A Single Supratherapeutic Dose of Vorinostat Does Not Prolong the QTc Interval in Patients with Advanced Cancer

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Abstract

Purpose: This dedicated QTc phase I study, conducted in advanced-stage cancer patients, assessed the effect of a single supratherapeutic dose (800 mg) of vorinostat on the QTc interval.

Experimental Design: A randomized, partially blind, placebo-controlled, two-period, crossover study was conducted. Patients (n = 25) received single doses of 800 mg vorinostat and placebo in the fasted state. Holter electrocardiogram monitoring was done before each treatment and for 24 h postdose. Blood samples for vorinostat concentration were collected through 24 h postdose following vorinostat treatment only. Prescribed electrocardiogram and blood sampling times were designed to capture the expected Cmax of vorinostat.

Results: Twenty-four of the 25 patients enrolled in the study were included in the QTc analysis. The upper bound of the two-sided 90% confidence interval for the QTcF interval for the placebo-adjusted mean change from baseline of vorinostat was <10 ms at every time point. No patient had a QTcF change from baseline value >30 ms. One patient had QTcF values >450 ms (seen after both vorinostat and placebo administration) and none had values >480 ms. Mean AUC0–∞ and Cmax values attained were on the order of ∼1.93- and ∼1.41-fold higher, respectively, compared with the 400 mg clinical dose. Based on assessment of clinical and laboratory adverse experiences, single doses of 800 mg vorinostat were generally well tolerated.

Conclusions: Administration of a single supratherapeutic dose of the histone deacetylase inhibitor vorinostat is not associated with prolongation of the QTc interval. A dedicated QTc study in advanced cancer patients is a robust means for assessing risk for ventricular repolarization prolongation. (Clin Cancer Res 2009;15(22):7077–84)

Histone deacetylase (HDAC) inhibitors are a new class of antineoplastic agent being developed for several oncologic indications. Vorinostat is a small-molecule inhibitor of class I and II HDAC enzymes (1), which binds directly to the catalytic pocket of HDAC enzymes and is orally bioavailable. It has shown preclinical activity in numerous cancer models both in vitro and in vivo (2). Clinical activity has been shown in patients with a variety of malignancies, including cutaneous T-cell lymphoma (CTCL), and vorinostat is currently marketed with an indication for the treatment of patients with CTCL who have progressive, persistent, or recurrent disease on or following two systemic therapies at a daily dose of 400 mg (3). Vorinostat is generally well tolerated at multiple doses and schedules. The most common adverse experiences associated with oral vorinostat in phase I and II trials have included diarrhea, fatigue, nausea, thrombocytopenia, anorexia, and dysgeusia (3). Cardiac-associated adverse experiences have not been reported commonly.

Cardiac rhythm and electrocardiogram (ECG) alterations have been suggested to be a class effect with HDAC inhibitors (4, 5); however, a specific hypothesis explaining the underlying mechanism(s) has yet to be determined. The finding of QT...
Translational Relevance

Vorinostat is an inhibitor of specific histone deacetylase enzymes and has shown clinical activity in patients with a variety of malignancies, including cutaneous T-cell lymphoma. Vorinostat is generally well-tolerated and cardiac-associated adverse experiences have not been reported commonly. However, cardiac rhythm and electrocardiogram alterations have been suggested to be a class effect with histone deacetylase inhibitors. A dedicated QTc assessment study was conducted in cancer patients to provide a more rigorous assessment of the potential for vorinostat to prolong ventricular repolarization. In 24 patients with advanced cancer, a single supratherapeutic 800 mg dose of vorinostat did not prolong the QTc interval (monitored over 24 h). Results indicate that a supratherapeutic single dose of vorinostat is not associated with significant prolongation of ventricular repolarization. This study was designed using many of the recommendations in the ICH E14 QT/QTc guidance and could be a more general approach for QTc evaluation of cancer drugs.

Prolongation is generally attributed to a direct effect on ion channel membranes in the myocardium, but in some instances this could be a secondary pharmacodynamic effect, for example, by changes in histone acetylation and gene expression alterations. Furthermore, ECG alterations maybe a misattribution based on early clinical studies and incomplete assessment. As more clinical experience is gained with HDAC inhibitors, the potential for these drugs to cause cardiac toxicities and the mechanism by which they occur will be better understood.

