STATISTICAL ANALYSIS PLAN

Protocol SET-101

A phase 1a/1b, open-label, multi-centre, two-part study of IPN60210, a SETD2 inhibitor, in participants with relapsed/refractory multiple myeloma (MM) or relapsed/refractory diffuse large B cell lymphoma (DLBCL)

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Version 1.0
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SIGNATURE PAGE

The undersigned have reviewed this plan and find it meets the protocol requirements for the reporting of this study.

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MODIFICATION HISTORY

After approval of version 1.0 of the statistical analysis plan, subsequent versions should be documented below with a brief description of the change from the previous version, as well as the rationale for the change.

Version, Date	Made by	Brief Description of Change and Rationale
1.0, 23JUL2024	PPD	Initial Version

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AEs	adverse events
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
$AUC_{0–t}$	area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration
QD	once daily
BMI	body mass index
BOR	best overall response
BOIN	Bayesian optimal interval
BOP2	Bayesian optimal phase 2
CI	confidence intervals
C_{max}	maximum plasma concentration
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DLBCL	diffuse large B cell lymphoma
DLTs	dose-limiting toxicities
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report forms
EZM0414	PH-EPZ-055-RS2-300, EPZ040414, or EPZ- 040414
FIH	first-in-human
GI	gastrointestinal
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLGT	high-level group term
HR	heart rate
HTLV-1	human T-cell lymphotropic virus 1
INR	international normalized ratio
IMWG	International Myeloma Working Group
IV	intravenously
LVEF	left ventricular ejection fraction

MedDRA	Medical Dictionary for Regulatory Activities
λ_z	terminal phase elimination rate constant
MM	multiple myeloma
MTD	maximum tolerated dose
MUGA	multi-gated acquisition
NCI	National Cancer Institute
NE	not evaluable
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
PT	preferred term
PTT	partial thromboplastin time
RECIST	response evaluation criteria in solid tumors
RP2D	recommended phase 2 dose
R/R	relapsed/refractory
SAEs	serious adverse events
SAP	statistical analysis plan
sCR	stringent complete response
SD	stable disease
SETD2	Su(var)3-9, Enhancer of zeste, Trithorax domain containing 2
SI	standardized using International System of Units
SOC	system organ class
SRC	Safety Review Committee
StdDev	standard deviation
t(4;14) translocation	part of chromosome 4 has swapped places with chromosome 14
TEAE	treatment-emergent adverse event
T-LBL/T-ALL	T-cell lymphoblastic lymphoma/T-cell acute lymphoblastic leukemia
$t_{1/2}$	terminal elimination half-life
T_{max}	time at C_{max}
VGPR	very good partial response
WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

Study SET-101 is a first in human (FIH), 2-part (Phase 1a: dose escalation; Phase 1b: dose expansion), open-label, multi-centre study in adult participants with R/R MM or R/R DLBCL. In the middle of phase 1a (dose escalation) conduct, this study was terminated by May 2024 based on a business decision.

This statistical analysis plan (SAP) is limited to the planned analyses for the phase 1a portion of Protocol SET-101 Amendment 3.0. Of note, this SAP should be read in conjunction with the study protocol and the electronic case report forms (eCRFs).

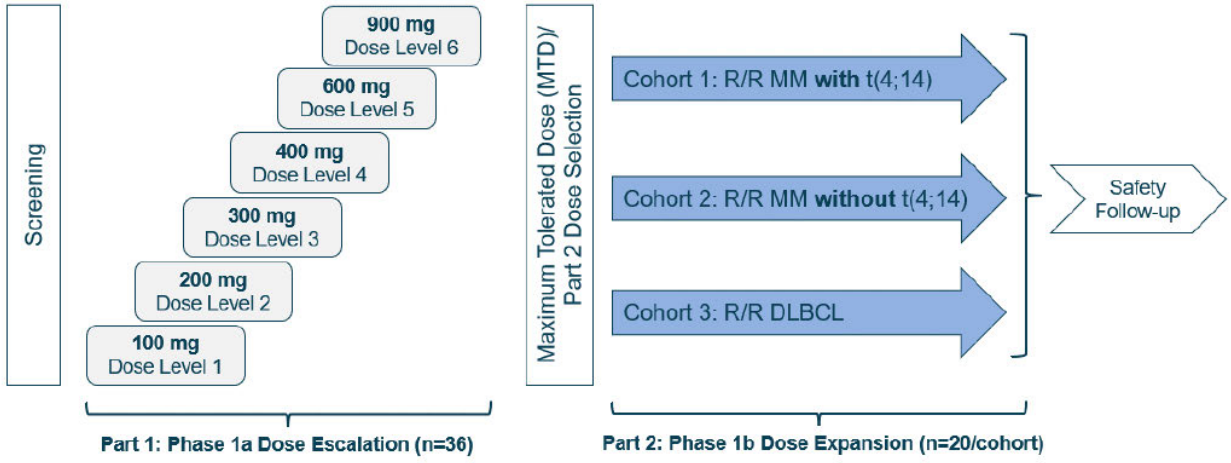
A clinical study report (CSR) will be prepared based on this SAP. Any deviations from this SAP, will be fully documented in the CSR with justification.

