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

NCT Number: NCT03330106

Protocol Approve Date: 26 June 2017

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

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

PROTOCOL

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

Sponsor: Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited
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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-1014

IND Number: 78,427 **EudraCT Number:** 2017-002610-31

Compound: Pevonedistat (MLN4924; TAK-924)

Date: 26 June 2017

1.0 ADMINISTRATIVE

1.1 Contacts

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

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

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

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

Contact Type/Role	United States and Rest-of-World Contacts
SAE and pregnancy reporting	See Sections 10.2 and 10.4.
Medical monitor (medical advice on protocol and compound)	Refer to Study Manual.
Responsible medical officer (carries overall responsibility for the conduct of the study)	Refer to Study Manual.

1.2 Approval

REPRESENTATIVES OF TAKEDA

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation 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.

PPD

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 Council for Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting SAEs defined in Section 10.2 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Responsibilities of the Investigator (Appendix B).

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

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

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, Randomized, Crossover Study to Evaluate the Effects of Pevonedistat on the QTc Interval in Patients With Advanced Solid Tumors	**IND No.:** 78427	**EudraCT No.:** 2017-002610-31
Study Number: Pevonedistat-1014	**Phase:** 1	

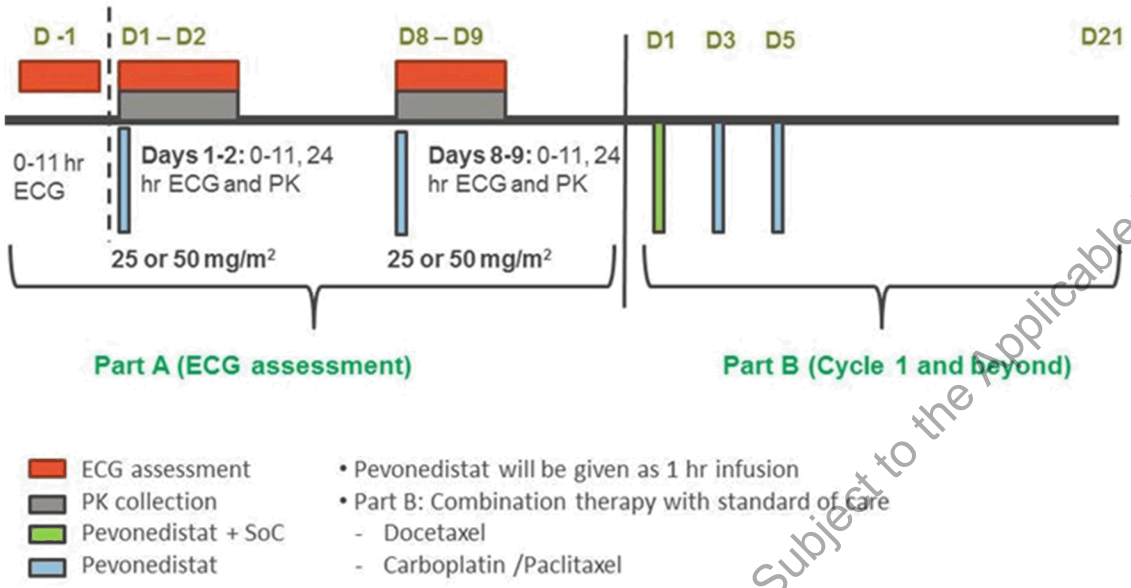
Study Design: This is a phase 1, 2-dose, crossover study to assess the effects of pevonedistat 25 and 50 mg/m^2 on the corrected QT (QTc) interval. A study flow chart is provided following the description of Parts A and B.

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

On Day 1, immediately following the collection of triplicate predose baseline ECG assessments, patients will be randomized in a crossover fashion to receive a single-dose, 1-hour intravenous (IV) infusion of 25 or 50 mg/m^2 pevonedistat and the other dose on Day 8 (approximately 18 patients per sequence). Serial blood samples for PK analysis of pevonedistat will be collected at prespecified time points over a 24-hour period (0-24 hours postdose). Patients will undergo Holter ECG monitoring on Day -1 (0-11 hours), Day 1 (0-11 hours), Day 2 (24 hours after Day 1 dosing), Day 8 (0-11 hours), and Day 9 (24 hours after Day 8 dosing), and triplicate ECGs will be extracted at matched PK time points to contribute to the analysis of the effects of pevonedistat on QT/QTc intervals. The clock time of pevonedistat infusion dosing initiation on Days 1 and 8 should coincide with that of the 0-hour time point on Day -1. On Days -1, 1, and 8 of Holter ECG sampling, patients will remain nothing by mouth (ie, no food or drink except water) from 2 hours before the 0-hour time point until completion of the 4-hour ECG/PK sample collection. Accordingly, patients will be advised to eat breakfast at least 2 hours before the 0-hour time point and to eat lunch after the 4-hour Holter ECG and PK blood sample collection. These meals will be administered at the same times on Days -1, 1, and 8 of Holter ECG monitoring. Safety will be assessed by monitoring vital signs, physical examinations, and clinical laboratory tests.

Part B: Continued Treatment With Pevonedistat in Combination With Standard of Care (Optional):

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



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

Primary Objective:

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

Secondary Objectives:

Part A:

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

Part B:

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

Safety Objectives:

Part A:

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

Part B:

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

Subject Population: Adult patients with histologically or cytologically confirmed metastatic or locally advanced solid tumors that are appropriate for treatment with one of the 2 combination therapies in Part B of this study, who have progressed despite standard therapy, or for whom conventional therapy is not considered effective.

Number of Subjects: Approximately 45 patients will be enrolled to obtain approximately 36 evaluable patients. Enrollment is defined as the time of the initiation of the first dose of study drug.	**Number of Sites:** Approximately 5 to 7 sites in the United States and/or rest of world
Dose Level(s): **Part A:** Pevonedistat is given IV at 25 or 50 mg/m^2 on Days 1 and 8 (administered in a 2-way crossover design). **Part B:** Pevonedistat is given IV at 25 mg/m^2 in combination with docetaxel 75 mg/m^2 or at 20 mg/m^2 in combination with carboplatin AUC5+paclitaxel 175 mg/m^2; pevonedistat is given in combination on Day 1 and as a single agent on Days 3 and 5 of each 21-day cycle.	**Route of Administration:** **Part A:** Pevonedistat: IV infusion **Part B (Optional):** Pevonedistat: IV infusion Docetaxel, carboplatin, and paclitaxel: IV infusion
Duration of Treatment: **Part A**: Pevonedistat is given as a single IV dose at 25 or 50 mg/m^2 on Days 1 and 8 (administered in a 2-way crossover design). **Part B (Optional):** Eligible patients may continue to receive treatment in Part B of this study until they experience symptomatic deterioration or disease progression, until treatment is discontinued for another reason, or until the study is stopped.	**Period of Evaluation:** Screening: 1 day during a 28-day period **Part A:** 10 days with an End-of-Study (EOS) visit at 30 (+10) days (safety follow-up) after the last dose of study drug for patients who do not continue on to optional Part B. **Part B (Optional):** 12 cycles of combination therapy. If the sponsor and investigator determine 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. All patients in optional Part B will attend an EOS visit at 30 (+10) days (safety follow-up) after the last dose of study drug or before the start of subsequent therapy for their disease, if that occurs sooner.
Main Criteria for Inclusion: • Adult patients with histologically or cytologically confirmed metastatic or locally advanced solid tumors that are appropriate for treatment with one of the 2 combination therapies in Part B of this study, who have progressed despite standard therapy, or for whom conventional therapy is not considered effective. • Cardiac, renal, and hepatic safety parameters to reflect the risk mitigation strategy in place in all ongoing pevonedistat studies and with special consideration to the safety profile of the standard-of-care agents (Part B of the study).	

Main Criteria for Exclusion:

- Patients requiring treatment with strong cytochrome P450 3A inducers within 14 days before receiving the first dose of study drug and/or requiring the use of these medications during the study.
- Patients taking QT-prolonging drugs with a risk of causing torsades de pointes (TdP). Patients taking drugs with a possible or conditional risk of QT prolongation or drugs that are to be avoided by patients with congenital long QT syndrome may be considered if on a stable dose, pending discussion and agreement between the investigator and the sponsor.
- Patients with a history of myocardial infarction, unstable symptomatic ischemic heart disease, any clinically significant cardiac arrhythmia (except for mild sinus tachycardia), thromboembolic, or any other cardiac condition within 6 months before receiving the first dose of study drug.
- Patients who have a history of Brugada syndrome, risk factors for TdP, or family history of long QT syndrome.
- Patients who have a 12-lead ECG at Screening indicating a second- or third-degree atrioventricular block or intermittent block or including 1 or more of the following: (1) QRS >110 milliseconds (msec); (2) QTcF >480 msec; (3) PR interval >200 msec.
- Patients with sustained systolic blood pressure (BP) >160 or <90 mm Hg, diastolic BP >100 or <65 mm Hg, or resting pulse rate <50 or ≥100 beats per minute (bpm) at Screening or predose.

Main Criteria for Evaluation and Analyses:

Primary endpoint:

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

Secondary endpoints:

Part A:

- Change from time-matched baseline in QTcI, QRS, PR, and HR following a single-dose IV administration of pevonedistat at 25 and 50 mg/m^2.
- PK parameters: maximum observed plasma concentration (C_{max}), area under the plasma concentration-time curve from time 0 to 24 hours, and half-life of pevonedistat following a single-dose IV administration at 25 and 50 mg/m^2.

Part B:

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

Safety endpoints:

Part A:

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

Part B:

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

Statistical Considerations:

The primary analysis will be based on the baseline-adjusted QTcF in Part A. A statistical analysis will be performed using a linear mixed-effects model with random subject effect. Additionally, a concentration effect analysis will be performed using a linear mixed-effects model with baseline-adjusted QTcF as the dependent variable, drug plasma concentration as the continuous predictor, and random intercept and slope per subject. Baseline-adjusted QTcF at the geometric mean C_{max} for the 2 dose levels from a regression analysis of baseline-adjusted QTcF as a function of pevonedistat concentration will be estimated.

If the mean ECG HR change from baseline at any time point after dosing is ≥+10 bpm, or if individual subject HR changes from baseline at ≥4 time points after dosing are ≥+15 bpm for more than 25% of subjects, analysis of the primary and secondary QTc endpoints will be performed using beat-to-beat comparison of QT postdose, with QT during Day -1 at matching respiratory rate value. The QTc beat-to-beat analysis will be performed as needed on the basis of the observed HR effects of pevonedistat.

Sample Size Justification:

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

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 for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Principal Investigator/Coordinating Investigator

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

3.3 List of Abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{24}	area under the plasma concentration-time curve from time 0 to 24 hours
AUC_{τ}	area under the plasma concentration-time curve during a dosing interval
BID	twice daily
BP	blood pressure
bpm	beats per minute
BSA	body surface area
C_{max}	maximum observed plasma concentration
CNS	central nervous system
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
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOS	End of Study
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GI	gastrointestinal
HCl	hydrochloride
HIV	human immunodeficiency virus
HR	heart rate
HR MDS	higher-risk myelodysplastic syndromes
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation

IEC	independent ethics committee
IRB	institutional review board
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
N	number of patients
NAE	NEDD8-activating enzyme
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NPO	nothing by mouth
NSCLC	non–small cell lung cancer
PD	progressive disease/disease progression
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PTE	pretreatment event
QTc	corrected QT interval
QTcF	Fridericia corrected QT interval
QTcI	individual corrected QT interval
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
ROW	rest of world
RP2D	recommended phase 2 dose
RR	respiratory rate
SAE	serious adverse event
SC	subcutaneous(ly)
SD	stable disease
SmPC	Summary of Product Characteristics
SoC	standard of care
SOE	Schedule of Events
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
$t_{1/2z}$	terminal disposition phase half-life
TdP	torsades de pointes
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeia
USPI	United States Package Insert

3.4 Corporate Identification

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

4.0 INTRODUCTION

4.1 Background

Pevonedistat is a cytotoxic agent and cannot be administered to healthy subjects. Pevonedistat is currently in phase 2/3 of clinical development in higher-risk myelodysplastic syndromes (HR MDS), chronic myelomonocytic leukemia, and low-blast acute myeloid leukemia (AML). The maximum tolerated dose (MTD) and recommended phase 3 dose of pevonedistat in this patient population is 20 mg/m^2 administered on Days 1, 3, and 5 in combination with azacitidine 75 mg/m^2 on Days 1 through 5, 8, and 9 in 28-day cycles. The MTD and recommended phase 2 dose (RP2D) of pevonedistat in combination with docetaxel is 25 mg/m^2 pevonedistat dosed on Days 1, 3, and 5, and docetaxel 75 mg/m^2 on Day 1 in 21-day cycles. The MTD and RP2D of pevonedistat in combination with paclitaxel plus carboplatin is 20 mg/m^2 pevonedistat dosed on Days 1, 3, and 5 and 175 mg/m^2 paclitaxel plus carboplatin (AUC5) on Day 1 in 21-day cycles. The RP2D of pevonedistat administered as a single agent in patients with advanced cancer is 50 mg/m^2 on Days 1, 3, and 5 in 21-day cycles.

