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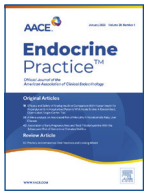

Original Article

Relacorilant, a Selective Glucocorticoid Receptor Modulator in Development for the Treatment of Patients With Cushing Syndrome, Does Not Cause Prolongation of the Cardiac QT Interval

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ABSTRACT

Objective: To assess the effect of relacorilant, a selective glucocorticoid receptor modulator under investigation for the treatment of patients with endogenous hypercortisolism (Cushing syndrome [CS]), on the heart rate–corrected QT interval (QTc).
Methods: Three clinical studies of relacorilant were included: (1) a first-in-human, randomized, placebo-controlled, ascending-dose (up to 500 mg of relacorilant) study in healthy volunteers; (2) a phase 1 placebo- and positive-controlled thorough QTc (TQT) study of 400 and 800 mg of relacorilant in healthy volunteers; and (3) a phase 2, open-label study of up to 400 mg of relacorilant administered daily for up to 16 weeks in patients with CS. Electrocardiogram recordings were taken, and QTc change from baseline (ΔQTc) was calculated. The association of plasma relacorilant concentration with the effect on QTc in healthy volunteers was assessed using linear mixed-effects modeling.
Results: Across all studies, no notable changes in the electrocardiogram parameters were observed. At all time points and with all doses of relacorilant, including supratherapeutic doses, ΔQTc was small, generally negative, and, in the placebo-controlled studies, similar to placebo. In the TQT study, placebo-corrected ΔQTc with relacorilant was small and negative, whereas placebo-corrected ΔQTc with moxifloxacin positive control showed rapid QTc prolongation. These results constituted a negative TQT study. The model-estimated slopes of the concentration-QTc relationship were slightly negative, excluding an association of relacorilant with prolonged QTc.

Abbreviations: CI, confidence interval; CS, Cushing syndrome; ECG, electrocardiogram; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; LS, least-squares; LV, left ventricular; MAD, multiple-ascending-dose; QTc, QT interval corrected for the heart rate; QTcF, QT interval corrected for the heart rate using the Fridericia formula; SAD, single-ascending-dose; TQT, thorough QT interval corrected for heart rate; ΔQTc, change from baseline QT interval corrected for the heart rate; ΔΔQTcF, placebo-corrected change from baseline QT interval corrected for the heart rate.

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Conclusion: At all doses studied, relacorilant consistently demonstrated a lack of QTc prolongation in healthy volunteers and patients with CS, including in the TQT study. Ongoing phase 3 studies will help further establish the overall benefit-risk profile of relacorilant.

Introduction

Delay of ventricular repolarization is an important risk factor for the development of cardiovascular comorbidities, including cardiac arrhythmia, syncope, and sudden cardiac arrest.[1-3] Delayed ventricular repolarization, detectable by electrocardiogram (ECG) as prolongation of the heart rate–corrected QT interval (QTc), can be caused or potentiated by numerous drugs.[4-7] In light of the association of QTc prolongation with the risk of ventricular arrhythmias, thorough studies of the effect of new drug candidates on QTc prolongation (thorough QT/QTc studies) are recommended by E14 guidance from the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).[8,9] QTc intervals between 330 and 450 milliseconds in males and between 390 and 460 milliseconds in females have been suggested as normal.[6]

Drug-induced QT interval prolongation may be of particular concern for patients with Cushing syndrome (CS). Patients with CS often present with ECG findings of left ventricular (LV) hypertrophy, remodeling, and dysfunction.[10-13] LV hypertrophy and remodeling are associated with increases in the QT interval duration as well as in QT dispersion, an indirect measure of abnormalities in ventricular repolarization.[14] Studies have demonstrated QTc prolongation and increased QTc dispersion in patients with CS compared with healthy individuals.[15,16] In the context of CS, both hypercortisolism and hypokalemia have been identified as independent risk factors for LV remodeling and dysfunction.[11,12] A study of patients with CS by Pecori Giraldi et al[17] found that QTc prolongation was present in 26% (5 of 19) of male patients with CS and was significantly associated with hypokalemia and hypogonadism or low testosterone levels. There were no instances of QTc prolongation among the female patients or healthy controls. The observed prevalence of QTc prolongation in this study was considerably greater than the estimated $\leq$2.5% prevalence in the general population.[18]

Importantly for the management of patients with CS, most medications approved or widely used off-label for the treatment of CS, including levoketoconazole, osilodrostat, pasireotide, pasireotide long-acting release (LAR), and mifepristone, are associated with QTc prolongation.[19-23] Therefore, drug-induced prolongation of the QTc interval is a concern that requires close monitoring, particularly, but not exclusively, in male patients with CS.

Relacorilant is an orally administered, selective glucocorticoid receptor modulator (SGRM) currently under investigation for the treatment of patients with endogenous CS and those with various tumor types. We analyzed the effect of relacorilant on the QTc interval using ECG data from 3 different studies: (1) a first-in-human phase 1 study in healthy volunteers,[24] (2) a phase 1 thorough QT/QTc study in healthy volunteers conducted in accordance with the ICH guidelines, and (3) a phase 2 dose-finding study in patients with endogenous CS.[25]

Methods

All studies were approved by the Institutional Review Board at each study center and were conducted in accordance with the World Medical Association Declaration of Helsinki and the ICH Good Clinical Practice guidelines. All participants provided written informed consent before the initiation of study procedures.

