Title: A Phase 1 Study to Evaluate the Effects of Rifampin on Pharmacokinetics of Pevonedistat in Patients with Advanced Solid Tumors

NCT Number: NCT03486314

SAP Approve Date: 11 June 2019

Certain information within this Statistical Analysis Plan has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable (PPD) information or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: Pevonedistat-1015

A Phase 1 Study to Evaluate the Effects of Rifampin on Pharmacokinetics of Pevonedistat in Patients with Advanced Solid Tumors

TAK-924/MLN4924: Effect of Rifampin (Strong Metabolic Enzyme Inducer) on 50 mg/m^2 dosing of Pevonedistat

PHASE 1

Version**:** Final

Date**:** 11 June 2019

Prepared by:

PPD

Based on:

Protocol Version: Protocol Amendment No. 02

Protocol Date: 04 September 2018

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

1.1 Approval Signatures

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

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

2.0 TABLE OF CONTENTS

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ALL	acute lymphoblastic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{∞}	AUC from time zero to infinity
AUC_{last}	AUC from time zero to time of the last quantifiable concentration
AUC_{τ}	AUC during a dosing interval
BSA	body surface area
CDL	cullin-dependent ubiquitin E3 ligases
CFR	Code of Federal Regulations
CLp	Systemic clearance
Cmax	maximum observed concentration
CR	complete response
CRO	contract research organization
CT	computed tomography
CV	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
DME	drug-metabolizing enzyme
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOS	End-of-Study
FDA (US)	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GI	gastrointestinal
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
IRB	institutional review board

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

IV	Intravenous(ly)
Millennium	Millennium Pharmaceuticals, Inc
pevonedistat	research name of pevonedistat hydrochloride; TAK-924
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NAE	NEDD8-activating enzyme
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer
PD	progressive disease
PK	pharmacokinetics
PR	partial response
QTc	rate-corrected QT interval
RECIST	Response in Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SC	subcutaneous(ly)
SmPC	Summary of Product Characteristics
SoC	standard of care
$t_{1/2z}$	terminal disposition phase half-life
TAD	time after dose (actual)
TEAE	treatment-emergent adverse event
t_{max}	time of first occurrence of Cmax
TRA	total radioactivity
ULN	upper limit of the normal range
US	United States
USP	United States Pharmacopeia

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

4.0 OBJECTIVES

4.1 Primary Objectives

The primary objective is to assess the effect of multiple-dose administration of rifampin on the single-dose PK of pevonedistat in adult patients with advanced solid tumors (Part A).

4.2 Secondary Objectives

The secondary objectives are as follows:

Part A

- To further characterize pevonedistat PK following a single dose at 50 mg/m^2 in the absence or presence of rifampin.

Part B

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

4.3 Safety Objectives

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 50 mg/m^2 in the absence or presence of rifampin.

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 Exploratory Objectives

None.

4.5 Study Design

This is a 2-part, open-label, DDI study in adult patients who have a histologically or cytologically confirmed metastatic or locally advanced solid tumor that is appropriate for treatment with pevonedistat in combination with either docetaxel or carboplatin+paclitaxel in Part B of this study, or have progressed, despite standard therapy, or for whom conventional therapy is not considered effective. Approximately 20 patients will be enrolled to obtain approximately 12 PK-evaluable patients.

4.5.1 Part A: Assessment of the effect of rifampin on pevonedistat pharmacokinetics (PK)

Eligible patients will receive a single dose of 50 mg/m^2 pevonedistat via a 1-hour intravenous (IV) infusion on Day 1. Plasma PK samples will be collected at a series of predetermined time points up to 48 hours (Day 3) following the single dose of pevonedistat. Patients will then

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

receive an oral dose of 600 mg rifampin once daily (QD) starting from Day 3 (after collecting the 48-hour PK sample) through Day 11. There will be no pevonedistat doses from Day 2 through Day 9. On Day 10, a single dose of 50 mg/m^2 pevonedistat will be administered, and plasma samples will be collected at predetermined time points up to 48 hours (Day 12) following the second single dose of pevonedistat. Study drug will be discontinued early if a patient experiences study drug–related toxicities.

Both doses of pevonedistat (Days 1 and 10) will be administered in the clinic, followed by the required PK sampling. Serial blood plasma samples for determination of the plasma concentration of pevonedistat will be obtained during Part A at prespecified time points. The first dose of rifampin will be given orally in the clinic on the morning of Day 3 after collection of the 48-hour PK sample. Patients will self-administer rifampin (oral capsules) QD on Days 4, 5, 6, 7, 8, and 9 at home. Patients are encouraged to take rifampin at approximately the same time each day (±2 hours from the time of first rifampin dose). On Days 10 and 11, patients will report to the clinic to continue to receive oral 600 mg rifampin co-administered with pevonedistat on Day 10, and at the time of the 24-hour pevonedistat PK sampling on Day 11. The last PK sampling is on Day 12 (48-hour post pevonedistat infusion on Day 10). There will be no pevonedistat dosing on Days 11 and 12. There will be no rifampin dosing on Day 12.

All doses of rifampin will be administered on an empty stomach with patients taking nothing by mouth (NPO) except for water and prescribed medications for 2 hours before and at least 1 hour after each rifampin dose. Patients who miss any rifampin doses on Days 3 to 9 will not be considered evaluable and pevonedistat dosing and PK sampling on Day 10 will not be required for these patients. Patients will have a washout period from the last dose of rifampin for at least 1 week to allow reversal of metabolic enzyme induction before the start of Part B of the study.

Patients may discontinue therapy at any time, for any reason. 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.

