Evaluation of CYP3A-Mediated Drug–Drug Interactions With Romidepsin in Patients With Advanced Cancer

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Abstract
Two multicenter, single-arm, single-infusion, open-label studies were conducted to evaluate the effect of ketoconazole (a strong CYP3A inhibitor) or rifampin (a strong CYP3A inducer) daily for 5 days on the pharmacokinetics (PK) and safety of romidepsin (8 mg/m² intravenous 4-hour infusion for the ketoconazole study or a 14 mg/m² intravenous 4-hour infusion for the rifampin study) in patients with advanced cancer. Romidepsin coadministered with ketoconazole (400 mg) or rifampin (600 mg) was not bioequivalent to romidepsin alone. With ketoconazole, the mean romidepsin AUC and Cmax were increased by approximately 25% and 10%, respectively. With rifampin, the mean romidepsin AUC and Cmax were unexpectedly increased by approximately 80% and 60%, respectively; this is likely because of inhibition of active liver uptake. For both studies, romidepsin clearance and volume of distribution were decreased, terminal half-life was comparable, and median Tmax was similar. Overall, the safety profile of romidepsin was not altered by coadministration with ketoconazole or rifampin, except that a higher incidence and greater severity of thrombocytopenia was observed when romidepsin was given with rifampin. The use of romidepsin with rifampin and strong CYP3A inducers should be avoided. Toxicity related to romidepsin exposure should be monitored when romidepsin is given with strong CYP3A inhibitors.

Keywords
romidepsin, ketoconazole, rifampin, drug–drug interaction, pharmacokinetics

Romidepsin (FK228, bicyclic depsipeptide) is a natural product histone deacetylase (HDAC) inhibitor originally isolated from Chromobacterium violaceum that is effective in the treatment of cutaneous T-cell lymphoma (CTCL) and peripheral T-cell lymphoma (PTCL).

Romidepsin was identified as an HDAC inhibitor based on its ability to arrest the cell cycle in both the G1 and G2/M phases, induce internucleosomal breakdown of chromatin, and inhibit intracellular HDAC activity, resulting in accumulation of acetylated histone species.

In vitro, romidepsin selectively induces apoptosis of malignant cells at concentrations in the nanomolar range. Currently, romidepsin is approved by the US Food and Drug Administration for the treatment of CTCL in patients who have received at least 1 prior systemic therapy and treatment of PTCL in patients who have received at least 1 prior therapy. Romidepsin is indicated at a dose of 14 mg/m², given as a 4-hour intravenous infusion on days 1, 8, and 15 of a 28-day cycle.

Romidepsin has been investigated in several phase 1 dose escalation studies in cancer patients. The pharmacokinetics (PK) of romidepsin are linear and dose-proportional over a dose range of 1.0 to 24.9 mg/m².

Romidepsin does not accumulate in plasma after repeated weekly administration. The maximal tolerated dose (MTD) ranges from 13.3 mg/m² when given on days 1, 8, and 15 of a 28-day cycle to 17.8 mg/m² when given on days 1 and 5 in a 21-day cycle. Dose-limiting toxicities include fatigue, nausea, vomiting, thrombocytopenia (transient and grade 3) and neutropenia. A population PK analysis in patients with CTCL and PTCL demonstrated no effect of sex, age, race, age, and geriatric status on the PK of romidepsin.
mild to severe renal impairment, or mild hepatic impairment on romidepsin PK.9

No mass balance study has been conducted in humans for romidepsin, but a rat radiolabel mass balance study showed that the majority (79.4%) of an administered intravenous dose is eliminated by biliary excretion.13 Romidepsin is extensively metabolized in liver S9 and microsomal fractions to at least 20 unique metabolites.13 In vitro metabolism studies in human liver microsomes indicate that romidepsin is primarily metabolized by cytochrome P450 3A4 (CYP3A4) with minor contributions for romidepsin is primarily metabolized by cytochrome metabolism studies in human liver microsomes indicate that CYP2B6, or CYP3A4.9,13 Romidepsin is taken up into hepatocytes by an active process, but in vitro studies have shown that it is not a substrate of the uptake transporters BCRP, BSEP, MRP2, OAT1, OAT3, OATP1B1, OATP1B3, or OCT2.9,13 In vitro, romidepsin was shown to be a substrate of the efflux transporter, P-glycoprotein (P-gp).9,13 Romidepsin is highly protein bound primarily to α1-acid-glycoprotein.9,13

Given the important role of CYP3A4 in the metabolism of romidepsin, it is possible that strong CYP3A inhibitors may increase and strong CYP3A inducers may decrease the systemic exposure to romidepsin. Thus, specific drug–drug interaction studies are warranted. The present studies were undertaken to determine the effects of a strong CYP3A inhibitor (ketonazole) and a strong CYP3A inducer (rifampin) on the PK and safety of romidepsin.

