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Original Article

Effect of Pevonedistat, an Investigational NEDD8-Activating Enzyme Inhibitor, on the QTc Interval in Patients With Advanced Solid Tumors

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Abstract

The purpose of this study was to assess the effect of pevonedistat, a neural precursor cell expressed, developmentally down-regulated protein 8 (NEDD8)-activating enzyme inhibitor, on the heart rate-corrected QT (QTc) interval in cancer patients. Patients were randomized 1:1 to receive pevonedistat 25 or 50 mg/m^2 on day 1 and the alternate dose on day 8. Triplicate electrocardiograms were collected at intervals over 0–11 hours and at 24 hours via Holter recorders on days −1 (baseline), 1, and 8. Changes from time-matched baseline values were calculated for QTc by Fridericia (QTcF), PR, and QRS intervals. Serial time-matched blood samples for analysis of pevonedistat plasma pharmacokinetics were collected and a concentration–QTc analysis conducted. Safety was assessed by monitoring vital signs, physical examinations, and clinical laboratory tests. Forty-four patients were included in the QTc analysis. Maximum least square (LS) mean increase from time-matched baseline in QTcF was 3.2 milliseconds at 1 hour postdose for pevonedistat at 25 mg/m^2, while the LSs mean change from baseline in QTcF was −1.7 milliseconds 1 hour postdose at 50 mg/m^2. The maximum 2-sided 90% upper confidence bound was 6.7 and 2.9 milliseconds for pevonedistat at 25 and 50 mg/m^2, respectively. Pevonedistat did not result in clinically relevant effects on heart rate, nor on PR or QRS intervals. Results from pevonedistat concentration–QTc analysis were consistent with these findings. Administration of pevonedistat to cancer patients at a dose of up to 50 mg/m^2 showed no evidence of QT prolongation, indicative of the lack of clinically meaningful effects on cardiac repolarization. ClinicalTrials.gov identifier: NCT03330106 (first registered on November 6, 2017).

Keywords

NEDD8-activating enzyme inhibitor, pevonedistat, pharmacokinetics, QTc interval

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Pevonedistat is a first-in-class, small molecule inhibitor of neural precursor cell expressed, developmentally down-regulated protein 8 (NEDD8)-activating enzyme (NAE) (Figure S1). NAE is an essential component of the NEDD8-conjugation pathway, which controls the activity of a subset of ubiquitin–proteasome system multiprotein complexes called E3 ligases, responsible for transferring ubiquitin molecules to protein substrates.[1,2] NEDD8 conjugation is essential for the activity of cullin-dependent ubiquitin E3 ligases, which control the ubiquitination of many proteins with important roles in DNA repair, cell cycle progression, and signal transduction.[3,4] As protein ubiquitination leads to proteasomal degradation, these cellular processes are relevant to tumor cell growth, proliferation, and survival.[5] As such, inhibitors of NAE activity may be of therapeutic value for various cancers.

The clinical safety and efficacy of pevonedistat as monotherapy or in combination with standard-of-care agents have been evaluated in multiple tumor types, including advanced solid tumors, melanoma, acute myeloid leukemia, myelodysplastic syndromes, multiple myeloma, and lymphoma.[6–11] The recommended clinical dose for pevonedistat as a single agent is 50 mg/m^2 administered on days 1, 3, and 5 in 21-day cycles. The maximum tolerated dose of pevonedistat was determined to be 25 mg/m^2 in combination with docetaxel, 20 mg/m^2 in combination with carboplatin plus paclitaxel, and 20 mg/m^2 in combination with azacitidine.[6,7] Pevonedistat demonstrated linear pharmacokinetics (PKs) over the dose range of 25–278 mg/m^2 based on a population PK analysis using data from more than 300 patients with hematologic malignancies or solid tumors. Body surface area (BSA) was identified as a clinically significant covariate for pevonedistat PK~~s~~, supporting the BSA-based dosing of pevonedistat.[12] A mass balance study conducted in cancer patients indicated that hepatic metabolism plays a major role in the overall clearance of pevonedistat, with renal clearance only representing approximately 2.5% of total plasma clearance.[13] In vitro metabolism (Takeda data on file) and clinical mass balance studies suggested that CYP3A played a major role in pevonedistat elimination pathways. However, co-administration with the strong CYP3A inhibitor itraconazole or metabolic enzyme inducer rifampin did not result in clinically meaningful changes in pevonedistat systemic exposures.[14,15] A physiologically based PK model for pevonedistat suggested that systemic exposure of pevonedistat was not sensitive to the modulations of enzyme activity if hepatic uptake was the rate-determining step of pevonedistat clearance.[15]

Prolongation of the heart-rate corrected QT (QTc) interval is a potential drug side effect associated with an increased risk of cardiac arrhythmias, particularly torsades de pointes (TdP), which may spontaneously lead to ventricular fibrillation and sudden death.[16] Blockade of the human cardiac K+ ether-à-go-go related gene (hERG) channel is usually associated with these clinical findings.[17] Although in vitro studies indicate a low risk for hERG channel inhibition by pevonedistat (inhibitory constant [K_i] = 17.3 μM, Takeda data on file), we have carried out a dedicated study to evaluate this risk in the clinical setting. Pevonedistat cannot be administered to healthy individuals due to its cytotoxicity, therefore this study was conducted in patients with advanced solid tumors. Accordingly, no placebo or a positive control (such as moxifloxacin, known to prolong QTc interval) was included, consistent with previous similar analyses.[18,19] The pevonedistat doses of 25 and 50 mg/m^2 evaluated in this study were selected to cover the relevant clinical dose range across the contexts of single agent and combination development. Additionally, the 50-mg/m^2 dose provided a 2.5-fold exposure multiple over the 20-mg/m^2 dose that was under evaluation in combination with azacitidine in a phase 3 trial in ~~in~~ patients with higher-risk myelodysplastic syndromes, chronic myelomonocytic leukemia, and low-blast acute myeloid leukemia.[20]

Methods

Study Design

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the International Conference of Harmonisation guidelines for Good Clinical Practice and the ethical principles of the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The clinical study protocol, the Investigator's Brochure, a sample informed consent form, and other study-related documents were reviewed and approved by the local or central Institutional Review Board of all study sites (WIRB, Chesapeake/Advarra, Brany, Integreview, Mary Crowley Cancer Research, Henry Ford; Table S1). All participants provided written informed consent prior to any study-related procedures.