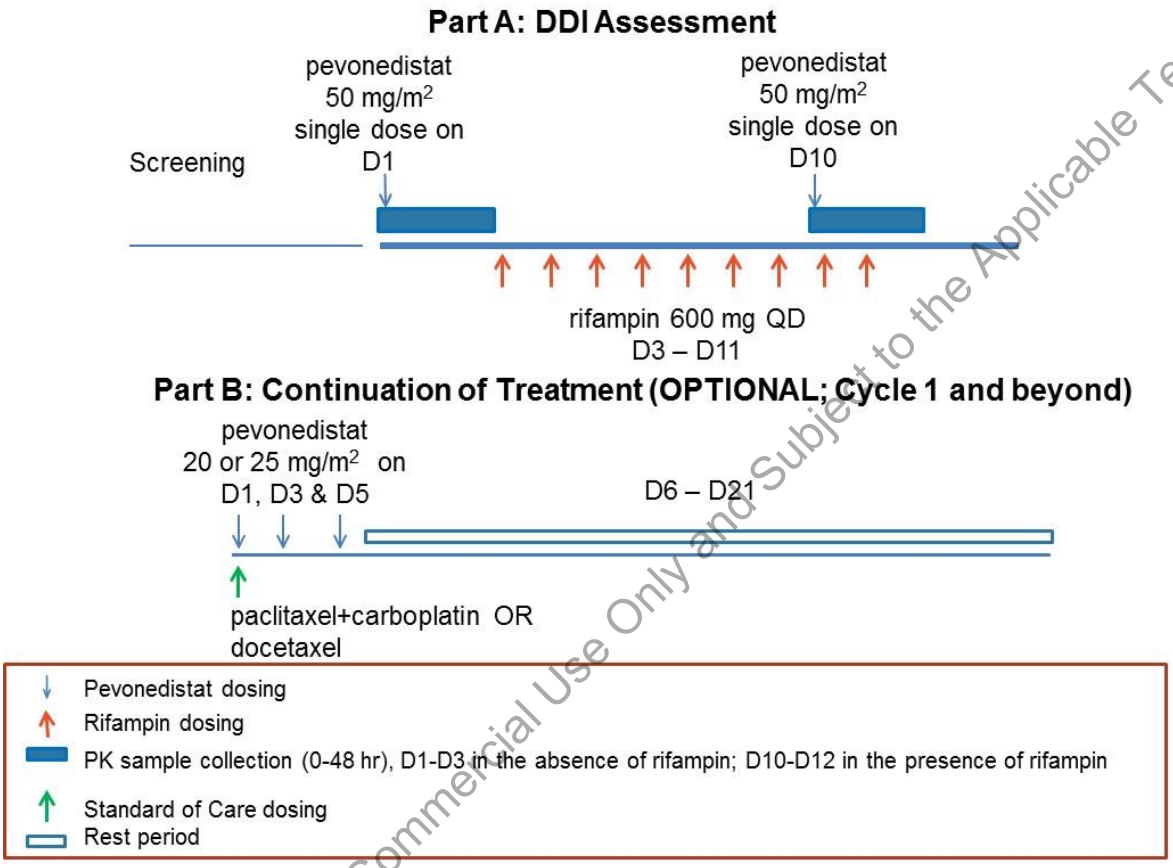
4.5.2 Part B (OPTIONAL): Continued Treatment with Pevonedistat in Combination with Standard of Care (SOC)

After completion of Part A of this study, patients will have the option of participating in Part B. Any patient who decides to participate in Part B will need to meet the continuation criteria of the study before treatment in Part B can begin. Patients will receive pevonedistat in combination with either docetaxel or carboplatin+paclitaxel, as recommended by the investigator. As in Part A, safety assessments will also be conducted in Part B of the study. In addition, Part B will conduct disease assessments using radiological evaluations (computed tomography scan or magnetic resonance imaging).

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

For an overview of the study design of Parts A and B, refer to Figure 4.a below.

Figure 4.a Study Overview



Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

The primary endpoint of the study is the ratios of geometric mean pevonedistat maximum observed plasma concentration (C_{max}), area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration (AUC_{last}), and area under the plasma concentration versus time curve from time 0 to infinity (AUC_{∞}) in the presence of rifampin in reference to C_{max}, AUC_{last}, and AUC_{∞} in the absence of rifampin and associated 90% confidence intervals (CIs).

5.2 Secondary Endpoints

The secondary endpoints are as follows:

Part A

- PK parameters: CL, volume of distribution at steady-state after intravenous administration (Vss), and $t_{1/2z}$ of pevonedistat following a single dose administration of 50 mg/m^2 on Day 1 (in the absence of rifampin) and Day 10 (in the presence of rifampin).

Part B

- Measures of disease response based on the investigator's assessment using the Response Evaluation Criteria in Solid Tumors (RECIST, Version 1.1) guideline.

5.3 Safety Endpoint

The safety endpoints for Part A of this study are AEs, serious adverse events (SAEs), assessments of clinical laboratory values, and vital signs measurements following a single-dose IV administration of pevonedistat at 50 mg/m^2 in the absence or presence of rifampin. The safety endpoint for Part B of this study are AEs, SAEs, assessments of clinical laboratory values, and vital signs measurements following administration of pevonedistat in combination with either docetaxel or carboplatin+paclitaxel.

5.4 Exploratory Endpoint

There are no exploratory or additional endpoints in this study.

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

6.0 DETERMINATION OF SAMPLE SIZE

The sample size calculation is based on the expected two-sided 90% CI for the difference in the paired, log-transformed AUC (or C_{max}) means of pevonedistat co-administered with rifampin and pevonedistat administered alone. Based on the preliminary data obtained from Study C15011, the within-subject coefficient of variation was estimated to be 13% for AUC and 58% for C_{max}, respectively. Assuming the AUC (or C_{max}) ratio is 1.0, with a sample size of 12 evaluable patients, the 90% CI of the ratio of geometric means is expected to be (0.907, 1.102) for AUC and (0.671, 1.49) for C_{max} based on the previously discussed variance assumptions. If the ratio is X, the 90% CI of the ratio of geometric means is expected to be within (0.907X, 1.102X) and (0.671X, 1.49X), respectively. Patients who are not PK evaluable will be replaced to ensure availability of approximately 12 PK-evaluable patients for the final analysis.