Methods

Both the ketoconazole and rifampin drug–drug interaction studies were conducted through the Sarah Cannon Research Institute according to good clinical practice and followed the ethical principles of the Declaration of Helsinki. Independent Ethics Committees approved the study protocol and all amendments. Written informed consent was signed by all the patients in both studies.

Study Population

The inclusion and exclusion criteria were the same for the rifampin and ketoconazole studies. Patients were male or female aged ≥ 18 years who had a diagnosis of advanced malignancy, who failed available standard-of-care therapies for their disease, and who had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Patients were excluded who had any significant medical condition or psychiatric illness, gastrointestinal disease, any known cardiac abnormalities, or clinically significant active infection or known infection with human immuno-deficiency virus (HIV), hepatitis B, or hepatitis C. Patients were also excluded who had hemoglobin < 9 g/dL, absolute neutrophil count ≤ 1.0 × 10⁹ cells/L, platelet count < 100 × 10⁹ cells/L or < 75 × 10⁹ cells/L if bone marrow disease was documented, total bilirubin > 1.5 upper limit of normal (ULN) or > 2.0 × ULN in the presence of demonstrable liver metastases, aspartate aminotransferase (AST)/SGOT and alanine aminotransferase (ALT)/SGPT > 1.5 × ULN or > 2x ULN in the presence of demonstrable liver metastases, and serum creatinine > 2.0 × ULN. Patients were not eligible for participation if they had major surgery within 2 weeks of study entry, had prior chemotherapy treatment within 3 weeks (6 weeks for nitrosoureas) of first day of study treatment, or had radiotherapy within 4 weeks prior to romidepsin treatment. Patients were excluded who had concomitant use of CYP3A strong inhibitors within 1 week of study medication, CYP3A strong inducers within 2 weeks of study medication, drugs that cause significant prolongation of the QTc, or any other anticancer therapy or investigational agent. Prior exposure to romidepsin or other HDAC inhibitors was allowed. Patients who were pregnant or breastfeeding were excluded.

Trial Design

A schematic of the design for both clinical studies is shown in Figure 1. Each study was a multicenter, open-label, single-arm, single-dose trial that included a screening period, a PK assessment period, and a closeout period. Patients were then offered enrollment into a rollover study to continue to receive romidepsin treatment. Within 3 weeks of the first dose, patients underwent screening procedures. All patients who met the inclusion and none of the exclusion criteria were reevaluated on day 1 for baseline assessments and confirmation of eligibility. A total of 15 and 14 patients with advanced cancer were enrolled in the ketoconazole and rifampin studies, respectively, to ensure 12 evaluable patients. The approved dose of romidepsin is 14 mg/m² infused intravenously over a 4-hour period on days 1, 8, and 15 or a 28-day cycle. For the ketoconazole study, the dose of romidepsin administered was 8 mg/m² (infused intravenously over a 4-hour period on days 1 and 8) because an interaction with a CYP3A inhibitor could potentially increase the concentrations of romidepsin. For the rifampin study, the approved dose of 14 mg/m² (infused intravenously over a 4-hour period on days 1 and 8) was used because an interaction could potentially reduce plasma concentrations of romidepsin. On days 15 to 20, patients returned to the clinic for study closeout assessments. Prior to romidepsin infusion, antiemetic drugs were given prophylactically to mitigate nausea and vomiting; serum potassium (K) and magnesium (Mg) levels were also determined. Supplements were administered to patients if their K levels were < 3.8 mmol/L or Mg levels were < 0.85 mmol/L. Serial blood samples (4 mL) were collected at time 0 (predose), at 1, 2, 3, and 4 hours (end of infusion), and 4.25, 4.5, 5, 6, 8, 10, 12, 24, and 48
hours after the initiation of the intravenous infusion for the determination of plasma concentrations of romidepsin. Plasma was stored frozen at −80°C until analysis.

