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# Effect of a Supratherapeutic Dose of Omaveloxolone on the Corrected QT Interval in Healthy Participants: A Randomized, Double-Blind, Placebo- and Active-Controlled, Three-Way Crossover Study

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**Received:** 25 October 2024 | **Revised:** 20 December 2024 | **Accepted:** 10 January 2025

**Funding:** This study was sponsored by Reata Pharmaceuticals. Reata was acquired by Biogen in 2023.

**Keywords:** omaveloxolone | pharmacokinetics | safety | thorough corrected QT interval | tolerability

## ABSTRACT

Omaveloxolone is approved for the treatment of Friedreich ataxia (FA) in patients aged ≥16 years at a dose of 150 mg once daily. This double-blind, randomized, placebo- and active-controlled, three-way crossover, thorough corrected QT interval (QTc) study (NCT05927649) evaluated the effect of supratherapeutic omaveloxolone exposure on QTc to exclude a clinically significant prolongation (defined as >10 ms). Healthy adults were randomized to one of six sequences of three single oral doses (omaveloxolone 450 mg, placebo, or moxifloxacin 400 mg [open-label positive control]) administered with an FDA high-fat meal. Serial pharmacokinetic blood sampling and time-matched electrocardiogram assessments were performed. The primary endpoint was placebo-corrected change from baseline in QTcF (ΔΔQTcF) following omaveloxolone administration. Secondary endpoints included pharmacokinetic parameters of omaveloxolone and its major plasma metabolites (M17 and M22) and safety. All 30 enrolled participants completed the study. The mean omaveloxolone $C_{max}$ was 319 ng/mL in this study (4.5-fold the mean steady-state $C_{max}$ [71.5 ng/mL] with the approved dose). The mean QTcF intervals were <450 ms, and mean changes from baseline were <10 ms at all timepoints following all doses. The upper limit of the 90% CIs of ΔΔQTcF following omaveloxolone administration was <10 ms at all timepoints. At the $C_{max}$ of omaveloxolone, M17, and M22, alone or combined, the upper limits of the 90% CIs of the model-predicted ΔΔQTcF were all <10 ms. No safety concerns were identified. Supratherapeutic omaveloxolone exposure that covers the worst-case clinical exposure did not cause a clinically significant QTc prolongation and was generally well tolerated.

## 1 | Introduction

Friedreich ataxia (FA) is a progressive, autosomal recessive neurodegenerative disorder characterized by difficulty with ambulation, coordination, and speech [1]. In addition to ataxia, FA has multisystem involvement that manifests clinically as cardiomyopathy, scoliosis, and diabetes, among others, contributing to the overall burden of the disease [2–4].

Omaveloxolone is an Nrf2 activator approved in the US and the EU for the treatment of FA in patients aged ≥16 years, at an oral dose of 150 mg once daily (QD), administered in the form of three 50-mg capsules or as capsule contents sprinkled on and

Scott M. Hynes: Employee at the time of development of this publication.

**Summary**

- What is the current knowledge on the topic?
  - Omaveloxolone is approved in patients with Friedreich ataxia (FA) aged ≥16 years at a dose of 150 mg once daily (QD) taken on an empty stomach. A previous concentration-corrected QT interval (QTc) analysis demonstrated a lack of QTc prolongation in healthy participants receiving omaveloxolone 150 mg QD in the fasted state or in the fed state (considered the worst-case clinical exposure, given that the maximum plasma concentration [$C_{max}$] was 4.5-fold higher when taken with a high-fat meal).
- What question did this study address?
  - This double-blind, placebo- and active-controlled, three-way crossover thorough QTc study further evaluated the effect of a supratherapeutic omaveloxolone dose (450 mg administered with a high-fat meal) on QTc to exclude a clinically significant prolongation (defined as > 10 ms).
- What does this study add to our knowledge?
  - At a mean omaveloxolone $C_{max}$ of 319 ng/mL achieved in this study (4.5-fold the mean steady-state $C_{max}$ [71.5 ng/mL] in patients with FA), omaveloxolone and its major plasma metabolites (M17 and M22, alone or combined) did not have a clinically significant effect on the QTc interval (based on the Fridericia formula [QTcF]). The upper limit of the 90% confidence intervals (CIs) of placebo-corrected change from baseline in QTcF (ΔΔQTcF) following omaveloxolone administration was < 10 ms at all timepoints. At $C_{max}$ of omaveloxolone, M17, and M22, alone or combined, the upper limit of the 90% CIs of the model-predicted ΔΔQTcF was < 10 ms. No new safety concerns were identified.
- How might this change clinical pharmacology or translational science?
  - Supratherapeutic omaveloxolone exposure covering the worst-case clinical exposure scenario did not have a clinically significant impact on the QTc interval and was generally well tolerated.

mixed in 2 tablespoons (30 mL) of applesauce, on an empty stomach ≥ 1 h before (US and EU) or 2 h after (EU) eating [5–7].

Following oral administration, omaveloxolone is slowly absorbed, with a median time to maximum plasma concentration ($t_{max}$) of 7–14 h in the fasted state [5, 8]. Omaveloxolone is primarily eliminated through feces and is metabolized by CYP3A4, and to a lesser extent, CYP2C8 and CYP2J2 [5, 8]. Omaveloxolone terminal elimination half-life ($t_{1/2}$) ranges from 32 to 90 h, with a mean $t_{1/2}$ of 57 h [5, 8]. There is a dose-proportional increase in the area under the plasma concentration versus time curve (AUC) at omaveloxolone doses ranging from 50 to 150 mg, but the maximum plasma concentration ($C_{max}$) increased in a slightly less than dose-proportional manner in healthy fasted participants [8].

The International Council for Harmonization of Technical Requirements for Human Use (ICH) 14 guideline calls for most drugs to be assessed for possible effects on cardiac repolarization through thorough QT (TQT) studies in the drug development process to confirm exclusion of clinically significant corrected QT interval (QTc) prolongation (defined as > 10 ms) [9, 10]. The safety pharmacology program demonstrated that the risk of adverse effects of omaveloxolone on the cardiovascular human ether-a-go-go-related gene (hERG) assay and conscious telemetered-monkey model, respiratory (rat model), and central nervous (rat model) systems of humans was considered to be minimal. In the monkey cardiovascular study, omaveloxolone at doses of up to 100 mg/kg did not produce meaningful changes in blood pressure, or qualitative or quantitative electrocardiogram (ECG) parameters (PR, RR, QRS, or QT interval; data on file). The mean $C_{max}$ at the 100-mg/kg dose corresponded to approximately five-times the maximal steady-state plasma omaveloxolone maximum plasma concentration at steady state ($C_{max,ss}$) in patients with FA administered an omaveloxolone dose of 150 mg. In a patch-clamp assay using human embryonic kidney (HEK) 293 cells stably expressing hERG, superfusion of omaveloxolone at concentrations of 0.75 and 1.2 μM produced minimal concentration-dependent blockage of hERG current, with approximately 6.73% ± 4.24% and 21.5% ± 5.4% inhibition, respectively, compared to 0.675% ± 2.120% for the vehicle control (physiological salt solution with 0.1% acetone) (data on file). The 0.75-μM omaveloxolone concentration corresponds to approximately 188-times the $C_{max,ss}$ in patients with FA administered an omaveloxolone dose of 150 mg. A previous omaveloxolone concentration versus QTc analysis predicted a lack of QTc prolongation in healthy participants receiving the therapeutic dose (150 mg QD administered in the fasted state) approved for patients with FA or worst-case clinical exposure (150 mg QD administered in the fed state) (Zahir, H., Hynes, S., Shinde, A. & Lohmer, L.R.L. ACoP14, 2023; abstract PMX-559). The upper bound of the bias-corrected 90% CI for concentration-related ΔQTcF at the highest predicted $C_{max}$ was 0.582 ms using the final model and 3.25 ms using the food effect sensitivity model from fasted data only. The upper bound of the 90% CI is < 10 ms for both models across the range of concentrations included in the analysis. Therefore, a 10-ms increase in QTc interval could be ruled out at the therapeutic dose of omaveloxolone recommended in patients with FA and clinical worst-case exposures. However, as there was minimum observed data at the clinical worst-case exposure, a TQTc study was conducted to evaluate the effect at the supratherapeutic dose and exposure of omaveloxolone on the QTc interval.

