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Evaluation of Eluxadoline Effect on Cardiac Repolarization

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Abstract

This study evaluated the effects of eluxadoline, a mixed μ-opioid receptor (OR) and κ-OR agonist and δ-OR antagonist, on cardiac repolarization. This evaluator-blinded, placebo- and positive-controlled, 4-period crossover study randomized healthy men and women to single oral doses of eluxadoline (therapeutic dose 100 mg or supratherapeutic dose 1000 mg), moxifloxacin 400 mg, or placebo. QT data were corrected using individual custom correction (QTcI). The primary endpoint was the change from baseline in QTcI intervals ($\triangle$QTcI) between eluxadoline and placebo ($\triangle\triangle$QTcI). An upper bound of the 95% confidence interval around $\triangle\triangle$QTcI of 10 milliseconds was considered clinically significant. Concentration–QTc data were analyzed using a repeated-measures, mixed-effects linear model. Sixty-four volunteers were treated, and 58 completed the study. Assay sensitivity was demonstrated with moxifloxacin (noted by $\triangle\triangle$QTcI of 11.94 milliseconds). The maximum $\triangle\triangle$QTcI for eluxadoline 1000 mg was 4.10 milliseconds 1 hour postdose (1-sided 95% upper confidence bound, 5.81 milliseconds), and for eluxadoline 100 mg was 1.20 milliseconds at 0.5 hours postdose (1-sided 95% upper confidence bound, 2.91 milliseconds). Primary $\triangle\triangle$QTcI results were confirmed using Fridericia's formula for QTc. Categorical, morphological, and concentration–QTc analyses were consistent with the primary and secondary findings. There were no significant gender effects on $\triangle\triangle$QTcI values. The most common adverse events were contact dermatitis and nausea (12.5% each) and dizziness (10.9%); adverse events were more frequent in the eluxadoline 1000 mg group. In conclusion, eluxadoline, at therapeutic or supratherapeutic doses, did not significantly prolong QT intervals, and was safe and generally well tolerated in this study population.

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder characterized by symptoms of abdominal discomfort or pain associated with altered bowel habits.[1] IBS is reported in approximately 5% to 15% of adults worldwide,[2–4] and women are reported to be at greater risk of IBS compared with men.[3] IBS can be classified into 4 main subtypes: IBS with chronic or recurrent diarrhea (IBS-D), IBS with constipation, IBS with mixed patterns of diarrhea and constipation, or unspecified IBS.[1]

Eluxadoline (Allergan plc, Madison, New Jersey) is a locally acting mixed μ-opioid receptor (OR) and κ-OR agonist and δ-OR antagonist,[5] approved by the US Food and Drug Administration (FDA) for the treatment of IBS-D in adults. The structure–activity relationship of eluxadoline has been previously reported, with preferential binding affinities at the μ- and δ-ORs and reduced binding affinity for the κ-OR.[6]

Eluxadoline exerts gastrointestinal transit activity through its activity at κ-, μ-, and δ-ORs expressed in the gastrointestinal tract, which regulate muscle tone, motility, and secretions.[7] The δ-OR antagonist activ-

ity of eluxadoline may mitigate the constipating effect of unopposed agonism of μ-ORs,[8,9] as may be seen with loperamide, an antidiarrheal agent that has historically been associated with the undesirable side effect of constipation.[10,11] In addition, simultaneous μ-/δ-OR binding may reduce other class effects of

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μ-OR agonists,[5] including the potential for abuse. In human abuse liability studies, eluxadoline has been demonstrated to have lower oral or intranasal abuse potential in humans than does the centrally acting μ-OR agonist oxycodone.[12]

Pharmacokinetic (PK) data from phase 1 studies in healthy adults showed peak plasma concentrations of eluxadoline at 1 to 2 hours following single-dose oral administration with low systemic exposure, and little to no accumulation observed.[13,14] The low systemic absorption of eluxadoline is due to both poor absorption and moderate hepatic first-pass extraction, and results in a high degree of variability in PK parameters.[14] OATP1B1-mediated hepatic uptake has been suggested as the primary mode of clearance of eluxadoline,[14] and although the metabolic pathways of eluxadoline remain unclear, caution is recommended with coadministration of strong cytochrome P450 (CYP) inhibitors (ie, ciprofloxacin, fluconazole, gemfibrozil).[15] Eluxadoline has demonstrated reduced clearance and increased exposure in patients with hepatic impairment[16] and is contraindicated in this patient group.

The efficacy, safety, and tolerability of eluxadoline have been previously reported in a phase 2 dose-ranging study[17,18] and in two large phase 3 trials,[18–20] and although infrequent, the most common adverse events (AEs) in these studies were constipation and nausea. Serious AEs of pancreatitis and sphincter of Oddi spasm events were infrequently reported in phase 2 and phase 3 clinical trials of eluxadoline.[18] Eluxadoline is contraindicated in patients without a gallbladder due to increased risk of sphincter of Oddi spasm, possibly due to increased sphincter of Oddi tone from μ-OR agonism, although the underlying mechanism for this remains unclear.[18] Eluxadoline was determined to have no effect on potassium channel currents in cells expressing the human *ether-à-go-go*-related gene (hERG): at concentrations of 10^{-7} M, 3×10^{-7} M, and 3×10^{-6} M, decreases in the rapidly activating delayed rectifier potassium channel (I_{Kr}) of 6.0% vs 3.8% with solvent, 12.8% vs 8.8% with solvent, and 17.5% vs 10.0% with solvent, respectively, were observed as measured by the whole-cell voltage clamp technique (unpublished observation). The present study was conducted to evaluate whether therapeutic and supratherapeutic plasma levels of eluxadoline had any relevant effects on cardiac repolarization as determined by measurement of the QT interval on surface electrocardiograms (ECGs), as recommended by regulatory guidance.