Safety was monitored throughout the study. Safety evaluations included adverse event (AE) reporting, physical examinations, vital sign measurements, concomitant medications/procedures, electrocardiograms (ECGs), and clinical laboratory safety tests.

Bioanalytical Methodology
Plasma samples were kept frozen at −70°C or colder prior to and following analysis. Samples were analyzed for romidepsin concentration using a validated method with a concentration range of 0.100 to 100 ng/mL. A 200-μL human plasma aliquot of each sample was fortified with 40 μL of internal standard (Boc-Met-Leu-Phe-OH) working solution at 100 ng/mL. Analytes were isolated from the unknown, standard, and quality control samples by liquid–liquid extraction using ethyl acetate. The eluate was evaporated under a nitrogen stream at approximately 40°C, and the remaining residue was reconstituted with 100 μL of 30:70 methanol/water, v/v. The final extract was analyzed via high-pressure liquid chromatography and tandem mass spectrometry detection using positive ion electrospray. A linear regression algorithm with [1/X^2] weighting was used to quantitate unknown samples.

Pharmacokinetic Analysis
Pharmacokinetic parameters were calculated by noncompartmental analysis using WinNonlin 5.3 (Pharsight Corp, Mountain View, California). Pharmacokinetic parameters included area under the plasma concentration–time curve from time zero to time t (AUC_t), the AUC from time zero to 24 hours (AUC_{24}), the AUC from time zero to infinity (AUC_{∞}), the maximum observed plasma concentration (C_{max}), and the time to maximum observed plasma concentrations (T_{max}). Actual sampling times were used in the calculations.

Safety Analysis
Safety was defined by type, severity, and relationship of AEs to romidepsin and clinically significant changes in physical examination, vital signs, ECG, concomitant medications, procedures, and laboratory findings.

Statistical Analysis
For C_{max} and AUC_{∞}, an analysis of variance (ANOVA) model was used to estimate the ratio of geometric means and 90% confidence intervals between romidepsin alone and romidepsin in the presence of ketoconazole or rifampin. The ANOVA model included treatment as the fixed effect and patient as the random effect. The bioequivalence between treatments (romidepsin in the presence of ketoconazole or rifampin and romidepsin alone) was indicated if the 90%CI of the ratio of geometric means between treatments was within the bioequivalence limits of 80%–125% for both AUC_{∞} and C_{max}. For T_{max}, the Wilcoxon signed-rank test, Hodges-Lehmann estimate, and its 90%CI were calculated for the median difference between treatments. Descriptive statistics were used to evaluate safety.

Results
Demographics and Disposition of Study Participants
A total of 15 patients were enrolled in the ketoconazole interaction study. Two patients prematurely discontinued the study, 1 patient because of an AE (pneumonia) and 1 patient who had disease progression. All 15 patients received at least 1 dose of romidepsin and had at least 1 evaluable PK profile, and thus were included in the PK and safety analysis. The mean age of the patients was 61.8 years (range, 38 to 80 years), and the mean weight was 78.4 kg (range, 50.8 to 113.4 kg). The majority of the patients were white (80.0%) and had disease progression (73.3%) and white (80.0%). The percentage of patients with an ECOG score of 0 or 1 was 46.7% and 53.3%, respectively.
A total of 14 patients were enrolled in the rifampin interaction study. One patient withdrew consent and did not complete the study. All 14 patients received at least 1 dose of romidepsin and had at least 1 evaluable PK profile and thus were included in the safety and PK analysis. The mean age of the patients was 63.6 years (range, 35 to 83 years), and the mean weight was 78.2 kg (range, 47.4 to 117.4 kg). The majority of the patients were female (64.3%) and white (92.9%). Half the patients had an ECOG score of 0, with the other half having an ECOG score of 1.

