"Population PK-QT Analysis Example"

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1 Introduction

The International Council for Harmonization (ICH) revised the E14 Q&A (R3) allowing a population PK-QT modeling to be used as primary analysis for assessing the QTc interval prolongation risk of new drug entities.

PK-QT analysis is intended to determine whether the studied drug has a threshold pharmacologic effect on cardiac repolarization, as detected by QTc prolongation.

2 Objectives

- To perform a population PK-QT analysis to characterize the exposure-response (E-R) relationship between moxifloxacin and the risk of cardiac repolarization, detected by QTc prolongation

3 Data Sources and Description

Moxifloxacin data were extracted from the IQ-CSRC study wherein 5 QT-prolonging drugs and 1 drug for which no QT prolongation was observed in a through QT (TQT) study were evaluated to demonstrate that E-R analysis could detect QT prolongation in small studies with healthy volunteers.

The data we will use today are from subjects administered moxifloxacin 400 mg orally (therapeutic dose) on Day 1 followed by 800 mg IV (supratherapeutic dose) on Day 2.

Study subjects were wearing a Holter monitor for electrocardiogram (ECG) recording for 24 hrs. Ten ECG recordings and blood samples for PK analysis were collected at each time point. All study treatments had identical sample collection time points. Placebo PK samples were only to be analyzed if deemed necessary.

Pharmacokinetic sampling and ECG assessments for placebo and moxifloxacin were done at predose, 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 hr post-dose. Pre-dose ECG assessments were done at -30, -20, -10, and right before dosing. Baseline ECG values were determined by the mean of the average of the 10 recordings collected at the scheduled times. Blood samples were taken after completion of ECG recordings.

3.1 ECG Acquisition and Measurements

Describe ECG collection methodology for your study here, e.g., manually overread at a core ECG lab, readers were/were not blinded to treatment, each subject's ECGs were read by the same reader to minimize between-rater variability, etc.

3.2 Data manipulation

Data were to be excluded if the paired ECG and PK samples were not collected within 15 min of one another and/or if ECG or PK data were missing for a particular time point (with the exception of baseline assessments and placebo treatment where PK is not collected or is zero).

4 Analysis Methods

4.1 Computational Software

The population PK-QT analysis was conducted using a population approach and linear mixed effects models. Estimation was conducted using R Studio using R version 4.0.0 (2020-04-24) (R Foundation for Statistical Computing, Vienna, Austria) [R Core Team, 2014] with the nlme package [Pinheiro et al., 2017] and maximum likelihood estimation or restricted maximum likelihood estimation. Data manipulation, post-processing, and graphics were conducted using R.

4.2 Model Strategy

Prior to starting modeling efforts, graphical and tabular summaries were created to check some basic assumptions that will drive the model development:

- Drug effect on HR: The potential of the drug to significantly increase or decrease HR. There is no clear consensus on the specific threshold effect on HR that could influence QTc assessment, however, mean increases or decreases of greater than 10 bpm have been considered problematic [Garnett et al., 2012]
- Demonstration of QT Correction: QTc interval is independent of HR for drug-free and/or placebo treatments. QTcF is usually sufficient correction method for drugs with insignificant effects on HR.
- Assessment of Time Delay Between Drug Concentration and ΔQTc: The default model assumption is a direct temporal relationship between drug concentration and QTc effect.

Following the basic model independent check the next steps are:

- Model Development
- Model adequacy

4.3 Effect of Moxifloxacin on Heart Rate

Prior to determining the most appropriate QT correction factor, the effect of studied drug treatment on heart rate (HR) was evaluated to support the assumption that the QT-HR relationship is the same regardless of the presence or absence of drug. Plots were generated of the mean change from baseline HR versus time grouped by treatment.

A linear mixed-effect model (LME) was used to evaluate the linear relationship between HR and moxifloxacin concentration.

$$\Delta HR_{ijk} = (\theta_j + \beta_{0k} + \eta_{0,i}) + \gamma \times (HR_{ij0} - \overline{HR}_{ij0}) + (\beta_1 + \eta_{1,i}) \times C_{ijk} + \epsilon_{ijk} \quad (1)$$

where ΔHR_{ijk} is the change from baseline HR for the i^{th} subject, in the j^{th} treatment, at the k^{th} time point (nominal) relative to dosing;j=1 for active drug (moxifloxacin) and j=0 for placebo; C_{ijk} is the concentration at the k^{th} time point for the j^{th} treatment in the i^{th} subject(C_{ijk}=0 for placebo); θ_j is the treatment-specific intercept (moxifloxacin versus placebo), β_{0k} is the population mean ΔHR (change from baseline) with placebo for time k (representing categorical fixed effect of time to account for diurnal variation); HR_{ij0} is the baseline HR for the i^{th} subject in the j^{th} treatment, $\overline{HR}_{ij0}$ is the overall population mean of all baseline HR (HR_{ij0}) values (from combined placebo

and active treatment periods), and γ is the influence of the baseline HR (centered on population baseline). β_1 is the slope which quantifies the relationship between Δ HR and concentration. $\eta_{0,i}$ and $\eta_{1,i}$ are the subject-specific random effects (inter-individual variability) for the intercept and slope, respectively, each with a mean of zero and variance ω^2, and ϵ_{ijk} is the residual error of the ith subject on the jth treatment at the kth time point with a mean of zero and variance σ^2.

4.4 Demonstration of QT Correction

The preferred QT correction (unless the studied drug has a significant effect on HR) is the Fridericia heart-rate corrected QT interval (QTcF). Unless drug-free QT data is collected in all subjects over a range of heart rates similar to the range of heart rates observed during treatment, the use of subject- and study-specific corrections is not generally recommended.

If studied drug was determined to have no effect on HR (or RR), then a fixed correction was applied to remove the underlying HR effect on the QT interval. The QTcF was the primary correction method in this analysis; if data suggested this method did not adequately correct for the relationship between HR and QT interval, a more appropriate correction could be estimated and reported.

For fixed corrections, QT interval corrected for heart rate equation is decribed below:

$$QTc = \frac{QT_{i,j}}{\left(\frac{RR_{i,j}}{1000}\right)^{\beta}} \tag{2}$$

where i represents the ith individual and j represents the jth measurement time for QT and RR (presented in milliseconds). The subject- and population-specific correction factor for calculation of QTcS could be estimated by fitting a LME model to only baseline (pre-dose values on Day 1) individual singlets (not the averaged triplicate) QT and RR measurements from all four study treatment periods as described in equation 3:

$$ln(QT_{i,j}) = (\theta_1 + \eta_{1,i}) + (\theta_2 + \eta_{2,i}) \cdot ln(RR_{i,j}) + \epsilon_{i,j} \tag{3}$$

where ln designates natural logarithmically transformed parameter, i represents the ith individual and j represents the jth measurement time for QT (milliseconds) and RR (seconds), θ_2 represent the study population specific estimate of the correction factor (β), and θ_1 is the intercept. $\eta_{1,i}$ and $\eta_{2,i}$ are the subject-specific random effects (inter-individual variability) for the intercept and slope, respectively, each with a mean of zero and variance ω^2, and ϵ is the residual error with a mean of zero and variance σ^2.

Thus, θ_2 and $\theta_2 + \eta_{2,i}$ represent the study- and subject-specific estimates of the correction factor (β), respectively.

The analysis dataset used in this workshop is insufficient for an appropriate estimation of individual- and/or study-specific corrections. Therefore, plots of QT, QTcF, and QTcB versus RR interval were generated using only baseline singlet data to assess the adequacy of each correction factor, to ensure that the correlation between QT and RR was adequately removed with the correction. Comparison of correction methods was made on the basis of the slope estimates from a LME model of QTc as a function of RR as follows:

$$QTc_{i,j} = (\theta_{int} + \eta_{int,i}) + (\theta_{slope} + \eta_{slope,i}) \cdot RR_{i,j} + \epsilon_{i,j} \tag{4}$$

Where QTc is the dependent variable (either QTcF, QTcB), i represents the ith individual and j represents the jth measurement time for QTc and RR, θ_{int} is the intercept, and θ_{slope} quantifies the

relationship between QTc and RR. $\eta_{int,i}$ and $\eta_{slope,i}$ are the subject-specific random effects (inter-individual variability) for the intercept and slope, respectively, each with a mean of zero and variance ω^2, and ϵ is the residual error with a mean of zero and variance σ^2.

The QTc associated with the regression that generated the smallest absolute value of the slope estimate was deemed the most appropriate HR adjusted QT method for use as the dependent variable in the subsequent E-R modeling; ideally the 95% CI for the slope should contain zero.