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

In general, summary tabulations will include the number of observations, (arithmetic) mean, standard deviation (SD), geometric mean and coefficient of variation (%CV) for PK related parameters, median, minimum, and maximum for continuous variables, and the number and percent (of non-missing) per category for categorical data, unless specified otherwise. Means and medians will be presented to 1 more decimal place than the recorded data. The standard deviations (SDs) will be presented to 2 more decimal places than the recorded data. Confidence intervals about a parameter estimate will be presented using the same number of decimal places as the parameter estimate.

Descriptive statistics will be presented with the same precision as the original data. The PK parameters will be summarized with a precision of 3 significant digits, while t_{max} is presented with the number of relevant decimal places to specify the sampling time. Percent CV and frequency percentages will be presented as integers.

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

7.1.1 Study Definitions

A Patient is considered to be enrolled when the first dose of study drug has been administered. Study start date is defined as the date of first dose of study drug for part A.

7.1.2 Definition of Study Days

Study Day 1 is defined as the date on which a subject is administered their first dose of the study drug. Other study days are defined relative to the Study Day 1 with Day 1 being Study Day 1 and Day -1 being the day prior to Study Day 1. Study day 1 definition is similarly for part B.

7.1.3 Definition 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 during Part A. For analysis of ECG data, the baseline value is the average of the screening and Part A Day 1 predose value if ECG is collected at both of the screening and Part A Day 1 predose. If ECG is collected at only one of these two time points, the baseline value takes the value of the one which is collected.

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.

Property of Takeda. For Non-Commercial Use Only and Subject to the Application Terms of Use

7.1.4 Windowing of Visits

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 post dose relative to the first dosing.

7.1.5 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.

7.1.6 Imputations for Missing Dates

Dates of initial diagnosis, prior therapy, surgery or radiation which are partially missing will be imputed as follows:

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

7.1.6.1 Analysis of Missing Adverse Event Dates

- 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 on or before the month and year of the date of the first dose of study drugs in Part B for patients who continue into Part B, and the end date of the event if not missing is on or after the date of first doseof study drug in part A.
  - 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, and the end date of the event if not missing is on or after the date of first dose of study drug in part B.
- 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 on or before the year of the date of the first dose of study drugs in Part B for patients who continue into Part B, and the end date of the event if not missing is on or after the date of first dose of study drug in part A.
  - treatment emergent for Part B if the year of the start date of the event are 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

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

date of the last dose of study drugs in Part B plus 30 days, and the end date of the event if not missing is on or after the date of first dose of study drug in part B.

- 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, and the end date of the event if not missing is on or after the date of first dose of study drug in part A.
  - 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, and the end date of the event if not missing is on or after the date of first dose of study drug in part A.
  - 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.

7.2 Randomization and Stratification

No randomization or stratification will be performed in this study.

7.3 Unblinding

As this is an open-label study, no unblinding methodology is required.

7.4 Statistical Software

SAS version 9.4 (or higher) will be used for all analyses.

7.5 Analysis Sets

7.5.1 Safety Analysis Set/ Population

The safety analysis set for Part A is defined as all enrolled patients who receive at least single pevonedistat dose 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 all patients who continue to Part B and receive at least 1 dose of study drugs administered during Part B. All safety analyses in Part B will be performed using the safety population for Part B.

7.5.2 Pharmacokinetic (PK)-Evaluable Population

The PK-evaluable population is defined as a) all enrolled patients who receive the protocol-specified single pevonedistat dose in Part A, b) did not receive any excluded medications throughout the completion of Part A, and c) have sufficient concentration-time data to permit reliable estimation of PK parameters. The patients to be included in the PK-evaluable population will be determined by the Takeda Clinical Pharmacologist upon review of the final data.

PK analyses during Part A will be performed using the PK-evaluable population.

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

7.5.3 Response-Evaluable Population

The response-evaluable population is defined as all 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 post-baseline disease assessment.

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

7.6 Disposition of Subjects

7.6.1 Patient Disposition

Separate tabulations of patient disposition data will be generated for Part A (including the washout period) and Part B.

A tabulation of patient disposition data for Part A will include the number of patients for the following categories: patients treated (safety population for Part A), patients in the PK-evaluable population, patients completing Part A, patients who discontinued study treatment during Part A the primary reason off study treatment, patients off study during Part A and the primary reason off study Patients will be considered to have completed Part A if they have completed the protocol-specified dose requirement and PK assessments to provide data necessary for assessment of effects of rifampin on pevonedistat PK within Part A of the protocol. The number of patients who are continuing into Part B of the study may also be tabulated. Percentages will be based on the number of patients in the safety populations for Part A

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

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

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

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

Summay table for screening failure and Primary Reason Subject Failed Screening will also be provided.Data concerning patient disposition (eg, primary reason off study treatment, patient population) will be presented in by-patient listings.

7.7 Demographic and Other Baseline Characteristics

7.7.1 Demographics

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

BSA is calculated for each patient using the following formula:

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

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 pre-dose 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.

No inferential statistics will be generated.

7.7.2 Baseline Disease Characteristics

Baseline disease characteristics (disease type, disease stage, sites of involvement, time since initial diagnosis (months), defined as the time of initial diagnosis to time of informed consent will be summarized for the safety population in Part A, and by SoC treatment and total for the safety population in Part B. ECOG performance status will be summarized similarly in the same table.

Information on prior therapies will be summarized for the safety population in Part A. Summarized information on prior therapies will include:

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

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

Missing dates will be imputed as described in section 7.1.6.

In addition, prior chemotherapy regimens will before Part A. List and categorization of prior chemotherapy regimens is described in Appendix 1.

