Title: A Randomized, Crossover Phase 1 Study to Evaluate the Effects of Pevonedistat on the QTc Interval in Patients with Advanced Solid Tumors

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: Pevonedistat-1014

A Randomized, Crossover Phase 1 Study to Evaluate the Effects of Pevonedistat on the QTc Interval in Patients with Advanced Solid Tumors

PHASE 1

Version**: Final**

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Prepared by:

PPD

Based on:

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1.1 Approval Signatures

Electronic signatures can be found on the last page of this document.

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ANC	absolute neutrophil count
AUC	area under the plasma concentration-time curve
AUC_{24}	area under the plasma concentration-time curve from time 0 to 24 hours
BP	blood pressure
BSA	body surface area
CI	Confidence Interval
C_{max}	maximum observed plasma concentration
CR	complete response
CT	computed tomography
CV	coefficient of variation
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOS	End of Study
GFR	glomerular filtration rate
HR	heart rate
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NPO	nothing by mouth
PD	progressive disease/disease progression
PK	pharmacokinetic(s)
PR	Partial response
QTc	corrected QT interval
QTcF	Fridericia corrected QT interval
QTcI	individual corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
SoC	standard of care
$t_{1/2}$	half-life
WHO	World Health Organization

4.0 OBJECTIVES

4.1 Primary Objective

The primary objective of the study is:

- To characterize the effects of 25 and 50 mg/m^2 pevonedistat on the QT interval with Fridericia correction method [QTcF] of the ECG.

4.2 Secondary Objectives

The secondary objectives for Part A are:

- To assess the effects of pevonedistat on individual corrected QT interval [QTcI], QRS, PR, and heart rate [HR] following a single IV dose at 25 and 50 mg/m^2.
- To characterize the pharmacokinetics [PK] profile of pevonedistat following a single IV dose at 25 and 50 mg/m^2.

The secondary objectives for Part B are:

- To evaluate the disease response that may be observed after treatment with pevonedistat in combination with either docetaxel or carboplatin+paclitaxel in patients with advanced solid tumors.

4.3 Safety Objective

The safety objective for Part A is:

- To evaluate the safety and tolerability of pevonedistat in patients with advanced solid tumors following a single IV dose at 25 and 50 mg/m^2.

The safety objective for Part B is

- To evaluate the safety and tolerability of pevonedistat in combination with either docetaxel or carboplatin+paclitaxel in patients with advanced solid tumors.

4.4 Study Design

This is a phase 1, 2-dose, crossover study to assess the effects of pevonedistat 25 and 50 mg/m^2 on the corrected QT [QTc] interval in patients with histologically or cytologically confirmed metastatic or locally advanced solid tumors that are appropriate for treatment with one of the 2 combination therapies described in Part B of this study, who have progressed despite standard therapy, or for whom conventional therapy is not considered effective.

Approximately 45 patients will be enrolled to obtain approximately 36 evaluable patients. Patients will be randomized 1:1 to receive pevonedistat 25 or 50 mg/m^2 on Day 1 in Part A and the other dose on Day 8. Study drug will be discontinued early if a patient experiences study drug–related toxicities. Patients may discontinue therapy at any time. Patients in Part A who do not continue to the optional Part B will attend an End-of-Study [EOS] visit 30 (+10) days after receiving their last dose of study drug in Part A.

Patients who continue to the optional Part B will attend an EOS visit 30 (+10) days after receiving their last dose of study drug in Part B or before the start of therapy subsequent to Part B participation, if that occurs sooner. Toxicity will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE], version 4.03, effective date 14 June 2010 [1]. Adverse event [AE] will be assessed, and laboratory values and vital signs will be obtained to evaluate the safety and tolerability of pevonedistat.

Part A: QT Assessment

For Part A of this study, qualifying adult patients will report to the clinical facility on the morning of Day -1 for collection of baseline measurements of serial triplicate ECGs (0-11 hours). Continuous 12-lead digital ECGs will be obtained using a Holter ECG recorder. Three Holter ECGs (approximately 1 minute apart) will be extracted at prespecified time points that match the times of Day 1 postdose PK/ECG sampling. As the Day -1 baseline evaluations are intended to serve as time-matched baseline for corresponding Day 1 and 8 PK/ECG evaluations, it is critical to ensure that the 0-hour time point on Day -1 is timed to coincide with the clock time of pevonedistat dosing on Days 1 and 8 (which will be considered the 0-hour time point on Days 1 and 8).

On Day 1, immediately following the collection of triplicate predose baseline ECG assessments, patients will be randomized in a crossover fashion to receive a single-dose, 1-hour IV infusion of 25 or 50 mg/m^2 pevonedistat and the other dose on Day 8 (approximately 18 patients per sequence). Serial blood samples for plasma PK analysis of pevonedistat will be collected at prespecified time points over a 24-hour period (0-24 hours postdose).

Patients will undergo Holter ECG monitoring on Day -1 (0-11 hours), Day 1 (0-11 hours), Day 2 (24 hours after Day 1 dosing), Day 8 (0-11 hours), and Day 9 (24 hours after Day 8 dosing); triplicate ECGs will be extracted at matched PK time points to contribute to the analysis of the effects of pevonedistat on QT/QTc intervals. The clock time of pevonedistat infusion dosing initiation on Days 1 and 8 should coincide with that of the 0-hour time point on Day -1. On Days -1, 1, and 8 of Holter ECG sampling, patients will remain nothing by mouth (NPO; ie, no food or drink except water) from 2 hours before the 0-hour time point until completion of the 4-hour ECG/PK sample collection. Accordingly, patients will be advised to eat breakfast at least 2 hours before the 0-hour time point and to eat lunch after the 4-hour Holter ECG and PK blood sample collection. These meals will be administered at the same times on Days -1, 1, and 8 of Holter ECG monitoring. Safety will be assessed by monitoring vital signs, physical examinations, and clinical laboratory tests.

For patients who cannot participate in the Day 8 dosing and Holter ECG assessment because of scheduling difficulty, a window of +2 days is permitted (ie, the originally scheduled Day 8 dosing and Holter ECG assessment may be conducted on Day 9 or 10).

Part B: Continued Treatment with Pevonedistat in Combination with SoC (Optional)

After completing Part A of this study, patients will have the opportunity to participate in the optional Part B. Any patient who decides to participate in Part B will be re-evaluated per the entry criteria before treatment in Part B can begin. Patients will receive pevonedistat in

combination with SoC agents, either docetaxel or carboplatin+paclitaxel, as recommended by the investigator. The dosing regimen will consist of pevonedistat in combination with the selected chemotherapy agent(s) on Day 1 and pevonedistat alone on Days 3 and 5 of each 21-day cycle. Safety and disease assessments will be conducted in Part B of the study. Disease assessments will be conducted using radiological evaluations (computed tomography [CT] scan or magnetic resonance imaging [MRI]) and will be based on the investigator's assessment using the Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1, guideline [2].

Pevonedistat will be administered IV at 25 mg/m^2 in combination with docetaxel 75 mg/m^2 or at 20 mg/m^2 in combination with carboplatin AUC5+paclitaxel (175 mg/m^2) on Day 1 in Part B. On Days 3 and 5 of each cycle, pevonedistat will be administered alone. Each cycle lasts 21 days. Eligible patients may continue to receive treatment in Part B of this study for 12 cycles or until they experience symptomatic deterioration or disease progression, treatment is discontinued for another reason, or until the study is stopped.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint

- Change from time-matched baseline in QTcF following a single-dose IV administration of pevonedistat at 25 and 50 mg/m^2.