The current TQT study was conducted in healthy participants to assess the effect of supratherapeutic plasma concentrations of omaveloxolone and major plasma metabolites (M17 and M22) on the QTc interval following the administration of a single 450-mg dose in the fed state that covers the worst-case clinical exposure scenario using concentration-QTc (CQTc) analysis. In addition, the safety and tolerability of this supratherapeutic dose of omaveloxolone, pharmacokinetic (PK) parameters of omaveloxolone and its major plasma metabolites (M17 and M22), and the effect on secondary ECG parameters were evaluated.

## 2 | Methods

### 2.1 | Study Design and Participants

This was a randomized, double-blind, placebo- and active-controlled, three-way crossover, corrected TQT study

(NCT05927649) in healthy adults. The study participants were healthy women and men, aged 18–55 years with a body mass index of 18–32 $kg/m^2$ at screening and no clinically significant findings based on medical history, physical examination, vital signs, laboratory profile, and a safety 12-lead ECG. Participants were excluded if they had ECG abnormalities at screening and baseline, including QTc of > 450 ms for men and > 460 ms for women, heart rate (HR) of < 45 or > 100 beats per min after 5 min in a supine position, PR interval of > 220 ms and QRS interval of > 110 ms, history of prolonged QTc, cardiac arrhythmia, or a first-degree relative with congenital long QT syndrome or unexplained sudden death at a young age. Further information on inclusion and exclusion criteria is in Appendix S1.

Following a 21-day screening period, eligible individuals were randomized to receive single oral doses of (A) omaveloxolone 450 mg, (B) placebo, or (C) moxifloxacin 400 mg (open-label positive control) in three separate periods, resulting in the following six sequences: ABC, ACB, BAC, BCA, CAB, and CBA to maintain blind dosing (Figure S1). There was a 14-day washout period after either omaveloxolone or placebo dosing and a 3-day washout period following administration of moxifloxacin. Study doses were administered 30 min after participants received the US Food and Drug Administration (FDA)–approved high-fat meal. All food and drink were prohibited from ≥ 10 h before study drug administration, except for water at 1 h before and 1 h after administration. No food and drinks (other than water) were allowed for approximately 5 h after omaveloxolone or placebo dosing.

A single 450-mg dose of omaveloxolone (nine 50-mg capsules) was administered with the FDA high-fat meal to achieve a supratherapeutic exposure. In the MOXIe registrational trial, the predicted mean $C_{max,ss}$ following the administration of omaveloxolone 150 mg QD (approved therapeutic dose) in the fasted state in patients with FA was 71.5 ng/mL [11]. In a food effect study (study 1703; NCT03664453), the administration of a single 150-mg dose of omaveloxolone with a high-fat meal in healthy participants resulted in a 4.5-fold increase in $C_{max}$ over that under fasted conditions [11, 12]. Assuming linear PK, it was estimated that a mean $C_{max}$ of approximately 357 ng/mL would be achieved in the present study following a single 450-mg dose of omaveloxolone in healthy participants when administered with a high-fat meal, which is approximately five-times the predicted mean $C_{max.ss}$ following the approved therapeutic dose of 150 mg QD taken under fasted conditions and covers the worst-case clinical exposure scenario. Concomitant medications, including other CYP3A4 modulators, were not allowed, except for the use of acetaminophen (≤ 2 g/day), aspirin, or nonsteroidal anti-inflammatory agents and 1% topical hydrocortisone for contact dermatitis at the discretion of the investigator. Participants were confined to the clinical unit from Study Day −1 to 32. Study participants received a standardized diet for all meals during the confinement period and were only permitted to consume the scheduled meals and water to quench thirst. All other food and drink were prohibited, including alcohol, grapefruit, grapefruit products, star fruit, star fruit products, Seville oranges, Seville orange products, caffeine, and herbal supplements of any kind. Alcohol, grapefruit and associated products, star fruit and associated products, and Seville oranges and associated products were not permitted to be consumed within the 72-h period before study drug administration on Study Day 1. Strenuous activity (e.g., heavy lifting, weight training, calisthenics, aerobics) was not permitted for ≥ 72 h before admission to the clinical research unit and through to the collection of the last protocol-specified blood sample.

## 2.2 | Study Endpoints

The primary endpoint was placebo-corrected change from baseline in the standard interval between the *Q* and *T* waves corrected for HR using the Fridericia formula (ΔΔQTcF). Secondary endpoints included ΔΔQTcF following administration of moxifloxacin (to determine assay sensitivity), safety, PK parameters of omaveloxolone and its major plasma metabolites (M17 and M22), and secondary ECG parameters (HR, PR interval, QRS interval, and *T*-wave morphology). Safety endpoints included the frequency of adverse events (AEs), including treatment-emergent AEs (TEAEs) and serious AEs, and findings from clinical laboratory tests, physical examinations, vital signs, and 12-lead ECGs. PK parameters included $C_{max}$, AUC from time 0 to the time of the last measurable concentration ($AUC_{0\text{-last}}$), and AUC from time 0 extrapolated to infinity ($AUC_{0\text{-}\infty}$). Additional PK parameters calculated for omaveloxolone included $t_{max}$, the terminal elimination rate constant ($\lambda_z$), the apparent plasma $t_{1/2}$, percent of AUC from time 0 extrapolated from $AUC_{0\text{-last}}$ to $AUC_{0\text{-}\infty}$, apparent total plasma clearance after extravascular administration, and apparent volume of distribution during the terminal elimination phase after extravascular administration. Additional PK parameters calculated for metabolites M17 and M22 included $C_{max}$, $t_{max}$, $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$, percent of AUC from time 0 extrapolated from $AUC_{0\text{-last}}$ to $AUC_{0\text{-}\infty}$, $\lambda_z$, $t_{1/2}$, and metabolite to parent ratio.

