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STATISTICAL ANALYSIS PLAN

PROTOCOL TITLE: A PHASE I, OPEN-LABEL MULTI-DOSE PHARMACOKINETIC AND SAFETY STUDY OF ORAL TAZEMETOSTAT IN SUBJECTS WITH MODERATE AND SEVERE HEPATIC IMPAIRMENT WITH ADVANCED MALIGNANCIES

EZH-1201

This statistical analysis plan (SAP) is based on:
PROTOCOL VERSION AND DATE: 6.2 – 10 JULY 2024

SAP Version	Date
Final Version 2.0	08 Apr 2025
Final Version 1.0	13 Nov 2020

APPROVAL PAGE

STUDY NUMBER:	EZH-1201
PROTOCOL TITLE:	A Phase I, Open-label Multi-dose Pharmacokinetic and Safety Study of Oral Tazemetostat in Subjects with Moderate and Severe Hepatic Impairment with Advanced Malignancies
SAP VERSION:	Final Version 2.0
SAP DATE:	08 Apr 2025

The undersigned agree that all required reviews of this document are complete, and approve this Statistical Analysis Plan:

Name	Company	Function	Date & signature
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HISTORY OF CHANGES

Version Number	Date	Description/Rational for change
1.0	13 Nov 2020	Not applicable (Initial version)
2.0	08 Apr 2025	Update the definition of study treatment exposure by cohorts, cycles and parts in section 5.7.2. Update the Study Endpoints section per protocol 6.0. Update the SAP to align with the protocol v6.2 and Ipsen SAP template

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	DEFINITION
AE	Adverse Events
AESI	Adverse Events of Special Interest
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Concentration-time Curve
BMI	Body Mass Index
C_{max}	Maximum concentration
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DSUR	Development Safety Update Report
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EZH	Enhancer of Zeste Homologue
HLGT	High-Level Group Term
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for the Registration of Medicinal Products for Human Use
LLN	Lower Limit of Normal
ULN	Upper Limit of Normal
MedDRA	Medical Dictionary for Regulatory Activities
mm	Millimeters
msec	Millisecond
NCI	National Cancer Institute
ODWG	Organ Dysfunction Working Group
PBRER	Periodic Benefit Risk Evaluation Report
PT	Preferred Term
PK	Pharmacokinetics
QTcF	QT interval corrected by Fridericia's formula
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation

ABBREVIATION	DEFINITION
SOC	System Organ Class
$t_{1/2}$	Apparent elimination half-life
TEAE	Treatment-Emergent Adverse Event
TFLs	Tables, Figures and Listings
t_{max}	Time to maximum plasma concentration
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to outline the planned analyses to be completed to support the completion of the Clinical Study Report (CSR) for protocol EZH-1201. It describes the rules and conventions to be used in the analysis and presentation of data, the data to be summarised and analysed, including specificities of the statistical analyses to be performed.

Exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc, or unplanned, analyses not identified in this SAP performed will be clearly identified in the respective CSR.

The initial SAP is to be finalised before first subject in. A separate shell will be provided for tables, figures and listings.

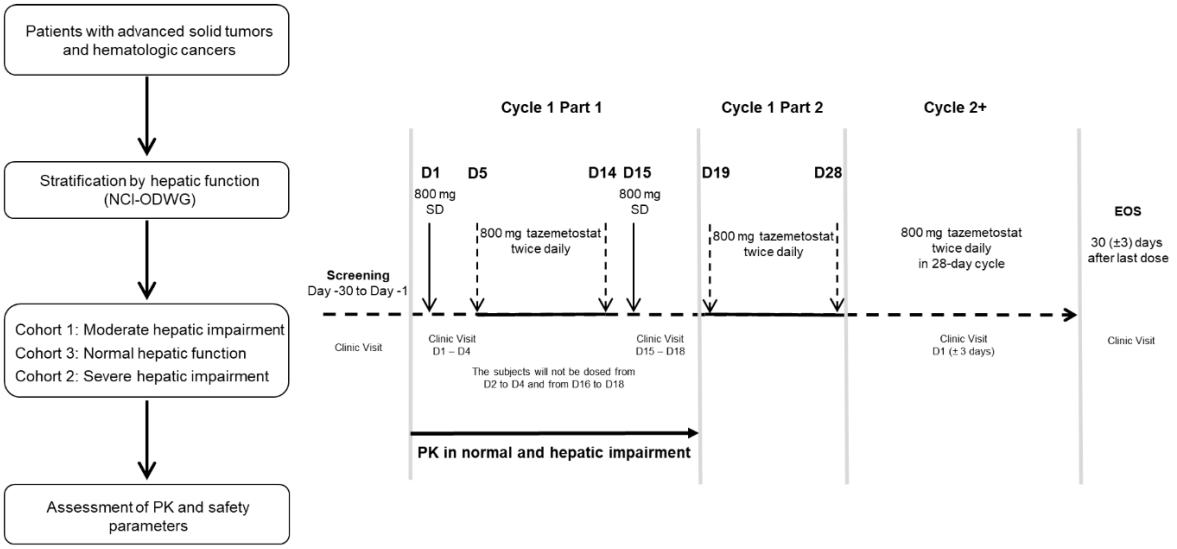
Any deviations from the SAP after database lock will be documented in the CSR (section 9.8 "Changes in the conduct of the study or planned analyses" as per International Council for Harmonisation of Technical Requirements for the Registration of Medicinal Products for Human Use (ICH) E3).

