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

NCT Number: NCT03486314

Protocol Approve Date: 04 September 2018

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information (PPD) 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.

PROTOCOL

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

Sponsor: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited
40 Lansdowne Street
Cambridge, MA 02139
USA
Telephone: +1 (617) 679-7000

Please note: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, may be referred to in this protocol as "Millennium," "Sponsor," or "Takeda".

Study Number: Pevonedistat-1015

IND Number: 78,427 **EudraCT Number:** Not Applicable

Compound: Pevonedistat (TAK-924/MLN4924)

Date: 04 September 2018 **Version/Amendment Number:** 02

Date	Amendment No.	Amendment Type	Region
29 November 2017	Initial Protocol	Not applicable	United States
28 February 2018	01	Substantial	United States
04 September 2018	02	Nonsubstantial	United States

1.0 ADMINISTRATIVE

1.1 Contacts

A separate contact information list will be provided to each site.

Serious adverse event and pregnancy reporting information is presented in Section 10.0, as is information on reporting product complaints.

Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited-sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each subject.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Contact Type/Role	United States of America (USA) Contact
Serious adverse event and pregnancy reporting	See Section 10.0
Medical Monitor (medical advice on protocol and compound)	Refer to Study Manual
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	Refer to Study Manual

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

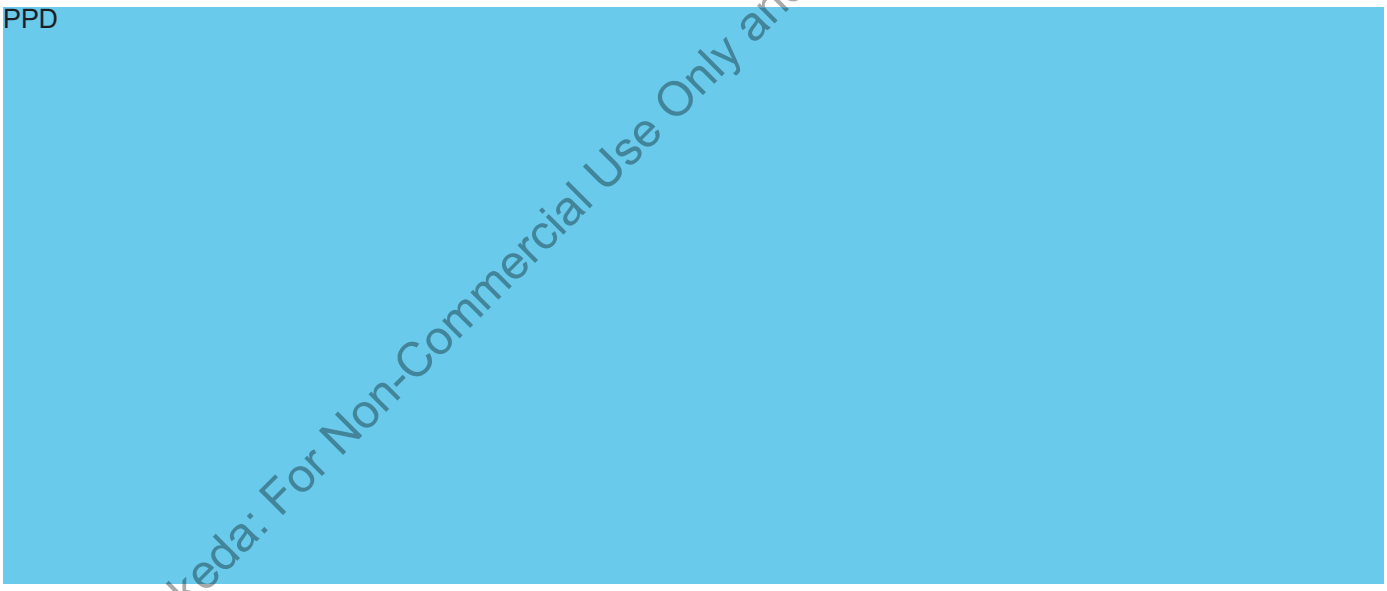
- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation (ICH) E6 Good Clinical Practice (GCP): Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer (and other signatories, as applicable) can be found on the signature page.

Electronic Signatures may be found on the last page of this document.

PPD



INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- ICH, E6 GCP: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Responsibilities of the Investigator (Appendix B).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix C of this protocol.

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State/Province)

_____

Location of Facility (Country)

1.3 Protocol Amendment 02 Summary of Changes

Rationale for Amendment 02

This document describes the changes in reference to the protocol incorporating Amendment 02. The primary reason for this amendment is to clarify the timing of the assessment of left ventricular ejection fraction (LVEF) as it relates to study eligibility.

Minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

For specific descriptions of text changes, the rationale for each change, and where the changes are located, see Appendix L.

Changes in Amendment 02

1. Clarify the exclusion criterion regarding the assessment of LVEF.
2. Delete the requirement that, for inclusion in the study, patients must have a tumor that is radiographically or clinically evaluable and/or measurable.
3. Change serious adverse event reporting from a paper-based system to electronic data capture.
4. Clarify the timing of chemistry and hematology laboratory assessments before administration of the Day 1 dose of pevonedistat in Part A (drug-drug interaction) of the study.

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2.0 STUDY SUMMARY

Name of Sponsor(s): Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited	**Compound:** Pevonedistat (TAK-924; MLN4924)	
Title of Protocol: A Phase 1 Study to Evaluate the Effects of Rifampin on Pharmacokinetics of Pevonedistat in Patients with Advanced Solid Tumors	**IND No.:** 78,427	**EudraCT No.:** Not applicable
Study Number: Pevonedistat-1015	**Phase:** 1	

Study Design:

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

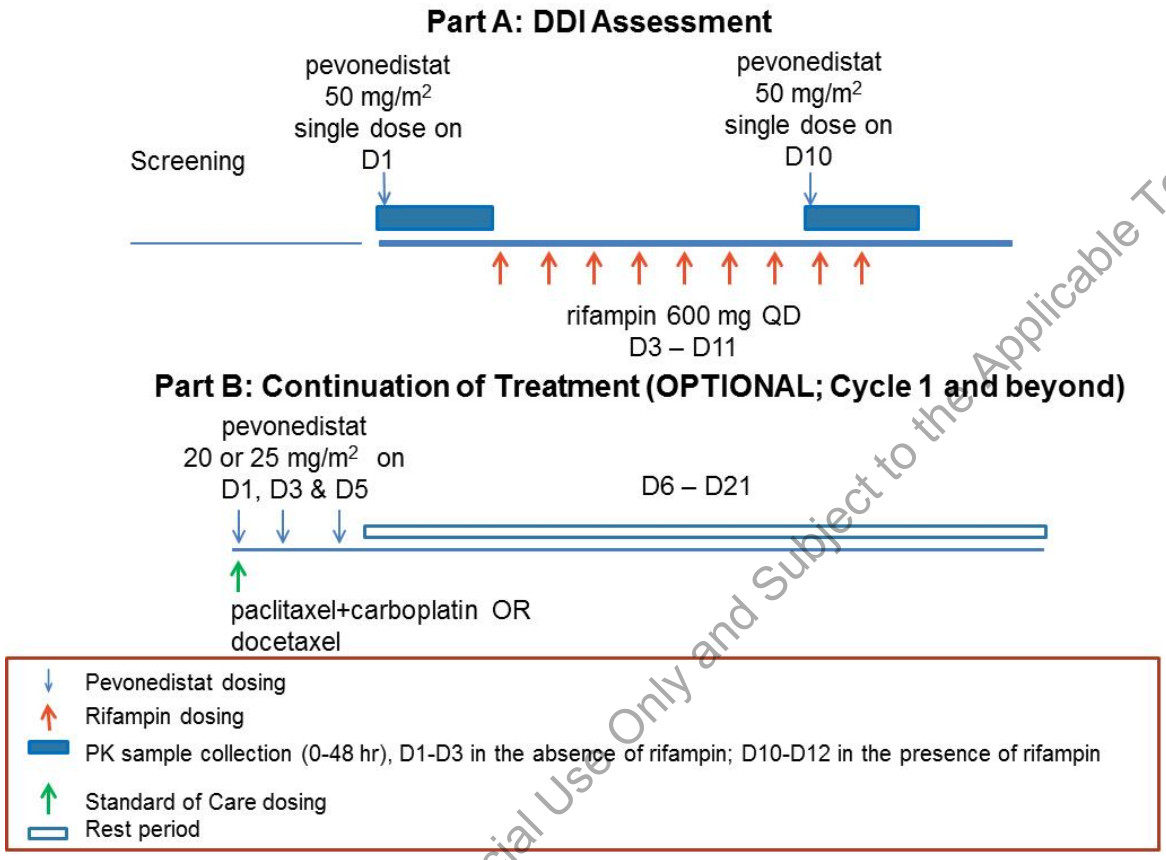
Eligible patients will receive a single dose of 50 mg/m^2 pevonedistat via a 1-hour intravenous (IV) infusion on Day 1. Plasma PK samples will be collected at a series of predetermined time points up to 48 hours (Day 3) following the single dose of pevonedistat. Patients will then receive an oral dose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

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).



Primary Objective:

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).

Secondary Objectives:

Part A: The secondary objective of Part A is to further characterize pevonedistat PK following a single dose at 50 mg/m^2 in the absence or presence of rifampin.

Part B: The secondary objective of Part B is 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.

Safety Objectives:

Part A: 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.

Part B: 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.

Subject Population: Adult patients, aged ≥18 years, 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.

Number of Subjects: Approximately 20 patients (for approximately 12 PK-evaluable patients).	**Number of Sites:** Estimated total: approximately 4 to 6 sites in the United States of America (USA).
Dose Level(s): **Part A:** Pevonedistat is given IV at 50 mg/m^2 on Day 1 and Day 10. Rifampin is given orally at 600 mg on Days 3 through 11; it is co-administered with pevonedistat on Day 10. **Part B:** Pevonedistat is given 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; pevonedistat is given in combination on Day 1 and as a single agent on Days 3 and 5 of each 21-day cycle.	**Route of Administration:** **Part A:** Pevonedistat: IV infusion Rifampin: oral dose **Part B (Optional):** Pevonedistat: IV infusion Docetaxel, carboplatin, and paclitaxel: IV infusion
Duration of Treatment: **Part A:** Single IV dose of pevonedistat at 50 mg/m^2 on Day 1 and Day 10, followed by a period of at least 1 week for washout and safety observation. **Part B (Optional):** Eligible patients may continue to receive treatment in Part B of this study until they experience symptomatic deterioration or disease progression, treatment is discontinued for another reason, or until the study is stopped. **Follow-up:** Patients will attend an End of Study (EOS) visit 30 days (+10 days) after the last dose of study drug or before the start of subsequent therapy in Part B, if that occurs sooner.	**Period of Evaluation:** Screening: Within 28 days before the first dose of study drug in Part A. **Part A:** 12 days with an EOS visit at 30 (+10) days (safety follow-up) after the last dose of study drug for patients who do not continue on to optional Part B. **Part B (Optional):** The duration of treatment for Part B is 12 cycles. If the sponsor and investigator determine that a patient would derive clinical benefit from continued treatment, the patient may remain on the current combination therapy or receive pevonedistat as a single agent beyond 12 cycles. Patients who have achieved clinical benefit from combination therapy (chemotherapy+pevonedistat) and who have developed intolerance that is reasonably attributable to the chemotherapy after 2 or more cycles may continue on single-agent pevonedistat at the same dose and schedule, upon request by the investigator and agreement by the sponsor. All patients in optional Part B will attend an EOS visit at 30 (+10) days (safety follow-up) after the last dose of study drug or before the start of subsequent therapy for their disease, if that occurs sooner.
Main Criteria for Inclusion: • Adult patients who have a histologically or cytologically confirmed metastatic or locally advanced solid tumor that is appropriate for treatment with 1 of the 2 combination therapies in Part B of this study, or have progressed despite standard therapy, or for whom conventional therapy is not considered effective. • Adequate renal, hepatic, and cardiac functions, and other safety parameters to reflect the risk mitigation strategy in place in all ongoing pevonedistat studies, and with special consideration to the safety profile of the SOC agents (Part B of the study).	

Main Criteria for Exclusion:

- Systemic treatment with strong metabolic enzyme inducers must be discontinued at least 14 days before the first dose of pevonedistat.
- Known gastrointestinal (GI) disease or GI procedure that could interfere with the oral absorption or tolerance of rifampin, including difficulty swallowing capsules.

Main Criteria for Evaluation and Analyses:

- **Primary**
- Ratios of geometric mean pevonedistat maximum observed plasma concentration (C_{max}), area under the plasma concentration versus time curve from time 0 to the 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% CIs.
- **Secondary**
- Part A:
  - PK parameters: total clearance after intravenous administration (CL), volume of distribution at steady state after intravenous administration (V_{ss}), and terminal disposition phase half-life ($t_{1/2z}$) 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.

Safety Endpoints:

Part A

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

Part B

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

Statistical Considerations:

Statistical analyses will be primarily descriptive and will be listed and/or summarized in tabular and/or graphical form. No formal statistical hypothesis testing will be performed. A formal statistical analysis plan will be developed and finalized before database lock.

Demographic and baseline characteristics will be summarized, including sex, age, race, ethnicity, weight, height, body surface area (BSA), baseline disease characteristics, and other parameters as appropriate.

All available efficacy and safety data will be included in data listings and/or tabulations and/or graphs.

Individual values and descriptive statistics of pevonedistat plasma concentration time data and PK parameters including but not limited to CL, V_{ss}, and $t_{1/2z}$ will be listed and tabulated by Day 1 (pevonedistat in the absence of rifampin) and Day 10 (pevonedistat in the presence of rifampin).

For pevonedistat-rifampin drug-drug interaction assessment, the ratios of geometric mean C_{max}, AUC_{last}, and AUC_{∞} of pevonedistat in the presence of rifampin versus C_{max}, AUC_{last}, and AUC_{∞} in the absence of rifampin and associated 90% CIs will be calculated.

Sample Size Justification: The sample size calculation is based on the expected two-sided 90% CI for the difference in the paired, log-transformed area under the plasma concentration-time curve (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.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Clinical Study Supplier List. The identified vendors in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Principal Investigator

Takeda will select a Signatory Coordinating Investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{∞}	area under the plasma concentration versus time curve from time 0 to infinity
AUC_{last}	area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration
BCRP	breast cancer resistance protein
BP	blood pressure
BSA	body surface area
CDLs	cullin-dependent ubiquitin E3 ligases
CL	total clearance after intravenous administration
C_{max}	maximum observed plasma concentration
CR	complete response
CrCl	creatinine clearance
CRO	contract research organization
CT	computed tomography
CYP	cytochrome P-450
DDI	drug-drug interaction
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOS	end of study
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GI	gastrointestinal
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IRB	institutional review board
IV	intravenous
LVEF	left ventricular ejection fraction

MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NAE	NEDD8-activating enzyme
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NEDD8	neural precursor cell expressed, developmentally down-regulated 8
NPO	nothing-by-mouth (nil per os)
NSCLC	non–small cell lung cancer
Pgp	P-glycoprotein
PD	progressive disease
PK	pharmacokinetic(s)
PR	partial response
PTA	post trial access
PTE	pretreatment event
QD	once daily
QTc	corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
RBC	red blood cell
RP2D	recommended phase 2 dose
SAE	serious adverse event
SC	subcutaneous
SD	stable disease
SOC	standard of care
SOE	Schedule of Events
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2z}$	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
USP	United States Pharmacopeia
USPI	United States package insert
V_{ss}	volume of distribution at steady state after intravenous administration
WBC	white blood cells

3.4 Corporate Identification

Millennium	Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

4.0 INTRODUCTION

4.1 Background

Pevonedistat is a cytotoxic agent and cannot be administered to healthy subjects. Pevonedistat is currently in phase 2/3 of clinical development for higher-risk myelodysplastic syndromes, chronic myelomonocytic leukemia, and low-blast acute myeloid leukemia (AML). The recommended phase 2 dose (RP2D) of pevonedistat administered as a single agent in patients with advanced hematologic malignancy is 50 mg/m^2 on Days 1, 3, and 5 in 21-day cycles. In solid tumors, the maximum tolerated dose (MTD) and RP2D of pevonedistat in combination with docetaxel is 25 mg/m^2 pevonedistat dosed on Days 1, 3, and 5, and docetaxel 75 mg/m^2 on Day 1 in 21-day cycles. The MTD and RP2D of pevonedistat in combination with paclitaxel+carboplatin is 20 mg/m^2 pevonedistat dosed on Days 1, 3, and 5 and 175 mg/m^2 paclitaxel+carboplatin (AUC5) on Day 1 in 21-day cycles.