## 2.3 | Cardiodynamic Assessments

Holter ECG monitoring (12-lead ECG recordings) was performed on Day 1 of each dosing period, with ECGs extracted in triplicate from continuous recordings by a central ECG laboratory. Extraction of ECGs for omaveloxolone- and placebo-treated participants occurred at 75, 65, and 45 min pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, and 24 h post dose. For moxifloxacin, extraction of ECGs occurred at 75, 65, and 45 min pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, and 24 h post dose. ECGs were measured using CalECG (AMPS LLC), and data were analyzed by qualified readers from the Celerion ECG core laboratory. To demonstrate the adequacy of QTcF, the QT interval correction was implemented using the Fridericia method for correction as follows, for which RR is 60/(HR):

$$QTcF = QT / (RR)^{1/3}$$

## 2.4 | PK Analysis

Within all study drug sequence groups, blood samples for the measurement of plasma concentrations of omaveloxolone, M17, and M22 were collected for PK analysis in Periods 1 and 2 at pre-dose and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 24, 36, 48, 72,

96, 120, 144, 168, 192, 216, 240, 288, and 336 h post dose. For dosing sequences ABC and BAC, the 336-h sample collected in Period 1 served as the pre-dose for Period 2; for dosing sequences CAB and CBA, the 336-h sample collected in Period 2 served as the pre-dose for Period 3. Blood samples for the measurement of moxifloxacin plasma concentrations were collected in Period 1 at pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, and 24 h post moxifloxacin dose. Sampling windows were within 60 min prior to dosing for the pre-dose sample timepoint; ±5 min for timepoints within the 0.5- to 2-h post-dose range; ±15 min for timepoints within the > 2- to 24-h post-dose range; and ±60 min for the > 24- to 336-h post-dose timepoints. Plasma concentrations of omaveloxolone, M17, M22, and moxifloxacin were determined using validated liquid chromatography–tandem mass spectrometry analytical methods at $Q^2$ Solutions. PK analyses were performed using Phoenix WinNonlin Version 8.3.4.

## 2.5 | Statistical Analysis

Thirty participants were randomized to ensure ≥ 24 evaluable participants (with a minimum of 10 men and 10 women). This would provide > 90% power to exclude omaveloxolone as a cause of a > 10-ms QTc effect at plasma levels that are clinically relevant, established by the upper bound of the two-sided 90% CI of the model-predicted ΔΔQTcF at the observed geometric mean $C_{max}$ of omaveloxolone in the study. It was assumed there would be a small underlying effect of omaveloxolone of 3 ms and SD of the ΔQTcF of 8 ms.

The safety analysis set included all participants who had received ≥ 1 dose of study drug (omaveloxolone, moxifloxacin, and placebo) and had ≥ 1 post-dose safety assessment. The PK analysis set included all participants who received ≥ 1 dose of investigational drug (omaveloxolone or moxifloxacin) and had ≥ 1 measurable concentration; it was used to generate the concentration-time profiles. The PK-evaluable analysis set included participants who received ≥ 1 dose of omaveloxolone and had enough corresponding measurable concentrations to estimate ≥ 1 PK parameter; it was used for the determination of PK parameter(s). The QT/QTc analysis set included all participants in the safety analysis set with QTc measurements at baseline and ≥ 1 post-dose timepoint (with a valid ΔQTcF value) following study drug administration. The PK/QTc analysis set included all participants in both the QT/QTc and PK analysis sets with ≥ 1 pair of post-dose concentrations and QTcF data at the same timepoint.

The baseline for ECG analyses was the average of the three pre-dose timepoints on Day 1 of each respective period. In the primary analysis, a linear mixed-effects modeling approach was used to establish the relationship between ΔQTcF and omaveloxolone and its metabolites (M17 and M22), with ΔQTcF as the dependent variable and time-matched concentration of omaveloxolone and its metabolites as a continuous covariate (i.e., 0 for placebo), centered baseline QTcF as an additional covariate, and study drug (active = 1 or placebo = 0) and time as categorical factors. Using the Kenward-Rogers method, the degrees of freedom for the model estimates were determined [13]. The slope of this model (i.e., the regression parameter for the concentration of omaveloxolone, M17, and M22) and the study drug effect–specific intercept (defined as the difference between active and placebo) were estimated together with two-sided 90% CIs.

The relationship between ΔQTc and omaveloxolone, M17, and M22 plasma concentrations was investigated in seven scenario models: (1) omaveloxolone only, (2) M17 only, (3) M22 only, (4) omaveloxolone, M17, and M22 combined, (5) omaveloxolone and M17 combined, (6) omaveloxolone and M22 combined, and (7) M17 and M22 combined. This was also investigated using a linear mixed-effects modeling approach with ΔQTc as the dependent variable; time-matched concentration of omaveloxolone, M17, and M22 as continuous covariates; centered baseline QTc as an additional covariate; study drug and time as categorical factors; and a random intercept and slope per participant. From the model, the slope and the study drug effect–specific intercept were estimated together with two-sided 90% CIs. The geometric mean of the individual $C_{max}$ values of omaveloxolone was determined together with the geometric mean concentration of M17 and M22 at the $t_{max}$ of omaveloxolone. Similarly, the geometric mean of the individual $C_{max}$ values of M17 was determined together with the geometric mean concentration

**TABLE 1** | Baseline characteristics.

| Category | Overall ($N = 30$) |
|---|---|
| Age (years) | |
| Mean ± SD | 35.4 ± 8.69 |
| Median (min, max) | 34.5 (18, 49) |
| Sex, *n* (%) | |
| Female | 10 (33.3) |
| Male | 20 (66.7) |
| Race, *n* (%) | |
| Asian | 1 (3.3) |
| Black or African American | 4 (13.3) |
| White | 25 (83.3) |
| Ethnicity, *n* (%) | |
| Hispanic or Latino | 25 (83.3) |
| Not Hispanic or Latino | 5 (16.7) |
| Body mass index (kg/m$^2$) | |
| Mean ± SD | 26.394 ± 3.1441 |
| Median (min, max) | 25.765 (20.18, 31.69) |
| Height (cm) | |
| Mean ± SD | 169.4 ± 9.35 |
| Median (min, max) | 171.0 (155, 186) |
| Weight (kg) | |
| Mean ± SD | 75.98 ± 11.807 |
| Median (min, max) | 75.65 (55.0, 94.2) |

*Note:* Descriptive statistics for body mass index, height, and weight were calculated using screening measurements.

of omaveloxolone and M22 at the individual $t_{max}$ of M17. Additionally, the geometric mean of the individual $C_{max}$ values of M22 was determined together with the geometric mean concentration of omaveloxolone and M17 at the individual $t_{max}$ of M22. The predicted effect and its two-sided 90% CI for ΔΔQTc (primary endpoint) (i.e., the product with the slope estimate + treatment effect from the linear mixed-effects model) at these geometric means of concentrations were obtained for the model with all analytes. The predicted effect at the geometric mean $C_{max}$ of the respective analyte was also obtained for the purpose of simplicity in the graphic display. If the upper bound of the two-sided 90% CI of the predicted effect at this plasma level was < 10 ms, it was concluded that omaveloxolone or its metabolites, M17 and M22, did not cause QTc prolongation of regulatory concern. These analyses were performed using the PK/QTc analysis set.

