



Title: A Phase 1 Study to Assess Mass Balance, Pharmacokinetics, and Metabolism of [14C]-Pevonedistat in Patients With Advanced Solid Tumors

NCT Number: NCT03057366

Protocol Approve Date: 29 November 2016

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PROTOCOL

**A Phase 1 Study to Assess Mass Balance, Pharmacokinetics, and Metabolism of
[¹⁴C]-Pevonedistat in Patients With Advanced Solid Tumors**

Sponsor: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda
Pharmaceutical Company Limited
40 Lansdowne Street
Cambridge, MA USA 02139

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-1013

Compound: Pevonedistat (MLN4924; TAK-924)

Date: 29 November 2016 **Final**

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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 or medication errors.

Takada Development Center 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 sites. Information on service providers is given in Section 3.1 and relevant guidelines provided to the sites.

Contact Type/Role	European 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 Conference on Harmonisation E6 Good Clinical Practice: 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.

Personally Protected Data	Date	Personally Protected Data	Date
Personally Protected Data	Date	Personally Protected Data	Date

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, package insert 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.
- International Conference on Harmonisation, E6 Good Clinical Practice: 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 10.0 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)

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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 (MLN4924; TAK-924)
Title of Protocol: A Phase 1 Study to Assess Mass Balance, Pharmacokinetics, and Metabolism of [¹⁴ C]-Pevonedistat in Patients With Advanced Solid Tumors	
Study Number: Pevonedistat-1013	Phase: 1
Study Design: This is a 2-part, open-label, multicenter, mass balance and absorption, distribution, metabolism, excretion (ADME) study in 4 to 6 pharmacokinetics (PK)-evaluable patients with advanced solid tumors. Part A: Mass Balance/ADME Assessment Part A represents the period for assessment of the mass balance, PK, metabolism, and elimination of pevonedistat in this population. Patients will be required to stay at the Part A study site for approximately 8 days or until the discharge criteria are met, with a maximum estimated confinement period of 9 to 14 days. Patients who meet all inclusion criteria and no exclusion criteria will be assigned a patient number and will be admitted to the Part A study site on the morning of Day -1 for predose assessments and to begin confinement. On the morning of Day 1, patients will receive a single dose of 25 mg/m ² (equivalent to approximately 43 mg for a typical individual of 1.73 m ² body surface area [BSA], up to a absolute maximum dose of 50 mg) [¹⁴ C]-pevonedistat intravenous (IV) solution (containing approximately 60-85 µCi [approximately 2.22-3.145 MBq] of total radioactivity [TRA]) via a 1-hour infusion. The actual amount of administered radioactivity and pevonedistat dose will be documented for each patient. Patients will be closely monitored for adverse events (AEs) throughout the study. Safety will be assessed by monitoring vital signs, physical examinations (including weight at Day 1 predose and End of Study [EOS]), electrocardiograms, and clinical laboratory tests. Blood will be collected at prespecified time points for analyses of pevonedistat and TRA PK and for metabolite profiles over the confinement period. Complete urinary and fecal output will be collected throughout the confinement period until discharge; urine samples will be analyzed for PK, TRA, and biotransformation and fecal samples will be analyzed for TRA and products of pevonedistat biotransformation. For patients who experience emesis during the first 24 hours after drug administration, the vomitus will be collected as much as possible and assayed for TRA. If a subject vomits more than once during the period, vomitus corresponding to each vomiting event will be collected in a separate labeled container and separately counted. Refer to the Study Manual for further details. To ensure defecation before release from the Part A study site, two 15 mL doses of oral lactulose will be administered, separated by approximately 2 hours, on the evening of Day 4; the second dose of lactulose will be withheld if the first dose was not tolerated. Patients will be required to stay at the Part A study site for approximately 8 days or until the discharge criteria are met, with a maximum estimated confinement period of 9 to 14 days. Company Confidential Information	
Part B: Continued Treatment With Pevonedistat in Combination With Chemotherapy (OPTIONAL) After completion of the mass balance/ADME assessment portion of the study, patients will have the opportunity to continue into Part B at a secondary study site, which can begin within approximately 2 weeks of the patient completing Part A (ie, when the patient has met the criteria to be discharged from the clinic). Participation in Part B is optional. Any patient who continues on to Part B will need to be re-evaluated for entry criteria before treatment in Part B can begin. Patients will receive pevonedistat in combination with either docetaxel or carboplatin+paclitaxel as recommended by the investigator. Safety and disease assessments will be conducted in Part B of the study. Disease assessments will be conducted using radiological evaluations (computed tomography scan or magnetic resonance	

<p>imaging as clinically indicated) to assess the status of the patient's underlying disease and will be part of the entry criteria for Part B.</p> <p>Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03, effective date 14 June 2010.</p>	
<p>Primary Objectives:</p> <p>The primary objectives are as follows:</p> <ul style="list-style-type: none"> To assess the mass balance (ie, cumulative excretion of TRA in urine and feces) of pevonedistat following a single 1-hour infusion of 25 mg/m² [¹⁴C]-pevonedistat IV solution containing approximately 60 to 85 μCi (approximately 2.22-3.145 MBq) of TRA in patients with advanced solid tumors in Part A. To characterize the PK of pevonedistat in whole blood, plasma, and urine, and of TRA in plasma and whole blood following a single 1-hour infusion of 25 mg/m² [¹⁴C]-pevonedistat IV solution containing approximately 60 to 85 μCi (approximately 2.22-3.145 MBq) of TRA in patients with advanced solid tumors in Part A. 	
<p>Secondary Objectives:</p> <p>The secondary objectives are as follows:</p> <ul style="list-style-type: none"> To collect samples for characterization of the metabolic profile of pevonedistat in plasma, urine, and feces following a single 1-hour infusion of 25 mg/m² [¹⁴C]-pevonedistat IV solution containing approximately 60 to 85 μCi (approximately 2.22-3.145 MBq) of TRA (maximum dose of 50 mg) in patients with advanced solid tumors in Part A. To evaluate the safety and tolerability of pevonedistat in patients with advanced solid tumors after a single dose in Part A and in combination with either docetaxel or carboplatin+paclitaxel in Part B. To evaluate disease response that may be observed with the combination of pevonedistat and docetaxel or pevonedistat and carboplatin+paclitaxel in patients with advanced solid tumors (Part B). 	
<p>Exploratory Objectives:</p> <p>Company Confidential Information</p>	
<p>Subject Population: Patients aged 18 years and older with advanced solid tumors.</p>	
<p>Number of Subjects:</p> <p>4 to 6 PK-evaluable patients</p>	<p>Number of Sites:</p> <p>Part A: Part A study site Part B: secondary study site</p>
<p>Dose Level(s):</p> <p>Part A: A single dose of 25 mg/m² (equivalent to approximately 43 mg for a typical individual of 1.73 m² BSA, up to a maximum absolute dose of 50 mg) [¹⁴C]-pevonedistat IV solution (containing approximately 60-85 μCi [approximately 2.22-3.145 MBq] of TRA) via 1-hour infusion.</p> <p>Part B (optional): Pevonedistat will be administered on Days 1, 3, and 5 of each cycle at the dose of 25 mg/m² in combination with docetaxel (75 mg/m²) or at the dose of 20 mg/m² in combination with carboplatin AUC5+ paclitaxel (175 mg/m²) on Day 1. On Days 3 and 5 of each cycle, only pevonedistat will be given. The duration of each cycle will be 21 days.</p>	<p>Route of Administration:</p> <p>Part A: Pevonedistat IV infusion</p> <p>Part B (optional): Pevonedistat: IV infusion Docetaxel, carboplatin, and paclitaxel: IV infusion</p>

<p>Duration of Treatment:</p> <p>Part A: single IV dose</p> <p>Part B (optional): Eligible patients may continue to receive treatment in Part B of this study until they experience symptomatic deterioration or progressive disease; treatment is discontinued for another reason; or until the study is stopped.</p>	<p>Period of Evaluation:</p> <p>Screening: within 28 days before the first dose of study drug in Part A.</p> <p>Part A: Patients will be required to stay at the Part A study site for approximately 8 days or until the discharge criteria are met, with a maximum estimated confinement period of 9 to 14 days.</p> <p>Part B (optional): 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.</p> <p>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.</p>
<p>Main Criteria for Inclusion:</p> <p>Male or female patients, aged 18 years or older, who have a histologically or cytologically confirmed metastatic or locally advanced and incurable solid tumor that is felt to be appropriate for treatment with one of the 2 chemotherapy regimens in Part B of this study (carboplatin+paclitaxel or docetaxel), 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.</p>	
<p>Main Criteria for Exclusion:</p> <p>Subjects who (1) have an inability to comply with study visits and procedures including required inpatient confinement; (2) have been treated with any systemic antineoplastic therapy or any investigational products within 21 days before the first dose of study treatment; (3) had radiotherapy within 14 days preceding the first dose of study treatment; (4) have known hypersensitivity, or history of severe intolerance or toxicity to chemotherapeutic agents used in Part B; (5) have a 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; (6) have irregular defecation patterns and/or history of urinary and/or fecal incontinence; (7) persistent diarrhea (\geqGrade 2) lasting >3 days within 2 weeks before the first dose of study treatment.</p>	
<p>Main Criteria for Evaluation and Analyses:</p> <p>The primary endpoints for this study are as follows:</p> <ul style="list-style-type: none">• Summary statistics of PK parameters of pevonedistat and TRA in plasma and whole blood: maximum observed concentration (C_{max}), time of first occurrence of C_{max} (t_{max}), and area under the concentration-time curve (AUC) from time zero to time of the last quantifiable concentration (AUC_{last}).• Cumulative percentage of urinary recovery, percentage of fecal excretion, and percentage of TRA in urine and feces over the entire period of collection.• Summary statistics of PK parameters of pevonedistat in urine: cumulative amount excreted in urine (Ae_{urine} and percentage of dose) and renal clearance (CL_R). <p>The secondary endpoints for this study are as follows:</p> <ul style="list-style-type: none">• Safety parameters: AEs, serious adverse events, and abnormal laboratory values reported.	

- Metabolite profiles in plasma, urine, and feces.
- Measures of disease response based on investigator's assessment using the Response in Evaluation Criteria in Solid Tumors guideline (Version 1.1).

Company Confidential Information

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, 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.

The following PK parameters will be calculated by noncompartmental analysis and tabulated for each individual:

- TRA in plasma and whole blood: C_{max} , t_{max} , AUC_{last} , and as permitted by data, terminal disposition phase half-life ($t_{1/2z}$) and AUC from time zero to infinity, calculated using the observed value of the last quantifiable concentration (AUC_{∞}).
- TRA in urine: amount of [^{14}C]-radioactivity excreted into urine per sampling interval ($Ae_{urine, t1-t2}^{14C}$ in ng-eq and percentage of dose) and cumulative amount of [^{14}C]-radioactivity excreted in urine up to the last sampling interval ($Ae_{urine, t}^{14C}$ in ng-eq and percentage of dose).
- TRA in feces: amount of [^{14}C]-radioactivity excreted into feces per sampling interval (daily excretion) ($Ae_{feces, t1-t2}^{14C}$ in ng-eq and percentage of dose) and cumulative amount of [^{14}C]-radioactivity excreted in feces up to the last sampling interval ($Ae_{feces, t}^{14C}$ in ng-eq and percentage of dose).
- The total cumulative excretion of [^{14}C]-radioactivity per interval and over the total collection period will be calculated as the sum of the cumulative excretion in urine and feces: total cumulative excretion of [^{14}C]-radioactivity from the body ($Ae_{total, t}^{14C} = Ae_{urine, t}^{14C} + Ae_{feces, t}^{14C}$) (in ng-eq and percentage of dose).
- Pevonedistat in whole blood and plasma: C_{max} , t_{max} , AUC_{last} , and as permitted by data, $t_{1/2z}$, AUC_{∞} , and clearance.
- Pevonedistat in urine (per sampling interval and total): cumulative amount excreted in urine ($Ae_{urine, t}$ and percentage of dose) and CL_R .

Additionally, one of the objectives of this study is to collect plasma, urine, and feces for metabolite profiling and identification. While the results of PK of pevonedistat and TRA, time course of excretion of TRA in urine and feces, and overall mass balance will be included in the clinical study report, the metabolite profiling and identification results will be reported separately.

Sample Size Justification: The sample size for this study is not based on statistical considerations. On the basis of the ALARA principle (As Low [radioactive burden] As Reasonably Achievable) set forth in the 96/29/EURATOM directive, a sample size of 4 to 6 PK-evaluable patients is considered sufficient to provide adequate characterization of the mass balance, PK, and metabolism of pevonedistat in patients with cancer. Patients will be replaced if they are not evaluable for PK.