This was a two-dose, crossover study to assess the effect of pevonedistat 25 and 50 mg/m^2 on the QTc interval in patients with advanced solid tumors (NCT03330106). Eligible adult patients reported to the clinical facility on the morning of day −1 for collection of baseline measurements, where serial triplicate electrocardiograms (ECGs) were collected for up to 11 hours. On days −1, 1, and 8 of Holter ECG sampling, patients were advised to have meals at least 2 hours before the 0-hour time point and after the 4-hour Holter ECG and blood sample collection. Meals

were administered at the same times on days −1, 1, and 8 of Holter ECG monitoring. On day 1, immediately after the collection of triplicate predose baseline ECGs, patients were randomized in a crossover manner to receive a single-dose, 1-hour intravenous (IV) infusion of pevonedistat 25 or 50 mg/m^2; the alternate dose was then given 1 week later on day 8. Holter ECG monitoring was carried out on days −1 (0–11 hours), 1 (0–11 hours postdose), 2 (24 hours after day 1 dosing), 8 (0–11 hours postdose), and 9 (24 hours after day 8 dosing); triplicate ECGs were extracted at time-matched PK sampling points to contribute to the analysis of the effects of pevonedistat on QT/QTc interval. Serial blood samples for the analysis of pevonedistat plasma PKs were collected at prespecified time points over a 24-hour period. Safety was assessed by monitoring vital signs, physical examinations, and clinical laboratory tests.

After completing ECG assessment, patients had the opportunity to continue receiving pevonedistat in combination with standard-of-care agents, either docetaxel or carboplatin plus paclitaxel, as recommended by the investigator. Safety and disease assessments of the combination therapy with standard-of-care agents are not reported here.

Patients

Eligible patients were male or female aged ≥18 years and had histologically or cytologically confirmed metastatic and/or advanced solid tumors which had progressed despite standard therapy or for which conventional therapy was not considered effective. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and had adequate renal and hepatic function. All patients had to provide written informed consent and comply with contraceptive requirements.

Exclusion criteria included treatment with any systemic antineoplastic therapy or any investigational products within 21 days prior to day 1. Patients were also excluded if they were taking QT-prolonging drugs with a risk of causing TdP, or if they had received strong CYP3A inducers within 14 days of day 1. Additionally, patients must have had no history of amiodarone use within 6 months prior to day 1, nor required the use of these medications during the study. Further exclusion criteria were a 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 of day 1; a history of polymorphic ventricular fibrillation or TdP, permanent atrial fibrillation, or persistent atrial fibrillation; a history of Brugada syndrome, risk factors for TdP, or family history of long QT syndrome; an abnormal 12-lead ECG at screening indicating a second- or third-degree atrioventricular block or intermittent block, or a QRS interval >110 milliseconds, QT interval with Fridericia's correction (QTcF) >480 milliseconds, PR interval >200 milliseconds, or any arrhythmia interpreted by the investigator to be clinically significant; or sustained systolic blood pressure >160 or <90 mmHg, diastolic blood pressure >100 or <65 mmHg, or resting heart rate <50 or >100 bpm at screening or predose.

PK Assessments

Serial blood samples for analysis of pevonedistat plasma concentrations were collected following dosing at 25 or 50 mg/m^2 over a 24-hour period. Plasma samples with dipotassium ethylenediaminetetraacetic acid anticoagulant were analyzed for pevonedistat using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method.[8] Briefly, TAK-924-d8 ($C_{21}H_{17}D_8N_5O_4S$) was used as the internal standard. The assay was performed by liquid–liquid extraction followed by LC-MS/MS using a gradient method at a flow rate of 0.3 mL/minute on a Genesis, C8, 2.1 × 50-mm, 4-μm column, with mobile phase A 0.1% formic acid in water and mobile phase B 0.1% formic acid in acetonitrile. Detection was performed by tandem MS using a Sciex API-4000 mass spectrometer, with ion spray in the positive mode. The quantitation range for the assay was 1–500 ng/mL. The assay precision, expressed as percentage coefficient of variation for quality control samples ranged from 2.3% to 4.4% and the mean accuracy, expressed as percentage bias, ranged from −4.3% to 3.4%.

Pevonedistat PK parameters were estimated using noncompartmental analysis with Phoenix™ 64 WinNonlin® Professional version 8.0 (Pharsight Corporation, Mountain View, California). The following PK parameters were calculated: maximum observed plasma concentration (C_{max}), area under the concentration–time curve from time 0 to the last quantifiable time point, area under the concentration–time curve from time 0 extrapolated to infinity ($AUC_{0\text{-inf}}$), terminal elimination half-life, clearance, and volume of distribution at steady state.

QTc Assessments

Continuous 12-lead digital ECGs were obtained using a Holter ECG recorder for 48 hours on days –1 and 1, and for 24 hours on day 8. Three Holter ECGs (approximately 1 minute apart) were extracted on each day at times that matched the times of day 1 postdose PK sampling (up to 11 hours on day –1 and up to 24 hours postdose on days 1 and 8). The day –1 triplicate ECGs served as time-matched baseline data.