Phase 1 First-in-Human Study of Relacorilant in Healthy Volunteers

The study design and methods of the phase 1, randomized, placebo-controlled, blinded, parallel-group, single-ascending-dose (SAD) or multiple-ascending-dose (MAD) first-in-human study of the safety, tolerability, pharmacokinetics, and pharmacologic effect of relacorilant in healthy volunteers have been published.[24] Briefly, volunteers with a family history of, or risk factors for, a form of ventricular tachycardia known as torsades de pointes (eg, familial long QT syndrome, heart failure, and hypokalemia), with a QT interval corrected for heart rate using the Fridericia formula (QTcF) of >450 milliseconds at screening or predose or with the use of concomitant medications that prolong QTcF, were excluded. Eighty-one study participants received a single dose of relacorilant (5-500 mg, n = 69) or placebo (n = 12) during the SAD phase. During the MAD phase, 46 participants received up to 14 days dosing with relacorilant (50-500 mg, n = 34) or placebo (n = 12). The primary ECG end point was placebo-corrected change from baseline QTcF (ΔQTcF). Ten-hour continuous (Holter) 12-lead ECG recordings were taken during the SAD phase and on MAD phase days 0, 1, 7, and 15, from approximately 2 hours before dosing until 8 hours after dosing. For both phases, up to 10 replicates were extracted from ECG recordings taken at 0 (predose), 1, 2, 4, and 8 hours after dosing and were measured centrally with the early precision QT technique.[26]

Analyses of QTcF were performed separately for the SAD and MAD phases and were based on a linear mixed-effects model with ΔQTcF as the dependent variable and time, treatment (dose of relacorilant or pooled placebo), and time-by-treatment interaction as the fixed effects, with baseline QTcF as a covariate. Blood samples for analysis of plasma concentration of relacorilant were taken from participants before dosing and at 0.5, 1, 2, 4, 8, 12, 24, 36, 48, 60, 72, 120, and 168 hours (SAD phase) and 0.5, 1, 2, 4, 6, 8, 12, and 24 hours (MAD phase). The concentration-QTc relationship between the relacorilant plasma concentration and placebo-corrected ΔQTcF (ΔΔQTcF) was assessed using a linear mixed-effects modeling approach.

Phase 1 Thorough QT/QTc Study of Relacorilant in Healthy Volunteers

A phase 1, dedicated thorough QT/QTc study of the effect of the therapeutic and supratherapeutic doses of relacorilant on cardiac repolarization in healthy volunteers was conducted, and full study details and results will be published separately. Briefly, 34 healthy male and female volunteers were enrolled in this partially blinded, randomized, placebo- and positive-controlled, multiple-dose, 4-way crossover study. The study exclusion criteria were as described earlier for the phase 1 first-in-human study and included the use of any strong CYP3A inhibitor or inducer within 4 weeks before the study or use of medications that could prolong the QT/QTc interval within 2 weeks before screening. Volunteers were also excluded if they had a history or family history of risk factors for torsades de

pointes, ECG abnormalities, or marked baseline prolongation of ECG intervals, including QTcF >450 milliseconds, PR interval of the ECG >200 milliseconds, or QRS >120 milliseconds, or with a resting heart rate <45 or >100 bpm. The primary ECG objective was to evaluate the potential cardiac toxicity of relacorilant by determining the effects of therapeutic and supratherapeutic plasma concentrations of relacorilant on ΔΔQTcF in comparison with placebo and with a positive control. Participants were randomized in a partial double-blind crossover manner to receive once-daily dosing of 400 mg of relacorilant (therapeutic dose), 800 mg of relacorilant (supratherapeutic dose), or placebo, each for 5 days, or placebo (double-blind) for 4 days followed by 400 mg of moxifloxacin (open-label positive control) for 1 day. Continuous ECG recording was performed for 25 hours on days 1 and 5 beginning 1 hour before dosing. Replicate ECGs were extracted at 3 time points before dosing on day 1 (45, 30, and 15 minutes before dosing) and at 1 time point before dosing on day 5. Up to 10 nonoverlapping postdose replicate ECGs were extracted at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours after dosing on days 1 and 5 (the 24-hour time point was recorded on days 2 and 6, respectively). ECG recordings were evaluated centrally and measured using the early precision QT technique.

The primary analysis of QTcF for relacorilant versus placebo was based on a linear mixed-effects model with ΔQTcF as the dependent variable with period, sequence, time (ie, nominal postbaseline time point, including postdose time points on days 1 and 5 as well as the predose time point on day 5), treatment (therapeutic dose of relacorilant, supratherapeutic dose of relacorilant, moxifloxacin, or placebo), and time by treatment as the interaction factors. The baseline QTcF was also included in the model as a covariate. Blood samples were drawn at approximately the same time points as the ECG extractions, and the concentration-QTc relationship was assessed as described earlier for the first-in-human study. In accordance with the ICH E14 guidance, the effect threshold for relacorilant was defined as an upper bound of the 2-sided 90% CI around the mean ΔΔQTcF of 10 milliseconds at the highest clinically relevant exposure.[27] Assay sensitivity was assessed using a concentration-QTc analysis of the effect of 400 mg of moxifloxacin vs placebo on ΔQTcF using the same model as the primary analysis.