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/Signatory Coordinating Investigator

Takeda will select only 1 principal investigator/signatory coordinating investigator for this study. Selection criteria will include having significant knowledge of the study protocol and the study medication, expertise in the therapeutic area, and expertise in the conduct of clinical research and study participation. The principal investigator/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

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
$Ae_{feces,^{14}C}$	cumulative amount of [^{14}C]-radioactivity excreted in the feces up to the last sampling interval
$Ae_{feces,^{14}C,t1-t2}$	amount of [^{14}C]-radioactivity excreted in feces in a sampling interval
$Ae_{total,^{14}C}$	total cumulative excretion of [^{14}C]-radioactivity from the body ($Ae_{total,^{14}C}=Ae_{urine,^{14}C}+Ae_{feces,^{14}C}$)
Ae_{urine}	cumulative amount of drug excreted in urine
$Ae_{urine,^{14}C}$	cumulative amount of [^{14}C]-radioactivity excreted in the feces/urine up to the last sampling interval
$Ae_{urine,^{14}C,t1-t2}$	amount of [^{14}C]-radioactivity excreted in feces in a sampling interval
ALL	acute lymphoblastic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{∞}	AUC from time zero to infinity, calculated using the observed value of the last quantifiable concentration
AUC_{last}	AUC from time zero to time of the last quantifiable concentration
AUC_t	AUC from time zero to time t
AUC_{τ}	AUC during a dosing interval
BID	twice daily
BSA	body surface area
CDL	cullin-dependent ubiquitin E3 ligases
CFR	Code of Federal Regulations
CL_R	renal clearance
C_{max}	maximum observed concentration
CR	complete response
CRO	contract research organization
CT	computed tomography
CV	coefficient of variation
CYP	cytochrome P450
DCSI	development core safety information
DDI	drug-drug interaction
DME	drug-metabolizing enzyme
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOS	End-of-Study
FDA	(US) Food and Drug Administration

FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GI	gastrointestinal
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
IRB	institutional review board
IV	Intravenous(ly)
MDS	myelodysplastic syndrome
Millennium	Millennium Pharmaceuticals, Inc
MLN4924	research name of pevedistat hydrochloride; TAK-924
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NAE	NEDD8-activating enzyme
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer
PD	progressive disease
pevedistat hydrochloride	salt form of MLN4924; TAK-924
PK	pharmacokinetics
PR	partial response
QTc	rate-corrected QT interval
RECIST	Response in Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SC	subcutaneous(ly)
SmPC	Summary of Product Characteristics
SoC	standard of care
$t_{1/2z}$	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
t_{max}	time of first occurrence of C_{max}
TRA	total radioactivity
ULN	upper limit of the normal range
US	United States
USP	United States Pharmacopeia

3.4 Corporate Identification

Millennium	Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited
TDC Japan	Takeda Development Center Japan
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd
TDC Americas	Takeda Development Center Americas, Inc
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	Millennium Pharmaceuticals, Inc, TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

4.0 INTRODUCTION

4.1 Background

4.1.1 Study Drug

Pevonedistat (MLN4924; TAK-924) is a first-in-class, small molecule inhibitor of the 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 by inhibiting the degradation of a subset of proteins that are regulated by the proteasome.

4.1.2 Nonclinical Background Information

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

Pevonedistat treatment of cultured tumor cells resulted in growth inhibition of a wide variety of cell lines and induced phenotypes consistent with NAE inhibition, including a decrease in NEDD8-cullin levels and a reciprocal increase in levels of known CDL substrates; DNA re-replication; cell cycle arrest; and ultimately death via apoptosis. In vitro experiments with pevonedistat administered in combination with hypomethylating agents azacitidine and decitabine demonstrated synergistic activity in acute myeloid leukemia (AML) cell lines.

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 (BID) 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.

In vitro assay results indicated a low risk for hERG channel inhibition by pevonedistat (inhibitory constant=17.3 μM) or its 3 major circulating metabolites (half-maximal inhibitory concentration >100 μM for all three).

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

The clinical pharmacokinetics (PK) of pevonedistat has been evaluated in 4 monotherapy phase 1 studies in 96 patients with solid tumors (C15001 and C15005) and 109 patients with hematologic malignancies (C15002 and C15003). These studies have evaluated the single- and multiple-dose PK of pevonedistat administered via IV infusion across a range of 25 to 278 mg/m² given at various daily or intermittent dosing schedules within 21-day treatment cycles.

Plasma concentrations of pevonedistat declined in a bi-exponential manner at the end of IV infusion, with little or no drug accumulation following intermittent dosing or once-daily dosing for 5 consecutive days of a 21-day cycle. Mean $t_{1/2z}$ was estimated to be approximately 10 hours (range 7.7-15.2) across doses and schedules. Consistent with in vitro data, pevonedistat is extensively partitioned in human blood (mean blood-to-plasma concentration ratio of approximately 65) with whole blood and plasma kinetics declining in parallel over time. Pevonedistat generally exhibited linear PK over the dose range studied. Observed interindividual variability was generally moderate with 18% to 41% coefficient of variation (CV) for the maximum observed concentration (C_{\max}), 12% to 56% CV for area under the plasma concentration-time curve (AUC) from time zero to 24 hours postdose (AUC_{24}), and 15% to 33% CV for the AUC during a dosing interval (AUC_{τ}) when pevonedistat was administered on Days 1, 3, and 5. Body size influences pevonedistat systemic clearance and volume of distribution, thus supporting body surface area (BSA)-normalized dosing to reduce variation in systemic exposure of pevonedistat in patients with cancer. Pevonedistat clearance tended to gradually decrease in elderly patients (by approximately 25% over the 30-90 years age range). There was also no apparent effect of renal function status (as assessed by estimated creatinine clearance >30 mL/min) on pevonedistat PK.

Additionally, evaluation of pevonedistat PK is ongoing for 2 studies of pevonedistat in combination with different standard-of-care therapies, and for a drug-drug interaction (DDI) study

evaluating the effects of cytochrome P450 (CYP)3A-mediated inhibition on pevedonidstat. Pevedonidstat PK was not altered in the presence of azacitidine when compared with historical single-agent data. Also, no obvious changes in the PK behavior of pevedonidstat in the presence of docetaxel or gemcitabine have been observed, whereas a trend toward increasing plasma concentrations of pevedonidstat in the presence of carboplatin+paclitaxel was evident. This apparent drug interaction effect, which cannot be explained at this time, warrants further understanding of the disposition properties of pevedonidstat in humans. Lastly, multiple doses of fluconazole, a moderate CYP3A inhibitor, had minimal effect (13% increase in mean AUC from time zero to infinity, calculated using the observed value of the last quantifiable concentration [AUC_∞]) on the single-dose IV PK of pevedonidstat, while pevedonidstat systemic exposure increased by 23% on average in the presence of the strong CYP3A inhibitor itraconazole.

Additional information on the clinical PK of pevedonidstat is provided in the current IB.

4.1.3.2 Clinical Experience

As of 22 January 2016, the clinical development program of pevedonidstat includes 8 clinical studies in patients with advanced malignancies. Four of the 8 clinical studies are completed phase 1 monotherapy studies (C15001, C15002, C15003, and C15005), and 2 are ongoing, phase 1b studies of pevedonidstat in combination with different standard of care (SoC) therapies (C15009 and C15010). A phase 1 DDI study (C15011) is also evaluating the effects of CYP3A-mediated inhibition on pevedonidstat. Thus, approximately 390 patients diagnosed with advanced malignancies including solid tumors, AML, melanoma, lymphoma, multiple myeloma, higher risk myelodysplastic syndrome (MDS), and acute lymphoblastic leukemia (ALL) have been enrolled in the overall clinical development program. Further details on these studies are provided in the current IB.

4.1.4 Potential Risks and Benefits

Pevedonidstat will be administered in Part A as a single 1-hour IV infusion of 25 mg/m² (equivalent to approximately 43 mg for a typical individual of 1.73 m² BSA, up to a maximum absolute dose of 50 mg) [¹⁴C]-pevedonidstat (containing approximately 60-85 μCi [approximately 2.22-3.145 MBq]) as the radioactive tracer to allow mass balance evaluation and quantitative metabolite profiling in plasma, urine, and feces. The safety of the dose of radioactivity is supported by dosimetry calculations based on quantitative whole body autoradiography studies in rats (Millennium: the Takeda Oncology Company, Report 96N-1213, 2012), while ensuring adequate sensitivity for radiometric detection in all biological matrices. Refer to Section 4.2.1 for the risks for [¹⁴C]-pevedonidstat.

It is anticipated that the chemotherapies used in Part B of this study may provide clinical benefit to patients. Study C15010 is an ongoing, open-label, dose-finding study to assess safety and tolerability of pevedonidstat+chemotherapy. Fifty-four patients evaluable for response have been treated with pevedonidstat in combination with docetaxel (N=22), carboplatin (N=6), or carboplatin+paclitaxel (N=26): 3 objective responses were seen in 22 patients treated in Arm 1 (pevedonidstat+docetaxel), and 9 partial responses (PRs)/complete responses (CRs) were seen in

32 patients treated in Arm 2 (pevonedistat+carboplatin or pevonedistat+carboplatin/paclitaxel) [1,2]. The overall response rate in the intent-to-treat population of Arm 1 was 13% and Arm 2 was 28%.

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 (DCSI) (Appendix A of the IB).

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 ($\geq 110 \text{ mg/m}^2$) than those being used in current clinical trials 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/m². 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 trials that are confounded by the patient's underlying medical condition, 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; the majority occurred in the setting of thrombocytopenia.

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, and increased diastolic blood pressure.

- 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) was 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.
- 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 (see Section 8.6.1). 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 Section 8.4 and Section 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.

Patients will be monitored closely when they are receiving this agent and for at least 30 days after their last dose for these anticipated and potential toxicities and for unanticipated toxicities.

Monitoring will include the following: laboratory assessments, physical examinations, serious adverse event (SAE) and adverse event (AE) reporting, and safety review (see Section 11.1). In addition, an independent data monitoring committee (IDMC) (see Section 11.2) is in place that will monitor the safety data from studies within the pevonedistat program.

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

4.1.4.2 Risks of Docetaxel Treatment

Treatment-related mortality increases with abnormal liver function, at higher doses, and in patients with non-small cell lung cancer (NSCLC) and prior platinum-based therapy receiving docetaxel at 100 mg/m².

Severe hypersensitivity, including very rare, fatal anaphylaxis, has been reported in patients who received dexamethasone premedication. Severe reactions require immediate discontinuation of docetaxel and administration of appropriate therapy.

Docetaxel is contraindicated if the patient has a history of severe hypersensitivity reactions to docetaxel or to drugs formulated with polysorbate 80.

Severe fluid retention may occur despite dexamethasone premedication.

For more details, refer to the docetaxel Summary of Product Characteristics (SmPC) [3].

Hepatotoxicity Warning

Docetaxel should not be given if total bilirubin is greater than the upper limit of the normal range (ULN) or if aspartate aminotransferase (AST) or alanine aminotransferase (ALT) is greater than 1.5 times the ULN. Liver function test elevations increase the risk of severe or life-threatening complications. Liver function tests should be obtained before each treatment cycle.

Hematologic Warning

Docetaxel should not be given if the absolute neutrophil count (ANC) is less than 1500 cells/mm³.

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 NSCLC and prior platinum-based therapy receiving docetaxel at 100 mg/m².

4.1.4.4 Risks of Carboplatin and Paclitaxel Therapy

See [Appendix H](#) for information on the hematologic toxicity of carboplatin alone and in combination with paclitaxel.

Carboplatin

Anaphylaxis-like reactions to carboplatin have been reported and may occur within minutes of carboplatin administration. Epinephrine, corticosteroids, and antihistamines have been employed to alleviate symptoms.

Vomiting is another frequent drug-related side effect.

Carboplatin injection is contraindicated in patients with a history of severe allergic reactions to cisplatin or other platinum-containing compounds.

Carboplatin injection should not be employed in patients with severe bone marrow depression or significant bleeding.

For more details, refer to the carboplatin SmPC [4].

Nephrotoxicity Warning

The renal effects of nephrotoxic compounds may be potentiated by carboplatin.

Hematologic Warning

Bone marrow suppression is dose related and may be severe, resulting in infection or bleeding. Peripheral blood counts should be frequently monitored during carboplatin treatment and, when appropriate, until recovery is achieved.

Anemia may be cumulative and may require transfusion support.

Paclitaxel

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment; angioedema; and generalized urticaria have occurred in 2% to 4% of patients receiving paclitaxel in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteroids, diphenhydramine, and H2 antagonists. Patients who experience severe hypersensitivity reactions to paclitaxel should not be rechallenged with the drug.

Severe conduction abnormalities have been documented in less than 1% of patients during paclitaxel therapy and, in some cases, require pacemaker placement. If patients develop significant conduction abnormalities during paclitaxel infusion, appropriate therapy should be administered, and continuous cardiac monitoring should be performed during subsequent therapy with paclitaxel.