4.5 Assessment of Time Delay Between Drug Concentration and ΔQTc

Concordance, or lack thereof, in the time course of studied drug concentrations and QTcF was evaluated by:

- Examining the mean concentration and placebo-corrected change from baseline QTcF (ΔΔQTcF) profiles by dose level.
- Linear QTc-drug concentration relationship: a QTc_drug concentration plot incorporating a trend line (i.e, loess or linear regression). The trend line does not reflect a model fit of data but rather is used to detect drug effect and linear assumption. If no delay between peak studied drug concentration and peak QTc effect (hysteresis) is apparent as assessed by visual inspection then a direct temporal relationship can be supported.

4.6 Characterization of Moxifloxacin Exposure-Response Relationship for QTc

Once the basic assumptions described in Section 4.2 were satisfied, then the relationship was evaluated with the pre-specified LME model shown below. In this model the change from baseline QTcF (ΔQTcF) and concentration data from both placebo and moxifloxacin treatment periods (therapeutic and supratherapeutic doses) were analyzed. This base model to describe the dependent variable, ΔQTc, includes the following fixed effect parameters: intercept, slope, the effect of treatment (categorical), time (categorical), and baseline QTc (continuous) on the intercept. Characterizing the placebo response at each nominal time point accounts for the effect of diurnal variation in QTc. Subject is included as a random effect on both the intercept and slope.

$$\Delta QTc_{ijk} = (\theta_j + \beta_{0k} + \eta_{0,i}) + \gamma \cdot (QTc_{ij0} - \overline{QTc}_{ij0}) + (\beta_1 + \eta_{1,i}) \cdot C_{ijk} + \epsilon_{ijk} \quad (5)$$

where $\Delta\, QTc_{ijk}$ is the change from baseline QTc interval for the i^{th} subject, in the j^{th} treatment, at the k^{th} time point (nominal) relative to dosing; j=1 for active drug (moxifloxacin) and j=0 for placebo; θ_j is the treatment-specific intercept (moxifloxacin versus placebo), β_{0k} is the population mean ΔQTc (change from baseline) in the placebo group at each time k (representing categorical fixed effect of time to account for diurnal variation); γ is the influence of the baseline QTc (centered on population baseline); QTc_{ij0} is the baseline QTc for the i^{th} subject in the the j^{th} treatment, $\overline{QTc}_{ij0}$ is the overall population mean of all baseline QTc (QTc_{ij0}) values (from combined placebo and active treatment periods), and C_{ijk} is the concentration in the i^{th} subject (and C_{i0k}=0 for placebo) for the j^{th} treatment at the k^{th} time point; β_1 is the slope which quantifies the relationship between ΔQTc and concentration. $\eta_{0,i}$ and $\eta_{1,i}$ are the subject-specific random effects (inter-individual variability) for the intercept and slope, respectively, each with a mean of zero and variance ω^2, and ϵ_{ijk} is the residual error of the i^{th} subject on the j^{th} treatment at the k^{th} time point with a mean of zero and variance σ^2.

The ΔQTc versus concentration model was used to compute the placebo-adjusted change from baseline QTc (ΔΔQTc) over the observed concentration range. The model-derived ΔΔQTc is the

difference between the model-derived ΔQTc at a given concentration under moxifloxacin treatment, and the model-derived ΔQTc under placebo treatment with drug concentration equal to zero. Using the contrast function (contrast package) [Kuhn et al., 2016] in R and the ΔQTc model object, the mean and two-sided 90% CI for the predicted population average ΔΔQTc at concentrations of interest (Cmax) can be computed as follows in Equations 6 and 7.

$$mean\Delta\Delta\overline{QTc}(C) = mean(\Delta\overline{QTc}_{ijk}|j=1; C_{ijk}=C) - mean(\Delta\overline{QTc}_{ijk}|j=0; C_{ijk}=0) \quad (6)$$

where $mean\Delta\Delta\overline{QTc}_{ijk}|j=1; C_{ijk}=$ C is the predicted population average ΔQTc under moxifloxacin treatment at plasma concentration C, and $mean\Delta QTc_{ijk}|j=0; C_{ijk}$ is the predicted population average ΔQTc in the absence of drug (i.e. placebo treatment where C = 0).

$$90\%CI = mean\Delta\Delta\overline{QTc}(C) \pm t(0.90, DF) \cdot SE(mean\Delta\Delta\overline{QTc}(C)) \quad (7)$$

where t is the critical value determined from the t-distribution, DF is the degrees of freedom, and SE is the standard error.

4.7 Model Adequacy

The evaluation of the model fit was based on several goodness-of-fit (GOFs) plots:

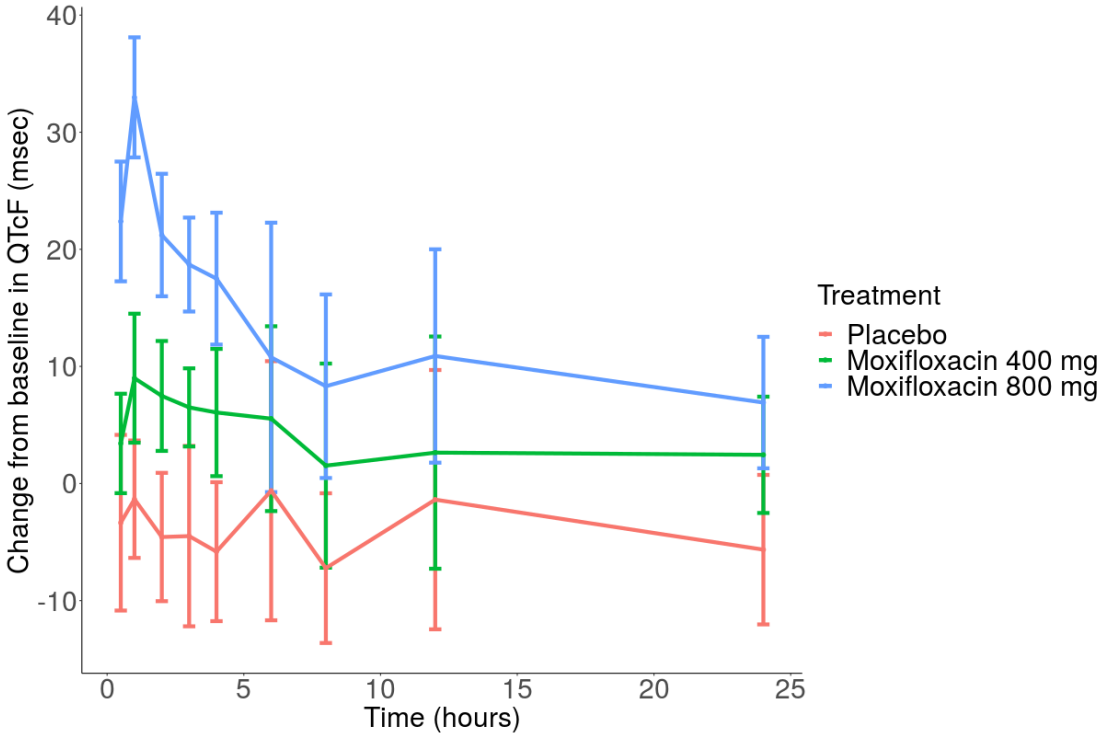
- Scatter plots of model predicted (population and individual) versus observed ΔQTc values with line of unity and loess line, to demonstrate any patterns suggestive of concentration dependent over/under prediction of ΔQTc
- Scatter plots of population and individual standardized (Pearson weighted) residuals versus ΔQTc and drug concentration,
- Boxplots of standardized residuals versus nominal time post dose and treatment (categorical variables) and quantile-quantile (Q-Q) plots of the standardized residuals to check that residuals follow normal distribution with mean of zero
- Scatter and quantile plots of concentration were used for displaying mean baseline corrected QTc (ΔQTc) and associated 90% CI derived from the observed data, with model predicted variables and the associated 90% CI overlayed. Systematic differences between the model predictions and observed data would suggest model misspecification

5 Results

A total of 13 subjects were enrolled, 6 subjects were administered with placebo and 9 subjects were administered with 2 doses of moxifloxacin. Out of the subjects administered with placebo, 2 received moxifloxacin. Time-matched ECG collections from the placebo treatment group were used to correct for diurnal patterns in QTc data.

The time course of the mean (±SD) change from baseline QTcF intervals by treatment is displayed in Figure 1.

Figure 1: Mean QTcF Change From Baseline Over Time by Treatment Group



Tables 1 and 2 display summary statistics for ΔQTcF intervals by timepoint for the placebo group and the 2 doses of moxifloxacin, respectively.