4.1.1 Nonclinical Background Information

Pevonedistat is a potent and selective, mechanism-based inhibitor of NEDD8-activating enzyme (NAE) activity. Pevonedistat also inhibits human carbonic anhydrase 2, which may explain the extensive partitioning of pevonedistat in red blood cells (RBCs) that has been observed in animal species and humans (see the current Investigator's Brochure [IB]).

Pevonedistat 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 cullin-dependent ubiquitin E3 ligase 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 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 human ether-a-go-go-related gene channel inhibition by pevonedistat (inhibitory constant=17.3 μM) or its 3 major circulating metabolites (half-maximal inhibitory concentration >100 μM for all 3).

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)/λz, 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.

4.1.2 Clinical Background Information

4.1.2.1 Clinical Pharmacokinetics

The clinical pharmacokinetics (PK) of pevonedistat has been evaluated in 4 monotherapy phase 1 studies in 96 patients with solid tumors (Studies C15001 and C15005) and 109 patients with hematologic malignancies (Studies 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/m^2 given at various daily or intermittent dosing schedules within 21-day treatment cycles.

Plasma concentrations of pevonedistat declined in a biexponential 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 plasma concentration (C_{max}), 12% to 56% CV for area under the plasma concentration-time curve (AUC) from time 0 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 in 2 studies of pevonedistat in combination with different standard-of-care (SoC) therapies and for a drug-drug interaction (DDI) study evaluating the effects of cytochrome P450 (CYP) 3A-mediated inhibition on pevonedistat. Pevonedistat PK was not altered in the presence of azacitidine when compared with historical

single-agent data. Also, no obvious changes in the PK of pevonedistat in the presence of docetaxel or gemcitabine have been observed, whereas a trend toward increasing plasma concentrations of pevonedistat in the presence of carboplatin+paclitaxel was evident. This apparent DDI effect, which cannot be explained at this time, warrants further understanding of the disposition properties of pevonedistat in humans. Lastly, preliminary PK evaluations from 26 patients (13 on fluconazole, 13 on itraconazole [Study C15011]) showed that multiple doses of fluconazole, a moderate CYP3A inhibitor, had minimal effect (13% increase in mean AUC from time 0 to infinity) on the single-dose IV PK of pevonedistat administered at a dose of 8 mg/m^2, while pevonedistat systemic exposure increased by approximately 23% in the presence of the strong CYP3A and P-glycoprotein (P-gp) inhibitor itraconazole. On the basis of these observations, additional patients were enrolled to evaluate the effects of itraconazole on pevonedistat PK at the clinical dose of 20 mg/m^2. Preliminary data from 11 patients who completed protocol-specified dosing and PK evaluations indicated that pevonedistat systemic exposures following IV administration at 20 mg/m^2 in the presence of itraconazole were similar to those in the absence of itraconazole. Therefore, strong and moderate CYP3A inhibitors and P-gp inhibitors are not excluded in this and other planned pevonedistat clinical studies. Additional information on the clinical PK of pevonedistat is provided in the current IB.

4.1.2.2 Clinical Experience

As of 22 January 2016, the clinical development program of pevonedistat 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 3 are ongoing, phase 1b studies of pevonedistat in combination with different SoC therapies (C15009, C15010, and P1012). A phase 1 DDI study (C15011) is also evaluating the effects of CYP3A-mediated inhibition on pevonedistat. Thus, approximately 390 patients diagnosed with advanced malignancies including solid tumors, AML, melanoma, lymphoma, multiple myeloma, HR MDS, and acute lymphoblastic leukemia have been enrolled in the clinical development program overall. Further details of these studies are provided in the current IB.

4.1.3 Potential Risks and Benefits

Pevonedistat will be administered in Part A of this study as a single 1-hour IV infusion of 25 or 50 mg/m^2.

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, phase 1b study evaluating the MTD and safety and tolerability of pevonedistat+chemotherapy. There were 4 treatment groups in this study: pevonedistat in combination with docetaxel, pevonedistat lead-in with AUC6 carboplatin, pevonedistat in combination with carboplatin and paclitaxel, and pevonedistat in combination with gemcitabine. As of 22 January 2016, enrollment was complete and 2 patients remained on study. Preliminary data are available for 64 patients who received at least 1 dose of pevonedistat in combination with SoC. These patients had completed a total of approximately 330 cycles, with a median number of 3.5 (range, 1-10) cycles for pevonedistat in combination with docetaxel and 6.0 (range, 1-21) cycles in combination with carboplatin and paclitaxel. Fifty-four patients

evaluable for response have been treated with pevonedistat in combination with docetaxel (number of patients [N]=22), carboplatin (N=6), or carboplatin+paclitaxel (N=26): 3 objective responses were seen in 22 patients treated in Arm 1 (pevonedistat+docetaxel), and 9 partial responses/complete responses (CRs) were seen in 32 patients treated in Arm 2 (pevonedistat+carboplatin or pevonedistat+carboplatin/paclitaxel) [1-8]. The overall response rate in the intent-to-treat population of Arm 1 was 13% and in that of Arm 2 was 28%.

4.1.3.1 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) (IB Appendix A).

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 (HR).
- Diarrhea.
- Nausea.
- Vomiting.
- Pyrexia.
- Liver function test abnormal.
- Musculoskeletal pain.
- Myalgia.

Potential Risks

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

Potential Risks From Phase 1 Studies (at High Doses)

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

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

Potential Risks Confounded by Underlying Disease or Malignancy

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

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

Potential Risks Primarily Based on Findings From Animal Studies

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

- Myocardial degeneration and thrombosis.
- Pulmonary hypertension.

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

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

Hepatotoxicity has been noted following administration of pevonedistat in patients with advanced malignancy, including elevations of liver transaminases, alkaline phosphatase (ALP), and bilirubin (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 Sections 8.4 and 8.5).

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

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

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

4.1.3.2 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) who received prior platinum-based therapy receiving docetaxel at 100 mg/m^2.

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) [7] or United States Package Insert (USPI) [8].

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/mm^3.

4.1.3.3 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 who received who received prior platinum-based therapy receiving docetaxel at 100 mg/m^2.

4.1.3.4 Risks of Carboplatin and Paclitaxel Therapy

See Appendix H for information on the hematologic toxicity of carboplatin alone and in combination with paclitaxel [4,9].

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 USPI [3] or SmPC [5].

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 studies. 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 USPI [4] or SmPC [6].

Paclitaxel injection therapy should not be given to patients with solid tumors who have baseline neutrophil counts of less than 1500 cells/mm^3. 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.

4.1.3.5 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 [10] (see Appendix H) may be potentiated by carboplatin.

Given limited existing clinical experience, it is not known whether patients will benefit from participation in this study. However, a number of patients treated with pevonedistat as a single agent did demonstrate clinical benefit based primarily on prolonged stable disease (SD). In

addition, it is anticipated that the SoC therapies used in Part B of this study may provide additional clinical benefit to patients. Forty-eight patients have been treated with pevonedistat in combination with docetaxel, carboplatin, or carboplatin+paclitaxel. On the basis of preliminary data, these combinations have shown evidence of clinical benefit in the form of multiple partial responses and extended durations of SD.

4.2 Rationale for the Proposed Study

The primary objective of this study is to characterize the effects of 25 and 50 mg/m^2 pevonedistat on the electrocardiogram (ECG) corrected QT (QTc) interval. Therefore, this study will include 12-lead Holter monitoring for collection of PK time-matched ECGs over 24 hours in Part A following a single-dose administration of pevonedistat on Days 1 and 8 with a predose time-matched baseline on Day -1. Because pevonedistat is a cytotoxic agent and cannot be administered to healthy subjects, this study is being performed in adult patients with histologically or cytologically confirmed metastatic or locally advanced solid tumors that are appropriate for treatment with one of the 2 combination therapies in Part B of this study, who have progressed despite standard therapy, or for whom conventional therapy is not considered effective. Accordingly, the intensive assessment of QTc intervals in this study will not include a placebo dosing period or administration of a positive control QT-prolonging agent such as moxifloxacin.

The MTD of pevonedistat in combination with either docetaxel or carboplatin plus paclitaxel is 25 and 20 mg/m^2, respectively. Coadministration of pevonedistat with carboplatin plus paclitaxel produces an 80% increase in pevonedistat systemic exposure. The MTD of pevonedistat in combination with azacitidine is 20 mg/m^2, and coadministration of azacitidine does not alter pevonedistat PK. Therefore, the pevonedistat dose of 25 mg/m^2 selected in this study provides exposure coverage for (1) pevonedistat in combination with azacitidine, and (2) pevonedistat in combination with docetaxel. In addition, the effects of pevonedistat (50 mg/m^2) on QTc interval will also be evaluated. Pevonedistat, at a dose of 50 mg/m^2, will provide a 2.5-fold margin of exposure coverage over pevonedistat (20 mg/m^2) in combination with azacitidine. The dose of 50 mg/m^2 is also considered the RP2D of pevonedistat as monotherapy. The half-life ($t_{1/2}$) of pevonedistat is estimated to be approximately 10 hours, and minimum accumulation was observed following multiple dosing.

4.2.1 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 therapy with pevonedistat and chemotherapy. Two chemotherapy regimens, docetaxel and carboplatin+paclitaxel, which have been previously studied as combination partners with pevonedistat, will be used in this study. On the basis of the MTDs determined in Study C15010, patients will receive pevonedistat 25 mg/m^2 in combination with docetaxel 75 mg/m^2 or pevonedistat 20 mg/m^2 in combination with carboplatin AUC5+paclitaxel 175 mg/m^2.

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

Paclitaxel is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Paclitaxel is also indicated for the second-line treatment of acquired immunodeficiency syndrome–related Kaposi's sarcoma. In addition, paclitaxel in combination with cisplatin is indicated for first-line treatment of NSCLC in patients who are not candidates for potentially curative surgery 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 USPIs or SmPCs for additional information [3-8].

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 are well recognized as SoC in a number of malignancies in first-line (carboplatin+paclitaxel) and various relapse settings (all 3 regimens).
- The safety profiles, risks, and benefits of these agents have been widely studied and reported.
- The additive/synergistic effects of these agents in combination with pevonedistat have been studied in a number of in vitro and in vivo models by the sponsor.
- The MTD and RP2Ds have been determined for the combination of pevonedistat+docetaxel or pevonedistat+carboplatin/paclitaxel.

On the basis of these considerations, 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 Objective

The primary objective of this study is to characterize the effects of 25 and 50 mg/m^2 pevonedistat on the Fridericia corrected QT interval (QTcF) of the ECG.

5.1.2 Secondary Objectives

The secondary objectives for Part A of this study are as follows:

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

The secondary objective for Part B of this study is to evaluate the disease response that may be observed after treatment with pevonedistat in combination with either docetaxel or carboplatin+paclitaxel in patients with advanced solid tumors.

5.1.3 Safety Objectives

The safety objective for Part A is to evaluate the safety and tolerability of pevonedistat in patients with advanced solid tumors following a single IV dose at 25 and 50 mg/m^2.

The safety objective for Part B is to evaluate the safety and tolerability of pevonedistat in combination with either docetaxel or carboplatin+paclitaxel in patients with advanced solid tumors.

5.1.4 Exploratory Objectives

None.

5.2 Endpoints

5.2.1 Primary Endpoint

The primary endpoint for this study is change from time-matched baseline in QTcF following a single-dose IV administration of pevonedistat at 25 and 50 mg/m^2.

5.2.2 Secondary Endpoints

The secondary endpoints for Part A of this study are as follows:

- Change from time-matched baseline in QTcI, QRS, PR, and HR following a single-dose IV administration of pevonedistat at 25 and 50 mg/m^2.
- PK parameters: C_{max}, AUC_{24}, and $t_{1/2}$ of pevonedistat following a single-dose IV administration at 25 and 50 mg/m^2.

The secondary endpoint for Part B of this study is measures of disease response based on the investigator's assessment using the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, guideline [11].

5.2.3 Safety Endpoints

The safety endpoint for Part A of this study is adverse events (AEs), serious adverse events (SAEs), assessments of clinical laboratory values, and vital signs measurements following a single-dose IV administration of pevonedistat at 25 and 50 mg/m^2.

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

5.2.4 Exploratory Endpoints

None.