Methods

The study protocol was reviewed and approved by the investigator's institutional review board, IntegReview,

Ltd (Austin, Texas). The study was carried out at PPD Phase I Clinic, Austin, Texas. All participants provided written, informed consent.

Study Objectives

The primary objective of this study was to assess the effects of eluxadoline at therapeutic and supratherapeutic doses on QT/corrected QT (QTc) intervals and ECG morphology in healthy male and female adult volunteers. Secondary objectives were to evaluate eluxadoline PK parameters to determine the relationship between eluxadoline plasma concentration and QT/QTc interval changes, and to assess the safety and tolerability of eluxadoline at a projected efficacious dose and a supratherapeutic dose.

Study Design

In accordance with regulatory guidance,[21] this was a randomized, evaluator-blinded, placebo- and positive-controlled, 4-period crossover study. A screening visit occurred up to 28 days before the first treatment. During the treatment phase, volunteers were randomly assigned to 1 of 4 treatment sequences, each consisting of 4 treatment periods (periods 1–4), with each period consisting of a single oral dose of 1 of the following treatments: eluxadoline 100 mg (maximum therapeutic dose in phase 3 studies[19]), eluxadoline 1000 mg (supratherapeutic dose; maximum plasma concentration [C_{max}] $\sim$8 times that of the therapeutic dose), positive-control moxifloxacin 400 mg, or placebo (Supplementary Table S1). The sequence of treatments that volunteers received was determined by a computer-generated randomization schedule, with a minimum 5-day washout interval between each period. The inclusion of the positive-control moxifloxacin 400 mg was designed to establish assay sensitivity in the study, as moxifloxacin is known to prolong the QT/QTc interval above 5 milliseconds (ie, an effect close to that representing historical regulatory concern). Single-dose administration of eluxadoline was selected based on the lack of accumulation of eluxadoline with repeat dosing, as agreed upon with the FDA. In accordance with FDA recommendation, volunteers were treated in the fasted state based on a phase 1 study of eluxadoline, which showed approximately 3-fold higher C_{max} in fasted volunteers compared with fed volunteers.[22] The posttreatment phase included an end-of-study visit 5 to 7 days following administration of the last dose of study drug. Total study duration was approximately 8 weeks from the beginning of screening to the completion of the posttreatment phase.

Inclusion and Exclusion Criteria

Key eligibility criteria were: men or women aged 18 to 55 years; if female participant, postmenopausal,

surgically sterilized, or using contraception, with negative plasma or serum beta human chorionic gonadotropin test; body mass index 18.0 to 32.0 kg/m^2 and body weight ≥ 50 kg; systolic blood pressure 90 to 140 mm Hg and diastolic blood pressure ≤ 90 mm Hg; and conventional 12-lead ECG recording in triplicate at screening and at day -2 of period 1 consistent with normal cardiac conduction and function, including normal sinus rhythm with heart rate 45 to 100 bpm, QT Fridericia correction (QTcF) 350 to 450 milliseconds for men and 350 to 470 milliseconds for women, QRS interval <120 milliseconds, PR interval ≤ 210 milliseconds, ECG morphology consistent with healthy ventricular conduction and normal rhythm, with QT measurement, and fewer than 30 premature ventricular beats per hour. Exclusion criteria included: tobacco use within the past 6 months; a history of or additional risk factors for torsades de pointes or the diagnosis or a family history of short or long QT syndrome; clinically significant abnormal values for clinical chemistry or hematology; alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin $>1.5 \times$ the upper limit of normal (ULN); a history of drug or alcohol abuse; and a history of sphincter of Oddi dysfunction. Study withdrawal was to be considered in the event of any of the following in any volunteer: ALT or AST $>8 \times$ ULN; ALT or AST $>5 \times$ ULN for more than 2 weeks; ALT or AST $>3 \times$ ULN and total bilirubin $>2 \times$ ULN or international normalized ratio >1.5; ALT or AST $>3 \times$ ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($>5\%$).

Pharmacodynamic Assessments

ECGs were acquired from a 12-lead Holter recorder using an ambulatory digital ECG recorder (H-12+[TM], Mortara Instrument, Inc., Milwaukee, Wisconsin) with a digital flashcard. Data from the digital flashcard were transmitted to the central ECG laboratory using the HolterGateway[TM] system (BioTelemetry, Inc., Rockville, Maryland). ECG recordings were collected in a quiet, supervised setting. Volunteers rested in a supine position for at least 20 minutes before each ECG time point, and during each of the 10-minute ECG extraction windows that immediately preceded the nominal time points where ECGs were extracted in triplicate. On day -1 of period 1 and on day 1 of all treatment periods, an ECG recorder was placed on all volunteers 1.5 hours before their assigned dosing time (25.5 hours before the first dose) and allowed to run until completion (24 hours and 22.5 hours, respectively). ECG extraction time points on day -1 and on day 1 occurred at 1, 0.5, and 0.25 hours before dosing, and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 15, 18, and 22.5 hours after dosing. Baseline values for each treatment period were obtained from the average of the 3 predose recordings (triplicate; total of 9 recordings).

