2 only) and time from initial diagnosis.

6.3.4 Prior Anticancer Drug Therapies and Surgeries

The number of prior anticancer drug therapies, prior anticancer radiotherapy and prior anticancer surgeries will be summarized in safety analysis set. The therapies with the same line number are counted as one prior therapy.

Previous anticancer medication will be summarized in the World Health Organization Drug Dictionary (WHO DD) preferred term, if data available.

6.3.5 Prior and Concomitant Medications

Prior and concomitant medications will be coded using WHO DD and will be further classified to the appropriate Anatomical Therapeutic Chemical (ATC) code.

The number (percentage) of patients reporting prior and concomitant medications will be summarized by ATC medication class and WHO DD preferred term by phase in the safety analysis set. Prior medications are defined as medications that stopped before the first dose date. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 30 days after the patient's last dose or initiation of a new anticancer therapy. A listing of prior and concomitant medications will be provided.

6.3.6 Medical History

Medical/disease history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 22.0 or higher). The number (percentage) of patients reporting a history of any medical condition, as recorded on the CRF, will be summarized by system organ class and preferred term in the safety analysis set. A listing of medical history will be provided.

6.4 EFFICACY ANALYSIS

A summary table for all the efficacy endpoints could be referred to in Table 1. Detailed information for each endpoint for each phase is elaborated in the following subsections.

Table 1. Summary table of efficacy endpoints and their corresponding analysis sets

Phase (Source)	Phase 1 (Investigator Review)			Phase 2 (Independent Review Committee)			Phase 2 (Investigator Review)		
Analysis Set[1]	A	B	C	A	B	C	A	B	C
ORR	Y	Y	-	Y	Y	-	Y	Y	-
DOR	Y[2]	-	-	Y[2]	-	-	Y[2]	-	-
PFS	-	Y	-	-	Y	-	-	Y	-
OS	-	-	-	-	-	-	-	Y	-
DCR	Y	Y	-	Y	Y	-	Y	Y	-
CBR	Y	Y	-	Y	Y	-	Y	Y	-
CA-125 response rate	-	Y[3]	Y[3]	-	-	-	-	Y[3]	Y[3]

Note: 1: A: Efficacy evaluable analysis set, B: Safety analysis set, C: CA-125 evaluable analysis set, Y: Yes. 2: only for responders. 3: only for HGOC patients.

6.4.1 Primary Efficacy (Phase 2)

Hypothesis testing of ORR will only be performed in the patients with high grade platinum-sensitive ovarian cancer (PSOC). The primary analysis will be carried out using IRC data in efficacy evaluable analysis set. Efficacy endpoints based on investigator assessed tumor response will be presented as the sensitivity analysis. ORR of pamiparib per IRC is assumed as 52% in patients with recurrent PSOC. The historical rate in a similar population is estimated as 30%. The null and alternative hypotheses are set as follows:

H_0: ORR=30%

H_a: ORR >30%

A binomial exact test will be performed for hypothesis testing in recurrent PSOC efficacy evaluable analysis set. If the obtained one-sided p-value is ≤ 0.025, it will be concluded that pamiparib monotherapy statistically significantly increases ORR compared with historical control. A two-sided binomial exact 95% CI of ORR will be constructed to assess the precision of the rate estimate.

The primary efficacy analysis will be conducted when mature response rate data have been observed, estimated as no more than 12 months after the last patient received the first dose of study drug.

ORR in evaluable recurrent high grade platinum-resistant ovarian cancer (PROC) will be summarized descriptively.

Sensitivity analysis of ORR will be carried out in the safety analysis set. Patients without postbaseline tumor assessment will be considered as non-responders in the safety analysis set and will be classified in category "not evaluated/not evaluable".

6.4.2 Secondary Efficacy (Phase 2)

Kaplan-Meier method will be used to estimate the key secondary endpoint, DOR, and corresponding quartiles (including the median) in the responders. A two-sided 95% CIs of median, if estimable, will be constructed with a generalized Brookmeyer and Crowley method.