Table 1: Summary of Baseline-Corrected (ΔQTcF) Intervals For the Placebo Treatment per Time-point

Day	Nominal Time (hrs)	N	Mean (SD)	Median (Max, Min)
1	0.5	6	-3.23 (6.82)	-3.52 (5.13 , -13.18)
1	1.0	6	-2.45 (5.37)	-2.81 (4.01 , -9.27)
1	2.0	6	-4.01 (6.09)	-5.01 (4.91 , -13.43)
1	3.0	6	-3.83 (4.37)	-4.91 (3.61 , -7.86)
1	4.0	6	-4.63 (5.75)	-6.86 (5.15 , -9.93)
1	6.0	6	1.68 (11.09)	1.64 (16.11 , -10.05)
1	8.0	6	-4.96 (5.88)	-6.79 (4.21 , -10.3)
1	12.0	6	-1.02 (12.24)	-1.66 (18.15 , -16.07)
1	24.0	6	-4.67 (4.86)	-6.13 (1.82 , -10.89)
2	0.5	6	-3.46 (8.79)	-5.96 (13.33 , -10.05)
2	1.0	6	-0.22 (4.85)	-1.78 (9.13 , -3.95)
2	2.0	6	-5.13 (5.31)	-5.82 (1.68 , -12.55)
2	3.0	6	-5.16 (10.51)	-9.04 (13.27 , -14.05)
2	4.0	6	-7 (6.41)	-8.81 (5.41 , -12.27)
2	6.0	6	-2.91 (11.57)	-3.96 (14.71 , -14.67)
2	8.0	6	-9.49 (6.56)	-11.69 (0.91 , -15.65)
2	12.0	6	-1.73 (10.94)	-1.52 (9.82 , -15.07)
2	24.0	6	-6.63 (7.99)	-8.81 (7.03 , -14.15)

Table 2: Summary of Baseline-Corrected (ΔQTcF) Intervals For Moxifloxacin per Dose and Time-point

Day	Nominal Time (hrs)	N	Mean (SD)	Median (Max, Min)
1	0.5	9	3.42 (4.25)	3.81 (8.38 , -3.99)
1	1.0	9	8.99 (5.51)	10.26 (14.36 , -2.22)
1	2.0	9	7.48 (4.69)	6.81 (16.17 , 1.19)
1	3.0	9	6.5 (3.34)	7.09 (11.92 , 0.88)
1	4.0	9	6.06 (5.43)	4.89 (16.87 , 0.4)
1	6.0	9	5.54 (7.89)	3.47 (18.77 , -5.77)
1	8.0	9	1.53 (8.71)	-0.65 (18.56 , -10.93)
1	12.0	9	2.64 (9.92)	4.86 (18.08 , -11.67)
1	24.0	9	2.45 (4.97)	1.91 (10.66 , -4.87)
2	0.5	9	22.38 (5.11)	23.13 (30.07 , 14.06)
2	1.0	9	32.98 (5.13)	32.22 (43.77 , 25.48)
2	2.0	9	21.22 (5.23)	19.87 (28.96 , 14.76)
2	3.0	9	18.7 (4.01)	19.71 (25.48 , 13.83)
2	4.0	9	17.5 (5.63)	14.49 (25.18 , 10.88)
2	6.0	9	10.77 (11.5)	9.66 (28.38 , -4.84)
2	8.0	9	8.31 (7.84)	7.68 (24.68 , -1.94)
2	12.0	9	10.89 (9.11)	13.98 (25.58 , -3.01)
2	24.0	9	6.91 (5.62)	6.77 (16.96 , -2.77)

Following administration of single PO doses of moxifloxacin 400 mg and 800 mg, peak plasma moxifloxacin concentration Cmax was achieved with a median time to maximum concentration (Tmax) of 1-3 hours post dose. The observed geometric mean (geometric coefficient of variation (CV)%) of Cmax in ng/mL at the 400 mg (therapeutic) and 800 mg (supratherapeutic) doses were 1862.14 (28.36) and 4576.13 (20.98), respectively. Mean moxifloxacin concentration-time profiles are presented in Figure 2. Table 3 presents summary statistics of moxifloxacin maximum concentration per dose group.

Figure 2: Mean Moxifloxacin Concentration-Time Profile by Dose Group

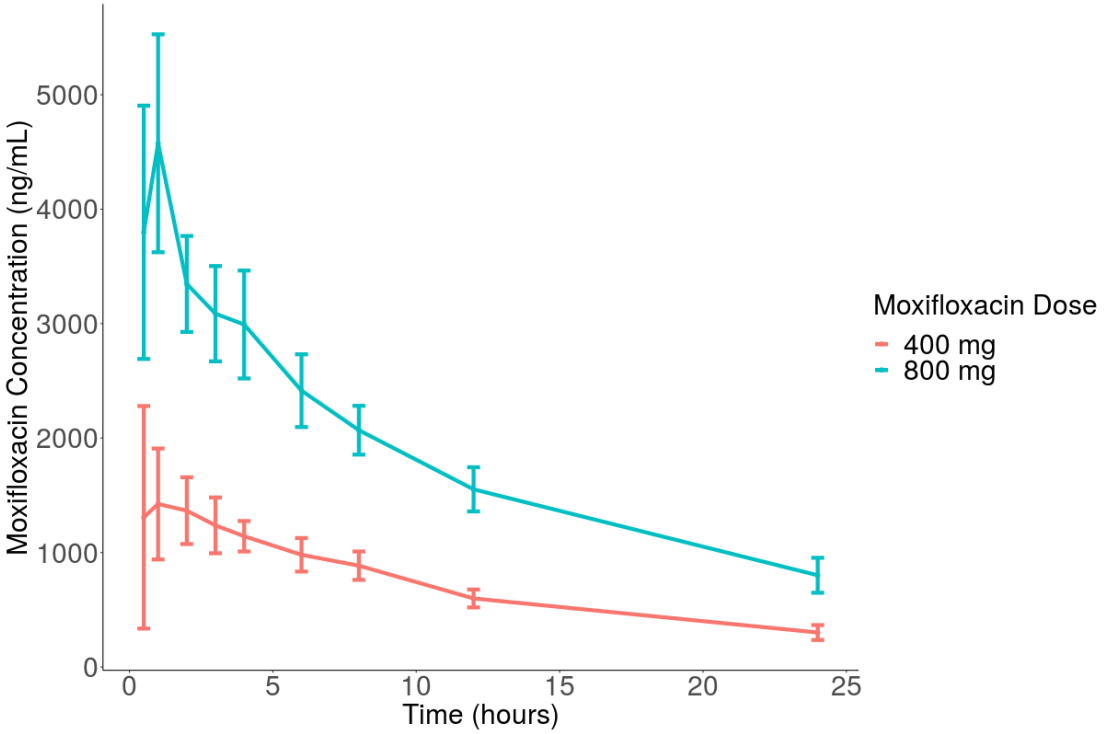


Table 3: Summary of Moxifloxacin Maximum Concentration by Dose

Tmax Median (Max, Min)	Geometric Mean (CV%)	Median (Max, Min)
1 (3 , 0.5)	1862.14 (28.36)	2030 (3130 , 1240)
1 (1 , 0.5)	4576.13 (20.98)	4240 (5800 , 3280)

5.1 Effect of Moxifloxacin on Heart Rate

The effect of moxifloxacin on heart rate (HR) was evaluated via a linear mixed-effects modeling with ΔHR as the dependent variable and moxifloxacin plasma concentration as independent variable.