This analysis plan does not cover pharmacokinetics (PK) analysis.

2 PROTOCOL OVERVIEW

This is a phase 1, 2-part, global, multi-center, open-label, PK, and safety study. This study is designed to characterize the PK of oral tazemetostat and its metabolite EPZ-6930 when administered as a single and twice daily dose (800 mg) in subjects with advanced malignancies and either normal hepatic function, moderate or severe hepatic impairment (Figure 1) based on the National Cancer Institute (NCI) Organ Dysfunction Working Group (ODWG) criteria (Shibata et al., 2013) .

Figure 1 Study Design



D: day; EOS: end of study; NCI-ODWG: National Cancer Institute Organ Dysfunction Working Group; PK: pharmacokinetics; SD: Single dose

NOTE: Subjects from the moderate hepatic impairment cohort and normal hepatic function cohort were dosed at 800 mg tazemetostat. Preliminary data from the normal and moderate hepatic impairment cohorts in this study and the tazemetostat safety profile (DSUR/PBRER) does not preclude treatment of subjects with severe hepatic

impairment. Therefore, the cohort of subjects with severe hepatic impairment will be enrolled in parallel to the cohort of subjects with moderate hepatic impairment.

2.1 Study Objectives and Hypotheses

2.1.1 Primary Objective

The primary objective of this study is to evaluate the PK of tazemetostat and its metabolite EPZ 6930, when administered as a single and twice daily oral dose in subjects with advanced malignancies and moderate or severe hepatic impairment (based on the NCI ODWG criteria), compared with subjects with advanced malignancies and normal hepatic function.

2.1.2 Secondary Objective

The secondary objective of this study is to evaluate the safety of tazemetostat and its metabolite EPZ 6930 when administered as a single and twice daily oral dose in subjects with advanced malignancies and moderate or severe hepatic impairment (based on the NCI ODWG criteria), compared with subjects with advanced malignancies and normal hepatic function.

2.2 Overall Study Design and Investigational Plan

This is a phase 1, 2-part, global, multicenter, multi-dose, open-label, PK, safety, and tolerability study of oral tazemetostat in subjects with either advanced solid tumors, or hematological malignancies and normal hepatic function or moderate, or severe hepatic impairment. The study will be conducted in 2 parts.

2.2.1 Part 1

A screening visit will occur within 30 days before day 1 after signing an informed consent form (ICF). Subjects will visit the clinical study unit on an out-patient basis from day 1 to day 4 and from day 15 to day 18. Subjects may be admitted to the clinical study unit or must agree to stay locally during their study participation. Prior to dosing on day 1, subject eligibility will be reconfirmed.

Subjects will be enrolled into one of 3 cohorts:

- Cohort 1: moderate hepatic impairment (NCI-ODWG)
- Cohort 2: severe hepatic impairment (NCI-ODWG)
- Cohort 3: normal hepatic function (NCI-ODWG)

2.2.2 Part 2

Subjects proceeding to Cycle 1 Part 2 will begin Part 2 on Cycle 1 day 19. Subjects continuing treatment in Part 2 will receive tazemetostat (oral 800 mg dose) tablets to be taken twice daily from day 19 – 28. Subjects in Cycle 2+ of the study will be treated twice daily in 28-day cycles until Investigator-assessed clinical progression per standard practice, or unacceptable toxicity, or until another discontinuation criterion is met.