Duration of response analysis will only include responders. Censoring rule for DOR will follow PFS censoring rule which will follow FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2018).

Table 2 shows the primary censoring rules for the derivation of PFS using RECIST v1.1 criteria based upon investigator's tumor assessment.

Table 2. Censoring Rules for Analysis of Progression-Free Survival Per RECIST v1.1

No.	Situation	Date of Progression or Censoring	Outcome
1	No baseline tumor assessments	Reference start date	Censored
2	Progression documented on scheduled visit or between scheduled visits	Date of first radiologic PD assessment	Progressed
3	No progression at the time of data cutoff or withdrawal from study	Date of last adequate radiologic assessment prior to or on date of data cutoff or withdrawal from study	Censored
4	Treatment discontinuation for undocumented progression	Date of last radiological assessment of measured lesions	Censored
5	New anticancer treatment started	Date of last radiological assessment of measured lesions prior to or on date of new anticancer treatment	Censored
6	Death before first PD assessment	Date of death	Progressed
7	Death between adequate assessment visits*	Date of death	Progressed
8	Death or progression after two or more consecutive missed visit**	Date of last adequate radiologic assessment before missed tumor assessments	Censored

Abbreviations: CR = complete response, PD = progressive disease, PR = partial response, SD = stable disease,

* Adequate tumor assessment is a radiologic assessment of CR, PR, SD, non-CR/non-PD or PD as determined by investigators.

**More than one missed visit is defined if the duration between the last tumor assessment and death or PD is longer than 2 scheduled visits.

Other time to event variables (PFS and OS) will be analyzed in the safety analysis set using the Kaplan-Meier method. The Kaplan-Meier estimates of PFS and OS will be plotted over time. The PFS time point estimates, defined as the percentages of patients in the analysis population who remain alive and progression-free at the specified time point (eg, 3 or 6 months), will be estimated using the Kaplan-Meier method along with the corresponding 95% CI constructed using Greenwood's formula. The OS time point estimates will be calculated similarly. For OS analysis, patient who has no death date in database will be censored at the last date the patient was known to be alive before/on cutoff date.

BOR is defined as the best response recorded from the start of pamiparib until data cutoff or start of new antineoplastic treatment. BOR and their 95% CIs will be summarized in the efficacy evaluable analysis set. Sensitivity analysis of BOR will be carried out in the safety analysis set. The proportion of each response category (CR, PR, SD, PD and NE) will be presented in the efficacy evaluable analysis set and safety analysis set.

DCR and CBR and their 95% CIs will be summarized in the efficacy evaluable analysis set and safety analysis set.

Time to response (TTR) is defined as time from first dose date to the date of earliest confirmed response (CR or PR) assessed using RECIST V1.1. Only responders were included in the analysis. TTR will be summarized descriptively.

All the efficacy endpoints in Phase 2 will be summarized by cohort. Assessments by IRC and investigator will be summarized separately.

The analysis of CA-125 response rate will be conducted on the CA-125 evaluable analysis set and safety analysis set. The analysis of change in CA-125 (the best percent change from baseline) will be conducted in the safety analysis set. Summary statistics, 2-sided 95% CIs, and graphical summaries will be generated for the percent change from baseline in CA-125. CA-125 definitions agreed by GCIG will be referred to calculate the CA-125 response rate.

6.4.3 Efficacy Analysis (Phase 1)

For phase 1, there will be no analysis for OS. No IRC assessment is available for Phase 1 portion. For the rest part of the efficacy analysis, Phase 1 will follow what Phase 2 does, including the analysis of CA-125.