2. OVERALL STUDY DESIGN

2.1. General Description

This is a FIH, open-label, multi-centre, Phase 1a/1b study to evaluate the safety, tolerability, PK, and efficacy of the oral SETD2 inhibitor, IPN60210, in adult participants with R/R MM or R/R DLBCL. The study schema is displayed in Figure 1 (See further details in Protocol Amendment 3).

Figure 1: Study Schema



NOTE: Participants who are treated at MTD in Phase 1a Dose Escalation AND do not experience any DLT will be rolled over to Phase 1b Dose Expansion until disease progression, occurrence of unacceptable toxicity, or withdrawal of consent.

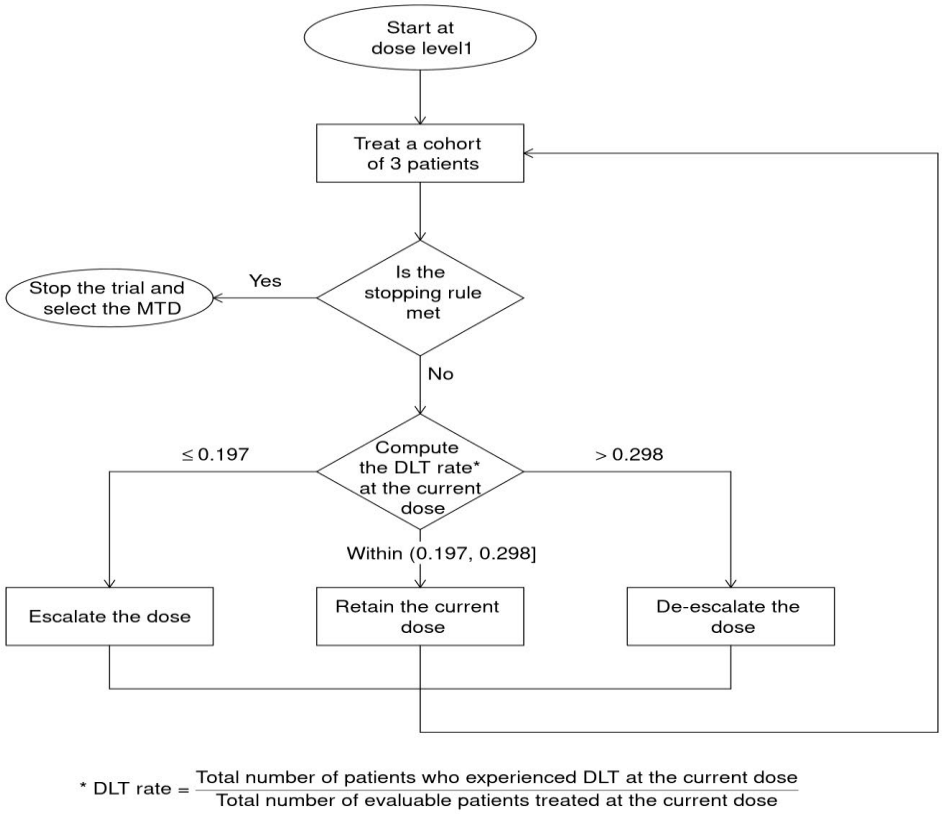
Approximately 96 participants (Phase 1a: 36; Phase 1b: 60) were planned to be enrolled into the study. All participants in this study would receive IPN60210 as monotherapy orally once daily (QD) in 28-day cycles.