2.3 Sample Size Determination and Power

Approximately 24 subjects will be enrolled in the study (8 evaluable subjects in each cohort, i.e., subjects who completed Cycle 1 Part 1 with adequate dosing of tazemetostat in accordance with the protocol and adequate PK sampling to enable PK parameter estimates).

2.4 Randomisation and Blinding (if applicable)

This is an open-label study, subjects will not be randomized or blinded to treatment.

2.5 Schedule of Assessments

Schedule of assessments is presented in section 8 from the protocol.

2.6 Change from Statistical Section of the Protocol

There is no change from the statistical section of the protocol.

3 PLANNED ANALYSES

3.1 Data Monitoring

No independent Data Monitoring Committee will be used in this study.

3.2 Interim Analysis / Primary Analysis

No interim analysis will be performed.

3.3 Final Analysis

Planned analyses will be done when all subjects complete study and after database lock.

4 ANALYSIS SETS

The **Enrolled population** is defined as all subjects who signed inform consent and met all inclusion/exclusion criteria.

The **Safety population** is defined as all subjects who received at least 1 dose or a partial dose of study drug. The safety population will be used for all baseline and safety analyses.

The **PK population** is defined as all subjects in the Safety population who have adequate dosing of tazemetostat in accordance with the protocol and sufficient (ie, to accurately assess the AUC0-8 and Cmax) post-dose samples collected to allow estimation of the PK parameters.

5 STATISTICAL METHODS/ANALYSES

The statistical analyses will be performed in accordance with ICH E9 guideline and guidelines presented in section 8.

5.1 General Considerations

The purpose of this SAP is to describe the endpoints and analyses, excluding PK, to be included in the CSR for the Phase 1 Protocol EZH-1201.

PPD will perform the statistical analysis of the safety and tolerability. Analyses of PK and the results will be presented in separate documents.

Unscheduled assessments won't be included in the table summaries but will be used in determining maximum/worst post-baseline values.

All statistical analyses will be performed using the Statistical Analysis System® software version 9.4 or higher.

5.1.1 Outputs Presentation

5.1.1.1 Tables Header

Depending on the type of data, the summary tables will be presented as follows:

- For disposition, demographic, baseline and safety data: by cohort and overall,
- For exposure data: by cycle, cohort and overall.

In case of several active doses, an overall active dose column should also be added for any tables.

- Only the cohort with no missing information will be display

5.1.1.2 Presentation of Cohort

Tables, Figures and Listings (TFLs) will be displayed using the following cohort labels, in the order presented:

Cohort	Cohort Label
Normal	normal hepatic function (NCI-ODWG)
Moderate	moderate hepatic impairment (NCI-ODWG)
Severe	severe hepatic impairment (NCI-ODWG)

5.1.1.3 Presentation of Visits

Summaries by visit will be presented using visit number as collected in the Electronic Case Report Form (eCRF).

5.1.2 Descriptive Statistics

All raw and derived variables will be listed and described using summary statistics. For categorical variables, summary statistics will be displayed using descriptive statistics by frequency count and percentages by category. The missing category will be presented if there is at least one missing category for at least one cohort. Unless otherwise specified, subjects with missing data will be included in the calculation of percentages. For quantitative variables, summary statistics will be displayed using descriptive statistics by number of observations, mean, standard deviation (SD), median, minimum and maximum. Frequency and proportion of missing data will be displayed.

5.1.3 Baseline value

Unless otherwise specified, baseline is defined as the last non-missing measurement taken on or prior to first Investigational Medicinal Product (IMP) administration (including unscheduled assessments).

5.1.4 Reference Start Date and Study Day

Reference start date is defined as the day of the first IMP administration.

The day of the first IMP administration will be Day 1. Study day will be calculated as:

- The difference between the event date and the reference date plus one day, if the event is on or after the reference date.
- The difference between the event date and the reference date, if the date of event is prior to the reference date.

Study day will appear in any listings where an assessment date or event date appears.

5.2 Disposition and Analysis Sets

Following disposition summaries and listings will be provided:.