Phase 2 Study of Relacorilant in Patients With CS

Treatment-emergent change in ECG was included as a safety end point in the prospective, phase 2, open-label, dose-finding study of relacorilant in 35 adult patients with endogenous CS and uncontrolled hypertension and/or hyperglycemia.[25] Briefly, patients were treated with low-dose relacorilant (100 mg/day uptitrated to 200 mg/day) for 12 weeks or with high-dose relacorilant (250 mg/day uptitrated to 400 mg/day) for 16 weeks. Patients with QTcF >450 milliseconds at screening or with a family history of risk factors for torsades de pointes were excluded. Triplicate ECG measurements were taken at screening, and duplicate measurements were taken 1.5 to 2.5 hours after dosing at weeks 2, 4, 6, 8, 10, and 12 (all patients) and weeks 14 and 16 (high-dose relacorilant patients only).

Results

First-in-Human Study of Relacorilant

ECG data were available from 42 and 12 participants randomized to relacorilant or placebo, respectively, during the SAD phase and from 34 and 12 participants randomized to relacorilant or placebo, respectively, during the MAD phase. The baseline mean (SD) QTcF values were within expectations for a healthy population (range, 378.9 [11.7] to 403.5 [9.4] milliseconds) and were similar in the respective relacorilant and placebo cohorts during the SAD and MAD study phases (Table). Relacorilant did not have a clinically relevant effect on QTcF during the SAD or MAD study phases. At all SAD and MAD postdose time points and for all doses of relacorilant, the least-squares (LS) mean ΔQTcF for relacorilant was similar to that for placebo. In both groups, the postdose LS mean ΔΔQTcF for relacorilant was small and mostly negative (Table). No obvious differences in ΔΔQTcF were observed for different relacorilant doses in the SAD and MAD study phases, and mean ΔΔQTcF did not exceed 5 milliseconds at any time point (Fig. 1). The relacorilant plasma concentration and QTcF data in the SAD and MAD phases were best fit with a linear model with population mean intercepts. For both phases, the model-estimated slopes (90% CI) were slightly negative (SAD, −0.59 [−2.14 to 0.97] × 10^{-3} milliseconds/ng/mL; MAD, −2.34 [−3.16 to −1.52] × 10^{-3} milliseconds/ng/mL). Therefore, a concentration-dependent effect of relacorilant on QTc prolongation was not identified. The exposure-response model-predicted results for mean ΔΔQTcF at peak plasma concentrations of relacorilant during the SAD and MAD phases also indicated that increasing doses of relacorilant were not associated with QT interval prolongation (Fig. 2 *A* and *B*). Based on the modeled SAD and MAD results, an effect of relacorilant on ΔΔQTcF exceeding the 10-millisecond threshold was excluded within the full observed range of plasma concentrations up to approximately 5500 ng/mL.

Highlights

- Three phase 1 or 2 clinical studies were analyzed to assess QT changes with relacorilant
- There were no notable electrocardiogram changes, including at the supratherapeutic relacorilant doses
- Ongoing phase 3 studies will further establish relacorilant's benefit-risk profile

Clinical Relevance

Drug-induced prolongation of the QT interval is a risk factor for arrhythmia and sudden cardiac arrest. Regulatory agencies recommend that all new drugs be evaluated for their effect on the QT interval. This analysis shows that relacorilant was not associated with QT prolongation in healthy individuals or patients with Cushing syndrome.

Thorough QT/QTc Study

ECG data were available from 25 participants administered therapeutic (400 mg) relacorilant, 28 participants administered supratherapeutic (800 mg) relacorilant, 29 participants who received placebo, and 28 participants who received the moxifloxacin positive control. For all participants, mean (SD) QTcF values at baseline were within expectations for a healthy population (range, 405.6 [15.33] to 407.2 [17.49] milliseconds). On both days and for all postdose time points with the therapeutic and supratherapeutic doses of relacorilant and with placebo, LS mean ΔQTcF was generally slightly negative (range, −11.7 to 2.0 milliseconds). In contrast, treatment with 400 mg of moxifloxacin positive control on day 5 produced a rapid increase from LS mean (90% CI) predose QTcF starting at 1 hour after dosing (5.7 [3.3 to 8.2] milliseconds) to a maximum observed value of 9.7 (7.2 to 12.2) milliseconds at 16 hours after dosing.

