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Effect of Vortioxetine on Cardiac Repolarization in Healthy Adult Male Subjects: Results of a Thorough QT/QTc Study

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ABSTRACT

This double-blind, randomized, placebo- and positive-controlled, parallel-group study evaluated the effect of vortioxetine (Lu AA21004), an investigational multimodal antidepressant, on QT interval in accordance with current guidelines of the International Conference on Harmonisation (ICH-E14). A total of 340 healthy men were randomized to receive 1 of 4 treatments for 14 days: (1) vortioxetine 10 mg once daily (QD), (2) vortioxetine 40 mg QD, (3) placebo QD, or (4) placebo QD on Days 1 through 13 followed by a single dose of moxifloxacin 400 mg (positive control). The primary endpoint was the largest time-matched, baseline-adjusted least-squares (LS) mean difference for the individual-corrected QT interval (QTcNi [linear]) between vortioxetine and placebo. Alternative QT correction formulas (i.e., Fredericia [QTcF], Bazett [QTcB], Framingham [QTcFm], and QTcNi [nonlinear]) were used as secondary endpoints. The upper bound of the 2-sided 90% confidence interval around the LS mean difference from placebo for baseline-adjusted QTcNi (linear), QTcF, QTcB, QTcFm, and QTcNi (nonlinear) did not exceed 10 ms at any time point after multiple doses of vortioxetine 10 mg (therapeutic) or 40 mg (supratherapeutic). Overall, the study results indicate that vortioxetine is unlikely to affect cardiac repolarization in healthy subjects.

Keywords

vortioxetine, Lu AA21004, repolarization, arrhythmia, QT, QTc

Vortioxetine (Lu AA21004; 1-[2-(2,4-dimethyl-phenyl-sulfanyl)-phenyl]-piperazine-hydrobromide)[1] is a novel multimodal antidepressant currently in Phase III development for the treatment of major depressive disorder. It works through a combination of two pharmacologic modes of action: reuptake inhibition and receptor activity. In vitro studies indicate that vortioxetine is a 5-HT_3 and 5-HT_7 receptor antagonist, 5-HT_{1B} receptor partial agonist, 5-HT_{1A} receptor agonist, and inhibitor of the 5-HT transporter.[1] In vivo nonclinical studies have demonstrated that vortioxetine enhances levels of the neurotransmitters serotonin, noradrenaline, dopamine, acetylcholine, and histamine in specific brain areas.[1] Because depression is a multifactorial disorder, agents such as vortioxetine with multiple therapeutic targets may have advantages over "selective agents."[2]

Prolongation of cardiac repolarization is a well-established, although imperfect, biomarker for the proarrhythmic potential of drugs.[3,4] Prolongation of the QT interval may predispose to potentially fatal arrhythmias,[5] with mean placebo-adjusted QTc prolongations of >20 ms considered a definite risk factor for torsade de pointes.[6] Although drug-induced arrhythmia is rare with noncardiovascular drugs, the seriousness of the event warrants evaluation.[7] Several drugs have been removed from the market or given precautionary warnings because they prolong QT and/or have been associated with proarrhythmic events.[3,7,8]

The International Conference on Harmonisation (ICH) formulated guidelines (E14) for performing "thorough QT/QTc" (TQT) studies to detect potential proarrhythmic

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effects of noncardiovascular drugs.[9] TQT studies are designed to determine whether the drug has a threshold pharmacologic effect on cardiac repolarization, as detected by QT/QTc prolongation.[9] The objective of this study was to evaluate the effects of vortioxetine on cardiac repolarization following multiple oral doses for 14 days in accordance with the current ICH-E14 guidelines.[9]

Materials and Methods

Subjects

The study included healthy men (aged 18–45 years) weighing ≥50 kg, whose body mass index ranged from 19 to 32 kg/m^2. Exclusion criteria were: history or manifestations of significant medical disorders such as cardiac disease, substance abuse, HIV infection, cancer, or abdominal, thoracic, or nonperipheral vascular surgery; abnormal screening electrocardiogram (ECG); and family history of long QT syndrome, abnormal blood pressure, or hypersensitivity to study medications or related compounds. Disallowed substances included selective serotonin or serotonin–norepinephrine reuptake inhibitors (SSRIs, SNRIs), monoamine oxidase inhibitors, tobacco (within 6 weeks), and products containing nicotine, caffeine, xanthine, alcohol, grapefruit, Seville-type oranges, or poppy seeds (for 72 hours).

Study Design

This was a Phase I, double-blind, randomized, parallel-group study. Subjects were randomly assigned to 1 of 4 treatment groups and received treatment for 14 days: (1) vortioxetine 10 mg once daily (QD), (2) vortioxetine 40 mg QD, (3) placebo QD, or (4) placebo QD for Days 1 through 13 followed by a single dose of moxifloxacin 400 mg on Day 14.

The parallel, multiple-dose design was chosen because vortioxetine and its metabolites have long half-lives (50–70 hours) and require a 14-day dosing period to reach their steady-state drug concentrations.[7] The study was conducted in men because previous vortioxetine studies had demonstrated limited tolerability in healthy young women at high (≥40 mg/day) multiple doses. The dose of 40 mg was selected as the supratherapeutic dose for vortioxetine because it is considered the highest dose achievable without significant intolerability in men. This dose covers the population and special subpopulation variations (e.g., concomitant use with a cytochrome P450 [CYP] 2D6 inhibitor; subjects who are poor metabolizers of CYP2D6; and subjects with hepatic or renal insufficiency)[9] with respect to the peak exposure of vortioxetine and its metabolites when used at anticipated therapeutic doses up to 20 mg QD.

Moxifloxacin was selected as the positive control because of its well-known prolongation of QT/QTc in humans,[3,7,10] typically ∼10–14 ms after a single 400-mg dose.[11]

The sample-size calculation assumed that the true difference in the largest time-matched mean change from baseline between vortioxetine and placebo groups did not exceed 4 ms, with a common standard deviation of 14 ms. A sample of 85 subjects per arm provides 90% power to show that the upper limit of the 2-sided 90% confidence interval (CI) for the comparison of vortioxetine versus placebo would fall below 10 ms.