Romidepsin (depsipeptide), another HDAC inhibitor that is currently in clinical development, is a bicyclic peptide and structurally distinct from the hydroxamate backbone of vorinostat. In nonclinical and clinical studies of romidepsin, there have been reports of cardiac abnormalities including ECG changes with QTc prolongation (4, 5). The mechanism of the cardiac effects of romidepsin is not fully understood; however, a suggestion was made that HDAC isozyme effect may be a contributor, but other external factors may be responsible. Montgomery et al. recently reported the involvement of HDAC1 and HDAC2 in the control of myocardial growth, morphogenesis, and contractility, with deletion re-expression of HDAC1 and HDAC2 in the control of myocardial growth, morphogenesis, and contractility. Furthermore, ECG alterations may be a misattribution based on early clinical studies and incomplete assessment. As more clinical experience is gained with HDAC inhibitors, the potential for these drugs to cause cardiac toxicities and the mechanism by which they occur will be better understood.

Although there has not been clear evidence of QTc prolongation due to vorinostat in either nonclinical or clinical studies to date, isolated rare events of QTc prolongation in previous vorinostat studies were observed (3). Due to these findings and the potential association of QTc prolongation in the HDAC inhibitor class, a dedicated QTc assessment study was conducted in cancer patients to provide a more rigorous assessment of the potential for vorinostat to prolong ventricular repolarization.

This study was designed using the recommendations in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E14 Guidance for Industry, Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs (10), a guidance document that provides recommendations regarding the design and analysis of clinical studies to assess the potential of a drug to delay cardiac repolarization. Performance of this study in cancer patients placed some notable restrictions on the study design; however, many of the recommended critical components were incorporated, resulting in a dedicated, robust study design evaluating the potential effect of an anticancer agent (not amenable for study in the healthy volunteer population) on ventricular repolarization.

Patients and Methods

This phase I randomized, partially blind, placebo-controlled, two-period, crossover study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol (PN070) was approved by the Western Institutional Review Board, the University of South Florida Office of Research, Division of Research Compliance Institutional Review Board, and the Ethical Review Committee of the University of Ghent. Every patient gave written informed consent to participate in the study. The clinical study was registered with ClinicalTrials.gov [Internet] (National Library of Medicine, NLM Identifier: NCT00632931).}

Eligibility criteria. Male and female patients ages ≥18 years, with histologically confirmed malignancies (including solid tumors, hematologic malignancies, and lymphoma) that were metastatic or unacceptable and for which standard curative or palliative measures did not exist or were no longer effective, were eligible for enrollment. Patients must also have had an Eastern Cooperative Oncology Group performance status ≤2 and a life expectancy of ≥3 months. Patients must not have received tumor directed immunological therapy, radiation therapy, surgery, or chemotherapy within 2 weeks of the study. Patients must not have received other experimental HDAC inhibitors or high-dose chemotherapy with stem cell rescue. Patients with a history of sick sinus syndrome, AV block, myocardial infarction, pulmonary congestion, cardiac arrhythmia, risk factors for Torsades de Pointes, or prolonged QTc interval were excluded. Patients were excluded if ECG intervals fell outside of the following ranges: PR >0.20 s, QRS >0.12 s, QTc (Fridericia) ≤450 ms, and RR >1.2 s. Other exclusion criteria included the following: participated in a study with an investigational agent or device within in 30 days, active central nervous system involvement of disease, active hepatitis B or C infection, HIV infection, pregnancy, lactation, history of unstable anemia, uncontrolled intercurrent illness, gastrointestinal resection, abnormal bone marrow function (hemoglobin <9 g/dL, absolute neutrophil count <1,500/µL, and platelets <100,000/µL), hepatic insufficiency [total bilirubin >1.5 times the upper limit of normal (ULN)], aspartate aminotransferase or alanine aminotransferase >2.5 times the ULN, alkaline phosphatase >5 times the ULN (if >2.5 times
the ULN, then liver fraction should be ≤2.5 times ULN), prothrombin time >1.5 times ULN (for patients not receiving anticoagulation), renal insufficiency [creatinine >1.5 times the ULN or creatinine clearance <60 mL/min (for patients with creatinine levels >1.5 times the ULN)], serum potassium and magnesium levels outside of normal limits, need for coadministration of a potent enzymatic inducing drug, and multiple or severe allergies or intolerability to drugs or food.