Central ECG laboratory-certified cardiologists were blinded to treatment allocation, dosing time, and volunteer identification. Ten-second ECG tracings were extracted from continuous data in triplicate at the predefined time points, and for each individual volunteer the same cardiologist read the ECGs in all 4 treatment periods and on day -1. Following each ECG extraction, single QTc values were determined by averaging triplicate ECG recordings taken at each time point. The average of the QTc values at each of the predefined time points was used for QTc study endpoint analyses in this treatment period. QTc values obtained on day 1 corresponded to the time of PK sampling to facilitate determination of the relationship between eluxadoline plasma concentration and QT/QTc interval changes. Heart rate, along with QT, RR, QRS, and PR intervals, was measured at baseline and during treatment using the superimposed representative complex method for manual overread in a blinded fashion. QTc was calculated using manually overread individual QT and RR values. QT data were corrected for heart rate using individual custom correction QTcI ($QTcI = QT/RR^{(b)}$) and Fridericia correction ($QTcF = QT/RR^{(1/3)}$) methods. For QTcI, all pairs of QT and RR interval data collected on day -2 of period 1 (baseline) for each volunteer were analyzed using the following linear regression: $\log (QT) = \log (a) + b^*\log (RR)$. The resulting slope ($b_i$) for the i-th volunteer was used to calculate the individual correction for that volunteer.

PK and Safety Assessments

The analytic methodology has previously been published.[14] Briefly, venous blood samples were collected for PK analysis in each treatment period within 0.75 hours predose, and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 15, 18, 22.5, 24, 36, and 48 hours after dosing. PK blood samples containing dipotassium ethylenediaminetetraacetic acid for analysis of plasma concentrations of eluxadoline were collected immediately after the 10-minute ECG extraction window at each predefined time point; plasma was separated and stored at $-20°C$ or colder and analyzed within 350 days. PK analyses used noncompartmental methods, with validated, specific, and sensitive liquid chromatography–tandem mass spectrometry method (LC-MS/MS). PK samples collected for moxifloxacin and placebo were not analyzed. Samples were fortified with an internal standard solution of JNJ-27018966-^{13}C,d$_3$. Analytes were isolated from plasma using acetonitrile precipitation. Extracts were evaporated under a nitrogen stream at approximately 45°C, and the remaining residue was reconstituted with a 20:80 ratio of mobile phase B (99.8:0.2:0.1 methanol/5.0 mM ammonium

acetate/formic acid, v/v/v) / mobile phase A (94.8:5:0.2:0.1 water/methanol/5.0 M ammonium acetate/formic acid, v/v/v/v) v/v, both at room temperature prior to the assay. A validated chromatography column (Phenomenex 5 μm Luna$^{\circledR}$ Phenyl-Hexyl, 2.0 mm × 50 mm, maintained at room temperature) was used for analysis. Samples were injected into a Sciex API 4000 triple quadrupole LC-/MS/MS in electrospray positive ion multiple-reaction monitoring mode (calibration curve range, 0.1–10.0 ng/mL). The peak area ratio of the m/z 574 eluxadoline ion was quantitated against the peak area of the internal standard using a linear, 1/concentration weighted, least squares regression algorithm. The lower limit of quantitation was 0.100 ng/mL. The quality control concentrations were 0.3, 0.8, 3.0, 12.5, and 75.0 ng/mL. During validation of the assay, intra-assay precision of the quality controls ranged from 1.29% to 10.0% and interassay precision ranged from 2.24% to 10.1%. During the analysis of eluxadoline, intra-assay precision was not calculated, as the quality controls per batch were analyzed in duplicate. Interassay precision of the quality controls ranged from 3.14% to 6.18%. Safety was assessed throughout the study and included incidence and type of AEs, coded using the Medical Dictionary for Regulatory Activities, version 11.0; changes in clinical laboratory tests; vital sign measurements; 12-lead ECGs; and physical examinations.

Pharmacodynamic Analysis

The primary variable was the change from baseline in QTcI intervals (ΔQTcI) and the difference in mean ΔQTcI between each dose of eluxadoline and placebo (ΔΔQTcI) at each time point of measurement. The primary QT correction method was QTcI, and QTcF was considered secondary. Categorical analyses for each QTc interval for each eluxadoline dose group and placebo group were presented as the number and percentage of volunteers meeting the following criteria at each scheduled ECG time point: absolute QTc interval prolongations (QTc interval >450, >480, and >500 milliseconds); ΔQTc interval (interval increases of >30 and >60 milliseconds); QRS interval (>120 milliseconds and 25% increase from baseline); and PR interval (>200 milliseconds and 25% increase from baseline). New ECG morphologies not present at baseline were summarized by treatment group.