Paclitaxel is contraindicated in patients who have a history of hypersensitivity reactions to paclitaxel or other drugs formulated in Cremophor EL (polyoxyethylated castor oil).

For more details, refer to the paclitaxel SmPC [5].

Hematologic Warning

Paclitaxel injection therapy should not be given to patients with solid tumors who have baseline neutrophil counts of less than 1500 cells/mm³. To monitor for the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving paclitaxel injection.

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 (see [Appendix H](#)) may be potentiated by carboplatin.

4.2 Rationale for the Proposed Study

Pevonedistat is currently in phase 2 of clinical development across multiple solid tumors, AML, and higher risk MDS. This study is intended to provide a quantitative characterization of the mass balance, rates and routes of excretion, and metabolic pathways of pevonedistat in humans. Such definitive characterization will help guide understanding of the potential for patient-specific (eg, renal function, hepatic function) or extrinsic (eg, concomitant medications with potential to affect drug metabolism) factors to affect pevonedistat PK and, thereby, is important to inform the need for future clinical pharmacology studies (eg, special population studies in patients with organ impairment).

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

Pevonedistat will be administered in Part A, the absorption, distribution, metabolism, excretion (ADME) portion of this study, as a single 1-hour IV infusion of 25 mg/m² (equivalent to approximately 43 mg for a typical individual of 1.73 m² BSA, up to a maximum absolute dose of 50 mg) [¹⁴C]-pevonedistat (containing approximately 60-85 μCi [approximately 2.22-3.145 MBq]) as the radioactive tracer to allow mass balance evaluation and quantitative metabolite profiling in plasma, urine, and feces. On the basis of the available results from studies with SoC therapies, the recommended phase 2 dose of the combinations was determined to be 20 mg/m² pevonedistat (plus azacitidine or carboplatin/paclitaxel) or 25 mg/m² pevonedistat (plus docetaxel). These dose levels were chosen to study the highest potential dose of pevonedistat (in combination with SoC) to be further investigated in clinical development in any tumor type. On the basis of previous clinical observations, it is anticipated that a single IV dose administration of 25 mg/m² pevonedistat as single agent will be well tolerated. Additionally, [¹⁴C]-pevonedistat will be supplied in glass vials, each containing compounded sterile solution, at a concentration of 1 mg/mL (as free base). It was therefore determined that the maximum absolute dose of pevonedistat that can be accurately administered via infusion to a patient from a single vial is 50 mg; using BSA-adjusted dosing, individuals with BSA values greater than 2 m² will receive no more than 50 mg of pevonedistat in Part A of this study. As the clinical PK of pevonedistat is dose linear, this maximum selected dose of 50 mg based on the above described practical considerations does not affect the scientific objectives of the study or interpretation of the results.

Furthermore, the safety of the dose of radioactivity is supported by dosimetry calculations based on the results of quantitative whole body autoradiography studies in rats, while providing adequate sensitivity for radiometric detection in plasma, urine, and feces. [¹⁴C]-pevonedistat-derived radioactivity in male Long-Evans rats was well distributed at the end of a single 30-minute IV infusion of [¹⁴C]-pevonedistat, at a target dose of 5 mg/kg, through 4 hours postdose. Tissue

concentrations declined steadily over the course of the study, and elimination of radioactivity was observed in most tissues (24 of 40 tissues), which were below the lower limit of quantitation at 72 hours postdose; by 672 hours, all tissue concentrations, except the eye uveal tract, were below the lower limit of quantitation. It was estimated that the administration of a 100 μCi (3.70 MBq) IV infusion of [^{14}C]-pevonedistat would expose adult male human subjects to a total maximum weighted effective dose equivalent of 1.1077 mrem (0.0111 mSv). This is approximately 0.04% of the 3000 mrem single dose limit specified for whole-body exposure by the United States (US) Code of Federal Regulations (21 CFR: part 361.1, section b, 3i) and 1.1% of the 1 mSv single dose limit specified for whole-body exposure by the International Commission on Radiological Protection. In conclusion, an excessive individual tissue or whole-body exposure of male human subjects to ^{14}C is not expected to occur with a single IV infusion of up to 100 μCi (3.70 MBq) of [^{14}C]-pevonedistat.

The mean $t_{1/2z}$ of pevonedistat as parent drug was estimated to be approximately 10 hours (range 7.7-15.2 hours) across doses and schedules in adult patients with advanced malignancies. The human $t_{1/2z}$ of metabolites of pevonedistat is not known; therefore, the $t_{1/2z}$ of total drug-related material (parent drug+metabolites) cannot be accurately estimated. The estimated assessment period of 8 days (greater than 5 $t_{1/2z}$) takes into account potential metabolites that may have $t_{1/2z}$ that are up to 2 times that of parent drug for characterizing the PK of total radioactivity (TRA) and excretion of drug-related material in urine and feces.

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 maximum tolerated doses (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 (one 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 to the SmPCs for additional information [3-5].

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 (all 3 regimens).
- Their 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 recommended phase 2 doses have been determined for the combination of pevonedistat+docetaxel or pevonedistat+carboplatin/paclitaxel.

Therefore, it is thought 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 objectives are as follows:

- To assess the mass balance (ie, cumulative excretion of total radioactivity [TRA] in urine and feces) of pevonedistat following a single 1-hour infusion of 25 mg/m² [¹⁴C]-pevonedistat IV solution containing approximately 60 to 85 μCi (approximately 2.22-3.145 MBq) of TRA in patients with advanced solid tumors in Part A.
- To characterize the PK of pevonedistat in whole blood, plasma, and urine, and of TRA in plasma and whole blood following a single 1-hour infusion of 25 mg/m² [¹⁴C]-pevonedistat IV solution containing approximately 60 to 85 μCi (approximately 2.22-3.145 MBq) of TRA in patients with advanced solid tumors in Part A.

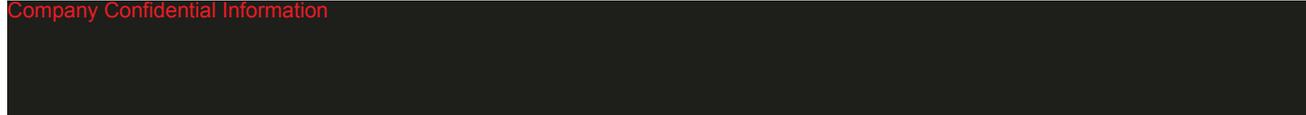
5.1.2 Secondary Objectives

The secondary objectives are as follows:

- To collect samples for characterization of the metabolic profile of pevonedistat in plasma, urine, and feces following a single 1-hour infusion of 25 mg/m² [¹⁴C]-pevonedistat IV solution containing approximately 60 to 85 μCi (approximately 2.22-3.145 MBq) of TRA (maximum dose of 50 mg) in patients with advanced solid tumors in Part A.
- To evaluate the safety and tolerability of pevonedistat in patients with advanced solid tumors after a single dose in Part A and in combination with either docetaxel or carboplatin+paclitaxel in Part B.
- To evaluate disease response that may be observed with the combination of pevonedistat and docetaxel or pevonedistat and carboplatin+paclitaxel in patients with advanced solid tumors (Part B).

5.1.3 Exploratory Objective

Company Confidential Information



5.2 Endpoints

5.2.1 Primary Endpoints

The primary endpoints are as follows:

- Summary statistics of PK parameters of pevonedistat and TRA in plasma and whole blood: C_{max} , time of first occurrence of C_{max} (t_{max}), and AUC from time zero to time of the last quantifiable concentration (AUC_{last}).
- Cumulative percentage of urinary recovery, percentage of fecal excretion, and percentage of TRA in urine and feces over the entire period of collection.
- Summary statistics of PK parameters of pevonedistat in urine: cumulative amount excreted in urine (A_{urine} and percentage of dose) and renal clearance (CLR).

5.2.2 Secondary Endpoints

The secondary endpoints are as follows:

- Safety parameters: AEs, SAEs, and abnormal laboratory values reported.
- Metabolite profiles in plasma, urine, and feces.
- Measures of disease response based on investigator's assessment using the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (Version 1.1) [6].

5.2.3 Exploratory Endpoint

Company Confidential Information



6.0 STUDY DESIGN

6.1 Overview of Study Design

This is a 2-part, open-label, multicenter, mass balance and ADME study in adult patients with advanced solid tumors. It is expected that approximately 4 to 6 PK-evaluable patients will be enrolled in this study. Once enrolled into the study, patients will be administered a single dose of [¹⁴C]-pevedistat via IV infusion.

In the first part of the study, patients will remain at the Part A study site for approximately 8 consecutive days (or until the discharge criteria are met, with a maximum estimated confinement period of 9-14 days) to measure mass balance and PK, followed by a washout period of approximately 2 weeks.

In the optional second part of the study, patients will receive pevedistat in combination with docetaxel or pevedistat in combination with carboplatin+paclitaxel at a secondary study site. Patients may receive pevedistat combination therapy for 12 cycles, or longer if the investigator and sponsor agree that a patient would benefit from continued treatment (see Section 6.3.4), or until discontinuation criteria are met (see Section 9.8). Patients will attend the End-of-Study (EOS) visit 30 days after receiving their last dose of study drug.

6.1.1 Part A: Mass Balance/ADME Assessment

Part A represents the period for assessment of the mass balance, PK, metabolism, and elimination of pevedistat in this population. Patients will be required to stay at the Part A study site for approximately 8 days or until the discharge criteria are met (see Section 9.5.17), with a maximum estimated confinement period of 9 to 14 days.

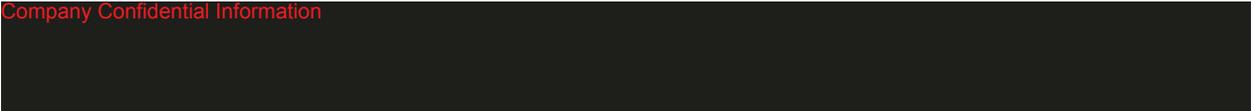
Patients who meet all inclusion criteria and no exclusion criteria will be assigned a patient number and will be admitted to the Part A study site on the morning of Day -1 for predose assessments and to begin confinement. On the morning of Day 1, patients will receive a single dose of 25 mg/m² (equivalent to approximately 43 mg for a typical individual of 1.73 m² BSA, with a maximum absolute dose of up to 50 mg) [¹⁴C]-pevedistat IV solution (containing approximately 60-85 μCi [approximately 2.22-3.145 MBq] of TRA) via a 1-hour infusion. The actual amount of administered radioactivity will be documented for each patient.

Patients will be closely monitored for AEs throughout the study. Safety will be assessed by monitoring vital signs, physical examinations (including weight at Day 1 predose and EOS), electrocardiograms (ECGs), and clinical laboratory tests.

Blood will be collected at prespecified time points in [Appendix A](#) for analyses of pevedistat and TRA PK and for metabolite profiles over the confinement period. Complete urinary and fecal output will be collected throughout the confinement period until discharge; urine samples will be analyzed for PK, TRA, and biotransformation, and fecal samples will be analyzed for TRA and products of pevedistat biotransformation. For patients who experience emesis during the first 24 hours after drug administration, the vomitus will be collected as much as possible and assayed

for TRA. If a subject vomits more than once during the period, vomitus corresponding to each vomiting event will be collected in a separate labeled container and separately counted. Refer to the Study Manual for further details. To ensure defecation before release from the Part A study site, two 15 mL doses of oral lactulose will be administered, separated by approximately 2 hours, on the evening of Day 4; the second dose of lactulose will be withheld if the first dose was not tolerated. Patients will be required to stay at the Part A study site for approximately 8 days or until the discharge criteria are met, with a maximum estimated confinement period of 9 to 14 days. See Section 9.5.17 for Part A discharge criteria.