Table 4: Summary of Baseline-Corrected (ΔHR) Intervals For Moxifloxacin Treatment per Timepoint and Dose Level

TRTG	DOSE	Day	Nominal Time (hrs)	N	Mean (SD)	Median (Max, Min)
D - moxifloxacin	400	1	0.5	9	2.26 (6.03)	4.48 (8.63 , -8.06)
D - moxifloxacin	400	1	1.0	9	1.2 (5.2)	0.85 (8.79 , -8.28)
D - moxifloxacin	400	1	2.0	9	-0.55 (3.46)	-1.07 (4.72 , -5.01)
D - moxifloxacin	400	1	3.0	9	-1.62 (4.14)	-1.47 (7.65 , -6.93)
D - moxifloxacin	400	1	4.0	9	-0.12 (5.38)	-0.73 (10.45 , -6.29)
D - moxifloxacin	400	1	6.0	9	9.48 (6.23)	10.41 (17.13 , -0.23)
D - moxifloxacin	400	1	8.0	9	6.16 (5.47)	4.11 (15.03 , -2.51)
D - moxifloxacin	400	1	12.0	9	11.22 (7.31)	12.69 (22.43 , -1.03)
D - moxifloxacin	400	1	24.0	9	0.65 (5.93)	-1.37 (10.11 , -8.93)
D - moxifloxacin	800	2	0.5	9	4.98 (7.8)	8.71 (14.59 , -6.91)
D - moxifloxacin	800	2	1.0	9	11.11 (8.26)	12.43 (21.69 , -0.34)
D - moxifloxacin	800	2	2.0	9	4.08 (6.75)	5.01 (14.39 , -5.03)
D - moxifloxacin	800	2	3.0	9	3.62 (6.75)	5.26 (14.76 , -6.33)
D - moxifloxacin	800	2	4.0	9	3.49 (5.56)	5.11 (10.49 , -5.83)
D - moxifloxacin	800	2	6.0	9	14.45 (4.93)	15.23 (21.39 , 6.31)
D - moxifloxacin	800	2	8.0	9	9.59 (5.49)	10.45 (16.39 , -1.61)
D - moxifloxacin	800	2	12.0	9	10.7 (6.15)	11.81 (18.69 , 0.17)
D - moxifloxacin	800	2	24.0	9	5.62 (6.24)	5.41 (17.09 , -2.47)

Figure 3: Overlay of Time course of Mean Moxifloxacin Concentration and Mean ΔHR by Dose and Treatment Group

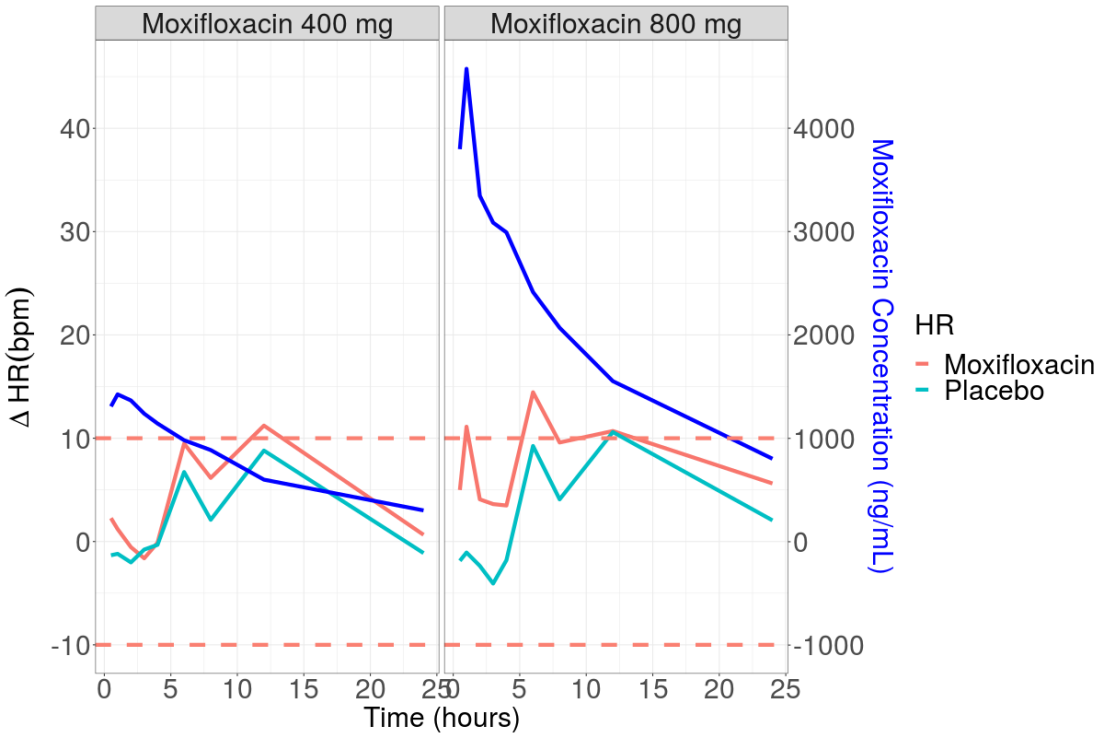
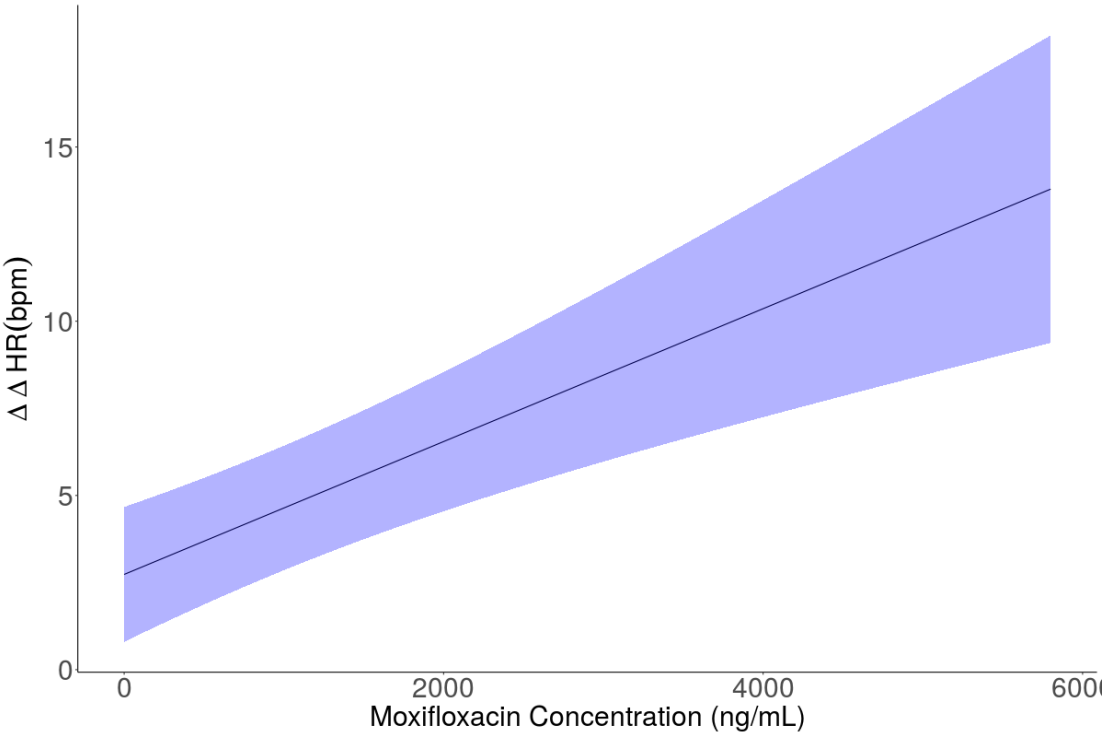