The efficacy analysis of Phase 1 will be presented by dose level and then separately, by cohort. The cohorts in Phase 1 will be:

- TNBC: triple negative breast cancer
- HGOC: high-grade epithelial, non-mucinous ovarian cancer, including fallopian cancer or primary peritoneal cancer

6.4.4 Subgroup Analyses (Phase 2)

Subgroup analyses of ORR will be conducted for PSOC patients in Phase 2. Table and forest plot of subgroup analysis in ORR will be provided based on the following subgroups:

- Age group (< 65 years vs. ≥ 65 years)
- Baseline ECOG performance status (0 vs. 1)
- Tumor stage at study entry (Stage I vs. II vs. III vs. IV vs. Unknown)
- BRCA mutation type (BRCA1 vs. BRCA2)
- Number of prior anticancer therapy lines (2 vs. 3 vs. ≥4)
- Number of prior systemic chemotherapy lines (2 vs. 3 vs. ≥4)
- Name of the last surgery (Optimal debulking, Sub-optimal debulking, unknown, other)
- Time to progression to last platinum-based systemic chemotherapy (6-12 months vs. ≥ 12 months)
- Target lesion diameter at study entry (<50 mm, ≥50 mm)
- CA-125 value at study entry (<70 kU/L) , ≥70 kU/L))

These planned subgroup analyses may not be explored if sufficient number of samples cannot be achieved for certain subgroups. The subgroup variables and the cutoff values are subject to change if warranted to better represent the data.

6.4.5 Exploratory Efficacy

[redacted]

6.5 SAFETY ANALYSES

All safety analyses will be performed by dose level in the Phase 1 portion of this study and by cohort in the Phase 2 portion of this study based on the safety analysis set. The incidence of treatment-emergent adverse events (TEAEs) and SAEs will be summarized. Laboratory test results, vital signs, ECG and their changes from baseline will be summarized using descriptive statistics (e.g., n, mean, standard deviation, median, Q1, Q3, minimum, maximum for continuous variables; n [%] for categorical variables). Abnormal values will be flagged.

Safety information will be summarized by phase separately.

6.5.1 Dose Limiting Toxicity (Phase 1)

DLTs are taken from the "Dose Limiting Toxicity (DLT)" form on the eCRF. All toxicities or AEs will be graded according to NCI CTCAE version 4.03. A DLT is a toxicity or AE occurring

in the first cycle (23 days), which is attributable to pamiparib and meets the criteria defined in Section 4.1.1.2 of the protocol (version 1.1).

All patients will be summarized by type of DLT and by dose level in the DLT Analysis Set.

6.5.2 Extent of Exposure

The number (and percentage) of patients requiring dose reductions, dose interruption, and treatment discontinuation will be summarized. One cycle is defined as 21 days of treatment except for the first cycle in the Phase 1 portion of this study.

The duration of treatment (months) will be summarized with descriptive statistics. It will be calculated as (Date of last non-zero dose – Date of first dose + 1) / 30.4375.

Number of patients with dose reductions and treatment discontinuation and their reasons, as well as number of patients with any dose modification will be summarized by counts and percentages according to study medication data. In addition, frequency of dose reductions and dose interruption will be summarized by categories (0, 1, ≥2).

Average dose intensity per patient (in mg/day) and relative dose intensity (total dose received / total dose planned) per patient will be summarized. Average dose intensity is calculated as the total dose (mg) taken by a patient divided by overall duration of exposure (= Date of last non-zero dose – Date of first dose + 1) for individual patient. Relative dose intensity is calculated as the total dose (mg) taken by a patient divided by the total dose planned for the patient by study design. To note, for the Phase 1 portion of the study, the planned dose for a patient will be a single dose on day 1 at a given dose level, no dose on day 2 and then twice daily for the next 21 days for Cycle 1; and then twice-daily for later treatment cycles. Patients in the Phase 2 portion of the study will always be treated on twice-daily administration at the prescribed dose level.

Patient data listings will be provided for all dosing records.