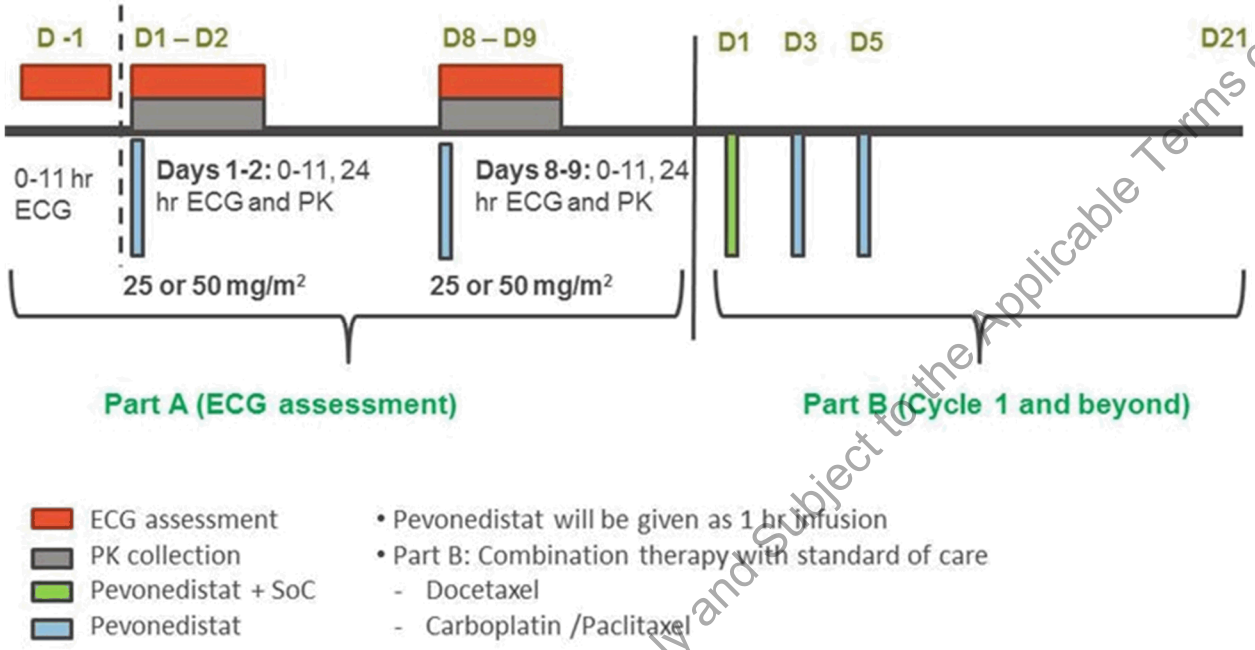
6.0 STUDY DESIGN

6.1 Overview of Study Design

This is a phase 1, 2-dose, crossover study to assess the effects of pevonedistat 25 and 50 mg/m^2 on the QTc interval in patients with histologically or cytologically confirmed metastatic or locally advanced solid tumors that are appropriate for treatment with one of the 2 combination therapies described in Part B of this study, who have progressed despite standard therapy, or for whom conventional therapy is not considered effective. Approximately 45 patients will be enrolled to obtain approximately 36 evaluable patients. Patients will be randomized 1:1 to receive pevonedistat 25 or 50 mg/m^2 on Day 1 in Part A and the other dose on Day 8. Study drug will be discontinued early if a patient experiences study drug–related toxicities. Patients may discontinue therapy at any time. Patients in Part A who do **not** continue to the optional Part B will attend an End-of-Study (EOS) visit 30 (+10) days after receiving their last dose of study drug in Part A.

Patients who continue to the optional Part B will attend an EOS visit 30 (+10) days after receiving their last dose of study drug in Part B or before the start of therapy subsequent to Part B participation, if that occurs sooner. The Schedules of Events (SOEs) are provided in Appendix A. 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 [12]. AEs will be assessed, and laboratory values and vital signs will be obtained to evaluate the safety and tolerability of pevonedistat. See Figure 6.a for an overview of the study design of Parts A and B.

Figure 6.a Study Overview



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

6.1.1 Part A: QT Assessment

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

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

Patients will undergo Holter ECG monitoring on Day -1 (0-11 hours), Day 1 (0-11 hours), Day 2 (24 hours after Day 1 dosing), Day 8 (0-11 hours), and Day 9 (24 hours after Day 8 dosing); triplicate ECGs will be extracted at matched PK time points to contribute to the analysis of the

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

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

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

After completing Part A of this study, patients will have the opportunity to participate in the optional Part B. Any patient who decides to participate in Part B will be re-evaluated per the entry criteria before treatment in Part B can begin (see Section 7.3). Patients will receive pevonedistat in combination with SoC agents, either docetaxel or carboplatin+paclitaxel, as recommended by the investigator. The dosing regimen will consist of pevonedistat in combination with the selected chemotherapy agent(s) on Day 1 and pevonedistat alone on Days 3 and 5 of each 21-day cycle. Safety and disease assessments will be conducted in Part B of the study. Disease assessments will be conducted using radiological evaluations (computed tomography [CT] scan or magnetic resonance imaging [MRI]) and will be based on the investigator's assessment using the RECIST, version 1.1, guideline [11].

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

6.2 Number of Patients

Approximately 45 patients will be enrolled at approximately 5 to 7 study sites in the United States (US) and/or rest of world (ROW) to obtain approximately 36 evaluable patients to provide the protocol-specified PK and time-matched ECG data to permit adequate assessment of the effects of pevonedistat on the QTc interval. Patients must meet the entry criteria and sign the informed consent form (ICF). Enrollment is defined as the time of the initiation of the first dose of study drug.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

6.3.1.1 Part A: QT Assessment

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

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

Eligible patients will have the **option** to continue to receive treatment in Part B of this study until discontinuation criteria are met (see Section 9.6). If a patient chooses to continue to Part B, that patient may enter Part B after meeting the entry criteria and within approximately 2 weeks of completing Part A; however, patients entering Part B must begin treatment within 8 weeks of completing Part A. The maximum duration of treatment will be 12 cycles; however, if it is determined, after discussion between the investigator and the sponsor, that a patient would derive benefit from continued treatment, the patient may remain on the current combination therapy or receive pevonedistat as a single agent beyond 12 cycles.

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

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

6.3.2 EOS/Study Completion Definition and Planned Reporting

Primary Completion/Study Completion

The analyses for the clinical study report may be conducted after all patients enrolled in the study have completed Part A, to meet the primary (QTc assessment) objective of the protocol, or have discontinued treatment. Patients still on therapy at this point will continue in the study through their EOS visit. The estimated time frame for primary completion is approximately 19.5 months, assuming an 18-month patient accrual period. The estimated time frame for study completion is approximately 28.5 months after the first patient is enrolled, assuming an 18-month patient accrual period. Once the study has been completed, an addendum to the study report will be prepared.

6.3.3 Time Frames for Primary and Secondary Endpoints to Support Disclosures

Refer to Table 6.a for disclosure information for all primary and secondary endpoints.

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

Endpoint	Definition	Maximum Time Frame (per Individual Patient)
Primary: change from time-matched baseline in QTcF following a single-dose IV administration of pevonedistat at 25 and 50 mg/m^2	Estimated maximum change in QTcF from time-matched baseline and 1-sided 95% CI	Up to 10 days
Secondary: change from time-matched baseline in QTcI, QRS, PR, and HR following a single-dose IV administration of pevonedistat at 25 and 50 mg/m^2	Estimated maximum change in QTcI, QRS, PR, and HR from time-matched baseline and 1-sided 95% CI	Up to 10 days
Secondary: PK parameters: C_{max}, AUC_{24}, and $t_{1/2}$ of pevonedistat following a single-dose IV administration at 25 and 50 mg/m^2	Maximum observed plasma concentration, area under the plasma concentration-time curve from time 0 to 24 hours postdose, and half-life	Up to 10 days

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

Endpoint	Definition	Maximum Time Frame (per Individual Patient)
Primary: not applicable	Not applicable	Not applicable
Secondary: measures of disease response based on the investigator's assessment using the RECIST, version 1.1, guideline [11]	Percentage of patients who achieve an objective response per investigator's assessment at end of treatment, according to the RECIST, version 1.1, guideline	Up to 12 months, depending on patient response

6.3.4 Total Study Duration

It is anticipated that this study will last for approximately 28.5 months, assuming an 18-month patient accrual period. The maximum duration of treatment in Part B will be 12 cycles; however, if it is determined, after discussion between the investigator and the sponsor, that a patient would derive benefit from continued treatment, the patient may remain on the current combination therapy or receive pevonedistat as a single agent beyond 12 cycles.

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

7.0 STUDY POPULATION

The patient population for this study will be adult patients with histologically or cytologically confirmed metastatic or locally advanced solid tumors that are appropriate for treatment with one of the 2 combination therapies in Part B of this study, who have progressed despite standard therapy, or for whom conventional therapy is not considered effective. Confirmation of eligibility must be obtained before the patient can enter the study. After completion of Part A, patients who elect to continue into the optional Part B must meet the entry criteria listed in Section 7.3.

7.1 Inclusion Criteria

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

1. Male or female patients aged 18 years or older.
2. Patients must have a histologically or cytologically confirmed metastatic or locally advanced solid tumor(s) appropriate for treatment with one of the 2 combination therapies in Part B of this study, have progressed despite standard therapy, or for whom conventional therapy is not considered effective.
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.
4. Expected survival longer than 3 months from enrollment in the study.
5. Recovered (ie, Grade ≤1 toxicity) from the reversible effects of prior anticancer therapy.
6. Clinical laboratory values, as specified below, within 3 days before the first dose of study drug:
   - Hemoglobin ≥9 g/dL; patients may be transfused to achieve this value.
   - Total bilirubin less than or equal to the ULN.
   - ALT, AST, and ALP ≤2.5 times the ULN; for patients to be treated with pevonedistat+docetaxel in Part B, AST and ALT must be ≤1.5 times the ULN, and total bilirubin should be within the normal range.
   - Calculated creatinine clearance ≥50 mL/min (creatinine clearance is defined in Section 9.4.13).
   - ANC ≥1000/mm^3.
   - Platelet count ≥75,000/mm^3.
   - Prothrombin time and aPTT ≤1.5 times the ULN.
   - Albumin ≥2.7 g/dL.
7. Suitable venous access for the study-required blood sampling (including PK sampling).
8. Female patients who meet any of the following:
   - Are postmenopausal for at least 1 year before the Screening visit (see Appendix J).
   - Are surgically sterile.

- If they are of childbearing potential, agree to practice 1 highly effective method of contraception and 1 additional effective (barrier) method of contraception (see Appendix K) at the same time, from the time of signing the ICF through <1 month or 5 half-lives (whichever is longer) after the last dose of study drug.
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

9. Male patients, even if surgically sterilized (ie, status postvasectomy), who meet either of the following:
   - Agree to practice effective barrier contraception during the entire study treatment period and through 120 days after the last dose of study drug.
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
10. Patients who are willing to refrain from donating blood for at least 90 days after their last dose of pevonedistat and (for male patients) willing to refrain from donating semen for at least 4 months after their last dose of pevonedistat.
11. Voluntary written consent must be given before performance of any study-related procedure that is 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. Female patients who are lactating and breastfeeding, have a confirmed positive serum pregnancy test during the Screening period, or have a confirmed positive pregnancy test 24 hours or sooner before the first dose of study drug.
2. Life-threatening illness or serious (acute or chronic) medical or psychiatric illness unrelated to cancer that may increase the risk associated with study participation or investigational product administration, interfere with the interpretation of study results, or (in the investigator's opinion) could potentially interfere with the completion of treatment according to this protocol.
3. Treatment with any systemic antineoplastic therapy or any investigational products within 21 days before the first dose of study drug.
4. Inability to comply with study visits and procedures, including required inpatient confinement.

5. Major surgery within 14 days before the first dose of study drug or scheduled surgery during Part A of the study.
6. Treatment with strong CYP3A inducers within 14 days before the first dose of pevonedistat. Patients must have no history of amiodarone use within 6 months before the first dose of pevonedistat nor require the use of these medications during the study
7. Prior treatment with pevonedistat; however, prior treatment with docetaxel, paclitaxel, and carboplatin is allowed.
8. Treatment with QT-prolonging drugs with a risk of causing torsades de pointes (TdP) (see Appendix L [13]). Patients taking drugs with a possible or conditional risk of QT prolongation or drugs that are to be avoided by patients with congenital long QT syndrome may be considered if on a stable dose, pending discussion and agreement between the investigator and the sponsor.
9. History of myocardial infarction, unstable symptomatic ischemic heart disease, thromboembolic events (eg, deep vein thrombosis, pulmonary embolism, or symptomatic cerebrovascular events), or any other cardiac condition (eg, pericardial effusion or restrictive cardiomyopathy) within 6 months before receiving the first dose of study drug.
10. History of polymorphic ventricular fibrillation or TdP, permanent atrial fibrillation (defined as continuous atrial fibrillation for ≥6 months), and persistent atrial fibrillation (defined as sustained atrial fibrillation lasting 7 days 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 a device (eg, pacemaker) or ablation, and is excluded. Patients with paroxysmal atrial fibrillation are permitted to enroll.
11. History of Brugada syndrome, risk factors for TdP, or family history of long QT syndrome.
12. Clinically significant abnormal 12-lead ECG at Screening indicating a second- or third-degree atrioventricular block/intermittent block or including 1 or more of the following:
    - QRS interval >110 msec.
    - QTcF >480 msec.
    - PR interval >200 msec.
    - Any arrhythmia (except for mild sinus tachycardia) interpreted by the investigator to be clinically significant.
13. Any of the following cardiovascular conditions or values within 6 months before the first dose of study drug:
    - A left-ventricular ejection fraction <40%.
    - New York Heart Association Class III or IV congestive heart failure with recent decompensation requiring hospitalization within 4 weeks before Screening [14] (see Appendix I).

