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Implementation on concentration-QTc modeling

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ABSTRACT

The International Council for Harmonization has updated the E14 guideline, endorsing concentration-QTc (C-QTc) modeling as a primary analytical method for evaluating the risk of QTc interval prolongation by new drugs. This paper delineates a comprehensive workflow for conducting a definitive QTc assessment in alignment with FDA recommendations. The workflow is centered around a pre-specified linear mixed effects model and encompasses the development of specifications, creation of the primary analysis dataset (ADCQT: Concentration-QTc Analysis Dataset), generation of exploratory plots to verify model assumptions, production of goodness-of-fit plots for model evaluation, compilation of tables, figures, and listings (TFLs) for presenting model outcomes, and preparation of e-Submission packages.

INTRODUCTION

In December 2015, the International Council for Harmonisation (ICH) revised the E14 Questions and Answers document, allowing concentration-QTc (C-QTc) modeling to be used as the primary analysis for assessing the risk of QTc interval prolongation in new drugs. This revision has significant implications for the design and analysis of thorough QT/QTc (TQT) studies. The TQT study aims to identify any significant pharmacological impact on cardiac repolarization, indicated by QTc interval prolongation. A regulatory threshold of concern is a around 5 ms increase, with a two-side 90% confidence interval upper limit of 10 ms for the mean QTc effect. TQT study results are used to determine whether the effect of a drug on the QT/ QTc interval in target patient populations should be studied intensively during later stages of drug development.

A well-designed and conducted QTc assessment in early Phase 1 studies, using C-QTc analysis, may suffice substitute for a TQT study to confidently rule out significant QTc alterations. The C-QTc modeling approach leverages data from all doses and time points, providing a robust sample size that supports reliable QTc prolongation assessments. This comprehensive data utilization can reduce the need for large TQT trials or allow these assessments to be conducted during early-phase clinical trials not specifically designed for QT effects. Consequently, sponsors can now perform smaller TQT studies or use C-QTc modeling with high-quality electrocardiogram (ECG) measurements in single/multiple dose escalation (SAD/MAD) studies during early clinical development.

For regulatory purposes, it is crucial that the quantitative methods used in C-QTc modeling are clearly described to ensure reproducibility. This includes detailing data sources, modeling specifics, structural models, assumptions, and criteria for assessing model robustness and goodness-of-fit in a pre-specified cardiac statistical analysis plan, and standardized reporting formats. Although the E14 implementation working group did not provide detailed technical guidance on performing and reporting C-QTc modeling, a scientific white paper published in the Journal of Pharmacokinetics and Pharmacodynamics in 2017 aims to fill that gap. The white paper was developed on the best modeling practices from industry, scientific literature, and the experiences from regulatory scientists. It offers recommendations for designing studies, conducting C-QTc analyses, and reporting results to support regulatory submissions. This paper focuses on the implementation of the pre-specified linear mixed effects model introduced in the white paper by Dizal.

STUDY DESIGN

When conducting C-QTc analysis, the following aspects need to be considered in the study design:

- Sample size: Early phase clinical trials usually do not perform specific sample size calculation for QTc assessment, but rather use all the dose and time point data for C-QTc analysis, providing sufficient sample size to support reliable QTc prolongation evaluation. If the trial design and execution meet the standards of optimized ECG quality control, drug exposure margin, and ECG collection and measurement, then a typical single/multiple dose escalation (SAD/MAD) trial

contained at least four dose cohorts, with each cohort having 4–8 subjects on drug and 2–4 subjects on placebo, may be enough to demonstrate that the mean QTc effect is less than 10ms.