4.1.1 Study Drug

Pevonedistat (TAK-924/MLN4924) is a first-in-class, small molecule inhibitor of neural precursor cell expressed, developmentally down-regulated 8 (NEDD8)-activating enzyme (NAE) under development for the treatment of malignancies. NAE, an E1 ligase, is an essential component of the NEDD8 conjugation pathway that controls the activity of a subset of ubiquitin E3 ligases, multiprotein complexes that transfer ubiquitin molecules to protein substrates that are then targeted to the proteasome for degradation. Cullin-dependent ubiquitin E3 ligases (CDLs) require conjugation to NEDD8 to be activated. CDLs control the timely ubiquitination and consequent proteasomal degradation of proteins with important roles in cell cycle progression and signal transduction, cellular processes that are integral to tumor cell growth, proliferation, and survival. Inhibitors of NAE activity may be of therapeutic value in the treatment of various cancers, such as solid tumors, by inhibiting the degradation of a subset of proteins that are regulated by the proteasome. Pevonedistat treatment results in tumor growth inhibition in mouse tumor xenografts models.

4.1.2 Nonclinical Background Information

Pevonedistat is a potent and selective inhibitor of NAE activity. Pevonedistat also inhibits human carbonic anhydrase II, which may explain the extensive partitioning of pevonedistat in red blood cells (RBCs) that has been observed in animal species and humans (see the current Investigator's Brochure [IB]).

Pevonedistat demonstrated antitumor activity in xenograft models when administered to immunocompromised mice by the subcutaneous (SC) route. The degree of the pharmacodynamic effect in HCT-116 xenograft tumors was dose dependent and correlated with dose-dependent antitumor activity after 21 consecutive days of twice-daily treatment. Pevonedistat also demonstrated a dose-dependent pharmacodynamic response in additional xenograft models (AML model HL-60, the Calu-6 lung tumor model, and 2 xenograft models of diffuse large B cell lymphoma: OCI-Ly10 and OCI-Ly19). Pevonedistat demonstrated antitumor activity in these

models with less frequent treatment, showing that continuous dosing is not necessary for antitumor activity.

Pevonedistat showed medium permeability in Caco-2 cells.

Plasma clearance ranged from relatively low in chimpanzees, to moderate in dogs and monkeys, to relatively high in rats. The plasma terminal disposition phase half-life ($t_{1/2z}$), calculated as $\ln(2)/\lambda z$, varied from <1 hour in rats to approximately 15 hours in monkeys.

The major elimination pathway of pevonedistat in animals is through the hepatic route. Urinary excretion of unchanged pevonedistat was negligible in rats, monkeys, and chimpanzees. After an intravenous (IV) dose of [^{14}C]-pevonedistat, radioactivity was primarily excreted in the feces in intact rats and in the bile in bile duct cannulated rats; excretion was almost complete by 24 hours postdose. No plasma metabolite accounted for more than 10% of the total plasma radioactivity, suggesting potentially low systemic exposure to metabolites.

Detailed information regarding the nonclinical pharmacology and toxicology of pevonedistat may be found in the current IB.

4.1.3 Clinical Background Information

4.1.3.1 Clinical Pharmacokinetics

Population pharmacokinetic (PK) analysis was conducted using data from pevonedistat single-agent studies (C15001, C15002, C15003, and C15005) and pevonedistat in combination with standard-of-care chemotherapy (C15009 and C15010) in patients with solid tumor or hematological malignancies. The database contained 335 subjects contributing 3768 PK observations. Pevonedistat plasma concentration-time profiles were well described by a 2-compartment model with linear elimination. Body surface area (BSA) was an important predictor of total clearance after intravenous administration (CL), distributional clearance, and both central and peripheral volumes. For a typical patient with a BSA of 1.73 m^2, an alpha half-life of 1.27 hours and a beta (elimination) half-life of 7.85 hours are estimated. Concurrent administration of carboplatin and paclitaxel decreased the CL of pevonedistat by approximately 44%, translating to an approximately 80% higher pevonedistat exposure (area under the plasma concentration-time curve [AUC]) during coadministration with carboplatin and paclitaxel, consistent with pevonedistat concentration data observed in C15010. Coadministration with azacitidine, gemcitabine, or docetaxel did not appear to affect the CL of pevonedistat. Race, sex, age, tumor type (hematologic vs solid), mild or moderate renal impairment (creatinine clearance [CrCl] ≥30 mL/minute), or mildly impaired liver function, to the extent represented in this dataset, had no impact on pevonedistat PK.

In a drug-drug interaction (DDI) study (C15011), preliminary data from 26 evaluable patients (13 from the itraconazole arm and 13 from the fluconazole arm) demonstrate that steady-state exposures to fluconazole had a minimal effect on the single-dose IV pevonedistat PK at 8 mg/m^2, while mean systemic exposure to pevonedistat increased by approximately 23% in the presence of itraconazole.

On the basis of these observations, additional patients were enrolled to evaluate the effects of itraconazole on pevonedistat PK at the clinical dose of 20 mg/m^2. Preliminary data from 11 patients who completed protocol-specified dosing and PK evaluations indicated that pevonedistat systemic exposures following IV administration at 20 mg/m^2 in the presence of itraconazole were similar to those in the absence of itraconazole (geometric mean ratio of 0.996 with an associated 90% CI of 0.913 and 1.09). These findings with established moderate and strong cytochrome P-450 (CYP)3A inhibitor probes indicate a minor contribution of CYP3A to pevonedistat metabolism in humans. On the basis of these results, moderate and strong CYP3A inhibitors and P-glycoprotein (Pgp) inhibitors can be used in patients receiving pevonedistat. For individual studies in the pevonedistat clinical program, reference should be made to the respective protocols for specific information relating to excluded and permitted medications.

4.1.3.2 Clinical Experience

As of 22 January 2017, the clinical development program includes 9 clinical studies in patients with advanced malignancies. Four of the 9 clinical studies are completed phase 1 monotherapy studies (C15001, C15002, C15003, and C15005) and 5 are ongoing phase 1/1b/2 studies (Studies C15009, C15010, C15011, Pevonedistat-1012, and Pevonedistat-2001). Pevonedistat is under development as a component of regimens with azacitidine (Study C15009, Pevonedistat-1012, and Pevonedistat-2001) and with docetaxel or in combination with carboplatin and paclitaxel (Study C15010), and DDIs of pevonedistat with fluconazole or itraconazole (Study C15011). Per the data available as of 22 January 2017, a total of approximately 451 patients received at least 1 dose of pevonedistat in the overall clinical development program.

4.1.4 Potential Risks and Benefits

Pevonedistat will be administered in Part A of this study as a single 1-hour IV infusion at 50 mg/m^2 on Days 1 and 10. Patients will also receive rifampin (Days 3 through 11), a strong CYP3A inducer. In vitro, pevonedistat is predominantly metabolized by the CYP isozyme 3A4; however, the in vivo contribution of CYP3A to overall clearance is inferred to be minimal, based on the lack of clinically meaningful effect of the strong CYP3A inhibitor itraconazole on pevonedistat PK. Because this is an induction DDI evaluation, it is hypothesized that the exposures of pevonedistat may be decreased upon co-administration with rifampin. The safety profile of this combination (pevonedistat+rifampin) is not known at this time.

It is anticipated that the chemotherapies used in Part B of this study may provide clinical benefit to patients. Study C15010 was an open-label, phase 1b study whose primary objective was to establish the MTD and assess the safety and tolerability of pevonedistat in combination with docetaxel, carboplatin, paclitaxel+carboplatin, or gemcitabine in patients with solid tumors. As of 22 January 2017, enrollment was complete. As of October 2017, 2 patients in complete response (CR) (still active in cycles 43+) remain on the study.

Data are available for 64 patients who received at least 1 dose of pevonedistat in combination with standard of care (SOC) (data cutoff: 15 February 2016). The safety profile of pevonedistat in combination with docetaxel (75 mg/m^2), in patients with solid tumors was favorable, and the study

objective to establish the MTD for pevonedistat (25 mg/m^2 on Days 1, 3, and 5 of a 21-day treatment cycle) was achieved. The safety profile of pevonedistat in combination with paclitaxel (175 mg/m^2) and carboplatin (AUC5) in patients with solid tumors was favorable. No new safety signals were observed for pevonedistat in this study compared to an earlier solid tumor study of pevonedistat as a single agent.

The most common (any grade) adverse event (AE) for patients in Arm 1 (pevonedistat+docetaxel) and Arm 2 (pevonedistat+carboplatin+paclitaxel) were fatigue (55%, 65%), nausea (36%, 54%), diarrhea (41%, 42%), anemia (32%, 46%), constipation (18%, 42%), increased aspartate aminotransferase (AST) (27%, 35%), vomiting (18%, 42%), and alopecia (23%, 38%), respectively. For patients who had an AE ≥ Grade 3 in Arm 1 and Arm 2, the most common events were decreased neutrophil count (27% each arm) and increased AST (18% and 23%), respectively.

Of the 54 response-evaluable patients diagnosed with a solid tumor, responses of stable disease (SD) or better were observed in 41 patients. Twelve patients experienced a best response of CR or partial response (PR); 15.8% in response-evaluable patients in Arm 1 (pevonedistat+docetaxel) and 34.8% in Arm 2 (pevonedistat+paclitaxel+carboplatin). For patients treated in Arm 2 (pevonedistat+paclitaxel+carboplatin), the median duration of response (CR and PR) was 7.375 months or 10 cycles (8 patients); and for Arm 1 (pevonedistat+docetaxel), the median duration of response (PR) was 3.060 months or 5 cycles (3 patients). For the 12 patients with a response of CR or PR, the time to response was between 1 and 3 months in all treatment arms. Two patients achieved a best response of CR that, at the time of data cutoff (15 February 2016), had durations of 6.57 (9 cycles) and 8.48 months (11 cycles), respectively, indicating that with repeat cyclic dosing of pevonedistat in combination with paclitaxel+carboplatin a complete response was feasible for at least 11 cycles.

The additional benefit in response rate derived from the combination of pevonedistat and SOC compared to historical data from SOC did not appear to be associated with additional toxicity with the exception of increased liver function tests. Broad-based activity in the various tumor types offers clinical benefit in variety of patient populations, including patients with adenocarcinoma and squamous carcinoma.

4.1.4.1 Risks of Pevonedistat Therapy

Safety information gained from single-agent clinical studies of pevonedistat and from toxicology studies in rats and dogs has been used to guide the safety evaluation of pevonedistat. Additional information on risks is provided in the current IB, which includes the development core safety information.

The risks of pevonedistat treatment, based on preliminary findings from the single-agent clinical studies and the toxicities noted in the toxicology studies done in rats and dogs, are presented below.

Identified Risks

- Increased heart rate.
- Diarrhea.
- Nausea.
- Vomiting.
- Pyrexia.
- Liver function test abnormal.
- Musculoskeletal pain.
- Myalgia.

Potential Risks

There are potential risks in the pevonedistat program that require further monitoring. While the potential toxicities listed below may be severe or life-threatening, it is anticipated that they can be managed by clinical monitoring and intervention. Patients will be monitored for these potential toxicities and for unanticipated toxicities for at least 30 days after their last dose of pevonedistat.

Potential Risks From Phase 1 Studies (at High Doses)

There are events that have been reported in phase 1 studies at doses and schedules substantially higher (≥110 mg/m^2) than those being used in current clinical studies of pevonedistat. These events are considered potential risks for the doses and schedules proposed in this study.

- Multi-organ failure that could result in death.
- Renal failure.
  - The events of multi-organ failure (hepatic, renal, and cardiac) with a fatal outcome, and renal failure alone, have been reported at doses of pevonedistat ranging from 110 to 278 mg/m^2. Refer to the current IB for additional information about multi-organ failure and dosing.
- Cardiac arrhythmias.
  - All events were supraventricular arrhythmias; all except 1 were unrelated. The case of atrial fibrillation, assessed by the investigator as related, occurred in a patient with a risk factor for cardiovascular disease (uncontrolled hypertension).
- Myelosuppression with increased susceptibility to infection, bleeding, and anemia.
- Acute phase response.
- Gastrointestinal (GI) toxicity including or resulting in dehydration and electrolyte imbalance.

- Hypophosphatemia.

Potential Risks Confounded by Underlying Disease or Malignancy

Events have been reported from clinical studies that are confounded by the patients' underlying medical conditions, including malignancy. These events are noted in the absence of randomized, controlled data:

- Fatigue.
- Chills.
- Decreased appetite.
- Neutropenia.
- Febrile neutropenia.
- GI bleeding.
  - All events were assessed by the investigator as unrelated; most occurred in the setting of thrombocytopenia.
- Multi-organ failure in the setting of infection.

Potential Risks Primarily Based on Findings From Animal Studies

Potential risks that are derived from findings in animal studies in rats and dogs include the following:

- Myocardial degeneration and thrombosis.
- Pulmonary hypertension.
- Cardiovascular changes that could result in tachycardia, decreased or increased systolic blood pressure (BP), and increased diastolic BP.
- Enteropathy (including dehydration and electrolyte loss) with secondary sepsis.
- Effects on the testes and ovaries that represent a reproductive hazard, including sterility.
- Increased developmental risk to the fetus or embryo.
- Decreased trabecular bone (graded minimal to moderate) noted in the femur and in the sternum in rats at all dose groups (low, medium, and high) but not in dogs. This finding was considered adverse in the high-dose group; however, no bone fractures were noted at any of the doses.
- Prolongation of the activated partial thromboplastin time (aPTT).
- Local tissue injury when administered SC.

It is possible that pevonedistat will have toxicities, which may be severe or fatal, that were not observed in or predicted from the studies completed in rats and dogs or have not yet been identified in patients.

Hepatotoxicity has been noted following administration of pevonedistat in patients with advanced malignancy, including elevations of liver transaminases, alkaline phosphatase (ALP), and bilirubin. Liver enzymes and liver function are frequently monitored during clinical studies of pevonedistat. Acetaminophen and acetaminophen-containing compounds may be used judiciously and should not exceed a dose of 2 g of acetaminophen in a 24-hour period (see Sections 8.4 and 8.5).

Patients must be carefully evaluated at screening and before each pevonedistat dose for early symptoms and signs of hemodynamic compromise or active infection. Particular attention should be paid to unexplained fever, tachycardia, hypotension, orthostasis, tachypnea, recent nausea and vomiting, and clinical evidence of dehydration. Guidance on rehydration is provided in Section 8.7.1.

These potential toxicities will be managed by careful, frequent monitoring and intervention, as needed, with supportive care. It is possible that pevonedistat will have toxicities that were not observed in or predicted from the studies completed in rats and dogs or have not yet been identified in patients.

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements (including International Council for Harmonisation [ICH] guidelines).

4.1.4.2 Risks of Docetaxel Treatment

Details of risks related to docetaxel treatment are provided in the applicable United States package insert (USPI).

4.1.4.3 Risks of Pevonedistat and Docetaxel as Combination Therapy

The following potential risks, based on the known individual safety profiles of pevonedistat and docetaxel, of combination therapy may apply: death, hypersensitivity, hepatotoxicity, neutropenia, and fluid retention (cardiac/pulmonary). With regard to docetaxel, treatment related mortality increases with abnormal liver function, at higher doses, and in patients with non–small cell lung cancer (NSCLC) who received prior platinum-based therapy receiving docetaxel at 100 mg/m^2.