Across day 1, the postdose LS mean (90% CI) ΔΔQTcF ranged from −3.6 (−7.1 to −0.1) to 1.3 (−2.1 to 4.7) milliseconds across

Table
ECG Parameters of Healthy Volunteers Randomized to Relacorilant or Placebo During the SAD and MAD Phases in the Phase 1 First-in-Human Study

ECG parameter, msec	SAD		MAD	
	Relacorilant[a] ($n = 42$)	Placebo ($n = 12$)	Relacorilant[b] ($n = 34$)	Placebo ($n = 12$)
Baseline QTcF, mean (SD)	378.9 (11.7) to 403.5 (9.4)	399.0 (14.2)	385.1 (14.1) to 401.8 (15.3)	391.1 (12.1)
ΔQTcF, LS mean (90% CI)	−5.4 (−10.0 to −0.8) to 1.1 (−1.6 to 3.9)	−2.7 (−6.4 to 1.1) to −1.7 (−4.0 to 0.6)	−16.9 (−22.6 to −11.2) to 1.7 (−2.7 to 6.2)	−9.0 (−12.1 to −5.9) to 3.5 (−0.2 to 7.2)[c]
ΔΔQTcF, LS mean (90% CI)	−3.5 (−7.2 to 0.2) to 2.8 (−0.8 to 6.4)	…	−12.3 (−20.2 to −4.5) to 1.4 (−5.0 to 7.9)	…

Abbreviations: ECG = electrocardiogram; LS = least-squares; MAD = multiple-ascending-dose; msec = millisecond; QTcF = QT interval corrected for heart rate using the Fridericia formula; SAD = single-ascending-dose; ΔQTcF = change from baseline QT interval corrected for the heart rate using the Fridericia formula; ΔΔQTcF = placebo-corrected change from baseline QT interval corrected for the heart rate using the Fridericia formula.

[a] Data represent the range of mean (SD) QTcF or LS mean (90% CI) values for healthy volunteers who received a single dose of 5, 15, 50, 150, 300, or 500 mg of relacorilant during the SAD phase.

[b] Data represent the range of mean (SD) QTcF baseline or LS mean (90% CI) values for healthy volunteers who received 50, 150, 250, or 500 mg/day of relacorilant for 14 days during the MAD phase.

[c] Data represent the range of LS mean (90% CI) ΔQTcF values for healthy volunteers who received placebo for 14 days during the MAD phase.

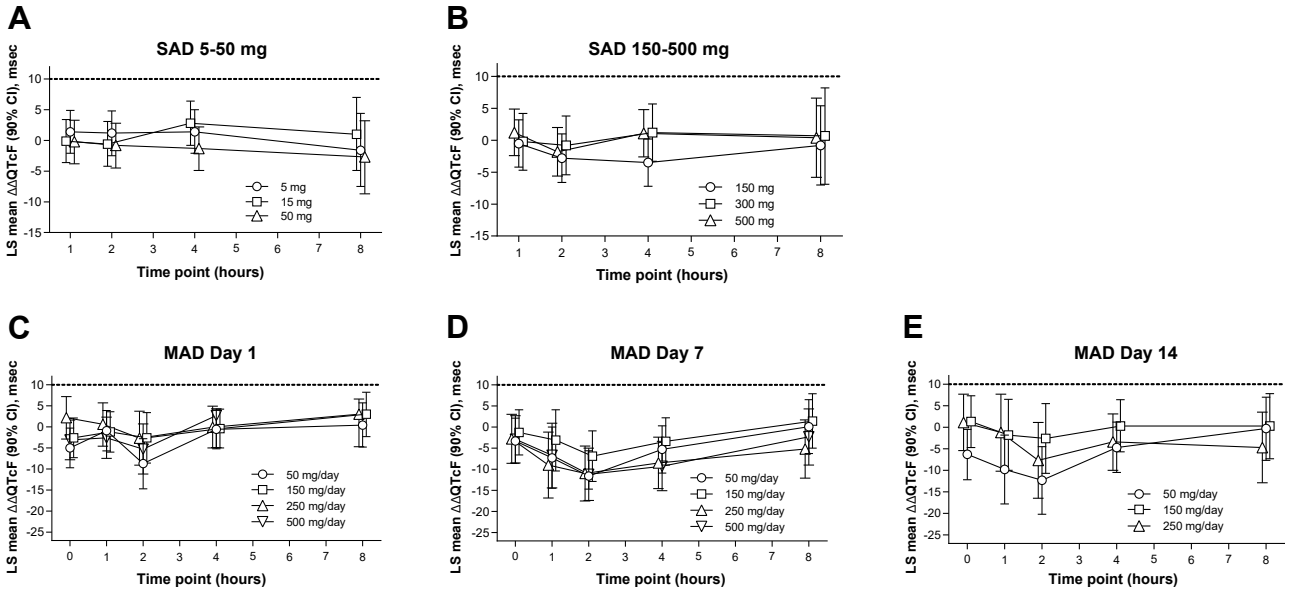

Fig. 1. Placebo-corrected change from baseline QT interval corrected for the heart rate using the Fridericia formula (QTcF) during the first-in-human single-ascending-dose (SAD) (*A* and *B*) and multiple-ascending-dose (MAD) (*C* through *E*) study phases. The least-squares (LS) mean and 90% confidence interval (CI) values were based on a linear mixed-effects model with ΔQTcF as the dependent variable and time (categorical), treatment (each dose of relacorilant), and time by treatment as the interaction factors. The baseline QTcF was included as a covariate. Day 14 data for the 500-mg/day dose (MAD) were not available (dosing terminated). *ΔΔQTcF* = placebo-corrected change in the baseline QT interval corrected for the heart rate using the Fridericia formula.