Study design. In two treatment periods, patients received a single 800 mg oral dose of vorinostat (Merck & Co.) or placebo to vorinostat in a randomized, crossover manner. Before the conduct of this study, a single 800 mg dose of vorinostat had not been tested but was expected to be adequately tolerated. The currently approved therapeutic dose for CTCL is 400 mg administered once daily (3). A total daily dose of 750 mg (250 mg administered three times daily) had been assessed and defined as one of the maximum tolerated dose levels (11). Experience with 600 mg showed that continuous once daily dosing was not tolerated; however, toxicities generally appeared after multiple dose administration (12). Furthermore, toxicities were generally rapidly reversible on discontinuation of the study drug. An intravenous formulation given at 900 mg/m²/d × 5 days was generally well tolerated (13). Based on the overall clinical experience with vorinostat and tolerability issues that were seen in a subgroup of patients at doses lower than the approved clinical dose of 400 mg, a dose ≥2-fold over the clinical dose was not recommended.

Vorinostat and placebo were administered following an 8-h fast to maintain consistency in the study and to reduce variability. There was a minimum 3-day washout interval between treatment periods. Twelve-lead ECGs were obtained by a Mortara H-12+ Holter recorder (Mortara Instrument) and extracted by a core ECG laboratory (Quintiles ECG Services). Blood samples were collected predose and at prespecified time points throughout the study following vorinostat administration only for up to 24 h postdose for determination of vorinostat serum concentrations.

ECG acquisition. Following completion of predose procedures, including physical examination and blood collection in each treatment period, patients rested in a supine position for Holter recorder attachment; recorders were activated 10 min before the anticipated dosing time. ECGs were simultaneously acquired (using dual-snap ECG electrodes) by the Mortara H-12+ Holter recorder (which continuously recorded and digitized 12-lead ECGs that were used for the primary analysis) and a bedside 12-lead ECG machine (which was used for safety monitoring during the study). These dual-snap ECG electrodes were placed on the six standard precordial positions on the chest; limb leads were placed in the modified foreshortened position. Patients were

<table>
<thead>
<tr>
<th>Table 1. Patient disposition</th>
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<tbody>
<tr>
<td>Characteristics</td>
</tr>
<tr>
<td>Gender/age</td>
</tr>
<tr>
<td>Male, n (age range), median age, y</td>
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<tr>
<td>Female, n (age range), median age, y</td>
</tr>
<tr>
<td>Body surface area (m²), mean (range), median</td>
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<tr>
<td>Performance status (Eastern Cooperative Oncology Group)</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
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<tr>
<td>2</td>
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<tr>
<td>Race</td>
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<td>Asian</td>
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<td>African American</td>
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<tr>
<td>Hispanic</td>
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<tr>
<td>White</td>
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<td>Ovarian</td>
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<tr>
<td>Colon</td>
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<tr>
<td>Lung</td>
</tr>
<tr>
<td>Mesothelioma</td>
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<tr>
<td>Uterine</td>
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<tr>
<td>Soft tissue sarcoma</td>
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<tr>
<td>Anal</td>
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<tr>
<td>Basal cell</td>
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<tr>
<td>Breast</td>
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<tr>
<td>Gastrointestinal stromal tumor</td>
</tr>
<tr>
<td>Pseudomyxoma peritonei</td>
</tr>
<tr>
<td>Pancreatic</td>
</tr>
<tr>
<td>Thyroid</td>
</tr>
<tr>
<td>Prior systemic anticancer therapies, n</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
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<tr>
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<td>Prior radiation therapies, n</td>
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<td>2</td>
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<td>≥3</td>
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asked to rest quietly in a supine position for 10 min before, as well as 5 min following, each prespecified ECG time point (baseline predose and 0.5, 1, 2, 3, 4, 8, and 12 h postdose). The time points were selected to capture the expected maximal concentration (C\text{max}) of vorinostat; based on the previously characterized serum concentration time profile, the time to maximal concentration (T\text{max}) is between 1 and 2 h (14).

Following completion of the 12 h procedures, the Holter monitor was disconnected with leads remaining in place. Twenty-four hour procedures, including the collection of the 24-h ECG reading, were completed the following morning. In each period, a single bedside 12-lead ECG was printed and reviewed by the investigators at 2, 4, 8, 12, and 24 h postdose for safety evaluation.