Assay sensitivity was also evaluated by analyzing the exposure response (ΔΔQTc) of 400 mg oral moxifloxacin, using the same model as the concentration-QTc primary analysis. Assay sensitivity was evaluated with ΔΔQTcF at the geometric mean $C_{max}$ value predicted from a linear mixed-effect model examining the relationship between QTc and moxifloxacin plasma concentrations. Sensitivity would be demonstrated if the moxifloxacin plasma concentration/ΔΔQTcF relationship was statistically significant ($\alpha = 0.10$) and the lower bound of the two-sided 90% CI of the predicted QT effect at the observed geometric mean $C_{max}$ was > 5 ms.

## 2.6 | Study Oversight

The study protocol was reviewed prior to study initiation by the Advarra institutional review board, which operates in compliance with FDA regulations. This study was conducted in accordance with the ICH E6 guidelines originally set out within the Declaration of Helsinki. Written informed consent was obtained from all participants prior to study initiation.

# 3 | Results

## 3.1 | Participant Disposition and Baseline Characteristics

A total of 30 participants were enrolled, and all completed study drug dosing. The mean age was 35.4 years, 67% were men, and 83% were White (Table 1).

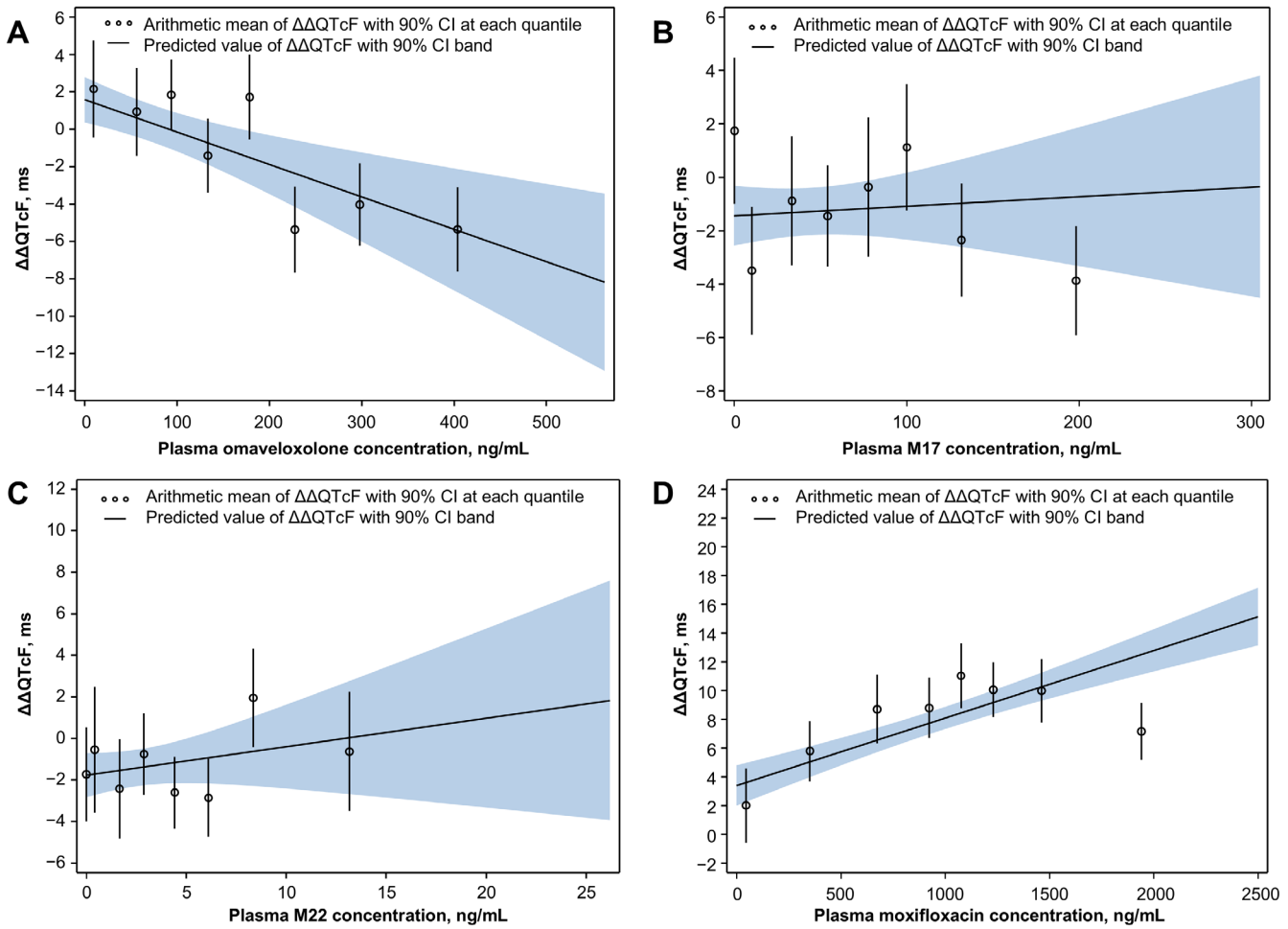


**FIGURE 1** | Exposure-response ΔΔQTcF versus concentration (study baseline) for (A) omaveloxolone, (B) M17, (C) M22, and (D) moxifloxacin (positive control). Predicted lines and 90% CIs (blue bands) are from the final linear model. ΔΔQTcF, placebo-corrected change from baseline in QT interval using Fridericia formula.

### 3.2 | Cardiodynamics

Following a single 450-mg dose of omaveloxolone in a fed state, mean triplicate-average 12-lead ECG parameters remained within normal limits for all post-dose timepoints, and changes from baseline were generally small for all doses. Overall mean triplicate-average QTcF intervals were < 450 ms and decreased from baseline at all timepoints (ranging from −5.8 ms at Hour 24 to −16.9 ms at Hour 2 compared with study baseline) following omaveloxolone dosing. For all timepoints, the central tendency of the upper bound of the two-sided 90% CI for omaveloxolone was < 10 ms (regulatory threshold). There were no individual triplicate-average QTcF intervals that exceeded 450 ms or individual QTcF interval increases from baseline of > 30 ms following all doses.

### 3.3 | Exposure-Response ΔΔQTcF versus Concentration

Quantiles of plasma concentration and ΔΔQTcF overlaid with the slope of the final model of each analyte for study baseline are presented in Figure 1 (this applied to single-analyte model scenarios). The mean concentrations of omaveloxolone, M17, and M22 for each quantile overlapped with the 90% confidence band associated with the model, indicating that the final selected model represents the actual observed data.