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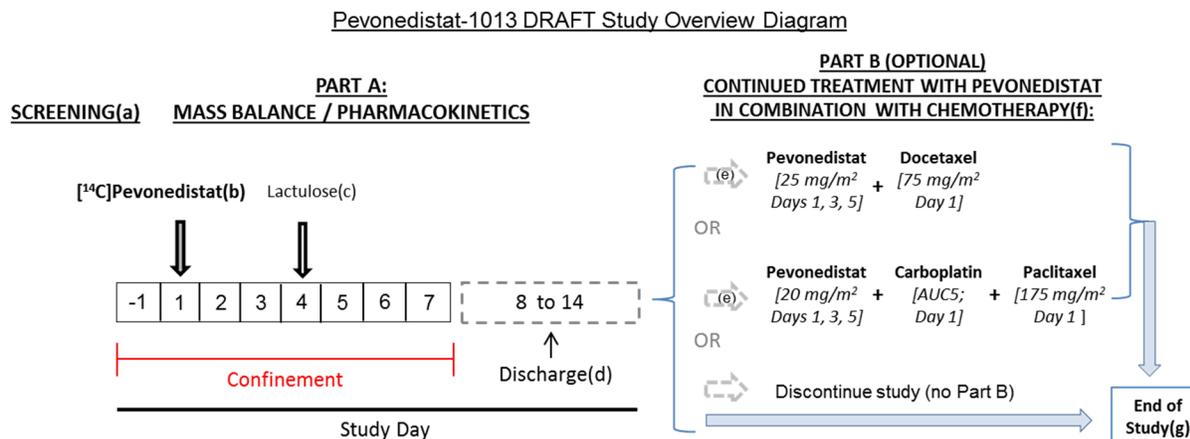
6.1.2 Part B: Continued Treatment With Pevonedistat in Combination With Chemotherapy (OPTIONAL)

After completion of the mass balance/ADME assessment portion of the study, patients will have the opportunity to continue into Part B at a secondary study site, which can begin within approximately 2 weeks of the patient completing Part A (ie, when the patient has met the Part A discharge criteria; see Section 9.5.17). Participation in Part B is optional. Any patient who continues on to Part B will need to be re-evaluated for entry criteria before treatment in Part B can begin. Patients will receive pevonedistat in combination with either docetaxel or carboplatin+paclitaxel as recommended by the investigator. On the basis of the MTDs determined in Study C15010, patients will receive pevonedistat on Days 1, 3, and 5 at the dose of 25 mg/m² in combination with docetaxel 75 mg/m² on Day 1 every 3 weeks, or pevonedistat on Days 1, 3, and 5 at the dose of 20 mg/m² in combination with carboplatin AUC5+paclitaxel 175 mg/m² every 3 weeks on Day 1. Safety and disease assessments will be conducted in Part B of the study. Disease assessments will be conducted using radiological evaluations (computed tomography [CT] scan or magnetic resonance imaging [MRI] as clinically indicated) to assess the status of the patient's underlying disease and will be part of the entry criteria for Part B (see Section 9.5.18).

Toxicity will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03, effective date 14 June 2010 [7]. Dose-limiting toxicities are defined in Section 8.3.

See Figure 6.a for an overview of the study design of Parts A and B.

Figure 6.a Study Overview



- (a) Screening assessments will be performed within 28 days before administration of [¹⁴C]-pevonedistat.
- (b) On the morning of Day 1, following the collection of Day 1 predose assessments, patients will receive a single dose of 25 mg/m² (equivalent to approximately 43 mg for a typical individual of 1.73 m² BSA up to a maximum absolute dose of 50 mg) [¹⁴C]-pevonedistat IV solution (containing approximately 60-85 μCi [approximately 2.22-3.145 MBq] of TRA) via a 1-hour infusion.
- (c) Two 15 mL doses of oral lactulose will be administered, separated by approximately 2 hours, on the evening of Day 4; the second dose of lactulose will be withheld if the first dose was not tolerated. Lactulose may also be administered as needed.
- (d) During Part A, patients will be required to stay at the Part A study site for approximately 8 days or until the discharge criteria are met, with a maximum estimated confinement period of 9 to 14 days.
- (e) Eligible patients may continue into Part B (optional), which can begin within approximately 2 weeks of the patient completing Part A (ie, when the patient has met the discharge criteria). Cycle length is 21 days. Treatment assignment in Part B will be based on recommendation by the investigator.
- (f) 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.
- (g) Patients will attend an EOS visit 30 days (+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.

6.2 Number of Patients

In this study, 4 to 6 PK-evaluable patients will be enrolled at the Part A study site in Europe. 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 or are not considered evaluable for PK will be replaced.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

Patients will be required to stay at the Part A study site for approximately 8 days or until the discharge criteria are met, with a maximum estimated confinement period of 9 to 14 days.

Eligible patients may have the **option** to continue to receive treatment at a secondary site in Part B of this study until discontinuation criteria are met (see Section 9.8). 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.

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.

Patients will attend an EOS visit 30 days (+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.

It is anticipated that an individual patient will participate in this study for approximately 8 days in Part A or a total of approximately 36 weeks for Parts A and B combined for those patients who participate in the optional Part B.

6.3.2 EOS/Study Completion Definition and Planned Reporting

Primary Completion/Study Completion

The analyses for the clinical study report may be conducted after all patients enrolled in the study have provided assessments in Part A to meet the primary (ADME) objectives 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 36 weeks for Parts A and B combined.

6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures

Refer to [Table 6.a](#) for disclosures information for all primary and secondary endpoints.

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame
Primary: Summary statistics of PK parameters of pevonedistat and TRA in plasma and whole blood	Maximum observed concentration (C_{max}) Time of first occurrence of C_{max} (t_{max}) Area under the plasma concentration-time curve from time zero to time of the last quantifiable concentration (AUC_{last})	Up to 168 hours postdose (± 4 hours)
Primary: Cumulative percentage of urinary recovery, percentage of fecal excretion, and percentage of TRA in urine and feces over the entire period of collection	Cumulative amount of [^{14}C]-radioactivity excreted in urine up to the last sampling interval ($Ae_{urine, ^{14}C}$). Cumulative amount of [^{14}C]-radioactivity excreted in feces up to the last sampling interval ($Ae_{feces, ^{14}C}$). Total cumulative excretion of [^{14}C]-radioactivity from the body ($Ae_{total, ^{14}C} = Ae_{urine, ^{14}C} + Ae_{feces, ^{14}C}$)	Up to 168 hours postdose (± 4 hours)
Primary: Summary statistics of PK parameters of pevonedistat in urine: cumulative amount excreted in urine ($Ae_{urine,t}$ and % of dose) and CL_R	Cumulative amount of pevonedistat excreted in urine (Ae_{urine} and percent of dose) Renal clearance (CL_R)	Up to 168 hours postdose (± 4 hours)
Secondary: Metabolite profiling	Determination of relative percentage of circulatory and excretory metabolites	Up to 168 hours postdose (± 4 hours)
Secondary: Safety parameters: AEs, SAEs, and abnormal laboratory values reported	Abnormal laboratory values are those outside of normal range. See Section 10.1 for AE and SAE definitions.	AEs recorded from start of study administration through 30 days (+10 days) after the last dose of study drug. This will include serious pretreatment events. SAEs will be reported from signing of the informed consent form through 30 days (+10 days) after the last dose of study drug. Laboratory tests up to EOS

6.3.4 Total Study Duration

It is anticipated that this study will last for approximately 36 weeks. 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.

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.

7.0 STUDY POPULATION

Confirmation of eligibility must be obtained before the patient can enter the study. After completion of Part A, patients who are to continue into Part B must meet the entry criteria listed in Section 9.5.18.

7.1 Inclusion Criteria

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

1. Male or female patients aged 18 years or older.
2. Patients must have a histologically or cytologically confirmed metastatic or locally advanced and incurable solid tumor that is felt to be appropriate for treatment with one of the 2 chemotherapy regimens in Part B of this study (carboplatin+paclitaxel or docetaxel), or have progressed despite prior standard therapy, or for whom conventional therapy is not considered effective. The tumor must be radiographically or clinically evaluable and/or measurable.
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.
4. Expected survival longer than 3 months from enrollment in the study.
5. Recovered (ie, \leq Grade 1 toxicity) from the effects of prior antineoplastic therapy.
6. Clinical laboratory values as specified below within 3 days before the first dose of study drug:
 - Hemoglobin \geq 9 g/dL. Patients may be transfused to achieve this value.
 - Total bilirubin \leq ULN.
 - ALT, AST, and ALP \leq 2.5 \times ULN.
 - For patients to be treated with pevonedistat+docetaxel in Part B, AST and ALT must be \leq 1.5 \times ULN, and total bilirubin should be within the normal range.
 - Calculated creatinine clearance \geq 50 mL/min (creatinine clearance is defined in Section 9.5.13.1).
 - ANC \geq 1,500/mm³.
 - Platelet count \geq 100,000/mm³.
 - Prothrombin time and activated partial thromboplastin time \leq 1.5 \times ULN.
 - Albumin \geq 2.7 g/dL.
7. Suitable venous access for the study-required blood sampling (including PK sampling).
8. Female patients who:
 - Are postmenopausal for at least 1 year before the Screening visit (see
 - [Appendix J](#)), or

- Are surgically sterile, or
 - If they are of childbearing potential, they and their male partners agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception (see [Appendix K](#)) 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:
- 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 for the female partner] 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 dose of pevonedistat and (for male patients) willing to refrain from donating semen for at least 4 months after their 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. Subject has irregular defecation patterns (less than 1 defecation per 2 days or excessive diarrhea) and/or has a history of changes in bowel habits with daily routine or environment changes.
3. Treatment with any systemic antineoplastic therapy or any investigational products within 21 days before the first dose of study treatment.
4. Major surgery within 14 days before the first dose of study treatment or scheduled surgery during Part A of the study.
5. Receiving antibiotic therapy within 14 days before the first dose of study treatment.
6. Radiotherapy within 14 days before the first dose of study treatment.

7. Prior treatment with radiation therapy involving $\geq 25\%$ of the hematopoietically active bone marrow.
8. Treatment with moderate or strong CYP3A inhibitors or inducers within 14 days before the first dose of pevedistat. Patients must have no history of amiodarone use in the 6 months before the first dose of pevedistat.
9. Prior treatment with pevedistat; however, prior treatment with docetaxel, paclitaxel, and carboplatin is allowed.
10. 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 pevedistat+docetaxel; history of hypersensitivity to carboplatin for patients to be treated with pevedistat+ carboplatin+paclitaxel; or history of severe hypersensitivity to paclitaxel (Cremophor-based formulations) for patients to be treated with pevedistat+carboplatin+ paclitaxel.
11. 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.
12. Active, uncontrolled infection or severe infectious disease, such as severe pneumonia, meningitis, septicemia, or methicillin-resistant *Staphylococcus aureus* infection within 2 weeks before dosing.
13. Known human immunodeficiency virus (HIV) 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.
14. History of urinary and/or fecal incontinence.
15. Persistent diarrhea (\geq Grade 2) lasting >3 days within 2 weeks before the first dose of study treatment.
16. Clinically significant central nervous system disease defined as newly diagnosed, untreated, progressive, or requiring steroids for control of symptoms.
17. Newly diagnosed or uncontrolled cancer-related central nervous system disease.
18. Known hepatic cirrhosis or severe pre-existing hepatic impairment.
19. Uncontrolled high blood pressure (ie, systolic blood pressure >180 mm Hg, diastolic blood pressure >95 mm Hg).
20. Left ventricular ejection fraction $<50\%$ as assessed by echocardiogram or radionuclide angiography.

21. 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. In addition, 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 I](#)) may enroll.
22. 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.
23. Prolonged rate corrected QT interval (QTc) ≥ 500 msec, calculated according to institutional guidelines.
24. Implantable cardioverter defibrillator.
25. 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).
26. Moderate to severe aortic stenosis, moderate to severe mitral stenosis, or other valvulopathy (ongoing).
27. Known moderate to severe chronic obstructive pulmonary disease, interstitial lung disease, pulmonary fibrosis, or pulmonary arterial hypotension.
28. 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.
29. 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.
30. Male patients who intend to donate sperm during the course of this study or 4 months after receiving their last dose of study drug.
31. Patient requiring chronic treatment with BCRP or P-gp inhibitors. Refer to [Table 8.b](#) for the list of known BCRP and P-gp inhibitors.

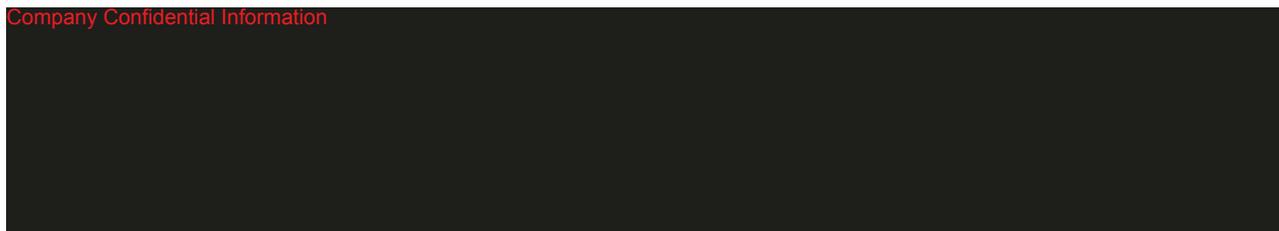
8.0 STUDY DRUG

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

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Patients will receive a single dose of pevonedistat given as an IV infusion on Day 1. The clinic will be supplied with vials containing approximately 60 to 98 μCi (approximately 2.22-3.626 MBq) of [^{14}C]-pevonedistat as the radioactive tracer.