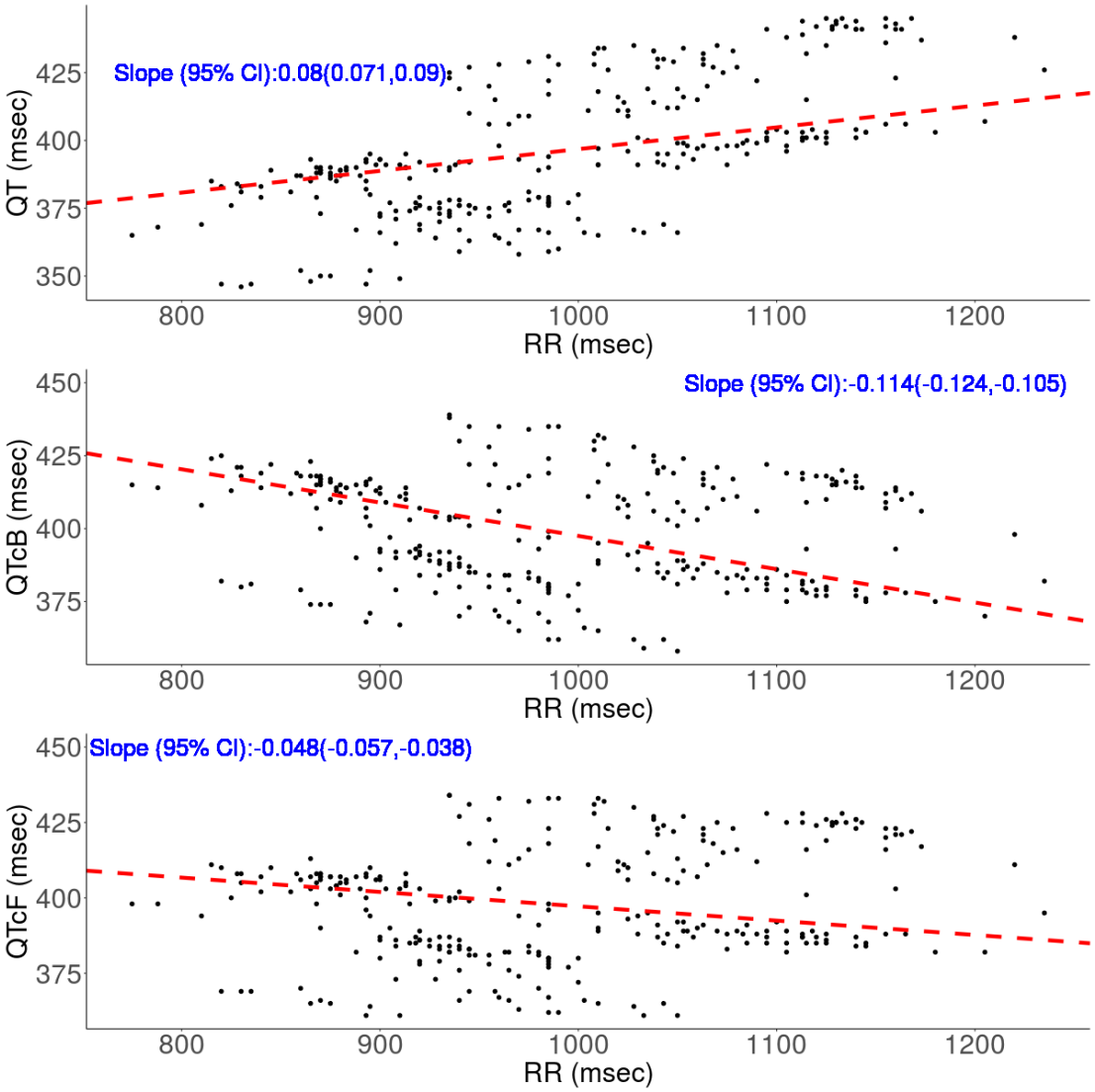
Figure 4: ΔΔHR versus Moxifloxacin Concentration with Model Slope and 90% Confidence Intervals



5.2 Assessment of Appropriate QT Correction Factor

As Shown in Figure 5, Bazett's method overcorrected for the trend between the QT and RR intervals (slope estimate of -0.114), and Fridericia's also did not completely remove the relationship, with a slope estimate (95% CI) which was statistically significantly different from zero (-0.048 [-0.057 to -0.038]).

Figure 5: Uncorrected and Fixed Correction Factors to Drug-Free QT intervals



5.3 Assessment of Time Delay Between Drug Concentration and Baseline Corrected QT Intervals

The presence of a delay in the time course of moxifloxacin cardiac repolarization effect relative to its PK profile was evaluated visually by plotting and comparing the mean moxifloxacin concentration and ΔΔQTcF profiles over time for both moxifloxacin dose levels (see Figure 6). Visual comparison of the mean moxifloxacin PK and ΔΔQTcF profiles revealed there was general concordance in the time course of both PK and cardiac repolarization, and no time dependency of the ΔΔQTcF on moxifloxacin plasma concentration was evident at either dose.
Figure 7 is a scatter plot of ΔQTcF and drug concentration data with loess smooth line and 95% confidence interval and a linear regression line indicating a direct effect between ΔQTc and moxifloxacin concentration.

Figure 6: Overlay of Time course of Mean Moxifloxacin Concentration and Mean ΔΔQTcF by Dose

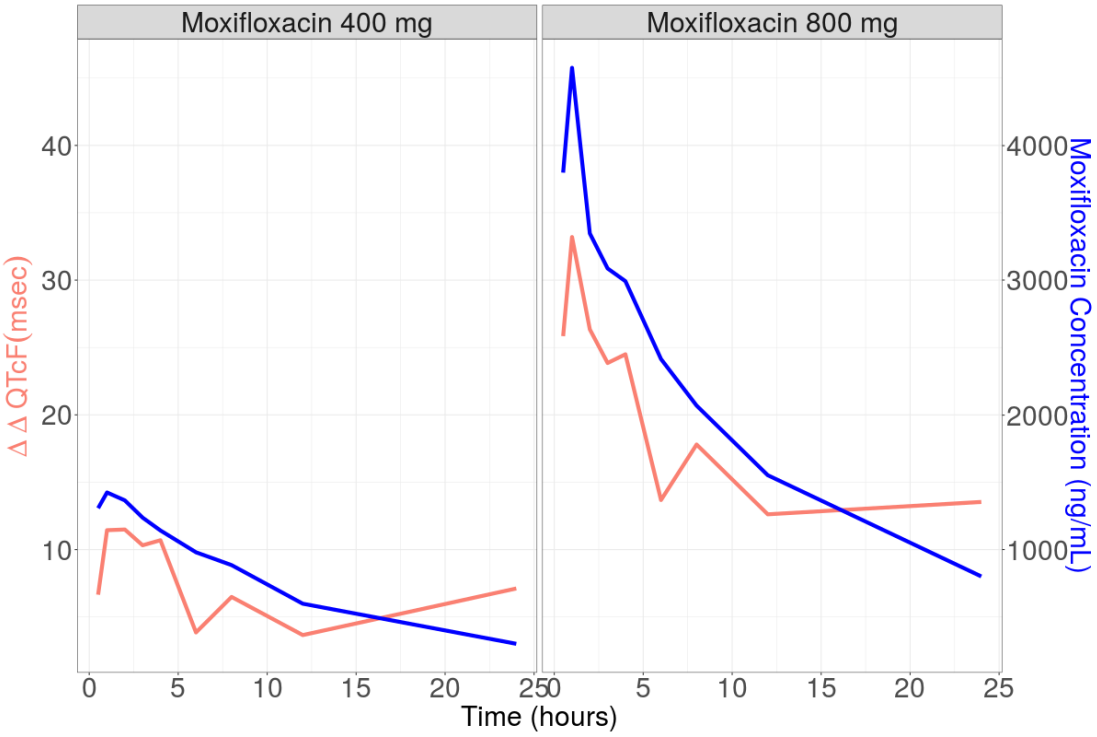
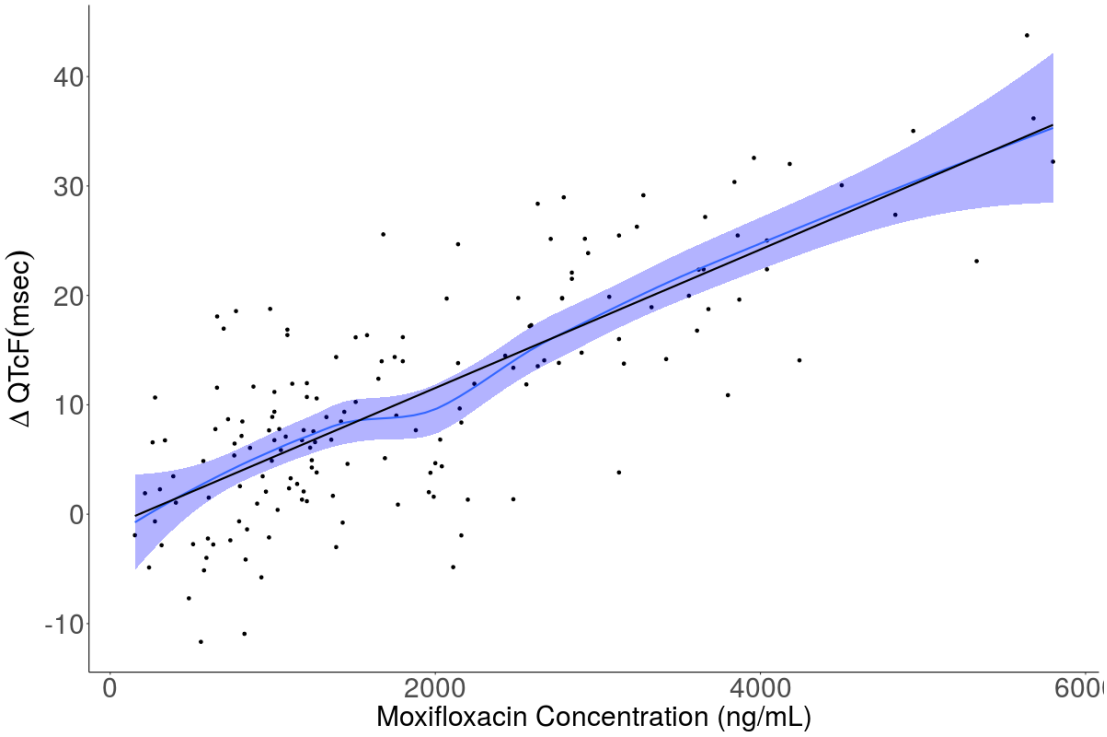


Figure 7: Scatter Plot of Paired Moxifloxacin Concentration and ΔQTcF



5.4 Characterization of Moxifloxacin Exposure-Response Relationship for QTc

The linear mixed-effects model was fitted to the ΔQTcF data for moxifloxacin and placebo as described in Section 4.6. The results from the model are displayed in Figure 8 and Table 5. The mean slope estimated was 0.006 msec/ng/mL, the 90% confidence interval around the slope estimate excludes zero indicating positive concentration-dependent effect of moxifloxacin on ΔQTcF intervals. At the therapeutic moxifloxacin dose of 400 mg, the estimated geometric mean moxifloxacin Cmax value was calculated to be 1862.1 ng/mL. The estimated mean change in ΔQTcF at the geometric mean Cmax was 15.74 msec with an 90% upper bound of 18.43. At the supratherapeutic moxifloxacin dose of 800 mg, the estimated mean change in ΔQTcF was 32.1 msec with an 90% upper bound of 36.21 at the geometric mean Cmax value of 4576.1 ng/mL.