**ECG analysis.** ECG data from each Holter recording session were analyzed in an ECG core laboratory (Quintiles ECG Services). Analysis procedures have been reported previously (15). In brief, each Holter recording was reviewed and annotated regarding any intervals of significant artifact, technical failure, or nonsinus beats. Ten-second periods of recording were extracted and ECGs were routed to an algorithm-assisted ECG annotation system. ECGs were then read by a cardiologist blinded to treatment, period, and time postdose. All ECGs from a subject were read by a single cardiologist. For replicate extraction at each time point, five 10-s windows centered on the nominal time point were extracted. In each ECG, all leads were evaluated, and the lead with the longest QT interval was used for analysis. In the lead with the longest QT interval, measurements were made in three consecutive complexes. To correct for the possible effect of heart rate, the Fridericia’s correction (QTcF = QT/ \sqrt{R}) was used. The sample size of the study was determined by the average of three consecutive complexes.

**Pharmacokinetic assessment.** Blood samples were drawn predose and following vorinostat treatment at 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 h after dosing. Blood collection procedures have been described previously (14). Serum was assessed for vorinostat using a turbulent flow online extraction format for analyte isolation followed by reverse-phase high-performance liquid chromatography with tandem mass spectrometric detection as described previously (16).

Serum pharmacokinetic parameter values of vorinostat that were calculated included area under the concentration-time curve from time 0 to infinity (AUC\text{0-\infty}), and from 0 to 24 h (AUC\text{0-24 h}), C\text{max}, T\text{max}, and apparent terminal half-life (t\text{1/2}). The software package WinNonlin Enterprise version 5.0.1 was used for the calculations. The apparent terminal t\text{1/2} was estimated from the best-fit parameters of a single exponential to the log-linear portion of the serum concentration-time curve using unweighted linear regression. AUC was calculated using the linear up/log down method up to the last measured concentration and the additional area for AUC\text{0-\infty} estimated from that concentration and the value of apparent terminal t\text{1/2} estimated for that administration. C\text{max} and T\text{max} were obtained by inspection of the concentration-time data.

**Safety and tolerability.** Safety and tolerability were assessed by physical examinations and measurements of vital signs, performance status, 12-lead ECGs, and routine laboratory safety tests (complete blood count, serum chemistries, coagulation profiles, and urinalyses). All clinical adverse experiences were evaluated by the investigator with respect to intensity (National Cancer Institute Common Terminology Criteria version 3.0), seriousness, action taken, and relationship to vorinostat.

**Statistical analysis.** The sample size of the study was determined by estimates of within-subject variance in QTc change from baseline based on prior studies done at Merck & Co. Based on a sample size of 24 patients and assuming that the true within-subject variance in QTc change from baseline would be 88.95 ms², the half-width of the 90% confidence interval for the mean difference of QTcF change from baseline was projected to be ~4.48 ms.

The QTcF value at each time point was calculated as the average of the five replicate QTcF values from the ECGs extracted around each nominal time point. QTcF change from baseline values were evaluated in a repeated-measures mixed model with treatment, time, treatment-by-time interaction, and period as fixed effects and patient as a random effect. Mean differences (vorinostat - placebo) along with two-sided 90% confidence intervals in QTcF change from baseline at all QTcF time points were calculated. A two-sided 95% confidence interval was constructed for mean QTcF at each combination of treatment and time point. Ninety-five percent confidence intervals were also constructed for the mean change from baseline in QTcF at each combination of time point and treatment.

Summary statistics for AUC\text{0-\infty}, AUC\text{0-24 h}, C\text{max}, T\text{max}, and apparent t\text{1/2} were calculated. Geometric means and corresponding 95% confidence intervals, medians and range, and harmonic means and jackknife SDs were provided as appropriate.

**Results**

**Patient disposition.** The baseline characteristics of the 25 patients enrolled in this study are shown in Table 1. All of the patients had a diagnosis of advanced stage cancer, and all had received at least two prior systemic anticancer therapies. One patient was withdrawn from the study following administration of 800 mg vorinostat in period 1 due to a protocol deviation of taking a concomitant medication (fluconazole) that was not allowed in the study due to its propensity to cause QTc prolongation. No QTc data were collected from this patient. A second patient withdrew consent following completion of period 1 procedures (dosed 800 mg vorinostat). All 25 patients were included in the analysis of safety and tolerability. Twenty-four of the 25 patients were included in the QTc analysis. Two patients had missing predose QTc measurements during the vorinostat treatment period and change from baseline could not be calculated. Overall, 22 patients had QTc data for analysis from the vorinostat treatment period and 23 patients had QTc data for analysis from the placebo treatment period.

**ECG analysis**

**Heart rate, PR and QRS intervals, and morphology.** Assessment of heart rate and PR and QRS interval change from baseline was done. By inspection, there was no clinically meaningful difference of heart rate or PR and QRS intervals between the treatment groups (Supplementary Tables S1 and S2). Exploratory assessment of T wave and U wave morphology revealed no statistically significant differences in T wave morphology between vorinostat and placebo either at specific time
points or overall; there was no evidence of U wave presence in either group. There was no evidence of clinically meaningful arrhythmias.