Patients will receive [^{14}C]-pevonedistat via a 60-minute (± 5 minutes) IV infusion. [^{14}C]-pevonedistat should be administered through central or peripheral venous access. The start and end times of the IV infusion should be recorded accurately. **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. All infusion times must be recorded. Refer to the Pharmacy Manual for the preparation of the IV infusion.

Samples will continue to be collected at 24-hour intervals until radioactivity in urine and feces combined is $\leq 1\%$ per day of the total administered radioactivity for at least 2 consecutive days or the excretion of radioactivity is $\geq 80\%$ of the administered radioactive dose. When radioactivity levels have fallen below these thresholds, patients can be discharged from the Part A study site. See Section 9.5.17 for Part A discharge criteria.

8.1.2 Part B

8.1.2.1 Pevonedistat Administration

Patients opting to continue into Part B will receive combination treatment with pevonedistat and chemotherapy. Two chemotherapy regimens, docetaxel and carboplatin+paclitaxel, will be used in this study as combination partners with pevonedistat.

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Concentrate is diluted in 5% dextrose for administration.

Patients will receive pevonedistat diluted with 5% dextrose in a 250 mL bag via a 60-minute 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 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.

8.1.2.2 Docetaxel Administration

On Day 1 of each cycle, when all study drugs are administered together, docetaxel 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 most recent SmPC for further details regarding docetaxel administration [3].

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 (Decadron, 4 mg BID 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 3 hours followed by carboplatin as a 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 most recent SmPC for further details regarding carboplatin administration [4].

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 due to overdosing. Using the Calvert formula described in the carboplatin label, the maximum doses can be calculated as:

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 most recent SmPC for further details regarding paclitaxel administration [5].
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 methylprednisone (solu-Medrol) 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 for each new cycle will be delayed until toxicity is reduced to ≤Grade 1 or 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 2 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. **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.

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 (to 15 mg/m²) 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.

The following are dose modification guidelines for specific toxicities:

- Alopecia of any duration will not lead to dose modification or treatment delay.
- Patients receiving pevonedistat+docetaxel may have a maximum of 2 dose modifications (if applicable) of chemotherapy agents as outlined below or modification of pevonedistat (see Section 8.3).
- 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 Section 8.3).
 - Paclitaxel is initially dosed at 175 mg/m². One dose reduction to 135 mg/m² 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 (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/ μ L on Day 1 of Cycles ≥ 2	Initiation (Day 1) of Cycles ≥ 2 should be delayed for up to 3 weeks (Section 8.3.4) until ANC is ≥ 1500 cells/ μ L. Consider use of growth factor or reduce chemotherapy by 1 dose level as appropriate.
	Grade ≥ 3 neutropenia lasting more than 7 days	Initiation (Day 1) of Cycles ≥ 2 should be delayed until ANC is ≥ 1500 cells/ μ L. Consider use of growth factor or reduce chemotherapy by 1 dose level as appropriate.
Hematologic: Platelets	Platelet count <100,000/ μ L on any dosing day of Cycles ≥ 2	Dosing in Cycles ≥ 2 should be delayed for up to 3 weeks (Section 8.3.4) until platelet count is $\geq 100,000$ cells/ μ L. Dose of chemotherapy may be reduced by 1 dose level as appropriate.
	Grade 4 thrombocytopenia lasting more than 7 days or platelet count <25,000 cells/ μ L at any time	Dosing in Cycles ≥ 2 should be delayed until platelet count is $\geq 100,000$ cells/ μ L (Section 8.3.4). Dose of chemotherapy may be reduced by 1 dose level as appropriate.
Hematologic: Anemia	\geq 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	\geq Grade 3	On days that both chemotherapy and pevonedistat are administered, hold all dosing for up to 3 weeks (Section 8.3.4) or until the toxicity returns to \leq Grade 1, then restart at the next lower dose of chemotherapy. On days when pevonedistat is given as a single agent, hold dosing of pevonedistat for up to 3 weeks (Section 8.3.4) or until the toxicity returns to \leq 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.

Table 8.a Dose Modification Guidelines for Specific Toxicities (continued)

Pathologic Condition	Severity	Action on Study Drug
Stomatitis	≥Grade 3	Hold treatment for up to 3 weeks until the stomatitis is ≤Grade 1 (Section 8.3.4). If acute ≥Grade 3 stomatitis occurs at any time, the dose of chemotherapy should be reduced 1 level. This is a permanent dose reduction.
Hepatic toxicity	ALT/AST ≥Grade 3 at any time	If ALT or AST is ≥Grade 3 at any time, withhold pevonedistat dosing until patient has recovered to ≤Grade 1 (see Section 8.3 for further details on dose modification of pevonedistat; also see Section 8.3.4 for discontinuation). In addition, if toxicity is felt to be attributable to the chemotherapy agent(s), consider dose reduction for chemotherapy also by 1 dose level.
Hepatic toxicity	Total bilirubin >1.5×ULN, regardless of ALT/AST	Hold all dosing for up to 3 weeks (Section 8.3.4) until bilirubin returns to within normal range and/or dose reduce chemotherapy by 1 level and/or modify pevonedistat dose (see Section 8.3).
Cardiac toxicity	Symptomatic arrhythmia during infusion	Stop infusion and manage arrhythmia according to institutional guidelines. Report as AE and discontinue further dosing.
Cardiac toxicity	Chest pain and/or symptomatic hypotension (<90/60 mmHg)	Stop infusion. Perform an ECG. Give IV diphenhydramine and dexamethasone if hypersensitivity is thought to be the etiology. Also, consider epinephrine or bronchodilators if chest pain is not thought to be cardiac. If >Grade 3, discontinue patient from the study.
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 (Section 8.3.4). This will be a permanent dose reduction. Carboplatin or pevonedistat are not to be dose modified.
Allergic reaction (paclitaxel or docetaxel only)	Moderate symptoms	Stop infusion. Give IV diphenhydramine 25 to 50 mg and IV dexamethasone 10 mg and/or treatment per institutional guidelines. Resume infusion after recovery of symptoms at a low infusion rate. If no further symptoms, resume full dose rate until infusion is complete. If symptoms recur, stop infusion and discontinue patient.
Allergic reaction (paclitaxel or docetaxel only)	Severe symptoms	Stop infusion. Give IV diphenhydramine and dexamethasone and/or treatment per institutional guidelines as above. Add epinephrine or bronchodilators if indicated. Report as an AE 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) of chemotherapy agents or modification of pevonedistat (see Section 8.3). 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 Excluded Concomitant Medications and Procedures (Part A)

Medications and procedures that are prohibited in Part A are listed in [Table 8.b](#).

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	eg, cyclosporine and eltrombopag (Promacta)
Moderate and strong CYP3A4 inhibitors and clinically significant CYP3A4 inducers	See Appendix F
Known P-gp inhibitors	eg, azithromycin (Zithromax), captopril, carvedilol, felodipine, quercetin, quinidine, ranolazine, ticagrelor

8.4.2 Excluded Concomitant Medications and Procedures (Part B)

Medications and procedures that are prohibited in Part B are listed in [Table 8.c](#).

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 (ie, cyclosporine and eltrombopag [Promacta])	Generally excluded during the study but may be used as specified in Table 8.e
Strong CYP3A4 inhibitors and clinically significant CYP3A4 inducers	Generally excluded during the study but may be used as specified in Appendix F
Systemic antineoplastic therapy unless specified in the protocol as part of the combination with pevonedistat	

This list is not all-inclusive; consult the docetaxel, carboplatin, and paclitaxel SmPCs [3-5] for additional information regarding precautions, warnings, and contraindications.

8.5 Permitted Concomitant Medications and Procedures

8.5.1 Permitted Concomitant Medications and Procedures (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	Whenever possible, caution should be used with nephrotoxic concomitant medications (Appendix H). Alternative concomitant non-nephrotoxic 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.
Red blood cell 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 red blood cell transfusions based on the patient's risk of inadequate oxygenation, underlying cardiopulmonary status, clinical judgment, and hospital guidelines. Red blood cell transfusions must be administered at least 1 day before administration of study drug. Each transfusion episode, including the type of transfusion (red blood cell), should be recorded.

8.5.2 Permitted Concomitant Medications and Procedures (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
Azole antifungal agents	Limited use of the azole antifungal agent, voriconazole, is permitted (if clinically necessary and no suitable alternative exists). The patient may receive voriconazole 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), Friday (Day 5) schedule, then voriconazole may be administered (if clinically necessary and no suitable alternative) from the Saturday after the Day 5 dose (Day 6) up to the Friday (Day 19) before the Monday dose of the next cycle.
Antiemetic agents	Antiemetic agents, including for prophylactic use, may be administered at the discretion of the investigator.
Known BCRP inhibitors (ie, cyclosporine and eltrombopag [Promacta])	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	Whenever possible, caution should be used with nephrotoxic concomitant medications (Appendix G). Alternative concomitant non-nephrotoxic medications should be used whenever possible.
Red blood cell 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 red blood cell transfusions based on the patient's risk of inadequate oxygenation, underlying cardiopulmonary status, clinical judgment, and hospital guidelines. Red blood cell transfusions must be administered at least 1 day before administration of study drug. Each transfusion episode, including the type of transfusion (red blood cell), 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 [8.4.1](#) and [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 group and male patients should use highly effective methods of contraception through defined periods during and after study treatment as specified below.

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

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2. Female patients must meet 1 of the following:
 - Postmenopausal for at least 1 year before the Screening visit (see [Appendix J](#)), or
 - Surgically sterile, or
 - If they are of childbearing potential (as defined in Section [9.5.7](#)), they and their male partners agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception (see [Appendix K](#)) 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.)
 - Female patients must agree to not donate eggs (ova) during the course of this study or 4 months after receiving their last dose of study drug.
3. Male patients, even if surgically sterilized (ie, status postvasectomy) must agree to 1 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, (if barrier methods are not locally approved to be used by males, then their female partners should use effective contraceptive methods as described in the above) 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.)
 - Male patients must agree to not donate sperm during the course of this study or 4 months after receiving their last dose of study drug.

8.6.2 Docetaxel

8.6.2.1 Pregnancy

Docetaxel is a pregnancy Category D drug. Refer to the docetaxel SmPC for more information [[3](#)].

Docetaxel can cause fetal harm when administered to a pregnant woman. Docetaxel caused embryo-fetal toxicities including intrauterine mortality when administered to pregnant rats and rabbits during the period of organogenesis. Embryo-fetal effects in animals occurred at doses as low as 1/50 and 1/300 the recommended human dose on a BSA basis.

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. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with docetaxel [3].

8.6.2.2 Geriatric Use

Refer to the docetaxel SmPC for additional information on geriatric use in different types of cancer [3].

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 in elderly patients.

8.6.3 Carboplatin

8.6.3.1 Pregnancy

Carboplatin is a pregnancy Category D drug. Refer to the carboplatin injection SmPC for more information [4].

Carboplatin injection may cause fetal harm when administered to a pregnant woman. Carboplatin has been shown to be embryotoxic and teratogenic in rats. There are no adequate and well-controlled studies in pregnant women. If this drug 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. Women of childbearing potential should be advised to avoid becoming pregnant [4].

8.6.3.2 Geriatric Use

Refer to the carboplatin SmPC for additional information on geriatric use [4].

Of the 789 patients in initial treatment combination therapy studies (National Cancer Institute of Canada and Southwest Oncology Group), 395 patients were treated with carboplatin in combination with cyclophosphamide. Of these, 141 were aged greater than 65 years and 22 were aged 75 years or older. In these trials, age was not a prognostic factor for survival. In terms of safety, elderly patients treated with carboplatin were more likely to develop severe thrombocytopenia than younger patients. In a combined database of 1942 patients (414 were aged ≥ 65 years) who received single-agent carboplatin for different tumor types, a similar incidence of AEs was seen in patients aged 65 years and older and in patients aged less than 65 years. Other reported clinical experience has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Because renal function is often decreased in the elderly, renal function should be considered in the selection of carboplatin dosage.

8.6.4 Paclitaxel

8.6.4.1 Pregnancy

Paclitaxel is a pregnancy Category D drug. Refer to the paclitaxel injection SmPC for more information [5].

Paclitaxel injection can cause fetal harm when administered to a pregnant woman. Administration of paclitaxel during the period of organogenesis to rabbits at doses of 3 mg/kg/day (about 0.2 the daily maximum recommended human dose on a mg/m² basis) caused embryo- and fetotoxicity, as indicated by intrauterine mortality, increased resorptions, and increased fetal deaths.

Maternal toxicity was also observed at this dose. No teratogenic effects were observed at 1 mg/kg/day (about 1/15 the daily maximum recommended human dose on a mg/m² basis); teratogenic potential could not be assessed at higher doses due to extensive fetal mortality.

There are no adequate and well-controlled studies in pregnant women. If paclitaxel injection 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. Women of childbearing potential should be advised to avoid becoming pregnant [5].