Ketoconazole Study Pharmacokinetics
Mean plasma concentrations of romidepsin were slightly higher after coadministration with ketoconazole than when administered alone as shown in Figure 2. A summary of the romidepsin plasma pharmacokinetic exposure parameters after both treatments is presented in Table 1. Following coadministration with ketoconazole, mean romidepsin $AUC_{\infty}$ and $C_{\text{max}}$ were increased by approximately 25% and 10%, respectively. The ratio of geometric least-squares means (90%CI) for $AUC_{\infty}$ was 124.6% (109.0%–142.2%) and for $C_{\text{max}}$ was 109.5% (94.9%–126.4%). Romidepsin $t_{1/2}$, $CL$, and $V_z$ PK parameters are listed in Table 2. Consistent with the increase in $AUC$, coadministration of romidepsin with ketoconazole decreased romidepsin clearance and volume of distribution. Terminal half-life of romidepsin was comparable for the 2 treatments, and median $T_{\text{max}}$ was similar, with no statistically significant difference between treatments (Table 3).

Rifampin Study Pharmacokinetics
Mean plasma concentrations of romidepsin were unexpectedly higher after coadministration with rifampin than when administered alone, as shown in Figure 3. A summary of the romidepsin plasma pharmacokinetic exposure parameters after both treatments is presented in Table 1. Following coadministration with rifampin, mean romidepsin $AUC_{\infty}$ and $C_{\text{max}}$ were increased by approximately 80% and 60%, respectively. The ratio of geometric least-squares means (90%CI) for $AUC_{\infty}$ was 179.6% (160.5%–201.0%) and for $C_{\text{max}}$ was 159.1% (135.8%–186.5%). Romidepsin $t_{1/2}$, $CL$, and $V_z$ PK parameters are listed in Table 2. The median $T_{\text{max}}$ values were the same when romidepsin was given alone or with rifampin (Table 3). When coadministered with rifampin, romidepsin clearance and volume of distribution were decreased by approximately 44% and 52%, respectively. Terminal half-life of romidepsin was comparable for the 2 treatments.

Safety
The safety profile of romidepsin (8 mg/m$^2$ infused over 4 hours) in the presence of ketoconazole (400 mg oral daily days 4 to 8) was consistent with previously reported safety data. The most frequently reported romidepsin-related treatment-emergent adverse events (TEAEs) were nausea, fatigue, decreased appetite, vomiting, headache, asthenia, and dysgeusia. No deaths occurred during the treatment period. Two patients who discontinued the study early died within 30 days of the last dose of the study drug, 1 patient because of general physical health deterioration after a treatment-emergent serious adverse effect (SAE) of pneumonia and 1 patient because of disease progression.

The safety profile of romidepsin (14 mg/m$^2$ infused over 4 hours) in the presence of rifampin (600 mg oral daily days 4 to 8) was also consistent with previously reported safety data, except for a higher incidence and greater severity of thrombocytopenia. The most frequently reported romidepsin-related TEAEs were nausea, decreased appetite, fatigue, vomiting, diarrhea, thrombocytopenia, anemia, dysgeusia, and hypokalemia. A total of 4 subjects had at least 1 grade 3/4 TEAE of thrombocytopenia that was determined to be related to romidepsin. No TEAE led to romidepsin discontinuation. Two patients had 8 treatment-emergent SAEs of anemia, fatigue, melena, nausea, thrombocytopenia, and vomiting. These SAEs, except melena and anemia, were suspected of being related to romidepsin, whereas 1 case of fatigue was suspected of being related to rifampin therapy.

Discussion
Romidepsin undergoes extensive hepatic metabolism in vitro by CYP enzymes, primarily CYP3A4, with minor contributions from CYP1A1, CYP2B6, and CYP2C19. Therefore, the potential exists for a decrease or increase in systemic exposure to romidepsin when coadministered with CYP3A inducers or inhibitors. A population PK analysis showed that polymorphic variants of CYP3A did not affect the systemic exposure to romidepsin in patients with CTCL or PTCL. Despite these data, a specific drug–drug interaction study was warranted because of the potential loss of efficacy if romidepsin were to be coadministered with a CYP3A inducer. In addition, coadministration with a CYP3A inhibitor could potentially result in higher romidepsin exposure and possible safety issues, as the indicated dose of romidepsin is at the MTD. To investigate CYP3A inhibition, ketoconazole was selected because it is a strong inhibitor of CYP3A known to increase the AUC of CYP3A substrates by $\geq$5-fold. A 400 mg/day dose of ketoconazole for 5 consecutive days was used, as this dose has previously been shown to inhibit the metabolism of CYP3A substrates. Rifampin was selected to evaluate CYP3A induction, as it is a strong inducer known to decrease the AUC of CYP3A substrates by $\geq$80.
Table 1. Statistical Analysis of Romidepsin Plasma Pharmacokinetic Parameters Following a Single Dose With or Without Ketoconazole or Rifampin