In the Phase 1a dose escalation portion of the study, participants were to receive one of six planned dose levels: 100 mg, 200 mg, 300 mg, 400 mg, 600 mg, and 900 mg, or optional step-down dose level of 75 mg (if applicable). Participants would be treated continuously until consent withdrawal, unacceptable toxicity, disease progression, or need for treatment prohibited on this study.

Part 1: Phase 1a (Dose Escalation)

Part 1 is a safety dose escalation study to determine the MTD for dose expansion in Part 2 of the study. Bayesian optimal interval (BOIN) design (Liu and Yuan, 2015; Yuan et al, 2016; Zhou, et al, 2017) would be used to evaluate the safety and tolerability of EZM0414 in participants with R/R MM and R/R DLBCL. The flowchart for trial conduct using the BOIN design is displayed in Figure 2.

Figure 2: Flowchart for Trial Conduct Using the BOIN Design



Note: Additional daily dose levels and/or dosing schedules (including BID regimen) may be studied based on clinical safety, tolerability, and PK data obtained during this study.

2.2. Changes to Analysis from Protocol

The study was terminated early based on a business decision. Only selected analysis detailed in the phase 1a portion of the protocol will be conducted.

3. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Part 1: Phase 1a Dose Escalation Phase	
Primary	
• To evaluate the safety and MTD of IPN60210 when administered as monotherapy in participants with R/R MM or R/R DLBCL.	• Adverse event assessment according to CTCAE 5.0, physical examination, vital signs (blood pressure, heart rate, respiration rate, and body temperature), 12-lead ECG, clinical laboratory tests (haematology including coagulation profile, serum chemistries, and urinalysis), ECOG performance status, concomitant medication monitoring, and DLTs.
Exploratory	
• To investigate pharmacodynamic biomarkers of target engagement in tumour/bone marrow biopsy and/or blood.	• Change from baseline of H3K36me3 in tumour/bone marrow biopsy and/or blood.
• To explore potential predictive biomarkers of response and other biomarkers associated with mechanism of action or resistance in bone marrow aspirates, tumour/bone marrow biopsies, and/or blood samples.	• Determination of biomarkers of response such as histones and histone methylation markers, genomic alterations such as somatic mutations, DNA methylation and other DNA alterations such as t(4;14), protein and gene expression, immune cells in bone marrow aspirates, tumour biopsies, and/or blood samples.
• To assess PK of IPN60210 when administered as monotherapy in participants with R/R MM or R/R DLBCL.	• PK parameters including but not limited to: AUC_{0-t}, C_{max}, T_{max}, and λ_z:

Abbreviations: λz: terminal phase elimination rate constant; AUC_{0-t}: area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration; C_{max}: observed maximum plasma concentration; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; DCR = disease control rate; DLBCL = diffuse large B cell lymphoma; DLT = dose limiting toxicity; DNA = deoxyribonucleic acid; DOR = duration of response; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; H3K36me3 = histone 3 trimethylation at lysine 36; IMWG = International Myeloma Working Group; MM = multiple myeloma; MTD = maximum tolerated dose; ORR = objective response rate; PD = progressive disease; PFS = progression-free survival; PK = pharmacokinetics; PR = partial response; R/R = relapsed/ refractory; sCR = suspected complete response; SD= stable disease; $t_{1/2}$: terminal elimination half-life. T_{max}: observed time at C_{max}; VGPR = very good partial response.

4. INTERIM ANALYSIS

Not applicable (NA).

5. SAMPLE SIZE DETERMINATION AND JUSTIFICATION

5.1. Sample Size Determination

The sample size of Phase 1a part was based on number of doses to be tested. Approximately 36 participants were planned to be enrolled in Phase 1a.