The study was conducted in accordance with Good Clinical Practice/ICH guidelines and approved by the independent investigational review board at the study site. All subjects provided written informed consent before any study-related procedures were started.

Assessments

ECG Assessments. Twelve-lead ECGs were obtained digitally (Mortara Instrument H-12) at baseline (Day −1) and on Day 14 of treatment. Triplicate 10-second 12-lead ECGs were extracted from continuous recordings ∼1 minute apart at predose, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, and 23.5 hours postdose on Day 14 for all treatment groups and at corresponding times at baseline (Day −1). The Mortara H-12 Holter monitor records ECG data onto an SD digital flashcard. The flashcard was forwarded to a central ECG laboratory for data analysis. A limited number of blinded qualified readers at the ECG central laboratory were assigned to this study, and a single reader assessed all ECGs for a particular subject. The study was assigned to a single US-certified cardiologist who supervised and reviewed the ECG annotations and qualified reader remarks. For each reading, the best three consecutive complexes in lead II were selected for measurement by the blinded central ECG reader, who analyzed all ECGs for a given subject using a high-resolution manual on-screen caliper method with annotations, according to the central ECG laboratory's standard procedures. In addition, all ECG tracings were interpreted by the cardiologist who was blinded to treatment assignment. Reader variability was assessed by quality assurance specialists who were blinded to all measurements performed in the study.

Because QT is dependent on heart rate, correction is required (QTc) to permit comparison of QT intervals for different heart rates. There is no optimal QT correction method, although several are available.[7] The primary endpoint of the current study was the individual-corrected QTc interval, based on linear regression (QTcNi [linear]) as recommended by the ICH-E14 guideline.[9] The ICH-E14 guideline states that, although the individually corrected methodology is suitable for thorough QT/QTc studies, other corrections also should be used.[9] Thus, the Fredericia (QTcF), Bazett (QTcB), Framingham (QTcFm), and QTcNi (nonlinear) formulas were included

as secondary endpoints. The following formulas for QT correction were used:

- QTcNi (linear) = QT + slope (1-RR), where the slope is obtained from fitting regression line of the form: QT = intercept + slope × RR for each subject
- $QTcF = QT/(RR)^{1/3}$
- $QTcB = QT/(RR)^{1/2}$
- QTcFm = QT + 0.154(1-RR)
- $QTcNi\ (nonlinear) = QT/RR^{\beta}$, where β was obtained from the equation $\log(QT) = \alpha + \beta\log(RR)$ for each subject.

Bioanalytical Methods for Vortioxetine and Metabolites. Blood samples for the determination of plasma concentrations of vortioxetine and its metabolites Lu AA34443 and Lu AA39835 in this study were collected in Vacutainers containing EDTA. Plasma samples were stored at −20°C or lower prior to the analysis at Aptuit Ltd., Edinburgh, Scotland. Plasma samples (250 μL) were prepared by solid phase extraction using Varian SPEC C8 cartridges in a 96-well plate format. Samples were diluted with 760 μL potassium dihydrogen phosphate (0.1 M, pH 3) and 950 μL and transferred to 96-well plates conditioned with 0.5 mL acetonitrile: 30 mM ammonium acetate (90:10, v:v) followed by 0.5 mL 0.1 M potassium dihydrogen phosphate (pH 3). After loading, the plate was washed with 0.5 mL methanol: water (20:80, v:v) and eluted with 0.35 mL of acetonitrile: 30 mM ammonium acetate (90:10, v:v). The eluate was dried under a stream of nitrogen gas at 40°C and reconstituted in 0.2 mL mobile phase.

Aliquots of the extract (5–50 μL) were injected onto a high-performance liquid chromatography tandem mass spectrometry (LC–MS/MS) system. Analytes were separated by an Ionospher 5C (5 μM, 50 × 2.1 mm, i.d.) ion exchange column with a Phenomenex SCX 4 mm × 2 mm guard column. The mobile phase consisted of 70 mM ammonium formate (pH 3) and acetonitrile (12:88). Retention times of the analyses were vortioxetine, 1.2 min; Lu AA34443, 202 min; and Lu AA39835, 1.4 min. Eluting compounds were detected by MRM tandem mass spectrometry (PE-Sciex API4000) with Turboionspray ionization in the positive ion mode. Mass transitions were vortioxetine, m/z 298.954 → 149.942; Lu AA34443, m/z 328.914 → 149.936; and Lu AA39835, m/z 314.858 → 165.873. The internal standards ($^{13}C_6$-labeled analogs of each of the three analytes) were detected at their corresponding mass transitions. The linear range for vortioxetine, Lu AA34443, and Lu AA39835 were 0.08–80 ng/mL (lower limit of quantitation [LLOQ] 0.08 ng/mL), 0.2–200 ng/mL (LLOQ 0.2 ng/mL), and 0.04–40 ng/mL (LLOQ 0.04 ng/mL), respectively. The accuracy and precision for these analytes were within 92.8–102% and 4.41–6.39% C.V. for vortioxetine; 93.7–101% and 3.86–10.4% C.V. for Lu AA34443; and 96.3–101% and 3.66–7.38% C.V. for Lu AA39835.

Bioanalytical Methods for Moxifloxacin. Blood samples for the determination of plasma concentrations of moxifloxacin were collected in Vacutainers containing EDTA. Plasma samples were stored at −20°C or lower prior to the analysis at PPD, Middleton, Wisconsin. An LC–MS/MS method previously published was used for determining moxifloxacin concentrations.[12] The linear range, accuracy, and precision of these analyses were considered adequate to determine the plasma concentrations of the interacting drug and metabolite(s) in these studies.

Pharmacokinetic Assessments. Serial blood samples were collected (at predose on Days 1, 11, 12, 13, and on Day 14 at predose and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 23.5, 36, 48, 72, 96, 120, 144, and 168 hours postdose) to determine plasma concentrations of vortioxetine, its metabolites (Lu AA34443, and Lu AA39835), and moxifloxacin. Whenever an ECG recording coincided with a blood draw, the ECG was performed first.