- Evidence of current uncontrolled cardiovascular conditions, including cardiac arrhythmias, congestive heart failure, angina, or ECG evidence of acute ischemia or active conduction system abnormalities.
- Patients with sustained systolic BP >160 or <90 mm Hg, diastolic BP >100 or <65 mm Hg, or resting pulse rate <50 or >100 beats per minute (bpm) at Screening or predose.

14. Implantable cardioverter defibrillator.
15. Cardiac pacemaker with HR set at a fixed rate and treatment with concomitant medication that may limit increase in HR in response to hypotension (eg, high-dose beta blocker).
16. Known moderate to severe aortic stenosis, moderate to severe mitral stenosis, or other valvulopathy (ongoing).
17. Known hypersensitivity or history of severe intolerance or toxicity to chemotherapeutic agents, including known history of severe hypersensitivity reactions to docetaxel (polysorbate 80–based formulations) for patients to be treated with pevonedistat+docetaxel; history of hypersensitivity to carboplatin for patients to be treated with pevonedistat+ carboplatin+paclitaxel; or history of severe hypersensitivity to paclitaxel (Cremophor-based formulations) for patients to be treated with pevonedistat+carboplatin+paclitaxel.
18. Active, uncontrolled infection or severe infectious disease such as severe pneumonia, meningitis, septicemia, or methicillin-resistant *Staphylococcus aureus* infection within 2 weeks before dosing.
19. Known human immunodeficiency virus (HIV) seropositive, 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.
20. Clinically significant central nervous system (CNS) disease defined as newly diagnosed, untreated, progressive, or requiring steroids for control of symptoms.
21. Newly diagnosed or uncontrolled cancer-related CNS disease.
22. Known hepatic cirrhosis or severe preexisting hepatic impairment.
23. Known moderate to severe chronic obstructive pulmonary disease, interstitial lung disease, pulmonary fibrosis, or pulmonary arterial hypertension.
24. 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.
25. Male patients who intend to donate sperm during the course of this study or 4 months after receiving their last dose of study drug.
26. Admission or evidence of illicit drug use, drug abuse, or alcohol abuse.

7.3 Entry Criteria for Continuation to Optional Part B

After completing Part A of the study, patients may choose to enter the optional Part B of the study. To be eligible for the optional Part B, patients must have completed Part A and be reassessed to determine if they meet the entry criteria for optional Part B. Only patients who meet the following criteria may enter into Part B:

- ECOG performance status of 0 to 1.
- ANC $\geq$1500/mm^3.
- Platelet count $\geq$100,000/mm^3.
- Laboratory values for hemoglobin, total bilirubin, ALT, AST, ALP, and serum creatinine or calculated/measured creatinine clearance, as specified in Section 7.1.
- Diarrhea symptoms resolved to Grade 1 or better.
- QTc interval <480 msec.
- CT scan or MRI of the chest, abdomen, and pelvis within 28 days of Cycle 1 Day 1.

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

For patients to begin dosing in optional Part B, their predose Cycle 1 Day 1 assessments in Part B must return to the baseline values of Part A or Grade $\leq$1 or to a level considered acceptable by the investigator, after discussion with the project clinician or designee, and must meet all the entry criteria specified in this section (Section 7.3). If after a maximum of 8 weeks from the last dose in Part A (eg, up to 8 weeks after the Day 8 visit), the predose Cycle 1 Day 1 assessments in Part B have not returned to Part A baseline values (or Grade $\leq$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** Part B 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.

8.0 STUDY DRUG

8.1 Study Drug Administration

8.1.1 Part A: Pevonedistat Administration

Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s). A single IV dose of pevonedistat at 25 or 50 mg/m^2 will be administered on Days 1 and 8 over a period of approximately 60 minutes (±5 minutes). Patients randomized to 25 mg/m^2 on Day 1 will receive 50 mg/m^2 on Day 8 and vice versa.

On all 3 days of Holter ECG sampling (Cycle 1 Days -1, 1, and 8), patients will remain NPO, except for water, from 2 hours before the 0-hour time point until completion of the 4-hour ECG/PK sample collection. Accordingly, patients will be advised to eat breakfast at least 2 hours before the 0-hour time point and to eat lunch after the 4-hour Holter ECG and PK blood sample collection.

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

All protocol-specified criteria for administration of study drug must be met and documented before study drug administration.

8.1.2 Part B: Pevonedistat in Combination With SoC Chemotherapy Agents

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

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

8.1.2.1 Pevonedistat Administration

For Part B, Pevonedistat (TAK-924/MLN4924) Concentrate for Solution for Infusion (referred to subsequently as Pevonedistat Concentrate) formulation CCI [redacted]

Patients will receive pevonedistat diluted CCI [redacted] 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.

On Day 1, patients will receive either pevonedistat 25 mg/m^2 in combination with docetaxel or pevonedistat 20 mg/m^2 in combination with carboplatin+paclitaxel. On Days 3 and 5, patients will receive pevonedistat alone.

8.1.2.2 Docetaxel Administration

On Day 1 of each cycle, when all study drugs are administered together, docetaxel 75 mg/m^2 will be administered first as a 1-hour IV infusion. After a mandatory approximately 15-minute time-out (pevonedistat-free period), pevonedistat will be administered IV. On Days 3 and 5, only pevonedistat will be given. The duration of each cycle will be 21 days. Refer to the most recent SmPC for further details regarding docetaxel administration [7,8].

Premedication for Docetaxel-Associated Hypersensitivity or Other Acute Reactions Guidelines

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

8.1.2.3 Carboplatin Plus Paclitaxel Administration

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

- Refer to the most recent SmPC/USPI for further details regarding carboplatin administration [3,5].

  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 follows:

  Total carboplatin dose (mg)=(target AUC)×(GFR+25) [Calvert formula]

  Maximum carboplatin dose (mg)=target AUC (mg×min/mL)×(150 mL/min)

The maximum dose is based on a GFR estimate that is capped at 125 mL/min for patients with normal renal function. No higher estimated GFR values should be used.

For a target AUC=5, the maximum dose is 5×150=750 mg.

For a target AUC=4, the maximum dose is 4×150=600 mg.

- Refer to the most recent SmPC/USPI for further details regarding paclitaxel administration [4,6].

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

8.2 Reference/Control Therapy

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

8.3 Dose Modification Guidelines (Part B)

8.3.1 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

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

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

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

8.3.2 Criteria for Dose Interruption During a Cycle

In Part B, the infusion may be slowed or stopped and restarted for any associated infusion-related reactions; however, this should be avoided in Part A. 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.

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/m^2) may also be considered for events

judged by the investigator to be directly related to pevonedistat or for chemotherapy-related toxicities that may have been exacerbated by pevonedistat in the combination setting.

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/m^2. One dose reduction to 135 mg/m^2 may be considered.
  - Carboplatin is initially dosed at AUC5. One dose reduction to AUC4 may be considered.
- The decision to treat at a reduced dose level of chemotherapy is at the discretion of the investigator. Discussions with the project clinician or designee are encouraged.

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

Table 8.a Dose Modification Guidelines for Specific Toxicities

Pathologic Condition	Severity	Action on Study Drug
Hematologic: ANC	Febrile neutropenia	Hold dosing on Day 1 of Cycles ≥2 up to 3 weeks (see Section 8.3.4) until febrile neutropenia is resolved, then resume dosing as appropriate. Consider use of growth factor or reduce chemotherapy by 1 dose level, as appropriate.
	ANC <1500 cells/µL on Day 1 of Cycles ≥2	Initiation (Day 1) of Cycles ≥2 should be delayed for up to 3 weeks (see Section8.3.4) until ANC is ≥1500 cells/µL. Consider use of growth factor or reduce chemotherapy by 1 dose level as appropriate.
	Grade ≥3 neutropenia lasting >7 days	Initiation (Day 1) of Cycles ≥2 should be delayed until ANC is ≥1500 cells/µL. Consider use of growth factor or reduce chemotherapy by 1 dose level as appropriate.
Hematologic: Platelets	Platelet count <100,000/µL on any dosing day of Cycles ≥2	Dosing in Cycles ≥2 should be delayed for up to 3 weeks (see Section 8.3.4) until platelet count is ≥100,000 cells/µL. Dose of chemotherapy may be reduced by 1 dose level as appropriate.
	Grade 4 thrombocytopenia lasting >7 days or platelet count <25,000 cells/µL at any time	Dosing in Cycles ≥2 should be delayed until platelet count is ≥100,000 cells/µL (see Section 8.3.4). Dose of chemotherapy may be reduced by 1 dose level as appropriate.

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

Pathologic Condition	Severity	Action on Study Drug
Hematologic: Anemia	Grade ≥1	No dose modification is allowed for anemia. Transfusion and/or erythropoietin may be given, as clinically indicated, for the treatment of anemia (see Section 8.7.3).
Nausea, emesis, or diarrhea despite maximal prophylaxis	Grade ≥3	On days when both chemotherapy and pevonedistat are administered, hold dosing for up to 3 weeks (see Section 8.3.4) or until the toxicity returns to Grade ≤1, then restart at the next lower dose of chemotherapy. On days when pevonedistat is given as a single agent, hold pevonedistat dosing for up to 3 weeks (see Section 8.3.4) or until the toxicity returns to Grade ≤1 before dosing is resumed. **Note**: Ensure that optimal prophylaxis has been employed before dose reduction. Supportive care with moderate or strong CYP3A inhibitors/inducers should be avoided.
Stomatitis	Grade ≥3	Hold treatment for up to 3 weeks until the stomatitis is Grade ≤1 (see Section 8.3.4). If acute Grade ≥3 stomatitis occurs at any time, the dose of chemotherapy should be reduced by 1 dose 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 reducing chemotherapy also by 1 dose level.
Hepatic toxicity	Total bilirubin >1.5× ULN, regardless of ALT/AST	Hold dosing for up to 3 weeks (see Section 8.3.4) until bilirubin returns to within normal range and/or reduce chemotherapy by 1 dose 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. If after review with sponsor, the arrhythmia is felt to be clearly unrelated to infused agent (eg, recurrent atrial fibrillation in patient with a remote history of intermittent atrial fibrillation), treatment may be restarted when the arrhythmia has resolved. Should the patient have a second incidence of symptomatic arrhythmia during infusion, the patient will be discontinued from the study.
Cardiac toxicity	Chest pain and/or symptomatic hypotension (<90/60 mm Hg)	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.

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

Pathologic Condition	Severity	Action on Study Drug
Neurotoxicity (paclitaxel or docetaxel only)	Grade ≥2	Hold treatment until patient recovers to Grade 1 toxicity, then resume treatment at the next lower dose level (see Section 8.3.4). This will be a permanent dose reduction. Carboplatin or pevonedistat dose is not to be modified.
Allergic reaction (paclitaxel or docetaxel only	Moderate symptoms	Stop infusion. Give IV diphenhydramine 25 to 50 mg, IV dexamethasone 10 mg, and/or treatment per institutional guidelines. After recovery of symptoms, resume infusion at a low infusion rate. If no further symptoms occur, resume full dose rate until infusion is complete. If symptoms recur, stop infusion and discontinue patient.
Allergic reaction (paclitaxel or docetaxel only)	Severe symptoms	Stop infusion. Give IV diphenhydramine, dexamethasone, and/or treatment per institutional guidelines as mentioned 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	Examples: cyclosporine and eltrombopag
Strong CYP3A4 inducers	See Appendix F.
QT prolonging drugs	See Appendix L.

BCRP=breast cancer resistance protein.

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 (eg, cyclosporine and eltrombopag)	Generally excluded during the study but may be used as specified in Table 8.e
Strong CYP3A4 inducers	Excluded during the study
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 [5-7] for additional information regarding precautions, warnings, and contraindications.
BCRP=breast cancer resistance protein.