8.6.4.2 Geriatric Use

Refer to the paclitaxel SmPC for additional information [5].

Of 2228 patients who received paclitaxel in 8 clinical studies evaluating its safety and effectiveness in the treatment of advanced ovarian cancer, breast carcinoma, or NSCLC, and 1570 patients who were randomized to receive paclitaxel in the adjuvant breast cancer study, 649 patients (17%) were aged 65 years or older, and 49 patients (1%) were aged 75 years or older. In most studies, severe myelosuppression was more frequent in elderly patients; in some studies, severe neuropathy was more common in elderly patients. In 2 clinical studies in NSCLC, elderly patients treated with paclitaxel had a higher incidence of cardiovascular events. Estimates of efficacy appeared similar in elderly patients and in younger patients; however, comparative efficacy cannot be determined with confidence because of the small number of elderly patients studied. In a study of first-line treatment of ovarian cancer, elderly patients had a lower median survival than younger patients, but no other efficacy parameters favored the younger group.

8.7 Management of Clinical Events

Specific recommendations for the management of pevonedistat clinical events that were identified from toxicology studies in dogs and rats and from early experience in ongoing clinical studies are outlined in the pevonedistat current IB, which includes the DCSI (Appendix A of the IB).

The most common adverse drug reactions for docetaxel and for paclitaxel+carboplatin are described in Section 4.1.4. Refer to the applicable SmPC for additional details regarding the management of clinical events attributed to these agents [3-5].

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, red blood cell 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 red blood cell 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. If granulocyte-colony stimulating factor is used, it should be used in accordance with the European Society for Medical Oncology guidelines [8].

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, red blood cell 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 red blood cell transfusion should be recorded in the eCRFs.

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

8.8 Blinding and Unblinding

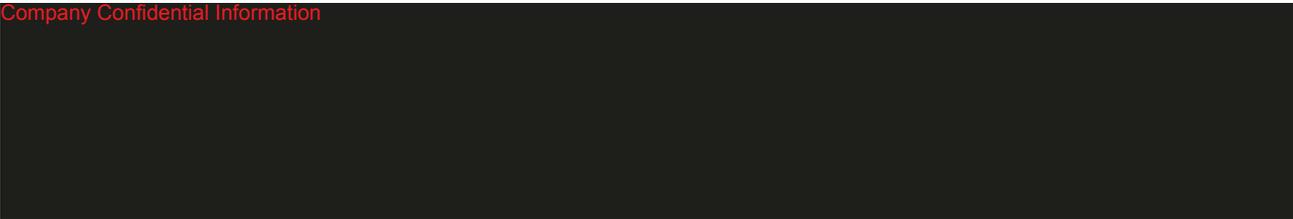
This is an open-label study.

8.9 Description of Investigational Agents

8.9.1 Pevonedistat

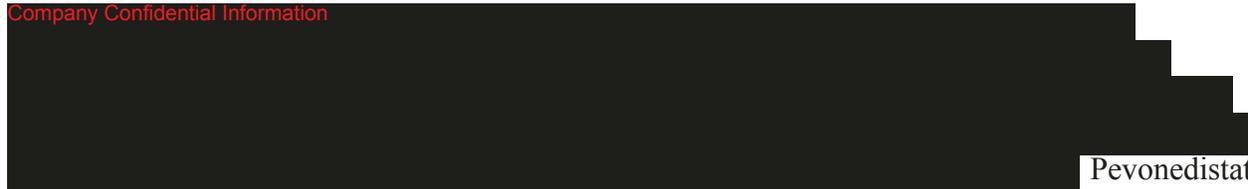
8.9.1.1 Part A

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8.9.1.2 Part B

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Pevonedistat

Concentrate is diluted in 5% dextrose for administration.

8.9.2 Docetaxel

Docetaxel is obtained from commercial sources according to local practice standards and is provided as a commercially available dosage formulation. Refer to the docetaxel SmPC [3].

8.9.3 Carboplatin

Carboplatin is obtained from commercial sources according to local practice standards and is provided as a commercially available dosage formulation. Refer to the carboplatin SmPC [4].

8.9.4 Paclitaxel

Paclitaxel is obtained from commercial sources according to local practice standards and it is provided as a commercially available dosage formulation. Refer to the paclitaxel SmPC [5].

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.

Pevonedistat, docetaxel, paclitaxel, and carboplatin are anticancer drugs, and as with other potentially toxic compounds, caution should be exercised when handling pevonedistat and 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, and Paclitaxel

Refer to the SmPCs for docetaxel, paclitaxel, and carboplatin for instructions and precautions regarding preparation [3-5].

8.11 Packaging and Labeling

8.11.1 Pevonedistat

[¹⁴C]-pevonedistat will be provided in USP Type I glass vials containing compounded sterile solution, at a concentration of 1 mg/mL (as free base), sealed with a coated butyl rubber stopper and oversealed with an aluminum seal.

8.11.2 Docetaxel, Carboplatin, and Paclitaxel

Docetaxel, paclitaxel, and carboplatin may be sourced locally by the clinical site when arrangements have been made and agreed to by Takeda and the clinical site 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 or storage will be communicated to the investigator and detailed in the Study Manual.

8.12 Storage, Handling, and Accountability

8.12.1 Pevonedistat

[¹⁴C]-pevonedistat will be provided in USP Type I glass vials containing 1 mg/mL of compounded sterile solution sealed with a coated butyl rubber stopper and oversealed with an aluminum seal. Vials should be stored at 5°C until use, allowed to reach room temperature (1 hour) before use, and used within 72 hours of manufacture.

8.12.2 Docetaxel, Carboplatin, and Paclitaxel

Refer to the SmPCs for the docetaxel, paclitaxel, and carboplatin for instructions and precautions regarding preparation [3-5].

8.13 Other Protocol-Specified Materials

Refer to the Pharmacy Manual.

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 contract research organization (CRO) team, and other vendors can be found in the Project Management Plan. 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).

9.3 Treatment Group Assignments

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

In optional Part B, patients will be assigned to pevonedistat 25 mg/m² in combination with docetaxel 75 mg/m² or pevonedistat 20 mg/m² in combination with carboplatin AUC5+paclitaxel 175 mg/m² as recommended by the investigator.

9.4 Confinement and Overnight Visits

In Part A, patients will check into the clinic on Day -1 and be confined from Day -1 to Day 7 as specified in the Schedule of Events ([Appendix A](#)). Patients will be required to stay at the Part A study site for approximately 8 days or until the discharge criteria are met (Section [9.5.17](#)), with a maximum estimated confinement period of 9 to 14 days.

9.5 Study Procedures

Refer to the Schedule of Events ([Appendix A](#)) for timing of assessments. Additional details are provided as necessary in the sections that follow.

9.5.1 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.

9.5.2 Patient Demographics

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

9.5.3 Medical History

During the Screening period, a complete medical history 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 8.5.

9.5.4 Physical Examination

Full and symptom-driven physical examinations will be completed per SoC at the times specified in the Schedule of Events ([Appendix A](#)).

9.5.5 Patient Height

Height will be measured only during Screening.

9.5.6 Vital Signs

Vital signs, including diastolic and systolic blood pressure, heart rate, weight, and body temperature, will be collected as indicated in the Schedule of Events ([Appendix A](#)) and as clinically indicated. All vital signs will be taken in the sitting position, as noted in the Schedule of Events ([Appendix A](#)).

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 Schedule of Events ([Appendix A](#)).

9.5.7 Pregnancy Test

A serum pregnancy test will be performed for women of childbearing potential at Screening, Day -1, and the EOS visit in Part A ([Appendix A](#)). In Part B, a pregnancy test must also be performed for women of childbearing potential at every cycle (typically performed on Day 1 of the 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 that cycle. A 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:

1. Those who have not undergone hysterectomy or bilateral oophorectomy, and
2. Those who have not had natural menopause ([Appendix J](#)) for 12 consecutive months or longer (eg, 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).

9.5.8 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 days (+10 days) after the last dose of study drug(s). See Sections 0 and 8.4 for additional details regarding excluded and permitted concomitant medications and procedures.

9.5.9 AEs

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the Schedule of Events. Refer to Section 10.0 for details regarding definitions, documentation, and reporting of pretreatment events, AEs, and SAEs.

For Part B only, refer to [Table 8.a](#) for dose modifications related to AEs.

9.5.10 Enrollment

Enrollment is achieved when the first dose of any study drug has been administered.

Procedures for completion of the enrollment information are described in the Pharmacy and Study Manuals.

9.5.11 Echocardiogram

An echocardiogram will be performed at Screening as indicated in the Schedule of Events ([Appendix A](#)).

9.5.12 ECG

A 12-lead ECG will be performed as indicated in the Schedule of Events ([Appendix A](#)). When the timing of ECG assessment coincides with the timing of a blood draw, ECG assessments will be completed before the collection of the blood sample unless otherwise noted in the Schedule of Events ([Appendix A](#)).

For Part B only, refer to [Table 8.a](#) for dose modifications related to cardiotoxicity.

9.5.13 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.

9.5.13.1 Clinical Chemistry, Hematology, and Urinalysis

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 Schedule of Events ([Appendix A](#)).

Table 9.a Clinical Chemistry and Hematology Tests

Hematology	Serum Chemistry	
Hemoglobin	ALT	Calcium
Hematocrit	ALP	Chloride
Leukocytes with differential	AST	Carbon dioxide (CO ₂)/Bicarbonate
Neutrophils (ANC)	Bilirubin (total)	Magnesium
Platelet (count)	Blood urea nitrogen (BUN)	
	Creatinine	
	Direct bilirubin	
	Glucose	
	Lactate dehydrogenase (LDH)	
	Phosphate Albumin	
	Potassium	
	Sodium	
	Urate	
<u>Part A Screening:</u>	<u>Part A Screening:</u>	<u>Parts A and B:</u>
Activated partial thromboplastin time	D-dimer	Coagulation panel, if applicable (a)
Coagulation panel (a)	Fibrinogen	
Prothrombin time (PT) international normalized ratio (INR)		

(a) If the initial coagulation screen is positive (ie, results are outside of 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, then no further coagulation studies need to be done.

Table 9.b Clinical Urinalysis Tests

Urinalysis	
Bilirubin	pH
Glucose	Protein
Ketones	Specific gravity
Leukocytes	Turbidity and color
Nitrite	Urobilinogen
Occult blood	
Microscopic assessment	

If creatinine clearance is to be estimated, the Cockcroft-Gault formula will be employed as follows:

$$\begin{aligned} & \textit{Estimated creatinine clearance} \\ & = [(140 - \textit{Age}) * \textit{Mass}(kg)] / [72 * \textit{serum creatinine}(mg/dL)] \end{aligned}$$

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

9.5.14 Disease Assessment

CT 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 every 3 cycles 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) [6].

9.5.15 PK Measurements

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

9.5.15.1 Blood Sampling

During Part A, blood samples (approximately 3 mL each) for TRA and PK assessments in whole blood and plasma will be drawn at the time points specified in Table A ([Appendix A](#)). Additional blood samples (approximately 5 mL) will be collected at each time point for metabolite profiling in plasma.

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.

To ensure that the measurements are representative of plasma exposure, blood draws will be conducted in the arm opposite to a 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.

9.5.15.2 Urine and Fecal Sampling

Urine and fecal output will be collected over the 7-day period or until discharge. Urine samples will be analyzed for PK, TRA, and biotransformation as specified in **Table B (Appendix A)**, and fecal samples will be analyzed for TRA and products of pevedistat biotransformation as specified in **Table B (Appendix A)**.

9.5.15.3 Vomitus Sampling

For patients who experience emesis during the first 24 hours after drug administration, the vomitus will need to be collected as much as possible and assayed for TRA. If a subject vomits more than once during the period, vomitus corresponding to each vomiting event will be collected in a separate labeled container and separately counted. Refer to the Study Manual for further details.

9.5.16 DNA Measurements

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9.5.17 Discharge Criteria for Part A

Samples will continue to be collected at 24-hour intervals until radioactivity in urine and feces combined is $\leq 1\%$ per day of the total administered radioactivity for at least 2 consecutive days or the excretion of radioactivity is $\geq 80\%$ of the administered radioactive dose. When radioactivity levels have fallen below these thresholds, patients can be discharged from the Part A study site.

If on Day 7 the criteria for discharge are not met, subjects will be required to remain confined for a maximum estimated period of 4 additional days (until Day 11) until the criteria are met (daily check by quick counts).

9.5.18 Entry Criteria for Continuation Into Part B

To be eligible for Part B, patients must meet the following entry criteria:

- ECOG performance status of 0 to 1.
- Laboratory values for hemoglobin, ANC, platelets, total bilirubin, ALT, AST, ALP, and serum creatinine or calculated/measured creatinine clearance as specified in Section 8.6.1.
- Diarrhea symptoms resolved to Grade 1 or better.
- QTc interval < 500 msec.
- CT scan or MRI of the chest, abdomen, and pelvis within 28 days of Cycle 1 Day 1.