- Drug exposure margin: To ensure adequate QTc assessment, the drug exposure in early phase clinical trials should be far higher than the maximum therapeutic exposure, to cover the potential impact of intrinsic and extrinsic factors on drug exposure, including unforeseen factors. If the drug has significant pharmacokinetic accumulation after repeated dosing, or the exposure of the drug or its active metabolite at the single maximum tolerated dose cannot reach or exceed the steady state supra-therapeutic exposure, then it is recommended to perform a repeated dose C-QTc analysis. In addition, if the maximum exposure in early phase clinical trials cannot reach twice the highest clinically relevant exposure, then a TQT trial with a positive control may still be needed to verify the sensitivity of the ECG measurement.
- Positive control: A limitation of performing QTc assessment in early phase clinical trials is the lack of a positive control to demonstrate the sensitivity of the ECG measurement. If a positive control cannot be replaced by the drug exposure margin, then it may be necessary to wait for a non-drug method to verify the sensitivity of the ECG measurement. Currently, there is no established universal non-drug positive control method to replace the positive control in the TQT trial.
- ECG collection and measurement: To ensure the accuracy and reliability of the C-QTc analysis, the ECG collection and measurement should follow some best practice principles, including using high-quality 12-lead ECG machines, performing standardized subject handling and ECG collection procedures, collecting at appropriate time points to capture the peak drug concentration and a wide range of concentrations, using automated algorithms or centralized manual readings to determine the QT interval, using appropriate heart rate correction methods to calculate the QTc interval, and evaluating other ECG parameters such as heart rate, PR interval, QRS duration.

CONCENTRATION-QTC ANALYSIS DATASET: ADCQT

At Dizal, we have developed a standard analysis dataset called ADCQT (Concentration-QTc Analysis Dataset) for C-QT analysis. This dataset is primarily based on the ADEG and ADPC datasets used in Clinical Study Reports (CSR). The majority of the data in ADCQT comes from ADEG, such as PARAMCD, AVAL, CHG, etc., while the time-matched concentrations of the investigational drug and/or its metabolites are extracted from ADPC. The development of ADCQT follows the FDA guideline Submitting Clinical Trial Datasets for Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential of Drugs released in 2019. Table 1 lists the additional variables not typically present in ADEG but essential for C-QT modeling. All the variables can be referred to in the Appendix 1.

Variable Name	Variable Label	Type	Code List / Controlled Term	Comments
QTFL	QT/QTc Analysis Set	Char	NY	Patient-level analysis populations for by timepoint relevant analysis, e.g., the statistical modeling in assumption 1. Example of definition: all patients who received at least 1 dose of study drug and had cardiodynamic ECG measurements at baseline as well as on-treatment with at least 1 post-baseline time point with a valid change-from-baseline value for at least 1 ECG parameter QTcF.
PKQTFL	PK/QTc Analysis Set	Char	NY	Patient-level analysis populations for C-QTc modeling analysis, e.g., all patients in the QT/QTc population who had at least 1 post-dose value of plasma concentration of study drug with at least 1 pair of post-dose PK concentration and ΔQTcF data from the same scheduled time point.
PTRTA	Pooled Actual Treatment	Char		If ADCQT.TRTA='Placebo' then ADCQT.PTRTA='Placebo'; else if ADCQT.TRTA is not missing then ADCQT.PTRTA='DRUGX', i.e., active treatment