- Summary table with the number and percentage of subjects enrolled, treated and not treated, and discontinued study drug and reason for discontinuation, completed safety follow-up, status at last contact for the Safety population,
- Listing of dates of discontinuation, first dose, last dose and primary reason for discontinuation from the study drug, death, reason for discontinued follow-up for the enrolled population.
- Summary table with the number and percentages of enrolled subjects per region EEA countries (including European Union member states, as well as Norway, Iceland, and Liechtenstein), vs. USA vs. other, country, and site, on the enrolled set.

5.3 Protocol Deviations

All protocol deviations will be listed for the safety population. Protocol deviations will be summarized by major and minor category, by cohort and overall, for the safety population. Predefined categories of major protocol deviations will include but might not be limited to:

- Violation of inclusion/exclusion criteria
- Prohibited medications
- Study drug compliance

Additional categories may be added during the study but will be determined prior to database lock.

5.4 Demography and Other baseline characteristics

The following demographic information will be presented: age, BMI, race, sex, ethnicity and Eastern Cooperative Oncology Group (ECOG) score.

Sex, race, ethnicity and age in category (<65, 65-75, >75) and baseline hepatic function per NCI organ dysfunction working group (NCI-ODWG) will be presented using number and percentage of subjects. Age, BMI and baseline total bilirubin will be summarized using number of subjects, mean, standard deviation, median, minimum and maximum. Baseline demographics will also be presented in a listing.

The use of alcohol will be summarized presenting the number and percentage of subjects in the never, current, and former categories. For current and former categories of daily, weekly, monthly and per year, descriptive statistics will be provided.

Baseline disease characteristics such as tumor type coded according to the of Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary version in use at the time of the analysis, stage and location will be tabulated by cohort by presenting number and percentage of subjects.

Drug and alcohol screening results will be presented in a listing.

5.5 Medical history, non-drug therapies, medications and surgical procedures

General and disease-specific medical history including a history of past and current medical conditions were to be recorded during screening. Current medical conditions were to be updated on day 1.

Medical history will be coded according to the MedDRA coding dictionary version in use at the time of the analysis and presented by system organ class (SOC) and PT as well as in a listing.

Surgical history will be summarized by the MedDRA high-level group term (HLGT) and PT.

Separate listings of surgical and medical history will be provided.

All prior medications administered 30 days before study drug were to be recorded.

Prior medications, cancer related surgery, radiotherapy, and anti-cancer therapy regimen will be summarized by cohort and overall and presented in listings on a subject level basis by cohort.

For prior medications, the medication/therapy, dose, frequency, route, indication and whether medication is ongoing, will be presented.

In the listing for cancer related surgery, the surgical procedure, whether it is concomitant or not, date of procedure and date of progression after surgery, if applicable, will be presented. The number of prior surgery and type of surgical procedure will be tabulated by the number and percentage of subjects.

The site of radiotherapy, type of radiation, start date and end date, total dose, and date of progression after radiation, if applicable, will be listed for prior radiotherapy. The number of prior courses of radiotherapy, site of radiotherapy and type of radiation will be summarized by presenting the number and percentage of subjects. Number of prior courses of radiotherapy will also be descriptively summarized.

Prior anti-cancer therapy will be presented in terms of number of prior regimens, type of therapy, therapy setting, dose, and number of cycles. In addition, the start and end date, best response, reason subject discontinued therapy, and whether patient progressed on therapy will be listed.

Prior anti-cancer therapies will also be summarized by number of prior regimens, type of therapy, therapy setting, best response and reason for discontinuing therapy by number and percentage of subjects, except for number of regimens which, will be descriptively summarized.

Concomitant medications were to be recorded throughout the study and will be coded using the World Health Organization (WHO) Drug Dictionary version in use at the time of the analysis.

Concomitant medications will be summarized by WHO Drug Anatomical Therapeutic Chemical (ATC) Classification level 4 and preferred term (PT), cancer related surgery and radiotherapy will be presented in a listing on subject level by cohort. The number and percentage of patients using at least one medication within each medication group will be tabulated.

5.6 Efficacy - Disease assessment

No efficacy analysis will be performed.

Disease assessment will be performed as outlined in the schedule of assessment in the protocol. Disease progression will be determined through Investigator assessed review of clinical status and patient scans. Assessment week, assessment date, whether patient had progressive disease and comments related to progression, if applicable, will be presented in a listing.

5.7 Safety

5.7.1 General Consideration

All safety summaries and analyses will be based upon the Safety Set.