In addition, patients will require at least a 2-week (may be extended up to 8 weeks) washout period after their last dose of [^{14}C]-pevedistat. For patients to begin dosing in Part B, their predose Cycle 1 Day 1 assessments in Part B must return to the baseline values of Part A (or \leq Grade 1) or

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to a level considered acceptable by the investigator after discussion with the project clinician or designee. If, after a maximum of 8 weeks from the last dose in Part A (eg, up to 8 weeks after the Day 1 visit), the predose Cycle 1 Day 1 assessments in Part B have not returned to Part A baseline values (or \leq Grade 1), the patient will not be eligible for Part B, and all assessments required for the EOS visit should be completed. The predose Cycle 1 Day 1 assessments for Part B do not need to be repeated if the Day 24 Part A results confirm that the patient is eligible for dosing in Part B AND Cycle 1 Day 1 occurs within 5 days from Part A Day 24; however, the liver function tests will need to be repeated within 3 days of Cycle 1 Day 1.

9.6 Completion of Study Treatment (for Individual Patients)

9.6.1 Part A

Patients will be considered to have completed Part A of the study if they have completed the protocol-specified assessments to provide data necessary for evaluation of mass balance and PK within Part A of the protocol.

9.6.2 Part B

Patients will be considered to have completed Part B of the study if they complete 12 cycles of treatment with study drug. 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.

9.7 Completion of Study (for Individual Patients)

9.7.1 Part A

Patients will be considered to have completed Part A of the study if they have completed the protocol-specified assessments to provide data necessary for evaluation of mass balance and 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 and vitals), laboratory assessments (hematology, chemistry, urinalysis), and 12-lead ECG. The EOS visit will be conducted 30 days (+10 days) after the last dose of study drug in Part A. If the EOS visit occurs before 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.

9.7.2 Part B

Patients will be considered to have completed Part B of the study if they complete 12 cycles of treatment with study drug or if treatment is discontinued for any of the reasons outlined in Section 9.8. The EOS visit will be conducted 30 days (+10 days) after the last dose of study drug in

Part B. If the EOS visit occurs before 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.

9.8 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.
- 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 Schedule of Events ([Appendix A](#)). The primary reason for study drug discontinuation will be recorded on the eCRF. In Part A of the study, patients who are not PK evaluable will be replaced.

Note: In Part B of the study, patients may receive pevonedistat until they experience progressive disease (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 by the sponsor.

9.9 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.

9.10 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 Pretreatment Event Definition

A pretreatment event 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 [7]. 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/mm³ 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 pretreatment events (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 of the 2 clinical study sites. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE or serious pretreatment event may be requested by Takeda. SAE report information must be consistent with the data provided on the eCRF.

SAE Reporting Contact Information

Cognizant

All Other Countries (Rest of World)

Personal Protected Data

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

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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 pretreatment events, 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 [7]. 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?”

10.3 Monitoring of AEs and Period of Observation

AEs, both nonserious and serious, will be monitored throughout the study as follows:

AEs will be reported from start of study administration through 30 days (+10 days) after administration of the last dose of study drug and recorded in the eCRFs.

SAEs will be reported as follows:

- Serious pretreatment events will be reported to the Takeda Global Pharmacovigilance department or designee from the time of the signing of the informed consent form (ICF) up to the first dose of study drug.
- Related and unrelated treatment-emergent SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the first dose of study drug through 30 days (+10 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 due to 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
Personally Protected Data			

Product complaints or medication errors in and of themselves are not AEs. If a product complaint or a medication error results in an SAE, an SAE form should be completed and sent to Cognizant (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 and any other applicable SAEs to regulatory authorities, including the European Medicines Agency, 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 (suspected unexpected serious adverse reactions) 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

Safety data will be reviewed and assessed periodically by an internal safety working group throughout the conduct of the study. These reviews will include a safety physician, a clinical physician from the study team, and other representation from the Clinical Research, Pharmacovigilance, Biostatistics, Clinical Pharmacology, Regulatory Affairs, Drug Safety Evaluation/Toxicology, and Clinical Operations departments at Takeda. Escalation of safety issues to a senior management cross-functional safety board will be performed on an ad hoc basis.

11.1 Sponsor Safety Assessments

Safety data will be reviewed and assessed periodically by an internal safety working group throughout the conduct of the study. These reviews will include a safety physician, a clinical physician from the study team, and other representation from the Clinical Research, Pharmacovigilance, Biostatistics, Clinical Pharmacology, Regulatory Affairs, Drug Safety Evaluation/Toxicology, and Clinical Operations departments at Millennium. Escalation of safety issues to a senior management cross-functional safety board will be performed on an ad hoc basis.

11.2 Independent Data Monitoring Committee

An IDMC has been formed to periodically monitor the overall conduct of studies within the pevonedistat program, including review of accumulating clinical study data and safety data (both clinical and nonclinical) and to make recommendations to Takeda to safeguard the interests of study participants. Additionally, the IDMC may make recommendations relating to the selection/recruitment/retention of study participants, patient management, improving adherence to protocol-specified regimens, and the procedures for data management and quality control. Further details regarding the IDMC are located in the IDMC charter.

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, pretreatment events, 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 the 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, Contract Research Organization partners, and regulatory authorities. The 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 sites.

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 sites 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 sites and filed with the original in the subject's chart

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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: patients who receive at least 1 dose of study drug. The safety population will be used for all safety analyses.
- PK population: patients who a) receive the protocol-specified single [¹⁴C]-pevonedistat dose in Part A; b) do not receive any excluded concomitant medications through the completion of Part A; and c) have sufficient concentration-time data to permit reliable estimation of PK parameters and mass balance.

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 chemotherapy will be based on the best overall response as determined by the investigator using RECIST Version 1.1 guidelines ([Appendix E](#)) [6]. 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

The PK analysis will be based on concentrations of pevonedistat. All data will be summarized using descriptive statistics and will be listed and summarized in tabular and/or graphical form.

The following PK parameters will be calculated by noncompartmental analysis and tabulated for each individual:

- TRA in plasma and whole blood: C_{max} , t_{max} , AUC_{last} , and as permitted by data, $t_{1/2z}$ and AUC_{∞} .
- TRA in urine: amount of [¹⁴C]-radioactivity excreted into urine per sampling interval ($Ae_{urine, ^{14}C, t1-t2}$ in ng-eq and percentage of dose) and cumulative amount of [¹⁴C]-radioactivity excreted in urine up to the last sampling interval ($Ae_{urine, ^{14}C}$ in ng-eq and percentage of dose).

- TRA in feces: amount of [¹⁴C]-radioactivity excreted into feces per sampling interval (daily excretion) ($Ae_{\text{feces},^{14}\text{C},t1-t2}$ in ng-eq and percentage of dose) and cumulative amount of [¹⁴C]-radioactivity excreted in feces up to the last sampling interval ($Ae_{\text{feces},^{14}\text{C}}$ in ng-eq and percentage of dose).
- The total cumulative excretion of [¹⁴C]-radioactivity per interval and over the total collection period will be calculated as the sum of the cumulative excretion in urine and feces: total cumulative excretion of [¹⁴C]-radioactivity from the body ($Ae_{\text{total},^{14}\text{C}} = Ae_{\text{urine},^{14}\text{C}} + Ae_{\text{feces},^{14}\text{C}}$) (in ng-eq and percentage of dose).
- Pevonedistat in whole blood and plasma: C_{max} , t_{max} , AUC_{last} , and as permitted by data, $t_{1/2z}$, AUC_{∞} , and clearance.
- Pevonedistat in urine (per sampling interval and total): cumulative amount excreted in urine (Ae_{urine} and percentage of dose) and CL_R .

Additionally, one of the objectives of this study is to collect plasma, urine, and feces for metabolite profiling and identification. While the results of the PK of pevonedistat and TRA, time course of excretion of TRA in urine and feces, and overall mass balance will be included in the clinical study report, the metabolite profiling and identification results will be reported separately.

13.1.5 Safety Analysis

A safety analysis will be conducted separately for Part A and Part B to respectively characterize the safety profiles of [¹⁴C]-pevonedistat and pevonedistat in combination with chemotherapy. 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 $\geq 10\%$ 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 $\geq 10\%$ 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.

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

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 for this study is not based on statistical considerations.

On the basis of the ALARA principle (As Low [radioactive burden] As Reasonably Achievable) set forth in the 96/29/EURATOM directive, a sample size of 4 to 6 PK-evaluable patients is considered sufficient to provide adequate characterization of the mass balance, PK, and metabolism of pevonedistat in patients with cancer. Patients will be replaced if they are not evaluable for PK.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study sites 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, 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 sites should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the sites 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. A Protocol Deviation Form should be completed by the sites and signed by the sponsor or designee for any significant deviation from the protocol.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study sites also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the sites 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 study site 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 US FDA and OGYEI [Hungarian Regulatory Authorities]). If the study sites are 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 country 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.

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 notify the study 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 notification (Part A) or drug (Part B), no protocol activities, including Screening, may occur.

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

The ICF 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 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 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 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 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 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 eCRF).

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. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

15.4.2 Clinical Trial Registration

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 the 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.

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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Appendix A Schedule of Events

Schedule of Events for Part A (ADME Portion of the Study)

	ADME Assessment Period											EOS (c)
	Screening (a)	Week 1 Confinement									Week 2 Discharge (b)	
		Day -1 Predose	Day 1 Predose	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Between Days 8 and 14	
Confinement (d)		X	X	X	X	X	X	X	X	X		
Study Drug Administration												
Single [¹⁴ C]-pevonedistat IV solution administration (e)				X								
Lactulose (f)							X					
Study Procedures												
Informed consent	X											
Inclusion/exclusion criteria	X											
Demographics	X											
Medical history/prior therapy	X											
Full physical examination	X										X	X
Symptom-directed physical examination		X	X									
Height	X											
Weight	X	X (g)	X (g)									X
Vital signs (h)	X	X		X							X	X
ECOG performance status	X										X	X
12-lead ECG (i)	X	X (g)	X (g)								X	X
Echocardiogram	X											
Monitoring of concomitant medications, therapies, and	Recorded from start of study administration through 30 days (+10 days) after the last dose of study drug											

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	ADME Assessment Period											EOS (c)
	Screening (a)	Week 1 Confinement									Week 2 Discharge (b)	
		Day -1 Predose	Day 1 Predose	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Between Days 8 and 14	
procedures												
AE reporting(j)	Recorded from start of study administration through 30 days (+10 days) after the last dose of study drug											
	SAEs will be reported from signing of the ICF through 30 days (+10 days) after the last dose of study drug.											
Samples/Laboratory Assessments												
Pregnancy test	X	X (g)										X
Hematology/chemistry (k) (l)	X	X (g)	X (g)				X				X	X
Urinalysis (m)	X	X (g)	X (g)								X	X
Blood sample collection	See Table A , Part A for Blood Sampling Collection Schedule											
Urine sample collection	See Table B , Part A for Urine Collection Sample Schedule											
Fecal sample collection	See Table B , Part A for Fecal Collection Sample Schedule											
Vomitus	Collect vomitus if event occurs during first 24 hours after dosing and collect at any other vomiting events afterward											
Buccal swabs for DNA analysis (optional)	X2											

X2=2 samples will be collected.

(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.

(b) Discharge criteria for Part A can be found in Section 9.5.17. Patients can be discharged any time between Days 8 and 14. The discharge assessments are done only once on the day of discharge.

(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) During Part A, patients will be required to stay at the Part A study site for approximately 8 days or until the discharge criteria are met, with a maximum estimated confinement period of 9-14 days.

(e) Patients will receive a single dose of pevonedistat 25 mg/m² (equivalent to approximately 43 mg for a typical individual of 1.73 m² BSA up to a maximum absolute dose of 50 mg) given as a 1-hour IV infusion on Day 1. The clinic will be supplied with vials containing approximately 60-98 µCi (approximately 2.22-3.626 MBq) of [¹⁴C]-pevonedistat as the radioactive tracer.

(f) To ensure defecation before release from the Part A study site, two 15 mL doses of oral lactulose will be administered, separated by approximately 2 hours, on the evening of Day 4; the second dose of lactulose will be withheld if the first dose was not tolerated. Lactulose may also be administered as needed.

(g) 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, with the

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exception of an ECG that must be repeated predose on Day 1.

(h) 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. All vital signs are measured with the patient in the sitting position. When the timing of vital signs assessment coincides with the timing of a blood draw, vital signs will be measured before blood sample collection.

(i) A 12-lead ECG will be performed during Screening and before administration (within 3 hours) of pevonedistat on Day 1 and immediately after the pevonedistat infusion is complete (± 20 min) on Day 1. When the timing of ECG measurements coincides with the timing of a blood draw, the ECG will be completed before the blood sample collection, with the exception of the end-of-infusion PK sample, which should be collected before the ECG is completed.