Statistical Analysis of QT/QTc

As previously noted, the threshold level of regulatory concern for delaying cardiac repolarization is a prolongation of the QT/QTc interval of around 5 milliseconds, as evidenced by an upper bound of the 95% confidence interval around ΔΔQTc of 10 milliseconds. Per FDA guidance, a negative QT/QTc study is therefore one in which the upper bound of the 95% 1-sided confidence interval for the largest ΔΔQTc excludes 10 milliseconds, as this provides assurance that the mean effect of the drug is not greater than around 5 milliseconds. The primary hypothesis of this study was that the largest ΔΔQTcI for each eluxadoline dose was 10 milliseconds, vs the alternative hypothesis that it was <10 milliseconds.

Based on an assumed intervolunteer standard deviation (using ΔQTcI) for change from baseline in QTc of 10 milliseconds, it was determined that 52 volunteers with analyses at each of 12 time points would provide 90% power to reject the null hypothesis and conclude a negative study if the true increase in ΔQTcI over placebo was no more than 2 milliseconds. The primary hypothesis was tested using a 1-sided 95% upper confidence bound placed on the mean ΔΔQTcI for each eluxadoline dose. If each of the upper confidence bounds was <10 milliseconds, the null hypothesis was rejected and the study was deemed negative. The primary analysis was a repeated-measures, mixed-effects linear model that included the effects of treatment sequence, volunteers within treatment sequence, study drug, study period, ECG time point, study drug-by-ECG time point interaction, and period-specific pre-dose baseline QTcI. The secondary QTc endpoint QTcF was analyzed in the same manner as QTcI. Gender interaction was analyzed by testing for a differential effect of eluxadoline on QTcI intervals between genders. To describe the concentration–QTc relationship, a linear mixed-effects model was fit to the ΔΔQTcI data from both doses of eluxadoline with concentration as a predictor and volunteer as a random effect. The predicted values of ΔΔQTcI (along with upper 95% confidence bounds) were estimated at relevant concentrations. For the regression analysis of placebo-subtracted changes from baseline in QTcI vs $\log_{10}$ eluxadoline plasma concentration, a nonlinear quadratic model was used.

All statistical analyses were performed using computer software (SAS$^{\circledR}$, version 9.1.3; SAS Institute Inc., Cary, North Carolina).

Results

Characteristics and Baseline Demographics

A total of 64 volunteers (35 women and 29 men) were enrolled and assigned to treatment (Table 1). Overall, the mean age was 33.8 years, mean volunteer weight was 75.04 kg, and mean body mass index was 26.08 kg/m^2. Fifty-eight volunteers completed the study; of the 6 who did not complete the study, 3 discontinued because of AEs, 2 chose to discontinue, and 1 was discontinued by the sponsor after experiencing premature ventricular contractions following dosing with

Table 1. Demographics and Baseline Characteristics

	Treatment Sequence[a]				
	ACDB (n = 16)	BDCA (n = 16)	CBAD (n = 16)	DABC (n = 16)	Total (N = 64)
Mean age, y (SD), [range]	31.6 (9.42) [19–54]	34.4 (7.35) [23–51]	32.9 (12.22) [21–55]	36.3 (10.14) [23–54]	33.8 (9.86) [19–55]
Sex, n (%)					
Men	8 (50.0)	9 (56.3)	6 (37.5)	6 (37.5)	29 (45.3)
Women	8 (50.0)	7 (43.8)	10 (62.5)	10 (62.5)	35 (54.7)
Race, n (%)					
White	11 (68.8)	10 (62.5)	12 (75.0)	12 (75.0)	45 (70.3)
Black	5 (31.3)	6 (37.5)	3 (18.8)	3 (18.8)	17 (26.6)
Asian	0	0	1 (6.3)	1 (6.3)	2 (3.1)
Mean weight, kg (SD), [range]	75.41 (11.61) [52.7–94.2]	71.44 (11.33) [52.6–95.0]	73.98 (15.39) [50.7–101.1]	79.32 (9.35) [65.2–96.9]	75.04 (12.17) [50.7–101.1]
Mean BMI, kg/m^2 (SD), [range]	26.33 (3.19) [21.0–30.7]	26.23 (2.61) [21.5–31.6]	24.75 (3.53) [19.1–30.7]	27.03 (2.72) [22.5–31.0]	26.08 (3.07) [19.1–31.6]

BMI, body mass index; SD, standard deviation.
[a] Treatment A: single 1000-mg oral dose of eluxadoline; Treatment B: single 100-mg oral dose of eluxadoline; Treatment C: single oral dose of placebo; Treatment D: single 400-mg oral dose of moxifloxacin.

Table 2. Mean Differences From Predose Baseline in QTcI for Moxifloxacin and Placebo (milliseconds)

	Placebo[a]		Moxifloxacin		Moxifloxacin − Placebo	
Hours Postdose	n	Mean	n	Mean	Mean	95% LCB
2	60	−1.58	62	10.36	11.94	10.25
3	60	−0.15	62	10.38	10.53	8.84
4	60	0.05	62	11.50	11.45	9.76

LCB, lower confidence bounds; QTcI, corrected QT interval using the volunteer-specific method.
[a] Least squares means from the primary analysis model.

moxifloxacin in period 2, which was considered to be possibly a previously undetected baseline condition.