4.1.4.4 Risks of Carboplatin and Paclitaxel Therapy

Details of risks related to carboplatin and paclitaxel therapy are provided in the applicable USPIs.

4.1.4.5 Risks of Pevonedistat and Carboplatin+Paclitaxel as Combination Therapy

The following potential risks, based on the known individual safety profiles of pevonedistat and carboplatin+paclitaxel, of combination therapy may apply: bone marrow suppression,

hypersensitivity/anaphylaxis reactions, and hepatotoxicity. Renal effects of nephrotoxic compounds [1] (see Appendix E) may be potentiated by carboplatin.

Given limited existing clinical experience, it is not known whether patients will benefit from participation in this study. However, a number of patients with solid tumors treated with pevonedistat as a single agent did demonstrate clinical benefit based primarily on prolonged SD. In addition, it is anticipated that the SOC therapies used in Part B of this study may provide additional clinical benefit to patients. Forty-eight patients have been treated with pevonedistat in combination with docetaxel, carboplatin, or carboplatin+paclitaxel. On the basis of preliminary data, these combinations have shown evidence of clinical benefit in the form of multiple PRs, limited CRs, and extended durations of SD.

4.2 Rationale for the Proposed Study

The primary objective of this study is to evaluate the effects of rifampin, a strong metabolic enzyme inducer, on the PK of pevonedistat. Pevonedistat is predominantly cleared via metabolism, based on in vitro and nonclinical in vivo data, and is also a substrate for the drug transporters Pgp and breast cancer resistance protein (BCRP). Strong inducers of metabolic enzymes and transporters, such as rifampin may be expected to result in decrease pevonedistat exposures and reduced efficacy. Current clinical studies prohibit use of strong enzyme inducers (eg, rifampin, carbamazepine, phenytoin). The results of this study will inform the risk assessment for potential DDIs with concomitant use of strong metabolic enzyme inducers during the clinical development of pevonedistat.

4.2.1 Rationale for Dose and Duration of PK Assessments in Part A

The pevonedistat dose of 50 mg/m^2 selected to be evaluated in this study is based on the consideration of 50 mg/m^2 as the RP2D of pevonedistat in the monotherapy setting and dose-linear PK of pevonedistat that should permit translation of the results of this study (ie, estimated magnitude of DDI) to lower doses such as those used in combination settings (eg, 20 mg/m^2 in combination with azacitidine). Approximately 12 evaluable patients will be required to provide the protocol-specified dosing and PK data in order to permit adequate assessment of the effects of rifampin on single-dose pevonedistat PK.

The elimination half-life of pevonedistat is approximately 9 hours. Serial PK sampling up to 48 hours following pevonedistat single dosing on Day 1 and Day 10 permits characterization of PK profiles of pevonedistat in the absence (Day 1) and in the presence (Day 10) of rifampin. Patients will begin to receive once daily (QD) doses of oral capsules of 600 mg rifampin on Days 3 through 11 in order to achieve steady-state of enzyme induction. The duration of PK assessment in Part A is approximately 12 days.

4.2.2 Rationale for Continued Treatment With Pevonedistat in Combination With Chemotherapy in Optional Part B

After completing Part A, patients will have the option to continue in the study by participating in Part B, where they will receive combination treatment with pevonedistat and chemotherapy. Two chemotherapy regimens, docetaxel and carboplatin+paclitaxel, which have been previously studied as combination partners with pevonedistat, will be used in this study. On the basis of the MTDs determined in Study C15010, patients will receive pevonedistat 25 mg/m^2 in combination with docetaxel 75 mg/m^2 or pevonedistat 20 mg/m^2 in combination with carboplatin AUC5+paclitaxel 175 mg/m^2.

Docetaxel is indicated as a single agent for locally advanced or metastatic breast cancer and for locally advanced or metastatic NSCLC after platinum therapy failure.

Paclitaxel is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Paclitaxel is also indicated for the second-line treatment of acquired immunodeficiency syndrome–related Kaposi's sarcoma. In addition, paclitaxel in combination with cisplatin is indicated for the first-line treatment of NSCLC in patients who are not candidates for potentially curative surgery and/or radiation therapy.

Carboplatin is indicated for the initial treatment of advanced ovarian carcinoma in combination with other approved chemotherapeutic agents (1 established combination regimen consists of carboplatin and cyclophosphamide). Carboplatin is also indicated for the palliative treatment of patients with ovarian carcinoma recurrent after prior chemotherapy, including patients who have been previously treated with cisplatin.

Docetaxel and paclitaxel+carboplatin are also approved in combination with other chemotherapeutic agents to treat other indications; refer the applicable USPIs.

In addition to the approved indications outlined above, these agents are widely used to treat a variety of malignancies in patients for whom prior therapies have failed. Paclitaxel+carboplatin is also widely used to treat patients with newly diagnosed NSCLC.

For a detailed description of each of these medications, see Section 8.9. The choice of the above chemotherapy agents in combination with pevonedistat in this study is based on the following considerations:

These chemotherapy agents have been well recognized as SOC in a number of malignancies in first-line (carboplatin+paclitaxel) or in various relapse settings (both regimens).

The safety profiles, risks, and benefits have been widely studied and reported.

Additive/synergistic effects of these agents in combination with pevonedistat have been studied in a number of in vitro and in vivo models by the sponsor.

The MTD and RP2Ds have been determined for the combination of pevonedistat+docetaxel and pevonedistat+carboplatin/paclitaxel.

Therefore, it is considered that the above chemotherapy agents will serve as reasonable partners in combination with pevonedistat for investigations in patients with various solid tumors in this study.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 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).

5.1.2 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.

5.1.3 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.

5.1.4 Exploratory/Additional Objectives

None.

5.2 Endpoints

5.2.1 Primary Endpoint

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).

5.2.2 Secondary Endpoints

The secondary endpoints are as follows:

Part A

- PK parameters: CL, volume of distribution at steady-state after intravenous administration (V_{ss}), 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.

5.2.3 Safety Endpoints

The safety endpoints for Part A of this study is 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 is AEs, SAEs, assessments of clinical laboratory values, and vital signs measurements following administration of pevonedistat in combination with either docetaxel or carboplatin+paclitaxel.

5.2.4 Exploratory/Additional Endpoints

There are no exploratory or additional endpoints in this study.

6.0 STUDY DESIGN

6.1 Overview of 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.

Eligible patients will receive a single dose of 50 mg/m^2 pevonedistat via a 1-hour 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 receive an oral dose of 600 mg rifampin 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.

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.

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 as described in Appendix A, Table A. 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.

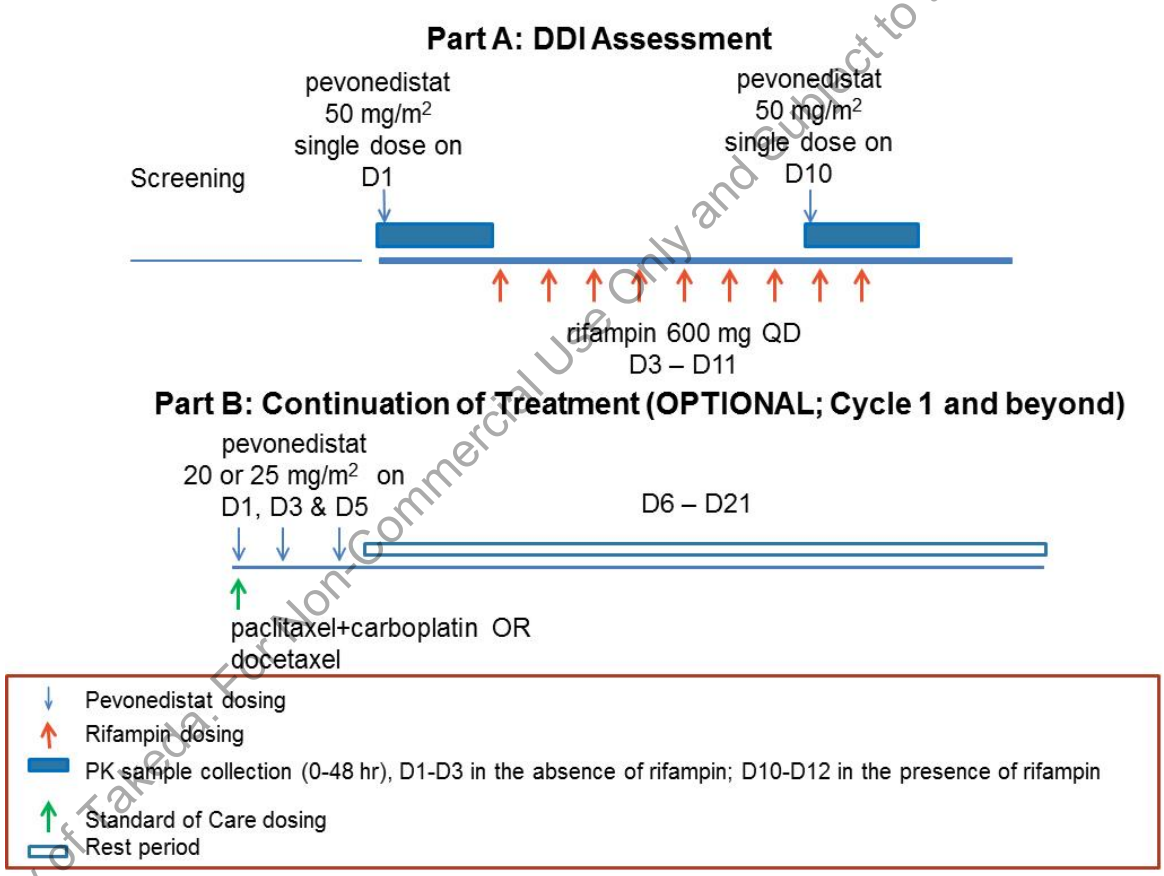
All doses of rifampin will be administered on an empty stomach with patients taking nothing-by-mouth (NPO) except for water and prescribed medications for 2 hours before and at least 1 hour after each rifampin dose. Patients who miss any rifampin doses on Days 3 to 9 will not be considered evaluable; hence, 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.

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**

(Section 7.3) 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 [CT] scan or magnetic resonance imaging [MRI]).

The Schedule of Events (SOEs) for Part A and Part B are provided in Appendix A. Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03, effective date 14 June 2010 [2]. AEs will be assessed, and laboratory values and vital signs will be obtained to evaluate the safety and tolerability of pevonedistat. See Figure 6.a for an overview of the study design of Parts A and B.

Figure 6.a Study Overview



D=day.

6.2 Number of Patients

Approximately 20 patients (for approximately 12 PK-evaluable patients) will be enrolled. A patient is considered to be enrolled when the first dose of any study drug has been administered. In Part A, patients who are withdrawn from treatment before completing protocol required procedures, or are not considered evaluable for Part A will be replaced. Four to 6 study centers in the US will are planned to participate in the study.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

6.3.1.1 Part A: PK Assessment

It is anticipated that an individual patient will participate in this study for approximately 12 days in Part A, with an EOS visit 30 (+10) days after receiving their last dose of study drug to permit the detection of any delayed treatment-related AEs. If patients continue to the optional part of the study, Part B, they will forgo the EOS visit after Part A and be evaluated per the Part B continuation criteria (see Section 7.3). At least 1 week washout will take place before the start of Part B.

6.3.1.2 Part B (Optional): Continued Treatment With Pevonedistat in Combination With SOC

Eligible patients will have the option to continue to receive treatment in Part B of this study until discontinuation criteria are met (see Section 9.6). If a patient chooses to continue to Part B, that patient may enter Part B after meeting the entry criteria and within approximately 1 week of completing Part A; however, patients entering Part B must begin treatment within 1 to 2 weeks of completing Part A. The maximum duration of treatment will be 12 cycles; however, if it is determined, after discussion between the investigator and the sponsor, that a patient would derive clinical benefit from continued treatment, the patient may remain on the current combination therapy or receive pevonedistat as a single agent beyond 12 cycles.

After completion of at least 6 cycles of treatment, patients will be permitted to take treatment breaks, at the investigator's discretion, that are no longer than 2 weeks in duration (up to 4 weeks after consulting with the sponsor); treatment breaks may not be taken consecutively. The investigator will confirm patient eligibility for continued treatment (Section 7.3) upon return from a treatment break, before resuming treatment.

Patients who have achieved clinical benefit from combination therapy (chemotherapy+pevonedistat) and who have developed intolerance that is reasonably attributable to the chemotherapy after 2 or more cycles may continue on single-agent pevonedistat at the same dose and schedule, upon request by the investigator and agreement by the sponsor.

Patients will attend an EOS visit 30 (+10) days (safety follow-up) after the last dose of study drug or before the start of subsequent therapy for their indication, if that occurs sooner.

6.3.2 EOS/Study Completion Definition and Planned Reporting

The analyses for the clinical study report may be conducted after all patients enrolled in the study have completed Part A, to meet the primary (PK assessment) objective of the protocol, or have discontinued treatment. Patients still on therapy at this point will continue in the study through their EOS visit. The estimated time frame for study completion is approximately 18 months for Parts A and B combined.

6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures

Please refer to Table 6.a for disclosures information for primary and secondary endpoints for Part A and Table 6.b for Part B, respectively.

Table 6.a Primary and Secondary Endpoints for Disclosures: Part A

Endpoint	Definition	Maximum Time Frame (per Individual Patient)
Primary: Pevonedistat C_{max}, AUC_{last}, and AUC_{∞} geometric mean ratios in the presence of rifampin in reference to C_{max}, $AUC_{0\text{-}last}$, and AUC_{∞} in the absence of rifampin (Section 5.2.1)	DDI assessment, ratios of geometric mean, 90% CIs.	Up to 12 days.
Secondary: PK parameters: CL, V_{ss} 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) (Section 5.2.2).	DDI assessment, descriptive statistics of PK parameters.	Up to 12 days.

Table 6.b Primary and Secondary Endpoints for Disclosures: Part B

Endpoint	Definition	Maximum Time Frame
Primary: not applicable	Not applicable	Not applicable
Secondary: 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 (Section 5.2.2)	Disease response to pevonedistat in combination with SOC, based on the best overall response as determined by the investigator using RECIST Version 1.1 guidelines.	Up to 12 months, depending on patient response.(a)

(a) The maximum duration of treatment will be 12 cycles; however, if it is determined, after discussion between the investigator and the sponsor, that a patient would derive benefit from continued treatment, the patient may remain on the current combination therapy or receive pevonedistat as a single agent beyond 12 cycles.

6.3.4 Total Study Duration

It is anticipated that this study will last for approximately 18 months for Part A and Part B combined. The maximum duration of treatment in Part B will be 12 cycles; however, if it is determined, after discussion between the investigator and the sponsor, that a patient would derive

benefit from continued treatment, the patient may remain on the current combination therapy or receive pevonedistat as a single agent beyond 12 cycles.

Patients who have achieved objective clinical benefit from combination therapy (chemotherapy+pevonedistat) and who have developed intolerance that is reasonably attributable to the chemotherapy after 2 or more cycles may continue on single-agent pevonedistat at the same dose and schedule, upon request by the investigator and agreement by the sponsor.

6.3.5 Post Trial Access

Currently, there is no post trial access (PTA) protocol available in the pevonedistat development program. If during conduct of the Pevonedistat-1015 study, an open-label, rollover PTA study should become an option and the investigator and the sponsor agree that a patient would derive benefit from continued treatment in Part B or would be harmed without continued access to the medication, the patient may be given the opportunity to enroll. Patients who participate in a rollover study will be considered to have completed Study Pevonedistat-1015. The patient would then be able to continue receiving his/her current study treatment (combination or single-agent pevonedistat).