6.5.3 Adverse Events

AEs will be graded by the investigators using CTCAE version 4.03. The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using MedDRA. Adverse events will be coded to the MedDRA, version 22.0 or higher, lower level term closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as an AE that had an onset date on or after the first dose of study drug up to 30 days following study drug discontinuation or was worsening in severity from baseline (pretreatment). All AEs will be included in the listings and only TEAEs will be included in the summary tables. SAEs, deaths, TEAEs with Grade 3 or higher, treatment-related TEAEs and TEAEs that led to treatment discontinuation, dose reduction or dose interruption will be summarized.

An overview table, including the incidence of and the number of patients with TEAEs, treatment-emergent serious adverse events (SAEs), treatment-related TEAEs, TEAEs with Grade 3 or higher, treatment-related treatment-emergent SAEs, TEAEs that led to death, and TEAEs that led to treatment discontinuation, dose reduction or dose interruption will be provided. Treatment-related TEAEs include those events considered by the investigator to be unlikely, possibly or probably or definitely- related to study drug or with missing assessment of the causal relationship.

The incidence of TEAEs will be reported as the number (percentage) of patients with TEAEs by SOC and PT. A patient will be counted only once by the highest severity grade according to CTCAE version 4.03 within an SOC and PT, even if the patient experienced more than 1 TEAE within a specific SOC and PT.

The number (percentage) of patients with treatment-emergent SAEs, treatment-related TEAEs, TEAEs with Grade 3 or higher, treatment-related treatment-emergent SAEs, TEAEs that led to death, and TEAEs that led to treatment discontinuation, dose reduction or dose interruption will be summarized by SOC and PT. TEAEs with grade 3 or higher will also be summarized by PT in descending order.

Patient data listings of all AEs, SAEs, treatment-related AEs, grade 3 or higher AEs, AEs that led to death and AEs that led to treatment discontinuation will be provided.

6.5.4 Laboratory Values

Laboratory safety tests (hematology, which is reviewed prior to pamiparib administration, serum chemistry assessed on Day 1 of every cycle, and pregnancy test assessed at screening and EOT) will be assessed in the trial.

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in Table 3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment will be summarized by visit using descriptive statistics. Qualitative parameters listed in Table 3 will be summarized using frequencies (number and percentage of patients), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of patients with non-missing baseline and relevant postbaseline results. Figures will be provided for better illustration, if needed.

Laboratory parameters will be categorized according to NCI CTCAE version 4.03 grades and shifts from baseline CTCAE grades to maximum and the last postbaseline grades will be assessed. Laboratory parameters will be summarized by worst postbaseline CTCAE grade as well. For the lab tests with both high and low abnormality, separate records of worst CTCAE grade (for high and low) will be generated.

Table 3. Clinical Laboratory Tests

Clinical Chemistry	Hematology
Alanine aminotransferase	Hemoglobin (Hgb)
Alkaline phosphatase	Platelet count
Aspartate aminotransferase	White blood cell count
Albumin	Lymphocyte count
Bilirubin (total)	Neutrophil count
Urea	
Calcium	
Chloride	
Creatinine	
Glucose	
Lactate dehydrogenase	
Magnesium	
Phosphate	
Potassium	
Sodium	
Total protein	

6.5.5 Vital Signs

Descriptive statistics for vital sign parameters (systolic and diastolic blood pressure [BP], pulse rate, temperature, and respiratory rate) and changes from baseline for all pre-dose assessments will be presented by visit. Vital signs will be listed by patients, visits and timepoints.

6.5.6 Electrocardiograms

ECG will be performed at the baseline and multiple time points after the start of treatment. ECG findings at baseline and all other pre-dose assessments on the first of the cycles will be summarized. For triplicated ECG, the averaged value will be used in the summary and additional concentration-QT analysis will be conducted and summarized separately. Patient listing of ECG will be provided for all ECG recordings with the indicator whether the abnormality is clinical significance.

6.5.7 ECOG Performance Status

ECOG scores will be summarized by visit.