Figure 8: ΔΔQTcF versus Moxifloxacin Concentration with Associated Predictions at the Observed Therapeutic and Supratherapeutic Geometric Mean Cmax

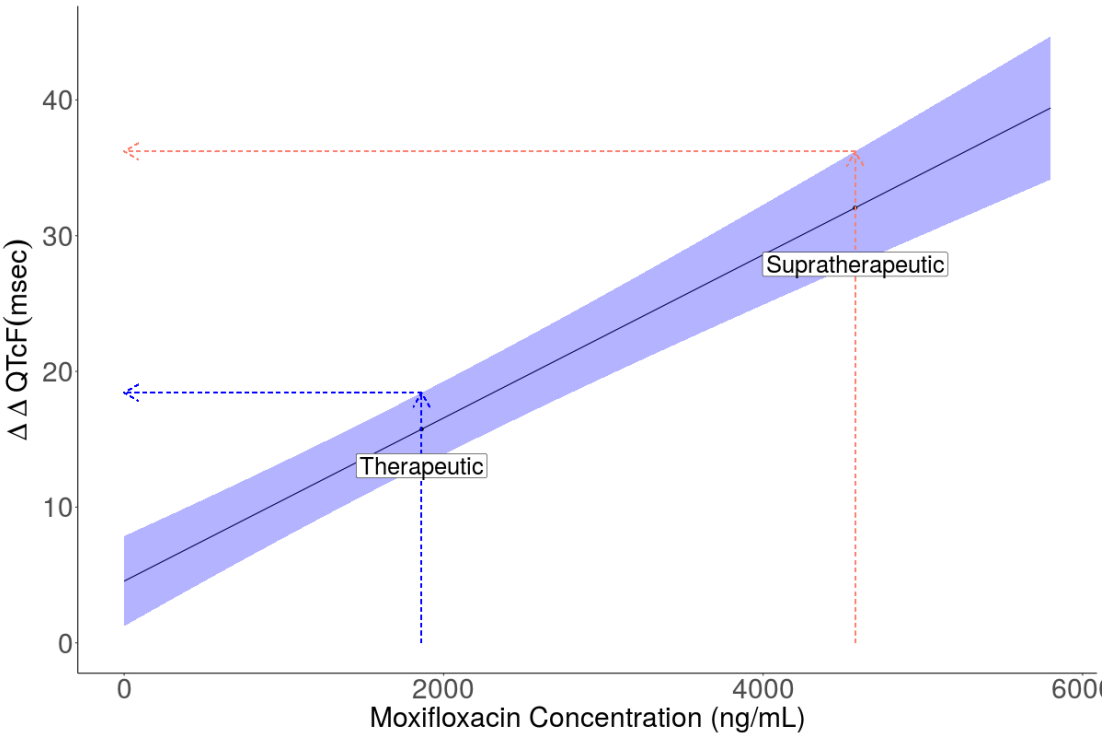


Table 5: Summary of Model Parameter Fit of ΔQTcF Versus Moxifloxacin Concentration

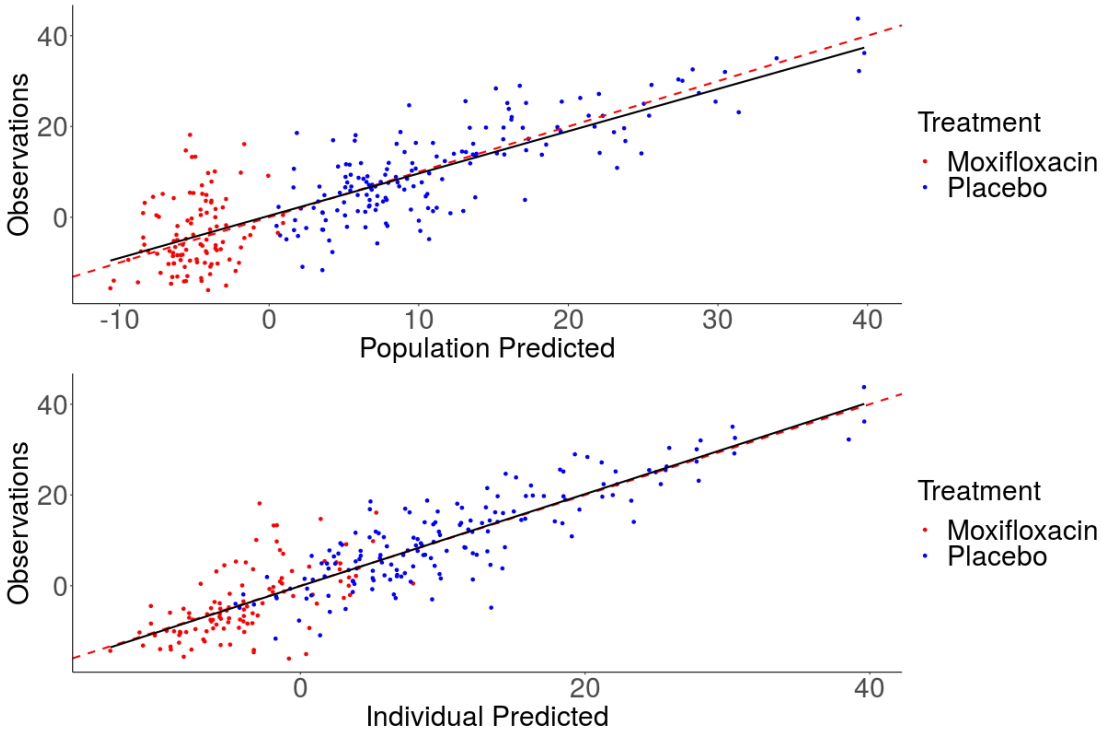
Parameter	Estimate	90% CI
TAFDHR 0.5	-6.676	(-10.832, -2.519)
TAFDHR 1	-3.433	(-7.599, 0.734)
TAFDHR 12	-3.644	(-7.876, 0.588)
TAFDHR 2	-4.743	(-8.915, -0.571)
TAFDHR 24	-4.130	(-8.4, 0.141)
TAFDHR 24.5	-4.498	(-8.862, -0.133)
TAFDHR 25	0.379	(-4.155, 4.913)
TAFDHR 26	-4.146	(-8.429, 0.137)
TAFDHR 27	-4.720	(-8.967, -0.472)
TAFDHR 28	-5.841	(-10.076, -1.607)
TAFDHR 3	-4.781	(-8.959, -0.603)
TAFDHR 30	-6.118	(-10.302, -1.934)
TAFDHR 32	-8.971	(-13.138, -4.804)
TAFDHR 36	-2.440	(-6.605, 1.726)
TAFDHR 4	-5.016	(-9.199, -0.833)
TAFDHR 48	-4.051	(-8.262, 0.16)
TAFDHR 6	-2.213	(-6.408, 1.982)
TAFDHR 8	-6.927	(-11.13, -2.725)
TRTGD - moxifloxacin	4.547	(1.23, 7.864)
CONC	0.006	(0.005, 0.007)
DBQTF	-0.055	(-0.196, 0.085)
Random Effects on Intercept	4.230	(2.567, 6.97)
Cor Intercept-concentration	-0.572	(-0.991, 0.884)
Random Effects on Concentration	0.001	(0, 0.003)
Residual Error	5.934	(5.422, 6.494)

5.5 Model Adequacy

5.5.1 Prediction_based Diagnostics

The scatter plots of model-predicted (population and individual) versus observed ΔQTc values with line of unity and loess line are presented in Figure 9 and do not suggest any patterns that indicate over or under model-predicted ΔQTc.