6.3.6 Duration of PTA

In the event of a rollover PTA study, continued access to pevonedistat for participants will be terminated for those individuals who no longer benefit from treatment (eg, they have completed the recommended course of therapy or their disease has improved or resolved), the benefit-risk no longer favors the individual, or an appropriate alternative therapy becomes available. PTA may be terminated in a country or geographical region where the development of pevonedistat has been suspended or stopped by the sponsor, or pevonedistat can no longer be supplied.

7.0 STUDY POPULATION

The patient population for this study will be 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. Confirmation of eligibility must be obtained before the patient can enter the study. After completion of Part A, patients who elect to continue into the optional Part B must meet the criteria for continuation listed in Section 7.3.

7.1 Inclusion Criteria

Each patient must meet all the following inclusion criteria to be enrolled in the study:

1. Male or female patients 18 years or older.
2. 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.
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 (Appendix D).
4. Expected survival of at least 3 months from the date of enrollment in the study.
5. Recovered (ie, ≤Grade 1 toxicity) from the effects of prior antineoplastic therapy.
6. Clinical laboratory values as specified below:
   - Hemoglobin ≥9 g/dL. Patients may be transfused to achieve this value.
   - Total bilirubin ≤ upper limit of normal (ULN).
   - Alanine aminotransferase (ALT), AST, and ALP ≤2.5×ULN.
     - For patients to be treated with pevonedistat+docetaxel in Part B, AST and ALT must be ≤1.5×ULN, and total bilirubin should be within the normal range.
   - Calculated CrCl ≥50 mL/min (CrCl is defined in Section 9.4.13).
   - Absolute neutrophil count (ANC) ≥1,500/mm^3.
   - Platelet count ≥100,000/mm^3.
   - Prothrombin time and aPTT ≤1.5×ULN.
   - Albumin ≥2.7 g/dL.
7. Suitable venous access for the study-required blood sampling (including PK sampling).
8. Female patients who meet any of the following:
   - Are postmenopausal for at least 1 year before the screening visit (see Appendix F).

- Are surgically sterile.
- If they are of childbearing potential, they and their male partners agree to practice 1 highly effective method of contraception (see Appendix G) and 1 additional effective (barrier) method at the same time, from the time of signing the informed consent through 4 months after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

9. Male patients, even if surgically sterilized (ie, status postvasectomy), who meet either of the following:
   - Agree to practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug, or
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
10. Patients who are willing to refrain from donating blood for at least 90 days after their last dose of pevonedistat and (for male patients) willing to refrain from donating semen for at least 4 months after their last dose of pevonedistat.
11. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

7.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Inability to comply with study visits and procedures including required inpatient confinement.
2. Treatment with any systemic antineoplastic therapy or any investigational products within 21 days before the first dose of study treatment.
3. Major surgery within 14 days before the first dose of study treatment or scheduled surgery during Part A of the study.
4. Prior treatment with radiation therapy involving ≥25% of the hematopoietically active bone marrow.
5. Use of strong CYP3A inducers within 2 weeks before the first dose of study drug. (The non-exhaustive list of clinically significant strong CYP3A inducers is provided in Appendix K.

6. Known hypersensitivity or history of severe intolerance or toxicity to chemotherapeutic agents including known history of severe hypersensitivity reactions to docetaxel (polysorbate 80-based formulations) for patients to be treated with pevonedistat+docetaxel; history of hypersensitivity to carboplatin for patients to be treated with pevonedistat+ carboplatin+paclitaxel; or history of severe hypersensitivity to paclitaxel (Cremophor-based formulations) for patients to be treated with pevonedistat+carboplatin+ paclitaxel.
7. Life-threatening illness or serious (acute or chronic) medical or psychiatric illness unrelated to cancer that may increase the risk associated with trial participation or investigational product administration or may interfere with the interpretation of trial results or, in the investigator's opinion, could potentially interfere with the completion of treatment according to this protocol.
8. Active, uncontrolled infection or severe infectious disease, such as severe pneumonia, meningitis, septicemia, or methicillin-resistant Staphylococcus aureus infection within 2 weeks before dosing.
9. Known human immunodeficiency virus seropositive or known hepatitis B surface antigen seropositive or known or suspected active hepatitis C infection. Note: patients who have isolated positive hepatitis B core antibody (ie, in the setting of negative hepatitis B surface antigen and negative hepatitis B surface antibody) must have an undetectable hepatitis B viral load.
10. Persistent diarrhea (≥Grade 2) lasting >3 days within 2 weeks before the first dose of study treatment.
11. Known hepatic cirrhosis or severe pre-existing hepatic impairment.
12. Uncontrolled high BP (ie, systolic BP >180 mm Hg, diastolic BP >95 mm Hg).
13. Left ventricular ejection fraction (LVEF) <50% within 6 months prior to study enrollment. If a result within this time frame is unavailable, LVEF must be determined by echocardiography at screening.
14. Patients with ischemic heart disease who have had acute coronary syndrome, myocardial infarction, or revascularization (eg, coronary artery bypass graft, stent) in the past 6 months are excluded. However, patients with ischemic heart disease who have had acute coronary syndrome, myocardial infarction, or revascularization greater than 6 months before screening and who are without cardiac symptoms may enroll. Patients with congestive heart failure (New York Heart Association Class III or IV) or New York Heart Association Class II with recent decompensation requiring hospitalization within 4 weeks before screening and patients with severe pulmonary arterial hypertension (see Appendix J) are excluded.
15. Arrhythmia (eg, history of polymorphic ventricular fibrillation or torsade de pointes, permanent atrial fibrillation defined as continuous atrial fibrillation for ≥6 months, and persistent atrial fibrillation, defined as sustained atrial fibrillation lasting 7 days and/or requiring cardioversion in the last 4 weeks before screening). However, patients with <Grade 3 atrial fibrillation for a period of at least 6 months may enroll. Grade 3 atrial fibrillation is

defined as symptomatic and incompletely controlled medically, or controlled with device (eg, pacemaker) or ablation, and is excluded. Patients with paroxysmal atrial fibrillation are permitted to enroll.

16. Prolonged rate corrected QT interval (QTc) ≥500 msec, calculated according to institutional guidelines.
17. Implantable cardioverter defibrillator.
18. Patients with a cardiac pace maker whose heart rate is set at a fixed rate and patients on concomitant medication that may limit increase in heart rate in response to hypotension (eg, high-dose beta blocker).
19. Moderate to severe aortic stenosis, moderate to severe mitral stenosis, or other valvulopathy (ongoing).
20. Known moderate to severe chronic obstructive pulmonary disease, interstitial lung disease, pulmonary fibrosis, or pulmonary arterial hypotension.
21. Female patients who are lactating and breastfeeding or who have a positive serum pregnancy test during the screening period or a positive urine pregnancy test on Day 1 before the first dose of study drug.
22. Female patients who intend to donate eggs (ova) during the course of this study or 4 months after receiving their last dose of study drug.
23. Male patients who intend to donate sperm during the course of this study or 4 months after receiving their last dose of study drug.
24. Patient requiring chronic treatment with BCRP inhibitors. Refer to Table 8.b for the list of known BCRP inhibitors.

7.3 Criteria for Continuation into Optional Part B

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 following criteria may continue into Part B:

1. ECOG performance status of 0 to 1.
2. ANC ≥1500/mm^3.
3. Platelet count ≥100,000/mm^3.
4. Laboratory values for hemoglobin, total bilirubin, ALT, AST, ALP, and serum creatinine or calculated/measured CrCl, as specified in Inclusion Criterion #6.
5. Diarrhea symptoms resolved to Grade 1 or better.
6. QTc interval <500 msec.

7. CT scan or MRI of the chest, abdomen, and pelvis within 28 days of Cycle 1 Day 1.

Radiological evaluations (CT scan or MRI) of the chest, abdomen, and pelvis are required as entry criteria for Part B to assess the status of the patient's underlying disease. If the patient has had appropriate imaging scans performed within 28 days before Cycle 1 Day 1 of Part B, the results of those scans may be used. During the study, CT scans or MRIs encompassing the known sites of disease will be performed at the end of Cycle 2 and every 3 cycles thereafter. An EOS/early termination CT scan does not need to be completed/repeated if a scan was performed within the previous 28 days.

For patients to begin dosing in optional Part B, their predose Cycle 1 Day 1 assessments in Part B must return to the baseline values of Part A or Grade ≤1 or to a level considered acceptable by the investigator, after discussion with the project clinician or designee, and must meet all the continuation criteria specified in this section (Section 7.3).

8.0 STUDY DRUG

8.1 Study Drug Administration

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

8.1.1 Part A: Pevonedistat and Rifampin Administration

8.1.1.1 Pevonedistat Administration

Patients will receive a single dose of 50 mg/m^2 pevonedistat via an approximate 1-hour (60±5 minutes) 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. The start and end times of the IV infusion should be recorded accurately. 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. Patients will not be considered evaluable and need to be replaced if, in the assessment of the Takeda clinical pharmacologist, the infusion interruption compromises PK evaluability. All infusion times must be recorded. Refer to the Pharmacy Manual for the preparation of the IV infusion.

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 via a 1-hour IV infusion, and plasma samples will be collected at predetermined time points up to 48 hours (Day 12) following the second single dose of pevonedistat.

Both doses of pevonedistat (Days 1 and 10) will be administered in the clinic, followed by the required PK sampling. There will be no pevonedistat dosing on Days 11 and 12.

8.1.1.2 Rifampin Administration

The first dose of rifampin 600 mg 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. There will be no rifampin dosing on Day 12.

All doses of rifampin will be administered on an empty stomach with patients taking 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; hence, pevonedistat dosing and PK sampling on Day 10 will not be required. 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.

8.1.2 Part B (Optional): Pevonedistat in Combination With SOC Chemotherapy Agents

Patients will be re-evaluated per the entry criteria before treatment in Part B can begin. Patients opting to continue into Part B will receive combination therapy with pevonedistat and SOC chemotherapy. Two SOC chemotherapy regimens, docetaxel and carboplatin+paclitaxel, will be used in this study in combination with pevonedistat, as recommended by the investigator.

Study drug(s) will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

8.1.2.1 Pevonedistat Administration

Patients will receive pevonedistat diluted with 5% dextrose in a 250 mL bag via an approximate 1-hour (60±5 minutes) IV infusion. Pevonedistat should be administered through central or peripheral venous access. The infusion may be slowed or stopped and restarted for any associated infusion-related reactions. All infusion times must be recorded. The total time from drug dilution in 5% dextrose to the end of infusion must not exceed 6 hours.

The entire contents of the pevonedistat IV bag will be infused at a constant rate over approximately 60 minutes. The start and end times of IV infusion should be recorded accurately. To ensure that all the pevonedistat is administered, the infusion line will be flushed with saline or 5% dextrose immediately after administration. The volume used for line flushing is not considered part of the volume of the pevonedistat IV bag to be documented.

On Day 1 of a 21-day cycle, patients will receive either pevonedistat 25 mg/m^2 in combination with docetaxel or pevonedistat 20 mg/m^2 in combination with carboplatin+paclitaxel. A time-out of approximately 15 minutes is required between the end of infusion of the chemotherapy regimen and the start of infusion of pevonedistat. On Days 3 and 5, patients will receive pevonedistat alone.

8.1.2.2 Docetaxel Administration

On Day 1 of each cycle, when all study drugs are administered together, docetaxel 75 mg/m^2 will be administered first as a 1-hour IV infusion. After a mandatory approximately 15-minute time-out (pevonedistat-free period), pevonedistat will be administered IV. On Days 3 and 5, only pevonedistat will be given. The duration of each cycle will be 21 days. Refer to the applicable USPI for further details regarding docetaxel administration.

Premedication for Docetaxel-Associated Hypersensitivity or Other Acute Reactions Guidelines

Premedication to prevent docetaxel-associated (hypersensitivity or other) reactions is recommended according to institutional guidelines or local practices. For example, patients may be treated with dexamethasone (4 mg twice daily for 3 days), which should start 24 hours before docetaxel administration.

8.1.2.3 Carboplatin+Paclitaxel Administration

On Day 1 of each cycle, when all study drugs are administered together, paclitaxel will be given first as an IV infusion over approximately 3 hours, followed by carboplatin as an approximately 30-minute IV infusion. After a mandatory approximately 15-minute time-out (pevonedistat-free period), pevonedistat will be administered IV. On Days 3 and 5, only pevonedistat will be given. The duration of each cycle will be 21 days.

- Refer to the applicable USPI for further details regarding carboplatin administration.
- If a patient's glomerular filtration rate (GFR) is estimated using serum creatinine measurements by the standardized isotope dilution mass spectrometry method, the US Food and Drug Administration (FDA) recommends that physicians consider capping the dose of carboplatin for desired exposure (AUC) to avoid potential toxicity caused by overdosing. Using the Calvert formula described in the carboplatin label, the maximum doses can be calculated as follows:
- Total carboplatin dose (mg)=(target AUC)×(GFR+25) [Calvert formula]
- Maximum carboplatin dose (mg)=target AUC (mg×min/mL)×(150 mL/min)
- The maximum dose is based on a GFR estimate that is capped at 125 mL/min for patients with normal renal function. No higher estimated GFR values should be used.
- For a target AUC=5, the maximum dose is 5×150=750 mg.
- For a target AUC=4, the maximum dose is 4×150=600 mg.
- Refer to the applicable USPI for further details regarding paclitaxel administration.

  Premedication to prevent paclitaxel-associated (hypersensitivity or other) reactions is recommended according to institutional guidelines or local practices. For example, patients may be treated with either dexamethasone (10 mg) 24 hours before and on the day of paclitaxel dosing or methylprednisolone immediately before paclitaxel dosing.

8.2 Reference/Control Therapy

No reference or placebo treatment will be used in this study. All eligible patients will receive treatment with pevonedistat in Part A. Participation in Part B of the study is optional.

8.3 Dose Modification Guidelines (Part B)

8.3.1 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

For individual patients experiencing specific toxicities, treatment in each new cycle will be delayed until toxicity is reduced to Grade ≤1, patient's baseline, or to a level considered acceptable by the investigator after discussion with the project clinician or designee.

Patients will receive pevonedistat in combination with chemotherapy on a dose regimen that has been established from Study C15010. If dosing with pevonedistat is held for toxicity during any given cycle, dosing may resume within that same cycle when toxicity is resolved (ALT/AST to Grade ≤1 or bilirubin within normal range). Alternatively, dosing may be held until the next cycle. The start of the next cycle may also be delayed for up to 3 weeks to allow patients to recover from any safety concerns, so that pevonedistat may be administered in combination with chemotherapy.

In Part B only, Day 1 dosing may be delayed by up to 2 days (of any cycle) to accommodate inclement weather, holidays, vacations, or other administrative reasons.

8.3.2 Criteria for Dose Interruption During a Cycle

- In Part B, the infusion may be slowed or stopped and restarted for any associated infusion-related reactions; however, this should be avoided in Part A. The exact date and time of each additional sample collection and the actual start and stop times of the infusion should be recorded accurately.

8.3.3 Criteria for Dose Reduction

When a dose modification is warranted for safety, consider dose reductions for chemotherapy first, if appropriate. Dose modification of pevonedistat (by 1 dose level=5 mg/m^2) may also be considered for events judged by the investigator to be directly related to pevonedistat or for chemotherapy related toxicities that may have been exacerbated by pevonedistat in the combination setting.

Alopecia of any duration will not lead to dose modification or treatment delay.

Patients receiving pevonedistat+docetaxel may have a maximum of 2 docetaxel dose modifications. Docetaxel is initially dosed at 75mg/m^2, dose reductions up to 60 mg /m^2 and 45 mg/m^2 may be considered (if applicable) or modification of pevonedistat (see above).

Patients receiving pevonedistat+carboplatin+paclitaxel may have no more than 1 dose modification (if applicable) of chemotherapy agents, as outlined below, or modification of pevonedistat (see above). Paclitaxel is initially dosed at 175 mg/m^2. One dose reduction to 135 mg/m^2 may be considered. Carboplatin is initially dosed at AUC5. One dose reduction to AUC4 may be considered.