5.2. Sample Size Justification

Bayesian optimal interval design (Liu, 2015; Yuan, 2016; Zhou, 2017) was to be used in the dose escalation part. Similar numbers of participants with R/R MM or R/R DLBCL were to be enrolled to determine the MTD. The target toxicity rate ($\emptyset_T$) for the MTD was set at **0.25** for both R/R MM and R/R DLBCL participants. The maximum number of participants for determination of the MTD will be 9 participants. A total of 6 dose levels ($j = 6$, ie, starting at 100 mg, then 200 mg, 300 mg, 400 mg, 600 mg, and 900 mg) as well as an optional step-down dose level of 75 mg will be investigated. Participants would be enrolled and treated in groups of at least 3, and up to 36 participants were to enrol into the dose-escalation part of the study so that it can evaluate at least 3 and up to 9 participants per dose level. At least 6 participants would be needed to determine the MTD. Dose limiting toxicities are defined in Section 7.5.1 of the protocol, and only those DLTs that occur within the first cycle will be used for dose escalation-related safety assessments. The BOIN design uses the following rules, optimized to minimize the probability of incorrect dose assignment, to guide dose escalation/de-escalation:

- if the observed DLT rate at the current dose is ≤ 0.197, escalate the dose to the next higher dose level;
- if the observed DLT rate at the current dose is ≥ 0.298, de-escalate the dose to the next lower dose level;
- otherwise, stay at the current dose.

For the purpose of overdose control, the current dose j and higher levels will be eliminated from further examination if $\Pr(p_j > 0.25|\text{ data}) > 0.8$ and at least 3 participants have been treated at the current dose level j, where p_j is the true DLT rate of dose level $j, j = 1,\cdots, 6$. This posterior probability is evaluated based on the beta-binomial model $y_j \mid p_j \sim \text{binomial}(p_j)$ with $p_j \sim \text{uniform}(0,1)$, where y_j is the number of participants experienced DLT at dose level j. When the lowest dose is eliminated, stop the trial for safety. The probability cut-off 0.8 is chosen to be consistent with the common practice when the target DLT rate ≤1/6, a dose with 2/3 participants experienced DLT is eliminated. The above dose escalation/de-escalation and elimination rule can be equivalently presented in, which will be used to conduct the trial.

Table 1: Dose Escalation/de-escalation Rule for the BOIN Design

Target Toxicity Rate	Pr (pj > target toxicity rate | data)	Actions	The number of evaluable patients at the current dose								
			1	2	3	4	5	6	7	8	9
0.25	0.8	Escalate if # of DLT ≤	NA	NA	0	0	0	1	1	1	1
		De-escalate if # of DLT ≥	NA	NA	1	2	2	2	3	3	3
		Eliminate if # of DLT ≥	NA	NA	2	2	2	3	3	3	4

BOIN = Bayesian Optimal Interval Design; DLT = Dose Limiting Toxicity; NA = Not Applicable
* When none of the actions (ie, escalate, de-escalate, or eliminate) is triggered, stay at the current dose for treating the next group of subjects. Note that "# of DLT" is the number of participants with at least 1 DLT, and "NA" means that a dose cannot be eliminated before treating 3 evaluable subjects.

Maximum tolerated dose will be determined based on isotonic regression as specified in Liu and Yuan (2015). When the isotonic estimate of toxicity rate $\tilde{p}_{j*}$ is closest to pre-set target DLT rate ($\emptyset_T$=0.25 for this study). If there are ties for $\tilde{p}_{j*}$ the higher dose with $\tilde{p}_{j*}$ < the target toxicity rate will be selected as MTD. Alternatively, the lower dose with $\tilde{p}_{j*} > \emptyset_T$ will be selected.

6. ANALYSIS POPULATIONS

6.1. Definition of Analysis Populations

6.1.1. Analysis Population in Part 1a Dose Escalation Part

Safety Population

The safety population is defined as all participants who have received at least one dose of study drug in Phase 1a (dose escalation part). The safety population will be used for all safety analysis in part 1a.

Dose-Limiting Toxicity (DLT) Evaluable Population

The DLT evaluable population is consist of dose escalation dose level participants in the Safety Population who received at least 80% of planned study treatment during cycle 1. Participants will be analysed according to the assigned dose level for the respective dose escalation cohort.

6.1.2. Pharmacokinetic (PK) Population in Both Phase 1a

Pharmacokinetic (PK) Population

The PK population will include all participants in the Safety population who have sufficient post-dose blood sample collected.

6.2. Statistical Analysis Groups

The Safety population of the study will be categorized to the 3 conducted dose levels (100 mg, 200 mg, 300 mg).

7. DEFINITIONS AND CONVENTIONS

7.1. Study Day

Study day will be calculated in reference to the first dose date of study drug as follows:

- Assessment date is on/after first dose date of study drug:

  Study Day = (date of event – first dose date of study drug) + 1

- Assessment date is prior to first dose date of study drug:

  Study Day = date of event – first dose date of study drug

For partial dates, Study Day will be missing in the listings.