Figure 9: Population and Individual Model Predictions Diagnostic Plots



5.5.2 Residual-Based Diagnostics

Figure 10 presents scatter plots of population and individual standarized residuals (Pearson weighted) versus population and individual model predictions of ΔQTcF and moxifloxacin plasma concentrations. In all cases, the residuals are randomly scattered around zero suggesting lack of model misspecification.

Figure 10: Population and Individual Standardized Residuals versus Population and Individual Model ΔQTc Predictions and Moxifloxacin Concentrations

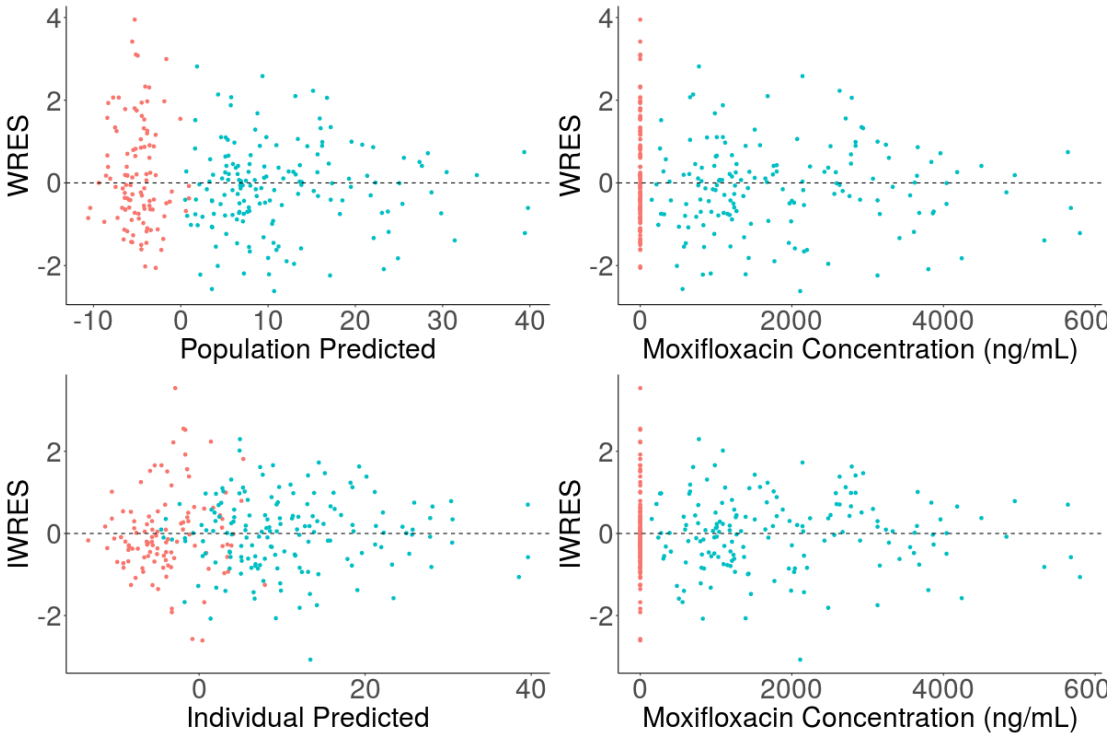
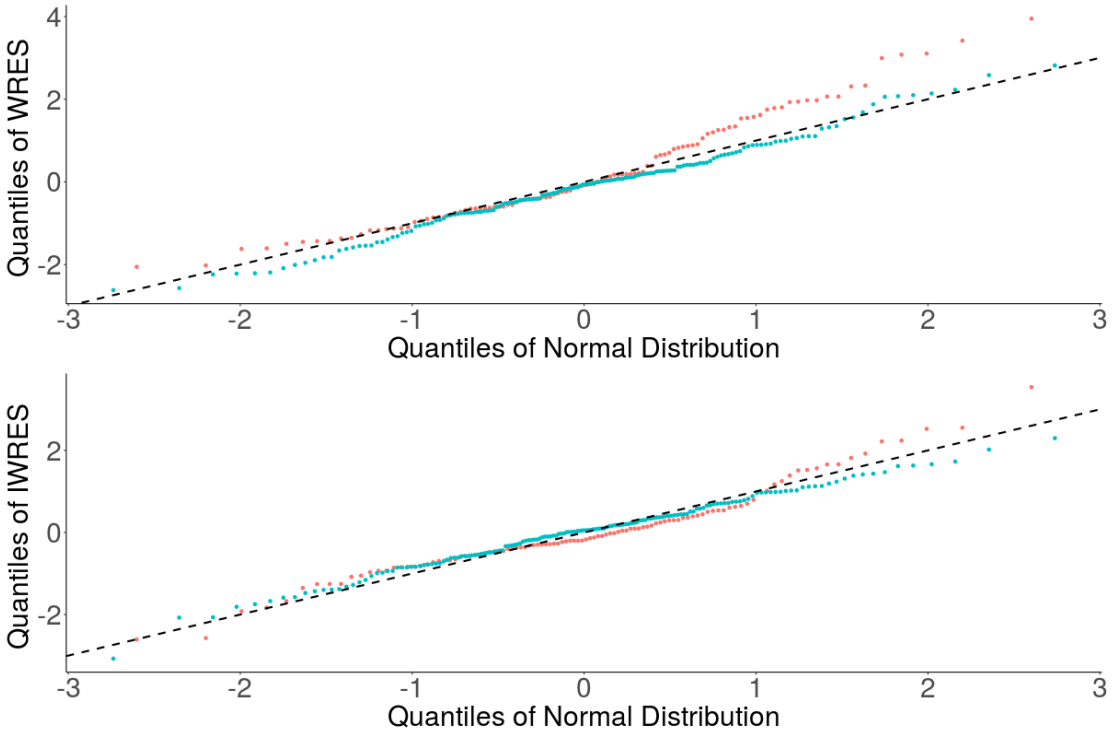


Figure 11 displays the quantile-quantile plots of residuals. The residuals fall in the line of unity with no heavy tails indicative of model misspecification. The residuals follow normal distribution with a mean of zero.

Figure 11: Quantile-Quantile (Q-Q) Plots of Pearson Weighted Standardized Residuals



Figures 12 and 13 are boxplots of population and individual model residuals versus the nominal timepoints for the assessments and versus treatment groups, placebo and moxifloxacin. Residuals are centered around zero not showing any particular pattern.