The decision to treat at a reduced dose level of chemotherapy is at the discretion of the investigator. Discussions with the project clinician or designee are encouraged.

Table 8.a outlines the dose modification guidelines for specific toxicities. Treatment cannot be withheld for longer than 3 weeks for any toxicity Grade >1, as indicated in Section 8.3.4.

Table 8.a Dose Modification Guidelines for Specific Toxicities

Pathologic Condition	Severity	Action on Study Drug
Hematologic: ANC	Febrile neutropenia	Hold dosing on Day 1 of Cycles ≥2 up to 3 weeks (see Section 8.3.4) until febrile neutropenia is resolved, then resume dosing as appropriate. Consider use of growth factor or reduce chemotherapy by 1 dose level, as appropriate.
	ANC <1500 cells/µL on Day 1 of Cycles ≥2	Initiation (Day 1) of Cycles ≥2 should be delayed for up to 3 weeks (see Section 8.3.4) until ANC is ≥1500 cells/µL. Consider use of growth factor or reduce chemotherapy by 1 dose level as appropriate.
	Grade ≥3 neutropenia lasting >7 days	Initiation (Day 1) of Cycles ≥2 should be delayed until ANC is ≥1500 cells/µL. Consider use of growth factor or reduce chemotherapy by 1 dose level as appropriate.
Hematologic: Platelets	Platelet count <100,000/µL on any dosing day of Cycles ≥2	Dosing in Cycles ≥2 should be delayed for up to 3 weeks (see Section 8.3.4) until platelet count is ≥100,000 cells/µL. Dose of chemotherapy may be reduced by 1 dose level as appropriate.
	Grade 4 thrombocytopenia lasting >7 days or platelet count <25,000 cells/µL at any time	Dosing in Cycles ≥2 should be delayed until platelet count is ≥100,000 cells/µL (see Section 8.3.4). Dose of chemotherapy may be reduced by 1 dose level as appropriate.
Hematologic: Anemia	Grade ≥1	No dose modification is allowed for anemia. Transfusion and/or erythropoietin may be given, as clinically indicated, for the treatment of anemia (see Section 8.7.3).
Nausea, emesis, or diarrhea despite maximal prophylaxis	Grade ≥3	On days when both chemotherapy and pevonedistat are administered, hold dosing for up to 3 weeks (see Section 8.3.4) or until the toxicity returns to Grade ≤1, then restart at the next lower dose of chemotherapy. On days when pevonedistat is given as a single agent, hold pevonedistat dosing for up to 3 weeks (see Section 8.3.4) or until the toxicity returns to Grade ≤1 before dosing is resumed. **Note**: Ensure that optimal prophylaxis has been employed before dose reduction. Supportive care with moderate or strong CYP3A inhibitors/inducers should be avoided.
Neurotoxicity (paclitaxel or docetaxel only)	Grade ≥2	Hold treatment until patient recovers to Grade 1 toxicity, then resume treatment at the next lower dose level (see Section Section 8.3.4). This will be a permanent dose reduction. Carboplatin or pevonedistat dose is not to be modified.
Allergic reaction (paclitaxel or docetaxel only	Moderate symptoms	Stop infusion. Give IV diphenhydramine 25 to 50 mg, IV dexamethasone 10 mg, and/or treatment per institutional guidelines. After recovery of symptoms, resume infusion at a low infusion rate. If no further symptoms occur, resume full dose rate until infusion is complete. If symptoms recur, stop infusion and discontinue patient.

8.3.4 Criteria for Discontinuation of Study Drug

Patients receiving pevonedistat+docetaxel may have a maximum of 2 dose modifications (if applicable) or modification of pevonedistat (see Section 8.3.3). Patients who require more than 2 dose modifications will be discontinued from the study.

Patients receiving pevonedistat+carboplatin+paclitaxel may have no more than 1 dose modification (if applicable) of chemotherapy agents or modification of pevonedistat (see Section 8.3). Patients who require additional dose modifications will be discontinued from the study.

Patients with unresolved toxicities Grade >1 lasting 3 weeks or longer from the date of the next scheduled treatment will be discontinued from the study.

For further details on discontinuation criteria for specific toxicities, see Section 8.7.

8.4 Excluded Concomitant Medications and Procedures

8.4.1 Part A

Table 8.b lists the medications and procedures that are prohibited during Part A of the study.

Table 8.b Excluded Concomitant Medications and Procedures During Part A

Drug Class/Therapy	Comment
Acetaminophen and acetaminophen-containing products	May be used judiciously and should not exceed a dose of 2 g in 24 hours
Any investigational agent other than pevonedistat	Excluded during the study
Known BCRP inhibitors	Examples: cyclosporine and eltrombopag
Strong CYP3A4 inducers	See Appendix K.

8.4.2 Part B

Table 8.c lists the medications and procedures that are prohibited in Part B.

Table 8.c Excluded Concomitant Medications and Procedures During Part B

Drug Class/Therapy	Comment
Acetaminophen and acetaminophen-containing products	May be used judiciously and should not exceed a dose of 2 g in 24 hours
Any investigational agent other than pevonedistat	Excluded during the study
Known BCRP inhibitors (eg, cyclosporine and eltrombopag)	Generally excluded during the study but may be used as specified in Table 8.e
Systemic antineoplastic therapy, unless specified in the protocol as part of the combination with pevonedistat	
Strong CYP3A4 inducers	See Appendix K.

This list is not all-inclusive; consult the docetaxel, carboplatin, and paclitaxel applicable USPIs for additional information regarding precautions, warnings, and contraindications.

8.5 Permitted Concomitant Medications and Procedures

8.5.1 Part A

Medications and procedures that are specifically permitted during Part A are listed in Table 8.d. Other supportive care medications are also permitted, unless specifically excluded in Section 8.4.1.

Table 8.d Permitted Concomitant Medications and Procedures During Part A

Therapy	Comment/Exceptions
Nephrotoxic medications, including nonsteroidal anti-inflammatory drugs	Caution should be used with nephrotoxic concomitant medications (see Appendix E). Alternative concomitant nonnephrotoxic medications should be used whenever possible.
Antiemetic agents	Antiemetic agents may be administered at the discretion of the investigator, but prophylactic antiemetic agents should not be administered if nausea or vomiting is not observed.
RBC transfusion	For all patients with anemia, and especially for patients with hemoglobin values <9 g/dL during the conduct of the study, consideration should be given for RBC transfusions based on the patient's risk of inadequate oxygenation, underlying cardiopulmonary status, clinical judgment, and hospital guidelines. RBC transfusions must be administered at least 1 day before administration of study drug. Each transfusion episode, including the type of transfusion (RBC), should be recorded.

8.5.2 Part B

Medications and procedures that are specifically permitted during Part B are listed in Table 8.e. Other supportive care medications are also permitted, unless specifically excluded in Section 8.4.2.

Table 8.e Permitted Concomitant Medications and Procedures During Part B

Therapy	Comment/Exceptions
Antiemetic agents	Antiemetic agents, including for prophylactic use, may be administered at the discretion of the investigator.
Known BCRP inhibitors (eg, cyclosporine and eltrombopag)	Limited use is permitted only if clinically necessary and no suitable alternative exists. The patient may receive a BCRP inhibitor from 24 hours after the last pevonedistat dose to 72 hours before the next pevonedistat dose. For example, if a patient receives pevonedistat on a Monday (Day 1), Wednesday (Day 3), and Friday (Day 5) schedule, then a BCRP inhibitor may be administered (if clinically necessary and no suitable alternative exists) from the Saturday after the Day 5 dose (Day 6) up to the Friday (Day 19) before the Monday dose of the next cycle.
Nephrotoxic medications, including nonsteroidal anti-inflammatory drugs	Caution should be used with nephrotoxic concomitant medications (see Appendix E). Alternative concomitant nonnephrotoxic medications should be used whenever possible.
RBC transfusion	For all patients with anemia, and especially for patients with hemoglobin values <9 g/dL during the conduct of the study, consideration should be given for RBC transfusions based on the patient's risk of inadequate oxygenation, underlying cardiopulmonary status, clinical judgment, and hospital guidelines. RBC transfusions must be administered at least 1 day before administration of study drug. Each transfusion episode, including the type of transfusion (RBC), should be recorded.

8.6 Precautions and Restrictions

Concomitant medications and procedures that are excluded or must be used with caution are described in Sections 8.4.1and 8.4.2 and Sections 8.5.1 and 8.5.2, respectively.

Certain situations may warrant further caution, such as modifying the dose of study drug(s). Dose modification guidelines are provided in Section 8.3.

8.6.1 Pevonedistat

It is not known what effects pevonedistat has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age and male patients should use highly effective methods of contraception through defined periods during and after study treatment, as specified below.

Use only contraceptive methods that are locally approved in each country.

Female patients must meet any of the following:

- Postmenopausal for at least 1 year before the screening visit (see Appendix F).
- Surgically sterile.
- If they are of childbearing potential (as defined in Section 9.4.7), they and their male partners agree to practice 1 highly effective method and 1 additional effective (barrier)

method of contraception (see Appendix G) at the same time, from the time of signing the informed consent form (ICF) through 4 months after the last dose of study drug.

- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
- Agree to not donate eggs (ova) during the course of this study or 4 months after receiving their last dose of study drug.

Male patients, even if surgically sterilized (ie, status postvasectomy), must agree to any of the following:

- Practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug. (If barrier methods are not locally approved to be used by males, then their female partners should use effective contraceptive methods, as described in above.)
- Practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
- Donate sperm during the course of this study or 4 months after receiving their last dose of study drug.

8.6.2 Rifampin

8.6.2.1 Pregnancy

There are no adequate and well-controlled studies of rifampin in pregnant women. Refer to the applicable USPI for additional information regarding pregnancy.

8.6.2.2 Geriatric Use

In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic function and of concomitant disease or other drug. Refer to the applicable USPI for further details relating to use with geriatric patients.

8.6.3 Docetaxel

8.6.3.1 Pregnancy

Docetaxel is a pregnancy Category D drug. There are no adequate and well-controlled studies in pregnant women using docetaxel. If docetaxel is used during pregnancy, or if the patient becomes

pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Refer to the applicable docetaxel USPI for more information.

8.6.3.2 Geriatric Use

In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Refer to the applicable docetaxel USPI for information relating to use in the geriatric population with different types of cancer.

8.6.4 Carboplatin

8.6.4.1 Pregnancy

Carboplatin is a pregnancy Category D drug. Carboplatin injection may cause fetal harm when administered to a pregnant woman. Refer to the applicable carboplatin injection USPI for more information.

8.6.4.2 Geriatric Use

Because renal function is often decreased in the elderly, renal function should be considered in the selection of carboplatin dosage. Refer to the applicable carboplatin USPI for additional information on geriatric use.

8.6.5 Paclitaxel

8.6.5.1 Pregnancy

Paclitaxel is a pregnancy Category D drug. Paclitaxel injection can cause fetal harm when administered to a pregnant woman. Refer to the applicable paclitaxel injection USPI for more information.

8.6.5.2 Geriatric Use

Refer to the applicable paclitaxel USPI for information regarding use in the geriatric population.

8.7 Management of Clinical Events

The most common adverse drug reactions for docetaxel and for paclitaxel+carboplatin are described in Section 4.1.4. Refer to the applicable USPIs for additional details regarding the management of clinical events attributed to these agents.

Patients who experience an AE with pevonedistat should be followed closely for a recurrence of similar or other AEs upon subsequent dosing of pevonedistat.

8.7.1 Guidance for Clinical Assessment and Management of Hemodynamic Compromise (Part A and Part B)

It is essential that the patient is carefully evaluated at screening and before each pevonedistat dose for early symptoms and signs of hemodynamic compromise and/or active infection. Particular attention should be paid to unexplained fever, tachycardia, hypotension, orthostasis, tachypnea, recent nausea and vomiting, and clinical evidence of dehydration.

For those patients for whom there is a concern of dehydration, the following guidance for rehydration before pevonedistat dosing may be considered: 500 mL/hour of 0.5 N saline given over 2 to 4 hours for a total of 1 to 2 L of fluid as clinically appropriate; each infusion of IV fluids should be recorded in the electronic case report forms (eCRFs).

For all patients with anemia, and especially for patients with hemoglobin values <9 g/dL at screening or during the conduct of the study, RBC transfusions should be considered before pevonedistat dosing on the basis of the patient's risk of inadequate oxygenation, underlying cardiopulmonary status, clinical judgment, and/or hospital guidelines; each RBC transfusion should be recorded in the eCRFs.

Patients who experience signs and symptoms of hemodynamic compromise after pevonedistat dosing (eg, tachycardia, hypotension, orthostasis, changes in mental status, syncope, and dizziness) should be followed closely and managed with supportive care, including hospitalization as clinically indicated.

Patients who experience an untoward reaction with pevonedistat should be followed closely on subsequent dosing.

8.7.2 Guidance for Use of Granulocyte-Colony Stimulating Factor

Use of growth factors such as granulocyte-colony stimulating factor are permitted at the investigator's discretion.

8.7.3 Guidance for Clinical Assessment and Management of Anemia

Transfusion and/or erythropoietin may be given as clinically indicated for the treatment of anemia. These should be recorded in the eCRFs.

For all patients with anemia, and especially for patients with hemoglobin values <9 g/dL at screening or during the conduct of the study, RBC transfusions should be considered before pevonedistat dosing on the basis of the patient's risk of inadequate oxygenation, underlying cardiopulmonary status, clinical judgment, and/or hospital guidelines; each RBC transfusion should be recorded in the eCRFs.

Use of erythropoietin may be considered at the investigator's discretion and according to institutional guidelines.

8.7.4 Guidance for Management of Extravasation

Based on nonclinical findings as detailed in the IB, pevonedistat is considered a nonvesicant drug. Although no published guidelines are available for extravasation of nonvesicants, the investigator is encouraged to follow institutional guidelines. Some general advice in case of extravasation includes immediately stopping drug infusion and elevating the affected limb to minimize swelling.

8.8 Blinding and Unblinding

This is an open-label study.

8.9 Description of Investigational Agents

8.9.1 Pevonedistat

Pevonedistat Concentrate for Solution for Infusion formulation consists of 10 mg/mL (as free base) of pevonedistat HCl in an aqueous solution containing citric acid (anhydrous), trisodium citrate dihydrate, and betadex sulfobutyl ether sodium (Captisol) at pH 3.3. Each United States Pharmacopeia (USP) Type I glass vial contains 5 mL compounded sterile solution, sealed with a fluoropolymer-coated butyl rubber stopper, and oversealed with an aluminum seal and a plastic cap. Pevonedistat Concentrate for Solution for Infusion needs to be diluted in 5% dextrose for administration.

8.9.2 Rifampin

Rifampin is a semisynthetic antibiotic derivative of rifamycin SV. Rifampin capsules for oral administration contain 300 mg of rifampin per capsule.

For precautions, warnings, contraindications, and AEs associated with rifampin therapy, refer to the applicable rifampin USPI. For this study, all doses of rifampin should be administered on an empty stomach, with patients remaining NPO except water from 2 hours before until at least 1 hour after rifampin dosing. Additionally, antacids should not be administered from 2 hours before rifampin dosing until at least 2 hours after dosing.

8.9.3 Docetaxel

Docetaxel is obtained from commercial sources according to local practice standards and is provided as a commercially available dose formulation. Additional details are provided in the applicable USPI for docetaxel.

8.9.4 Carboplatin

Carboplatin is obtained from commercial sources according to local practice standards and is provided as a commercially available dose formulation. Additional details are provided in the applicable USPI for carboplatin.

8.9.5 Paclitaxel

Paclitaxel is obtained from commercial sources according to local practice standards, and it is provided as a commercially available dose formulation. Additional details are provided in the applicable USPI for paclitaxel.