7.7.3 Inclusion/Exclusion Criteria

All inclusion/exclusion information on enrolled patients will be included in by-patient listings. After completing Part A of the study, patients may choose to enter the optional part of the study, Part B. To be eligible for Part B, patients must have completed Part A and be reassessed to determine if they meet the continuation criteria for Part B. Only patients who meet the criteria may continue into Part B. Eligibility criteria for participation in (optional) 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. Patient pregnancy test results will be included in a separate by-patient listing. 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 separately 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".

7.7.4 Medical History

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

7.7.5 Concomitant Medications

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 for the safety population in Part A, and by SoC treatment 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 (pre-dose) 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 medications with start or end dates that are completely or partially missing will be analyzed using the same imputation rules as adverse events.

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

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

7.8 Study Drug Exposure and Compliance

7.8.1 Study Drug Exposure

There will only be 2 doses scheduled for Part A, therefore the assessment for Extent of Exposure will be performed for Part B only. The analysis will be done for Part B safety population only and by SoC treatment.

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 SoC 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 during the 21 days of that cycle. Percentages will be calculated by SoC treatmentarm, and total for Part B.

For pevonedistat, calculation of Percent Dosing Intensity will use equations as specified below 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.

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

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

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

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:

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

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

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

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.

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

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

For chemotherapy, Daily Expected Dose, Daily prepared dose, Daily dose received, Total Dose Received, Total Dose Expected, and Percent 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.

7.8.2 Treatment Compliance and Modifications

The actions on study drugs (Dose Held, Dose Reduced, Dose Interrupted, DoseDelayed, or Discontinued Permanently) will be summarized for the safety population by SoC treatment and total in Part B. For Part B, data will be summarized for all treatment cycles. A patient will count only once for each type of action within each cycle.

7.9 Efficacy Analyses (Part B)

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 disease response of pevonedistat in combination with SoC. 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]) and in overall response rate (CR + PR, and CR+PR+SD) will be presented by SoC treatment arm. Percentages will also be calculated for the total in Part B. Confidence interval will be calculated using exact binomial distribution All evaluations of response will be conducted using the response-evaluable population.

For each patient, the best percent change (ie, largest reduction) from baseline in the sum of the longest diameter will be calculated and displayed in a waterfall plot to show the distribution of response in each SoC treatment. 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 are the time from the date of

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

first documented response per the investigator response assessment to the date of first documentation of PD, or death if no prior PD is documented, or the date of last disease assessment if the patient discontinues treatment before PD. The duration of response (in months), will be summarized descriptively by SoC treatment arm for all response-evaluable patients.

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

Results from all disease response assessments and whether there was symptomatic deterioration will be presented in by-patient listings. Other measures of response (eg, patients with SD or better for ≥5 Cycles) will also be presented in by-patient listings.

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

7.10 Pharmacokinetic/ Pharmacodynamic Analysis

7.10.1 Pharmacokinetic Analysis (Part A)

During Part A of the study, serial blood samples (approximately 3 mL each) for PK analysis of pevonedistat will be collected in Part A predose and prespecified time points on Day 1 and Day 10 and over a 48-hour period on Days 1, 2 (24 hours after the Day 1 dose) and 3 (48 hours after the Day 1 dose), 10, 11 (24 hours after the Day 10 dose) and 12 (48 hours after the Day 10 dose) as indicated below:

	Time Point (hour)	Plasma Sample Collection
Study Day	**Matrix**	**Plasma (PK)**
Day 1	Predose(a)	X
Day 1	EOI (b) (–5 to +1 min)	X
Day 1	0.5 hour postinfusion (c) (±5 min)	X
Day 1	1 hour postinfusion (c) (±15 min)	X
Day 1	2 hours postinfusion (c) (±15 min)	X
Day 1	3 hours postinfusion (c) (±30 min)	X
Day 1	4 hours postinfusion (c) (±45 min)	X
Day 1	8 hours postinfusion (c) (±1 hour)	X
Day 1	10 hours postinfusion (c) (±1 hour)	X
Day 2	24 hours postdose (d) (±1 hour)	X
Day 3	48 hours postdose (d) (±1 hours)	X
Day 10	Predose(e)	X
Day 10	EOI (f) (–5 to +1 min)	X
Day 10	0.5 hour postinfusion (g) (±5 min)	X

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

	Time Point (hour)	Plasma Sample Collection
Study Day	**Matrix**	**Plasma (PK)**
Day 10	1 hour postinfusion (g) (±15 min)	X
Day 10	2 hours postinfusion (g) (±15 min)	X
Day 10	3 hours postinfusion (g) (±30 min)	X
Day 10	4 hours postinfusion (g) (±45 min)	X
Day 10	8 hours postinfusion (g) (±1 hour)	X
Day 10	10 hours postinfusion (g) (±1 hour)	X
Day 11	24 hours postdose (h) (±1 hour)	X
Day 12	48 hours postdose (h) (±1 hours)	X

EOI=end of infusion.
(a) The sample is to be collected within 1 hour before the start of pevonedistat infusion on Day 1.
(b) The window for collection of the EoI time point is between 5 minutes before completion of infusion and 1 minute after completion of infusion. If, during Part A, IV infusion of study drug is interrupted or slowed, contact the project clinician or designee as soon as possible for consideration of patient replacement, as appropriate. If the IV infusion is interrupted, 2 additional PK samples (1 sample drawn when the infusion is stopped and 1 sample drawn when the infusion is restarted) should be collected so that the patient may be considered evaluable. The exact date and time of each additional sample collection and the actual start and stop times of the infusion should be recorded accurately.
(c) Time points listed on Day 1 are in reference to the end of pevonedistat IV infusion on Day 1.
(d) Time points listed on Day 2 and Day 3 are in reference to the initiation of the pevonedistat IV infusion on Day 1.
(e) The sample is to be collected within 1 hour before the start of pevonedistat infusion on Day 10.
(f) The window for collection of the EoI time point is between 5 minutes before completion of infusion and 1 minute after completion of infusion. If, during Part A, IV infusion of study drug is interrupted or slowed, contact the project clinician or designee as soon as possible for consideration of patient replacement, as appropriate. If the IV infusion is interrupted, 2 additional PK samples (1 sample drawn when the infusion is stopped and 1 sample drawn when the infusion is restarted) should be collected so that the patient may be considered evaluable. The exact date and time of each additional sample collection and the actual start and stop times of the infusion should be recorded accurately.
(g) Time points listed on Day 10 are in reference to the end of pevonedistat IV infusion on Day 10.
(h) Time points listed on Day 11 and Day 12 are in reference to the initiation of the pevonedistat IV infusion on Day 10.