Statistical Analysis

The ECGs were read centrally and all QTc data represented the means of the three replicates at each time point. Two correction methods were used for all analyses of QTc: Fridericia's correction ($QTcF = QT/RR^{(1/3)}$) and individual patient correction ($QTcI = QT/RR^{b}$). For QTcI, all pairs of QT and RR interval data collected on day −1 and the day 1 predose measurement were analyzed by linear regression to define a slope b for each patient, which was then used to calculate the individual correction for that patient. Heart rate, PR interval, QRS duration, and ECG morphologies were also analyzed.

The ECG data set comprised all available ECGs extracted from the Holter monitor from all patients who were dosed on day 1. The primary endpoint was change from the time-matched day −1 baseline in QTcF following a single dose of pevonedistat. This change was calculated for each patient by subtracting the day −1 mean QTcF from the time-matched days 1 or 8 mean QTcF. The secondary endpoint was change from baseline in QTcI. Additionally, categorical analyses for each QTc interval were also conducted for days 1 and 8, including absolute QTc>450, >480, or >500 milliseconds, and change from baseline in QTc of >30 or >60 milliseconds, QRS duration >110 milliseconds and 25% increase from baseline, and PR interval >200 milliseconds and 25% increase from baseline.

The primary analysis was a repeated-measures, linear mixed-effects model and all inferences were based on least squares (LSs) means. For each time point, a 2-sided 90% upper confidence bound on the mean change from baseline was estimated. All statistical analyses were conducted using Statistical Analysis System version 9.2 (SAS Institute, Cary, North Carolina). Approximately 45 patients were planned to be enrolled to obtain approximately 36 evaluable patients, which would provide at least 80% power to show that the upper limit of the 2-sided 90% confidence interval (CI) for the comparison of change from baseline in QTcF falls below 10 milliseconds. This calculation was based on the assumption that the true difference in the largest time-matched mean change from baseline in QTcF was no more than 1.0 milliseconds, with a standard deviation of less than 10 milliseconds.

Pevonedistat Concentration–dQTc Analysis

The relationships between pevonedistat plasma concentrations and corresponding change from time-matched baseline QTcF (dQTcF), QTcI (dQTcI), and heart rate were analyzed using nonlinear mixed-effects modeling (NONMEM version 7.4; Icon Development Solutions, Dublin, Ireland). Sex, baseline ECOG score, and baseline body mass index (BMI) were evaluated as potential covariates. The final models were used to simulate the predicted size of the effect of pevonedistat on changes from baseline of QTc.

Table 1. Summary of Key Plasma PK Parameters of Pevonedistat Following a 1-Hour IV Infusion at 25 or 50 mg/m^2

PK Parameter (Unit)	Pevonedistat 25 mg/m^2 (N = 44)	Pevonedistat 50 mg/m^2 (N = 43)
C_{max} (ng/mL)	212 (82.0)	540 (192)
$AUC_{0\text{-last}}$ (h* ng/mL)	1220 (268)[a]	2580 (651)
$AUC_{0\text{-inf}}$ (h* ng/mL)	1340 (296)[a]	2740 (661)[b]
$t_{1/2}$ (hour)	7.21 (1.35)[a]	6.73 (1.15)[b]
CL (L/h)	36.5 (10.1)[a]	36.1 (10.6)[b]
CL/BSA (L/h/m^2)	19.5 (4.4)[a]	19.3 (4.6)[b]
V_{dss} (L)	330 (122)[a]	280 (93.4)[b]
V_z (L)	380 (128)[a]	346 (100)[b]
V_{dss}/BSA (L/m^2)	176 (56.6)[a]	150 (41.1)[b]
V_z/BSA (L/m^2)	203 (60.6)	185 (40.8)

Parameters are presented as arithmetic mean (SD). $AUC_{0\text{-inf}}$, area under the plasma concentration–time curve from time 0 extrapolated to infinity; $AUC_{0\text{-last}}$, area under the plasma concentration–time curve from time 0 to the last quantifiable time point; CL, clearance; CL/BSA, body surface area-normalized CL; C_{max}, maximum observed plasma concentration; IV, intravenous; PK, pharmacokinetic; SD, standard deviation; $t_{1/2}$, terminal elimination half-life; V_{dss}, volume of distribution at steady state; V_{dss}/BSA, body surface area-normalized V_{dss}; V_z, volume of distribution at elimination phase; V_z/BSA, body surface area-normalized V_z.
[a] N = 43.
[b] N = 42.

Results

Patient Disposition and Demographics

A total of 44 patients were enrolled and randomized 1:1 to receive pevonedistat 25 mg/m^2 and then 50 mg/m^2 (sequence AB, n = 22), or pevonedistat 50 mg/m^2 and then 25 mg/m^2 (sequence BA, n = 22). All 44 patients received at least one dose of pevonedistat. One patient randomized to sequence BA was excluded from the QT analysis due to missing baseline ECG data and therefore 43 (97.7%) patients were analyzed. All 44 patients had sufficient dosing and PK assessments to permit reliable estimation of PK parameters.

Thirty-one (70.5%) patients were women and the majority of patients (33 [75%]) were white. Median age was 62 years (range 29–78 years) and median BSA was 1.83 m^2 (range 1.3–2.3 m^2) (Table S2).

Pharmacokinetics

Following IV infusion at 25 and 50 mg/m^2, pevonedistat AUC increased in an approximately dose-proportional manner (Table 1). The terminal elimination half-life of pevonedistat was approximately 7 hours. Pevonedistat concentration–time profiles following single dose at 25 and 50 mg/m^2 are presented in Figure 1.

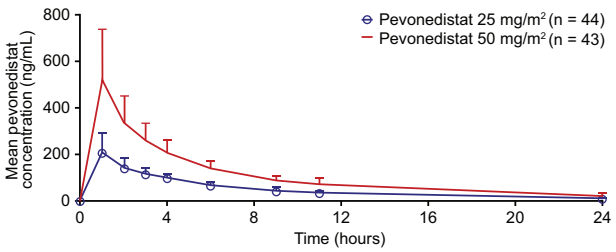

Figure 1. Mean (+ standard deviation) plasma concentration–time profiles for pevonedistat following single-dose administration at 25 or 50 mg/m^2.