Plasma pharmacokinetic parameters of vortioxetine, Lu AA34443, Lu AA39835, and moxifloxacin for each treatment group were determined from the concentration–time profiles for subjects in the pharmacokinetic set. Actual sampling times relative to time of study drug administration, rather than scheduled sampling times, were used in all computations involving sampling times. Plasma concentration profiles were used to compute standard pharmacokinetic parameters using noncompartmental methods, including area under the plasma concentration–time curve from time 0 to 24 hours (AUC[0–24]), maximum plasma concentration (C_{max}), minimum plasma concentration during a dose interval (C_{min}), time to C_{max} (t_{max}), elimination half-life ($t_{1/2}$), apparent oral clearance (CL/F), and apparent volume of distribution at steady state (V_{ss}/F).

Safety. Safety was assessed by spontaneous adverse event (AE) recording, clinical laboratory tests, vital signs, physical examinations, and a safety review of ECG data. AEs were identified by the investigator (or designee) and by subject reports and were coded using the Medical Dictionary for Regulatory Activities (MedDRA; Version 11.1). AEs were also assessed for severity and relationship to study drug.

Blood pressure and pulse were measured after 5 minutes of rest in a supine position and after standing for ∼1 minute. Blood pressure and pulse were obtained at screening; check-in (Day −2); predose at baseline (Day −1); predose and 4, 6, and 10 hours postdose on Days 1 through 13; predose on Day 14; and at the final assessment. Additional pulse and blood pressure readings, in the supine position only, were recorded on Day

−1 at 4, 6, and 10 hours postdose, and on Day 14 at 4, 6, 10, 12, and 24 hours postdose, respectively.

Data Analysis and Statistical Methods. The primary endpoint for ECG analysis was the largest time-matched, baseline-adjusted least-squares (LS) mean difference for QTcNi (linear) between vortioxetine and placebo at the post-treatment ECG collection times. Secondary ECG endpoints included the largest time-matched, baseline-adjusted LS mean difference in QTc analysis using alternative correction methods (i.e., QTcF, QTcB, QTcFm, and QTcNi [nonlinear]) and the absolute change from baseline in the QTcNi (linear) interval and intervals using alternative correction methods assessed at prespecified time points on Day 14.

Descriptive statistics were used to summarize ECG variables and change from baseline. Mixed-effects models with treatment, time, and treatment-by-time interaction as fixed effects, baseline QT/QTc as covariate, and repeated measure analysis with AR(1) covariance structure and subject as a random effect were used to model change from baseline in QT/QTc on Day 14. Within the framework of the analyses of variance, LS mean estimates and their corresponding 90% CIs of vortioxetine treatments to placebo difference were calculated at each assessment time on Day 14. To assess the assay sensitivity, 90% CIs for the difference in LS means between moxifloxacin and placebo treatments was also obtained.

An analysis similar to the one described above was also performed on QT/QTc based on the average of three measurements around the time to maximum plasma concentration (t_{max}) for vortioxetine, Lu AA34443, and Lu AA39835; this analysis included only the vortioxetine treatment groups and placebo. In addition, the time-matched, baseline-adjusted LS mean difference in the absolute ECG interval measurements (heart rate; PR and QRS intervals) between the treatments was analyzed.

A categorical analysis of the number of subjects meeting threshold QTc intervals was performed. This included the number of subjects with an absolute QTc interval >450, >480, and >500 ms, and the number with an interval increase from baseline of >30 and >60 ms. The percentage of subjects who showed abnormal T and U waves was also documented.

The concentration–QT relationship was evaluated using a linear regression model that followed the approach described by Florian et al[13] and Garnett et al.[14] This model considers the baseline-adjusted QTcNi (linear) values, denoted by ΔQTcNi as function of vortioxetine concentrations using a linear relationship, that is, $\Delta QTcNi = \text{intercept} + \text{slope} \times \text{concentration}$.

The point estimate of the slope of the linear regression model along with the corresponding 90% upper and lower confidence limits for the slope were generated. Using the estimated linear relationship between ΔQTcNi and the vortioxetine concentrations, ΔQTcNi at the mean maximum concentration values were obtained for both the 10- and 40-mg dose. Descriptive statistics were used to summarize pharmacokinetic parameters and AEs.

Results

Subjects

A total of 606 subjects were screened, 340 of whom satisfied study entrance criteria and were randomized to 1 of the 4 treatment arms (Figure 1); all received the baseline placebo dose at Day −1 and were included in the safety data set. Of these, 328 completed the study. The

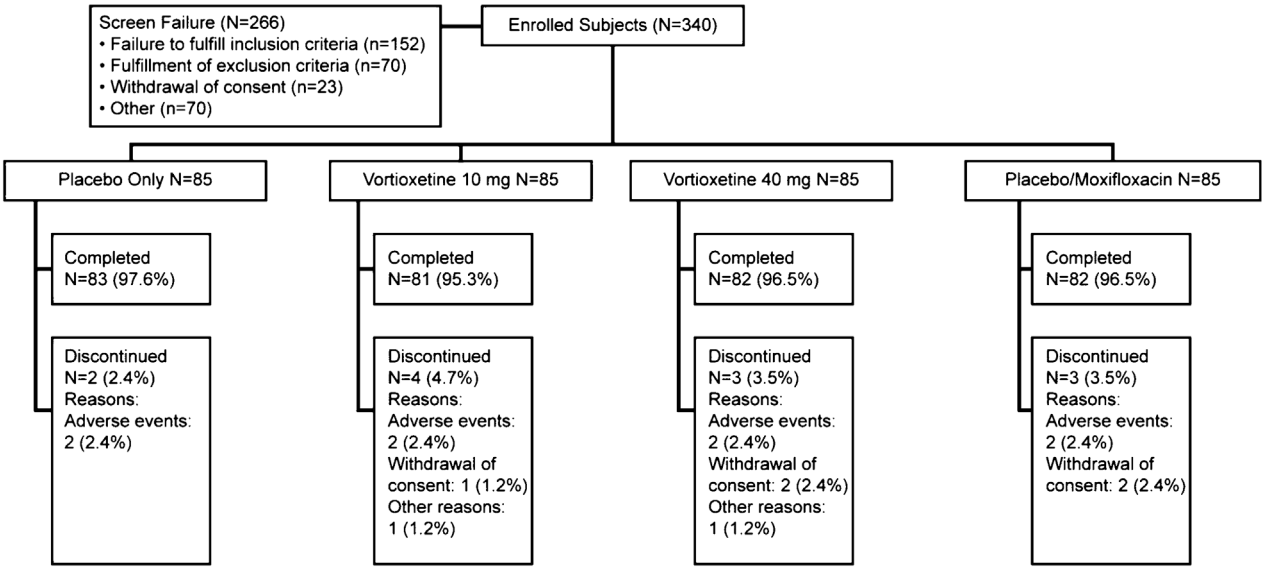

Figure 1. Subject disposition.