both relacorilant dose groups (Fig. 3). On day 5, the LS mean (90% CI) ΔΔQTcF with both doses of relacorilant was negative at all postdose time points, ranging from −8.0 (−11.5 to −4.6) to −3.9 (−7.3 to −0.5) milliseconds. At all postdose time points and with both doses of relacorilant, the upper bound of the 90% CI around the LS mean ΔΔQTcF was below the 10-millisecond ICH E14 threshold. On day 5, the LS mean (90% CI) ΔΔQTcF for 400 mg of moxifloxacin increased to a peak value of 10.7 (7.3 to 14.1) milliseconds at 1.5 hours after dosing (Fig. 3).

As in the first-in-human study, a linear model with a treatment effect-specific intercept provided the best fit to the relacorilant concentration and ΔΔQTcF data. The estimated slope (90% CI) of relacorilant plasma concentration in the concentration-QTc relationship was shallow and slightly negative (−0.97 [−1.68 to −0.25] × 10^{-3} milliseconds/ng/mL) with a small treatment effect-specific intercept (90% CI) of −1.25 milliseconds (−2.00 to −0.51). At the geometric mean peak relacorilant concentration, the predicted effects on QTcF were −3.02 milliseconds (90% CI, −4.16 to −1.88) and −3.87 milliseconds (90% CI, −5.56 to −2.17) for the 400-mg dose (maximum concentration, 1831.6 ng/mL) and 800-mg dose (maximum concentration, 2705.5 ng/mL), respectively (Fig. 4). Based on the concentration-QTc modeling results, an effect on ΔΔQTcF exceeding the 10-millisecond threshold within the full observed range of relacorilant plasma concentrations (up to approximately 4500 ng/mL with supratherapeutic dosing) could be excluded. In contrast, at the geometric mean peak concentration of moxifloxacin on day 5 (1869.4 ng/mL), the estimated slope (90% CI) of the concentration-QTc relationship was positive and statistically significant (2.6 × 10^{-3} milliseconds/ng/mL [0.00057 to 0.00466], $P = 0.0361$). The lower bound of the 90% CI of the predicted effect on ΔΔQTcF was >5 milliseconds (predicted effect, 8.9 milliseconds [5.96 to 11.85 milliseconds]), thereby demonstrating assay sensitivity.[27]

Phase 2 Study of Relacorilant in Patients With CS

The low- and high-dose relacorilant groups included 17 and 18 patients, respectively. At baseline, the mean (SD) QTcF values ranged from 393.6 (16.5) to 394.2 (16.2) milliseconds in the low-dose group and from 403.4 (36.3) to 409.9 (27.2) milliseconds in the high-dose-group, confirming the absence of QT prolongation at

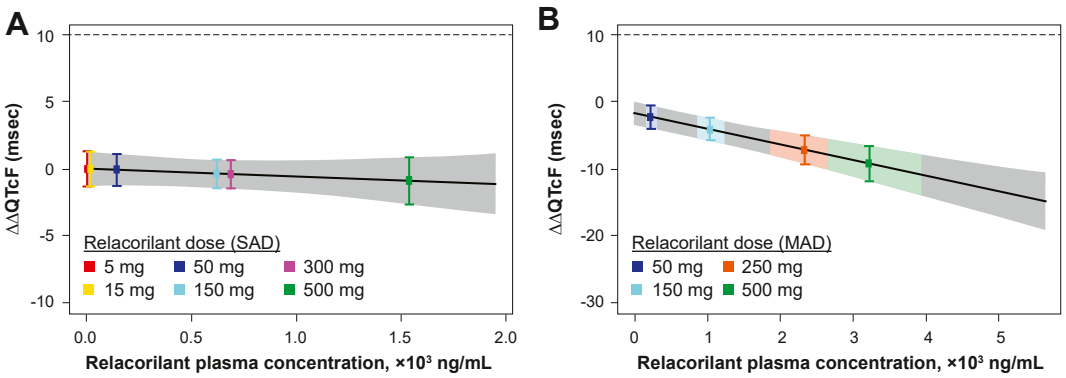

Fig. 2. Model-predicted placebo-corrected change from baseline QT interval corrected for the heart rate using the Fridericia formula (ΔΔQTcF) at geometric mean peak relacorilant concentrations during single-ascending-dose (SAD) (*A*) and multiple-ascending-dose (MAD) (*B*) study phases. The solid black lines and gray-shaded areas show the predicted mean ΔΔQTcF with 90% CI calculated from the equations ΔΔQTcF = −0.005 (milliseconds) − 0.588 (milliseconds/ng/mL) × relacorilant concentration (ng/mL) (*A*) and ΔΔQTcF = −1.804 (milliseconds) − 2.341 (milliseconds/ng/mL) × relacorilant concentration (ng/mL) (*B*). The colored markers and error bars show the predicted mean (90% CI) ΔΔQTcF at the observed relacorilant geometric mean peak concentrations during the SAD and MAD phases. (*B*) The blue-, light blue−, orange-, and yellow-shaded areas denote the predicted mean (90% CI) ΔΔQTcF at the geometric mean (90% CI) maximum concentrations (C_{max}) of 50, 150, 250, and 500 mg/day of relacorilant, respectively. The dashed lines show the 10-millisecond ΔΔQTcF effect threshold.