7.2. Baseline Assessments

Unless otherwise specified, baseline is defined as the last non-missing (including unscheduled) assessment value prior to the initial administration of the study drug. If an assessment is performed on the same day as the first dose of study drug, and time is not collected, the assessment will be considered baseline. If there is more than one value on or prior to the initial administration of the study drug, the value closest to and prior to the receipt of the first dose, whether scheduled or unscheduled, will be used as the baseline value.

AEs and medications reported with a start date on the date of first dose will be considered to have occurred after the start of treatment. For vital signs (excluding weight and height) and ECG measures, baseline results will be identified for the set. Baseline will be determined separately for each laboratory analyte.

7.3. Multicentre Studies

The centre effect will not be considered for this study.

7.4. Multiple Comparisons/Multiplicity

NA for this study.

7.5. Common Conventions

- 1 pound = 0.454 kg
- 1 inch = 2.54 cm
- 1 year = 365.25 days. Year is calculated as (days / 365.25) and will be rounded up to 1 significant digit for purposes of presentation
- 1 month = 30.4375 days. Month is calculated as (Days / 30.4375) and will be rounded up to 1 significant digit for purposes of presentation
- Body mass index (BMI) calculated as [weight (kg)/height $(m)^2$]
- BMI calculated as [weight (lb) / height $(in)^2$] × 703

- Post baseline duration in days = end date – start date + 1 (divide by 7 to convert to weeks, divide by 30.4375 to convert to months, and divide by 365.25 to convert to years; round result to 1 decimal place).
- Listings typically will be sorted by study phase, dose level, study treatment, subject identification number (concatenated site and subject number), visit, date, and time, if collected.
- Any date in the listings will use the *date9.* format, for example, 07MAY2002.

7.6. Missing Data

Unless noted otherwise, missing data will not be imputed.

7.7. Statistical Analysis Software

All statistical analyses for this study will be performed using SAS® version 9.4 or higher (SAS® Institute Inc., Cary NC).

8. STATISTICAL ANALYSIS

Phase 1a:

Data for the first three dose levels of phase 1a will be listed.

Phase 1b:

NA

8.1. Disposition of Subjects

Phase 1a:

A subject listing indicating analysis population will be presented for the safety population.

Subject disposition, including primary reasons for treatment and study withdrawal and vital status, will be listed based on the safety population.

Phase 1b:

NA

8.2. Demographics and Baseline Disease Characteristics

The subject listings for demographic and baseline characteristics will be provided for all the related data.

- Age
- Sex (male, female)
- Race (American Indian or Alaska Native, Asian, Black of African American, Native Hawaiian or Other Pacific Islander, White, Other, Not Reported)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, Not Reported)

- Body mass index
- Performance status – will be presented using the Eastern Cooperative Oncology Group (ECOG) scale.
- Primary cancer diagnosis (standardized term)
- Tumor stage at initial diagnosis (DLBCL) (Stage 0, I, II, III, IV, Not applicable, Unknown)
- Tumor stage at study entry (DLBCL) (Stage 0, I, II, III, IV, Not applicable, Unknown)
- Time to initial diagnosis
- Myeloma diagnosis and subtype at study entry (IgG, IgA, IgE, IgD, IgM, Light chain myeloma, and Non-secretory)
- ISS stage initial diagnosis (MM) (I, II, II, and Unknown)
- ISS stage study entry (MM) (I, II, II, and Unknown)
- Is there a history of CNS involvement? (MM) (Yes, No)

8.2.1 Prior Anti-cancer Therapies

Patient level listing for prior cancer related therapy will be provided.

8.2.2 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA V24.0) coding dictionary in use at the time of the analysis and presented by system organ class (SOC) and preferred term (PT). Medical history will be listed by the MedDRA high-level group term (HLGT) and PT.

8.3. Efficacy Analyses

NA

8.3.1 Analysis of Primary Efficacy Endpoint

NA

8.3.2 Analysis of Secondary Efficacy Endpoints

NA

8.4. Safety Analyses

8.4.1 General Considerations

Safety of EZM0414 including DLT for the Phase 1a dose escalation part and all safety events data in phase 1a (dose escalation part)

DLT evaluation will be performed based on the DLT Population (Section 6.1) and the other safety listings will be provided on the Safety Population.