### 3.4 | Model-Predicted ΔΔQTcF and 90% CI at Geometric Mean $C_{max}$ of Omaveloxolone and Metabolites

The model-predicted relationship between ΔΔQTcF (from study baseline) versus time-matched plasma concentrations of the analytes following a single oral dose of omaveloxolone is presented in Figure 2A–C. At geometric mean $C_{max}$ of omaveloxolone, M17, and M22, the predicted ΔΔQTcF was −3.593, −0.877, and −0.301 ms at study baseline, respectively (Table 2). The upper bounds for the two-sided 90% CI were −1.223, 1.117, and 1.870 ms for omaveloxolone, M17, and M22, respectively, which fall below the regulatory threshold of 10 ms, indicating no significant QTc prolongation. Similar results were reported for omaveloxolone and its major plasma metabolites, M17 and M22, based on period baseline, with the upper bounds for the two-sided 90% CI being −1.226, 1.053,

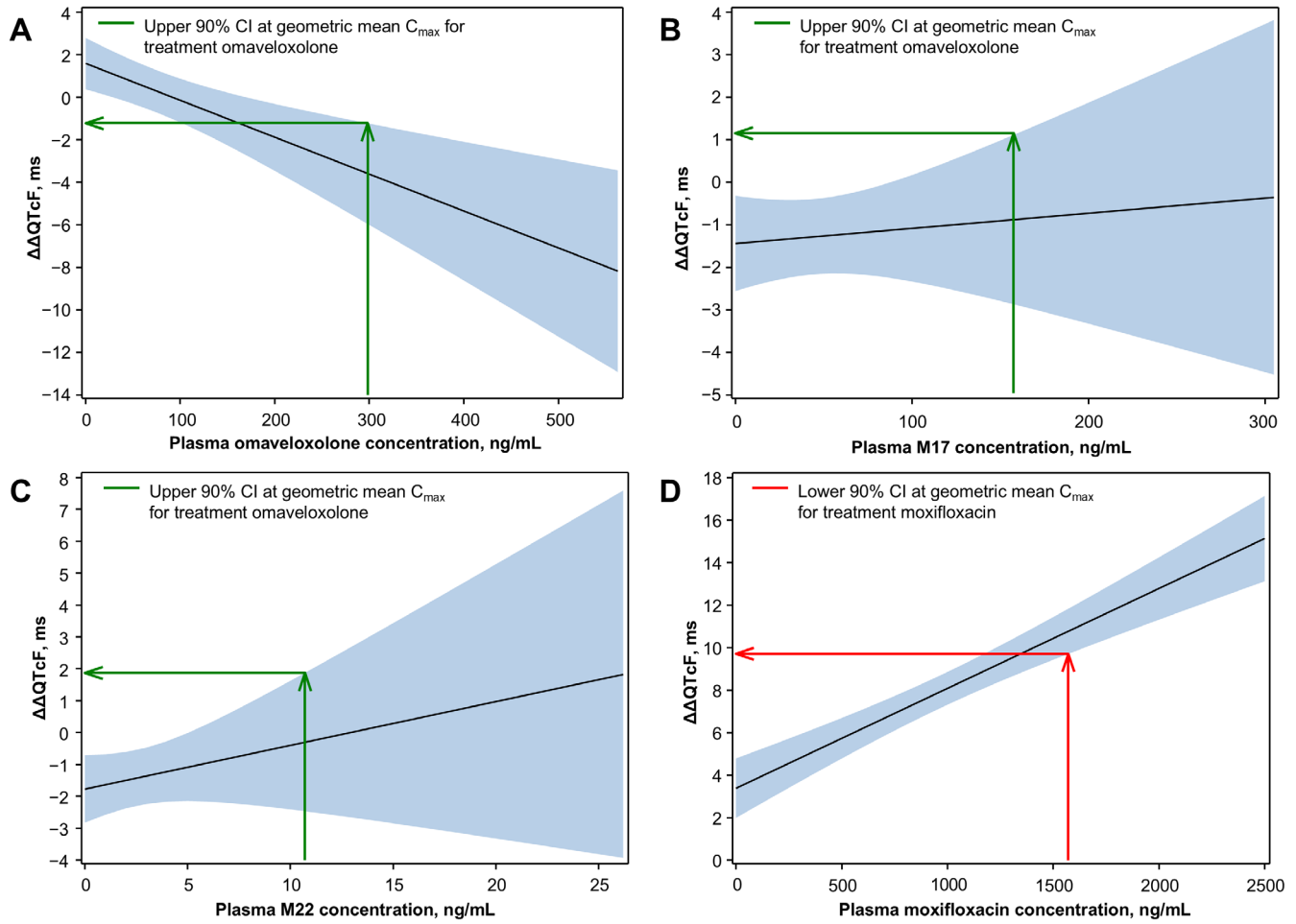


**FIGURE 2** | Predicted ΔΔQTcF versus time-matched plasma concentrations for (A) omaveloxolone, (B) M17, (C) M22 concentrations, and (D) moxifloxacin (study baseline) (PK/QTc analysis set). Predicted lines and 90% CIs (blue bands) are from the final linear model. The upper 90% CI of ΔΔQTcF at geometric mean $C_{max}$ of omaveloxolone, M17, or M22 is determined by interpolation (shown by green arrows). The lower 90% CI of ΔΔQTcF at geometric mean $C_{max}$ of moxifloxacin is determined by interpolation (shown by red arrows). $C_{max}$, maximum plasma concentration; PK, pharmacokinetics; QTc, corrected QT interval; ΔΔQTcF, placebo-corrected change from baseline in QT interval using Fridericia formula.

and 1.864, respectively (Table 2). Further combined final predicted scenario models of omaveloxolone and its metabolites at geometric $C_{max}$ showed that the predicted ΔΔQTcF at study baseline and period baseline fell below the regulatory threshold of 10 ms, and the upper bounds for the two-sided 90% CIs were also < 10 ms (Table 2). This further indicates that omaveloxolone and its metabolites (alone or combined) did not cause clinically significant QTc prolongation.

### 3.5 | Assay Sensitivity

The predicted ΔΔQTcF at the geometric mean $C_{max}$ of moxifloxacin (1571 ng/mL) was 10.77 ms based on study baseline and 9.24 ms based on period baseline. The lower bounds of the 90% CIs were 9.71 ms based on study baseline (Figure 2D) and 8.24 ms based on period baseline; a value of > 5 ms indicated QTcF prolongation, which meant that assay sensitivity was established.

### 3.6 | Pharmacokinetics

#### 3.6.1 | Mean Plasma Omaveloxolone and Metabolite Concentrations Over Time

The arithmetic mean peak plasma omaveloxolone concentration (280.7 ng/mL) was reached by 6 h post dose; concentrations in all participants were quantifiable by the first post-dose sample at 0.5 h and were maintained throughout the entire 336-h collection period (Figure 3A). The arithmetic mean $C_{max}$ of M17 (160.8 ng/mL) was reached by 10 h (Figure 3B). Among 30 participants, M17 concentrations were quantifiable in five, 29, and all 30 participants by 0.5, 1, and 2 h post dose, respectively, and were maintained in all but two participants throughout the 336-h collection period. The arithmetic mean $C_{max}$ of M22 (10.54 ng/mL) was reached by 12 h (Figure 3C). Among 30 participants, M22 concentrations were quantifiable in 0, 13, 29, and all 30 participants by 0.5, 1, 2, and 3 h post dose, respectively. M22 concentration remained quantifiable in all participants through 168 h and in 26, 27, 21, 14, and six participants by 192, 216, 240, 288, and 336 h post dose, respectively.