5.7.2 Extent of exposure

Descriptive statistics will be used to present drug exposure.

Drug exposure will be summarized as duration on treatment and extent of exposure to tazemetostat, by cohorts, cycles and parts.

Cycle 1 Part 1:

- Cumulative dose received (mg) for Cycle 1 Part 1 = 200 mg x number of tablets taken during the days of actual single daily dose + actual twice daily dose.
- Cumulative planned dose (mg) for Cycle 1 Part 1 = (planned single daily dose x number of days on planned single daily dose) + (planned twice daily dose x number of days on planned twice daily dose x 2), i.e. (800 mg x 2) + (800 mg x 10 x 2) = 17600 mg.

  Note: In Cycle 1 Part 1, number of days on planned single daily dose = 2 (i.e. Day 1 and Day 15), number of days on planned twice daily dose = 10 (i.e. Day 5 to Day 14 inclusive), and the number of days on actual single/twice daily dose is determined by the

actual start date and end date of single/twice daily dose. The planned single/twice daily dose is 800mg.

Cycle 1 Part 2:

- Cumulative dose received (mg) for Cycle 1 Part 2 = 200 mg x number of tablets taken during the days of actual twice daily dose.
- Cumulative planned dose (mg) for Cycle 1 Part 2 = (planned twice daily dose x number of days on planned twice daily dose x 2). i.e. (800 mg x 10 x 2) = 16000 mg.

  Note: In Cycle 1 Part 2, the number of days on planned twice daily dose = 10 (i.e. Day 19 to Day 28 inclusive), and the number of days on actual twice daily dose is determined by the actual start date and end date of twice daily dose. The planned single/twice daily dose is 800mg.

Cycle 2+ onwards:

- Cumulative dose received (mg) for Cycle 2+ = 200 mg x number of tablets taken during the days of actual twice daily dose.
- Cumulative planned dose (mg) for Cycle 2+ = (planned twice daily dose x 2 x number of cycles x 28).

  Note: In Cycle 2+, number of days on actual twice daily dose = last dose date – first dose date + 1. Each planned cycle has 28 days. The planned twice daily dose is 800mg.

The drug accountability information will be used to determine the actual dose where one tablet = 200 mg. The number of tablets taken = number of dispensed tablets – number of returned tablets. The number of tablets taken is set to missing when dispensed or returned tablets is not done.

Relative Dose Intensity (%) = [cumulative dose received / cumulative planned dose] x 100.

Compliance (%) = [cumulative dose received / adjusted cumulative planned dose] x 100.

- Adjusted cumulative planned dose = planned daily dose x (number of planned days – days of dose reductions due to AE) + ∑ (Each reduced daily dose due to AE x number of days on the reduced daily dose).

Measures of extent of exposure to tazemetostat include the cumulative dose received, cumulative planned dose, number of treatment cycles for cycle 2+, number of subjects with any missed or modified doses.

Compliance and relative dose intensity will be summarized. The reasons for study treatment dose missed or modified will be summarized.

A listing of study drug exposure and compliance will be provided.

5.7.3 Adverse Event

An overview summary table of subjects with TEAEs, which are defined as AEs that started or worsened in severity on or after the day of the first dose of study drug through 30 days after the end of study drug will be summarized by cohort and overall, and will include the number of subjects with any TEAE, TEAEs of Grade 3 or 4, any treatment related TEAE, any treatment related TEAEs of grade 3 or 4, serious TEAEs, treatment related serious TEAEs, non-serious TEAEs (frequency >5%), TEAEs leading to study drug discontinuation, TEAEs leading to dose interruptions, TEAEs leading to dose reductions, AESI and deaths(all causes), deaths related to study treatment.

Severity of all adverse events were evaluated by the Investigator based on the NCI CTCAE, version 5.0 and coded to PT, HLGT, and SOC using the MedDRA, version in use at the time of the analysis. Each summary table will include the number and percentage of subjects reporting any TEAE and will be presented by MedDRA SOC and PT, relationship to study treatment, and severity. TEAEs will also be presented by PT only.

Additional separate listings of SAEs, TEAEs leading to discontinuation of study drug, and TEAEs leading to dose modifications (interruption and dose reduction). A listing of TEAEs of special interest will also be provided.

Adverse events with CTCAE Grade 5 or outcome of death are excluded from AE summary tables and summarized under death related tables.