primary reasons for premature discontinuation (some subjects had multiple reasons) were AEs (n = 8), withdrawal of consent (n = 5), and other (n = 2). The demographic and baseline characteristics of the study groups were similar (Table 1). The ECG analysis included all subjects who received any treatment and had valid digital ECG data collected before dosing (sufficient to estimate the algebraic constant for calculating the QTcNi [linear] interval at ≥5 time points on Day 14; n = 327).

QTc Analyses

Baseline-adjusted, time-matched differences between active treatment and placebo for QTc intervals using the QTcNi (linear) correction (primary endpoint) are presented in Table 2 and Figure 2. As shown in these graphics, the upper bound of the 2-sided 90% CI around the LS mean difference from placebo for baseline-adjusted QTcNi (linear) did not exceed 10 ms at any time point after administration of vortioxetine 10 mg or 40 mg on Day 14. Values ranged from 3.0 to 4.9 ms for the 10-mg dose and 5.6 to 8.4 ms for the 40-mg dose. The lower bound of the 2-sided 90% CI around the LS mean difference from placebo for baseline-adjusted QTcNi (linear) exceeded 5 ms from 2 to 4 hours postdose after a single 400-mg dose of moxifloxacin.

Analyses using other correction methods (i.e., QTcF, QTcB, QTcFm, and QTcNi [nonlinear]) produced similar results. The upper bound of the 2-sided 90% CI around the LS mean difference from placebo did not exceed 10 ms at any time after administration of vortioxetine 10 or 40 mg on Day 14 for any alternative correction method. Results for QTcF are illustrated in Figure 3.

The point estimate of the slope of the linear model was estimated to be −0.07093 (SE = 0.04727). The slope was a random effect. The corresponding 90% upper and lower confidence limits for the slope were −0.1491 and 0.007233, respectively. The *P*-value for testing a significant linear relationship between the concentrations and ΔQTcNi was $P = .1353$, suggesting that the slope is not different from zero, and thus indicating the lack of a relationship between ΔQTcNi and vortioxetine concentrations (Figure 4). The estimated values of ΔQTcNi at the mean maximum concentration values for the 10- and 40-mg doses of ΔQTcNi were estimated to be 1.530239 and −1.768716, respectively.

The QT correction methods were evaluated by assessing the relationship between uncorrected QT and QTc using each method and the RR interval using the mean sum of squared slopes criteria.[15] No clear correlation was observed for QTcNi (linear), QTcFm, QTcF, or QTcNi (nonlinear) versus RR. The QTcFm method provided the best heart rate correction for all groups except placebo, but differences from the primary endpoint (QTcNi [linear]) were very small. A slight overcorrection was observed with QTcB, an effect that has been well documented for this method.[7]

No positive U waves were reported during the study, and the percentage of subjects with abnormal T-wave morphology was small and equally distributed among treatment groups at baseline and after 14 days of dosing. There were no notable treatment-related differences in the proportion of subjects with predefined outlier events for PR interval, QRS interval, tachycardia, or bradycardia. The variability analysis revealed a high degree of correlation between the original and over-read results with inter-observer mean differences of −0.46 (PR), 1.65 ms (QRS), 2.68 ms (QT), and 0.17 ms (RR).

The categorical analysis showed that no recipient of vortioxetine at either the 10- or 40-mg dose experienced a QTcNi (linear) >450 ms or a change from baseline >60 ms. Isolated changes from baseline >30 ms were observed in 1, 4, 4, and 9 subjects, respectively, in the placebo, vortioxetine 10 mg, vortioxetine 40 mg, and placebo/moxifloxacin groups. According to ICH-E14 analysis criteria,[9] there were no differences between vortioxetine and placebo for categorical events.

Pharmacokinetics

Plasma pharmacokinetic parameters of vortioxetine and its metabolites and moxifloxacin are summarized in Tables 3 and 4. The pharmacokinetic parameters of vortioxetine, its metabolites, and moxifloxacin (i.e.,

Table 1. Demographics and Baseline Characteristics (Mean [SD])

Characteristic	Placebo only (n = 85)	Vortioxetine 10 mg (n = 85)	Vortioxetine 40 mg (n = 85)	Placebo/moxifloxacin (n = 85)
Age (year)	31.7 (7.93)	32.6 (7.69)	33.6 (7.28)	32.6 (8.02)
Weight (kg)	77.8 (9.27)	77.4 (10.50)	83.1 (11.24)	80.7 (10.74)
Height (cm)	172.7 (6.37)	173.1 (7.00)	176.0 (5.95)	174.7 (6.67)
BMI (kg/m^2)	26.1 (2.74)	25.8 (2.90)	26.8 (2.97)	26.4 (2.95)
Race, n (%)				
White	66 (77.6)	71 (83.5)	71 (83.5)	69 (81.2)
Black/AA	19 (22.4)	14 (16.5)	13 (15.3)	16 (18.8)
AIAN	0	0	1 (1.2)	0

AA, African American; AIAN, American Indian or Alaska Native; BMI, body mass index.
Data for age, weight, height, and BMI are presented as mean (SD).