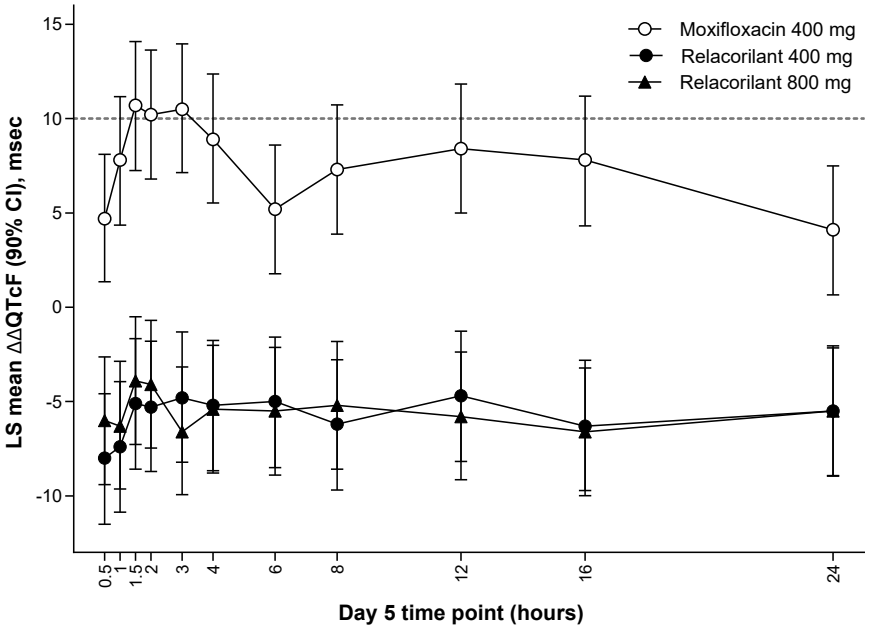

Fig. 3. Placebo-corrected change from baseline QT interval corrected for heart rate using the Fridericia formula (QTcF) in the thorough QT/QTc study on day 5. The baseline QTcF is the mean of data extracted from electrocardiogram recordings taken at 45, 30, and 15 minutes before dosing. The least-squares (LS) mean and 90% CI values were based on a linear mixed-effects model with ΔQTcF as the dependent variable and period, sequence, time, treatment, and time-by-treatment interaction as the fixed effects, with baseline QTcF as a covariate. The unstructured covariance matrix failed to converge, and an autoregressive structure was used to specify the repeated measures at postdose time points for each participant during treatment. The gray dashed line shows the 10-millisecond placebo-corrected change from baseline QTcF (ΔΔQTcF) effect threshold.

baseline. Throughout the study, the median QTcF did not change appreciably in either group (Fig. 5). In both groups and for all doses of relacorilant, the mean (SD) ΔQTcF values were small and not statistically significant (range, −2.2 [13.5] to 1.8 [24.4] milliseconds, all $P>0.3$). In both groups, abnormal sinus tachycardia was the most common postbaseline ECG finding and was observed in 3 patients (17.6%) in the low-dose group and 2 patients (11.1%) in the high-dose group.

Discussion

Drug-induced prolongation of the QTc interval is a risk factor for cardiovascular comorbidities including torsades de pointes, ventricular tachycardia, stroke, and sudden cardiac arrest.[4,28,29] Accordingly, regulatory authorities recommend thorough evaluation of QTc interval prolongation and proarrhythmic potential of all new drug candidates.[8,9] To date, most of the drugs approved or widely used for treatment of CS are associated with QTc interval prolongation,[19-23] and there is, therefore, a need for treatments that do not prolong the QTc interval. We have described here the ECG results for relacorilant, an investigational drug for CS, from 3 studies: (1) a first-in-human study in healthy volunteers, (2) a thorough QT/QTc study in healthy volunteers performed in accordance with regulatory guidance, and (3) a phase 2 study over up to 16 weeks in patients with CS. Overall, the results presented here demonstrate that relacorilant administration, including up to supratherapeutic doses, has no effect on QTc interval prolongation in healthy volunteers or patients with endogenous CS. In the