Effect of Pevonedistat on ECG Parameters

QTcF and QTcI. Following a 1-hour IV infusion of pevonedistat 25 mg/m^2, the mean change in QTcF from baseline was between −2.5 milliseconds (24 hours postdose) and 2.3 milliseconds (1 hour postdose). Following a 1-hour IV infusion of pevonedistat 50 mg/m^2, the mean change in QTcF from baseline was between −8.5 milliseconds (11 hours postdose) and −1.5 milliseconds (predose). The maximum mean increase in QTcF of 2.3 milliseconds was observed at 1 hour postdose (end of infusion) at 25 mg/m^2 (Table S3).

The maximum LS mean increase from baseline in QTcF was 3.2 milliseconds for pevonedistat 25 mg/m^2 at 1 hour postdose, while the LS mean changes from baseline in QTcF were all negative at 50 mg/m^2. The maximum 2-sided 90% upper confidence bound was 6.7 milliseconds for pevonedistat 25 mg/m^2 at 1 hour postdose. The maximum 2-sided 90% upper confidence bound at 50 mg/m^2 was 2.9 milliseconds at 1 hour postdose (Figure 2A).

The findings for QTcI (Table S4) were similar to those for QTcF. At a pevonedistat dose of 25 mg/m^2, the mean change in QTcI from baseline was between −0.5 milliseconds (24 hours postdose) and 3.3 milliseconds (predose). Following a 1-hour IV infusion of pevonedistat 50 mg/m^2, the mean change in QTcI from baseline was between −6.3 milliseconds (11 hours postdose) and −0.3 milliseconds (3 hours postdose). The maximum mean increase in QTcI of 3.3 milliseconds was observed predose for the 25 mg/m^2 dose. The range of LS mean change from baseline in QTcI was −1.9 and 3.8 milliseconds with pevonedistat 25 mg/m^2, and −5.3 and 1.9 milliseconds with pevonedistat 50 mg/m^2. The maximum 2-sided 90% upper confidence bound was 8.8 milliseconds with pevonedistat 25 mg/m^2 at 4 hours postdose. The maximum 2-sided 90% upper confidence bound with pevonedistat 50 mg/m^2 was 6.8 milliseconds at 3 hours postdose (Figure 2B).

Heart Rate, PR, and QRS. The mean change from time-matched baseline in heart rate was between −1.0 bpm (4 hours postdose) and 5.7 bpm (24 hours postdose) following IV administration of pevonedistat 25 mg/m^2, and between −0.3 bpm (1 hour postdose) and 7.9 bpm (24 hours postdose) following the 50 mg/m^2 dose. The range of LS mean changes from time-matched baseline was −2.1–4.4 bpm following pevonedistat dosing at 25 mg/m^2 and −1.6–7.6 bpm at 50 mg/m^2. The minimum lower bound of the 2-sided 90% confidence bound was −5.3 bpm (1 hour postdose) at 25 mg/m^2 and −4.8 bpm (1 hour postdose) at 50 mg/m^2. The maximum upper bound was 7.7 bpm (24 hours postdose) at 25 mg/m^2 and 10.9 bpm at 50 mg/m^2 (24 hours postdose) (Figure 2C).

The mean change from time-matched baseline in PR interval was between −4.9 milliseconds (24 hours postdose) and 1.5 milliseconds (1 hour postdose) following IV administration of pevonedistat 25 mg/m^2, and between −6.5 milliseconds (24 hours postdose) and 3.6 milliseconds (1 hour postdose) following the 50 mg/m^2 dose. The range of LS mean changes from time-matched baseline was −5.2–1.2 milliseconds following pevonedistat dosing at 25 mg/m^2 and −6.5–3.4 milliseconds at 50 mg/m^2. The minimum lower bound of the 2-sided 90% confidence bound was −10.6 milliseconds (24 hours postdose) at 25 mg/m^2 and −11.9 milliseconds (24 hours postdose) at 50 mg/m^2. The maximum upper bound was 6.5 milliseconds (1 hour postdose) at 25 mg/m^2 and 8.7 milliseconds at 50 mg/m^2 (1 hour postdose).

The mean change from baseline in QRS was between −1.1 milliseconds (4 hours postdose) and 1.4 milliseconds (1 hour postdose) following IV administration of the pevonedistat dose at 25 mg/m^2, and between −0.5 milliseconds (3 and 11 hours postdose) and 0.9 milliseconds (1 hour postdose) milliseconds following the 50 mg/m^2 dose. The range of LS mean changes from time-matched baseline was −1.1–1.4 milliseconds following pevonedistat dosing at 25 mg/m^2 and −0.8–0.9 milliseconds at 50 mg/m^2. The minimum lower bound of the 2-sided 90% confidence bound was −3.3 milliseconds (4 hours postdose) at 25 mg/m^2 and −3.0 milliseconds (11 hours postdose) at 50 mg/m^2. The maximum upper bound was 3.7 milliseconds (1 hour postdose) at 25 mg/m^2 and 3.1 milliseconds at 50 mg/m^2 (1 hour postdose).