6.6 PHARMACOKINETIC ANALYSES

Concentration of pamiparib and PK parameters will be summarized and listed for Phase 1 and Phase 2 separately. Dose proportionality will be assessed for Phase 1 portion. All other PK related analysis like concentration-QTc analysis, PK analysis on renal impairment population, PK analysis on hepatic impairment population, etc. will be presented separately and will not be included in the study-level CSR.

6.6.1 Phase 1 Portion

PLASMA CONCENTRATIONS

For Phase 1 portion, plasma samples for pamiparib will be collected on Cycle 1 Day 1, 2 and 3 after a single dose and on Cycle 1 Day 10, Cycle 2 Day 1 and Cycle 3 Day 1 during BID dosing. Pharmacokinetic blood sampling time points will occur at pre-dose, then at 0.5, 1, 2, 4, 6, 9, 12, 24 and 48 hours post first dose, pre-dose, 0.5, 1, 2, 4, 6, 9 and 12 hours postdose on Cycle 1 Day 10, and predose, 2 hours postdose on Cycle 2 Day 1 and Cycle 3 Day 1.

Plasma pamiparib concentration-time data will be summarized and displayed in both tabular and graphical form. Concentration-time data will be analyzed with standard non-compartmental and/or compartmental methods. Pharmacokinetic concentration data for pamiparib will be listed including the dose level, relative time to dosing, actual sample collection time. The concentration data will also be summarized with descriptive statistics for each time point by dose level. The number of patients with non-missing plasma concentration, mean, standard deviation, minimum, median, maximum, geometric coefficient of variation and geometric mean will be included in the summary.

The following figures will be provided:

- Individual patient's plasma concentration profiles will be plotted over time on linear scale.
- Individual patient's plasma concentration profiles will be plotted over time on semi-log scale.
- Mean of pamiparib plasma concentration on linear scale will be plotted over time by dose level.
- Mean of pamiparib plasma concentration on semi-log scale will be plotted over time by dose level.

PHARMACOKINETIC PARAMETERS

PK parameters will be derived using standard non-compartmental methods with WinNonlin Professional, version 5.2 or higher (Pharsight Corp., Mountain View, California). Actual sampling times will be used in the final PK parameter calculations.

Where possible, the following PK parameters will be determined for pamiparib and possibly its major metabolite(s) on Cycle 1 Days 1, 2, 3:

$AUC_{0\text{-}inf}$	Area under the plasma concentration-time curve from zero extrapolated to infinity calculated using the linear up/log down trapezoidal method
$AUC_{0\text{-}12}$	Area under the plasma concentration-time curve from zero to 12 hours post dose

AUC_{last}	Area under the plasma concentration-time curve from zero to last time point of administration
C_{max} and $C_{max,ss}$	Maximum observed plasma concentration
T_{max} and $T_{max,ss}$	Time of maximum observed plasma concentration
$t_{1/2}$	Elimination half-life
CL/F	Apparent clearance
V_z/F	Apparent volume of distribution during the terminal phase
RAC	Accumulation ratio based on AUC or C_{max}

Additional PK parameters may be calculated if deemed appropriate.

The PK parameters for a single dose profile (AUC_{0-12}, AUC_{0-inf}, AUC_{last}, C_{max}, T_{max}, $t_{1/2}$, CL/F, and V_z/F) and after steady-state ($AUC_{0-12,ss}$, $AUC_{last,ss}$, $C_{max,ss}$, $T_{max,ss,}$ C_{trough}), will be calculated, if there are sufficient data. Individual patient parameter values, as well as a descriptive summary (mean, standard deviation, median, minimum, maximum, geometric coefficient of variation and geometric mean) when appropriate by dose level will be reported. Individual patient parameter values will be plotted against dose.