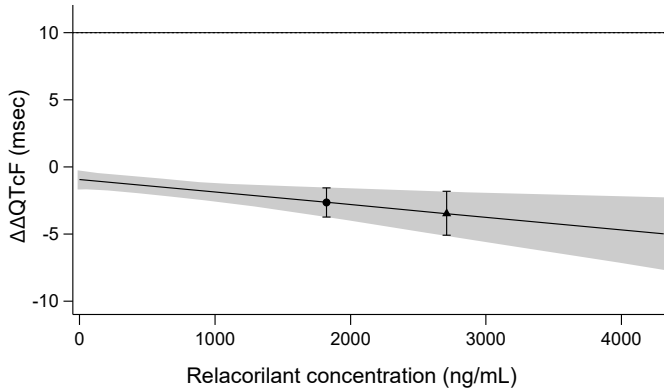

Fig. 4. Model-predicted placebo-corrected change from baseline QT interval corrected for heart rate using the Fridericia formula (ΔΔQTcF) at geometric mean peak relacorilant concentrations in the thorough QT/QTc study. The solid black line and gray-shaded area denote the model-predicted mean ΔΔQTcF and 90% CI, which was calculated from the equation ΔΔQTcF = −1.2501 (milliseconds) − 0.97 ($\times 10^{-3}$ milliseconds/ng/mL) × relacorilant concentration (ng/mL). The data points and error bars denote the estimated mean (90% CI) ΔΔQTcF at geometric mean relacorilant maximum concentration (C_{max}) with therapeutic dosing (400 mg, circle) and supratherapeutic dosing (800 mg, triangle), respectively. The gray dashed line shows the 10-millisecond ΔΔQTcF effect threshold.

first-in-human study in healthy volunteers, there was no meaningful clinical effect of relacorilant on QTcF over the range of doses administered during the SAD and MAD phases. There was no discernable dose dependency, and LS mean ΔΔQTcF did not exceed 5 milliseconds at any point during the SAD and MAD study phases. The results of the concentration-QTc modeling further indicated that an effect on ΔΔQTcF exceeding 10 milliseconds could be excluded for the range of the observed plasma concentrations of relacorilant, up to approximately 5500 ng/mL.

These results were confirmed in the dedicated placebo- and positive-controlled thorough QT/QTc study of relacorilant at therapeutic and supratherapeutic doses. As seen in the first-in-human study, the effect of both therapeutic and supratherapeutic relacorilant on ΔQTcF at all postdose time points was similar to that of placebo. Also, for both doses, ΔΔQTcF was consistently small and generally slightly negative. Importantly, the upper bound of the 2-sided 90% CI around the LS mean ΔΔQTcF for both doses of relacorilant was <10 milliseconds at all postdose time points. In addition, the results of concentration-QTc modeling excluded an effect on ΔΔQTcF exceeding 10 milliseconds within the full range of observed relacorilant plasma concentrations, up to approximately 4500 ng/mL noted with supratherapeutic dosing. The ability of the thorough QT/QTc study to detect small increases in QTcF was confirmed by a lower bound >5 milliseconds of the 90% CI for the predicted effect on ΔΔQTcF for the moxifloxacin positive control. Taken together, these results constitute a negative QT/QTc study, as described by the ICH E14 clinical regulatory guidance.[27]

In both the first-in-human and thorough QT/QTc studies, relacorilant administration was accompanied by slight downward trends in placebo-corrected ΔQTc. The QTc intervals 390 to 450 milliseconds in males and 390 to 460 milliseconds in females have been suggested as the normal ranges,[6] and it should be noted that all participants in the relacorilant studies had a normal QTc interval at screening and remained within the normal range while on treatment.

The findings and conclusions of the 2 studies of relacorilant in healthy volunteers were additionally confirmed by the ECG results from the 16-week phase 2 study of relacorilant in patients with endogenous CS. At all time points and for all doses of relacorilant, mean ΔQTcF values for relacorilant were small and not statistically significant.

The absence of QTc prolongation with relacorilant presented here stands in contrast to most of the currently approved or widely prescribed therapies for CS. In the 12-month phase 3 study of pasireotide, QTc prolongation (QTc interval >480 milliseconds) occurred in 2% of the patients.[30] Similar results were observed during the clinical studies of pasireotide LAR, with QTc >480 milliseconds reported for 1.3% of the patients.[31] Importantly, QTc prolongation has been observed with both therapeutic and supratherapeutic doses of pasireotide and pasireotide LAR.[21,22] In a phase 2 proof-of-concept study of osilodrostat in 19 patients with Cushing disease, QT interval prolongation, reported as a serious adverse event and presumed to be related to study drug, was reported in 1 patient (5.3%).[32] Similarly, during the phase 3 open-label trial of levoketoconazole in patients with CS, QT prolongation occurred in 5 of 94 (5.3%) patients, with 2 of these events considered serious and related to the study drug.[33] The glucocorticoid receptor antagonist mifepristone is also associated with QTc prolongation, and use of mifepristone should be avoided in patients with concomitant use of QT interval prolonging drugs or with familial long QT syndrome.[23] Based on preclinical studies, ketoconazole inhibits the rapidly activating component of the cardiac delayed rectifier potassium current and may prolong the QT interval, and ketoconazole is not recommended in patients receiving concomitant treatment with drugs that prolong QTc.[34]