Categorical Analysis and Morphology Findings

A summary of ECG abnormalities over all time points following administration of pevonedistat at 25 or 50 mg/m^2 is presented in Table 2. A QTcF of >450 milliseconds was observed in 4/43 (9.3%) and 1/41 (2.4%) patients who received pevonedistat 25 and 50 mg/m^2, respectively. There were no patients with a QTcF >480 or >500 milliseconds at either of the pevonedistat doses. No trends

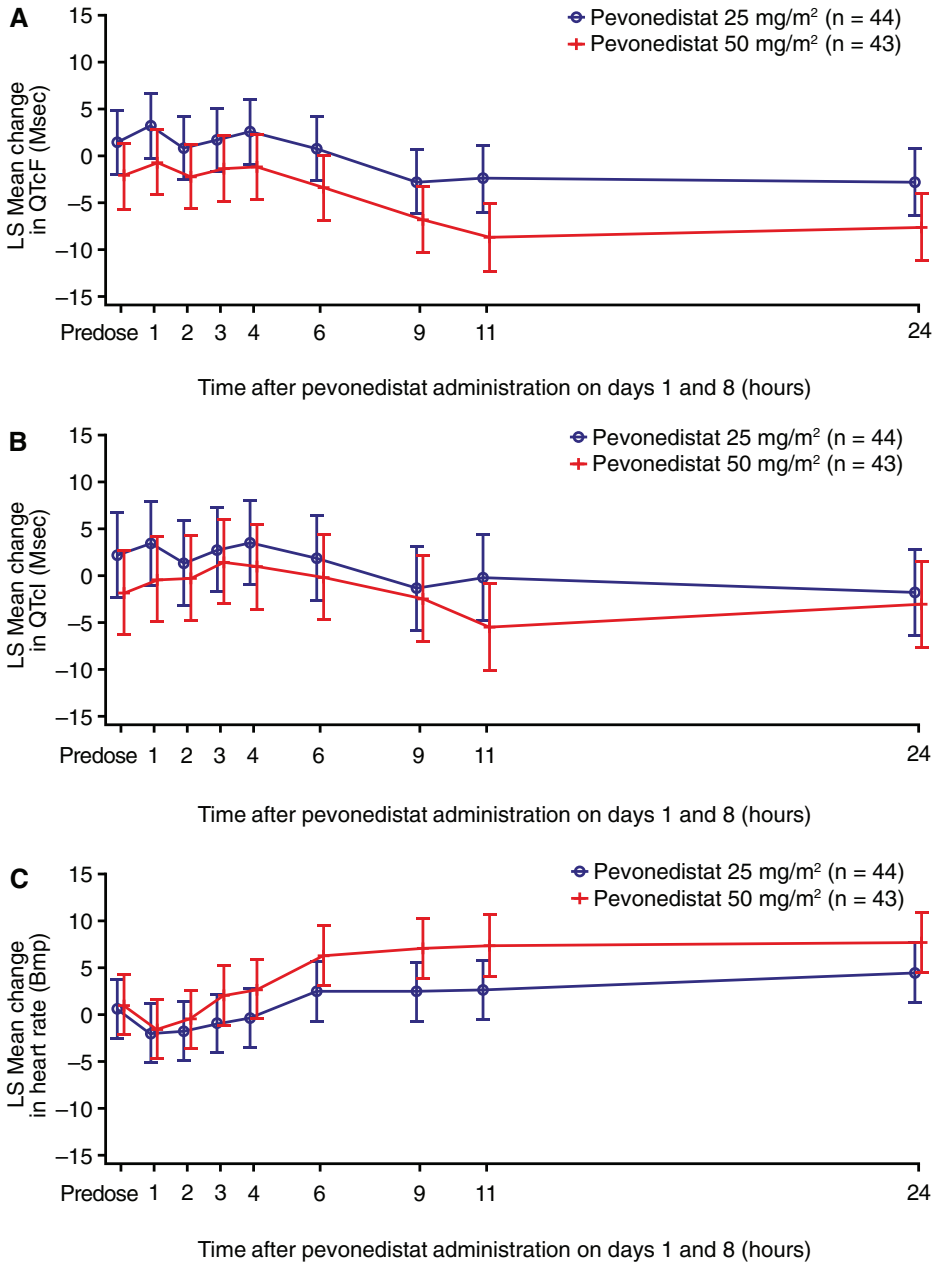

Figure 2. Least squares mean change from time-matched baseline and 2-sided 90% confidence intervals in QTcF (A), QTcI (B), and heart rate (C). LS, least square; QTcF, QT interval with Fridericia's correction; QTcI, QT interval with individual patient correction.

were noted for variation across the time points. A QTcI >450 milliseconds was observed in 8/42 (19.0%) and 6/41 (14.6%) patients who received pevonedistat 25 and 50 mg/m^2, respectively. One of 42 (2.4%) and 3/41 (7.3%) patients had a QTcI >480 milliseconds with pevonedistat 25 and 50 mg/m^2, respectively. One of 42 (2.4%) patient had a QTcI >500 milliseconds with the 50 mg/m^2 dose; this reflected the generally higher values for QTcI and was of no clinical consequence.

There were 4/42 (9.5%) patients with QTcF changes from baseline >30 milliseconds over all time points following the 25 mg/m^2 dose. No patients experienced a QTcF change from baseline >30 milliseconds over all time points following the 50 mg/m^2 dose. No change in QTcF or QTcI exceeded 60 milliseconds following either of the two pevonedistat doses.

Treatment-emergent nonspecific ST wave changes were found in one patient at two time points after the pevonedistat dose of 25 mg/m^2. Treatment-emergent nonspecific T wave changes were noted in three patients at 25 mg/m^2 and in the same three patients plus one additional patient while treated with 50 mg/m^2 pevonedistat.

Table 2. Summary of Electrocardiogram Abnormalities Over All Time Points Following IV Infusion of Pevonedistat at 25 or 50 mg/m^2

	Pevonedistat 25 mg/m^2			Pevonedistat 50 mg/m^2		
	n	N	%	n	N	%
QTcF >450 ms	4	43	9.3	1	41	2.4
QTcF >480 ms	0	43	0	0	41	0
QTcF >500 ms	0	43	0	0	41	0
QTcI >450 ms	8	42	19.0	6	41	14.6
QTcI >480 ms	1	42	2.4	3	41	7.3
QTcI >500 ms	0	42	0	1	41	2.4
QTcF increase >30 ms	4	42	9.5	0	41	0
QTcF increase >60 ms	0	42	0	0	41	0
QTcI increase >30 ms	1	42	2.4	2	41	4.9
QTcI increase >60 ms	0	42	0	0	41	0
PR >200 ms and >25% increase from baseline	0	42	0	0	40	0
QRS >110 ms and >25% increase from baseline	0	42	0	0	41	0

IV, intravenous; QTcF, QT interval with Fridericia's correction; QTcI, QT interval with individual patient correction.