Individual pevonedistat plasma concentration-time data obtained on Day 1 and Day 10 will be analyzed by noncompartmental methods using WinNonlin version 8.1.

The PK-evaluable population will be used for the description of the concentration-time profiles, and for the estimation of pevonedistat PK parameters.

Plasma concentration values below the lower limit of quantification (<BLQ) of the bioanalytical assay will be set to zero for analysis. Actual PK sampling times will be used in the derivation of PK parameters. The exact date and time of each sample collection, as well as the actual start and stop times of the infusion, should be recorded accurately, and particular care should be given to the recording of blood sampling times that occur close to the infusion. Actual time after dosing (TAD) will be set to zero for pre-infusion samples and calculated as the difference between the sample collection date/time and the start date/time of the IV infusion.

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

The following plasma PK parameters will be estimated, as permitted by the data:

Parameters	Definition	Units
C_{max}	Maximum observed concentration (theoretically end-of-infusion concentration)	ng/mL
T_{max}	First time at which C_{max} occurs	hr
AUC_{last}	Area under the plasma concentration-time curve from time zero to the time of the last measurable concentration	hr*ng/mL
AUC_{0-48hr}	Area under the plasma concentration-time curve from time zero to 48 hours post-dose	hr*ng/mL
AUC_{0-inf}	Area under the plasma concentration-time curve extrapolated to infinity	hr*ng/mL
$lambda_z$	Terminal disposition phase rate constant	1/hr
$t_{1/2}$	Terminal disposition phase half-life	hr
CL_p	Systemic clearance	L/hr
Vss	Volume of distribution at steady-state	L

For pevonedistat-rifampin DDI assessment, the ratios of geometric mean C_{max}, AUC_{0-last} and AUC_{0-inf} of pevonedistat in the presence of rifampin on Day 10 versus in the absence of rifampin on Day 1 and associated 90% CIs will be calculated based on mixed-model analysis of variance. Estimates for each PK parameter were obtained using a mixed effects model of log(PK parameter) with fixed terms for the rifampin effect and random terms for patient. Subject will be treated as a random effect in the model. Point estimates and adjusted 90% confidence intervals for the difference in the log ratios will be constructed. The point estimate and adjusted 90% confidence intervals will then be exponentially back transformed to provide point and confidence interval estimates for the ratios of interest appropriately (eg, C_{max} of pevonedistat with rifampin vs. C_{max} of pevonedistat).

Individual pevonedistat plasma concentration-time data (including nominal, actual and elapsed times relative to dosing; TAD) and individual plasma PK parameters will be listed and summarized descriptively on Day 1 and Day 10.

Summary statistics (N, arithmetic mean, standard deviation, geometric mean, coefficient of variation [CV], median, minimum, and maximum) will be calculated if there is less than 50% of the values missing. The arithmetic mean and geometric mean will be reported on at least 2 non-missing values; and the median, standard deviation and CV will be reported on at least 3 non-missing values. For $T_{max,}$ only N, median, minimum, and maximum will be calculated.

Individual (single-subject plots with Day 1/Day 10) and mean pevonedistat plasma concentration-time data will be plotted against time after the start of the infusion by study Day. Linear and logarithmic scales will be used. Individual comparison of Cmax and AUCs vs Day plots will also be provided.

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

7.10.2 Pharmacodynamic Analysis

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 SoC treatment using the safety population for Part B defined in section 7.4.1.

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 (pre-dose) 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 (SOC), high level term (HLT), and preferred term (PT). Summary tabulations include the following subsets:

- Treatment-emergent AEs.
- Drug-related treatment-emergent AEs.
- Grade 3 or higher treatment-emergent AEs(presented by grade and overall).
- Grade 3 or higher drug-related treatment-emergent AEs (presented by grade and overall).
- Treatment-emergent AEs resulting in study drug discontinuation.
- SAEs.
- Treatment-emergent drug-related SAEs.
- On Study Deaths.

A listing of TEAEs resulting in study drug discontinuation will be provided.

By-patient listing of treatment emergent adverse events will be provided.

Most commonly reported (at least 10% of all patients) treatment-emergent AEs will be presented by preferred term in part A and separately by SoC treatment in part B.

All adverse events will include the variable AE onset window (ie, days of onset of AE from first and last dose).

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

Adverse events with start dates that are completely or partially missing will be analyzed as described in 7.1.6:

7.11.2 Overall Summary

The number and percentage of patients who experience any of the following treatment emergent adverse events will be summarized

- Any adverse event.
- Drug-related adverse event.
- Grade 3 or higher 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 dose interruption.
- On-study deaths.

Percentages will be calculated for the Part A total, by SoC treatment for Part B and the Part B total.

7.11.3 Serious Adverse Events

The number and percentage of patients experiencing at least one treatment emergent serious AE (SAE) will be summarized by MedDRA SOC, HLT, and PT. 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, severity and causality will be indicated) .The drug-related SAEs will also be presented.

7.11.4 Deaths

By-subject listings of the deaths will be presented, causality will be indicated. All deaths occurring on-study will be displayed. On-study death is defined as the death that occurs between the first dose of study drug and 30 days after the last dose of study drug.