ACCUMULATION RATIO

AUC accumulation ratio is defined as the ratio of AUC at steady state to the AUC for single dose of pamiparib. Accumulation ratio will be normalized for dose level in the following model with repeated measurements for subject i at day j:

$$\mathbf{log(AUC)_{ijk} = \mu + subject_i + dose_j + day_k + dose_i*day_k}$$

where the categorical variable, day, distinguishes daily AUC on day 1 ($AUC_{day\ 1}$ as single dose) and AUC at steady state (AUC_{ss} when dosing day is greater than 1). A subject effect will be included as a random effect. For each dose, the estimate of accumulation ratio will be obtained by applying an exponential function on the difference of least square (LS) means of $log(AUC_{ss})$ and $log(AUC_{day\ 1})$. Similarly, a 95% CI for the accumulation ratio will be obtained by applying the exponential function on the 95% CI for the mean of $log(AUC_{ss})$ - $log(AUC_{day\ 1})$.

The same analysis will be conducted for C_{max}.

PK parameters will be analyzed only for Cycle 1. No data beyond Cycle 1 will be included in the analysis. If patient has dose modification (including dose interruption and reduction) from Cycle 1 Day 3 till Cycle 1 Day 10, data on Cycle 1 Day 10 for that patient will not be included in the analysis.

DOSE PROPORTIONALITY

Dose proportionality of $AUC_{0\text{-}inf}$, $AUC_{last,ss}$, C_{max}, and $C_{max,ss}$ for pamiparib will be assessed using the power model as described below:

$$Log(PK)_i = \alpha + \beta \times log(Dose_i) + \varepsilon_i.$$

where log(•) is the function of natural logarithm, ε_i is a normally distributed random error with mean 0, and PK represents PK parameters AUC, $AUC_{last,ss}$, C_{max} and $C_{max,ss}$. A minimum of 3 values of PK parameters per dose must be available for a given PK parameter. The power model will be estimated by a least square regression method. Point estimates and corresponding 2-sided 95% CIs for the slope parameter and the intercept parameter will be provided.

Dose proportionality will be analyzed only for Cycle 1. No data beyond Cycle 1 will be included in the analysis. If patient has dose modification (including dose interruption and reduction) from Cycle 1 Day 3 till Cycle 1 Day 10, data on Cycle 1 Day 10 for that patient will not be included in the analysis.

6.6.2 Phase 2 Portion

PLASMA CONCENTRATIONS

Sparse PK samples (pre-dose and 2 hour post-dose) will be collected for all patients at sites with the capacity to collect PK samples for determination of pamiparib and possibly its major metabolite(s). Four blood samples (2 mL each) will be collected on Cycle 1 Day 1 and Cycle 2 Day 1 at the following time points: pre-dose (within 1 hour before pamiparib administration) and 2 hours postdose for sparse PK sample collection.

For sparse PK, the number of patients with non-missing plasma concentration, mean, standard deviation, minimum, median, maximum, geometric coefficient of variation and geometric mean will be summarized by visit and time point. A listing will include relative time to dosing, actual sample collection time and time deviation from the relative time point.

Serial PK samples (full PK profile) will be collected in approximately 15 patients at selected sites with the capacity to collect serial PK samples. For PK participating in serial PK collection, on Cycle 1 Day 1 and Cycle 2 Day 1, blood samples (2 mL each) will be collected at the following time points: 0.5, 1, 2, 4, 6, 9 and 12 hours postdose for serial PK sample collection.

For serial PK, the same analysis for concentration will be conducted as Phase 1 portion. Plasma pamiparib concentration-time data will be summarized and displayed in both tabular and graphical form.

PHARMACOKINETIC PARAMETERS

Only patients with serial PK sampling will be included in the analysis for PK parameters. Where possible, the following PK parameters will be determined for pamiparib and possibly its

major metabolite(s) on Cycle 1 Day 1 and Cycle 2 Day 1:

AUC_{0-12}	Area under the plasma concentration-time curve from zero to 12 hours post dose
C_{max}	Maximum observed plasma concentration
T_{max}	Time of maximum observed plasma concentration

Additional PK parameters may be calculated if deemed appropriate.