5.2 Secondary Endpoints

The secondary endpoints for Part A are:

- Change from time-matched baseline in QTcI, QRS, PR, and HR following a single-dose IV administration of pevonedistat at 25 and 50 mg/m^2.
- PK parameters: C_{max}, AUC24, and $t_{1/2}$ of pevonedistat following a single-dose IV administration at 25 and 50 mg/m^2.

The secondary endpoint for Part B is:

- Measures of disease response based on the investigator's assessment using the RECIST, version 1.1, guideline.

5.3 Safety Endpoints

The safety endpoint for Part A is:

- AEs, serious adverse events [SAEs], assessments of clinical laboratory values, and vital signs measurements following a single-dose IV administration of pevonedistat at 25 and 50 mg/m^2.

The safety endpoint for Part B is:

- AEs, SAEs, assessments of clinical laboratory values, and vital signs measurements following administration of pevonedistat in combination with either docetaxel or carboplatin+paclitaxel.

6.0 DETERMINATION OF SAMPLE SIZE

Approximately 45 patients will be enrolled to obtain approximately 36 evaluable subjects. Thirty-six evaluable patients will provide at least 80% power to show that the upper limit of the 1-sided 95% CI for the comparison of change from baseline in QTcF falls below 10 msec. This calculation is based on the assumption that the true difference in the largest time-matched mean change from baseline in QTcF is no more than 1.0 msec, with a standard deviation of less than 10 msec. This sample size also provides more than 90% power to show that the upper limit of the 1-sided 95% CI for the comparison of change from baseline in QTcF falls below 20 msec, assuming that the true difference for QTcF is a 5 msec change from baseline, with a standard deviation of 13 msec.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

All statistical analyses will be conducted using SAS® Version 9.4.

In general, summary tabulations will include the number of observations, (arithmetic) mean, standard deviation, geometric mean and percent coefficient of variation [CV] for PK related parameters, median, minimum, and maximum for continuous variables, and the number and percentage (of non-missing) for categorical data, unless specified otherwise.

Means and medians will be presented to 1 more decimal place than the recorded data. The SD will be presented to 2 more decimal places than the recorded data. The PK parameters will be summarized with a precision of 3 significant digits. Percent CV and frequency percentages will be presented as integers.

Summary statistics will be calculated by time point, if applicable.

7.1.1 Randomization and Stratification

Randomization is performed only in Part A, not in Part B. A single IV dose of pevonedistat at 25 or 50 mg/m^2 will be administered on Days 1 and 8 over a period of approximately 60 minutes (±5 minutes). Patients will be randomized 1:1 to receive pevonedistat 25 or 50 mg/m^2 on Day 1 in Part A. Patients randomized to 25 mg/m^2 on Day 1 will receive 50 mg/m^2 on Day 8 and vice versa.

After completing Part A of this study, patients will have the opportunity to participate in Part B, which is optional. Any patient who decides to participate in Part B will be re-evaluated per the entry criteria before treatment in Part B can begin. Patients will receive pevonedistat in combination with either docetaxel or carboplatin+paclitaxel, as recommended by the investigator. The dosing regimen will consist of pevonedistat in combination with the selected chemotherapy agent(s) on Day 1 and pevonedistat alone on Days 3 and 5 of each 21-day cycle.

7.1.2 Methods for Handling Missing Data

All available data will be presented. Data that are potentially spurious or erroneous will be examined under the auspices of standard data management operating procedures. Every effort will be made to avoid missing/partial date in on-study data.

In general, missing data will be treated as missing and no data imputation will be applied.

Pevonedistat concentration values missing the corresponding sampling date and time records will be excluded from PK analysis.

7.1.2.1 Missing/Partial Dates in Screening Visit

The following rules apply to dates recorded in the screening visits.

- If only the day-component is missing, the first day of the month will be used if the year and the month are the same as those for the first dose of study drug. Otherwise, the 15th will be used.
- If only a year is present, and it is the same as the year of the first dose of study drug, the 15th of January will be used unless it is later than the first dose, in which case the date of the first of January will be used, unless other data indicate that the date is earlier.
- If only a year is present, and it is not the same as the year of the first dose of study drug, the 15th of June will be used, unless other data indicates that the date is earlier.

7.1.2.2 Missing/Partial Dates in Subsequent Therapies

Subsequent therapies with start dates that are completely or partially missing will be analyzed as follows:

1. When month and year are present and the day is missing,
   a) If the onset month and year are the same as the month and year of last dose with study drug, the day of last dose + 1 will be imputed.
   b) If the onset month and year are not the same as the month and year of last dose with study drug, the first day of the month will be imputed.
2. When only a year is present,
   a) If the onset year is the same as the year of last dose with study drug, the date of last dose + 1 will be imputed.
   b) If the onset year is not the same as the year of last dose with study drug, the first day of the year will be imputed.
3. If no components of the onset date are present, the date of last dose + 1 will be imputed.

7.1.2.3 Conventions for Missing Adverse Event Dates

Missing or partial AE start dates will be imputed according to the following rules.

Non-missing	Missing	Estimated
Month and Year	Day	Day of first dose date of STUDY DRUG, if month and year of onset date are the same as month and year of date of first dose. The last day of the month, if the month and year of onset date are before the month and year of date of first dose of STUDY DRUG. The first day of the month, if the month and year of onset date are after the month and year of date of first dose of STUDY DRUG.
Year	Day and Month	Day and month of first dose date of STUDY DRUG, if the year of onset date is the same as the year of date of first dose of STUDY DRUG. December 31st, if the year of onset date is prior to the year of date of first dose of STUDY DRUG. January 1st, if the year of onset date is after the year of date of first dose of STUDY DRUG.
	Day, Month and Year	Date of first dose of STUDY DRUG

Missing or partial AE stop dates will be imputed according to the following rules. If only the day is missing, use 15th of the month; if both month and day are missing, use June 30th. For a record with a complete start date and a partial stop date, if the estimated stop date would become earlier than the start date, the stop date will not be estimated.

If AE stop date is not missing and AE stop date < estimated start date, let estimated onset date = AE stop date.

All dates presented in listings are recorded dates without imputation.

7.1.3 Definitions of Baseline Values

Part A

Unless otherwise specified, the baseline value is defined as the value collected at the time closest to, but prior to, the start of study drug administration within each period during Part A. If Day 8 predose is missing then the baseline for day 8 dose will be the last observation prior to Day 1 dose. For ECG, baseline for Day 1 and Day 8 dose will be last value collected prior to Day 1 dose.

Part B

Similarly, the baseline value is defined as the value collected at the time closest to, but prior to, the start of study drug administration during Part B. Since there is no screening visit for Part B, the baseline value for ECG is also the one collected at the time closest to, but prior to, the start of study drug administration during Part B.

7.1.4 Definition of Study Visit Windows

All data will be categorized based on the scheduled visit at which they were collected. The analysis of PK data and determination of PK parameters will be based on the actual elapsed time postdose relative to the start of first dosing.

7.1.5 Definition of Study Start Date

Study start date is defined as the date of the signing of the informed consent.

7.1.6 Pooling

All data from all sites will be pooled. Study center or treatment-by-center interaction will not be included in any statistical analysis.