8.10 Preparation, Reconstitution, and Dispensation

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration, whenever solution and container permit.

Docetaxel, paclitaxel, and carboplatin are anticancer drugs, and as with other potentially toxic compounds, caution should be exercised when handling pevonedistat and these chemotherapy agents.

8.10.1 Pevonedistat

For a detailed preparation of the infusion, refer to the Pharmacy Manual. The bag, needle, and syringe must be disposed of in a proper biohazard container.

8.10.2 Docetaxel, Carboplatin, Paclitaxel and Rifampin

For instructions and precautions regarding preparation, refer to the applicable USPIs for docetaxel, paclitaxel, carboplatin, and rifampin.

8.11 Packaging and Labeling

8.11.1 Pevonedistat

The drug product is labeled Pevonedistat (TAK-924/MLN4924) Concentrate for Solution for Infusion.

Pevonedistat Concentrate for Solution for Infusion will be provided in USP Type I glass vials. Each Pevonedistat Concentrate for Solution for Infusion vial contains 50 mg Pevonedistat, as free base.

Pevonedistat Concentrate for Solution for Infusion will be supplied by the sponsor as detailed in the Study/Pharmacy Manual.

8.11.2 Docetaxel, Carboplatin, and Paclitaxel

Docetaxel, paclitaxel, carboplatin may be sourced locally by the clinical site when arrangements have been made and agreed to by Takeda and when regulations allow for clinical site sourcing, appropriate labeling, and compliance with local and regional regulations. As required by local regulations, any modifications to the plan for drug supply.

8.11.3 Rifampin

Rifampin will be provided by the sponsor as oral capsules. As required by local regulations, any modifications to the plan for drug supply or storage will be communicated to the investigator and detailed in the pharmacy manual.

8.12 Storage, Handling, and Accountability

8.12.1 Pevonedistat

Pevonedistat injection is an investigational anticancer drug. As with other potentially toxic compounds, caution should be exercised when handling pevonedistat. Refer to institutional guidelines regarding the proper handling and disposal of toxic agents.

Pevonedistat Concentrate vials should be stored at 2°C to 8°C. The vials are suitable for use up to 6 hours after removal from the storage condition of 2°C to 8°C. If the drug product vial is not to be used within the 6-hour time frame, the vial should be returned to storage. Each vial is for single use only.

Once Pevonedistat Concentrate is diluted in 5% dextrose, the prepared pevonedistat IV bag must be used within 6 hours if stored at ambient temperature or else must be discarded. Alternatively, the prepared pevonedistat IV bag may be stored for up to 18 hours at 2°C to 8°C, after which the prepared IV bag can be used within 3 hours upon removal from 2°C to 8°C storage or must be discarded.

The vial must not be shaken at any time during dose preparation.

Discard bags, needles, and syringes in a proper biohazard container according to institutional guidelines.

Detailed reconstitution and dosage preparation instructions are provided in the Directions for Use located in the Pharmacy Manual.

8.12.2 Docetaxel, Carboplatin, Paclitaxel and Rifampin

For instructions and precautions regarding preparation, refer to the applicable USPIs for docetaxel, paclitaxel, carboplatin, and rifampin.

8.13 Other Protocol-Specified Materials

Refer to the Pharmacy Manual for any other protocol-specified materials to be used in the study.

9.0 STUDY CONDUCT

This trial will be conducted in compliance with the protocol, GCP, applicable regulatory requirements, and ICH guidelines.

9.1 Study Personnel and Organizations

The contact information for the project clinician for this study, the central laboratory and any additional clinical laboratories, the coordinating investigator for each member state/country, the interactive voice response system/interactive web response system provider, and the contract research organization (CRO) team may be found in the Study Manual. A full list of investigators is available in the sponsor's investigator database. For 24-hour contact information, refer to the Project Management Plan.

9.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the institutional review board (IRB)/independent ethics committee (IEC). Any other arrangements will be described in the Study Manual.

9.3 Treatment Group Assignments

All patients will receive the same study treatment in Part A.

In optional Part B, patients will be assigned, as recommended by the investigator, to pevonedistat 25 mg/m^2 in combination with docetaxel 75 mg/m^2 or pevonedistat 20 mg/m^2 in combination with carboplatin AUC5+paclitaxel 175 mg/m^2.

9.4 Study Procedures

Refer to the SOE (Appendix A) for timing of assessments. Additional details are provided as necessary in the sections that follow.

9.4.1 Informed Consent

Each patient must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

9.4.2 Patient Demographics

The date of birth, race, ethnicity, and sex of the patient are to be recorded during screening.

9.4.3 Medical History

During the screening period, a complete medical history, including prior therapy, will be compiled for each patient. The history will emphasize the background and progress of the patient's

malignancy and include a description of prior therapies for it. In addition, concomitant medications will be recorded as specified in Section 9.4.8.

9.4.4 Physical Examination

A complete physical examination or symptom-directed physical examination will be completed per SOC at the times specified in the SOE (Appendix A).

9.4.5 Patient Height

Height will be measured only during screening.

9.4.6 Vital Signs

Vital signs, including diastolic and systolic BP, heart rate, weight, and body temperature, will be collected as indicated in the SOE (Appendix A) and as clinically indicated.

When the timing of vital signs assessment coincides with the timing of a blood draw, vital signs will be completed before the collection of the blood sample, unless otherwise noted in the SOE (Appendix A).

9.4.7 Pregnancy Test

A serum pregnancy test will be performed for women of childbearing potential at screening. In Part A, a serum or urine pregnancy test will be performed on Day 1 predose, Day 10 predose, and at the EOS visit (Appendix A). In Part B, a serum or urine pregnancy test must also be performed for women of childbearing potential at every cycle (typically performed on Day 1 predose of each cycle; however, if a serum pregnancy test is used, this may be performed up to 3 days before Day 1), with negative results available before the first dose is administered in the respective cycle. A serum or urine pregnancy test will also be performed for women of childbearing potential at the EOS/Early Termination visit in Part B. Pregnancy tests may also be repeated during the study if requested by an IEC/IRB or if required by local regulations.

Women of childbearing potential are defined as any sexually active female subjects who meet the following criteria:

- Those who have not undergone hysterectomy or bilateral oophorectomy.
- Those who have not had natural menopause (Appendix F) for 12 consecutive months or longer (ie, follicle-stimulating hormone [FSH] ≥40 IU/L and no menopausal period for at least 12 consecutive months; loss of menopausal periods following chemotherapy may not rule out childbearing potential).

9.4.8 Concomitant Medications and Procedures

Concomitant medications, therapies, and procedures will be recorded in the eCRF from the time of the first dose of any study drug through 30 (+10) days after the last dose of study drug(s). See

Sections 8.4 and Section 8.5 for additional details regarding excluded and permitted concomitant medications and procedures.

9.4.9 AEs

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the SOEs (Appendix A). Refer to Section 10.1 for details regarding definitions, documentation, and reporting of pretreatment events (PTEs), AEs, and SAEs.

For Part B only, refer to Table 8.a for dose modifications related to AEs.

9.4.10 Enrollment

Enrollment is achieved when the first dose of any study drug has been administered. Procedures for completing the enrollment information are described in the Pharmacy and Study Manuals.

9.4.11 Electrocardiogram

A 12-lead electrocardiogram (ECG) will be administered at screening (Part A only), on Day 1 (predose), and at the EOS visit.

9.4.12 Echocardiogram

If no historical data for LVEF within 6 months prior to study enrollment are available, LVEF should be assessed by echocardiography at screening.

9.4.13 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally. Handling and shipment of clinical laboratory samples will be outlined in the Study Manual. Clinical laboratory evaluations will be performed as outlined below.

For Part B only, refer to Table 8.a for dose modifications related to abnormal laboratory evaluations.

Blood samples for analysis of the clinical chemistry and hematologic parameters shown in Table 9.a and urine samples for analysis of the parameters shown in Table 9.b will be obtained as specified in the SOE (Appendix A).

Table 9.a Clinical Chemistry and Hematology Tests

Hematology	**Serum Chemistry**	
Hemoglobin	ALT	Lactate dehydrogenase
Hematocrit	Albumin	Phosphate
Leukocytes (white blood cells) with differential	ALP	Potassium
Neutrophils (ANC)	AST	Sodium
Platelet (count)	Bilirubin (total)	Urate
	Blood urea nitrogen	Calcium
	Creatinine	Chloride
	Direct bilirubin	Carbon dioxide/bicarbonate
	Glucose	Magnesium
Part A Screening:		
aPTT		
Coagulation panel (a)		
Prothrombin time international normalized ratio		
D-dimer		
Fibrinogen		
Parts A and B:		
Coagulation panel, if applicable (a)		

(a) If the initial coagulation screen is positive (ie, results are outside the laboratory's normal range) in Part A, coagulation studies in Part B should include a full coagulation panel. If the initial coagulation screen is negative (ie, results are within the laboratory's normal range) in Part A, no further coagulation studies need to be done.

Table 9.b Clinical Urinalysis Tests

Urinalysis	
Leukocytes	pH
Nitrite	Protein
Occult blood	Specific gravity
Microscopic assessment	

If CrCl is to be estimated, the Cockroft-Gault formula will be employed as follows:

$$Estimated\ CrCL\ =\ [(140 - Age) * Mass(kg)\ ]\ /\ [72 * serum\ creatinine(mg/dL)]$$

For female patients, the result of the formula above should be multiplied by 0.85.

9.4.14 Disease Assessment

Computed tomography scans with IV contrast (unless medically contraindicated), or MRI, of the chest, abdomen, and pelvis will be performed as entry criteria for Part B.

CT scans with IV contrast encompassing the known sites of disease will also be performed at the end of Cycle 2 and as specified in the Schedules of Events thereafter. A scan should be taken at the EOS visit if a scan has not been completed within the past 28 days.

If CT scan does not provide adequate imaging, MRI may be used to evaluate sites of disease. If the patient has had appropriate imaging scans performed within 28 days of Cycle 1 Day 1, then the results of those scans may be used to satisfy the entry criteria for Part B. For each site of disease, the imaging modality (CT scan or MRI) used at entry for Part B must be used throughout the study. Tumor response will be assessed by the investigator at these times using the RECIST guideline (Version 1.1) [3].

9.4.15 Biomarker, Pharmacodynamic, and PK Samples

9.4.15.1 Primary Specimen Collection

Specimen Name is Schedule of Procedures	Primary Specimen	Description of Intended Use	Sample Collection
Plasma Sample for Pevonedistat PK	Plasma	PK measurements	Mandatory

9.4.16 PK Measurements

Details regarding the preparation, handling, and shipping of samples are provided in the Study and Laboratory Manuals.

As shown in the table in Appendix A, 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).

The exact date and time of each sample collection and the actual start and stop times of the infusion should be recorded accurately, with particular care given to the recording of blood sampling times that occur close to the infusion. 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.

There is no protocol-specified PK sampling for Part B.

The primary purpose of PK sampling in this study is to measure pevonedistat concentrations in plasma. However, these PK samples may also be used for the exploratory measurement of plasma

concentrations of metabolites of pevonedistat, if technically feasible and considered necessary for further understanding the metabolism of pevonedistat in patients with cancer.

To ensure that the measurements are representative of plasma exposure, blood draws will be conducted in the arm opposite to the patient's IV infusion. If only a single arm is available, blood should be drawn as distal to the site of the IV infusion as feasible, and the site of the blood draw should be documented.

9.4.17 Pharmacodynamic Measurements

Not applicable to this study.

9.4.18 DNA Measurements

Not applicable to this study.

9.4.19 Banked Tumor Specimen Measurements

Not applicable to this study.

9.4.20 Immunogenicity Sample Collection

Not applicable to this study.

9.5 Completion of Study Treatment (for Individual Patients)

9.5.1 Part A

Patients will be considered to have completed Part A of the study 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.

An EOS visit is needed in Part A only if the patient does not continue into Part B for any reason. The EOS visit will include physical examination (including ECOG performance status, vital signs, and weight); pregnancy test; laboratory assessments (hematology, chemistry, and urinalysis); 12-lead ECG; monitoring of concomitant mediations, therapies, and procedures; and recording of AEs/SAEs. The EOS visit will be conducted 30 (+10) days after the last dose of study drug in Part A. If the EOS visit occurs earlier than 30 days after the last dose of pevonedistat, the patient should be contacted via telephone on Day 30 to assess for any new or ongoing AEs or SAEs that may have occurred since the previous visit.

9.5.2 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 reasons outlined in Section 9.6. Patients who have completed Part A and participate in a rollover study (see Section 6.3.5) will be considered to have completed Study Pevonedistat-1015. If the patient continues into Part B, the EOS visit will occur 30 (+10) days after the last dose of study drug(s) in

Part B or before the start of subsequent therapy for the patient's indication, if that occurs sooner. If the EOS visit occurs earlier than 30 days after the last dose of pevonedistat, the patient should be contacted via telephone on Day 30 to assess for any new or ongoing AEs or SAEs that may have occurred since the previous visit. Patients in Part B may also be considered to have completed Study Pevonedistat-1015 if they a enter roll-over or PTA study (see Section 6.3.5).

9.6 Discontinuation of Treatment With Study Drug and Patient Replacement

Study drug may be permanently discontinued for patients meeting any of the following criteria:

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

Once study drug has been discontinued, all study procedures outlined for the EOS visit will be completed as specified in the SOE (Appendix A). The primary reason for study drug discontinuation will be recorded in the eCRF. In Part A of the study, patients who are not PK evaluable will be replaced.

Note: In optional Part B of the study, patients may receive pevonedistat until they experience PD or unacceptable pevonedistat-related toxicities or discontinue treatment for any reason.

Patients who have achieved objective clinical benefit from combination therapy (chemotherapy+pevonedistat) and who have developed intolerance that is reasonably attributable to the chemotherapy after 2 or more cycles may continue on single-agent pevonedistat at the same dose and schedule, upon request by the investigator and agreement with the sponsor.

9.7 Withdrawal of Patients From Study

A patient may be withdrawn from the study for any of the following reasons:

- Lost to follow-up.
- Study terminated by sponsor.
- Withdrawal by subject.
- Completed study.

- Death.
- Other.
- PD.
- Initiation of hematopoietic stem cell transplant.

The consequence of study withdrawal is that no new information will be collected from the withdrawn patient and added to the existing data or any database.

9.8 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

The clinical team and the clinical research associate will review treatment compliance during investigational visits and at the completion of the study. Tests and procedures should be performed on schedule, but unless otherwise specified, occasional changes are allowable within a 2-day window for holidays, vacations, and other administrative reasons. If the study schedule is shifted, both assessments and dosing must be shifted to ensure that collection of assessments is completed before dosing. This 2-day window is allowed for Part B but does not apply for Part A.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 PTE Definition

A PTE is any untoward medical occurrence in a patient or subject who has signed informed consent to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 AE Definition

AE means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

10.1.3 SAE Definition

SAE means any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of an existing hospitalization (see clarification in the paragraph in Section 10.2 on planned hospitalizations).
- Results in persistent or significant disability or incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.
- Is a medically important event. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home,

blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010 [2]. Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.2 Procedures for Recording and Reporting AEs and SAEs

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

Regardless of causality, SAEs and serious PTEs (as defined in Section 10.1) must be reported (see Section 10.3 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee within 24 hours of becoming aware of the event.

This will be done by transmitting an electronic data capture (EDC) SAE report. If transmission of an EDC SAE report is not feasible, then a facsimile of the completed Takeda paper-based SAE form will be sent. A sample of the paper-based SAE form and processing directions are in the Study Manual. Information in the SAE report or form must be consistent with the data provided on the eCRF.

If information not available at the time of the first report becomes available at a later date, the investigator will transmit a follow-up EDC SAE report (or a paper-based SAE form if an EDC SAE report is not feasible) or provide other documentation immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs and serious PTEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial *or* before study drug was given are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (eg, surgery was performed earlier or later than planned).