A subject will be counted once within an SOC, even if the subject experienced more than one TEAE within a specific SOC (likewise for PT).

Subject deaths will be summarized and listed as follows:

- Summary and listing of subjects who died during and till 30 days after last dose of study drug
- Summary and listing of subjects who died during and till 30 days after last dose of study drug with treatment-related TEAEs
- Summary and listing of subjects who died after 30 days after the last dose of study drug with treatment-related TEAEs.

The summary and listing will include the reason for death:

- Any AE (by MedDRA PT)
- Any treatment related TEAE
- Progressive Disease
- Unknown/Other causes.

Patient death will be listed by subject by presenting date of death, primary cause of death, treatment duration (days), AE associated PT (if available) and relation to study drug, time from last dose date to death date (days) and whether an autopsy was performed.

5.7.4 Laboratory Data

Clinical laboratory data (chemistry, hematology and coagulation, and urinalysis) values will be classified by toxicity grade based on the NCI CTCAE, version 5.0, irrespective signs or symptoms. Where CTCAE grading applies, shift from baseline value to worst post-baseline result will be summarized. Where CTCAE grading does not apply, shift from baseline to worst post-baseline value that is < 0.25 x lower limit of normal (LLN) or >2.5 x upper limit of normal (ULN) will be summarized.

Blood smear morphology assessment and bone marrow biopsy/aspirate results will be listed by cohort and subject.

Listings of all laboratory data, grade 3 or 4 laboratory data and laboratory results <0.25 x LLN or > 2.5 x ULN, for hematology and coagulation, blood chemistry and urinalysis will be provided.

Laboratory values that are reported as ‘below the detectable limit’ of an assay will be analysed as half the detectable limit when required for analysis purposes but listed as originally reported (e.g bilirubin= “<0.2” use 0.1 mg/dL)

For GFR, if only qualitative values are reported (e.g., “>60”), impute a default value of 75.0 mL/min for analysis purposes but listed as originally reported.

5.7.5 Vital Signs

Vital signs for systolic blood pressure (mmHg), diastolic blood pressure (mmHg), sitting heart rate (bpm), respiratory rate (breaths/min), and temperature (ºC) will be summarized and listed. Summaries of heart rate, temperature, systolic blood pressure, and diastolic blood pressure will be based on markedly abnormal criteria defined below in Table 1:

Table 1: Markedly abnormal criteria for vital signs

Vital Sign	Markedly Abnormal Criteria
Heart rate (bpm)	• < 60 bpm • > 100 bpm
Temperature (ºC)	• ≤ 35 ºC • ≥ 38 ºC
Systolic blood pressure (mmHg)	• 120-139 mmHg, inclusive (CTCAE grade 1) • 140–159 mm Hg, inclusive (CTCAE grade 2) • ≥ 160 mmHg (CTCAE Grade 3)
Diastolic blood pressure (mmHg)	• 80–89 mmHg, inclusive (CTCAE grade 1) • 90–99 mm Hg, inclusive (CTCAE grade 2) • ≥ 100 mmHg (CTCAE grade 3)

Incidence of markedly abnormal worst-case values will be presented. For heart rate and temperature, both high and low values will be presented separately such that subjects can be counted in both categories. Vital signs will also be presented in a listing.

5.7.6 Electrocardiogram (ECG)

12-Lead ECG measures (singlets and triplicates) will be collected according to the schedule of events in the protocol. When triplicates are collected, the averages will be used in the summaries.

The investigator will provide an overall interpretation of the ECG (i.e. normal; abnormal – not clinically significant; abnormal – clinically significant; unevaluable). For the Fridericia correction of QT interval for heart rate (QTcF), markedly abnormal criteria will be defined as described in Table 2 below.

ECG values, the investigator's interpretation of the ECG, and other information collected will be listed. QTcF values meeting markedly abnormal criteria will be flagged as in Table 2.

The following summaries will be provided for QTcF:

- Quantitative 12-lead ECG measurements: Shift from baseline to worst post-baseline in QTcF status categorized as markedly abnormal or not (defined in the table below).
- Quantitative 12-lead ECG measurements: Number and percentage of subjects whose worst-case changes from baseline in QTcF measurements meet markedly abnormal criteria (described in the table below for changes from baseline).