7.1.7 Withdrawals, Dropouts, Loss to Follow-up

Patients who are not PK-evaluable will be replaced. Generally, no additional patients will be enrolled due to withdrawals, dropouts, or loss to follow-up.

7.2 Analysis Sets

7.2.1 QT Population

QT population is defined as patients who receive the protocol-specified pevonedistat dosing and have sufficient ECG assessments in the baseline period (Day -1) and at least one period of assessment of effect of pevonedistat (Day 1 or Day 8) to permit reliable analysis.

7.2.2 Pharmacokinetic Population

The PK population is defined as patients who receive the protocol-specified pevonedistat dosing during Part A and have sufficient PK assessments to permit reliable estimation of PK parameters.

7.2.3 Safety Population

The safety population for Part A is defined as patients who receive at least 1 dose of pevonedistat during Part A.

All safety analyses in Part A will be performed using the safety population for Part A.

The safety population for Part B is defined as patients who continue to Part B and receive at least 1 dose of study drugs during Part B.

All safety analyses in Part B will be performed using the safety population for Part B.

7.2.4 Disease-response Population

The disease-response population is defined as patients who receive at least 1 dose of study drug in Part B, have measurable disease as entry criteria for Part B, and have at least 1 postbaseline disease assessment.

Response analyses for Part B will be performed using the disease-response population.

7.3 Disposition of Subjects

Separate tabulations of patient disposition data will be generated for Part A and Part B.

A tabulation of patient disposition data for Part A will include the number and percentage of patients for the following categories: patients treated (safety population for Part A) during Part A, patients in the QT population, patients in the PK population, patients completing Part A, patients who discontinued study treatment during Part A (including the washout period), the primary reason off study treatment during Part A (including the washout period). Patients will be considered to have completed Part A of the study if they have completed the protocol-specified assessments to provide data necessary for evaluation of ECGs and PK within Part A of the protocol. Percentages will be based on the number of enrolled patients in the planned treatment sequence group for Part A.

A tabulation of patient disposition data by treatment arm and Part B total for Part B will also be generated to include the following categories: patients treated (safety population for Part B) in Part B, patients in the disease-response population for Part B, patients completing Part B, patients who discontinue study treatment from Part B, and the primary reason off study treatment during Part B. Patients will be considered to have completed Part B of the study if they have completed 12 cycles of treatment with study drug, or if treatment is discontinued for any of the following reasons:

- Adverse event.
- Protocol deviation.
- Progressive disease.
- Symptomatic deterioration.
- Unsatisfactory therapeutic response.
- Study terminated by sponsor.
- Withdrawal by subject.
- Lost to follow-up.
- Other (to be specified).

Percentages in the table of disposition data for Part B will be based on the number of patients in the enrolled populations for Part B.

Data concerning patient disposition (e.g. primary reason off study treatment, patient population) will be presented in by-patient listings.

7.4 Demographic and Other Baseline Characteristics

7.4.1 Demographics

Demographics will be summarized by dose and total for the randomized population in Part A and by treatment arm and total for the safety population in Part B. Demographic data to be evaluated will include age at the date of informed consent, sex, ethnicity, race, height, weight and body surface area [BSA].

BSA is calculated for each patient using the following formula:

$$\mathbf{BSA} = \sqrt{\frac{Height\,(cm) \times Weight\,(kg)}{3600}}$$

OR

$$\mathbf{BSA} = \sqrt{\frac{Height\,(in) \times Weight\,(lbs)}{3131}}$$

Both Part A and Part B use Height collected at screening. Part A uses weight collected at screening. If a weight at screening is not available, the Part A Day 1 predose weight can be used. Part B uses weight collected at the visit closest, but prior to the Part B Cycle 1 Day 1 study drug administration. For Part B, BSA will be calculated on Cycle 1, Day 1 or at subsequent visits if the patient experiences a >10% change in body weight from the weight used for the most recent BSA calculation.

No inferential statistics will be generated.

Demographic data will also be presented in a by-patient listing.

7.4.2 Inclusion/Exclusion Criteria

All inclusion/exclusion information on enrolled patients will be included in a by-patient listing for Part A. Eligibility criteria for dosing during Part B for patients who continue into Part B will be presented in a separate listing. These listings will include whether all criteria were satisfied. For patients who did not satisfy the criteria, the criteria number will be listed with the deviation.

In addition, all protocol deviations will be reviewed, and major protocol deviations will be identified and summarized by Part A and Part B in a table. Any enrolled patients who did not meet inclusion or exclusion criteria will be summarized under the category "Not meeting study inclusion/exclusion criteria".

Patient pregnancy test results will be included in a separate by-patient listing.

7.4.3 Baseline Disease Status

Baseline disease characteristics (disease type, disease stage, sites of involvement, time since initial diagnosis) will be summarized for the randomized population in Part A, and by treatment arm and total for the safety population in Part B, if applicable. ECOG performance status will be summarized similarly in the same table. Separate by-patient listings will also be presented by Part A and Part B for baseline disease characteristics and ECOG performance status.

Dates of initial diagnosis which are partially missing will be imputed as follows:

- If the date of initial diagnosis has a month and year but the day is missing, the 15th will be inserted as the day.
- If the date of initial diagnosis has a year but the month and the day are missing, June 30th will be inserted.

7.5 Medical History and Concurrent Medical Conditions

Patients with a medical (and/or surgical) history will be presented in a by-patient listing, including the medical and surgical history, date of onset and the outcome status (whether it is resolved or ongoing).

7.6 Medication History and Concomitant Medications

Medication history will be summarized for the randomized population in Part A, and by treatment arm and total for the safety population in Part B. Summarized information on medication history will include:

- Number of patients with prior chemotherapy.
- Months from last dose of prior chemotherapy to first study dose.
- Number of patients with prior radiation.
- Months from last prior radiation to first study dose.
- Number of patients with prior surgery or non-radiation procedures.
- Number of patient with prior transplant.

If a day of the month is not provided for the date of prior therapy, prior radiation, or prior surgery, then the 15th will be inserted as the day. If neither a day nor month is provided, then June 30th will be inserted.

Medication history will also be presented in by-patient listings.

All concomitant medications will be mapped to generic terms according to the World Health Organization [WHO] drug dictionary. The number and percentage of patients taking concomitant medications will be tabulated by WHO drug generic term, presented by dose and total for the safety population in Part A, and by treatment arm and total for the safety population in Part B.

Patients are counted once for each WHO drug generic term. Concomitant procedures will not be coded.

Concomitant medication for Part A is defined as any medication that occurs after administration of the first dose of study treatment during Part A and up through 30 days after the last dose of study drug during Part A for patients who do not continue into Part B or up through Part B C1D1 (predose) for patients who continue into Part B.

Concomitant medication for Part B is defined as any medication that occurs after administration of the first dose of study treatment during Part B and up through 30 days after the last dose of study drug during Part B.

Concomitant therapies with start or end dates that are completely or partially missing will be analyzed using the same imputation rules as adverse events.

Concomitant medications and procedures will be presented in separate by-patient listings.

7.7 Study Drug Exposure and Compliance

7.7.1 Study Treatments

Part A

During Part A, patients will receive a single dose of pevonedistat at 25 or 50 mg/m^2 given as an IV infusion on Day 1 and Day 8 over a period of approximately 60 minutes (±5 minutes). Patients randomized to 25 mg/m^2 on Day 1 will receive 50 mg/m^2 on Day 8 and vice versa.