(j) Including serious pretreatment events; see Section 10.1.1.

(k) Hematology samples will be collected during Screening and before dosing with study drug on Day 1. These 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, samples will be taken on Day 1 predose and postdose, at the time of discharge, and at the EOS visit.

(l) Clinical chemistry samples will be collected during Screening, before dosing with study drug, and 3 hours (± 30 min) after completion of the pevonedistat infusion. Predose samples can be drawn within 24 hours predose. If dosing falls on a Monday, the collection window may be extended to collect samples on the previous Friday. In addition, samples will be taken on Day 1 predose and postdose, at the time of discharge, and at the EOS visit.

(m) Urinalysis samples (with microscopic analysis) will be analyzed at the Part A study site's local laboratory.

Table A Blood Sampling Schedule (Part A, ADME)

Study Day	Time Point (hour)	Whole Blood Sample Collection	Plasma Sample Collection
	Matrix	Blood 1 (a) Blood 2 (a)	Plasma 1 (b) Plasma 2 (b) Plasma 3 (b)
Day 1	Predose(c)	X2	X3
Day 1	EOI (d) (-5 to +1 min)	X2	X3
Day 1	0.5 hour postinfusion (e) (± 5 min)	X2	X3
Day 1	1 hour postinfusion (e) (± 15 min)	X2	X3
Day 1	2 hours postinfusion (e) (± 15 min)	X2	X3
Day 1	3 hours postinfusion (e) (± 30 min)	X2	X3
Day 1	4 hours postinfusion (e) (± 45 min)	X2	X3
Day 1	8 hours postinfusion (e) (± 1 hour)	X2	X3
Day 1	12 hours postinfusion (e) (± 1 hour)	X2	X3
Day 2	24 hours postdose (f) (± 1 hour)	X2	X3
Day 3	48 hours postdose (f) (± 2 hours)	X2	X3
Day 4	72 hours postdose (f) (± 3 hours)	X2	X3
Day 5	96 hours postdose (f) (± 4 hours)	X2	X3
Day 6	120 hours postdose (f) (± 4 hours)	X2	X3
Day 7	144 hours postdose (f) (± 4 hours)	X2	X3
Day 8	168 hours postdose (f) (± 4 hours)	X2	X3

EOI=end of infusion, X2=2 samples will be collected, X3=3 samples will be collected.

(a) For determination of TRA (Blood 1) and pevonedistat (Blood 2).

(b) For determination of TRA (Plasma 1), pevonedistat (Plasma 2), and metabolite profiling (Plasma 3).

(c) The sample is to be collected within 1 hour before the start of pevonedistat infusion on Day 1.

(d) 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.

(e) Samples are to be collected after **completion** of pevonedistat IV infusion on Day 1.

(f) Samples are to be collected after **initiation** of the pevonedistat IV infusion on Day 1.

Table B Urine and Fecal Sample Schedule (Part A, ADME)

Study Day	Time Interval (hour) (a)	Urine Sample Collection	Feces Sample Collection
	Matrix	Urine 1, Urine 2 (b)	Fecal (c)
Day -1	0 (predose)	X2	X
Day 1	0-6 hours	X2	X (0-24 hours)
Day 1	6-12 hours	X2	
Day 2	12-24 hours	X2	
Day 3	24-48 hours	X2	X
Day 4	48-72 hours	X2	X
Day 5	72-96 hours	X2	X
Day 6	96-120 hours	X2	X
Day 7	120-144 hours	X2	X
Day 8	144-168 hours (d)	X2	X

X=1 sample collected, X2=2 samples will be collected.

(a) Sampling times are relative to the initiation of the IV infusion on Day 1.

(b) For determination of TRA and metabolite profiling (Urine 1); pevonedistat (Urine 2).

(c) For determination of TRA and metabolite profiling (Feces).

(d) Samples will continue to be collected at 24-hour intervals until radioactivity in urine and feces combined is $\leq 1\%$ per day of the total administered radioactivity per day for at least 2 consecutive days or the excretion of radioactivity is $\geq 80\%$ of the administered radioactive dose. When radioactivity levels have fallen below these thresholds, patients can be discharged from the Part A study site.

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).

Schedule of Events for Optional Continued Treatment With Pevonedistat+Chemotherapy (Part B) (All Cycles)

	Pevonedistat+Chemotherapy Treatment 21-Day Cycle					EOS/ Early Termination (b)
	Day 1 Predose (a)	Day 1	Day 3	Day 5	Day 8	
Study Drug Administration						
Chemotherapy administration (c)		X				
Pevonedistat administration (c)		X	X	X		
Study Procedures						
Inclusion/exclusion criteria	X					
Full physical examination	X					X
Symptom-directed physical examination		X	X	X	X	
ECOG performance status	X (d)	X (d)			X	X
Weight	X					X
Vital signs (e)	X	X	X	X		X
12-Lead ECG (f)	X	X				
Tumor assessments (g)	To be completed before dosing in Part B, end of Cycle 2, and every 3 cycles thereafter					X
Monitoring of concomitant medications, therapies, and procedures	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 reporting (h)	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 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					

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	Pevedonistat+Chemotherapy Treatment 21-Day Cycle					EOS/ Early Termination (b)
	Day 1 Predose (a)	Day 1	Day 3	Day 5	Day 8	
Samples/Laboratory Assessments						
Pregnancy test (i)	X					X
Hematology/chemistry (j) (k)	X	X (k)	X	X	X	X
Urinalysis (l)	X					X

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 pevedonistat+chemotherapy (Part B), they must meet certain entry criteria (see Section 9.5.18).

(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 pevedonistat. On Day 1, when pevedonistat and chemotherapy agents are both administered, chemotherapy will be administered first, followed by pevedonistat. The infusion of pevedonistat may be slowed or stopped and restarted for any associated infusion-related reactions. The dose of pevedonistat 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 pevedonistat.**

(d) If ECOG performance status is measured at Screening, it does not need to be repeated on Day 1 predose and Day 1. Only 1 ECOG measurement is needed on Day 1 predose and Day 1.

(e) On days when study drug is administered, vital signs are to be measured predose (20 minutes [± 10 min]) before the infusion of chemotherapy (when pevedonistat and chemotherapy agents are both administered) or pevedonistat; 30 minutes (± 10 min) after the start of pevedonistat dosing; and 1 hour (± 10 min) after the completion of pevedonistat dosing. All vital signs are measured with the patient in the sitting position. When the timing of vital signs assessment coincides with the timing of a blood draw, vital signs will be measured before blood sample collection.

(f) A 12-lead ECG will be performed on Day 1 before administration (within 3 hours) of the chemotherapy regimen and immediately after the infusion of pevedonistat is complete (± 10 min). When the timing of ECG measurements coincides with the timing of a blood draw, the ECG will be completed before the collection of the blood sample, with the exception of the end of infusion PK sample, which should be taken before the ECG is completed.

(g) Radiological evaluations (CT scan or MRI) of the chest, abdomen, and pelvis 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. 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.

(h) Including serious pretreatment events in Part A; see Section 10.1.1.

(i) A pregnancy test must also be performed for women of childbearing potential at every cycle (typically performed on Day 1 of the 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 that cycle. A pregnancy test will also be performed for women of childbearing potential at the EOS/Early Termination visit. Pregnancy tests may also be repeated during the study if requested by an IEC/IRB or if required by local regulations.

(j) 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. On dosing days, samples can 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, samples will be taken on Day 8 and at the EOS visit.

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- (k) 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. If dosing falls on a Monday, the collection window may be extended to collect samples on the previous Friday. On Cycle 1 Day 1, an additional sample will be taken 3 hours (± 30 mins) after the completion of the pevonedistat infusion. In addition, samples will be taken on Day 8 and at the EOS visit.
- (l) Urinalysis samples (with microscopic analysis) will be analyzed at the Part A study site's local laboratory.

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:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, before the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to ICH, and local regulatory requirements.
6. 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.
7. Ensure that requirements for informed consent, as outlined in ICH and local regulations, are met.
8. 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.
9. 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.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.

11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
12. 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 [9].

Appendix E 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 one or more nontarget lesion(s) or/and maintenance of tumor marker level above the normal limits.
PD	Appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions.

Source: Eisenhauer, et al, 2009 [6].

SD=stable disease.

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 [6].

SD=stable disease.

Appendix F Excluded CYP3A Inhibitors and Inducers

Note that HIV medications that are strong or moderate CYP3A inhibitors or inducers are not included in this list because HIV-positive patients are excluded from study participation.

Classification of CYP3A Inhibitors

Use of moderate and strong CYP3A inhibitors listed in the table below should be avoided during pevedistat therapy. The moderate CYP3A inhibitor amiodarone has a long $t_{1/2}$ (mean of 58 days); consequently, amiodarone must be discontinued 6 months before the first dose of pevedistat.

In Vivo Inhibitors of CYP3A

Strong (a)	Moderate (a)
5-fold increase in AUC	2-fold, but <5-fold Increase in AUC
Clarithromycin	Amiodarone
Itraconazole	Aprepitant
Ketoconazole	Diltiazem
Nefazodone	Erythromycin
Voriconazole	Ciprofloxacin
Posaconazole	Cimetidine
Telithromycin	Fluconazole
Conivaptan	Verapamil
	Tofisopam
	Dronedarone
	Isavuconazole

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.

(a) Azole antifungal agents are CYP3A inhibitors and are excluded during Part A of the study. During Part B of the study, if the patient's clinical condition requires the use of an azole antifungal agent, the patient may receive voriconazole and fluconazole from 24 hours after the last pevedistat dose to 72 hours before the next pevedistat dose. For example, if a patient receives pevedistat on a Monday (Day 1), Wednesday (Day 3), Friday (Day 5) schedule, an azole may be administered (if clinically necessary and no suitable alternative) from the Saturday after the Day 5 dose (Day 6) up to the Friday (Day 19) before the Monday dose of the next cycle.

Classification of CYP3A Inducers

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

In Vivo Inducers of CYP3A

Strong Inducers ≥80% Decrease in AUC	Moderate Inducers 50%-80% Decrease in AUC
Carbamazepine	Bosentan
Phenytoin	Efavirenz
Phenobarbital	Modafinil
Primidone	Nafcillin
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 G 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 [10].

NCIC CTG=National Cancer Institute of Canada Clinical Trials Group, SWOG=Southwest Oncology Group.

In a randomized clinical trial, 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

Toxicity	Set	N	NCI CTC Grade, %						N	NCI CTC Grade, %					Difference (a) in the Proportions of Patients With Grades 3/4 Toxicity, %	
			Paclitaxel+Carboplatin Arm							Cisplatin+Paclitaxel Arm					E	95% CI
			0	1	2	3	4		0	1	2	3	4			
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	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 [11].

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.

The symbol "--" denotes "not defined".

(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; 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.

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Appendix H 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	Cardiovascular agents
Nonsteroidal anti-inflammatory drugs	Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers
Antidepressants/mood stabilizers	Clopidogrel (Plavix), ticlopidine (Ticlid)
Lithium	Contrast dye
Antimicrobials	Diuretics
Acyclovir (Zovirax)	Loops, thiazides
Aminoglycosides	Triamterene (Dyrenium)
Amphotericin B (Fungizone; deoxycholic acid formulation more so than the lipid formulation)	Herbals
Beta lactams (penicillins, cephalosporins)	Chinese herbals with aristocholic acid
Foscarnet (Foscavir)	Others
Ganciclovir (Cytovene)	Allopurinol (Zyloprim)
Pentamidine (Pentam)	Gold therapy
Quinolones	Haloperidol (Haldol)
Rifampin (Rifadin)	Pamidronate (Aredia)
Sulfonamides	Phenytoin (Dilantin)
Vancomycin (Vancocin)	Quinine (Qualaquin)
Antiretrovirals	Zoledronate (Zometa)
Adefovir (Hepsera), cidofovir (Vistide), tenofovir (Viread)	
Indinavir (Crixivan)	
Calcineurin inhibitors	
Cyclosporine (Neoral)	
Tacrolimus (Prograf)	

Source: Modified from Naughton, 2008 [12].

Appendix I 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 [13].

Appendix J 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. Please refer to the following source for additional information: European Heads of Medicines Agencies Clinical Trial Facilitation Group; see hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

Appendix K 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:

- 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
- Vasectomised 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:

- 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 Vasectomised 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 vasectomised 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 trial 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) are also considered acceptable, but not highly effective, birth control methods.

A Phase I Study to Assess Mass Balance, Pharmacokinetics, and Metabolism of [14C]-Pevonedistat in Patients with Advanced Solid Tumors

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
Personally Protected Data	Clinical Science Approval	30-Nov-2016 20:38 UTC
	Biostatistics Approval	30-Nov-2016 21:10 UTC
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