| Parameter | Romidepsin (8 mg/m²) + Ketoconazole (400 mg) | Romidepsin (8 mg/m²) | Statistical Comparison |
|-----------|---------------------------------------------|---------------------|-----------------------|
|           | Geometric Least-Squares Mean |                         |                       |
| n Value  |                             | n Value             | Ratio (%) | 90%CI of Ratio (%) |
| Cmax (ng/mL) | 13 | 250.9                         | 15 | 229.0 | 109.5 (94.9–126.4) |
| AUC (ng·h/mL) | 13 | 1140.6                        | 15 | 915.3 | 124.6 (109.0–142.4) |

Geometric Least-Squares Mean

| Parameter | Romidepsin (14 mg/m²) + Rifampin (600 mg) | Romidepsin (14 mg/m²) | Statistical Comparison |
|-----------|--------------------------------------------|---------------------|-----------------------|
|           | Geometric Least-Squares Mean |                         |                       |
| n Value  |                             | n Value             | Ratio (%) | 90%CI of Ratio (%) |
| Cmax (ng/mL) | 13 | 909.0                         | 14 | 571.2 | 159.1 (135.8–186.5) |
| AUC (ng·h/mL) | 13 | 4005.5                        | 14 | 2229.8 | 179.6 (160.5–201.0) |

Romidepsin was given as a single intravenous infusion over 4 hours on days 1 and 8.
Ketoconazole was administered as an oral daily 400-mg dose on days 4 to 8.
Rifampin was given as an oral daily 600-mg dose on days 4 to 8.
A 600 mg/day dose of rifampin for 5 consecutive days has been shown to induce the metabolism of CYP3A substrates. Plasma concentrations of ketoconazole or rifampin were not measured; thus, attainment of steady state was not verified. For the rifampin interaction study, the indicated dose of romidepsin was selected because if an interaction occurred, romidepsin levels were expected to decrease. For the ketoconazole interaction study, a lower dose of romidepsin was selected because if an interaction occurred, romidepsin levels were expected to increase.

The romidepsin coadministered with ketoconazole treatment and the romidepsin-alone treatment were not bioequivalent, as the 90%CI ranges for AUC∞ and Cmax were not contained within the 80%–125% limits. A modest increase in romidepsin exposure was observed with ketoconazole coadministration, indicating that romidepsin is not a sensitive substrate of CYP3A4, which is defined as a >5-fold increase in AUC when coadministered with a known CYP inhibitor. These findings also suggest that other CYPs (CYP1A1, CYP2B6, and CYP2C19) that were shown to be minor contributors to romidepsin metabolism in vitro may contribute more to the in vivo metabolism of romidepsin when the CYP3A pathway is inhibited. The safety profile of romidepsin did not change when coadministered with ketoconazole compared with when given alone in this small study. However, concurrent use of a strong CYP3A inhibitor may modestly increase romidepsin exposure and warrant close patient monitoring for potential toxicity. There were no changes in romidepsin clearance or volume of distribution when coadministered with ketoconazole.

Ketoconazole use has been associated with serious hepatotoxicity. Increases in liver enzymes AST or ALT were not observed in this study, but 1 subject who did not have a history of liver disease had an elevated total bilirubin. Drug interactions of ketoconazole that result in prolongation of the QT interval have been observed. No effect on the QT interval was observed in this study, but 1 subject experienced a treatment-emergent serious AE of atrial fibrillation that was confirmed by ECG assessment.

The romidepsin coadministered with rifampin treatment and the romidepsin-alone treatment were not bioequivalent as the 90%CI ranges for AUC∞ and Cmax were not contained within the 80%–125% limits. Systemic exposure to romidepsin was unexpectedly increased when romidepsin was coadministered with rifampin. Rifampin is an inducer of hepatic CYP enzymes (CYP3A and CYP2C) as well as the efflux transporter P-gp because of its potent activation of the human pregnane X receptor. Rifampin is also an inhibitor of the hepatic uptake transporters OATP1B1 and OATP1B3. OATP1B1 and OATP1B3 are located on the basal lateral membrane and facilitate the uptake of drugs into the liver. Differential effects of rifampin on the pharmacokinetics of romidepsin were observed. Rifampin administration was associated with a modest increase in romidepsin exposure.