Part B

During Part B, for Arm 1 (Pevonedistat + Docetaxel), patients will be administered docetaxel at a dose of 75 mg/m^2 IV over 1 hour on Day 1 of each cycle. After a mandatory approximately 15-minute time out (pevonedistat-free period), pevonedistat at mg/m^2 will be administered IV. On Days 3 and 5, only pevonedistat will be given. The duration of each cycle will be 21 days.

For Arm 2 (Pevonedistat + Paclitaxel + Carboplatin), patients will be administered all three drugs on Day 1 of each cycle. Paclitaxel will be given first at a dose of 175 mg/m^2 IV over 3 hours, followed by carboplatin AUC5 IV over 30 minutes. After a mandatory approximately 15-minute time out (pevonedistat-free period), Pevonedistat at 20 mg/m^2 will be administered IV. On Days 3 and 5, only pevonedistat will be given. The duration of each cycle will be 21 days.

All dosing information for each visit will be presented by Part A and Part B in a by-patient listing.

7.7.2 Extent of Exposure

Extent of exposure will be reported separately for Part A and for Part B by treatment arm.

Part A

The exposure to pevonedistat during Part A will be characterized by the number of doses received, Total Dose Received, Total Dose Expected, and Percent Dosing Intensity.

Percent Dosing Intensity will be calculated using the following equations for Daily Expected Dose (mg), Daily Prepared Dose (mg), and Daily Dose Received (mg):

$$\text{Daily Expected Dose} = \text{Dose Level Assigned at each dosing day } (mg/m^2) * \text{Body Surface Area } (m^2)$$

$$\text{Daily Prepared Dose} = \text{Scheduled Dose Level } (mg/m^2) \text{ at each dosing day} * \text{Body Surface Area } (m^2)$$

$$\text{Daily Dose Received} = \text{Daily prepared Dose} * \frac{\text{Volume of IV bag actually infused (mL)}}{\text{Prepared volume (mL)}}$$

The scheduled dose level will be collected on the electronic case report form (eCRF) for each dosing day. BSA will be calculated on Day 1.

Total Dose Received, Total Dose Expected, and Percent Dosing Intensity for pevonedistat will be based on the following formulas:

Total Dose Received = Sum of Daily Dose Received over all days during Part A.

Total Dose Expected = Daily Expected Dose at Day 1+ Daily Expected Dose at Day 8.

$$\text{Percent Dosing Intensity} = \frac{\text{Total Dose Received}}{\text{Total Dose Expected}} * 100$$

The extent of exposure to pevonedistat during Part A will be summarized.

Part B

The extent of exposure to pevonedistat will be based on the number of cycles received and the mean number of doses administered per cycle. The distribution of the number of cycles received will be presented by treatment arm for all patients treated in Part B. Patients will be considered to have been treated for a cycle if they receive at least one dose of pevonedistat during the 21 days of that cycle. Percentages will be calculated by treatment arm, and total for Part B.

The mean number of doses per cycle will be calculated for each patient and summarized by treatment arm, and total for Part B.

For pevonedistat, calculation of Percent Dosing Intensity will use similar equations as specified in Part A for Daily Expected Dose (mg), Daily Prepared Dose (mg), and Daily Dose Received (mg). Daily Expected Dose and Daily Prepared Dose may differ if there are dose decreases.

BSA will be calculated on Cycle 1, Day 1, and at subsequent visits if the patient experiences a >5% change in body weight from the weight used for the most recent BSA calculation.

Total Dose Received, Total Dose Expected, and Percent Dosing Intensity for pevonedistat during Part B will be based on the following formulas:

$$\text{Total Dose Received} = \text{Sum of Daily Dose Received on all days in Part B}$$

$$\text{Total Dose Expected} = \text{Daily Expected Dose} * 3 \text{ doses per cycle} * \text{number of treated cycles}$$

$$\text{Percent Dosing Intensity} = \frac{\text{Total Dose Received}}{\text{Total Dose Expected}} * 100$$

Total dose expected will be calculated based on the BSA measured at baseline for Part B. If there are dose increases, the Dosing Intensity may exceed 100%. The number of patients with 100% intensity, 80% - <100%, 50 - <80, and <50% intensity will be summarized by treatment arm, and total for Part B.

For each of the standard of care drugs, the extent of exposure will be summarized in a similar manner as pevonedistat. The number of cycles of standard of care drug administered will also be summarized.

The mean number of doses per cycle will be calculated for each patient and summarized by treatment arm, and total for Part B.

Daily Expected Dose, Total Dose Received, Total Dose Expected, and Dosing Intensity for each standard of care drug will be based on the following formulas:

$$\text{Daily Expected Dose (Docetaxel and Paclitaxel)} = \text{Dose Level Assigned at Study Entry (mg/m}^2\text{)} * \text{Body Surface Area (m}^2\text{)}$$

$$\text{Daily Expected Dose (Carboplatin)} = \text{Dose Level Assigned AUC at Study Entry (mg x min/mL)} * (\text{Glomerular filtration rate (mL/min)} + 25)$$

$$\text{Daily Prepared Dose (Docetaxel and Paclitaxel)} = \text{Scheduled Dose Level (mg/m}^2\text{)} * \text{Body Surface Area (m}^2\text{)}$$

$$\text{Daily Prepared Dose (Carboplatin) (mg)} = \text{Scheduled Dose Level (AUC)} * (\text{Glomerular filtration rate} + 25)$$

$$\text{Daily Dose Received} = \text{Daily Prepared Dose} * \left(\frac{\text{Volume of IV bag actually infused (mL)}}{\text{Prepared Volume}} \right)$$

AUC is the area under the free carboplatin plasma concentration versus time curve.

Dosing intensity for each standard of care drug will be summarized by treatment arm, and total for Part B, in a similar manner to pevonedistat dosing intensity.

Dosing administration data for both Part A and Part B (including SoC) will also be presented in separate by-patient listings.

7.7.3 Treatment Compliance and Modifications

The actions on study drugs (Dose Reduced, Dose Increased, Dose Held, Dose Missed, Dose Interrupted, Dose Delayed, or Discontinued Permanently) will be summarized for the randomized population in Part A, and by treatment arm and total in Part B. For Part B, data will be summarized for Cycle 1 only as well as all cycles combined. A patient will count only once for each type of action.

7.8 Efficacy Analysis

Efficacy analysis is only conducted for Part B, where efficacy is not a primary endpoint. A summary of the best overall response as determined by the investigator using the RECIST version 1.1 guidelines will be presented as a measure of antitumor activity of pevonedistat in

combination with standard of care drugs. The number and percentage of patients in each disease response category (e.g., complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD], overall response rate (CR + PR) and CR+PR+SD) will be presented by treatment arm. Percentages will also be calculated for the total in Part B. All evaluations of response will be conducted using the disease-response population.

For each patient, the best percent change (i.e. largest reduction) from baseline in the sum of the longest diameter of target lesions will be calculated and displayed in a waterfall plot to show the distribution of response in each arm. Unscheduled visits will also be included in such displays.

The duration of disease response (CR or PR) will be presented in a by-patient listing for all response-evaluable patients with CR or PR. Duration of response is the time from the date of first documented response per the investigator response assessment to the date of first documentation of PD, or death, or the date of last disease assessment if the patient discontinues treatment before PD or still ongoing. In addition, the date of first response and the date of first documentation of PD after the first response will be shown. The duration of response (in treatment cycle and months), will also be summarized descriptively by treatment arm for all disease-response patients.