All deaths will be summarized for Part A, by SoC treatment for Part B, including deaths occurring on-study and death during follow-up separately.

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

7.11.5 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 SOC, HLT, and PT.

By-patient listing of AEs resulting in discontinuation of study drug will be presented, severity and causality will be indicated. All AEs resulting in discontinuation of study drug occurring during the study will be displayed

7.11.6 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, severity and causality will be indicated. All AEs resulting in dose reduction of study drug occurring on-study will be displayed.

7.11.7 Adverse Events Resulting in Dose Modification

The number and percent of patients experiencing at least one adverse event resulting in dose modification (including dose Reduction, Delay or Permanent Discontinuation) will be summarized by MedDRA SOC, HLT, and PT.

A by-patient listing of AEs resulting in dose modification of study drug will be presented, severity and causality will be indicated. All AEs resulting in dose reduction of study drug occurring on-study will be displayed.

7.11.8 Myalgia Events and Musculoskeletal Pain and Discomfort

A listing of patients who experience treatment emergent myalgia (PT) event or treatment-emergent musculoskeletal pain and discomfort (PT)will be presented, severity and causality will be indicated.

7.11.8.1 Hemorrhages SMQ

By-patient line listing for patients who have Thrombocytopenia/Platelet Count Decreased and concurrent Hemorrhages (defined by SMQ Hemorrhages) with both events occurred within 5 days will be provided.

7.11.8.2 Acute Renal Failure SMQ

A listing of treatment-emergent acute renal failure events will be generated, severity and causality will be indicated.

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

7.11.8.3 Liver Function Test (LFT) Elevations

A listing of treatment-emergent LFT elevations will be generated, severity and causality will be indicated. The corresponding preferred and high level 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).

7.11.8.4 Tachycardia Events

A listing of treatment-emergent tachycardia events will be generated, severity and causality will be indicated. The corresponding preferred terms are listed as below:

- Heart rate increased.
- Rebound tachycardia.
- Sinus tachycardia.
- Supraventricular tachyarrhythmia.
- Tachyarrhythmia.
- Tachycardia.
- Tachycardia paroxysmal.
- Palpitations.

7.11.8.5 Hypotension

A listing of treatment-emergent hypotension will be generated, severity and causality will be indicated. The corresponding preferred terms are listed as below:

- 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.

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

7.11.8.6 Anemia

A listing of treatment-emergent anemia will also be generated, severity and causality will be indicated. The corresponding preferred terms are listed as below:

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

7.11.8.7 Neutropenia

A listing of treatment-emergent neutropenia will also be generated, severity and causality will be indicated. 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.
- Neutropenia.
- Neutropenic infection.
- Neutropenic sepsis.
- Neutrophil count abnormal.
- Neutrophil count decreased.
- Neutrophil percentage abnormal.
- Neutrophil percentage decreased.

By- patient line listing for patients who have Febrile neutropenia and concurrent Infections (defined by SOC Infections and Infestations. or HLGT Respiratory Tract Infections, or HLT Lower Respiratory Tract Inflammatory and Immunologic Conditions) with both events occurred within 5 days will be generated.

By- patient line listing for Patients who have Grade 3 or Higher TEAE of Neutropenia (defined by PT Neutropenia, PT Neutrophil Count Decreased, PT White Cell Count Decreased) and Infections (defined by SOC Infections and Infestations. or HLGT Respiratory Tract Infections, or HLT Lower Respiratory Tract Inflammatory and Immunologic Conditions) with both events occurred within 5 days will be generated.

7.11.8.8 Dose Modifications due to LFT Abnormalities

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+)

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

7.11.8.9 Dose Modifications due to Renal Abnormalities

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+)

7.11.8.10 Dose Modifications due to Myelosuppression

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 7.11.7.6 Anaemia.
- PTs from section 7.11.7.7. neutropenia.
- Thrombocytopenia.
- Platelet count decreased.

7.11.9 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 (v4.03: June 14, 2010) from baseline to the post baseline worst CTCAE grade will be generated. If necessary, graphical displays will be used to show changes in laboratory measures over time for each individual patient; (1) line graphs of individual tests over time for each patient; and (2) scatter plots of baseline versus worst post-baseline values.

In addition, the lines of mean and median estimates over time may be graphed for a selected list of test parameters. The box plots of creatinine and platelet may be graphed too. By patient listings of desired lab parameters may be generated, if deemed necessary. For complete list of lab analytes, see appendix 2.

Graphical displays will be used to show changes in laboratory measures over time for patients separately for Part A and Part B:

- Box graphs of individual tests over time by SoC treatment.
- Scatter plots of baseline versus worst post-baseline values for all patients. Separate plotting characters will be used for SoC treatment. These will be generated for only selected labs in Table 7.a.

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

Table 7.a Selected Labs

Panel	Test	CTCAE Shift Table	Box Graphs	Scatter Plots	Summary Tables
Chemistry	Albumin	X	X		
	ALT	X	X		X
	AST	X	X		X
	Alkaline Phosphatase	X	X		
	Carbon Dioxide		X		
	Direct Bilirubin	X	X		
	Total Bilirubin	X	X		X
	Blood urea nitrogen		X	X	
	Calcium	X	X		
	Chloride		X	X	
	Creatinine	X	X		
	Creatinine Clearance		X	X	X
	Glucose	X	X		
	Lactate dehydrogenase (LDH)		X	X	
	Magnesium	X	X		
	Phosphate	X	X		X
	Potassium	X	X		X
	Sodium	X	X		
	Urate	X	X		
Hematology	Platelets	X	X		X
	Hemoglobin	X	X		
	Hematocrit		X		
	White Blood Cells	X	X		
	Lymphocyte Count	X	X		
	Leukocytes	X	X		
	Neutrophils (ANC)	X	X		X
	Monocytes		X		
	Basophils		X		
Additional	Reticulocyte		X		X
	Ferritin		X		X