Variable Name	Variable Label	Type	Code List / Controlled Term	Comments
PTRTAN	Pooled Actual Treatment (N)	Num		The numeric value for ADCQT.PTRTA; 0 for placebo, 1 for active treatment.
AVISTPT	Analysis Visit and Timepoint	Char		Concatenate the ADEG.AVISIT and ADEG.ATPT if there are multiple visits involved in C-QT analysis
AVISTPTN	Analysis Visit and Timepoint (N)	Num		The numeric value for ADCQT.AVISTPT
ACOMPFL	Comparator Record Flag	Char	Y_NULL	If record is part of the comparator treatment (e.g., placebo) then ACOMPFL="Y" else ACOMPFL is null, e.g., if ADCQT.TRTA='Placebo' then ADCQT.ACOMPFL="Y" else ADCQT.ACOMPFL is null.
COMP	Comparator Value	Num		If DTYPE ne "AVERAGE" then null else if ACOMPFL eq "Y" then COMP=AVAL; else COMP value is based on the corresponding COMPTYPE (similar as BASETYPE).
COMPBASE	Baseline Value of the Comparator	Num		If DTYPE ne "AVERAGE" then null else if ACOMPFL eq "Y" then COMPBASE=BASE; else COMPBASE value is based on the corresponding COMPTYPE.
COMPCHG	Change from Baseline in the Comparator	Num		If DTYPE ne "AVERAGE" then null else if ACOMPFL eq "Y" then COMPCHG=CHG else COMPCHG value is based on the corresponding COMPTYPE.
CCOMPCHG	Comparator corrected change from BL	Num		If DTYPE ne "AVERAGE" then null else if ACOMPFL ne "Y" then CCOMPCHG=CHG – COMPCHG else null.
COMPTYPE	Comparator Type	Char		Encodes the key that allows for identifying comparator treatment (e.g., placebo) rows used to compute the comparator and baseline corrected changes (i.e., double deltas) from each DTYPE = "AVERAGE" and ACOMPFL ne "Y". This is like BASETYPE. Example values as 'Placebo group at 0.5 h', 'Placebo group at 2 h', etc.
CBASE	Centralized Baseline	Num		For ADCQT.DTYPE='AVERAGE' and ADCQT.PARAMCD='QTCF', ADCQT.CBASE is mapped for individual participant. ADCQT.CBASE=ADCQT.BASE minus the population mean baseline QTcF for all participants in PK/QTc population.
ANALY1	Analyte 1	Char		The analyte in ADPC.PARAMCD that corresponding to ADCQT.CONC1, i.e. study treatment 'DRUGX'
A1DTM	Analyte 1 Analysis Datetime	Num		Fetch the datetime (ADPC.ADTM) of the time-matched PK samples corresponding to ADCQT.CONC1
A1RRLT	Relative Time from Analyte 1 Datetime	Num		Relative Time of ECG collection datetime to time-match PK sampling datetime, e.g., ADCQT.A1RRLT=(ADCQT.ADTM - ADCQT.A1DTM) / 3600
A1RRLTU	Relative Time from Analyte 1 DT Units	Char	UNIT	
A1OUTWFL	Analyte 1 Out of Window Flag	Char	Y_NULL	Define the window of ECG collection datetime and PK sampling datetime through SAP, e.g., 1 hour, if ADCQT.A1RRLT > 1, then ADCQT.A1OUTWFL = 'Y'. The out-of-window records should be excluded from C-QTc analysis.