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

8.5.2 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
Antiemetic agents	Antiemetic agents, including for prophylactic use, may be administered at the discretion of the investigator.
Known BCRP inhibitors (eg, cyclosporine and eltrombopag)	Limited use is permitted only if clinically necessary and no suitable alternative exists. The patient may receive a BCRP inhibitor from 24 hours after the last pevonedistat dose to 72 hours before the next pevonedistat dose. For example, if a patient receives pevonedistat on a Monday (Day 1), Wednesday (Day 3), and Friday (Day 5) schedule, then a BCRP inhibitor may be administered (if clinically necessary and no suitable alternative exists) from the Saturday after the Day 5 dose (Day 6) up to the Friday (Day 19) before the Monday dose of the next cycle.
Nephrotoxic medications, including nonsteroidal anti-inflammatory drugs	Whenever possible, caution should be used with nephrotoxic concomitant medications (Appendix H). Alternative concomitant nonnephrotoxic medications should be used whenever possible.
RBC transfusion	For all patients with anemia, and especially for patients with hemoglobin values <9 g/dL during the conduct of the study, consideration should be given for RBC transfusions based on the patient's risk of inadequate oxygenation, underlying cardiopulmonary status, clinical judgment, and hospital guidelines. RBC transfusions must be administered at least 1 day before administration of study drug. Each transfusion episode, including the type of transfusion (RBC), should be recorded.

BCRP=breast cancer resistance protein.

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 and male patients should use highly effective methods of contraception through defined periods during and after study treatment, as specified below.

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

Female patients must meet any of the following:

- Postmenopausal for at least 1 year before the Screening visit (see Appendix J).
- Surgically sterile.
- If they are of childbearing potential (as defined in Section 9.4.8), 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 ICF through 4 months after the last dose of study drug.
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, and postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
- Agree to not donate eggs (ova) during the course of this study or 4 months after receiving their last dose of study drug.

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

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

- Donate sperm during the course of this study or 4 months after receiving their last dose of study drug.

8.6.2 Docetaxel

8.6.2.1 Pregnancy

Docetaxel is a pregnancy Category D drug. Refer to the docetaxel SmPC/USPI for more information [7,8].

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 [7,8].

8.6.2.2 Geriatric Use

Refer to the docetaxel SmPC/USPI for additional information on geriatric use in different types of cancer [7,8].

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/USPI for more information [3,5].

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 [3,5].

8.6.3.2 Geriatric Use

Refer to the carboplatin SmPC/USPI for additional information on geriatric use [3,5].

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 older than 65 years, and 22 patients were

older than 75 years. In these studies, 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 older than 65 years) who received single-agent carboplatin for different tumor types, a similar incidence of AEs was seen in patients older than 65 years and in patients younger 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/USPI for more information [4,6].

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 times the daily maximum recommended human dose on a mg/m^2 basis) caused embryotoxicity 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/m^2 basis); teratogenic potential could not be assessed at higher doses because of extensive fetal mortality.

There are no adequate and well-controlled studies of paclitaxel 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 [4,6].

8.6.4.2 Geriatric Use

Refer to the paclitaxel SmPC/USPI for additional information [4,6].

Of the 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 of the 1570 patients who were randomized to receive paclitaxel in the adjuvant breast cancer study, 649 patients (17%) were older than 65 years and 49 patients (1%) were older than 75 years. 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 and 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 current pevonedistat IB, which includes the DCSI (IB, Appendix A).

The most common adverse drug reactions for docetaxel and for paclitaxel+carboplatin are described in Section 4.1.3.4. Refer to the applicable SmPC/USPI for additional details regarding the management of clinical events attributed to these agents [3-8].

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 (Parts A and B)

It is essential that patients are 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. Patients may enter the optional Part B within approximately 2 weeks of completion of Part A if they meet the entry criteria for Part B. If a patient chooses to enter Part B, they must do so within 8 weeks of completing Part A.

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 0.5N saline given over 2 to 4 hours, for a total of 1 to 2 L of fluid, as clinically appropriate; each infusion of IV fluids should be recorded in the electronic case report forms (eCRFs).

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

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

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

8.7.2 Guidance for Use of Granulocyte-Colony Stimulating Factor

Use of growth factors such as granulocyte-colony stimulating factor is 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 [15].

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

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

8.7.4 Guidance for Management of Extravasation

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

8.8 Blinding and Unblinding

This is an open-label study.

8.9 Description of Investigational Agents

8.9.1 Pevonedistat

Pevonedistat Concentrate formulation consists of 10 mg/mL (as free base) of pevonedistat HCl in an aqueous solution of 7.45 mg/mL anhydrous citric acid, 3.29 mg/mL trisodium citrate dihydrate, and 100 mg/mL betadex sulfobutyl ether sodium (Captisol) at pH 3.3. Each United States Pharmacopeia (USP) Type I glass vial contains compounded sterile solution, sealed with a fluoropolymer-coated butyl rubber stopper, and oversealed with an aluminum seal and a plastic cap. 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 dose formulation. Refer to the docetaxel SmPC/USPI [7,8].

8.9.3 Carboplatin

Carboplatin is obtained from commercial sources according to local practice standards and is provided as a commercially available dose formulation. Refer to the carboplatin SmPC/USPI [3,5].

8.9.4 Paclitaxel

Paclitaxel is obtained from commercial sources according to local practice standards, and it is provided as a commercially available dose formulation. Refer to the paclitaxel SmPC/USPI [4,6].

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/USPIs for docetaxel, paclitaxel, and carboplatin for instructions and precautions regarding preparation [3-8].

8.11 Packaging and Labeling

8.11.1 Pevonedistat

Pevonedistat Concentrate will be provided in USP Type I glass vials nominally containing 5 mL of compounded sterile solution at a concentration of 10 mg/mL (as free base), sealed with a fluoropolymer-coated butyl rubber stopper, and oversealed with an aluminum seal and a plastic cap.

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 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

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

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

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

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

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

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

8.12.2 Docetaxel, Carboplatin, and Paclitaxel

Refer to the SmPCs/USPIs for the docetaxel, paclitaxel, and carboplatin for instructions and precautions regarding preparation [3-8].

8.13 Other Protocol-Specified Materials

Refer to the Pharmacy Manual.

9.0 STUDY CONDUCT

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

9.1 Study Personnel and Organizations

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

9.2 Arrangements for Recruitment of Patients

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

9.3 Treatment Group Assignments

In Part A, patients will be randomized 1:1 in a crossover fashion to receive a single dose of 25 or 50 mg/m^2 pevonedistat on Day 1 and the alternate dose on Day 8.

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

9.4 Study Procedures

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

9.4.1 Informed Consent

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

9.4.2 Patient Demographics

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

9.4.3 Medical History

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

malignancy and include a description of prior therapies for it. In addition, concomitant medications will be recorded as specified in Section 8.5.

9.4.4 Physical Examination

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

9.4.5 Patient Height

Height will be measured only during Screening.

9.4.6 Vital Signs

Vital signs, including diastolic and systolic BP, HR, weight, and body temperature, will be collected as indicated in the SOEs (Appendix A) and as clinically indicated. All vital signs will be taken in the supine position, as noted in the SOEs (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 SOEs (Appendix A).

9.4.7 ECOG Performance Status

ECOG performance status [16] (Appendix D) will be assessed during Screening for Part A, on Day 1 predose in Part B of the study, and at the EOS visit.

9.4.8 Pregnancy Test

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

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

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

9.4.9 Concomitant Medications and Procedures

Concomitant medications, therapies, and procedures will be recorded in the eCRF from the time of the first dose of any study drug through 30 (+10) days after the last dose of study drug(s). See Sections 8.4 and 8.5 for additional details regarding excluded and permitted concomitant medications and procedures.

9.4.10 AEs

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the SOEs (Appendix A). Refer to Section 10.0 for details regarding definitions, documentation, and reporting of pretreatment events (PTEs), AEs, and SAEs.

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

9.4.11 Enrollment

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

9.4.12 ECG

For Part A of the study, there are 2 types of ECGs: 12-lead safety ECGs and 12-lead Holter monitoring (see Section 9.4.16 for Holter monitoring). 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 (Appendix A).

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

9.4.12.1 Twelve-Lead Safety ECG

The first type of ECG acquired for this study consists of ECG tracings that are acquired using a standard 12-lead digital ECG machine. This includes ECGs that are taken as described in the table in Appendix A. These tracings are all to be reviewed by the investigator or trained designee at the site. The ECG printout of parameters (including HR, PR, QRS, QT, and QTc intervals) is acceptable for the purposes of check-in and safety before dosing. All machine-generated tracings should be acquired in the supine position after the patient has been resting for 5 minutes. These ECGs are not included in the final analysis of effects of pevonedistat on triplicate ECG parameters of this study.

9.4.12.2 Pharmacodynamic Measurements: 12-Lead Holter Monitoring ECG

The study ECGs that are included in the final statistical analysis will be acquired from the 24-hour Holter recorders using the H-12 Plus ambulatory ECG recorder (Mortara Instruments, Milwaukee, Wisconsin), with high-frequency flashcards and a sampling rate of 1000 samples per second (see Section 9.4.16).

9.4.13 Clinical Laboratory Evaluations

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

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

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

Blood samples for the analysis of clinical laboratory parameters shown in Table 9.b will be obtained as specified in the SOEs (Appendix A).

Table 9.a Clinical Chemistry and Hematology Tests

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

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

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

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

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

Table 9.b Clinical Urinalysis Tests

Urinalysis	
Leukocytes	pH
Nitrite	Protein
Occult blood	Specific gravity
Microscopic assessment	

9.4.14 Disease Assessment

Radiological evaluations (CT scans, with IV contrast unless medically contraindicated, or MRI) of the chest, abdomen, and pelvis will be required as entry criteria for Part B (see Section 7.3) to assess the status of the patient's underlying disease. If the patient has had appropriate imaging scans performed within 28 days before Cycle 1 Day 1 of Part B, 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. For each site of disease, the imaging modality (CT scan or MRI) used at entry for the optional Part B must be used throughout the study. Tumor response will be assessed by the investigator at these times using the RECIST, version 1.1, guideline (Appendix E).

9.4.15 PK Measurements

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

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

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

The primary purpose of PK sampling in this study is to measure pevonedistat concentrations in plasma. However, these PK samples may also be used for the exploratory measurement of plasma concentrations of metabolites of pevonedistat, if technically feasible and considered necessary for further understanding the metabolism of pevonedistat in patients with cancer.

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

9.4.16 Pharmacodynamic Measurements for Analysis of Effects of Pevonedistat on Triplicate ECG Parameters

As shown in the table in Appendix A, patients will undergo Holter ECG monitoring for collection of triplicate ECGs for baseline measurement (Day -1) and pre- and post pevonedistat administration (Days 1, 2, 8, and 9). Triplicate ECGs will be extracted on Day -1 (drug-free baseline) Days 1, 2, 8, and 9 at matched PK time points to contribute to the analysis of the effect of pevonedistat on QT/QTc intervals. As Day -1 is timed to coincide with the clock time of the dosing time of pevonedistat on Day 1 and Day 8.

On all 3 days of Holter ECG sampling (Days -1, 1, and 8), patients will remain NPO, except for water, from 2 hours before the 0-hour time point until completion of collection of the 4-hour ECG/PK samples. Accordingly, patients will be advised to eat breakfast at least 2 hours before the 0-hour time point and to eat lunch after the 4-hour Holter ECG and PK blood sample collection. At least 1.5 hours must elapse between completing the meal and the onset of the next ECG time point that occurs 6 hours postdose. This is necessary to avoid an autonomic effect on the QT interval duration. Meal times on Days -1, 1, and 8 should be kept the same.

Before each nominal triplicate ECG sampling time point listed in Appendix A, the patient must maintain at supine bed rest for 15 minutes. The triplicate ECGs will be extracted during the final 10 minutes of that rest period (the ECG extraction of 10-minute window). The time-matched PK blood draws will occur immediately following the completion of the ECG extractions on Days 1, 2, 8, and 9. The 12-lead ECGs are extracted by the Core ECG Laboratory in triplicate, free from artifact, wandering, and at a time when the HR has been stabilized at ±2 bpm. All QT intervals will be measured using the representative beat in the 12-lead global display. The measurements of QT, respiratory rate (RR), PR, and QRS intervals are initiated in semiautomatic mode and then adjusted appropriately by cardiovascular physicians. Thereafter, they are visually validated or manually adjusted and interpreted by certified cardiologists who are subject specific and remain blinded to treatment sequence.

9.5 Completion of Study (for Individual Patients)

9.5.1 Part A

Patients will be considered to have completed Part A of the study if they have completed the protocol-specified assessments to provide data necessary for evaluation of ECGs 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 vital signs), laboratory assessments (hematology, chemistry, and urinalysis), and 12-lead ECG; monitoring of concomitant mediations, therapies, and procedures; and recording of AEs/SAEs. The EOS visit will be conducted 30 (+10) days after the last dose of study drug in Part A. If the EOS visit occurs earlier than 30 days after the last dose of pevonedistat, the patient should be contacted via telephone on Day 30 to assess for any new or ongoing AEs or SAEs that may have occurred since the previous visit.