The duration of SD or better will be presented in a by-patient listing for all response-evaluable patients with SD or better. Duration of SD or better is the time from the date of first documented SD or better to the date of first documentation of PD or death, or the date of last disease assessment if the patient discontinues treatment before PD. In addition, the date of first dose, the date of first SD or better, the date of first documentation of PD, and the number of cycles with SD or better will be shown. The duration of SD or better (in months) and the number of cycles with SD or better will also be summarized descriptively by treatment arm for all response-evaluable patients.

A separate listing will be generated for patients who are on treatment for at least 4 cycles during Part B. This listing should include disease type, number of cycles on treatment, duration of stable disease or better, and prior therapies.

Results from all disease response assessments and whether there was symptomatic deterioration will be presented in by-patient listings.

Any tumor assessments after the alternate antineoplastic therapies or after disease progression will be excluded in the analyses.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

Pharmacokinetic analysis will be conducted using the PK population.

In Part A, serial blood samples for PK analysis of pevonedistat will be collected from each patient at prespecified time points: predose on Day1 and Day 8 and over a 24-hour period (0-24 hours postdose) on Days 1, 2 (24 hours after the Day 1 dose), 8, and 9 (24 hours after the Day 8 dose). Time points are based on the start of the infusion.

7.9.1.1 Pharmacokinetic Concentrations

Mean concentrations will be calculated based on nominal sample times for each dose level of pevonedistat. For the calculation of mean concentration time profiles, concentrations reported as being below the limit of quantitation (BLQ) will be assigned a value of zero if they preceded quantifiable samples prior to the first measurable concentration. A BLQ concentration that occurs after quantifiable concentrations, or is embedded between two quantifiable points will be set to missing. If more than half the concentrations at a nominal time are reported as being BLQ or if there are fewer than 3 measurable concentrations at a nominal time, a mean concentration value will not be calculated for that nominal time.

Individual listings of the concentration time data will be provided. Concentration-time data for pevonedistat will be summarized by dose level using descriptive statistics (n, arithmetic mean, geometric mean, median, arithmetic standard deviation, minimum, maximum, and arithmetic coefficient of variation [%]) at each scheduled collection time. If more than 50% of the individual concentrations are BLQ per scheduled collection time, then only the minimum and maximum pevonedistat concentrations will be reported.

Plots of individual concentrations versus time by dose level will be generated on a linear and semi-log scale. Plots of mean concentrations versus nominal time by dose level will be generated on a linear and semi-log scale.

7.9.1.2 Pharmacokinetic Parameter Analysis

Concentration-time data for pevonedistat will be analyzed by noncompartmental analysis (NCA) using the software program Phoenix WinNonlin (Phoenix WinNonlin Professional version 6.4, Certara Inc., Mountain View, CA). The NCA parameters will not be reported to any greater accuracy than that of the observed concentration data. Default reporting in text and tables is 3 significant figures with the exception of time-related parameters.

A listing of the planned NCA parameters is presented in Table 7.a. In order to conduct NCA, at least 3 measurable concentrations, two of which must occur after the peak concentration, must be available in a concentration-time profile in the relevant study period. Actual sampling times will be used in the NCA. Tables of individual parameter values will be provided by dose level and Study day. Summary statistics of parameter values by dose level will be generated.

Table 7.a Summary of NCA PK Parameters

Parameter	Description
C_{max}	Maximum observed concentration, determined directly from individual concentration-time data
AUC_{inf}	Area under the pevonedistat concentration-time curve from the start of dosing for each dose interval to infinity.
AUC_{last}	Area under the pevonedistat concentration-time curve from the start of dosing for each dose interval until the last measurable concentration during that dose interval.
C_{max}/Dose	Dose-normalized C_{max}
AUC_{inf}/Dose	Dose-normalized AUC_{inf}
$t_{1/2}$	Terminal elimination half-life
CL	Clearance
V_{ss}	Volume of distribution at steady-state

7.9.2 Pharmacodynamic Analysis

7.9.2.1 Primary Endpoint: By-timepoint Analysis of Central Tendency of Time-matched QTcF Change from Baseline

An ANOVA model that includes the effects of subjects overall in one mode will be performed. The initial model will be as follows:

proc mixed;

class time dose subject ;
model ΔQTcF =baselineQTcF dose time dose*time/ddfm=satterth;
repeated time/ type=un sub= subject;

In the above model, time indicates the time in relation to dose, dose indicates the dose groupings, and ΔQTcF represents the change from individual subject time-matched baseline.

If the above is not convergent, a model for each timepoint separately will be explored, using dose group as a class variable.

All inferences will be based on the least square means estimated from the mixed effects model. For each timepoint, a 2-sided 90% confidence interval on the mean change from baseline will be presented, defined as: estimate ± Student t*the estimated standard error. Primary attention will be placed on the largest upper bound of the confidence interval on the mean change in QTcF from time-matched baseline using the algorithm stated above.

If the upper bounds of the CIs at all timepoint are <20 msec, then no clinically meaningful QTc interval prolongation will be concluded.

Findings will be displayed in a table giving the least square mean ΔQTcF values and upper limits of the 2-sided 90% CIs by timepoint and dose; and in graphs of the same data, with a reference line superimposed on the figure at 20 msec.

7.9.2.2 Primary Endpoint: QTcF-Concentration Analysis

The plasma concentration and time-matched ΔQTcF data collected in this study will be analyzed using mixed effects model as implemented by the computer program NONMEM Version 7.3 or higher (Icon Development Solutions, Dublin, Ireland). The R data analysis language (Version 3.3.1 or higher) will be used for most graphical output and data manipulation. The remaining graphical output and data manipulation will be performed using Microsoft® Excel 2003 or later.

All modeling work will be conducted using the first order conditional estimation method (FOCE) of NONMEM™. Conditional weighted residuals (CWRES) will be used for model evaluation as appropriate for the FOCE estimation method.

The ΔQTcF-Concentration relationships will be examined by linear drug effect models $\Delta QTc = Intercept + Slope*Cp$. In this model, C_p is the plasma concentration of pevonedistat at the time of each ECG measurement. Other models may be evaluated if deemed appropriate. The unexplained inter-individual variability in parameters will also be evaluated through incorporation of random effects in the mixed effects model. After the base model is selected, covariates (e.g., sex) will be assessed for their influence on the pharmacodynamic effects of pevonedistat on the ΔQTcF. Continuous covariates will be modeled using the following equation:

$$TPV = P_{pop} * \prod_{i=1}^{n} cov_i^{\theta_i}$$

where TPV represents the model predicted parameter (e.g. slope or intercept) for the "typical" individual with covariate value(s) cov_i, P_{pop} represents the population central tendency for the parameter TPV, cov_i represents the individual value for the covariate (e.g., body mass index) normalized for the population median, and θ_i represents a scale factor. With this type of model, if $\theta_i=0$, the influence of the covariate is dropped from the model; if $\theta_i=1$, a direct proportional relationship is specified; and if θ_i is less than or greater than 1, a non-linear relationship is specified. Negative θ_i values specify a non-linear inverse relationship. Diagnostic plots will be examined during development of the model to assess the appropriateness of covariate models. Categorical covariates, such as sex, will be modeled using the following equation:

$$TPV = P_{pop} * (1 + cov_i * \theta_i)$$

In this equation, θ_i is a direct proportionality constant. With this type of model, θ_i is fixed to 0 for the reference subgroup (e.g., males) where the covariate value is set to 0, and estimated for the test subgroup (e.g., females) where the covariate value is set to 1. The covariates will be determined to be in the final model through two steps. The first step is to evaluate if a single covariate is significant by considering only one covariate in the base model at one time. Covariate is set to be significant with a reduction in the minimum objection function ≥7.9. Covariates found to be significant in the first step will all be added to the base model. The second step is to evaluate which covariates among those significant covariates will remain in the model using iterative backward deletion method. The final model will be used to simulate the predicted size of the effect of pevonedistat on ΔQTcF. The mean predicted change in QTcF and

associated 1-sided 95% confidence intervals will be calculated over a range of concentrations up to the upper end of concentrations evaluated in the analysis. ΔQTcF predictions will be summarized for the geometric mean steady-state C_{max} at 25 and 50 mg/m^2. Furthermore, a graph of concentration versus ΔQTcF with associated confidence intervals based on model predictions will be constructed. Reference lines for 10 msec and 20 msec change from baseline will be added.

As the study design for P1014 includes a time-matched baseline on Day -1 and the endpoint being analyzed is change in QTc from time-matched baseline, time will not be incorporated as a factor variable in the linear mixed effects model. Plots of CWRES vs time will be examined. If any trends are observed in these plots suggestive of a need to consider time effects, models including time points as factor variables will be evaluated.

7.9.2.3 Secondary Endpoint: By-timepoint Analysis of QTcI

A by-timepoint analysis of change from time-matched baseline in QTcI will be determined using the same model as for QTcF, see Section 7.9.2.1. For ΔQTcI, if the upper bounds of the CIs at all timepoint are <20 msec, then supplemental evidence of no clinically meaningful QTc interval prolongation will be concluded.

Findings will be displayed in a table giving the least square mean ΔQTcI values and upper CIs; and in graphs of the same data with a reference line superimposed on the figure at 20 msec.

7.9.2.4 Secondary Endpoint: QTcI-Concentration Analysis

The plasma concentration effect analysis will be performed for ΔQTcI, using the same methods as for ΔQTcF, see Section 7.9.2.2.

7.9.2.5 Secondary Endpoint: By-timepoint Analysis of HR, PR and QRS

A by-timepoint analysis of change from time-matched baseline in HR, PR and QRS will be determined using the same model as for QTcF, see Section 7.9.2.1. No formal statistical hypotheses will be tested. Findings for will be displayed in a table giving the least square means and CI interval ranges; and in graphs of the same data.

7.9.2.6 Secondary Endpoint: HR-Concentration Analysis

A concentration effect analysis will be performed for HR, using the same method as for QTcF, see Section 7.9.2.2.

7.9.2.7 Categorical Analysis

The following categorical analyses for both QTcF and QTcI, and for PR interval and QRS duration will be summarized as the number and percent of subjects by dose level at each scheduled ECG timepoint and overall:

- Absolute QTc interval prolongation:
  - QTc interval >450 msec.

- QTc interval >480 msec.
- QTc interval >500 msec.

- Change from predose baseline:
  - QTc interval increase from predose baseline >30 msec.
  - QTc interval increase from predose baseline >60 msec.
  - PR interval >200 msec and 25% increase from baseline.
  - QRS duration >110 msec and 25% increase from baseline.

7.9.2.8 Morphology Analysis

New ECG morphologies, not present at the baseline, will be summarized as the number and percent of subjects by dose level at each scheduled ECG timepoint and overall. New ECG morphologies, not present at the baseline, will be summarized. Diagnostic findings that represent findings based solely on interval abnormalities will not be included. Attention will be directed at findings possibly indicative of repolarization abnormalities, especially abnormalities of ST segments, T waves and U waves.

7.9.2.9 Contingent QT Analysis

In the case where there is a marked increase in the HR for a majority of subjects, an alternate method of QT correction, namely "beat-to-beat correction" (QT_{btb}), will used as an exploratory analysis. QT_{btb} is a method that does not utilize any correction factors but compares QT intervals after treatment with those associated with beats extracted from the 24-hour baseline at similar RR intervals.[1]

For each subjects, all QT-RR pairs on Day -1 are assessed algorithmically and the median QT determined at each value of RR without regard to time of day. QT_{btb} is determined as the difference between the postdose ECG uncorrected QT and the median value of the QT on Day -1 at the matching RR. QT_{btb} is equivalent to a change from baseline. Once determined for single ECGs, the mean value of QT_{btb} is calculated for the triplicate ECGs at each timepoint.

A marked increase in HR is defined as the presence of either of the criteria below:

Criterion 1:

The mean ECG HR for either dose level increases from baseline at any timepoint after dosing by ≥10 bpm;

Criterion 2:

[1]Fossa, A. A., Langdon, G., Couderc, J-P., Zhou, M., Darpo, B., Wilson, F., Davis, J. D. The use of beat-to-beat electrocardiogram analysis to distinguish QT/QTc interval changes caused by moxifloxacin from those caused by vardenafil. Clin Pharmacol Ther 2011; 90:449-454.

More than 25% of subjects have HR values that increase from baseline by ≥15 bpm at 4 or more timepoints after dosing.

If either of these criteria is met, all analyses noted above for QTcF will be repeated substituting QT_{btb} for ΔQTcF. QT_{btb} findings will supplement conclusions from the primary endpoints.

7.10 Other Outcomes

Not Applicable.

7.11 Safety Analysis

Safety analyses will be conducted separately for Part A and Part B.

Safety evaluations will be based on the incidence, severity, type of AEs, clinically significant changes or abnormalities in the patient's physical examination, vital signs, ECG, and clinical laboratory results.

These analyses for Part A will be performed using the safety population for Part A. Safety analyses for Part B will be performed by treatment arm using the safety population for Part B who continue from Part A into Part B with at least one dose administration of study drugs during Part B.

7.11.1 Adverse Events

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

A treatment-emergent AE for Part A is defined as any AE that occurs after administration of the first dose of study treatment during Part A and up through 30 days after the last dose of study drug during Part A for patients who do not continue into Part B or up through Part B C1D1 (predose) for patients who continue into Part B.

A treatment-emergent AE for Part B is defined as any AE that occurs after administration of the first dose of study treatment during Part B and up through 30 days after the last dose of study drug during Part B.

AEs will be tabulated by system organ class, high level term, and preferred term for Part A, and for Part B by treatment arm. Percentages will be calculated for the Part A total, arm totals for Part B and the Part B total. Summary tabulations include the following subsets:

- Treatment-emergent AEs.
- Drug-related treatment-emergent AEs.
- Grade 3 or higher treatment-emergent AEs.
- Grade 3 or higher drug-related treatment-emergent AEs.
- Treatment-emergent AEs resulting in study drug discontinuation.
- Treatment-emergent AEs resulting in study drug dose delayed.

- Treatment-emergent AEs resulting in study drug dose reduction.
- Treatment-emergent AEs resulting in study drug interruption.
- SAEs.
- Treatment-emergent drug-related SAEs.