Table 3. Final Pevonedistat Concentration–dQTcF Model Parameters

Parameter		Population Mean (SE%)	Additive Omega IIV (Shrinkage)
dQTcF intercept (ms)	Θ_1	0 FIXED	31.0 (8.5%)
dQTcF slope (ms/[ng/mL])	Θ_2	–0.00143 (132.9%)	–
Residual variability (ms)	σ_1	79.5 (5.4%)	(2.8%)

dQTcF, change in Fridericia-corrected QT interval; IIV, interindividual variability; SE, standard error.

Concentration–dQTc Analysis

The final parameters for the pevonedistat concentration and change in QTcF from the baseline (pevonedistat concentration–dQTcF) model are shown in Table 3. None of the evaluated covariates (sex, baseline ECOG score, or baseline BMI) were identified to be significant predictors of dQTcF intercept or slope. The effect size of pevonedistat concentration on dQTcF was calculated using the linear model. The mean and 90%CI for dQTcF were constructed by nonparametric bootstrapping (Figure 3). The estimated dQTcF at C_{max} of pevonedistat modeled dose levels of 20, 25, and 50 mg/m^2 showed a nominal (<1 milliseconds) decrease in QTcF based on the mean values (Table 4).

The effect size was also evaluated by simulations (N = 5000) using the original dataset and final pevonedistat concentration–dQTcF model. These simulation results were used to determine whether each simulated patient experienced a dQTcF value greater than 30 or 60 milliseconds. The proportion of patients at each daily dose level was calculated as the percentage of all simulated patients administered that dose. Following a dose of pevonedistat 25 and 50 mg/m^2, 1.44% and 1.51% of patients, respectively, would be expected to have a QTcF increase of 30 milliseconds. None of the patients would be expected to have a QTcF increase of >60 milliseconds.

Table 4. Pevonedistat Concentration–dQTcF Model Simulations of Predicted Effect Sizes (dQTcF) for Pevonedistat C_{max} at 20, 25, and 50 mg/m^2

Dose (mg/m^2)	C_{max} (ng/mL)	Mean	90%CI
20	164	–0.238	(–0.763 to 0.294)
25	197	–0.286	(–0.916 to 0.353)
50	509	–0.738	(–2.367 to 0.911)

CI, confidence interval; C_{max}, maximum observed plasma concentration; dQTcF, change in Fridericia-corrected QT interval.

Safety

Single doses of pevonedistat 25 and 50 mg/m^2 administered 1 week apart in crossover fashion were well tolerated. Thirty-seven of the 44 patients (84.1%) experienced at least one treatment-emergent adverse event (TEAE), including 18 (81.8%) patients randomized to sequence AB and 19 (86.4%) randomized to sequence BA. The most common TEAEs were gastrointestinal in nature (nausea, diarrhea, and vomiting)

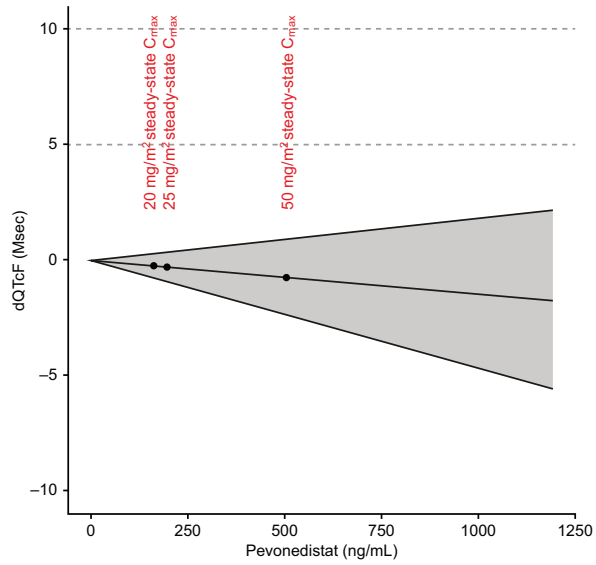

Figure 3. Model predicted mean change from baseline in QTcF versus pevonedistat concentration and associated 90% confidence interval (CI). The mean and 90%CI for dQTcF were computed by nonparametric bootstrap results. The center line is the mean predicted dQTcF versus pevonedistat concentration and the shaded area is the 90%CI around the mean. The dQTcF for C_{max} at 20, 25, and 50 mg/m^2 are displayed. C_{max}, maximum observed plasma concentration; dQTcF, change in Fridericia-corrected QT interval; QTcF, QT interval with Fridericia's correction.

or liver enzyme elevations (increased aspartate aminotransferase and alanine aminotransferase). None of the three on-study deaths were considered to be study drug-related.