9.5.2 Optional Part B

Patients will be considered to have completed Part B of the study if they have completed 12 cycles of treatment with study drug, or if treatment is discontinued for any of the reasons outlined in Section 9.6. If the patient continues into Part B, the EOS visit will occur 30 (+10) days after the last dose of study drug(s) in Part B or before the start of subsequent therapy for the patient's indication, if that occurs sooner. If the EOS visit occurs earlier than 30 days after the last dose of pevonedistat, the patient should be contacted via telephone on Day 30 to assess for any new or ongoing AEs or SAEs that may have occurred since the previous visit.

9.6 Discontinuation of Treatment With Study Drug and Patient Replacement

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

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

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

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

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

9.7 Withdrawal of Patients From Study

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

- Lost to follow-up.
- Study terminated by sponsor.

- Withdrawal by subject.
- Completed study.
- Death.
- Other.
- PD.
- Initiation of hematopoietic stem cell transplant.

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

9.8 Study Compliance

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

The clinical team and the clinical research associate will review treatment compliance during investigational visits and at the completion of the study. Tests and procedures should be performed on schedule, but (unless otherwise specified) occasional changes are allowed 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 in the optional Part B of the study.

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

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 PTE Definition

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

10.1.2 AE Definition

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

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, or 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, requires medical or surgical intervention to prevent one 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 [12]. Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4) because the terms *serious* and *severe* are **not** synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is **not** the same as *serious*, which is based on patient/event outcome or action criteria described above and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000/mm^3 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 in the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

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

SAE Reporting Contact Information

Cognizant

United States

PPD

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the study *or* before study drug was given are not to be considered AEs

unless the condition deteriorated in an unexpected manner during the study (eg, surgery was performed earlier or later than planned).

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

Severity (toxicity grade) for each AE, including any lab abnormality, will be determined using the NCI CTCAE, version 4.03, effective date 14 June 2010 [12]. The criteria are provided in the Study Manual.

The **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 the signing of informed consent through 30 (+10) days after administration of the last dose of study drug and recorded in the eCRFs.

SAEs will be reported as follows:

- Serious PTEs will be reported to the Takeda Global Pharmacovigilance department or designee from the time of the signing of the ICF up to the first dose of study drug and will also be recorded in the eCRF.
- 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 (+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 email addresses provided below.

Call Center	Phone Number	Email	Fax
Dohmen Life Science Services	1-844-662-8532 Non–toll-free number: 1-510-740-1273	GlobalOncologyMedinfo@takeda.com	1-800-881-6092

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to 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 (SUSARs) 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 will be submitted to the regulatory authorities as an expedited report within 7 days for fatal and life-threatening events and within 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 study. 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

11.1 Sponsor Safety Assessment

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

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. If selected for coding, AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). 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 sponsor's 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, CRO 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, the 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 sponsor's 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), eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or sponsor's designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of

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

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

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator and the head of the institution 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

13.1.1.1 Part A: QT Assessment

The populations used for analysis of Part A will include the following:

- QT population: patients who receive the protocol-specified pevonedistat dosing and have sufficient ECG assessments to permit reliable analysis.
- PK population: patients who receive the protocol-specified pevonedistat dosing and have sufficient PK assessments to permit reliable estimation of PK parameters.
- Safety population: patients who receive at least 1 dose of pevonedistat during Part A; the safety population will be used for all safety analyses.

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

The populations used for analysis of Part B will include the following:

- Disease-response population: patients who receive at least 1 dose of study drug in Part B, have measurable disease as entry criteria for Part B, and have at least 1 postbaseline disease assessment.
- Safety population: patients who continue to Part B and receive at least 1 dose of study drug during Part B; the safety population will be used for all safety analyses.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics (including sex, age, race, ethnicity, weight, height, and BSA) will be summarized for all subjects. Summary statistics (eg, number of subjects, mean, median, standard deviation, and range) will be generated for continuous variables (eg, age and weight), and the number and percentage of subjects within each category will be presented for categorical variables.

13.1.3 Efficacy Analysis

In Part B, analysis of disease response will be based on the investigator's assessment using the RECIST, version 1.1, guideline [11] (Appendix E). The primary analysis of efficacy measures will be descriptive. Survival analysis and other statistical modeling may be used as needed. The primary analysis will be based on the best overall response.

13.1.4 PK Analysis

The PK analysis in Part A will be based on noncompartmental analysis of the concentration-time data of pevonedistat in individual patients. Concentration-time data will be listed for individual patients by dose and summarized using descriptive statistics in tabular and graphical forms. PK parameters will be listed for individual patients by dose and summarized using descriptive statistics in tabular form.

The following PK parameters will be calculated by noncompartmental analysis and listed by dose for each individual and tabulated using descriptive statistics by dose: C_{max}, AUC_{24}, and $t_{1/2}$ of pevonedistat following single-dose administration at 25 and 50 mg/m^2.

13.1.5 Pharmacodynamic Analysis of the Effects of Pevonedistat on Triplicate ECG Parameters

Holter triplicate ECG data will be centrally read and will contribute to an integrated analysis of the effects of pevonedistat on triplicate ECG parameters.

The primary analysis will be based on the baseline-adjusted QTcF in Part A. A statistical analysis will be performed using a linear mixed-effects model with random subject effect. Additionally, a concentration effect analysis will be performed using a linear mixed-effects model with baseline-adjusted QTcF as the dependent variable, drug plasma concentration as the continuous predictor, and random intercept and slope per subject. Baseline-adjusted QTcF at the geometric mean C_{max} for the 2 dose levels from a regression analysis of baseline-adjusted QTcF as a function of pevonedistat concentration will be estimated.

The methods for calculating QTc parameters are described below:

- Fridericia correction: $QTcF=QT/RR^{1/3}$.
- Individual correction: QTcI will be derived from linear regression modeling using QT-RR pairs recorded by Holter on all baseline assessments: $\log(QT)=\log(a)+b_{LOG}(RR)$, whose RR coefficient for each subject, b, will then be used to calculate the individual corrected QT for each subject, as follows: $QTcI=QT/RR^b$. Each individual QT interval and RR interval pair will be used to calculate a QTcI interval. These individual QTc intervals will then be averaged for analysis. For the change from time-matched baseline QTcI at each time point, 1-sided 95% CIs will be constructed.

The following categorical analyses of QTcF, QTcI, PR interval, and QRS duration will be performed at each ECG time point and overall for each patient:

- Absolute QTc interval prolongation:
  - QTc interval >450 msec.
  - QTc interval >480 msec.
  - QTc interval >500 msec.

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

If the mean ECG HR change from baseline at any time point after dosing is ≥+10 bpm, or if individual subject HR changes from baseline at ≥4 time points after dosing are ≥+15 bpm for more than 25% of subjects, analysis of the primary and secondary QTc endpoints will be performed using beat-to-beat comparison of QT postdose, with QT during Day -1 at matching RR value. The QTc beat-to-beat analysis will be performed, as needed, on the basis of the observed HR effects of pevonedistat.

Additional details regarding analyses will be provided in the statistical analysis plan.

13.1.6 Safety Analysis

AEs will be summarized using the safety analysis set. No statistical testing or inferential statistics will be generated.

All AEs will be coded using the MedDRA. Data will be summarized by preferred term and primary system organ class.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

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

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or sponsor's 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 site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or sponsor's designee (and IRB or IEC, 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 site 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 site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the US FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

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

15.1 IRB and/or IEC Approval

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

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

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

Patient incentives should not exert undue influence for participation. Payments to patients must be approved in advance by the IRB or IEC and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

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

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

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

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

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

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

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

15.3 Subject Confidentiality

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

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, US 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 studies reaches the public in a timely manner and to comply with applicable laws, regulations, and guidance, Takeda will, at a minimum, register interventional clinical studies it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites on or before the start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for America's 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 studies via registries, as needed. In certain situations/registries, Takeda may assist participants or potential participants to find a clinical trial by helping them locate study sites closest to their homes by providing the investigator name, address, and phone number via email/phone or other methods to callers requesting study information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the study. The investigative sites are encouraged to handle the study inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of study 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 studies 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

1. Bauer T, Harvey R, Lee C, Aggarwal C, Cohen R, Sedarati F, et al. Investigational NEDD8-activating enzyme inhibitor pevonedistat plus chemotherapy in patients with solid tumors (phase 1b study): Activity of pevonedistat plus carboplatin/paclitaxel. Annual Meeting of the American Society of Clinical Oncology (ASCO); June 03-07, 2016; Chicago, IL. 2580.
2. Lockhart A, Bauer T, Harvey R, Lee C, Aggarwal C, Cohen R, et al. Phase 1b trial of investigational NEDD8-activating enzyme (NAE) inhibitor pevonedistat (TAK-924/MLN4924) in combination with docetaxel, paclitaxel/carboplatin, or gemcitabine in patients with solid tumors. AACR-NCI-EORTC Molecular Targets and Cancer Therapeutics Conference; November 5-9, 2015; Boston, MA.
3. CARBOPLATIN - carboplatin injection, solution [package insert]. Princeton, NJ: Sandoz Inc, 2011.
4. PACLITAXEL [package insert]. Lake Forest, IL: Hospira, Inc, 2007.
5. Carboplatin 10 mg/mL concentrate for infusion (Summary of Product Characteristics). SmPC. East Sussex, United Kingdom: TEVA UK Limited, 26 April, 2016.
6. ABRAXANE (paclitaxel) 5 mg/mL powder for suspension for infusion [Summary of Product Characteristics]. SmPC. Uxbridge, United Kingdom: Celgene Europe Ltd, January 2013.
7. TAXOTERE (docetaxel) 20 mg/0.5 mL concentrate and solvent for solution for infusion [Summary of Product Characteristics]. SmPC. Antony Cedex, France: Aventis Pharma S.A., November, 2005.
8. TAXOTERE (docetaxel) [package insert]. Bridgewater, NJ 08807: Sanofi-Aventis, 2014.
9. du Bois A, Luck HJ, Meier W, Adams HP, Mobus V, Costa S, et al. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. J Natl Cancer Inst 2003;95(17):1320-9.
10. Naughton CA. Drug-induced nephrotoxicity. Am Fam Physician 2008;78(6):743-50.
11. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.
12. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. U.S. Department of Health and Human Services National Cancer Institute. 14 June 2010.
13. Woosley R, Heise C, Romero K. QTdrugs List, AZCERT, Inc. Updated 24 June, 2012. Accessed May 24, 2017. CredibleMeds.org.
14. The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9 ed. Boston, MA: Little, Brown & Co; 1994.

15. Crawford J, Caserta C, Roila F, Group EGW. Hematopoietic growth factors: ESMO Clinical Practice Guidelines for the applications. Ann Oncol 2010;21 Suppl 5:v248-51.

16. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5(6):649-55.

Appendix A SOEs

SOE (Part A)

Procedure	Screening (a)	Day -1	Day 1 Predose	Day 1	Day 2	Day 8 Predose	Day 8	Day 9	EOS (b)
Pevonedistat dosing (25 or 50 mg/m^2) (c)				X			X		
Randomization			X						
Informed consent	X								
Demographics	X								
Medical history/prior therapy	X								
Physical examination	X		X						X
Symptom-directed physical examination		X		X	X		X	X	
Height	X								
Weight	X		X						X
Vital signs (d)	X	X	X	X		X	X		X
ECOG performance status	X								X
12-lead safety ECGs (e,f)	X	X		X			X		X
Serial triplicate ECGs for continuous 12-lead Holter monitoring (g)		X (0-11 hr)	X	X (0-11 hr)	X (24 hr)	X	X (0-11 hr)	X (24 hr)	
Monitoring of concomitant medications, therapies, and procedures		Recorded from the time of the first dose of any study drug through 30 (+10) days after the last dose of study drug							
AE/SAE reporting		Reported from the signing of the ICF through 30 (+10) days after the last dose of study drug							
		Serious PTEs will be reported from the signing of the ICF up to the first dose of study drug. In addition, related and unrelated treatment-emergent SAEs will be reported from the first dose of study drug through 30 (+10) days after administration of the last dose of study drug. After this period, only related SAEs must be reported.							

SOE (Part A)									
Procedure	**Screening (a)**	**Day -1**	**Day 1 Predose**	**Day 1**	**Day 2**	**Day 8 Predose**	**Day 8**	**Day 9**	**EOS (b)**
Samples/laboratory assessments									
Pregnancy test (e)	X	X							X
Hematology (e,h)	X	X				X			X
Chemistry (i)	X	X	X		X	X		X	X
Urinalysis (j)	X								X
Plasma samples for Pevonedistat PK			X	X	X	X	X	X	

Tests and procedures should be performed on schedule, but occasional changes are allowable (±2 days) for holidays, vacations, and other administrative reasons. If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled action within this time, the patient may continue the study only with the written permission of the project clinician.

(a) Unless otherwise noted, the Screening visit must occur within 28 days before Day -1 in Part A.