#### 3.6.2 | Plasma Omaveloxolone and Metabolite PK Parameters

Table 3 shows PK parameters for omaveloxolone and its metabolites M17 and M22. A supratherapeutic 450-mg dose of omaveloxolone in the fed state resulted in a mean plasma $C_{max}$ of 319 ng/mL, which is 4.5-fold the predicted mean plasma omaveloxolone $C_{max,ss}$ in patients with FA (71.5 ng/mL). The geometric mean plasma omaveloxolone $C_{max}$, $AUC_{0\text{-last}}$, and $AUC_{0\text{-}\infty}$ were approximately 298 ng/mL, 5589 ng·h/mL, and 5725 ng·h/mL, respectively, with a median $t_{max}$ of 5 h and an arithmetic mean plasma omaveloxolone $t_{1/2}$ of approximately 81.1 h. The geometric mean plasma M17 $C_{max}$, $AUC_{0\text{-last}}$, and $AUC_{0\text{-}\infty}$ were approximately 158 ng/mL, 2991 ng·h/mL, and 3024 ng·h/mL, respectively, with a median $t_{max}$ of 10 h and an arithmetic mean plasma $t_{1/2}$ of approximately 79.7 h, similar to the rate of elimination for omaveloxolone. The geometric mean plasma M22 $C_{max}$, $AUC_{0\text{-last}}$, and $AUC_{0\text{-}\infty}$ were approximately 10.7 ng/mL, 300.4 ng·h/mL, and 305.6 ng·h/

**TABLE 2** | Model-predicted ΔΔQTcF and 90% CI at geometric mean $C_{max}$ of omaveloxolone and metabolites.

| | Study baseline | | Period baseline | |
|---|---|---|---|---|
| | Predicted maximum ΔΔQTcF (ms) | 90% CI (ms) | Predicted maximum ΔΔQTcF (ms) | 90% CI (ms) |
| Omaveloxolone (at $C_{max}$) | −3.593 | −5.962 to −1.223 | −3.549 | −5.871 to −1.226 |
| M17 (at $C_{max}$) | −0.877 | −2.871 to 1.117 | −1.011 | −3.074 to 1.053 |
| M22 (at $C_{max}$) | −0.301 | −2.472 to 1.870 | −0.215 | −2.295 to 1.864 |
| Omaveloxolone (at $C_{max}$) + M17 | −4.225 | −6.763 to −1.687 | −4.250 | −6.661 to −1.839 |
| Omaveloxolone + M17 (at $C_{max}$) | 0.099 | −1.807 to 2.004 | 0.306 | −1.530 to 2.142 |
| Omaveloxolone (at $C_{max}$) + M22 | −4.158 | −6.628 to −1.688 | −4.086 | −6.393 to −1.779 |
| Omaveloxolone + M22 (at $C_{max}$) | 1.291 | −0.558 to 3.140 | 1.222 | −0.641 to 3.085 |
| M17 (at $C_{max}$) + M22 | −0.819 | −2.752 to 1.115 | −0.703 | −2.758 to 1.352 |
| M17 + M22 (at $C_{max}$) | 0.109 | −1.976 to 2.194 | −0.202 | −2.486 to 2.083 |
| Omaveloxolone (at $C_{max}$) + M17 + M22 | −3.027 | −4.028 to −2.026 | −3.487 | −4.466 to −2.508 |
| Omaveloxolone + M17 (at $C_{max}$) + M22 | −0.040 | −1.220 to 1.140 | 0.409 | −0.746 to 1.563 |
| Omaveloxolone + M17 + M22 (at $C_{max}$) | 0.523 | −0.748 to 1.794 | 0.155 | −1.088 to 1.399 |

Abbreviations: $C_{max}$, maximum plasma concentration; ΔΔQTcF, placebo-corrected change from baseline in QT interval using Fridericia formula.

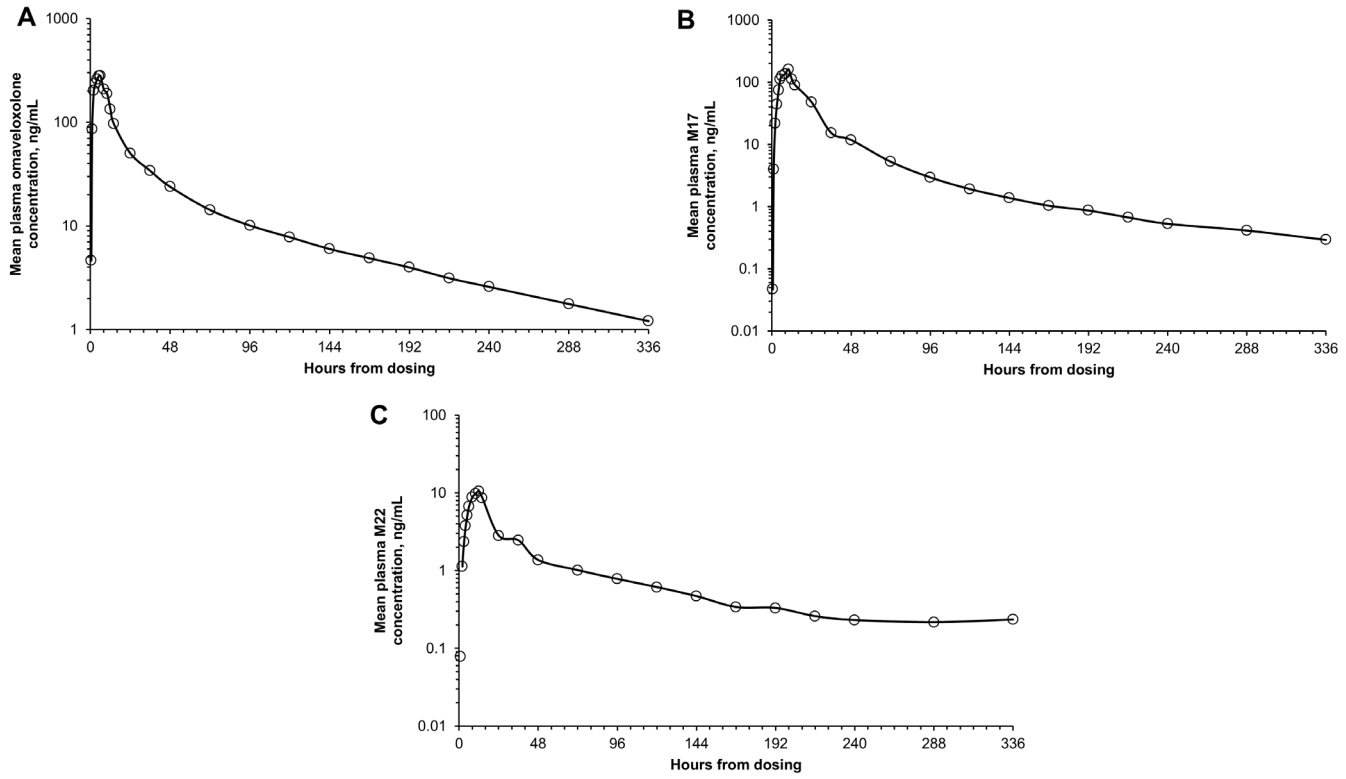


**FIGURE 3** | Arithmetic mean plasma (A) omaveloxolone, (B) M17, and (C) M22 concentrations over time (semi-log scale) (PK analysis set). PK, pharmacokinetics.