Discussion

Based on the review of New Drug Applications (NDAs)/Biological License Application for all oncology New Molecular Entities (NMEs) that were approved by the US Food and Drug Administration between 2011 and early 2017, three different approaches for evaluating effects of NMEs on QTc were identified among the 56 NDAs/Biological License Application submissions: concentration–QTc analysis, dedicated QT study and thorough QT study.[21–24] Dedicated QT studies were conducted for nine (16%) of 56 NMEs, including five of 39 (13%) small molecules. Concentration–QTc analyses were performed for 33 (59%) of the total NMEs using cross-study PK/QTc data, specifically for 21 of 39 (54%) small molecules. Similarly, a comprehensive analysis of QT prolongation evaluation of small-molecule NDAs approved in oncology between 2011 and 2019 found that among a total of 64 small-molecule NMEs, concentration–QTc studies were used in the majority of cases (59%), with fewer thorough QT studies (20%) and dedicated QT studies (21%).[25] These findings reinforce the value of concentration–QT analyses as the leading approach for QT risk assessment. In this dedicated QT study, we evaluated the effect of pevonedistat 25 and 50 mg/m^2 on the QTc interval in 44 patients with advanced malignancies. In addition, concentration–QT analyses were performed to confirm the lack of effects of pevonedistat on the QTc interval at the doses for clinical investigation. Based on the by-time point analysis of central tendency of time-matched QTcF change from baseline, the maximum 2-sided 90% upper bound for the LS mean increase in QTcF was less than 10 milliseconds, indicating that treatment with pevonedistat 25 and 50 mg/m^2 showed no evidence of QT prolongation indicative of cardiac repolarization abnormalities. Analyses using two correction methods (QTcF and QTcI) consistently supported the conclusion that administration of pevonedistat up to a dose of 50 mg/m^2 does not cause QT prolongation. The steady-state unbound C_{max} of pevonedistat 50 mg/m^2 was 15.5 ng/mL in this study (based on a total C_{max} of 509 ng/mL and pevonedistat in vitro free fraction of 0.03) and the observed lack of effect of pevonedistat on QTc is consistent with nonclinical findings in which pevonedistat exhibited minimal activity against hERG gene current (K_i = 17.3 μM, or 7673 ng/mL, which is 15- and 495-fold of steady-state total and unbound pevonedistat plasma C_{max}, respectively, at a pevonedistat dose of 50 mg/m^2). Overall, treatment with IV infusion of pevonedistat up to 50 mg/m^2 in patients with advanced solid tumors showed no evidence of QT prolongation, indicative of the lack of clinically meaningful effects on cardiac repolarization.

Following IV infusion of pevonedistat at doses of 25 and 50 mg/m^2, systemic exposures of pevonedistat increased in a dose-proportional manner, as evidenced by the similar dose-normalized AUC at these two dose levels. The estimated half-life of 7 hours for pevonedistat supported the washout period of 7 days between the two single doses. The geometric mean clearance of pevonedistat in this study was 35 L/h, consistent with that previously estimated in a population PK analysis.[12]

Concentration–QT analyses are often performed to evaluate the concentration-relatedness in the effects of a drug on QTc intervals.[26] In this study, population-based models were used to examine the relationships between dQTcF, dQTcI and heart rate, and pevonedistat concentrations. The Fridericia method adequately corrected for the relationship between the QT interval and heart rate. To evaluate the predicted effect sizes of pevonedistat concentration on dQTcF, the linear concentration–dQTcF model was selected. Pevonedistat was shown to decrease dQTcF by approximately −0.00143 milliseconds per ng/mL with a 90%CI of −0.00465 to −0.00179. The mean change of QTcF from

baseline at pevonedistat C_{max} following 25 mg/m^2 dose was −0.286 milliseconds with 90%CI of −0.916–0.353. The mean change of QTcF from baseline at C_{max} of 50 mg/m^2 dose was −0.738 milliseconds with 90%CI of −2.367–0.911. Simulations from the final pevonedistat concentration–dQTcF model indicated that less than 2% of patient populations would have QTcF changes from baseline above the threshold of 30 milliseconds following administration of pevonedistat at 25 and 50 mg/m^2, respectively, and no patients would have QTcF changes from baseline above the threshold of 60 milliseconds following administration of pevonedistat at 25 and 50 mg/m^2, which was consistent with the result from the categorical analysis. No pevonedistat concentration–effect relationships were detected from these model-based analyses, consistent with findings from the statistical and categorical analyses that support a lack of effect on the QT interval.

In conclusion, the current study and analyses demonstrate that pevonedistat up to a dose of 50 mg/m^2 does not cause QT prolongation indicative of the lack of clinically meaningful effects on cardiac repolarization.

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Conflicts of Interest

Xiaofei Zhou and Neeraj Gupta are employees of Takeda Development Center Americas, Inc (TDCA). Diane R. Mould is a consultant of Takeda Development Center Americas, Inc., (TDCA). Debra L. Richardson serves on advisory boards for Mersana, AstraZeneca, Genetech, GlaxoSmithKline, Immunogen, and Deciphera. Solmaz Sahebjam had research funding from Bristol-Myers Squibb, Merck, and Brooklyn ImmunoTherapeutics and received an advisory board fee from Merck and Boehringer-Ingelheim. James Strauss has stocks with AbbVie, Abbott Laboratories, Bristol-Myers Squibb, Intuitive Surgical, Johnson & Johnson, Merck and Regneron, serves on advisory boards for Synlogic and Binhui Biopharmaceuticals Ltd., and has a leadership role at Dialectic Therapeutics. The remaining authors declare no conflicts of interest.

Data Availability Statement

The datasets, including the redacted study protocol, redacted statistical analysis plan, and individual participants' data supporting the results reported in this article, will be made available within 3 months from initial request to researchers who provide a methodologically sound proposal. The data will be provided after its de-identification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