**QTcF.** For QT interval assessment, Fridericia’s correction to QT was made to correct for heart rate. The appropriateness of the correction factor (\(\text{QTcF} = \frac{\text{QT}}{\text{RR}^{1/3}}\)) was assessed via a simple linear regression of QTcF versus RR interval using placebo data. Although not formally tested, an observed slope of 0 would indicate that Fridericia’s correction is adequate. The performed regression resulted in a slope (and 95% confidence interval) of 0.0740 (0.057-0.091), indicating that Fridericia’s correction is indeed adequate.

The QTcF interval placebo-adjusted change from baseline means and corresponding 90% confidence intervals are summarized in Fig. 1 and Table 2. The upper limit of the 90% confidence interval for the placebo-adjusted mean change from baseline of vorinostat was <10 ms at every time point examined. Categorical analyses on both the raw QTcF values and the change from baseline QTcF values also provided evidence, per ICH E14 guidance, that vorinostat does not prolong the QTc interval. After averaging the five replicates, 1 patient had QTcF values >450 ms (seen both after administration of vorinostat to cause delayed ventricular repolarization (QT/QTc ∼1.6) and for \(\text{ALICo}_{24\text{h}}\) was 7.20 (5.96-9.34) and for \(\text{ALICo}_{24\text{h}}\) was 2.1 h (0.5, 6.0), and the harmonic mean apparent \(t_{1/2}\) (jackknife SD) was 2.08 h (1.56). As expected, the exposures attained with the 800 mg dose of vorinostat were ~2-fold higher than those attained with the standard clinical dose of 400 mg/d (14).

**Safety and tolerability.** Vorinostat administered at the supratherapeutic dose of 800 mg (single-dose administration) was generally well tolerated in patients with advanced cancer. No serious clinical or laboratory adverse experience was reported and no patient discontinued because of an adverse experience. Of the 25 patients enrolled, 13 reported a total of 34 nonserious clinical adverse experiences; 7 of which were considered either possibly or probably drug related. Of the 7 drug-related adverse experiences, 6 were reported following vorinostat administration and 1 was reported with placebo. The most commonly reported drug-related clinical adverse experience (reported by >2 patients) was nausea. Of the 34 nonserious clinical adverse experiences, the most common were nausea (reported by 4 patients) and cough, dyspnea, and fatigue (each reported by 3 patients). In the comparison of vorinostat administration versus placebo, 11 (44%) patients and 5 (21.7%) patients, respectively, reported clinical adverse experiences. Two patients experienced a total of 4 nonserious laboratory adverse experiences; 2 of which were considered possibly drug-related (increased international normalized ratio and increased prothrombin time, both seen in a single patient). All adverse experiences reported were judged to be grade 1 or 2 in severity with the exception of 1 patient with grade 3 adverse experiences that were not related to study drug.

**Discussion**

Alterations in cardiac rhythm have been suggested to be a class effect for HDAC inhibitors such as vorinostat (4, 5). In addition to the current clinical study, the potential risk of vorinostat to cause delayed ventricular repolarization (QT/QTc prolongation) in humans was investigated using several nonclinical assays, including cellular electrophysiologic evaluations.
Table 3. Number of patients with at least one QTcF value >450 ms after administration of single-dose 800 mg vorinostat or placebo to male and female patients with advanced cancer

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total patients</th>
<th>&gt;450 and ≤480 ms</th>
<th>≥480 and &lt;500 ms</th>
<th>&gt;500 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>800 mg vorinostat</td>
<td>24</td>
<td>1*</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Placebo</td>
<td>23</td>
<td>1*</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*The same patient had a QTcF value >450 ms in both treatment periods (periods 1 and 2).