Table 2. Baseline-Adjusted, Time-Matched LS Mean Difference (90% CI) Between Active Treatment and Placebo for QTcNi (Linear)

Time postdose (hour)	Vortioxetine 10 mg QD versus placebo (ms)			Vortioxetine 40 mg QD versus placebo (ms)			Moxifloxacin 400 mg single dose versus placebo (ms)		
	LS mean difference	SE for LS mean difference	90% CI	LS mean difference	SE for LS mean difference	90% CI	LS mean difference	SE for LS mean difference	90% CI[a]
(Predose)	0.4	2.122	−3.1, 3.9	4.9	2.121	1.4, 8.4	1.7	2.128	−1.8, 5.2
1	−0.4	2.123	−3.9, 3.1	4.0	2.122	0.5, 7.5	7.2	2.129	3.7, **10.7**
2	0.7	2.121	−2.8, 4.2	3.8	2.121	0.3, 7.3	10.1	2.128	**6.6**, **13.6**
3	1.0	2.122	−2.5, 4.5	3.8	2.121	0.3, 7.3	11.0	2.128	**7.5**, **14.6**
4	1.4	2.122	−2.1, 4.9	4.4	2.121	0.9, 7.9	10.6	2.128	**7.1**, **14.1**
5	0.5	2.121	−3.0, 4.0	3.1	2.123	−0.4, 6.6	7.6	2.128	4.1, **11.1**
6	0.8	2.122	−2.7, 4.3	3.2	2.121	−0.3, 6.7	7.8	2.128	4.3, **11.3**
7	0.5	2.123	−3.0, 4.0	2.2	2.121	−1.3, 5.7	6.8	2.128	3.3, **10.3**
8	−0.4	2.123	−3.9, 3.1	2.4	2.121	−1.1, 5.9	5.6	2.128	2.1, 9.1
9	0	2.123	−3.5, 3.5	2.1	2.121	−1.4, 5.6	6.1	2.128	2.6, 9.6
10	0.3	2.122	−3.2, 3.8	3.8	2.121	0.3, 7.3	7.9	2.128	4.4, **11.4**
12	1.3	2.124	−2.2, 4.8	4.4	2.121	0.9, 7.9	6.0	2.128	2.5, 9.5
16	−0.3	2.127	−3.8, 3.2	3.3	2.123	−0.2, 6.8	6.2	2.129	2.7, 9.7
23.5	−0.6	2.126	−4.1, 3.0	4.4	2.121	0.9, 7.9	5.6	2.128	2.1, 9.1

LS, least-squares; QD, once daily.
[a]Numbers in boldface type denote values ≥5 for the lower bound of the 2-sided 90% CI or ≥10 for the upper bound.

t_{max}, C_{max}, and area under the plasma concentration–time curve over the dosing interval [AUC(0–24)]) were consistent with those observed in a previous study.[16]

Effect of Vortioxetine on Heart Rate

The mean time-matched, baseline-adjusted change in heart rate observed on Day 14 in the placebo and moxifloxacin 400-mg treatment groups ranged from 5.5 to 8.9 beats per minute and 7.5 to 11.1 beats per minute, respectively (Figure 5). The mean time-matched, baseline-adjusted changes in heart rate in the vortioxetine 10- and 40-mg groups ranged from 2.9 to 5.6 beats per minute and from 1.3 to 5.1 beats per minute, respectively. The mean changes in heart rate in subjects who received vortioxetine 10 or 40 mg were not considered clinically significant. There was no correlation between baseline-adjusted, time-matched changes in heart rate and plasma concentrations of vortioxetine or its metabolites.

Adverse Events

The overall incidences of AEs were 68.2%, 70.6%, 74.1%, and 67.1% for placebo, vortioxetine 10 mg, vortioxetine 40 mg, and placebo/moxifloxacin, respectively. AEs that occurred in >2% of subjects are listed in Table 5. Two subjects in each treatment group withdrew because of AEs. The most common AE was contact dermatitis, relating to application of the ECG electrodes. AEs that occurred in ≥5% of subjects who received vortioxetine (either dose), and were twice as common as in the placebo group, were nausea, diarrhea, headache, constipation, and pruritus. Most AEs were mild or moderate in severity. No deaths or other serious AEs were reported, and there were no clinically significant changes in serum chemistry, hematology, urinalysis values, vital signs, physical findings, or ECGs.

Discussion

The ICH-E14 guidelines provide recommendations for conducting TQT studies with the objective of identifying drugs that require further assessment.[7] The goal is to prevent rare but serious AEs (e.g., sudden cardiac death, torsade de pointes) associated with prolonged cardiac repolarization. This is established by excluding the possibility that the drug prolongs the QTc ≥10 ms at the 1-sided upper bound 95% CI (which corresponds to upper confidence limit of a 2-sided 90% CI).[7]

The current study was designed in accordance with ICH-E14 guidelines. A parallel design is appropriate because vortioxetine and its metabolites have long half-lives (>50–70 hours) and require a 14-day dosing period to reach steady-state drug concentrations.[7] Moxifloxacin was chosen as the positive control because of its well-characterized effect on cardiac repolarization and its wide use as the positive control in TQT studies.[3] The moxifloxacin-induced prolongation of QT observed in the present study (LS mean difference vs. placebo of 10–11 ms at specified time points) is consistent with that in other studies, thereby validating the study procedure.[11,17,18]

The present study evaluated two doses of vortioxetine: 10 mg (potentially therapeutic dose) and 40 mg