References

1. Podust VN, Brownell JE, Gladysheva TB, et al. A NEDD8 conjugation pathway is essential for proteolytic targeting of p27^{Kip1} by ubiquitination. *Proc Natl Acad Sci U S A*. 2000;97(9):4579-4584.
2. Read MA, Brownell JE, Gladysheva TB, et al. NEDD8 modification of cul-1 activates SCF$^{\beta TrCP}$-dependent ubiquitination of IκBα. *Mol Cell Biol*. 2000;20(7):2326-2333.
3. Enchev RI, Schulman BA, Peter M. Protein neddylation: beyond cullin-RING ligases. *Nat Rev Mol Cell Biol*. 2015;16(1):30-44.
4. Mansour MA. Ubiquitination: friend and foe in cancer. *Int J Biochem Cell Biol*. 2018;101:80-93.
5. Rousseau A, Bertolotti A. Regulation of proteasome assembly and activity in health and disease. *Nat Rev Mol Cell Biol*. 2018;19(11):697-712.
6. Swords RT, Coutre S, Maris MB, et al. Pevonedistat, a first-in-class NEDD8-activating enzyme inhibitor, combined with azacitidine in patients with AML. *Blood*. 2018;131(13):1415-1424.
7. Lockhart AC, Bauer TM, Aggarwal C, et al. Phase Ib study of pevonedistat, a NEDD8-activating enzyme inhibitor, in combination with docetaxel, carboplatin and paclitaxel, or gemcitabine, in patients with advanced solid tumors. *Invest New Drugs*. 2019;37(1):87-97.
8. Sarantopoulos J, Shapiro GI, Cohen RB, et al. Phase I study of the investigational NEDD8-activating enzyme inhibitor pevonedistat (TAK-924/MLN4924) in patients with advanced solid tumors. *Clin Cancer Res*. 2016;22(4):847-857.
9. Bhatia S, Pavlick AC, Boasberg P, et al. A phase I study of the investigational NEDD8-activating enzyme inhibitor pevonedistat (TAK-924/MLN4924) in patients with metastatic melanoma. *Invest New Drugs*. 2016;34(4):439-449.
10. Shah JJ, Jakubowiak AJ, O'Connor OA, et al. Phase I study of the novel investigational NEDD8-activating enzyme inhibitor pevonedistat (MLN4924) in patients with relapsed/refractory multiple myeloma or lymphoma. *Clin Cancer Res*. 2016;22(1):34-43.

11. Sekeres MA, Watts J, Radinoff A, et al. Randomized phase 2 trial of pevonedistat plus azacitidine versus azacitidine for higher-risk MDS/CMML or low-blast AML. *Leukemia*. 2021;35(7):2119-2124.
12. Faessel HM, Mould DR, Zhou X, Faller DV, Sedarati F, Venkatakrishnan K. Population pharmacokinetics of pevonedistat alone or in combination with standard of care in patients with solid tumours or haematological malignancies. *Br J Clin Pharmacol*. 2019;85(11):2568-2579.
13. Zhou X, Sedarati F, Faller DV, et al. Phase I study assessing the mass balance, pharmacokinetics, and excretion of [(14)C]-pevonedistat, a NEDD8-activating enzyme inhibitor in patients with advanced solid tumors. *Invest New Drugs*. 2021;39(2):488-498.
14. Faessel H, Nemunaitis J, Bauer TM, et al. Effect of CYP3A inhibitors on the pharmacokinetics of pevonedistat in patients with advanced solid tumours. *Br J Clin Pharmacol*. 2019;85(7):1464-1473.
15. Zhou X, Vaishampayan U, Mahalingam D, et al. Phase 1 study to evaluate the effects of rifampin on pharmacokinetics of pevonedistat, a NEDD8-activating enzyme inhibitor in patients with advanced solid tumors. *Invest New Drugs*. 2022;40(5):1042-1050.
16. Darpo B, Nebout T, Sager PT. Clinical evaluation of QT/QTc prolongation and proarrhythmic potential for nonantiarrhythmic drugs: the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use E14 guideline. *J Clin Pharmacol*. 2006;46(5):498-507.
17. Kang J, Wang L, Chen X-L, Triggle DJ, Rampe D. Interactions of a series of fluoroquinolone antibacterial drugs with the human cardiac K+ channel HERG. *Mol Pharmacol*. 2001;59(1):122.
18. Rock EP, Finkle J, Fingert HJ, et al. Assessing proarrhythmic potential of drugs when optimal studies are infeasible. *Am Heart J*. 2009;157(5):827-836.
19. Sarapa N, Britto MR. Challenges of characterizing proarrhythmic risk due to QTc prolongation induced by nonadjuvant anticancer agents. *Expert Opin Drug Saf*. 2008;7(3):305-318.
20. ClinicalTrials.gov. Pevonedistat plus azacitidine versus single-agent azacitidine as first-line treatment for participants with higher-risk myelodysplastic syndromes (HR MDS), chronic myelomonocytic leukemia (CMML), or low-blast acute myelogenous leukemia (AML) (PANTHER). Accessed April 20, 2022. https://clinicaltrials.gov/ct2/show/NCT03268954
21. Faucette S, Wagh S, Trivedi A, Venkatakrishnan K, Gupta N. Reverse translation of US Food and Drug Administration reviews of oncology new molecular entities approved in 2011–2017: lessons learned for anticancer drug development. *Clin Transl Sci*. 2018;11(2):123-146.
22. Lester RM. Update on ICH E14/S7B cardiac safety regulations: the expanded role of preclinical assays and the "Double-Negative" scenario. *Clin Pharmacol Drug Dev*. 2021;10(9):964-973.
23. Darpo B, Ferber G. The new S7B/E14 question and answer draft guidance for industry: contents and commentary. *J Clin Pharmacol*. 2021;61(10):1261-1273.
24. Strauss DG, Wu WW, Li Z, Koerner J, Garnett C. Translational models and tools to reduce clinical trials and improve regulatory decision making for QTc and proarrhythmia risk (ICH E14/S7B updates). *Clin Pharmacol Ther*. 2021;109(2):319-333.
25. Cohen-Rabbie S, Berges AC, Rekić D, Parkinson J, Dota C, Tomkinson HK. QT prolongation risk assessment in oncology: lessons learned from small-molecule new drug applications approved during 2011–2019. *J Clin Pharmacol*. 2021;61(8):1106-1117.
26. Gupta N, Huh Y, Hutmacher MM, Ottinger S, Hui AM, Venkatakrishnan K. Integrated nonclinical and clinical risk assessment of the investigational proteasome inhibitor ixazomib on the QTc interval in cancer patients. *Cancer Chemother Pharmacol*. 2015;76(3):507-516.

Supplemental Information

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