Table 2: Markedly abnormal criteria for QTcF measurements

QTcF Measure	Markedly Abnormal Criteria
Observed	• 450–480 msec, inclusive (CTCAE grade 1) • 481–500 msec, inclusive (CTCAE grade 2) • > 500 msec (CTCAE grade 3 or higher)
Change from Baseline	• 31–60 msec, inclusive, increase from baseline • >60 msec increase from baseline

ECOG performance status at baseline and follow-up will be listed by subject for each cohort. Analyses presenting the shift from baseline to best and worst on-study ECOG will be tabulated. In addition, a listing of ECOG results will be provided.

5.7.7 Physical Examination

Physical examination results at each visit will be listed by subject for each cohort.

5.8 Pharmacokinetic Analysis

All pharmacokinetic analyses will be performed based on the PK population. PK concentration data will be listed.

All PK analysis details and results will be described in a separate PK report.

6 DATA HANDLING

6.1 Unscheduled Visits, Retest, Withdrawal Visit,

All listings will include retests and unscheduled visits, while for the description by visit in the tables, only the scheduled visits according to the protocol will be described.

Unscheduled visit and retest measurements will be used to provide a measurement for a baseline data or endpoint value (e.g. worst value), if appropriate according to their definition. These measurements will also be used to determine abnormal laboratory, vital signs values or ECG.

If a value requires a retest (for laboratory values, vital signs and ECG) the closest non-missing reliable value to the scheduled visit will be used in the summary tables.

7 DERIVED DATA

Baseline, change from baseline

Baseline is defined as the last non-missing value before the initial administration of the study drug. If an assessment is performed on the same day as first dose of study drug, and time is not collected, the assessment will be considered baseline. Change from baseline will be defined as the value at post-baseline visit minus value at baseline.

ECOG evaluation

Worst on-study ECOG is defined as the highest score on the ECOG scale for performance status evaluation and best on-study ECOG is defined as the lowest score on the ECOG scale for performance status evaluation, please see the Table 3 below.

Table 3: Performance status: ECOG

Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.
5	Dead

Prior/Concomitant Medications

Prior medications will include medications taken with a stop date prior to first dose of study drug.

Concomitant medications are defined as medications that started before the date of first dose of study drug and ongoing at the date of first dose of the study drug or with a start date on or after the date of first dose of the study drug and stopped date prior to discontinuation of study drug, or with a stop date on or after the date of the first study drug dose.

In the case of missing or partial medication start and end dates, medications will be assumed to be concomitant if they could have started or ended between first and last study drug dose date.

8 REFERENCES

ICH E3: Structure and Content of Clinical Study Reports

ICH E6 (R2): Good Clinical Practice

ICH E9: Statistical Principles for Clinical Trials

Standard Ipsen Study Data Tabulation Model (SDTM) user guide

Standard Ipsen Analysis Data Model (ADaM) user guide

Ipsen Global Style guide

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9 APPENDIX

9.1 List of PCSA criteria

The baseline hepatic function per NCI organ dysfunction working group (NCI-ODWG) criteria for hepatic dysfunction:

- Normal, Total bilirubin ≤ ULN and AST≤ ULN

- Moderate dysfunction, Total bilirubin >1.5 to 3 times ULN
- Severe dysfunction Total bilirubin > 3 times ULN and up to 5×ULN

9.2 Programming Convention for Outputs

All text fields must be left justified and numeric or numeric with some text specification (e.g.: not done, unknown, <4.5, …) must be decimal justified.

Decimal places:

• The mean, median, lower quartile, upper quartile will be reported to one decimal place greater than the raw data recorded in the database. The SD will be reported to two decimal place greater than the raw data recorded in the database.

• The minimum and maximum values will be reported with the same number of decimal places as the raw data recorded in the database.

• In general, the maximum number of decimal places reported should be four for any summary statistic.

Percentages will be presented to one decimal place (e.g.: xx.x). Percentages will not be presented for zero counts. Percentages 100 will be presented as (100) instead of (100.0). Percentage will be calculated using n as denominator. The denominator n will be specified in a footnote for clarification if necessary.

Dates will be presented in the format [ddmmmyyyy] and times in the format [hh:mm].

Conversions to weeks, to months, year will be days/7, days/30.4375, days/365.25, respectively.

Any listings will contain at least the following data: subject identifier, age, race and gender. When dates are presented, the associated study days should be included. They should be sorted by cohort then subject identifier. For multicenter studies, listings should be broken down by centre and cohort.