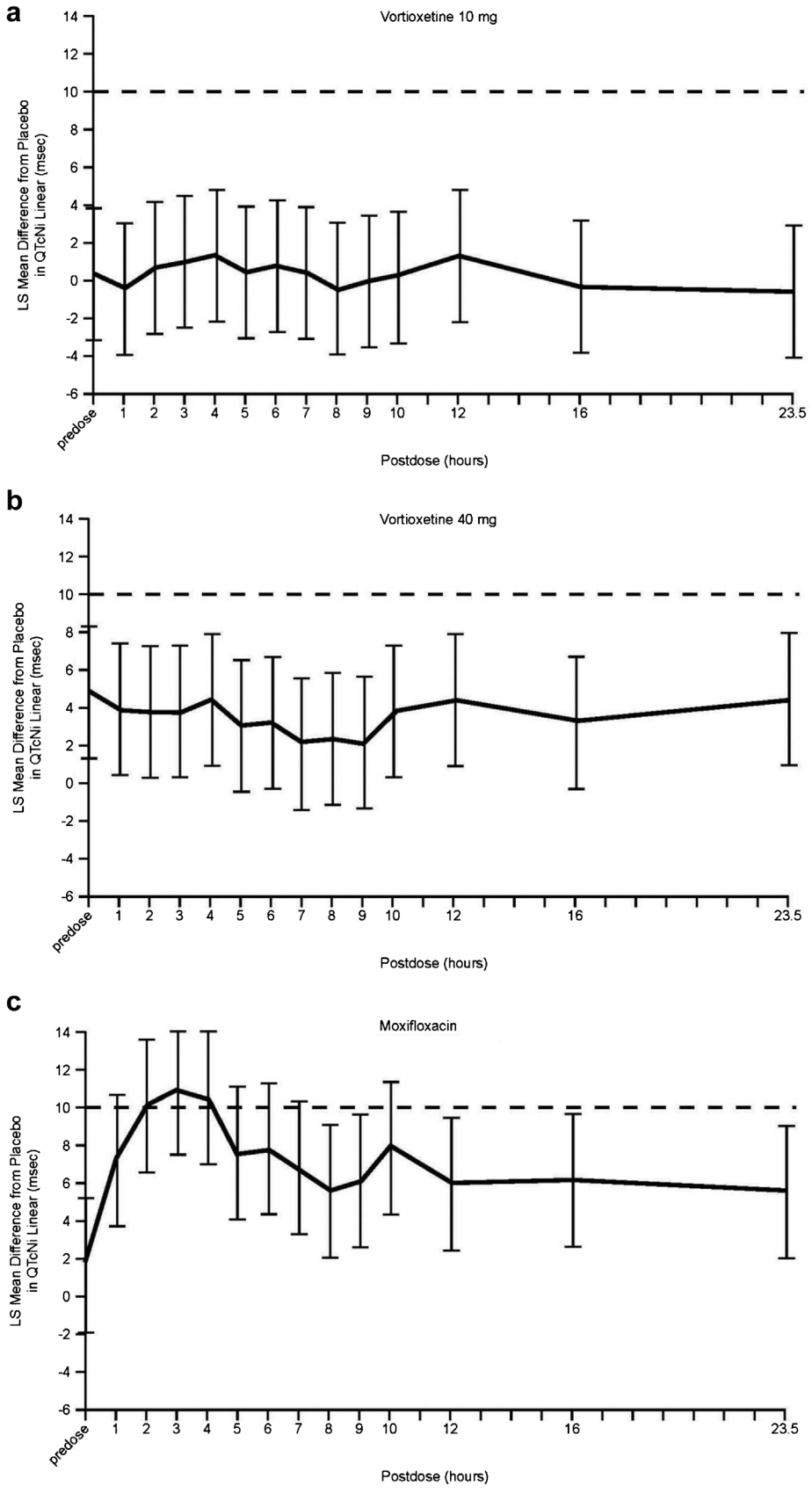

Figure 2. Least-squares (LS) mean difference (90% CI) from placebo in QTcNi (linear) over 24 hours on Day 14.