Creatinine clearance will be derived using one of the Cockcroft-Gault and CKD-epi formulas as follows:

Property of Takeda For Non-Commercial Use Only and Subject to the Applicable Terms of Use

Cockcroft-Gault equation:

For males:

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

OR

$$\text{Creatinine Clearance (mL/min)} = \frac{(140 - \text{age[years]}) \times \text{weight [kg]}}{72 \times (\text{serum creatinine [mg/dL]})}$$

For females:

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

OR

$$\text{Creatinine Clearance (mL/min)} = \frac{0.85 \times (140 - \text{age[years]}) \times \text{weight [kg]}}{72 \times (\text{serum creatinine [mg/dL]})}$$

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

CKD-EPI equation (http://nephron.com/epi_equation):

For males:

$$\text{GFR (mL/min/1.73 m}^2) = 141 \text{ x } \min(\text{Scr}/0.9, 1)^{-0.411} \text{ x } \max(\text{Scr}/0.9, 1)^{-1.209} \text{ x } 0.993^{\text{Age}}$$

where Scr = serum creatinine (mg/dL).

For black males:

$$\text{GFR(mL/min/1.73 m}^2) = 141 \text{ x } \min(\text{Scr}/0.9, 1)^{-0.411} \text{ x } \max(\text{Scr}/0.9, 1)^{-1.209} \text{ x } 0.993^{\text{Age}} \text{ x } 1.159$$

where Scr = serum creatinine (mg/dL).

For females:

$$\text{GFR (mL/min/1.73 m}^2) = 141 \text{ x } \min(\text{Scr}/0.7, 1)^{-0.329} \text{ x } \max(\text{Scr}/0.7, 1)^{-1.209} \text{ x } 0.993^{\text{Age}} \text{ x } 1.018$$

where Scr = serum creatinine (mg/dL).

For black females:

$$\text{GFR (mL/min/1.73 m}^2) = 141 \text{ x } \min(\text{Scr}/0.7, 1)^{-0.329} \text{ x } \max(\text{Scr}/0.7, 1)^{-1.209} \text{ x } 0.993^{\text{Age}} \text{ x } 1.018 \text{ x } 1.159$$

where Scr = serum creatinine (mg/dL).

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

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

7.11.10 Vital Signs

Tables will be used to show changes in vital sign parameters, including oral temperature, heart rate, and systolic and diastolic blood pressure, over time.

Change from baseline and by-patient listing will also be presented.

7.11.11 12-Lead ECGs

A 12-lead electrocardiogram (ECG) will be summarized over each time point, separately for Part A, and for Part B by SoC treatment arm. QTc intervals (QTcF and QTcB) will be derived by the Sponsor 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. Shift tables of the change from baseline to the post baseline worst will be generated.

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

7.11.12 Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG shifts from baseline to post-baseline assessment over time will be tabulated for both parts.

7.12 Interim Analysis

No interim analysis is planned

7.13 Changes in the Statistical Analysis Plan

Reference materials for this statistical plan include Clinical Study Protocol Pevonedistat-1015 Amend 02 (dated 04 September 2018), and the accompanying data collection documents (Annotated Case Report Form [CRF], version 1.0 and 2.0 dated 09 March 2017).

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

8.0 REFERENCES

1. U.S. Department of Health and Human Services, National Institutes of Health National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.03. 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.

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

9.0 DATA LISTINGS

The below subject-level listings will be generated:

1. Screen Failures.
2. Subject Disposition (Part A, Part B).
3. Inclusion/Exclusion Criteria (Part A).
4. Continuation Criteria (Part B).
5. Significant protocol deviation (Part A, Part B)).
6. Analysis Set (Part A, Part B).
7. Demographics and Baseline Characteristics (Part A, Part B).
8. Baseline Disease Characteristics (Part A).
9. Prior Therapy (Part A).
10. Prior Radiation (Part A).
11. Prior Transplant (Part A).
12. Prior Surgery (Part A).
13. Medical History and Concurrent Medical Condition (Part A).
14. Concomitant Medications (Part A, Part B).
15. Concomitant Procedures (Part A, Part B).
16. Study Drug Administration (Part A, Part B).
17. Extent of Exposure (Part B).
18. Plasma Concentration of Pevonedistat (Part A).
19. PK parameters of Pevonedistat (Part A).
20. Duration of Disease Response (Part B).
21. Duration of SD or Better (Part B).
22. Duration of SD or Better among Subjects with 5 or More Cycles of SD or Better (Part B).
23. Treatment-Emergent Adverse Events (Part A, Part B).
24. Serious Adverse Events (Part A, Part B).
25. Overview Listing of Subject Deaths.
26. Treatment-Emergent Adverse Events Resulting in Death (Part A. Part B).
27. Subject Survival Status (Part A. Part B).
28. Adverse Events Resulting in Discontinuation of Study Drug (Part A, Part B).

Property of Takeda. For Non Commercial Use Only and Subject to the Applicable Terms of Use

29. Adverse Events Resulting in Dose Reduction (Part A, Part B).
30. Adverse Events Resulting in Dose Modification (Part A, Part B).
31. Myalgia Events and Musculoskeletal Pain and Discomfort (Part A, Part B).
32. Acute Renal Failure Events (Part A, Part B).
33. Liver Function Test Elevations (Part A, Part B).
34. Tachycardia Events (Part A, Part B).
35. Hypotension Events (Part A, Part B).
36. Anaemia Events (Part A, Part B).
37. Neutropenia Events (Part A, Part B).
38. Febrile Neutropenia and Concurrent Infections with both events occurred within 5 days (Part A, Part B).
39. Grade 3 or Higher TEAE of Neutropenia and Infections with both events occurred within 5 days (Part A, Part B).
40. Thrombocytopenia/ Platelet Count Decreased and concurrent Hemorrhages with both events occurred within 5 day (Part A, Part B).
41. Hydration (Part B).
42. Dose Modifications due to LFT Abnormalities (Part B).
43. Dose Modifications due to Renal Abnormalities (Part B).
44. Dose Modifications due to Myelosupression (Part B).
45. Hematology Results and Change from Baseline (Part A, Part B).
46. Chemistry Results and Change from Baseline (Part A, Part B).
47. Vital Signs (Part A, Part B).
48. Electrocardiogram Results (Part A, Part B).
49. Electrocardiogram Interpretation (Part A, Part B).
50. ECOG Results (Part A, Part B).
51. Pregnancy Test Results.