**TABLE 3** | Summary of plasma omaveloxolone and metabolite PK parameters.

| | Omaveloxolone ($N=30$) | M17 ($N=30$) | M22 ($N=30$) |
|---|---|---|---|
| Geometric mean $C_{max}$ (ng/mL) | 298.4 | 157.8 | 10.71 |
| $t_{max}$ (h)[a] | 5.0 (1.0, 10.0) | 10.0 (5.0, 12.0) | 12.0 (5.0, 14.0) |
| $AUC_{0\text{-last}}$ (ng·h/mL)[b] | 5589 (35.9) | 2991 (28.7) | 300.4 (35.4) |
| $AUC_{0\text{-}\infty}$ (ng·h/mL)[b] | 5725 (36.3) | 3024 (29.0) | 305.6 (34.3) |
| $AUC_{\%extrap}$ (%)[c] | 2.4 ± 1.2 | 1.1 ± 1.1 | 3.2 ± 1.3[d] |
| $t_{1/2}$ (h)[c] | 81.1 ± 16.0 | 79.7 ± 26.5 | 58.5 ± 17.7[d] |
| CL/$F$ (L/h)[c] | 83.4 ± 29.0 | — | — |
| $V_z/F$ (L)[c] | 9678 ± 3803 | — | — |
| MPR $AUC_{0\text{-last}}$(%)[c] | — | 53.89 ± 14.86 | 5.41 ± 1.88 |
| MPR $AUC_{0\text{-}\infty}$(%)[c] | — | 53.19 ± 14.67 | 5.35 ± 1.82[d] |

Abbreviations: $AUC_{\%extrap}$, percent of area under the plasma concentration versus time curve from time zero extrapolated from $AUC_{0\text{-last}}$ to $AUC_{0\text{-}\infty}$; $AUC_{0\text{-}\infty}$, area under the concentration versus time curve from time 0 extrapolated to infinity; $AUC_{0\text{-last}}$, area under the plasma concentration versus time curve from time 0 to the time of the last measurable concentration; CL/$F$, apparent total plasma clearance after extravascular administration; $C_{max}$, maximum plasma concentration; MPR, metabolite-to-parent ratio; PK, pharmacokinetics; $t_{1/2}$, apparent plasma terminal elimination half-life; $t_{max}$, time to achieve $C_{max}$; $V_z/F$, apparent volume of distribution during the terminal elimination phase after extravascular administration.
[a]Median (min, max).
[b]Geometric mean (geometric CV%).
[c]Mean ± SD.
[d]$N=29$.

mL, respectively, with a median $t_{max}$ of 12.0 h and an arithmetic mean plasma $t_{1/2}$ of approximately 58.5 h. Metabolite-to-parent ratio $AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$ for M17 were similar at 53.89% and 53.19%, respectively, and were higher than those for M22 at 5.41% and 5.35%.

### 3.7 | Safety

There were no deaths, serious AEs, or discontinuations due to AEs in this study. Overall, TEAEs were minimally reported, with a total of 21 experienced by 10 participants in the

**TABLE 4** | Safety summary.

| Adverse event, *n* (%) | Study drug | | | Overall (*N* = 30) |
|---|---|---|---|---|
| | Omaveloxolone (*N* = 30) | Placebo (*N* = 30) | Moxifloxacin (*N* = 30) | |
| Number of participants with TEAEs | 6 (20.0) | 6 (20.0) | 0 | 10 (33.3) |
| Eye disorders | 2 (6.7) | 0 | 0 | 2 (6.7) |
| Ocular hyperemia | 1 (3.3) | 0 | 0 | 1 (3.3) |
| Vision blurred | 1 (3.3) | 0 | 0 | 1 (3.3) |
| Gastrointestinal disorders | 2 (6.7) | 2 (6.7) | 0 | 3 (10.0) |
| Abdominal pain upper | 0 | 1 (3.3) | 0 | 1 (3.3) |
| Constipation | 1 (3.3) | 1 (3.3) | 0 | 2 (6.7) |
| Diarrhea | 1 (3.3) | 0 | 0 | 1 (3.3) |
| Nausea | 2 (6.7) | 0 | 0 | 2 (6.7) |
| General disorders and administration site conditions | 2 (6.7) | 0 | 0 | 2 (6.7) |
| Feeling hot | 2 (6.7) | 0 | 0 | 2 (6.7) |
| Nervous system disorders | 1 (3.3) | 2 (6.7) | 0 | 2 (6.7) |
| Headache | 1 (3.3) | 1 (3.3) | 0 | 2 (6.7) |
| Somnolence | 0 | 1 (3.3) | 0 | 1 (3.3) |
| Psychiatric disorders | 0 | 1 (3.3) | 0 | 1 (3.3) |
| Insomnia | 0 | 1 (3.3) | 0 | 1 (3.3) |
| Renal and urinary disorders | 0 | 1 (3.3) | 0 | 1 (3.3) |
| Dysuria | 0 | 1 (3.3) | 0 | 1 (3.3) |
| Respiratory, thoracic, and mediastinal disorders | 2 (6.7) | 1 (3.3) | 0 | 3 (10.0) |
| Nasal congestion | 0 | 1 (3.3) | 0 | 1 (3.3) |
| Oropharyngeal pain | 1 (3.3) | 0 | 0 | 1 (3.3) |
| Rhinorrhea | 1 (3.3) | 0 | 0 | 1 (3.3) |
| Skin and subcutaneous tissue disorders | 1 (3.3) | 0 | 0 | 1 (3.3) |
| Erythema | 1 (3.3) | 0 | 0 | 1 (3.3) |

*Note:* Omaveloxolone: 450 mg (nine 50-mg capsules) administered orally as a single dose with an FDA high-fat meal. Placebo: visually matching omaveloxolone; administered orally as a single dose with an FDA high-fat meal. Moxifloxacin: 400-mg tablet (open label) administered orally as a single dose with an FDA high-fat meal. Although a participant may have had ≥ 2 AEs, the participant is counted only once within a category. The same participant may appear in different categories. AEs are classified according to MedDRA version 23.1.
Abbreviations: FDA, US Food and Drug Administration; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

study, with six participants reporting events following dosing with omaveloxolone and six participants following placebo (see Table S1 for a complete list of AEs per participant in the study); all TEAEs were reported by ≤ 2 participants (6.7%) each (Table 4). Seventeen events (omaveloxolone [*n* = 12], placebo [*n* = 5]) were considered mild in severity, and four events (omaveloxolone [*n* = 1], placebo [*n* = 3]) were considered to be of moderate severity. Fourteen events (omaveloxolone [*n* = 10], placebo [*n* = 4]) were considered to be related, five events to be possibly related (omaveloxolone [*n* = 2], placebo [*n* = 3]), one event unlikely related, and one event unrelated to the study drug. The frequency of TEAEs for each preferred term was low (≤ 2 events following either omaveloxolone or placebo administration). The most common TEAEs following omaveloxolone administration were nausea and feeling hot. No TEAEs were reported after moxifloxacin treatment. All TEAEs resolved before the end of the study, and the TEAE with the longest duration resolved within 11.3 days. There were no clinically significant findings in the assessments for clinical laboratory tests, vital signs, and 12-lead ECGs.