The study design incorporated ECG evaluation after a supratherapeutic single-dose administration of 800 mg vorinostat. The dose of vorinostat currently approved in the United States for the treatment of CTCL is 400 mg administered once daily. An oral dose of 800 mg has not been studied previously but was found in this study to be generally well tolerated after single-dose administration. Mean AUC0-24 h and Cmax values attained after 800 mg administration (7.46 μmol/L h and 1.58 μmol/L, respectively) were on the order of ~1.93- and ~1.41-fold higher, respectively, compared with historical data after 400 mg single-dose administration in a fasted state (3.87 μmol/L h and 1.12 μmol/L, respectively; ref. 14). In comparison with historical pharmacokinetic data after 400 mg multiple dose administration with food, which yields slightly higher exposure values compared with fasting (AUC0-24 h 6.46 μmol/L h and Cmax 1.13 μmol/L), 800 mg single-dose administration results in an increase of ~1.12- and ~1.40-fold for AUC0-24 h and Cmax respectively (14). Therefore, the dose of 800 mg satisfied the criterion to assess a supratherapeutic dose that provides plasma concentrations higher than that of the currently approved efficacious dose of 400 mg for the treatment of CTCL.

Five replicate ECGs were collected at each time point to reduce variability in the measurement of the QTcF interval. Furthermore, a centralized core laboratory was employed to measure QTcF intervals manually. The QTcF value at each

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time point was calculated as the average of the five replicate QTcF values from ECGs extracted around each nominal time point. The QTcF assessment results of the study indicated that a single supratherapeutic dose of vorinostat does not prolong the QTcF interval. The upper limit of the 90% confidence interval for the placebo-adjusted mean change from baseline was <10 ms at every time point. This cutoff is defined in the ICH E14 guidance as the threshold that defines a clinically meaningful effect. Additional categorical analyses on both the raw QTcF values and the change from baseline QTcF values also supported this conclusion.

Vorinostat is cleared primarily by metabolism resulting in two circulating inactive metabolites (O-glucuronide of vorinostat and 4-anilino-4-oxobutanoic acid) seen at higher concentrations than parent (3- to 4-fold and 10- to 13-fold higher, respectively; ref. 14). Previous pharmacokinetic data revealed that the apparent t1/2 of the O-glucuronide is similar to that of vorinostat with no meaningful accumulation projected with the supratherapeutic dose, while the 4-anilino-4-oxobutanoic acid accumulates to some extent (~44%) with multiple-dose administration but to a lower degree with respect to Cmax; T1/2 is ~3 h for this metabolite relative to ~1.5 h for vorinostat. Metabolite concentrations were not measured in this study; however, ECG evaluations were done at projected peak serum concentrations for both of the vorinostat metabolites, assuring adequate QTc evaluation. Multiple-dose administration was not conducted due to potential issues of toxicity at the 800 mg dose, and as such, steady-state concentrations of the 4-anilino-4-oxobutanoic acid were not achieved. However, it is likely that metabolite concentrations reached after administration of the supratherapeutic 800 mg dose of vorinostat are similar to that attained after steady-state administration of the therapeutic dose based on the known accumulation ratio (14). Overall, adequate assessment of QTc effects was assessed with respect to the metabolites.

Although a thorough QTc study as outlined by the ICH E14 guidance could not be conducted due to limitations outlined above, this dedicated study design was sufficient to evaluate ventricular prolongation potential and may be applicable for other compounds with similar clinical limitations. The study lacked a positive control that limits assessment of assay sensitivity; however, past clinical experience with similar monitoring techniques have consistently shown positive findings of QTc prolongation with positive controls (such as moxifloxacin), suggesting that this may not be a major deficiency (15, 17–21). Additionally, blood draws during placebo administration were not done, which may have led to potential unblinding of study therapy to patients. However, it should be noted that ECG readings were done in a blinded manner.

Investigation of a single supratherapeutic dose without the assessment of ECG effects of the therapeutic dose was done. This method of investigation has been documented as a generalizable study design (15). If there were findings seen at the supratherapeutic dose, use of modeling and simulation could characterize concentration effects and dose-response relationships. Despite the lack of characterization of a dose response, the supratherapeutic dose of vorinostat sufficiently characterized maximal effects, which is of most value with regard to identification of safety issues.

In conclusion, data from this dedicated QTc study indicate that a supratherapeutic single dose of vorinostat is not associated with significant prolongation of ventricular repolarization. These data are consistent with nonclinical and clinical cardiac data collected for vorinostat to date. In addition, these data support the overall safety profile of vorinostat use in cancer patients. A dedicated QTc study in advanced cancer patients is a robust means for assessing risk for ventricular repolarization prolongation.

Disclosure of Potential Conflicts of Interest

E.H. Rubin, E. Friedman, J.K. Patterson, K. Van Dyck, X. Li, W. Comisar, J.A. Chodakewitz, J.A. Wagner, and M. Iwamoto, employees, stockholders, ownership interest, Merck & Co. The other authors report no conflicts of interest.

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