For both serious and nonserious AEs, the investigator must determine both the severity (toxicity grade) of the event and the relationship of the event to study drug administration. For serious PTEs, the investigator must determine both the severity (toxicity grade) of the event and the causality of the event in relation to study procedures.

Severity (toxicity grade) for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010 [2]. The criteria are provided in the Study Manual.

Relationship of the event to study drug administration (ie, its causality) will be determined by the investigator responding yes (related) or no (unrelated) to this question: "Is there a reasonable possibility that the AE is associated with the study drug?" If the event is considered "not related" to study drug administration, an alternate etiology must be provided.

10.3 Monitoring of AEs and Period of Observation

AEs, both nonserious and serious, will be monitored throughout the study.

- AEs will be reported from the start of study drug administration through 30 days (+10 days) days after administration of the last dose of study drug and recorded in the eCRFs.
- SAEs will be reported as follows:
- Serious PTEs will be reported to the Takeda Global Pharmacovigilance department or designee from the time of the signing of the ICF up to first dose of study drug, and will also be recorded in the eCRF.
- Related and unrelated treatment-emergent SAEs and serious PTEs will be reported to the Takeda Global Pharmacovigilance department or designee from the signing of the ICF in Part A through 30 days (+10 days) days after administration of the last dose of study drug and recorded in the eCRF. After this period, only related SAEs must be reported to the Takeda Global Pharmacovigilance department or designee. SAEs should be monitored until they are resolved or are clearly determined to be caused by a patient's stable or chronic condition or intercurrent illness(es).

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee (see Section 10.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee (see Section 10.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

10.5 Procedures for Reporting Product Complaints or Medication Errors (Including Overdose)

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately report this via the phone numbers or e-mail addresses provided below.

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. Whereas overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error (including overdose) situation should immediately report this via the phone numbers or e-mail addresses provided below.

Call center	Phone number	E-mail	Fax
CCI [redacted]			

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to CCI [redacted] (refer to Section 10.2)

10.6 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as an expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal product's administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

Sponsor Safety Assessment

Safety data will be reviewed and assessed periodically by a global pharmacovigilance team and a cross-functional safety management team throughout the conduct of the study. These cross functional reviews will include a global safety lead from the study team, and other representation from other departments at Millennium such as Clinical Research, Pharmacovigilance, Biostatistics, Clinical Pharmacology, and Clinical Operations.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. If selected for coding, AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities. Drugs will be coded using the World Health Organization Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each subject who signs an ICF.

The sponsor or its designee will supply investigative sites with access to eCRFs and will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor, CRO partners, and regulatory authorities. Investigative sites must complete eCRFs in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Any change of, modification of, or addition to the data on the eCRFs should be made by the investigator or appropriate site personnel. Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the principal investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated ICFs, subject authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain

essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan will be prepared and finalized before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

13.1.1 Analysis Sets

The populations used for analysis will include the following:

- Safety population will include patients who receive at least 1 dose of study drug. The safety population will be used for all safety analyses.
- PK population will include patients who:
  - Receive the protocol-specified single pevonedistat dose in Part A.
  - Do not receive any excluded concomitant medications through the completion of Part A.
  - Have sufficient concentration-time data to permit reliable estimation of PK parameters.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized, including sex, age, race, ethnicity, weight, height, BSA, baseline disease characteristics, and other parameters as appropriate.

13.1.3 Efficacy Analysis

Analysis of all efficacy measures collected during Part B will be descriptive. Disease response to pevonedistat in combination with SOC will be based on the best overall response as determined by the investigator using RECIST Version 1.1 guidelines (Appendix H). The duration of response will be defined in patients with disease response (CR or PR) as the time between the first documentation of response and PD. Responders without PD will be censored at the last clinical assessment of response.

13.1.4 PK Analysis

Individual values and summary descriptive statistics of pevonedistat plasma concentration time data and PK parameters will be listed and tabulated as follows:

- Day 1 (pevonedistat [in the absence of rifampin])
  - Pevonedistat C_{max}, AUC_{last}, AUC_{∞}, CL, V_{ss}, and $t_{1/2z}$.
- Day 10 (pevonedistat in the presence of rifampin)
  - Pevonedistat C_{max}, AUC_{last}, AUC_{∞}, CL, V_{ss}, and $t_{1/2z}$.

For pevonedistat-rifampin DDI assessment, the ratios of geometric mean C_{max}, AUC_{last}, and AUC_{∞} of pevonedistat in the presence of rifampin versus C_{max}, AUC_{last}, and AUC_{∞} in the absence of rifampin and associated 90% CIs will be calculated based on mixed-model analysis of variance.

13.1.5 Safety Analysis

A safety analysis will be conducted separately for Part A and Part B to respectively characterize the safety profile of pevonedistat in combination with SOC. The safety population will be used for the safety analysis. Safety will be evaluated on the basis of the incidence of AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, weight, and clinical laboratory values using the safety population. Exposure to study drug and reasons for discontinuation will be tabulated.

A treatment-emergent adverse event (TEAE) in Part A is defined as any AE that occurs after administration of the first dose of study treatment in Part A and up through 30 days after the last dose of study drug in Part A for patients who do not continue into Part B; or up through Part B Cycle 1 Day 1 (predose) for patients who continue into Part B.

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

AEs will be tabulated according to Medical Dictionary for Regulatory Activities by System Organ Class, High-Level Term, and Preferred Term and will include the following categories:

- TEAEs.
- Drug-related TEAEs.
- Treatment-emergent Grade 3, 4, and 5 AEs (presented by grade and overall).
- Treatment-emergent drug-related Grade 3, 4, and 5 AEs (presented by grade and overall).
- The most commonly reported TEAEs (ie, those events reported by ≥10% of all patients).
- SAEs.
- Drug-related SAEs.

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

The most commonly reported TEAEs (ie, those events reported by ≥10% of all patients) will be tabulated by System Organ Class and Preferred Term. Tabulation also will be provided that enumerates AEs by maximum intensity. Deaths, SAEs, and AEs resulting in study drug discontinuation will be tabulated.

Descriptive statistics for the actual values of clinical laboratory parameters (and change from baseline in clinical laboratory parameters) will be presented for all scheduled measurements over time. Mean laboratory values over time will be plotted for key laboratory parameters.

Shift tables for laboratory parameters will be generated to show changes in NCI CTCAE grade from baseline to the worst postbaseline value. Graphical displays of key safety parameters, such as

scatter plots of baseline versus worst postbaseline values, may be used to understand the pevonedistat safety profile.

Graphical displays will be used to show vital sign parameters over time separately for Part A and for Part B.

All concomitant medications collected from screening throughout the study period will be classified to Preferred Terms according to the World Health Organization Drug Dictionary.

Additional safety analyses may be performed to enumerate rates of toxicities and to further define the safety profile of pevonedistat.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 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 may be replaced to ensure availability of approximately 12 PK-evaluable patients for the final analysis.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those American sites unwilling to provide names and titles of all members because of privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the IB, a copy of the ICF, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. The sponsor will ship drug/notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives [drug/notification] no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The ICF and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and if applicable, the subject authorization form. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor before use.

The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the ICF, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the ICF and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and before the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the ICF and subject authorization (if applicable) at the time of consent and before subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed ICF, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised ICFs must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the

revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised ICF.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's [e]CRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites on or before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

As needed Takeda and Investigator/site contact information may be made public to support participant access to trials via registries. In certain situations/registries, Takeda may assist participants or potential participants to find a clinical trial by helping them locate trial sites closest to their homes by providing the investigator name, address, and phone number via email/phone or other methods callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites (including the Takeda corporate site) and registries, as required by Takeda Policy/Standard, applicable laws and/or regulations.

Data Sharing:

The sponsor is committed to responsible sharing of clinical data with the goal of advancing medical science and improving patient care. Qualified independent researchers will be permitted to use data collected from patients during the study to conduct additional scientific research, which may be unrelated to the study drug or the patient's disease. The data provided to external researchers will not include information that identifies patients personally.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

16.0 REFERENCES

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4. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. American Journal of Clinical Oncology 1982;5(6):649-55.
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Appendix A Schedules of Events

SOE for Treatment Part A (DDI)

	Screening (a)	Day 1 Predose	Day 1	Day 2	Day 3 (b)	Day 4 (b)	Day 10 Predose	Day 10	Day 11	Day 12	EOS (c)
Study Drug Administration											
Pevonedistat IV solution administration (d)			X					X			
Rifampin administration (e)					**Day 3 through Day 11**						
Study Procedures											
Informed consent	X										
Inclusion/exclusion criteria	X										
Demographics	X										
Complete medical history	X										
Physical examination	X										X
Symptom-directed physical examination		X (f)					X				
ECOG performance status	X										X
Height	X										
Weight	X	X (f)					X				X
Vital signs (g)	X	X	X	X	X		X	X	X	X	X
12-Lead ECG	X	X									X
Echocardiogram (h)	X										
Pregnancy test (i)	X	X					X				X
Hematology	X	X (f)			X		X			X	X
Chemistry	X	X (f)			X		X		X	X	X
Urinalysis	X										X
Plasma sample for pevonedistat PK (j)		X	X	X	X		X	X	X	X	
Monitoring of concomitant medications and procedures	To be recorded in the eCRF from the time of the first dose through 30 (+10) days after the last dose of study drug.										
AE/SAE reporting	Treatment-emergent AEs will be reported from administration of the first dose through 30 (+10) days after the last dose of study drug.										
	Serious PTEs will be reported from the signing of the ICF up to the first dose of study drug. In addition, related and unrelated treatment-emergent SAEs will be reported from the first dose of study drug through 30 (+10) days after administration of the last dose of study drug. After this period, only related SAEs must be reported.										

Footnotes are on the last table page.

(a) Unless otherwise noted, the screening visit must occur within 28 days before the day of the first dose of study drug in Part A. Screening clinical laboratory values must be as specified in Inclusion Criterion #6 for patients to be eligible for the study.
(b) Patients can be discharged from clinic any time after all Day 3 PK samples have been collected (Days 3-4) and return to the clinic on Day 10.
(c) An EOS visit is needed in Part A only if the patient does not continue into Part B. The EOS visit will occur 30 days (+10 days) after the last dose of study drug or before the start of subsequent therapy for the patient's indication, if that occurs sooner.
(d) Patients will receive a single dose of pevonedistat 50 mg/m^2 (equivalent to approximately 86 mg for a typical individual of 1.73 m^2 BSA) given as an approximate 1-hour (60±5 minutes) IV infusion on Day 1 and Day 10.
(e) The first dose of rifampin 600 mg 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.
(f) Procedures conducted during screening that are performed within 3 days of Day 1 can also be used as the Day 1 predose evaluation and do not need to be repeated. Predose clinical laboratory values must be as specified in Inclusion Criterion #6 to administer the Day 1 dose of pevonedistat.
(g) On days when pevonedistat is administered, vital signs are to be measured predose (20 minutes [±10 min]) before the infusion of pevonedistat; 30 minutes (±10 min) after the start of pevonedistat dosing; and 1 hour (±10 min) and 3 hours (±30 min) after the completion of pevonedistat dosing. When the timing of vital signs assessment coincides with the timing of a blood draw, vital signs will be measured before blood sample collection.
(h) Echocardiography will be performed at screening to determine LVEF only for patients who have no historical LVEF data within 6 months prior to study enrollment.
(i) In Part A, a serum pregnancy test will be performed for women of childbearing potential at screening, and a serum or urine pregnancy test be performed on Day 1 predose, Day 10 predose, and at the EOS visit.
(j) Time points for blood samples for PK analysis will be collected as specified in Table A.

Eligible patients may continue into optional Part B, which can begin within approximately 2 weeks of the patient completing Part A (ie, when the patient has met the discharge criteria).

SOE for Optional Continued Treatment With Pevonedistat+Chemotherapy, Part B

	Pevonedistat+Chemotherapy Treatment 21-Day Cycle				EOS/ Early Termination (b)
	Day 1 Predose (a)	Day 1	Day 3	Day 5	
Study Drug Administration					
Chemotherapy administration (c)		X			
Pevonedistat administration (c)		X	X	X	
Study Procedures					
Part B entry criteria/retreatment (d)	X				
Full physical examination	X (e)				X
Symptom-directed physical examination (e)	X				
ECOG performance status (f)	X				X
Weight	X				X
Vital signs (g)	X	X	X	X	X
12-Lead ECG (f)	X				X
Tumor assessment for solid tumors by RECIST, version 1.1 (h)	To be completed before dosing in Part B, end of Cycle 2, Cycle 5, and every 6 cycles thereafter				X
Monitoring of concomitant medications, therapies, and procedures	To be recorded from start of study administration in Part A through 30 days (+10 days) after the last dose of study drug in Part B				
AE/SAE reporting (i)	Treatment-emergent AEs will be recorded from start of study administration in Part A through 30 days (+10 days) after the last dose of study drug in Part B.				
	SAEs (regardless of causality) will be reported from signing of the ICF in Part A through 30 days (+10 days) after the last dose of study drug in Part B. After this period, only related SAEs must be reported.				
Samples/Laboratory Assessments					
Pregnancy test (j)	X				X
Hematology (k)	X		X predose	X predose	X
Chemistry (l)	X		X predose	X predose	X
Urinalysis	X				X

Footnotes are on the following page.

Tests and procedures should be performed on schedule, but occasional changes are allowable (±2 days) for holidays, vacations, and other administrative reasons.
(a) For patients to be eligible for dosing with pevonedistat+chemotherapy (Part B), they must meet certain entry criteria (see Section 7.3).
(b) If the patient continues into Part B, the EOS visit will occur 30 days (+10 days) after the last dose of study drug(s) in Part B or before the start of subsequent therapy for the patient's indication, if that occurs sooner.
(c) The investigator will select which chemotherapy (docetaxel or carboplatin+paclitaxel) that each patient will receive in combination with pevonedistat. On Day 1, when pevonedistat and chemotherapy agents are both administered, chemotherapy will be administered first, followed by pevonedistat. The infusion of pevonedistat may be slowed or stopped and restarted for any associated infusion-related reactions. The dose of pevonedistat may be reduced because of toxicities in accordance with Section 8.3.3. The chemotherapeutic agent may be dose reduced because of toxicities in accordance with Section 8.3.3. See Section 8.1 for the details of study drug administration. **NOTE: a time-out of approximately 15 minutes is required between the end of infusion of the chemotherapy regimen and the start of infusion of pevonedistat.**
(d) For patients to be eligible for dosing with pevonedistat+chemotherapy (Part B), they must meet certain entry criteria (see Section 7.3). For Cycle 2 and beyond, patients must meet the criteria for beginning a new cycle of treatment (Section 8.3.1).
(e) A full physical examination is required on Day 1 (predose) of Cycle 1. For Cycle 2 and beyond, a symptom-directed physical examination is to be performed on Day 1 predose.
(f) Predose assessment may be performed 1 day in advance if necessary.
(g) On days when study drug is administered, vital signs are to be measured predose (20 minutes [±10 min]) before the infusion of chemotherapy (when pevonedistat and chemotherapy agents are both administered) or pevonedistat; 30 minutes (±10 min) after the start of pevonedistat dosing; and 1 hour (±10 min) after the completion of pevonedistat dosing. When the timing of vital signs assessment coincides with the timing of a blood draw, vital signs will be measured before blood sample collection.
(h) Radiological imaging (as CT scan or MRI) will be required as entry criteria for Part B to assess the status of the patient's underlying disease. If the patient has had appropriate imaging scans performed within 28 days of Cycle 1 Day 1 of Part B, then the results of those scans may be used; otherwise, the first assessment will take place before Cycle 1 Day 1. Tumor assessment will be performed before the start of Part B and at the completion of Cycle 2, Cycle 5, and every 6 cycles thereafter. Patients will undergo CT (with IV contrast, except for patients with an allergy to contrast agents), MRI, x-ray, and/or bone scanning to monitor and assess disease progression. If the anatomic region cannot be adequately imaged by CT, MRI may be used instead; see Section 9.4.14. Response will be determined according to RECIST version 1.1.
(i) Including serious PTEs in Part A; see Section 10.1.1.
(j) In Part B, a serum or urine pregnancy test must also be performed for women of childbearing potential at every cycle (typically performed on Day 1 predose of each cycle; however, if a serum pregnancy test is used, this may be performed up to 3 days before Day 1), with negative results available before the first dose is administered in the respective cycle. A serum or urine pregnancy test will also be performed for women of childbearing potential at the EOS/Early Termination visit in Part B. Pregnancy tests may also be repeated during the study if requested by an IEC/IRB or if required by local regulations.
(k) Hematology samples will be collected as part of the entry criteria for Part B and before dosing with study drug on Days 1, 3, and 5. Samples may be drawn up to 1 day before dosing. If dosing falls on a Monday, the collection window may be extended to collect samples on the previous Friday. In addition, a sample will be taken at the EOS visit.
(l) Clinical chemistry samples will be collected as part of the entry criteria for Part B and before dosing with study drug on Days 1, 3, and 5. On Days 1, 3, and 5, samples may be drawn up to 1 day before dosing. In addition, a sample will be taken at the EOS visit.