Assay Sensitivity
The least squares mean ΔQTcI between positive-control moxifloxacin and placebo at 2, 3, and 4 hours following dosing ranged from 10.53 to 11.94, with 95% lower confidence bounds for each of the prespecified time points exceeding 5 milliseconds, confirming assay sensitivity (Table 2). The 24-hour profile for moxifloxacin was as expected from its PK profile (Figure 1).

Pharmacodynamics—QTcI
Mean ΔΔQTcI over time is presented for each dose of eluxadoline in Figure 2. The largest ΔΔQTcI for the eluxadoline 1000-mg dose was 4.10 milliseconds at 1 hour after dosing, with a 1-sided 95% upper confidence bound of 5.81 milliseconds. For the eluxadoline 100-mg dose, the largest ΔΔQTcI was 1.20 milliseconds at 0.5 hours after dosing, with a 1-sided 95% upper confidence bound of 2.91 milliseconds. Because the largest

upper confidence bound determined was <10 milliseconds (5.81 milliseconds), the study is deemed negative for QT interval prolongation. These results are consistent with the finding that eluxadoline has no significant effect on membrane potassium channel currents in cells expressing hERG. Findings for ΔΔQTcI using the QTcF correction method confirmed the primary results.

Categorical Analyses
In the categorical analysis of QTc, 2 volunteers receiving placebo each had a single QTcI >450 milliseconds at 18 hours after dosing, while no volunteers had a QTcI >450 milliseconds after receiving either dose of eluxadoline. One volunteer receiving placebo had a QTcF >450 milliseconds at 3 different time points following dosing, and a QTcF >450 milliseconds at 18 hours after dosing with each dose of eluxadoline. There were no volunteers with QTc >480 milliseconds following dosing with either placebo or eluxadoline.
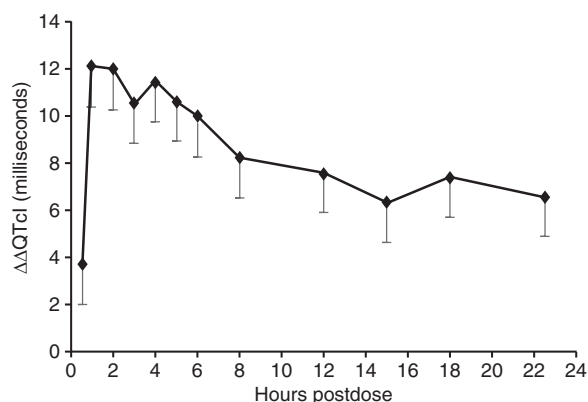
Figure 1. Mean moxifloxacin time-matched QTcI differences from placebo in change from predose baseline over 24 hours. Error bars show 95% lower confidence bounds. QTcI, corrected QT interval using the volunteer-specific method; ΔQTcI, change from baseline in QTcI intervals; $\Delta\Delta$QTcI, the difference in mean ΔQTcI between each dose of moxifloxacin and placebo.

Figure 2. Mean eluxadoline time-matched QTcI differences from placebo in change from predose baseline. Error bars show 95% upper confidence bounds. QTcI, corrected QT interval using the volunteer-specific method; ΔQTcI, change from baseline in QTcI intervals; $\Delta\Delta$QTcI, the difference in mean ΔQTcI between each dose of eluxadoline and placebo.

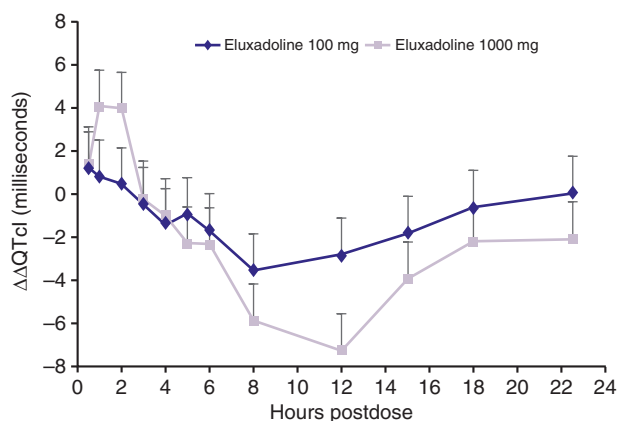These findings were consistent with the primary and secondary analyses of QTc.

For ΔQTc, 1 volunteer had an increase in QTcI from 399 to 450 milliseconds and an increase in QTcF from 400 to 440 milliseconds at 2 hours following dosing with eluxadoline 1000 mg. No other increase in ΔQTc >30 milliseconds was observed in any volunteer. Following dosing with placebo or either dose of eluxadoline, no volunteers had a PR interval >200 milliseconds that was also a 25% increase from baseline, or a QRS duration >120 milliseconds that was also a 25% increase from baseline.

Sex Analysis

The effect of eluxadoline on QTcI intervals was inconsistent between men and women, with a single significant sex-by-treatment interaction at 15 hours following dosing ($P = .029$) and 1 borderline significant interaction at 5 hours following dosing ($P = .058$). In all cases, the mean difference from placebo was either negative or <0.5 milliseconds; therefore, it was concluded that these sex effects, which were found only at times when negative or minor increases in QTcI were observed, did not require further analysis.