(b) An EOS visit is needed in Part A only if the patient does not continue into the optional Part B. The EOS visit will occur 30 (+10) days after the last dose of study drug for patients not enrolling in the optional Part B. If the EOS visit occurs earlier than 30 (+10) days after the last dose of study drug, the EOS visit may be conducted by telephone.

(c) Patients will be randomized in a crossover fashion to receive a single-dose, 1-hour IV infusion of 25 or 50 mg/m^2 pevonedistat and the other dose on Day 8.

(d) On days when pevonedistat is administered, vital signs are to be measured predose (20 [±10] minutes) before the infusion of pevonedistat, 30 (±10) minutes after the start of pevonedistat dosing, and 1 hour (±10 minutes) and 3 hours (±30 minutes) after the completion of pevonedistat dosing. All vital signs are measured with the patient in supine 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.

(e) Procedures conducted during Screening that are performed within 3 days before Day -1 can also be used as the Day -1 evaluation and do not need to be repeated. Pregnancy test at Screening must be a serum pregnancy test; at other time points, a urine pregnancy test is acceptable per local regulations.

(f) A 12-lead safety ECG will be performed during Screening; on Day -1, Day 1 (2-4 hours postdose), and Day 8 (2-4 hours postdose); and at the EOS visit for patients who choose not to continue to Part B. When the timing of ECG measurements coincides with the timing of a blood draw, the ECG will be completed before the blood sample collection.

(g) Before each nominal triplicate ECG sampling time point, the patient must be maintain at supine bed rest for 15 minutes. The triplicate ECGs will be extracted during the final 10 minutes of that rest period (the ECG extraction of 10-minute window). The time-matched PK blood draws will occur immediately following the completion of the ECG extractions on Days -1, 1, 2, 8, and 9.

(h) Blood samples for clinical hematology tests will be collected during Screening within 3 days before the start of dosing (Day 1). 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, Day 8 predose, and at the EOS visit.

(i) Clinical chemistry samples will be collected during Screening, on Day -1, and before dosing with study drug. Predose samples must be drawn within 24 hours predose. In addition, samples will be taken on Day 1 predose, Day 2, Day 8 predose, Day 9, and at the EOS visit.

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

Twelve-Lead Safety ECGs Collected (Part A)

Study Day/Period	
Screening	X
Day -1	X
Day 1 (2-4 hours postdose)	X
Day 8 (2-4 hours postdose)	X
EOS	X

The 12-lead safety ECG will be conducted at the EOS visit only if patients choose not to continue to Part B.

Plasma Sample Collection Times for PK (Part A)

Cycle 1	Day 1	Day 2	Day 8	Day 9
Predose within 1 hr before dose	X		X	
1 hr postdose (±10 min)	X		X	
2 hr postdose (±10 min)	X		X	
3 hr postdose (±10 min)	X		X	
4 hr postdose (±10 min)	X		X	
6 hr postdose (±10 min)	X		X	
9 hr postdose (±10 min)	X		X	
11 hr postdose (±10 min)	X		X	
24 hr postdose (±1 hr)		X		X

All time points listed in this table are in reference to the start of the pevonedistat infusion.

Triplicate Holter ECG Collection Times (Part A)

	Day -1 (a)	Day 1	Day 2	Day 8	Day 9
Predose (within 1 hr before dose)	X	X		X	
1 hr postdose (±10 min)	X	X		X	
2 hr postdose (±10 min)	X	X		X	
3 hr postdose (±10 min)	X	X		X	
4 hr postdose (±10 min)	X	X		X	
6 hr postdose (±10 min	X	X		X	
9 hr postdose (±10 min)	X	X		X	
11 hr postdose (±10 min)	X	X		X	
24 hr postdose (±10 min)			X		X

All time points listed in this table for Days 1 and 8 are in reference to the start of the pevonedistat infusion.
(a) There is no drug administration on Day -1. As the Day -1 evaluations are intended to serve as time-matched, drug-free baseline for corresponding Days 1 and 8 PK/ECG evaluations, it is critical to ensure that the 0-hour time point on Day -1 is timed to coincide with the clock time of pevonedistat dosing on Days 1 and 8 (which will be considered the 0-hour time point on Days 1 and 8).

Eligible patients may continue into optional Part B, which can begin within approximately 2 weeks of completing Part A.

SOE for Optional Continued Treatment With Pevonedistat+SoC Chemotherapy (Part B) (All Cycles)

	Pevonedistat+SoC 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						
Entry criteria for optional Part B (d)	X					
Full physical examination	X					X
Symptom-directed physical examination		X	X	X	X	
ECOG performance status	X (e)					X
ECG monitoring (f)		X				
Weight	X					X
Vital signs (g)	X	X	X	X	X	X
Tumor assessments (h)	To be completed before dosing in Part B, at the end of Cycle 2, and every 3 cycles thereafter					X
Monitoring of concomitant medications, therapies, and procedures	Recorded from the time of the first dose of any study drug in Part A through 30 (+10) days after the last dose of study drug					
AE/SAE reporting (i)	Reported from the signing of the ICF through 30 (+10) days after the last dose of study drug					
	Serious PTEs will be reported from the signing of the ICF up to the first dose of study drug. In addition, related and unrelated treatment-emergent SAEs will be reported from the first dose of study drug through 30 (+10) days after administration of the last dose of study drug. After this period, only related SAEs must be reported.					

SOE for Optional Continued Treatment With Pevonedistat+SoC Chemotherapy (Part B) (All Cycles)

	Pevonedistat+SoC 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 (j)	X					X
Hematology (k)	X			X predose		X
Chemistry (l)	X		X predose	X predose		X
Urinalysis	X					

Tests and procedures should be performed on schedule, but (unless otherwise specified) occasional changes are allowed (±2 days) for holidays, vacations, and other administrative reasons.

(a) For patients to be eligible for dosing with pevonedistat+chemotherapy (Part B), they must meet certain entry criteria (see Section 7.3).

(b) If the patient continues into Part B, the EOS visit will occur 30 (+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 SoC chemotherapy regimen (docetaxel or carboplatin+paclitaxel) each patient will receive in combination with pevonedistat. On Day 1, when pevonedistat and chemotherapy agents are both administered, chemotherapy will be administered first, followed by pevonedistat. For the pevonedistat+docetaxel regimen, on Day 1 of each cycle, when all study drugs are administered together, docetaxel 75 mg/m^2 will be administered first as a 1-hour IV infusion. After a mandatory approximately 15-minute time-out (pevonedistat-free period), pevonedistat will be administered IV. For the pevonedistat+ carboplatin+paclitaxel regimen, on Day 1 of each cycle, when all study drugs are administered, paclitaxel will be given first as an IV infusion over approximately 3 hours, followed by carboplatin as an approximately 30-minute IV infusion. After a mandatory approximately 15-minute time-out (pevonedistat-free period), pevonedistat will be administered IV. In both regimens, the infusion of pevonedistat may be slowed or stopped and restarted for any associated infusion-related reactions. The dose of pevonedistat may be reduced because of toxicities in accordance with Section 8.3.3. The chemotherapeutic agent(s) dose may be reduced because of toxicities in accordance with Section 8.3.3. See Section 8.9 for the details of study drug administration.

(d) Criteria include 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 9.4.13; diarrhea symptoms resolved to Grade 1 or better; QTc interval <480 msec; and CT scan or MRI of the chest, abdomen, and pelvis within 28 days before Cycle 1 Day 1.

(e) ECOG performance status is needed only on Day 1 predose and at the EOS visit.

(f) A 12-lead ECG will be performed on Day 1 immediately after the infusion of pevonedistat has been completed (±10 minutes). In Part B, further ECG monitoring is optional after 3 cycles of treatment if there has been no significant QTc prolongation.

(g) On days when any of the study drugs are administered, vital signs are to be measured predose (20 [±10] minutes) before the infusion of chemotherapy (when pevonedistat and chemotherapy agents are both administered) or pevonedistat; 30 (±10) minutes after the start of pevonedistat dosing; and 1 hour (±10 minutes) after the completion of pevonedistat dosing. All vital signs are measured with the patient in the supine 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.

(h) 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 before 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.

(i) Including serious PTEs in Part A; see Section 10.1.1.
(j) A serum or urine pregnancy test must be performed for women of childbearing potential at every cycle (typically performed predose 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.
(k) Hematology samples will be collected as part of the entry criteria for Part B and before dosing with study drug on Days 1, 3, and 5. On dosing days, samples can be drawn up to 24 hours 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 5 predose, and at the EOS visit.
(l) Clinical chemistry samples will be collected as part of the entry criteria for Part B and before dosing with study drug on Days 1, 3, and 5. On Days 1, 3, and 5, samples may be drawn up to 1 day before dosing.

Appendix B Responsibilities of the Investigator

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

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

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

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

Appendix C Investigator Consent to Use of Personal Information

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

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

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

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical study 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 [16].

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.
Partial response	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 partial response 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 [11].

Overall Disease Response Criteria

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	Partial response
CR	Not evaluated	No	Partial response
PR	Non-PD or not all evaluated	No	Partial response
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 [11].

Appendix F Excluded Strong CYP3A4 Inducers

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

Classification of Strong CYP3A4 Inducers

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

Strong Inducers
Carbamazepine
Phenytoin
Phenobarbital
Primidone
Rifabutin
Rifampin
Rifapentine
St. John's wort

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 2011 [3].
NCIC CTG=National Cancer Institute of Canada Clinical Trials Group, SWOG=Southwest Oncology Group.

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

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

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

Source: du Bois et al, 2003 [9].
The symbol "--" denotes "not defined."
C=maximum grade over all courses, G-CSF=granulocyte colony-stimulating factor, E=estimate, N=number of courses in set C and number of patients in set P, NCI CTC=National Cancer Institute Common Toxicity Criteria, P=maximum grade over all courses within a patient, pRBCs=packed red blood cells, WBC=white blood cell.
(a) Differences are calculated by subtracting the paclitaxel+carboplatin arm proportion from the cisplatin+paclitaxel arm proportion; statistically significant differences in proportions between the 2 treatment arms are in bold font. All percentages are rounded to 1 decimal place; therefore, the estimates may differ by ±1 from the difference of the percentages of the treatment arm columns.
(b) Transfusion of pRBCs and use of antibiotics and G-CSF were not assessed for the last treatment cycle within a patient. Use of antibiotics and use of G-CSF are graded in the same fashion as transfusion of pRBCs. Use of antibiotics/application of G-CSF is coded as a toxicity of Grade 3; a Grade 0 is applied otherwise.

Appendix 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
- Nonsteroidal anti-inflammatory drugs

Antidepressants/mood stabilizers
- Lithium

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

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

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

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

Contrast dye

Diuretics
- Loops, thiazides
- Triamterene (Dyrenium)

Herbals
- Chinese herbals with aristolochic acid

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

Source: Modified from Naughton, 2008 [10].

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 [14].

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. Refer to the following sources for additional information: European Heads of Medicines Agencies Clinical Trial Facilitation Group and hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_ CTFG_Contraception.pdf.

Appendix 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 the following:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (a).
  - Oral.
  - Intravaginal.
  - Transdermal.
- Progestogen-only hormonal contraception associated with inhibition of ovulation (a).
  - Oral.
  - Injectable.
  - Implantable (b).
- Intrauterine device (b).
- Intrauterine hormone-releasing system (b).
- Bilateral tubal occlusion (b).
- Vasectomized partner (b,c).
- Sexual abstinence (d).

Methods Considered Less Highly Effective

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

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action.
- Male or female condom with or without spermicide (e).
- Cap, diaphragm, or sponge with spermicide (e).

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

Appendix L Exclusionary QT-Prolonging Drugs

The following table contains a list of QT-prolonging drugs according to the Arizona Center for Education and Research on Therapeutics. QT-prolonging drugs with a risk of TdP are exclusionary in this study until all protocol-specified ECG monitoring is completed. Patients on a stable dose of drugs with a conditional or possible risk of QT prolongation or drugs that are to be avoided by patients with congenital long QT syndrome may be considered, pending discussion and agreement with the project clinician. Note that some of the drugs in this list are also associated with nephrotoxicity (see Appendix H).

Note that the following table was last updated 17 May 2017 and accessed online on 24 May 2017. The source is provided in the table footnote. This information is routinely updated, with new drugs being added and other drugs being removed from the list, and risk categories changing. The current online list should be checked if there is any question.