## 4 | Discussion

This randomized, double-blind, placebo- and active-controlled, three-way crossover TQT study in healthy adults evaluated the effect of oral omaveloxolone on QTcF when administered at a supratherapeutic dose of 450 mg with an FDA high-fat meal. Pharmaceutical agents from a wide range of therapeutic settings have an established risk of causing QTc interval prolongation, resulting in increased susceptibility to cardiac arrhythmia [14]. In the present study, mean triplicate-average 12-lead ECG parameters remained within normal limits for all post-dose timepoints following exposure to supratherapeutic omaveloxolone concentrations. For all doses, mean triplicate-average QTcF intervals were < 450 ms at all post-dose timepoints, and mean changes from baseline were < 10 ms. None of the individual triplicate-average QTcF intervals exceeded 450 ms, and individual increases from baseline were < 30 ms following all doses.

Using time-matched and concentration-QTc analysis, a QTc effect (ΔΔQTcF) greater than the regulatory threshold of 10 ms could be excluded for supratherapeutic omaveloxolone concentrations that were 4.5-fold greater than the $C_{max,ss}$ in patients with FA, signifying that omaveloxolone does not cause a significant QTc prolongation. While the ΔΔQTcF was negative and significantly different from zero for the parent compound, this was small in magnitude and unlikely to be clinically significant. We observed similar trends for metabolites M17 and M22, whether alone or combined with each other or omaveloxolone, where the upper bounds of the two-sided 90% CI estimates were less than the regulatory threshold of concern of 10 ms (based on both study baseline and period baseline analyses). QTc effects for all model-predicted ΔΔQTcF at geometric $C_{max}$ for omaveloxolone, M17, and M22 were ≤ 1.291 ms, far below the 10-ms threshold of concern. Each of the analytes, parent and metabolites, has a well-separated $t_{max}$. As no QTc prolongation was observed at any of the timepoints in the by-timepoint analysis, the by-timepoint analysis also confirms that QTc prolongation risk caused by the parent and individual metabolites can be excluded.

The predicted geometric mean plasma omaveloxolone $C_{max}$ and $AUC_{0-\infty}$ values (357 ng/mL and 3930 ng·h/mL, respectively) for a single 450-mg dose of omaveloxolone administered in the fed state based on PK following a dose of 150 mg in the fed state, compared with the actual geometric mean plasma $C_{max}$ and $AUC_{0-\infty}$ values in this study (298 ng/mL and 5725 ng·h/mL, respectively), suggested that the increase in omaveloxolone $C_{max}$ was approximately dose proportional, while the increase in $AUC_{0-\infty}$ was greater than dose proportional. The mean omaveloxolone $C_{max}$ (319 ng/mL) in this study was 4.5-fold the post hoc predicted mean omaveloxolone $C_{max,ss}$ (71.5 ng/mL) in patients with FA in the MOXIe study and covers the worst-case clinical exposure (i.e., a 4.5-fold increase in $C_{max}$ was observed when omaveloxolone was administered to healthy participants at the therapeutic dose of 150 mg with a high-fat meal in study 1703 [NCT03664453]) [12].

ICH E14 guidance advises the use of a positive control to establish assay sensitivity in TQT studies, assuming the control prolongs the mean QTc interval by 5 ms, which would ensure that the study is able to detect an effect of the study drug [9, 10, 15]. In this study, moxifloxacin 400 mg, the most widely used positive control in studies of this type, was used, with a linear mixed-effects model and predicted ΔΔQTcF geometric $C_{max}$ of 10.770 ms at study baseline. The lower bounds of the 90% CI were 9.709 ms, greater than the 5 ms required to show significant prolongation, indicating that assay sensitivity was obtained and further supporting the validity of this study.

Consistent with the previously demonstrated favorable safety profile of omaveloxolone, administration of a single dose of 450 mg was safe and generally well tolerated [16]. Omaveloxolone has been shown to not increase blood pressure and has not been associated with any other AEs on ECG parameters, including ejection fraction, ventricular heart rate, and QTcF, the significance of which cannot be understated due to the presence of cardiomyopathy in patients with FA [16]. A potential limitation of this study is the enrollment of a healthy adult population, which may not share the same comorbidities or predisposed exposure to cardiomyopathy that is prevalent in patients with FA [17].

In conclusion, this study is the first report to provide conclusive data demonstrating that omaveloxolone and its major plasma metabolites (M17 and M22) did not prolong the QT interval. A supratherapeutic dose of omaveloxolone (450 mg administered in the fed state) that covers the worst-case clinical exposure scenario did not have a clinically significant effect on QTcF and was generally safe and well tolerated.

### Author Contributions

H.Z., M.M., L.W., M.V., and S.M.H. wrote the manuscript. H.Z., M.M., L.W., M.V., and S.M.H. designed the research. H.Z., M.V., and S.M.H. performed the research. H.Z., M.M., L.W., M.V., and S.M.H. analyzed the data.

### Acknowledgments

Medical writing support was provided by James Glen, MRes, and Eric Deutsch, PhD, CMPP, of Nucleus Global, and was funded by Biogen. This manuscript was developed in accordance with Good Publication Practice (GPP2022) guidelines. Authors had full control of the content and made the final decision on all aspects of this publication.

### Conflicts of Interest

Hamim Zahir, Masako Murai, and Lucy Wu are employees of and may hold stock in Biogen. Scott Hynes was an employee of and may have held stock in Biogen at the time of the development of this publication. Michelle Valentine is an employee of Celerion Inc., which was commissioned by Reata Pharmaceuticals to conduct the study; Reata was acquired by Biogen in 2023.

### Data Availability Statement

Individual participant data collected during the trial may be shared after anonymization and on approval of the research proposal. Biogen commits to sharing patient-level data, study-level data, CSRs, and protocols with qualified scientific researchers who provide a methodologically sound proposal. Biogen reviews all data requests internally based on the review criteria and in accordance with our Clinical Trial Transparency and Data Sharing Policy. Deidentified data and documents will be shared under agreements that further protect against participant reidentification. To request access to data, please visit https://vivli.org/.

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## Supporting Information

Additional supporting information can be found online in the Supporting Information section.