ECG Morphology

Of the new ECG abnormalities not seen on any day -1 of period 1, ectopic atrial rhythm was the only morphologic finding that occurred in more than 1 volunteer per treatment, occurring in 2 volunteers in the placebo group. There were no instances of T-wave changes, and there was a single occurrence of nonspecific ST changes in 1 volunteer in the eluxadoline 1000-mg group.

Table 3. Mean (CV) Plasma Pharmacokinetic Parameters of Eluxadoline

	Eluxadoline 1000 mg (n = 58)	Eluxadoline 100 mg (n = 59)
AUC_{0-t}, ng·h/mL	168.04 (54.3)	21.94 (81.3)
AUC_{0-inf}, ng·h/mL	156.62 (64.2)[a]	23.54 (77.6)[b]
C_{max}, ng/mL	31.45 (66.9)	3.03 (88.1)
T_{max}, h[c]	1.00 [0.50, 6.00]	3.00 [0.50, 8.07]
$t_{1/2}$, alpha, h	2.56 (27.8)	2.71 (37.4)
$t_{1/2}$, beta, h	18.50 (38.7)[a]	5.03 (108.7)[b]

AUC_{0-t}, area under the concentration vs time curve from time zero to time of the last quantifiable concentration; AUC_{0-inf}, area under the concentration vs time curve from time zero to infinity; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; $t_{1/2}$, apparent terminal elimination half-life; T_{max}, time to reach maximum observed plasma concentration.
[a] n = 21.
[b] n = 55.
[c] For T_{max}, median [minimum, maximum] values are presented.

Pharmacokinetics

Eluxadoline was rapidly absorbed, with median times to reach C_{max} of 1 hour and 3 hours for the eluxadoline 1000-mg and 100-mg doses, respectively. Mean total exposures of eluxadoline as assessed by area under the concentration vs time curve from time zero to time of the last quantifiable concentration were 168.04 ng · h/mL and 21.94 ng · h/mL for single doses of eluxadoline 1000 mg and eluxadoline 100 mg, and mean C_{max} values were 31.45 ng/mL and 3.03 ng/mL, respectively (Table 3). The relative total exposure of the supratherapeutic dose was approximately 7- to 8-fold greater than that of the therapeutic dose, and the relative peak
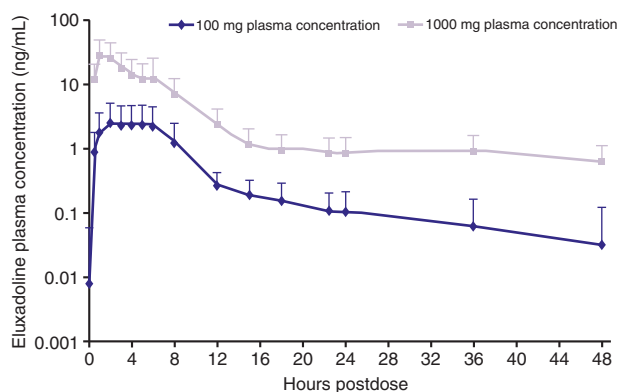
Figure 3. Mean eluxadoline plasma concentrations over time. Error bars show standard deviation.

exposure of the supratherapeutic dose was approximately 10-fold that of the therapeutic dose.

Concentration Analysis

The largest $\Delta\Delta$QTcI was observed at the time of the highest plasma concentration of eluxadoline 1000 mg at 1 hour following dosing (Figure 3). This result was consistent with the previous observation that eluxadoline showed greater, although not significant, decreases in I_{Kr} at higher concentrations. For the eluxadoline 100 mg dose, the largest $\Delta\Delta$QTcI occurred 0.5 hours after dosing, while the maximum plasma concentration was reached at 2 hours following dosing. Whereas the plasma concentration remained almost unchanged at 6 hours postdosing, the mean $\Delta\Delta$QTcI decreased to -1.69 milliseconds.

Figure 4 presents the results of the repeated-measures regression of $\Delta\Delta$QTcI vs $\log_{10}$ eluxadoline plasma concentration using a quadratic model to best fit the data. There was an increase in $\Delta\Delta$QTcI (4.9 milliseconds) only at the highest concentration of eluxadoline (94.1 ng/mL) with an upper confidence bound of 6.7 milliseconds. Thus, the concentration analysis supports the negative findings of the other study endpoints.

Safety

Exposure. A total of 58 volunteers received a single oral dose of eluxadoline 1000 mg, eluxadoline 100 mg, placebo, and moxifloxacin 400 mg on day 1 of each period. Of the 6 volunteers who discontinued the study, 1 received a single dose of moxifloxacin 400 mg, 1 received single doses of eluxadoline 100 mg, placebo, and moxifloxacin 400 mg, 1 received a single dose of placebo, 1 received single doses of eluxadoline 1000 mg and moxifloxacin 400 mg, 1 received single doses of eluxadoline 100 mg and moxifloxacin 400 mg, and 1 received single doses of eluxadoline 1000 mg and placebo.