Drug Class	Risk of TdP (a) Name (Brand Name)	Conditional or Possible Risk of TdP (b) Name (Brand Name)	Congenital QTc Name (Brand Name)
Adrenergic prodrug			Droxidopa (Northera)
Alkylating agent		Bendamustine (Treanda, Treakisym)	
Alpha1-blocker		Alfuzosin (Uroxatral)	
Analgesic		Hydrocodone - ER (Hysingla ER, zohydro ER)	
Anesthetic, general	propofol (Diprivan, Propoven) sevoflurane (Ultane, Sojourn)		
Antianginal		Ivabradine (Procoralan, Coralan) ranolazine (Ranexa, Ranozex)	
Antiarrhythmic	amiodarone (Cordarone, Pacerone) disopyramide (Norpace) dofetilide (Tikosyn) flecainide (Tambocor, Almarytm) ibutilide (Corvert) procainamide (Pronestyl, Procan) quinidine (Quinaglute, Duraquin) sotalol (Betapace, Sotalex)	Pilsicainide (non-US only; Sunrythm)	

Drug Class	Risk of TdP (a) Name (Brand Name)	Conditional or Possible Risk of TdP (b) Name (Brand Name)	Congenital QTc Name (Brand Name)
Antibiotic	azithromycin (Zithromax, Zmax) ciprofloxacin (Cipro, Cipro-XR) clarithromycin (Biaxin, Prevpac) erythromycin (E.E.S., Robimycin) levofloxacin (Levaquin, Tavanic) moxifloxacin (Avelox, Avalox) roxithromycin (Rulide; only on non-US market)	Bedaquiline (Sirturo) delamanid (non-US only; Deltyba) garenoxacin (non-US only; Geninax) gemifloxacin (Factive) metronidazole (Flagyl) norfloxacin (Noroxin, Ambigram) ofloxacin (Floxin) telavancin (Vibativ) telithromycin (Ketek)	Trimethoprim-sulfamethoxazole (Septra, Bactrim)
Anticancer	arsenic trioxide (Trisenox) vandetanib (Caprelsaa)	Capecitabine (Xeloda) lenvatinib (Lenvima) tamoxifen (Istubal) necitumumab (Portrazza)	
Anticonvulsant/seizure		Felbamate (Felbatol) ezogabine (retigabine; Potiga, Trobalt)	

Drug Class	Risk of TdP (a) Name (Brand Name)	Conditional or Possible Risk of TdP (b) Name (Brand Name)	Congenital QTc Name (Brand Name)
Antidepressant	citalopram (Celexa, Cipramil) escitalopram (Lexapro, Cipralex)	Amitriptyline (Tryptomer) clomipramine (Anafranil) desipramine (Pertofrane, Norpramine) doxepin (Sinequan, Silenor) fluoxetine (Prozac, Sarafem) imipramine (melipramine; Tofranil) mirtazapine (Remeron) nortriptyline (Pamelor, Sensoval) paroxetine (Paxil) sertraline (Zoloft) trazodone (Oleptro) trimipramine (Surmontil, Rhotrimine) venlafaxine (Effexor)	
Antiemetic	ondansetron (Zofran, Anset)	Dolasetron (Anzemet) granisetron (Kytril, Sancuso) metoclopramide (Reglan, Afipran) tropisetron (non-US only; Navogan, Setrovel)	
Antifungal	fluconazole (Diflucan, Trican) pentamidine (Pentam)	Amphotericin B (Fungilin, Fungizone) itraconazole (Sporanox) ketoconazole (Nizoral) posaconazole (Noxavil, Posamol) voriconazole (Vfend)	
Antihistamine	astemizole (Hismanal) terfenadine (Seldane)	Diphenhydramine (Benadryl, Nytol) hydroxyzine (Atarax, Vistaril)	

Drug Class	Risk of TdP (a) Name (Brand Name)	Conditional or Possible Risk of TdP (b) Name (Brand Name)	Congenital QTc Name (Brand Name)
Antihypertensive/diuretic		Isradipine (Dynacirc) ketanserin (non-US only; Sufrexal) moexipril/HCTZ (Uniretic, Univasc) nicardipine (Cardene)	
Antimalarial	chloroquine (Aralen) halofantrine (Halfan)	Artenimol+piperaquine (non-US only; Eurartesim) quinine sulfate (Qualaquin) hydroxychloroquine (Plaquenil, Quineprox)	
Antimania		Lithium (Eskalith, Lithobid)	
Antinausea	domperidone (Motilium, Motillium)		
Antineoplastic agent	oxaliplatin (Eloxatin)		

Drug Class	Risk of TdP (a) Name (Brand Name)	Conditional or Possible Risk of TdP (b) Name (Brand Name)	Congenital QTc Name (Brand Name)
Antipsychotic	chlorpromazine (Thorazine, Largactil) droperidol (Inapsine, Droleptan) haloperidol (Haldol) levomepromazine (non-US only; Nosinan, Nozinan) pimozide (Orap) sulpiride (non-US only; Dogmatil, Dolmatil) sultopride (non-US only; Barnetil, Barnotil) thioridazine (Mellaril, Novoridazine)	Amisulpride (Solian) aripiprazole (Abilify, Aripiprex) asenapine (Saphris, Sycrest) clozapine (Clozaril) cyamemazine (cyamepromazine, non-US only; Tercian) iloperidone (Fanapt, Fanapta) melperone (non-US only; Bunil, Buronil) olanzapine (Zyprexa, Zydis) paliperidone (Invega) pimavanserin (Nuplazid) perphenazine (non-US only; Trilafon, Etrafon/Triavil) pipamperone (non-US only; Dipiperon, Propitan promethazine (Phenergan) prothipendyl (non-US only; Dominal, Largophren) quetiapine (Seroquel) risperidone (Risperdal) sertindole (non-US only; Serdolect, Serlect) ziprasidone (Geodon) zotepine (non-US only; Losizopilon, Lodopin)	

Drug Class	Risk of TdP (a) Name (Brand Name)	Conditional or Possible Risk of TdP (b) Name (Brand Name)	Congenital QTc Name (Brand Name)
Antiretroviral/HIV infection		Efavirenz (Sustiva)	
Antisense oligonucleotide		Nusinersen (Spinraza)	
Antiviral		Amantadine (Symmetrel, Symadine) atazanavir (Reyataz, Evotaz) nelfinavir (Viracept) rilpivirine (Edurant, Complera) ritonavir (Norvir) saquinavir (Invirase [combo]) telaprevir (Incivo, Incivek)	
Appetite suppressant/dieting, weight loss			Phentermine (Adipex) phenylpropanolamine (Acutrim, Dexatrim)
β3 adrenergic antagonist		Mirabegron (Myrbetriq)	
Bladder antispasmodic			Tolterodine (Detrol LA, Detrol)

Drug Class	Risk of TdP (a) Name (Brand Name)	Conditional or Possible Risk of TdP (b) Name (Brand Name)	Congenital QTc Name (Brand Name)
Bronchodilator			Albuterol (salbutamol; Proventil, Ventolin) arformoterol (Brovana) formoterol (Foradil, Oxeze) indacaterol (Arcapta Neohaler) isoproterenol (Medihaler-Iso, Isuprel) levalbuterol (levsalbutamol; Xopenex, Levolin) metaproterenol (orciprenaline; Metaprel, Alupent) olodaterol (Striverdi Respimat) salmeterol (Serevent, Advair) terbutaline (Brethine, Bricanyl) vilanterol/fluticasone furoate (Breo Ellipta) ephedrine (Broncholate, Rynatuss)
Catecholamine			Epinephrine (adrenaline; Bronkaid, Primatene)
Cholinesterase inhibitor/ dementia, Alzheimer disease	donepezil (Aricept)	Galantamine (Reminyl, Nivalin)	
CNS stimulant/ADHD			Amphetamine (Adderall, Dexedrine) dexmethylphenidate (Focalin, Attenade) dextroamphetamine (Dexedrine) lisdexamfetamine (Vyvanse) methamphetamine (Desoxyn, Pervitin) methylphenidate (Concerta, Ritalin)
Cyclin-dependent kinase inhibitor		Ribociclib (Kisqali)	

Drug Class	Risk of TdP (a) Name (Brand Name)	Conditional or Possible Risk of TdP (b) Name (Brand Name)	Congenital QTc Name (Brand Name)
Decongestant/allergies, sinusitis, asthma			Pseudoephedrine (PediaCare, Sudafed)
Diuretic		Furosemide (frusemide; Lasix, Fusid) hydrochlorothiazide (Apo-Hydro, Aquazide H) indapamide (Lozol, Natrilix) torasemide (Demadex, Diuver) bendroflumethiazide or bendrofluazide (non-US only; Aprinox)	
Dopamine 2 and 5-HT2A antagonist		Flupentixol (non-US only; Depixol, Fluanxol)	
Dopamine 2 antagonist		Apomorphine (Apokyn, Ixense)	
Estrogen agonist/antagonist		Toremifene (Fareston)	
Gonadotropin receptor agonist/antagonist		Leuprolide (Lupron, Eligard)	
Gonadotropin-releasing hormone agonist/antagonist		Degarelix (Firmagon)	
H2-receptor antagonist		Famotidine (Pepcid, Fluxid)	
Histone deacetylase inhibitor		Panobinostat (Farydak) romidepsin (Istodax) vorinostat (Zolinza)	
Imaging contrast agent/ echocardiography		Perflutren lipid microspheres (Definity, Optison)	
Immunosuppressant		Tacrolimus (Prograf, Advagraf)	
Inotropic agent/heart failure, hypotension, shock			Dobutamine (Dobutrex) dopamine (Intropine)

Drug Class	Risk of TdP (a) Name (Brand Name)	Conditional or Possible Risk of TdP (b) Name (Brand Name)	Congenital QTc Name (Brand Name)
Kinase inhibitor		Ceritinib (Zykadia) crizotinib (Xalkori) dabrafenib (Tafinlar) lapatinib (Tykerb, Tyverb) nilotinib (Tasigna) sunitinib (Sutent) vemurafenib (Zelboraf)	
Local anesthetic	cocaine (Cocaine)		
Microtubule inhibitor		Eribulin mesylate (Halaven)	
Monoamine transporter inhibitor		Tetrabenazine (Nitoman, Xenazine)	
Muscle relaxant	terodiline (non-US only; Micturin, Mictrol [not bethanechol])	Solifenacin (Vesicare) tizanidine (Zanaflex) tolterodine (Detrol, Detrusitol)	
Norepinephrine reuptake inhibitor/ADHD		Atomoxetine (Strattera)	
Opiate		Loperamide (Imodium)	
Opioid agonist	methadone (Dolophine, Symoron)		
Opioid receptor modulator		Buprenorphine (Butrans, Belbuca)	
Oxytocic		Oxytocin (Pitocin, Syntocinon)	
Phosphodiesterase 3 inhibitor	anagrelide (Agrylin, Xagrid) cilostazol (Pletal)		
Phosphodiesterase 5 inhibitor		Vardenafil (Levitra)	
Progesterone antagonist		Mifepristone (Korlym, Mifeprex)	
Proteasome inhibitor		Bortezomib (Velcade, Bortecad)	

Drug Class	Risk of TdP (a) Name (Brand Name)	Conditional or Possible Risk of TdP (b) Name (Brand Name)	Congenital QTc Name (Brand Name)
Proton-pump inhibitor		Esomeprazole (Nexium, Nexum) lansoprazole (Prevacid) omeprazole (Losec, Prilosec) pantoprazole (Protonix)	
Sedative		Chloral hydrate (Noctec) dexmedetomidine (Precedex, Dexdor)	
Selective D2, D3 dopamine antagonist		Tiapride (non-US only; Tiapridal, Italprid)	
Selective serotonin reuptake inhibitor		Fluvoxamine (Faverin, Fevarin)	
Somatostatin analog		Pasireotide (Signifor)	
Sphingosine phospate receptor modulator		Fingolimod (Gilenya)	
Tyrosine kinase inhibitor		Bosutinib (Bosulif) dasatinib (Sprycel) osimertinib (Tagrisso) pazopanib (Votrient) sorafenib (Nexavar)	
Vasoconstrictor	terlipressin (non-US market only; Teripress, Glypressin)		Midodrine (ProAmatine, Gutron) phenylephrine (Neosynephrine)
Vasconstrictor, inotrope/shock, low BP			Norepinephrine (Levophed)
Vasoconstrictor, decongestant/ low BP			Phenylephrine (neosynephrine) midodrine (ProAmatine)

Source: Woosley, et al, 2012 [13].
Exclusions applicable only to listed drugs. Drugs often have more than one brand name. Only the more common brand names are included.
Medicines on this list are reviewed on an ongoing basis to assure that the available evidence supports their continued placement on this list. The list changes regularly, and we recommend checking the website at crediblemeds.org for the most up-to-date information. There may be many additional brand names that are not listed on this form.
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ADHD=attention-deficit/hyperactivity disorder, ER=extended release, HCTZ= hydrochlorothiazide.
(a) Drugs that are generally accepted by authorities to have a risk of causing TdP.
(b) Drugs that may prolong the QT interval but at this time lack substantial evidence for causing TdP.
(c) Drugs to be avoided, if possible, by patients with congenital long QT syndrome.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Approval	28-Jun-2017 14:11 UTC
	Biostatistics Approval	28-Jun-2017 14:24 UTC
	Clinical Pharmacology Approval	28-Jun-2017 14:26 UTC
	Clinical Approval	29-Jun-2017 00:24 UTC