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

10.0 APPENDICES

10.1 APPENDIX 1

Prior Chemotherapy Regimens Categories:

Taxane-containing regimens	BEVACIZUMAB+CARBOPLATIN+PACLITAXEL
	BEVACIZUMAB+CISPLATIN+DOCETAXEL
	BEVACIZUMAB+CISPLATIN+PACLITAXEL
	BEVACIZUMAB+PACLITAXEL
	CAPECITABINE+DOCETAXEL
	CAPECITABINE+PACLITAXEL
	CARBOPLATIN+PACLITAXEL
	CARBOPLATIN+PACLITAXEL+TRASTUZUMAB
	CISPLATIN+DOCETAXEL
	CISPLATIN+DOCETAXEL+FLUOROURACIL
	CISPLATIN+PACLITAXEL
	CYCLOPHOSPHAMIDE+DOCETAXEL
	CYCLOPHOSPHAMIDE+DOCETAXEL+DOXORUBICIN
	CYCLOPHOSPHAMIDE+DOXORUBICIN+PACLITAXEL
	DOCETAXEL (TAXOTERE)
	DOCETAXEL+DOXORUBICIN
	DOCETAXEL+FLUOROURACIL
	DOXORUBICIN+PACLITAXEL
	FLUOROURACIL+PACLITAXEL
	GEMCITABINE+PACLITAXEL
	PACLITAXEL (ABRAXANE FOR INJECTABLE SUSPENSION; APO-PACLITAXEL)
	PACLITAXEL+TRASTUZUMAB
Regimens containing a taxane but not a platinum	BEVACIZUMAB+PACLITAXEL
	CAPECITABINE+DOCETAXEL
	CAPECITABINE+PACLITAXEL
	CYCLOPHOSPHAMIDE+DOCETAXEL
	CYCLOPHOSPHAMIDE+DOCETAXEL+DOXORUBICIN
	CYCLOPHOSPHAMIDE+DOXORUBICIN+PACLITAXEL
	DOCETAXEL (TAXOTERE)
	DOCETAXEL+DOXORUBICIN
	DOCETAXEL+FLUOROURACIL
	DOXORUBICIN+PACLITAXEL
	FLUOROURACIL+PACLITAXEL
	GEMCITABINE+PACLITAXEL
	PACLITAXEL (ABRAXANE FOR INJECTABLE SUSPENSION; APO-PACLITAXEL)

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use

	PACLITAXEL+TRASTUZUMAB
Regimens containing a platinum but not a taxane	CAPECITABINE+CISPLATIN CAPECITABINE+CISPLATIN+EPIRUBICIN CAPECITABINE+EPIRUBICIN+OXALIPLATIN CAPECITABINE+OXALIPLATIN CARBOPLATIN (PARAPLATIN-AQ) CARBOPLATIN+ETOPOSIDE CARBOPLATIN+FLUOROURACIL CETUXIMAB+CISPLATIN+VINBLASTINE CETUXIMAB+CISPLATIN+VINORELBINE CISPLATIN (PLATINOL) CISPLATIN+EPIRUBICIN+FLUOROURACIL CISPLATIN+ETOPOSIDE CISPLATIN+FLUOROURACIL CISPLATIN+FLUOROURACIL+LEUCOVORIN CALCIUM CISPLATIN+GEMCITABINE CISPLATIN+IRINOTECAN CISPLATIN+PEMETREXED CISPLATIN+VINBLASTINE FLUOROURACIL+LEUCOVORIN CALCIUM+OXALIPLATIN FLUOROURACIL+OXALIPLATIN OXALIPLATIN (ELOXATIN)
Regimens containing both a platinum and a taxane	BEVACIZUMAB+CARBOPLATIN+PACLITAXEL BEVACIZUMAB+CISPLATIN+DOCETAXEL BEVACIZUMAB+CISPLATIN+PACLITAXEL CARBOPLATIN+PACLITAXEL CARBOPLATIN+PACLITAXEL+TRASTUZUMAB CISPLATIN+DOCETAXEL CISPLATIN+DOCETAXEL+FLUOROURACIL CISPLATIN+PACLITAXEL

10.2 APPENDIX 2

Panel	Test	CTCAE Shift Table	MTD Box Plots	Spaghetti Plots	Scatter Plots
Chemistry	Albumin	X	X		
	Alanine aminotransferase (SGPT)	X	X	X	
	Aspartate aminotransferase (SGOT)	X	X	X	
	Alkaline Phosphatase	X	X	X	

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

Panel	Test	CTCAE Shift Table	MTD Box Plots	Spaghetti Plots	Scatter Plots
	Carbon Dioxide	X	X		
	Direct Bilirubin	X	X	X	
	Total Bilirubin	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
	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	
	Potassium	X	X		
	Sodium	X	X		
	Urate	X	X		
Hematology	Platelets	X	X	X	
	Hematocrit		X		
	Hemoglobin	X	X	X	
	White Blood Cells	X	X	X	
	Lymphocyte Count	X	X		
	Neutrophils (ANC)	X	X	X	
	Monocytes		X		
	Eosinophils		X		
	Basophils		X		

Property of Takeda. For Non-Commercial Use Only and Subject to the Applicable Terms of Use

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	12-Jun-2019 15:23 UTC

Property of Takeda: For Non-Commercial Use Only and Subject to the Applicable Terms of Use