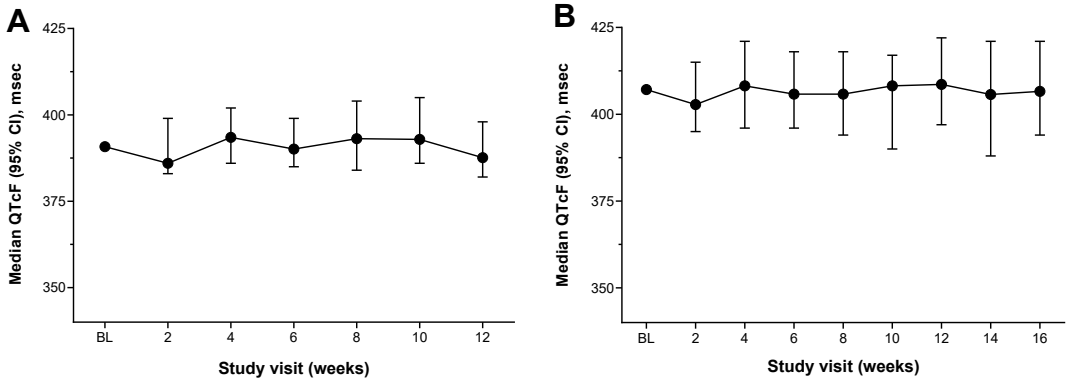

Fig. 5. QT interval corrected for heart rate using the Fridericia formula (QTcF) over time in patients with Cushing syndrome who received low-dose (*A*) and high-dose (*B*) relacorilant in the phase 2 study. Data are the median QTcF at baseline and median (95% CI) QTcF at weeks 2 to 16 and are based on 13 to 17 patients in the low-dose group and 9 to 17 patients in the high-dose group. Baseline was defined as the mean of the triplicate readings at the last visit before the first dose of study drug. Low-dose relacorilant included 100 mg/day for 4 weeks, 150 mg/day for 4 weeks, and then 200 mg/day for 4 weeks. High-dose relacorilant included 250 mg/day for 4 weeks, 300 mg/day for 4 weeks, 350 mg/day for 4 weeks, and then 400 mg/day for 4 weeks.

Hypokalemia, a relatively common finding in patients with endogenous CS,[35,36] has been shown to be an independent risk factor for LV dysfunction in CS[12] and for QTc prolongation in male patients with CS.[17] During the open-label trial of mifepristone in patients with endogenous CS, hypokalemia was reported in 34% of the patients.[37] Importantly, in the phase 2 study of relacorilant in patients with CS described here, there were no reported cases of hypokalemia among patients who received low- or high-dose relacorilant.[25]

Given the apparent relationship between CS and LV abnormalities, it is perhaps surprising that the prevalence of QTc prolongation in patients with CS has not been more extensively studied. An ECG study of 79 patients with Cushing disease found a significant association of LV hypertrophy and prolonged QTc dispersion.[16] A study of 54 patients with Cushing disease found that QTc was significantly prolonged in male, but not female, patients, compared with healthy controls.[17] The phase 2 study of relacorilant in patients with CS described here excluded patients with QTcF >450 milliseconds at screening; therefore, the negative findings of this study cannot be extended to patients with CS who may have prolonged QTc, although it is worth noting that QTcF remained stable in both dosing groups over the duration of the study.

The reported studies have some limitations that should be considered. Two of the studies, including the thorough QT/QTc study, were conducted in healthy volunteers rather than in patients with CS. It should be noted that the assessment of drug effects on QTc interval is consistent with ICH guidance on thorough QT/QTc studies. Furthermore, participants with pre-existing QTc prolongation, a family history of or risk factors for torsades de pointes, or the use of concomitant medications that prolong QTcF were excluded from all 3 studies. Therefore, the effect of relacorilant in patients with CS and a QTc interval of >450 milliseconds and/or with the aforementioned risk factors cannot be determined from these studies. Additional studies of relacorilant in patients with QTc prolongation will be helpful in assessing the risks and benefits of relacorilant in these patients.

The negative thorough QT/QTc study and the other studies presented here provide evidence that relacorilant treatment, even at supratherapeutic doses, does not result in QTc prolongation and suggest that relacorilant should not present a risk of torsades de pointes and related sequelae, including ventricular fibrillation and sudden cardiac arrest, in treated patients. Ongoing phase 3 studies of relacorilant up to 400 mg daily in patients with endogenous CS and those with cortisol-secreting adrenal adenomas or adrenal hyperplasia and relacorilant 150 mg in patients with ovarian, primary peritoneal, or fallopian tube cancer should help confirm the cardiac safety and overall benefit-risk profile for chronic administration of relacorilant.

Disclosure

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Author Contributions

R.P., K.D, B.D., J.C., A.L.H., and A.G.M. conceived and designed the studies; D.M.D., R.P., A.S., P.L., T.K., E.M., E.G., R.G., C.N.M., and R.F. provided study materials and/or patients; and D.M.D., R.P., K.D., B.D., H.X., J.M.C., A.L.H., and A.G.M. analyzed and/or interpreted data. All authors wrote or critically revised the manuscript for content, and all authors reviewed the final version and gave approval for submission.

Data Availability

Deidentified data sets for the results reported in this publication may be made available to qualified researchers following submission of a methodologically sound proposal to datarequests@corcept.com. Data will be made available by Corcept Therapeutics, Inc, for such requests following the online publication of this article and for 1 year thereafter in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

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