Table A Blood Sampling Schedule (Part A)

Study Day	Time Point (hour) Matrix	Plasma Sample Collection 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
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.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform study-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those study-related duties and functions and should implement procedures to ensure the integrity of the study-related duties and functions performed and any data generated.
4. Ensure that study related procedures, including study specific (non routine/non standard panel) screening assessments are NOT performed on potential subjects, before the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
13. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix D ECOG Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Source: Oken, et al, 1982 [4].

Appendix E Drugs Associated With Nephrotoxicity

The drugs listed in the table below are permitted to be used during the conduct of this study but should be used with caution.

Drugs Associated With Nephrotoxicity

Analgesics
- Nonsteroidal anti-inflammatory drugs

Antidepressants/mood stabilizers
- Lithium

Antimicrobials
- Acyclovir (Zovirax)
- Aminoglycosides
- Amphotericin B (Fungizone; deoxycholic acid formulation more so than the lipid formulation)
- Beta lactams (penicillins, cephalosporins)
- Foscarnet (Foscavir)
- Ganciclovir (Cytovene)
- Pentamidine (Pentam)
- Quinolones
- Rifampin (Rifadin)
- Sulfonamides
- Vancomycin (Vancocin)

Antiretrovirals
- Adefovir (Hepsera), cidofovir (Vistide), tenofovir (Viread)
- Indinavir (Crixivan)

Calcineurin inhibitors
- Cyclosporine (Neoral)
- Tacrolimus (Prograf)

Cardiovascular agents
- Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers
- Clopidogrel (Plavix), ticlopidine (Ticlid)

Contrast dye

Diuretics
- Loops, thiazides
- Triamterene (Dyrenium)

Herbals
- Chinese herbals with aristolochic acid

Others
- Allopurinol (Zyloprim)
- Gold therapy
- Haloperidol (Haldol)
- Pamidronate (Aredia)
- Phenytoin (Dilantin)
- Quinine (Qualaquin)
- Zoledronate (Zometa)

Source: Modified from Naughton, 2008 [1].

Appendix F Definition of Postmenopausal

Definition of Postmenopausal

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. Refer to the following sources for additional information: European Heads of Medicines Agencies Clinical Trial Facilitation Group and hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_ CTFG_Contraception.pdf.

Appendix G Acceptable Methods of Contraception Considered Highly Effective

Birth control methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered to be highly effective. Such methods include the following:

Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (a).

- Oral.
- Intravaginal.
- Transdermal.

Progestogen-only hormonal contraception associated with inhibition of ovulation (a).

- Oral.
- Injectable.
- Implantable (b).

Intrauterine device (b).

Intrauterine hormone-releasing system (b).

Bilateral tubal occlusion (b).

Vasectomized partner (b,c).

Sexual abstinence (d).

Methods Considered Less Highly Effective

Acceptable birth control methods that result in a failure rate of more than 1% per year include the following:

Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action.

Male or female condom with or without spermicide (e).

Cap, diaphragm, or sponge with spermicide (e).

(a) Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method.
(b) Contraception methods that, in the context of this guidance, are considered to have low user dependency.
(c) Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential participant of the study and that the vasectomized partner has received medical assessment of the surgical success.
(d) In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject.
(e) A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods) is also considered an acceptable, but not a highly effective, birth control method.

Appendix H Response Criteria

Disease Response Criteria for Target and Nontarget Lesions

Evaluation of Target Lesions	
CR	Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm.
PR	At least a 30% decrease from baseline in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.
PD	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered progression.
SD	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.
Evaluation of Nontarget Lesions	
CR	Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (<10 mm short axis).
Non-CR/ Non-PD	Persistence of 1 or more nontarget lesion(s) or/and maintenance of tumor marker level above the normal limits.
PD	Appearance of 1 or more new lesions and/or unequivocal progression of existing nontarget lesions.

Source: Eisenhauer, et al, 2009 [3].

Overall Disease Response Criteria

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Inevaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Source: Eisenhauer, et al, 2009 [3].

Appendix I Hematologic Toxicity of Carboplatin Alone and in Combination With Paclitaxel

In 2 prospectively randomized, controlled studies conducted by the National Cancer Institute of Canada Clinical Trials Group and the Southwest Oncology Group, 789 chemotherapy-naïve patients with advanced ovarian cancer were treated with carboplatin or cisplatin in combination with cyclophosphamide every 28 days for 6 courses before surgical re-evaluation. See the table below for the hematologic adverse experiences of patients treated with carboplatin in combination with cyclophosphamide.

Hematologic Adverse Experiences of Patients With Ovarian Cancer Treated With Carboplatin in Combination With Cyclophosphamide

Adverse Experience	Laboratory Value	NCIC CTG Study % Patients (N=447)	SWOG Study % Patients (N=342)
Bone Marrow			
Thrombocytopenia	<100,000/mm^3	70	59
	<50,000/mm^3	41	22
Neutropenia	<2000 cells/mm^3	97	95
	<1000 cells/mm^3	81	84
Leukopenia	<4000 cells/mm^3	98	97
	<2000 cells/mm^3	68	76
Anemia	<11 g/dL	91	88
	<8 g/dL	18	8
Infections		14	18
Bleeding		10	6
Transfusions		42	25

Source: Carboplatin US Package Insert 2011 [5].
NCIC CTG=National Cancer Institute of Canada Clinical Trials Group, SWOG=Southwest Oncology Group.

In a randomized clinical study, 798 patients with ovarian cancer were treated with either cisplatin+paclitaxel or paclitaxel+carboplatin therapy at 3-week intervals for 6 courses. See the table below for the hematologic adverse experiences of patients treated with paclitaxel/carboplatin.

Hematologic Toxicities and Associated Supportive Care in Patients With Advanced Ovarian Cancer Stratified by Treatment Arm and Toxicity Grade

		NCI CTC Grade, %												Difference (a) in the Proportions of Patients With Grades 3/4 Toxicity, %	
		Paclitaxel+Carboplatin Arm						Cisplatin+Paclitaxel Arm							
Toxicity	**Set**	**N**	**0**	**1**	**2**	**3**	**4**	**N**	**0**	**1**	**2**	**3**	**4**	**E**	**95% CI**
Hemoglobin	C	2209	29.1	49.4	20.1	1.3	0.1	2095	33.6	49.5	16.1	0.8	0.0	-0.6	-1.3 to 0.0
	P	388	9.0	40.7	44.3	5.4	0.5	382	14.7	44.2	37.2	3.9	0.0	-2.0	-5.1 to 1.1
Platelets	C	2193	71.9	19.9	5.2	2.5	0.5	2082	93.4	6.2	0.2	0.2	0.0	**-2.9**	**-3.6 to -2.1**
	P	388	43.3	31.2	12.6	10.1	2.8	382	78.3	19.4	1.3	1.0	0.0	**-11.8**	**-15.3 to -8.4**
Transfusions pRBCs (a)	C	1868	94.3	--	--	5.7	--	1766	97.2	--	--	2.8	--	**-2.9**	**-4.2 to -1.6**
	P	383	81.7	--	--	18.3	--	370	89.5	--	--	10.5	--	**-7.7**	**-12.7 to -2.8**
Leukocytes (WBC)	C	2200	37.0	22.6	29.3	10.8	0.3	2073	56.4	23.3	17.3	2.9	0.0	**-8.1**	**-9.6 to -6.6**
	P	388	13.4	16.0	38.7	30.4	1.5	382	31.4	35.1	32.7	10.5	0.3	**-21.2**	**-26.8 to -15.6**
Neutrophils	C	1842	56.9	12.9	12.8	12.4	5.0	1864	70.9	10.6	9.8	6.4	2.3	**-8.7**	**-10.8 to -6.5**
	P	371	31.3	12.9	18.9	21.6	15.4	373	48.0	13.1	16.9	15.0	7.0	**-14.9**	**-21.4 to -8.5**
Febrile neutropenia	C	2228	98.3	--	--	1.7	0.0	2110	99.3	--	--	0.7	0.0	**-0.9**	**-1.6 to -0.3**
	P	388	92.0	--	--	8.0	0.0	384	96.4	--	--	3.6	0.0	**-4.3**	**-7.6 to -1.1**
Supportive care: antibiotics (b)	C	1868	98.3	--	--	1.7	--	1768	97.9	--	--	2.1	--	0.4	-0.5 to 1.3
	P	383	93.2	--	--	6.8	--	370	90.5	--	--	9.5	--	2.7	-1.2 to 6.6
Supportive care: G-CSF (b)	C	1868	94.0	--	--	6.0	--	1767	98.2	--	--	1.8	--	-4.2	**-5.5 to -3.0**
	P	383	85.6	--	--	14.4	--	370	95.4	--	--	4.6	--	-9.8	**-13.9 to -5.7**

Source: du Bois et al, 2003 [6].
The symbol "--" denotes "not defined."
C=maximum grade over all courses, G-CSF=granulocyte colony stimulating factor, E=estimate, N=number of courses in set C and number of patients in set P, NCI CTC=National Cancer Institute Common Toxicity Criteria, P=maximum grade over all courses within a patient, pRBCs=packed red blood cells, WBC=white blood cell.
(a) Differences are calculated by subtracting the paclitaxel+carboplatin arm proportion from the cisplatin+paclitaxel arm proportion; statistically significant differences in proportions between the 2 treatment arms are in bold font. All percentages are rounded to 1 decimal place; therefore, the estimates may differ by ±1 from the difference of the percentages of the treatment arm columns.
(b) Transfusion of pRBCs and use of antibiotics and G-CSF were not assessed for the last treatment cycle within a patient. Use of antibiotics and use of G-CSF are graded in the same fashion as transfusion of pRBCs. Use of antibiotics/application of G-CSF is coded as a toxicity of Grade 3; a Grade 0 is applied otherwise.

Appendix J New York Heart Association Classification of Cardiac Disease

The following table presents the New York Heart Association classification of cardiac disease.

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease

Source: The Criteria Committee of New York Heart Association, 1994 [7].

Appendix K Excluded Strong CYP3A Inducers

Use of the CYP3A inducers listed in the table below should be avoided during pevonedistat therapy unless otherwise noted in the protocol.

In Vivo Inducers of CYP3A

Strong Inducers ≥80% Decrease in AUC
Carbamazepine
Phenytoin
Phenobarbital
Primidone
Rifabutin
Rifampin
Rifapentine
St. John's Wort

This is not an exhaustive list; refer to the following sources: medicine.iupui.edu/flockhart/table.htm and fda.gov/CDER/drug/drugInteractions/tableSubstrates.htm for additional information.

Appendix L Detailed Description of Amendments to Text

The primary section(s) of the protocol affected by the changes in Amendment 02 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Clarify the exclusion criterion regarding the assessment of LVEF.

The primary change occurs in Section 7.2, Exclusion Criteria.

Initial wording:	13. Left ventricular ejection fraction <50% as assessed by echocardiogram or radionuclide angiography.
Amended or new wording:	13. Left ventricular ejection fraction (LVEF) <50% ~~as assessed by echocardiogram or radionuclide angiography~~ within 6 months prior to study enrollment. If a result within this time frame is unavailable, LVEF must be determined by echocardiography at screening.

Rationale for Change:

The intent of the protocol has been to allow sites to use historical LVEF data, if available, or perform an echocardiogram, if needed, to determine patient eligibility for the study. This point has been clarified in this protocol amendment.

The following sections also contain this change:

- Section 9.4.12 Echocardiogram.
- Appendix A Schedules of Events (SOE for Treatment Part A [DDI]).

Change 2: Delete the requirement that, for inclusion in the study, patients must have a tumor that is radiographically or clinically evaluable and/or measurable.

The change occurs in Section 7.1, Inclusion Criteria.

Deleted text:	2.	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. ~~The tumor must be radiographically or clinically evaluable and/or measurable.~~

Rationale for Change:

As this is a phase 1 DDI study, the requirement for measurable disease is not considered essential.

Change 3: Change serious adverse event reporting from a paper-based system to electronic data capture.

The change occurs in Section 10.2, Procedures for Recording and Reporting AEs and SAEs.

Initial wording:

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

Regardless of causality, SAEs and serious PTEs (as defined in Section 10.1) must be reported (see Section 10.3 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee (contact information provided below). This should be done by faxing the SAE Form within 24 hours after becoming aware of the event. The SAE Form, created specifically by Takeda, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE or serious PTE may be requested by Takeda. SAE report information must be consistent with the data provided on the eCRF.

SAE Reporting Contact Information*

CCI

Amended or new wording:

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

Regardless of causality, SAEs and serious PTEs (as defined in Section 10.1) must be reported (see Section 10.3 for the period of observation) by the investigator to the Takeda Global Pharmacovigilance department or designee ~~(contact information provided below).~~ **within 24 hours of becoming aware of the event.** ~~This should be done by faxing the SAE Form within 24 hours after becoming aware of the event. The SAE Form, created specifically by Takeda, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE or serious PTE may be requested by Takeda. SAE report information must be consistent with the data provided on the eCRF.~~

~~**SAE Reporting Contact Information***~~

~~CCI~~ [redacted]

This will be done by transmitting an electronic data capture (EDC) SAE report. If transmission of an EDC SAE report is not feasible, then a facsimile of the completed Takeda paper-based SAE form will be sent. A sample of the paper-based SAE form and processing directions are in the Study Manual. Information in the SAE report or form must be consistent with the data provided on the eCRF.

If information not available at the time of the first report becomes available at a later date, the investigator will transmit a follow-up EDC SAE report (or a paper-based SAE form if an EDC SAE report is not feasible) or provide other documentation immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs and serious PTEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

Rationale for Change:

SAEs are being reported by EDC in this study; the amended text reflects only a change in **procedure** for reporting SAEs.

Change 4: Clarify the timing of chemistry and hematology laboratory assessments before administration of the Day 1 dose of pevonedistat in Part A (drug-drug interaction) of the study.

The primary change occurs in Section 7.1 Inclusion Criteria.

Deleted text: 3. Clinical laboratory values as specified below ~~within 3 days before the first dose of study drug~~:

Rationale for Change:

To clarify that the clinical laboratory values specified in Inclusion Criterion #6 may be determined within the 28-day screening period to determine patient eligibility for the study. If these assessments have been performed within 3 days of Day 1, these results can also be used as the Day 1 predose evaluation to determine whether the patient can receive study drug and do not need to be repeated.

Appendix A Schedules of Events (SOE for Treatment Part A [DDI]) Footnotes (a) and (f) also contain this change.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Pharmacology Approval	05-Sep-2018 17:08 UTC
	Clinical Science Approval	05-Sep-2018 17:48 UTC
	Clinical Approval	05-Sep-2018 18:16 UTC
	Biostatistics Approval	05-Sep-2018 20:37 UTC