Data from the phase 1a will be presented.

8.4.2 Study Drug Exposure

Study drug exposure and compliance in the phase 1b will be listed for the Safety population.

Compliance will be calculated as: [(total number of dose of drug administered during treatment period)/ (total number of dose planned to administer during treatment period)] *100%

8.4.3 Adverse Events

Listings will be provided for all reported treatment-emergent adverse events (TEAEs), defined as AEs that started or worsened in severity on or after the date of the first dose of study drug through 30 after the end of treatment, or prior to initiation of another investigational agent or cytotoxic chemotherapy. Missing or partially missing start and end dates for AEs and SAEs will not be imputed. For cases in which it is not possible to ascertain treatment-emergence, the event will be classified as treatment-emergent.

The reported AE term will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.0. The severity of each AE will be graded by the Investigator based on version 5.0 of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE). If a severity grading scale does not exist for an AE, the Investigator will classify the severity as mild, moderate, severe, life-threatening/debilitating, or fatal based on the criteria described in the study protocol. The causal relationship between the occurrence of an AE and study drug will be judged by the Investigator as “probable”, “possible”, “unlikely”, or “unrelated”.

The following listings will be presented for part 1a:

- All TEAEs
- Treatment-emergent serious adverse events (SAEs)
- TEAEs leading to discontinuation of study drug

8.4.4 Laboratory Values

Laboratory assessments and specific clinical laboratory tests are described in detail in Section 13.1.8 of Protocol. Blood samples for the following clinical laboratory tests were collected:

- Hematology: Hemoglobin, hematocrit, WBC, differential blood count with ANC, platelet count, RBC.
- Serum chemistries: alkaline phosphatase, ALT, AST, total bilirubin, blood urea nitrogen, creatinine, bicarbonate, albumin, calcium, magnesium, glucose, phosphorus, total protein, and triglycerides.
- Coagulation: partial thromboplastin, partial thromboplastin time (PTT), aPTT, and international normalized ratio (INR).
- Urinalysis: glucose, blood, protein, and pH.

- Viral serology: HBV, HCV, HIV, and human T-cell lymphotropic virus 1 (HTLV-1).

The following listings for hematology, chemistry and coagulation, and urinalysis will be provided:

- Subject listings of all lab values
- Subject listings for Grade 3 and 4 lab values
- Subject listings for laboratory results < 0.25 x LLN or > 2.5 x ULN

8.4.5 Vital Signs

Subject listing of heart rate, temperature, systolic blood pressure, and diastolic blood pressure will be provided:

8.4.6 Electrocardiograms (ECGs)

NA

8.4.7 ECOG

NA

8.4.8 Physical Examination

NA

8.4.9 Prior and Concomitant Medications and Procedures

The following definition will be used to define prior and concomitant medications:

- Prior medications will include medications which stopped prior to the first dose of study drug.
- Concomitant medications are defined as medications that were started prior to first dose of study drug or at any time after the start of first dose of study drug and stopped prior to the discontinuation of study drug.

The reported medication term will be coded using the World Health Organization (WHO) Drug Dictionary in effect at the time of the analysis. The number and percentage of participants taking concomitant medications will be summarized by dose level/Cohorts and generic name, sorted in decreasing order of frequency. All reported prior and concomitant medications will be listed by subject.

8.4.10 Subsequent Anticancer Therapy

NA

9. PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSIS

9.1. Analysis of Pharmacokinetics

Plasma concentrations will be listed based on the PK population.

9.2. Analysis of Pharmacodynamics

No pharmacodynamic analysis will be conducted in this study.

10. REFERENCES

1. Liu S, Yuan Y. Bayesian optimal interval designs for phase I clinical trials. *Journal of the Royal Statistical Society: Series C (Applied Statistics).* 2015; 64(3):507-523.
2. Yuan Y, Hess KR, Hilsenbeck SG, et al. Bayesian Optimal Interval Design: A Simple and Well-Performing Design for Phase I Oncology Trials. *Clinical Cancer Research: an official Journal of the American Association for Cancer Research.* 2016; 22(17):4291-4301.
3. Zhou H, Lee JJ, Yuan Y. BOP2: Bayesian optimal design for phase II clinical trials with simple and complex endpoints. *Statistics in Medicine.* 2017; 36(21):3302-3314.