### Table 2. Geometric Mean (Geometric CV%) of Romidepsin Plasma Pharmacokinetic Parameters Following a Single Dose With or Without Ketoconazole or Rifampin

| Parameter | Ketoconazole Study | Rifampin Study |
|-----------|-------------------|----------------|
|           | Romidepsin (8 mg/m²) | Romidepsin (14 mg/m²) |
|           | Romidepsin (8 mg/m²) + Ketoconazole (400 mg) | Romidepsin (14 mg/m²) + Rifampin (600 mg) |
| n         | 15 | 14 |
| t1/2 (h)  | 9.7 (26.4) | 9.7 (27.9) |
| CL (L/h)  | 16.9 (77.7) | 11.59 (78.1) |
| Vz (L)    | 236.4 (88.7) | 161.5 (78.6) |

Romidepsin was given as a single intravenous infusion over 4 hours on days 1 and 8. Ketoconazole was administered as an oral daily 400-mg dose on days 4 to 8. Rifampin was administered as an oral daily 600-mg dose on Days 4 to 8.

### Table 3. Statistical Analysis of Romidepsin T_{max} Following a Single Dose With or Without Ketoconazole or Rifampin

| Treatment         | n | Median T_{max} | Median Difference | 90%CI of Median Difference | P Value |
|-------------------|---|----------------|------------------|----------------------------|---------|
| Romidepsin + ketoconazole | 13 | 3.25 | 0 | (−0.485–0.095) | .7422 |
| Romidepsin        | 15 | 3.5  | 0   | 0.0  | 0.0   | 0.0   |
| Romidepsin + rifampin | 13 | 2.985 | 0.15 | (−1.0–1.01) | .7910 |
| Romidepsin        | 14 | 2.985 | 0   | 0.0  | 0.0   | 0.0   |

Romidepsin was given as a single intravenous infusion over 4 hours on days 1 and 8 at a dose of 8 mg/m² (ketoconazole study) and 14 mg/m² (rifampin study). Ketoconazole was administered as an oral daily 400-mg dose on days 4 to 8. Rifampin was administered as an oral daily 600-mg dose on days 4 to 8.

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drugs that are both substrates of CYPs and transporters can occur depending on duration of dosing and timing of administration.26–29 Romidepsin was shown to be primarily metabolized in vitro by CYP3A4, and it is also a substrate of the efflux transporter P-gp. Romidepsin is actively taken up into the liver, but in vitro data indicated that it is not a substrate of the liver uptake transporters OATP1B1 or OATP1B3.9,13 The increase in romidepsin exposure after intravenous administration is likely because of inhibition of active liver uptake. Although in vitro data do not indicate that romidepsin is a substrate of the liver uptake transporters OATP1B1 or OATP1B3, it is possible that rifampin inhibits an undescribed liver transporter. The mechanism by which rifampin increased the concentrations of romidepsin remains uncertain.

The design of the current study was adequate to assess the CYP3A induction potential of rifampin, as the 600-mg daily dose of rifampin has previously been shown to increase clearance of CYP3A substrates.30 The safety profile of romidepsin when coadministered with rifampin was consistent with the profile when romidepsin was given alone. However, thrombocytopenia at a higher incidence and with greater severity was observed following rifampin coadministration. Based on these observations, administration of romidepsin with rifampin should be avoided.

In conclusion, systemic exposure (AUC) to romidepsin was increased modestly (25%) when given with ketoconazole, so toxicity related to increased romidepsin exposure should be monitored when romidepsin is given with strong CYP3A inhibitors. Systemic exposure
to romidepsin was increased by 60% ($C_{\text{max}}$) and 80% (AUC) when given with rifampin; thus, the use of romidepsin with rifampin should be avoided. Also, in this study, because of the unknown mechanism by which romidepsin concentrations are increased, the effect on romidepsin PK due to CYP3A inducers could not be evaluated, and the administration of romidepsin with potent CYP3A inducers should be avoided.

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**Declaration of Conflicting Interests**

E.L. and L.L. are employees of Celgene Corporation. M.P., J.I., C.L., S.F.J., H.W.B., and H.T.A have nothing to disclose.

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