Treatment-emergent AEs will be tabulated by system organ class, HLT, PT, and highest intensity. Most commonly reported (at least 5% of patients at each dose level) treatment-emergent AEs will be presented by preferred term. Most commonly reported (at least 5% of all patients at each dose level) treatment-emergent AEs by preferred term will also be summarized by dose for Part A, and by treatment cycles for Part B. Additionally, tabulations of AE (by system organ class, high level term, and preferred term) vs grade intensity will be made separately for Part A, and for Part B by treatment arm. All adverse events will also be reported in by-patient listings separately for Part A, and Part B, which will include the variable AE onset window (i.e., "Part A' or "Part B").

During Part B, all adverse events for patients who have dose modification in the standard of care treatments will be included in a by-patient listing. This listing should additionally include reduced doses during AE occurrence and omitted doses during AE occurrence. Reduced doses during AE occurrence refer to any dose level, administered during the period of AE onset date to AE ending date, which is lower than the dose closest but prior to AE onset date. Omitted doses during AE occurrence refer to any scheduled dose which is omitted during the period of AE onset date to AE ending date.

Adverse events with start dates that are completely or partially missing will be analyzed as follows:

- If the start date has month and year but day is missing, the event will be considered
  - treatment emergent for Part A if both the month and year of the start date of the event are on or after the month and year of the date of the first dose of study drug in Part A, and on or before the month and year of the date of the last dose of study drugs in Part A plus 30 days for patients who do not continue into Part B or the date of the first dose of study drugs in Part B for patients who continue into Part B.
  - treatment emergent for Part B if both the month and year of the start date of the event are on or after the month and year of the date of the first dose of study drugs in Part B, and on or before the month and year of the date of the last dose of study drugs in Part B plus 30 days.
- If the start date has year, but day and month are missing, the event will be considered:
  - treatment emergent for Part A if the year of the start date of the event is on or after the year of the date of the first dose of pevonedistat in Part A, and on or before the year of the date of the last dose of study drugs in Part A plus 30 days for patients who do not continue into Part B or the date of the first dose of study drugs in Part B for patients who continue into Part B.

  - treatment emergent for Part B if the year of the start date of the event is on or after the year of the date of the first dose of study drugs in Part B, and on or before the year of the date of the last dose of study drugs in Part B plus 30 days.

- If the start date of an event is completely missing, the event will be considered:
  - treatment emergent for Part A for patients who do not continue into Part B.
  - treatment emergent for Part A for patients who continue into Part B if the ending date of the event is before the date of the first dose of study drugs in Part B.
  - treatment emergent for both Part A and Part B for patients who continue into Part B if the ending date does not reflect whether the AE ends prior to the first dose of study drug in Part B.

7.11.1.1 Serious Adverse Events

The number and percentage of patients experiencing at least one treatment emergent SAEs will be summarized by MedDRA system organ class, high level term, and preferred term, and separately for Part A, and for Part B by treatment arm. Similar summary will be generated for treatment emergent drug-related SAEs.

By-patient listings of the SAEs will be presented (the patient listing will contain all SAEs regardless of treatment-emergent AE status) separately for Part A, and for Part B by treatment arm.

The drug-related SAEs will also be presented separately for Part A and for Part B by treatment arm in by-patient listings.

Listings of treatment emergent SAEs on the first dose of pevonedistat will be generated for Part A.

7.11.1.2 Deaths

By-subject listings of the deaths will be presented separately for Part A and for Part B by treatment arm. All deaths occurring on-study will be displayed (regardless of treatment-emergent AE status). Deaths with start dates that are completely or partially missing will be imputed to the date of last contact. An on-study death is defined as a death that occurs between the first dose of study drug in Part A and 30 days after the last dose of study drug.

7.11.1.3 Adverse Events Resulting in Discontinuation of Study Drug

The number and percentage of patients experiencing at least one adverse event resulting in discontinuation of study drug will be summarized by MedDRA system organ class, high level term, and preferred term and separately for Part A, and for Part B by treatment arm.

By-patient listing of AEs resulting in discontinuation of study drug will be presented separately for Part A and Part B. All AEs resulting in discontinuation of study drug occurring on-study will be displayed (regardless of treatment emergent AE status).

7.11.2 Adverse Events Resulting in Dose Reduction

The number and percent of patients experiencing at least one adverse event resulting in dose reduction will be summarized by MedDRA MedDRA SOC, HLT, and PT.

A by-patient listing of AEs resulting in dose reduction of study drug will be presented. All AEs resulting in dose reduction of study drug occurring on-study will be displayed.

7.11.2.1 Myalgia Events

Listings of patients who experience treatment emergent myalgia events will be presented separately for Part A, and Part B. The corresponding preferred terms include myalgia, musculoskeletal pain, and musculoskeletal discomfort.

7.11.2.2 Acute Renal Failure Events (SMQ Acute renal failure)

Listings of treatment-emergent acute renal failure events will be generated separately for Part A and Part B.

7.11.2.3 Liver Function Test Elevations

Listing of treatment-emergent liver function test elevations will be generated separately for Part A and Part B. The corresponding preferred terms are listed as below:

- Acute hepatic failure (PT).
- Blood alkaline phosphatase (PT).
- Blood alkaline phosphatase abnormal (PT).
- Blood alkaline phosphatase increased (PT).
- Hyperbilirubinemia (PT).
- Hepatic function abnormal (PT).
- Liver function analyses (HLT).

7.11.2.4 Tachycardia Events

Listings of treatment-emergent tachycardia events will be generated separately for Part A and Part B. The corresponding preferred terms are listed as below:

- Heart rate increased.
- Rebound tachycardia.
- Sinus tachycardia.
- Supraventricular tachyarrhythmia.
- Tachyarrhythmia.

- Tachycardia.
- Tachycardia paroxysmal.
- Palpitations.

7.11.2.5 Hypotension

Listings of treatment-emergent hypotension will be generated separately for Part A and Part B.

- Blood pressure ambulatory decreased.
- Blood pressure decreased.
- Blood pressure diastolic decreased.
- Blood pressure orthostatic abnormal.
- Blood pressure orthostatic decreased.
- Blood pressure systolic decreased.
- Hypotension.
- Orthostatic hypotension.

7.11.2.6 Anaemia

Listings of treatment-emergent anaemia will also be generated separately for Part A and Part B.

- Anaemia of chronic disease.
- Anaemia of malignant disease.
- Anaemia.
- Red blood cell count decreased.
- Hemoglobin decreased.
- Mean cell hemoglobin decreased.
- Hematocrit decreased.

7.11.2.7 Neutropenia

Listings of treatment emergent neutropenia will also be generated separately for Part A and Part B. The corresponding preferred terms are listed as below:

- Agranulocytosis.
- Granulocyte count decreased.
- Band neutrophil count decreased.
- Band neutrophil percentage decreased.

- Febrile neutropenia.
- Idiopathic neutropenia.
- Leukopenia.
- Febrile neutropenia.
- Neutropenia.
- Neutropenic infection.
- Neutropenic sepsis.
- Neutrophil count abnormal.
- Neutrophil count decreased.
- Neutrophil percentage abnormal.
- Neutrophil percentage decreased.

7.11.2.8 Overall Summary

The number and percentage of patients who experience any of the following treatment-emergent adverse events will be summarized separately for Part A and for Part B by treatment arm:

- Any adverse event.
- Grade 3 or higher adverse event.
- Drug-related adverse event.
- Drug-related Grade 3 or higher adverse event.
- Serious adverse event.
- Drug related serious adverse event.
- Adverse events resulting in study drug discontinuation.
- Adverse events resulting in study drug dose delayed.
- Adverse events resulting in study drug dose reduction.
- Adverse events resulting in study drug interruption.
- On-study deaths.