Individual patient parameter values, as well as a descriptive summary (mean, standard deviation, median, minimum, maximum, geometric coefficient of variation and geometric mean) will be reported, as appropriate.

6.7 AD HOC ANALYSES

Protocol version 5.0 was released on 21 September 2018, which was in the middle of study conduct. The new version of the protocol was mainly aiming to provide more proactive dose modification algorithm and closer hematology monitoring in early stage of drug administration in order to improve the hematological safety management.

The analysis of hematological safety data comparison of pamiparib between pre- and post-protocol amendment (PA) for patients in phase 2 is proposed. Post-PA subgroup is defined as patients signed the first ICF under protocol version 5.0 and Pre-PA subgroup includes patients who signed ICF under at least one previous protocol version. The detailed description of the analysis is in Appendix 10.2.

As a consequence of dose reduction, a proportion of patients will end up with lower dose levels, other than the starting dose level, for their rest of treatment. An analysis of ORR, DCR, CBR, TTR, DOR and PFS will be summarized by most recent prescribed dose level (60mg, 40mg and 20mg) by IRC for PSOC patients in phase 2.

7 INTERIM ANALYSIS

No interim analysis is planned.

8 CHANGES IN THE PLANNED ANALYSIS

No changes are identified at this point.

9 REFERENCES

Brookmeyer R, Crowley J. A Confidence interval for the median survival time. Biometrics. 1982; 38: 29-41.

Clopper, C. and Pearson, ES. The use of confidence or fiducial limits illustrated in the case of the binomial, Biometrika 1934;26: 404-413.

Collett D. Modelling survival data in medical research. New York: Chapman & Hall; 1994.

Common Terminology Criteria for Adverse Events (CTCAE). Version 4.0. United States Department of Health and Human Services, National Institutes of Health, National Cancer Institute, Washington, DC, USA, May 28, 2009.

Eisenhauer EA, Therasse P, Bogaerts J Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-47.

Food and Drug Administration Center for Drug Evaluation Research CDER and Center for Biologics Evaluation and Research. FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, 2018.

Greenwood M. "The natural duration of cancer". Reports on Public Health and Medical Subjects (London: Her Majesty's Stationery Office). 1926; 33:1-26.

Gordon John Sampson Rustin, etc. Definitions for Response and Progression in Ovarian Cancer Clinical Trials Incorporating RECIST 1.1 and CA 125 Agreed by the Gynecological Cancer Intergroup (GCIG). Int J Gynecol Cancer. 2011;21: 419-423.

Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. Washington, DC: United States Food and Drug Administration; 2007.

Kaplan E, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958;53:457-81.

10 APPENDIX

10.1 IMPUTATION OF PARTIAL DATES FOR AEs/MEDICATIONS/THERAPIES/PROCEDURES

IMPUTATION FOR AEs WITH MISSING OR PARTIAL DATES

If AE start/end date are missing or partial missing, the following imputation rules apply.
If end date of an adverse event is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month
- If the imputed end date > death date, then set to death date

If year of the end date is missing or end date is completely missing, do not impute.

If start date of an adverse event is partially missing, impute as follows:

- If both month and day are missing and year = year of treatment start date, then set to treatment start date
- If both month and day are missing and year ≠ year of treatment start date, then set to January 01
- If day is missing and month and year = month and year of treatment start date, the set to treatment start date
- If day is missing and month and year ≠ month and year of treatment start date, the set to first of the month

If year of the start date is missing or start date is completely missing, do not impute.

If the imputed start date > death date, then set to death date. If the imputed start date > the end date (or the imputed end date), set the imputed start date = end date (or the imputed end date).