Adverse Events. Of the 64 volunteers included in the safety analysis, 35 (54.7%) reported a total of 100 AEs

(Table 4), the majority of which were mild in severity. The most commonly observed AEs were contact dermatitis and nausea (12.5% each), dizziness (10.9%), and headache and muscle tightness (7.8% each) (Table 4). Gastrointestinal disorders were reported in 14 volunteers (21.9%) and, other than nausea as mentioned, included dry mouth in 4 volunteers (6.3%); dry lip in 2 volunteers (3.1%); and abdominal discomfort, upper abdominal pain, constipation, diarrhea, flatulence, oral paresthesia, and vomiting in 1 volunteer (1.6%) each. Overall, the greatest proportion of volunteers reporting AEs (38.3%) was in the eluxadoline 1000 mg treatment group, and nausea was the most common AE in any individual treatment group, reported in 7 volunteers (11.7%) in the eluxadoline supratherapeutic dose group (Table 4). In general, the majority of remaining AEs tended to be more common in the eluxadoline supratherapeutic dose group compared with the therapeutic dose and moxifloxacin groups, although these were relatively infrequent (<7% at the treatment group level).

No deaths or serious AEs were reported in this study. A significant AE was reported in 1 volunteer who received a single dose of moxifloxacin on day 1 of period 1; the volunteer experienced an AE of acute hepatitis C infection that was mild in severity and was not considered drug related. The volunteer was discontinued from the study, and the AE remained ongoing at the end of the study. Additionally, 1 volunteer who received a single dose of moxifloxacin on day 1 of period 1 and a dose of eluxadoline 1000 mg on day 1 of period 2 experienced severe epigastric pain within 1.5 hours of eluxadoline dosing. The volunteer was discontinued from the study on day 5 of period 2, and the AE was considered resolved within 1 day after onset.

Discussion

Eluxadoline, a mixed μ-OR and κ-OR agonist and δ-OR antagonist, FDA-approved for the treatment of IBS-D in adults, is rapidly absorbed following single-dose oral administration with low systemic exposure and little to no accumulation,[13] and its safety and efficacy have been previously reported.[17–19] As part of the required safety evaluation of new drugs,[21] the present thorough QTc study was conducted and results demonstrate that the oral administration of a single dose of eluxadoline 100 mg (currently approved dose for IBS-D) and 1000 mg (supratherapeutic dose) did not prolong the QTc interval in healthy volunteers. QTc intervals did not show any significant prolongation (>5 milliseconds) with either dose of eluxadoline, with upper 95% confidence bounds <10 milliseconds for all $\Delta\Delta$QTcI between eluxadoline and placebo, thereby fulfilling the ICH E14 criteria for a negative QT/QTc
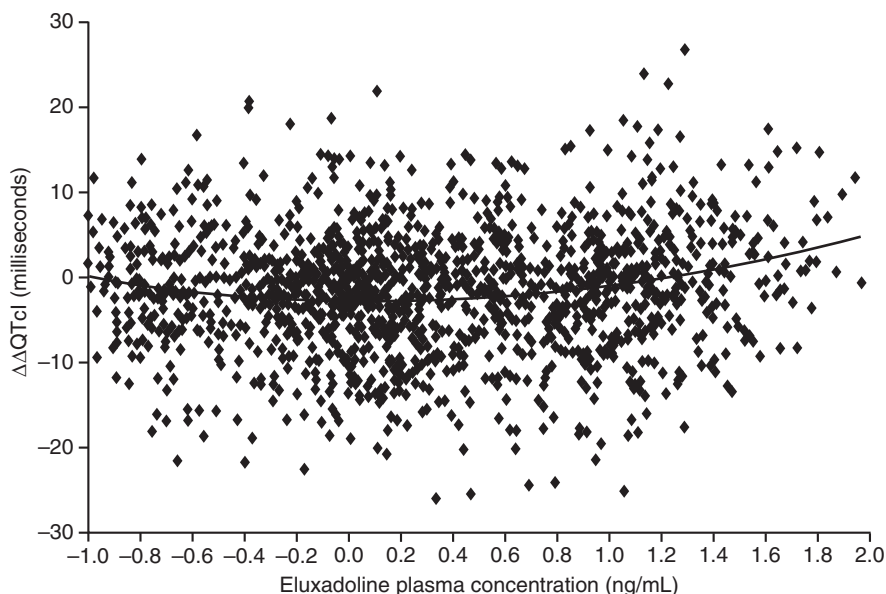
Figure 4. Mean time-matched differences from placebo in changes from predose baseline in QTcI vs $\log_{10}$ eluxadoline plasma concentration. QTcI, corrected QT interval using the volunteer-specific method; ΔQTcI, change from baseline in QTcI intervals; $\Delta\Delta$QTcI, the difference in mean ΔQTcI between each dose of eluxadoline and placebo.