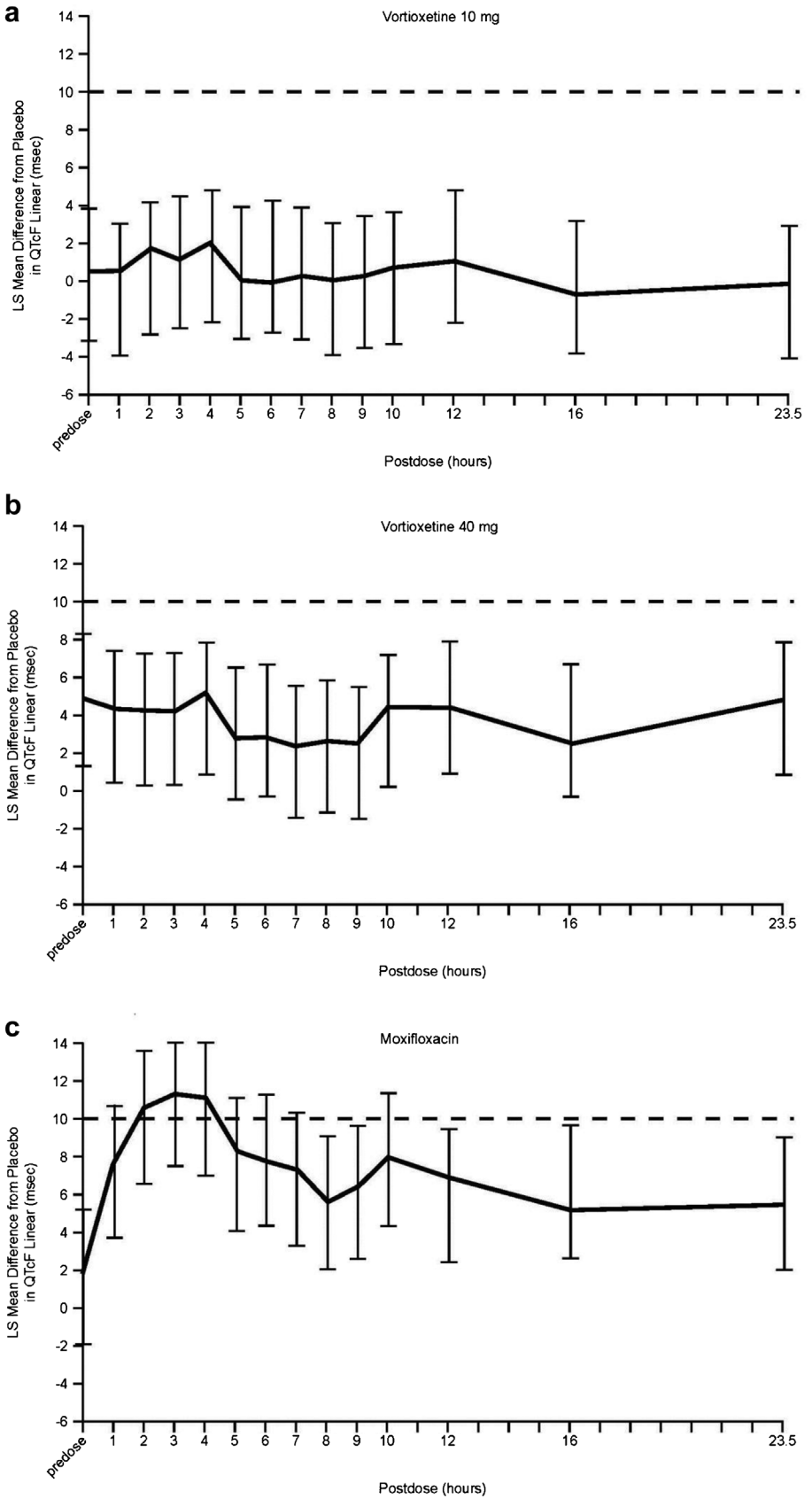

Figure 3. Least-squares (LS) mean difference (90% CI) from placebo in QTcF over 24 hours on Day 14.

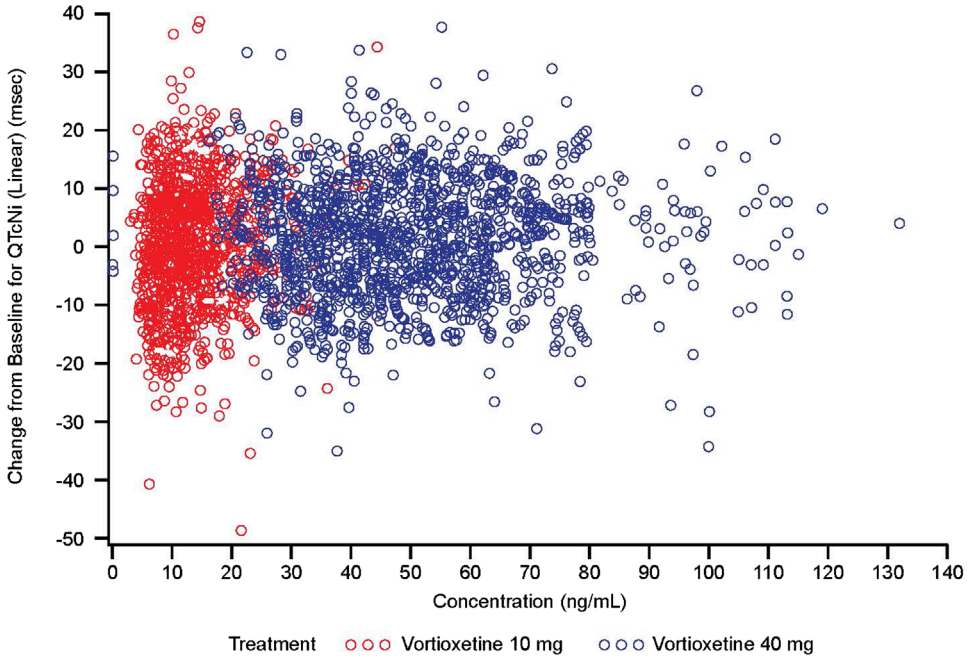

Figure 4. Relationship between vortioxetine plasma concentrations and QTcNi (linear) over time.

Table 3. Plasma Pharmacokinetic Parameters of Vortioxetine and its Metabolites

	Vortioxetine 10 mg (n = 82)		Vortioxetine 40 mg (n = 82)	
Parameter	No. of subjects[a]	Arithmetic mean (% CV)	No. of subjects[a]	Arithmetic mean (% CV)
Vortioxetine				
AUC(0–24) (ng hr/mL)	82	316.85 (46.04)	82	1177.80 (33.65)
C_{max} (ng/mL)	82	16.84 (44.36)	82	63.35 (35.19)
C_{min} (ng/mL)	82	10.23 (47.20)	82	37.13 (38.25)
t_{max}[b] (hr)	82	8.10 (0, 16.10)	82	8.10 (4.10, 23.60)
$t_{1/2}$ (hr)	77	58.58 (47.93)	82	56.41 (36.19)
CL/F (L/hr)	82	37.42 (40.52)	82	37.94 (33.97)
Vd(area) (L)	80	768.98 (45.19)	82	803.24 (38.00)
Lu AA34443				
AUC(0–24) (ng hr/mL)	82	290.73 (36.84)	82	1180.80 (27.11)
C_{max} (ng/mL)	82	17.86 (43.70)	82	73.27 (32.57)
C_{min} (ng/mL)	82	8.32 (35.17)	82	33.06 (28.64)
t_{max}[b] (hr)	82	5.10 (3.10, 16.10)	82	4.10 (3.10, 8.10)
$t_{1/2}$ (hr)	78	60.83 (43.63)	82	56.13 (33.90)
Lu AA39835				
AUC(0–24) (ng hr/mL)	82	10.29 (29.66)	82	47.12 (26.08)
C_{max} (ng/mL)	82	0.53 (33.98)	82	2.46 (27.09)
C_{min} (ng/mL)	82	0.36 (27.86)	82	1.56 (30.99)
t_{max}[b] (hr)	82	7.10 (0.00, 16.10)	82	7.10 (3.10, 12.10)
$t_{1/2}$ (hr)	76	64.71 (40.94)	82	61.85 (36.85)

AUC(0–24), area under the plasma concentration–time curve from time 0 to 24 hours; CL/F, apparent oral clearance; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration during a dose interval; CV, coefficient of variation; t_{max}, time to C_{max}; $t_{1/2}$, elimination half-life; Vd (area), volume of distribution based on area.

[a]Several subjects did not have a complete dataset for specific pharmacokinetic parameters.

[b]Median (range).