Figure 12: Boxplots of Standardized Residuals Versus Nominal Time Postdose

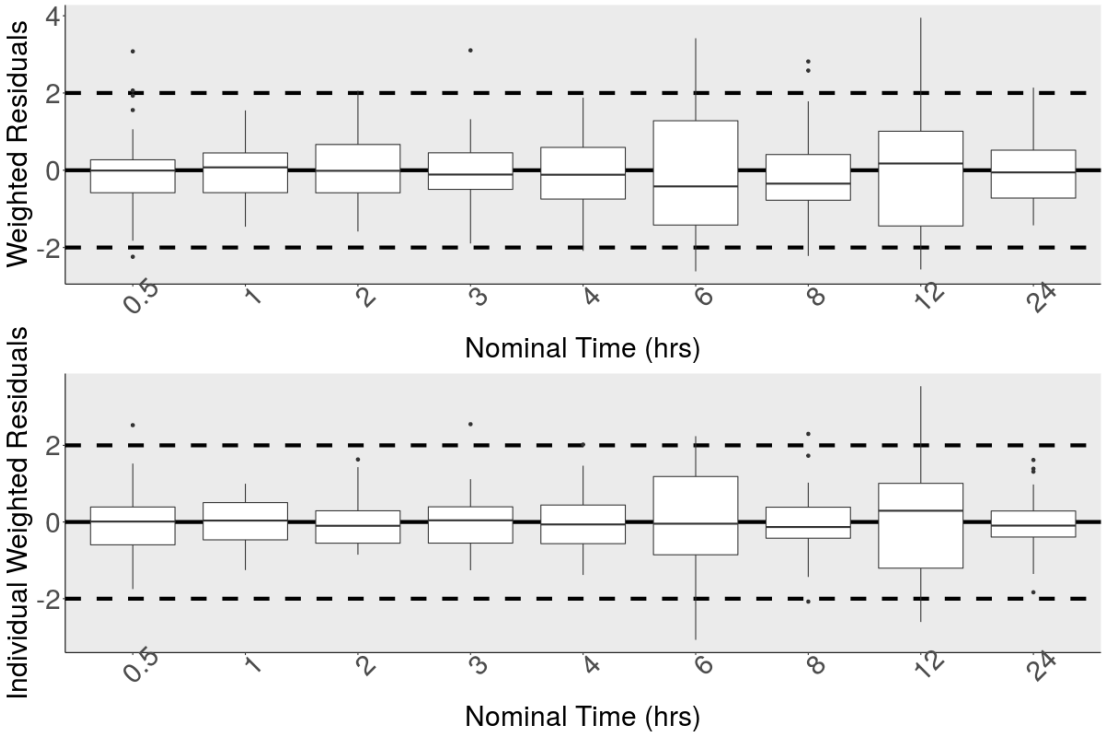
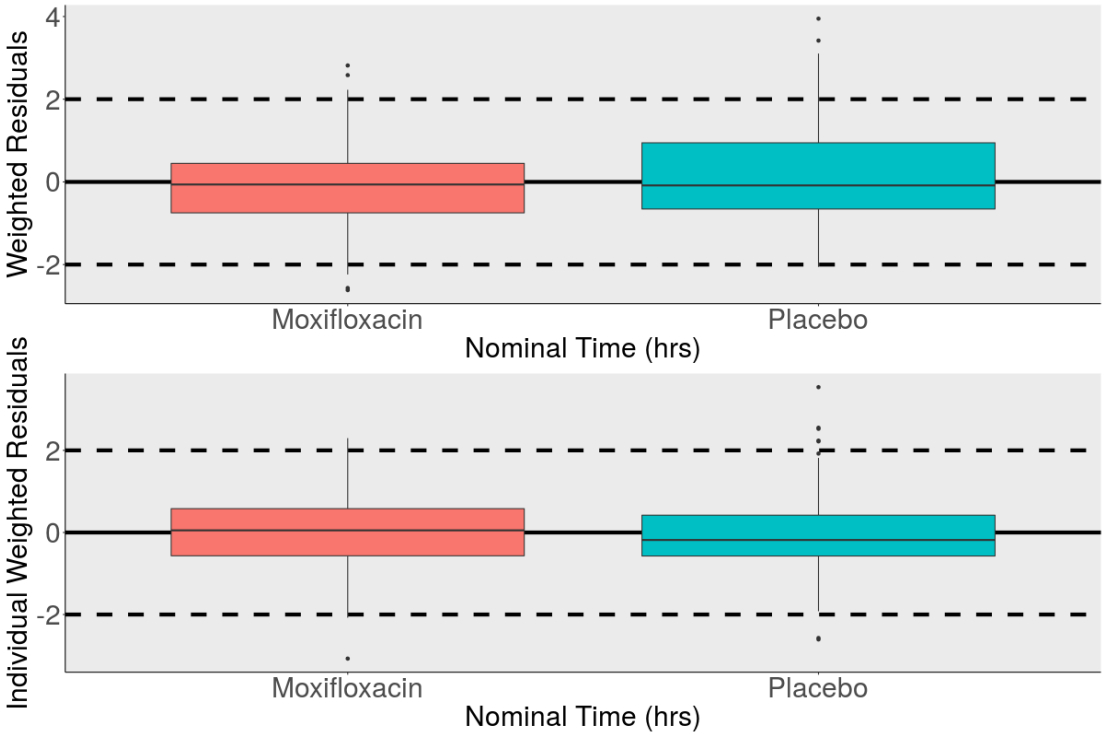


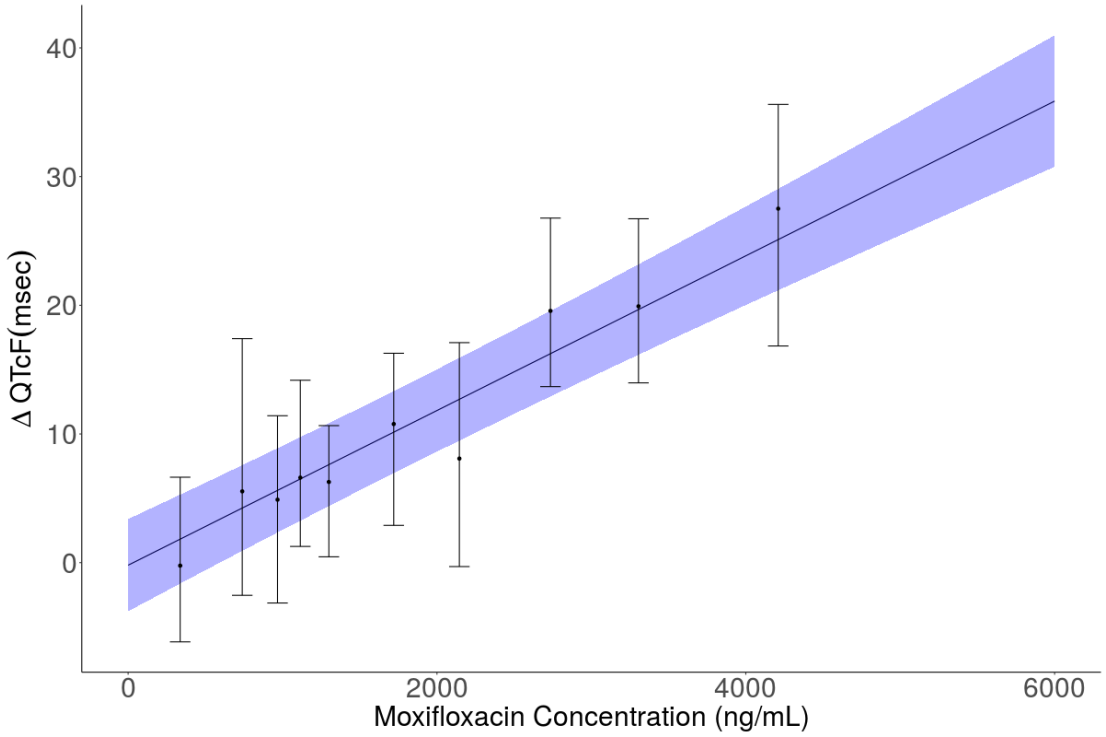
Figure 13: Boxplots of Standardized Residuals Versus Treatment



5.5.3 Evaluation of Linear Mixed-Effects Model for ΔQTc-Drug Concentration Relationship

Figure 14 corresponds to the evaluation of the final model. Mean baseline-corrected QTcF (ΔQTcF) versus moxifloxacin concentration quantiles derived from the observed data with model-predicted variables and the associated 90% CI overlayed.

Figure 14: ΔQTcF versus Moxifloxacin Concentration Quantile Plot



6 Discussion

The ICH E14 Q&A (R3) document was revised in December 2015 to confirm concentration-QTc (C-QT) analyses as an acceptable primary analysis methodology for definitive QTc characterization. Subsequently, a scientific white paper on concentration-QTc modeling was published collaboratively by regulatory and industry representatives. This paper described the critical design elements for the studies suitable for such analysis, as well as modeling and reporting aspects corresponding to regulatory submissions involving such concentration-QTc analyses. The definitive C-QT analysis of data in early phase studies following ICH E14 Q&A (R3) implementation has alleviated the need for Thorough QT/QTc (TQT) studies for multiple development programs. In this example report we used moxifloxacin data from the IQ-CSRC study .
The results of the analysis for the moxifloxacin IQ-CSRC study indicated the presence of the expected effect of moxifloxacin on the QTcF interval at the therapeutic and supratherapeutic doses, as the upper bound of the 2-sided 90% CIs was above the pre-specified criterion of 10 msec.

7 Conclusions

This analysis represents the quantitative evaluation of the relationship between changes in the placebo-adjusted change from baseline QTc interval and plasma concentrations of moxifloxacin.

- Moxifloxacin does not have a meaningful effect on heart rate (change in the RR interval); the fixed corrections (QTcF) utilized in this analysis was considered sufficient to correct for the underlying relationship between RR and QT intervals.
- The final QTc_Concentration model for ΔQTcF indicated a mean estimate of a 0.006 msec

increase from baseline in QTcF per ng/mL of moxifloxacin. At the geometric mean therapeutic Cmax value observed in patients (400 mg dose), the mean predicted increase in placebo-adjusted change from baseline QTcF is 15.74 msec, and the upper bound of the 90% CI of ΔΔQTcF is above 10 msec (18.43).

- At the geometric mean supratherapeutic moxifloxacin Cmax value observed in patients (800 mg dose), the mean predicted increase in placebo-adjusted change from baseline QTcF is 32.05 msec and the upper bound of the 90% CI of ΔΔQTcF is above the 10 msec threshold (36.21).

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