Table 4. Summary of AEs Occurring in $\geq$2 Volunteers Overall

	Eluxadoline 1000 mg (n = 60)	Eluxadoline 100 mg (n = 60)	Placebo (n = 61)	Moxifloxacin 400 mg (n = 62)	Total (N = 64)
Total number of AEs	57	20	6	17	100
Number of volunteers with $\geq$1 AEs, n (%)	23 (38.3)	14 (23.3)	4 (6.6)	10 (16.1)	35 (54.7)
AEs, n (%)					
Contact dermatitis	3 (5.0)	4 (6.7)	2 (3.3)	1 (1.6)	8 (12.5)
Nausea	7 (11.7)	1 (1.7)	0	1 (1.6)	8 (12.5)
Dizziness	4 (6.7)	2 (3.3)	0	2 (3.2)	7 (10.9)
Headache	3 (5.0)	1 (1.7)	0	1 (1.6)	5 (7.8)
Muscle tightness	3 (5.0)	2 (3.3)	0	1 (1.6)	5 (7.8)
Asthenia	3 (5.0)	1 (1.7)	0	0	4 (6.3)
Dry mouth	4 (6.7)	0	0	0	4 (6.3)
Dysphonia	3 (5.0)	0	0	0	3 (4.7)
Sensation of heaviness	3 (5.0)	0	0	0	3 (4.7)
Somnolence	1 (1.7)	1 (1.7)	1 (1.6)	0	3 (4.7)
Hyperventilation	2 (3.3)	0	0	0	2 (3.1)
Hypoesthesia	2 (3.3)	0	0	0	2 (3.1)
Dry lip	1 (1.7)	0	0	1 (1.6)	2 (3.1)
Palpitations	1 (1.7)	0	0	1 (1.6)	2 (3.1)
Paresthesia	2 (3.3)	0	0	0	2 (3.1)
Decreased respiratory rate	2 (3.3)	0	0	0	2 (3.1)

AE, adverse event.

study.[21] The greatest $\Delta\Delta$QTcI (the primary endpoint) observed in this study was 4.10 milliseconds with the supratherapeutic dose of eluxadoline 1000 mg, at 1 hour after dosing, with a 1-sided 95% upper confidence bound of 5.81 milliseconds. The largest $\Delta\Delta$QTcI

for the therapeutic dose of eluxadoline 100 mg was 1.20 milliseconds at 0.5 hours after dosing, with a 1-sided 95% upper confidence bound of 2.91 milliseconds. Dosing with eluxadoline 1000 mg caused a larger change in QTcI than the therapeutic dose

of 100 mg, although the $\Delta\Delta$QTcI with either dose was below that of the moxifloxacin positive control (10.53–11.94 milliseconds).

The primary QTcI findings were reinforced by the secondary QTcF endpoint. In addition, the paucity of outlier values from the categorical analyses of QTc, change in QTc, and change in PR and QRS intervals further confirm that this was a negative QT/QTc study. Results from the gender analysis showed no significant gender effects on QTcI intervals between eluxadoline and placebo, which is notable considering the female predominance of IBS.[3] The lack of emergent morphology findings, particularly the absence of emergent T-wave changes, indicates a lack of effect of eluxadoline on repolarization and further supports the primary endpoint findings.

PK analysis showed that the relative total exposure of the supratherapeutic dose of eluxadoline was approximately 7- to 8-fold greater than that of the therapeutic dose, and that the relative peak exposure of the supratherapeutic dose was approximately 10-fold that of the therapeutic dose. Discrepancy was observed in the beta half-life values between the two doses, which is likely due to the high observed variability; furthermore, the terminal phase was difficult to resolve for both concentrations. Although the maximum effect of eluxadoline on QTcI interval was observed with the highest plasma concentration of eluxadoline (1000 mg dose, 1 hour postdosing), concentration analysis did not reveal a relationship between eluxadoline plasma concentration and changes in QT interval. The concentration analysis therefore supported the negative findings of the other study endpoints.

Single doses of moxifloxacin 400 mg, a positive control,[23] established that the study had adequate sensitivity to detect a QTc prolongation of clinical importance. The 24-hour QTcI profile of moxifloxacin was consistent with the previously reported profile of moxifloxacin, with maximum prolongation of QT interval approximately corresponding with maximum reported plasma concentration ($\sim$2.5 hours).[24]

A potential limitation of this study is that although the demographics and baseline characteristics of the study population generally reflected those of the phase 3 IBS-D population,[19] the volunteers in this study did not have IBS-D. Thus, these participants do not present with the same comorbidities that are expected in the IBS-D population.[25] However, in line with regulatory guidance, QTc studies are performed in healthy volunteers to minimize any extraneous variables.[21] In addition, the proportion of men included here was slightly greater than in the phase 3 population (45% vs $\sim$32%–35%, respectively).

Overall, the therapeutic and supratherapeutic doses of eluxadoline were safe and generally well tolerated,

and the most common AEs were contact dermatitis, dizziness, and nausea. The majority of AEs were mild in severity, and no serious AEs or deaths were reported. The supratherapeutic dose of eluxadoline was associated with an increased incidence of AEs, particularly nausea (in 7 volunteers in the eluxadoline 1000 mg group; 11.7%), compared with the other treatments. Eluxadoline in single oral doses of 100 mg was thus considered to be safe and well tolerated in this study population.

Conclusions

In conclusion, results from this thorough QTc study demonstrate that eluxadoline at a therapeutic dose of 100 mg and a supratherapeutic dose of 1000 mg did not cause QT interval prolongation in healthy male and female volunteers, and are supportive of the overall favorable safety profile of eluxadoline for the pharmacological treatment of IBS-D in adults.

Disclosures

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Supporting Information

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