Table 4. Pharmacokinetics of Moxifloxacin

Parameter	Placebo/moxifloxacin (n = 82)	
	No. of subjects[a]	Arithmetic mean (% CV)
AUC(0–24) (ng hr/mL)	82	20,716 (14)
C_{max} (ng/mL)	82	1,703 (16)
t_{max}[a] (hr)	82	2.10 (1.0, 5.10)
$t_{1/2}$ (hr)	82	16.69 (26.08)

CV, coefficient of variation; AUC(0–24), area under the plasma concentration–time curve from time 0 to 24 hours; C_{max}, maximum plasma concentration; t_{max}, time to C_{max}; $t_{1/2}$, elimination half-life.
[a]Median (range).

(supratherapeutic dose). This practice is common in TQT studies and permits a reasonable approximation of the higher drug exposure expected in certain clinical situations (e.g., concomitant use with a CYP2D6 inhibitor; subjects who are poor metabolizers of CYP2D6; and subjects with hepatic or renal insufficiency).[10] Use of a supratherapeutic dose is also noted in the ICH-E14 guidelines, which emphasize the importance of characterizing concentration–response relationships for QT/QTc prolongations.[9]

These findings indicate that once-daily vortioxetine (10 and 40 mg) for 14 days has no clinically significant effect on cardiac repolarization in healthy individuals. The largest LS mean difference for QTcNi (linear) between vortioxetine and placebo was <5 ms at all time points, and the upper bound of the 2-sided 90% CI did not exceed 10 ms at any point for either dose. No drug concentration–QTc relationship was observed, an important confirmatory finding for regulatory review.[13] Although no effect was observed in healthy individuals, these results should not be generalized to other patient populations not evaluated in this study, such as women, patients with heart disease, and certain ethnic/racial groups (e.g., East and South Asian populations).

There are several ways to perform heart rate corrections to the QT interval, and no method has been accepted universally.[3,7,19] QTcF and QTcNi (linear) are considered effective for evaluating drugs that have no clear effect on heart rate. However, as consensus is lacking on the most appropriate correction method, studies should use multiple methods.[9] The consistent results across the various correction methods provide further confidence in the robustness of the results.

Categorical analysis is important because of the consensus that increases of >60 ms from baseline should raise concern.[20] ICH-E14 guidelines state that all subjects with a QTc interval ≥450 ms and those with prolongations ≥30 ms must be reported as outliers.[9] The categorical QTcNi (linear) analysis showed that no subject who received vortioxetine had a QTc interval ≥450 ms or a prolongation ≥60 ms.

Pharmacokinetic results from this study of vortioxetine, its metabolites (Lu AA34443 and Lu AA39835), and moxifloxacin were consistent with those observed in previous studies; this indicates that sufficient levels of drug exposure were achieved.

This study demonstrates that vortioxetine at clinically relevant doses does not prolong the QTc interval and is unlikely to affect cardiac repolarization in healthy men.

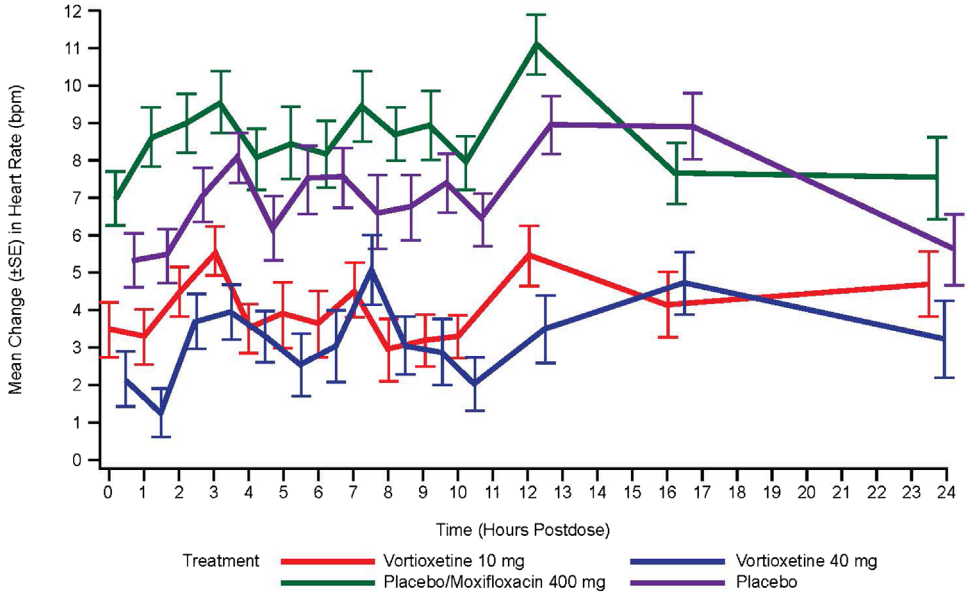

Figure 5. Change from baseline in heart rate versus time.

Table 5. Treatment-Emergent Adverse Events (≥2% in Any Group)

Event, n (%)	Placebo only (n = 85)	Vortioxetine 10 mg (n = 85)	Vortioxetine 40 mg (n = 85)	Placebo/moxifloxacin (n = 85)
Any TEAE	58 (68.2)	60 (70.6)	63 (74.1)	57 (67.1)
Contact dermatitis	39 (45.9)	38 (44.7)	33 (38.8)	36 (42.4)
Headache	5 (5.9)	9 (10.6)	12 (14.1)	5 (5.9)
Diarrhea	4 (4.7)	7 (8.2)	12 (14.1)	4 (4.7)
Nausea	0	9 (10.6)	14 (16.5)	4 (4.7)
Dizziness	5 (5.9)	4 (4.7)	6 (7.1)	3 (3.5)
Increased blood pressure	4 (4.7)	4 (4.7)	6 (7.1)	3 (3.5)
Sinus tachycardia	4 (4.7)	3 (3.5)	5 (5.9)	1 (1.2)
Lip dry	5 (5.9)	0	0	4 (4.7)
Tachycardia	1 (1.2)	3 (3.5)	2 (2.4)	2 (2.4)
Pruritus	2 (2.4)	1 (1.2)	5 (5.9)	0
Constipation	0	0	5 (5.9)	3 (3.5)
Abdominal pain	1 (1.2)	1 (1.2)	4 (4.7)	1 (1.2)
Dyspepsia	0	2 (2.4)	4 (4.7)	1 (1.2)

TEAE, treatment-emergent adverse event.

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