IMPUTATION FOR MEDICATIONS/THERAPIES/PROCEDURES WITH MISSING OR PARTIAL DATES

When the start date or end date of a medication/therapy/procedure is partially missing, the date will be imputed to determine whether the medication/therapy/procedure is prior or concomitant. The following rules will be applied to impute partial dates for medication/therapy/procedure:

If start date of a medication/therapy/procedure is partially missing, impute as follows:

- If both month and day are missing, then set to January 01
- If only day is missing, then set to the first of the month
- If the imputed start date > death date, then set to death date

If end date of a medication/therapy/procedure is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month
- If the imputed end date > death date, then set to death date

- For prior anticancer therapy, the imputed end date should be the first dose date – 15 at the latest after imputation.

If the year of start date or year of end date of a medication/therapy/procedure is missing, or the start date or end date is completely missing, do not impute.

For detailed imputation rule for new anti-cancer therapy and death date, etc., please refer to a separate document "Standard Definitions and Derivation Rules of Key Variables_V1".

10.2 PRE- AND POST- PROTOCOL AMENDMENT (PA) HEMATOLOGICAL ANALYSES

The following safety data is considered for this analysis of comparison between pre- and post-PA:

C1. Summary of Hematology Laboratory Values

The hematological laboratory values at baseline will be summarized descriptively. The incidence of abnormal hematology values at baseline and any postbaseline visits, and number of patients (%) with shifts in hematology results of ≥ 2 toxicity grades from baseline to worst postbaseline grade will be summarized. The hematological laboratory parameters (unit) of interest for these summaries are: Hemoglobin (g/L), Leukocytes (10^9/L), Lymphocytes (10^9/L), Neutrophils (10^9/L), Platelets (10^9/L).

C2. Summary of Hematological TEAEs

An overall summary of hematological TEAEs will summarize the number (%) of patients. Summaries of the following hematological TEAEs will be provided:

- All hematological TEAEs by preferred terms
- Hematological TEAEs grade 3 or higher by preferred terms
- Serious hematological TEAEs by preferred terms

Hematological TEAE preferred terms are Anemia, Leukopenia, White blood cell count decreased, Neutropenia, Neutrophil count decreased, Thrombocytopenia, Platelet count decreased, Lymphopenia, Lymphocyte count decreased, Haemoglobin decreased, Erythropenia, Red blood cell count decreased, Bone marrow failure, and Febrile neutropenia.

C3. Extent of Exposure and Dose Modification

The following measures of overall extent of study drug exposure in patients between pre- and post-PA will be summarized:

- Duration of treatment (months), defined as (earlier of date of last nonzero dose and data cutoff date – date of first dose + 1) / 30.4375

- Number (%) of patients in each treatment duration category
- Number (%) of patients with dose modification (interruption and reduction)
- Number (%) of patients with dose interruptions and reasons of dose interruptions
- Number (%) of patients with dose reductions and reasons of dose reductions
- Time to first dose reduction (weeks), defined as (earlier of date of first nonzero dose date – date of first dose + 1) / 30.4375 for patients with dose reduction

C4. Concomitant Medications for Anemia

Erythropoietin and Red Blood Cell Transfusion related concomitant medications coded by the WHO-DD drug codes are identified as concomitant medications to cure anemia and will be further classified to the grouping drug name for this analysis of comparison on patients between pre- and post-PA. The number (%) of patients reporting concomitant medications for anemia will be summarized by two grouping drug names and its corresponding WHO-DD preferred terms as following:

EPO (Erythropoietin)
- Erythropoietin Human
- Erythropoietin
- Epoetin Beta

Red Blood Cell Transfusion
- Red Blood cells, Concentrated
- Human Red Blood Cells
- Blood, Whole
- Red Blood Cells
- Erythrocyte
- Red Blood Cells, Leucocyte Depleted

10.3 PROGRAMMING RULE

For detailed programming rule, please refer to a separate document “Standard Definitions and Derivation Rules of Key Variables_V1”.