Percentages will be calculated for the Part A total, arm totals for Part B and the Part B total.

7.11.2.9 Dose Modifications due to LFT Abnormalities (part B)

A listing of patient that required dose modification of due to LFT abnormalities during study to display trend over time (Week 1-4, Week 5-8, Week 9-12, and Week 13+).

7.11.2.10 Dose Modifications due to Renal Abnormalities (part B)

A listing of patients that required dose modification due to renal abnormalities during study to display trend over time (Week 1-4, Week 5-8, Week 9-12, and Week 13+).

7.11.2.11 Dose Modifications due to Myelosupression (part B)

A listing of patient that required dose modification due to myelosuppression during study to display trend over time (Week 1-4, Week 5-8, Week 9-12, and Week 13+). +). Corresponding PT terms include:

- PTs from section 7.11.2.6 Anaemia.
- PTs from section 7.11.2.7 neutropenia.
- Thrombocytopenia.
- Platelet count decreased.

7.11.3 Clinical Laboratory Evaluations

For the purposes of summarization, all laboratory values will be converted to standardized units. If a lab value is reported using a non-numeric qualifier (eg, less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summarization, ignoring the non-numeric qualifier.

If a subject has repeated laboratory values for a given time point, the value from the last evaluation will be used.

Shift tables of the change in NCI CTCAE from baseline to the post baseline worst CTC grade will be generated for relevant measurements, separately for Part A and Part B. Graphical displays will be used to show changes in laboratory measures over time, separately for Part A, and Part B:

1. Box graphs of individual tests over time by dose for Part A, and by treatment arm for Part B.
2. Spaghettis plot of selected lab tests over time by treatment arm for Part B.
3. Scatter plots of baseline versus worst postbaseline values by dose for Part A and by treatment arm for Part B. Separate plotting characters will be used for each subgroup. These will be generated for only selected labs (see table below).

Panel	Test	CTCAE Shift Table	Box Plots	Spaghetti Plots	Scatter Plots	Summary table
Chemistry	Albumin	X	X			
	Alanine aminotransferase (SGPT)	X	X	X		X
	Aspartate aminotransferase (SGOT)	X	X	X		X
	Alkaline Phosphatase	X	X	X		
	Carbon Dioxide	X	X			
	Direct Bilirubin	X	X	X		
	Total Bilirubin	X	X	X		X
	Blood urea nitrogen		X		X	
	Blood urea nitrogen (mg/dL)/Creatinine (mg/dL)		X		X	
	Calcium	X	X			
	Chloride	X	X			
	Creatinine	X	X	X		
	Creatinine clearance		X		X	X
	Glomerular filtration rate (estimated)		X		X	
	Glucose	X	X			
	Gamma-glutamyl-transpeptidase	X	X	X		
	Lactate dehydrogenase	X	X			
	Magnesium	X	X			
	Phosphate	X	X	X		X
	Potassium	X	X			X
	Sodium	X	X			
	Urate	X	X			
Hematology	Platelets	X	X	X		X
	Hematocrit		X			
	Hemoglobin	X	X	X		
	White Blood Cells	X	X	X		
	Lymphocyte Count	X	X			
	Neutrophils (ANC)	X	X	X		X
	Monocytes		X			
	Eosinophils		X			
	Basophils		X			

For patients with neutrophil lab results reported as segmented neutrophils and neutrophil bands, ANC will be calculated by the Sponsor (or designee) as:

ANC=total leukocyte count × total percentage of neutrophils (segmented neutrophils + band neutrophils)

Example:

If total leukocyte count = 4.3 x 10^3; segmented neutrophils = 48%; band neutrophils = 2% Then: 4300 × (0.48 + 0.02) = 4300 × 0.5 = ANC of 2150

Creatinine clearance and estimated glomerular filtration rate (GFR) will be derived by the Sponsor (or designee) using the Cockcroft-Gault and chronic kidney disease epidemiology collaboration (CKD-epi) formulas as follows:

Cockcroft-Gault equation:

For males:

$$\text{Creatinine Clearance} = \frac{((140 - \text{age[years]}) * \text{weight[kg]})}{0.81 * (\text{serum creatinine } [\mu\text{mol/L}])}$$

For females:

$$\text{Creatinine Clearance} = \frac{0.85 * ((140 - \text{age[years]}) * \text{weight[kg]})}{0.81 * (\text{serum creatinine } [\mu\text{mol/L}])}$$

A cap value of 125 will be set to creatinine clearance values (calculated from Cockcroft-Gault equation) higher than 125.

CKD-epi equation:

For males:

$$\text{GFR} = 141 * \min(\text{serum creatinine}/0.9, 1)^{-0.411} * \max(\text{serum creatinine}/0.9, 1)^{-1.209} * 0.993^{\text{Age}} * 1.159[\text{if race} = \text{black}]$$

For females:

$$\text{GFR} = 141 * \min(\text{serum creatinine}/0.7, 1)^{-0.329} * \max(\text{serum creatinine}/0.7, 1)^{-1.209} * 0.993^{\text{Age}} * 1.018 * 1.159[\text{if race} = \text{black}]$$

For purposes of the scatterplots, the worst value will be the largest value observed after baseline for BUN and BUN/creatinine ratio. The worst value will be the smallest value observed after baseline for creatinine clearance and GFR.

All chemistry and hematology lab data will also be presented in by-patient listings separately for Part A and Part B.

7.11.4 Vital Signs

Vital signs, including diastolic and systolic BP, HR, height, weight, and body temperature, will be collected. All vital signs will be taken in the supine position.

Graphical displays will be used to show vital sign parameters over time, separately for the Part A by dose, and for Part B by treatment arm:

- Individual patient line graphs of temperature, diastolic BP, systolic BP, and HR over time for each dose level. These will be summarized for measurements taken in the supine position.

- Box plots over time for temperature, diastolic BP, systolic BP and HR during Cycle 1 will be generated. These will be summarized for measurements taken in the supine position.

Vital signs data will also be presented in by-patient listings, separately for Part A and Part B.

7.11.5 Electrocardiograms

The number and percentage of patients experiencing abnormal ECG results will be summarized over each time point, separately for Part A by dose, and for Part B by treatment arm.

QTc intervals (QTcF and QTcB) will be derived by the Sponsor (or designee) using the following formulas.

$$QTcF = \frac{QT_{uncorrected}}{\left(\frac{60}{Ventricular\ Rate}\right)^{1/3}} \qquad QTcB = \frac{QT_{uncorrected}}{\sqrt{\frac{60}{Ventricular\ Rate}}}$$

ECG findings will also be presented in by-patient listings separately for Part A, and Part B.

ECG Parameter	Abnormal values
QTcF and QTcB	New absolute values >450, >480 and >500
	Changes from baseline >30 and >60
HR	Decrease from baseline >25% and to a HR <50
	Increase from baseline >25% and to a HR >100
PR	Increase from baseline >25% and to a value >200
QRS	Increase from baseline >25% and to a value >110

7.11.6 Other Observations Related to Safety

Not applicable.

7.12 Interim Analysis

Not applicable.

7.13 Changes in the Statistical Analysis Plan

Not applicable.

8.0 REFERENCES

1. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. U.S. Department of Health and Human Services National Cancer Institute. 14 June 2010.
2. 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(2):228-47.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	13-Mar-2019 13:45 UTC