Variable Name	Variable Label	Type	Code List / Controlled Term	Comments
CONC1	Concentration of Investigator Production	Num		Fetch the time-matched concentration of investigator production (ADPC.AVAL for investigator production). Example of definition: Map for ADCQT.PARAMCD='QTCF' and ADCQT.ECGPKFL='Y', get the corresponding timepoint investigator production concentration from ADPC; if ADCQT.TRTA='Placebo', then ADCQT.CONC1=0; if the pre-dose concentration is below the quantifiable limit, set ADCQT.CONC1=0; if the post-dose concentration is below the quantifiable limit, set ADCQT.CONC1=quantifiable limit/2
CONC1U	Conc. of Investigator Production Units	Char		ADPC.AVALU for investigator production
ANALY2	Analyte 2	Char		Same as ADCQT.ANALY2 but for metabolites of investigator production
A2DTM	Analyte 2 Analysis Datetime	Num		Same as ADCQT.A2DTM but for metabolites of investigator production
A2RRLT	Relative Time from Analyte 2 Datetime	Num		Same as ADCQT.A2RRLT but for metabolites of investigator production
A2RRLTU	Relative Time from Analyte 2 DT Units	Char		Same as ADCQT.A2RRLTU but for metabolites of investigator production
A2OUTWFL	Analyte 2 Out of Window Flag	Char	Y_NULL	Same as ADCQT.A2OUTWFL but for metabolites of investigator production
CONC2	Concentration of <Metabolite 1>	Num		Same as ADCQT.CONC2 but for metabolites of investigator production
CONC2U	Concentration of <Metabolite 1> Units	Char		Same as ADCQT.CONC2U but for metabolites of investigator production
ECGPCFL	ECG Matching PK Flag	Char	Y_NULL	Populate with “Y” if there is a matching nominal PK sample time point for the nominal ECG time point (i.e., if there are time-matched PK measures in ADPC for this ECG).
IUTANLFL	Intersection Union Test Analysis Flag	Char	Y_NULL	Record-level analysis flag. Set to “Y” if the record is used in the intersection union test (i.e., by-time in assumption 1) analysis or null otherwise.
CATANLFL	Categorical Analysis Flag	Char	Y_NULL	Record-level analysis flag. Set to “Y” if the record is used in the categorical analysis or null otherwise.
CQTANLFL	Concentration QT Analysis Flag	Char	Y_NULL	Record-level analysis flag. Set to “Y” if the record is used in the concentration (investigator production)-QT analysis or null otherwise.
M1QTANFL	<Metabolite 1> Conc. QT Analysis Flag	Char	Y_NULL	Record-level analysis flag. Set to “Y” if the record is used in the concentration (metabolite of investigator production)-QT analysis or null otherwise.
CMQTANFL	IP and Metabolite Conc. QT Analysis Flag	Char	Y_NULL	Record-level analysis flag. Set to “Y” if the record is used in the concentration (both parent and metabolite of investigator production included)-QT analysis or null otherwise.
ANL01	Analysis 01	Char		A text string describing the analysis number 01, which is reserved for the primary analysis (e.g., assessment of investigational drug treatment QT effects).
ANL01FL	Analysis Flag 01	Char	Y_NULL	Selection variable to identify the exact set of records used in the analysis number 01 corresponding to ANL01.

Variable Name	Variable Label	Type	Code List / Controlled Term	Comments
ANL02	Analysis 02	Char		A text string describing the analysis flag number 02, which is reserved for the assay sensitivity analysis (e.g., assessment of positive control QT effects).
ANL02FL	Analysis Flag 02	Char	Y_NULL	Selection variable to identify the exact set of records used in the analysis number 02 corresponding to ANL02.

Table 1. Additional essential variables for C-QT modeling

PRE-SPECIFIED LINEAR MIXED EFFECTS MODEL

When using a C-QTc analysis as the primary basis for decisions to classify the risk of a drug, the upper bound of the two-sided 90% confidence interval for the QTc effect (model-derived ΔQTc/ΔΔQTc) should be less than 10 ms at the highest clinically relevant exposure (refer to ICH E14 Section 2.2.4). This threshold indicates that an expanded ECG safety evaluation in later stages of drug development is unnecessary. The white paper recommends a pre-specified linear mixed effects model (LME) (See Equation 1) as the primary analysis to exclude a 10-ms QTc prolongation effect. The default dependent variable of the model is ΔQTcF, which represents the change from baseline in QTc interval corrected using Fridericia's formula. The fixed effect parameters include intercept, slope, baseline influence on intercept, treatment (active = 1, placebo = 0), and nominal time from the first dose. The subject is included as an additive random effect on both intercept and slope terms.

$$\Delta QTcF_{ijk} = (\theta_0 + \eta_{0,i}) + \theta_1 TRT_j + (\theta_2 + \eta_{2,i}) C_{ijk} + \theta_3 TIME_j + \theta_4 (QTcF_{ij0} - \overline{QTcF_0}) \quad (1)$$

- $\Delta QTcF_{ijk}$ is the change from baseline in QTcF for subject i in treatment j at time k, denoted by CHG when PARAMCD is QTCFAG in ADCQT;
- θ_0 is the population mean intercept in the absence of a treatment effect;
- $\eta_{0,i}$ is the random effect of subject i associated with the intercept term θ_0;
- θ_1 is the fixed effect associated with treatment TRT_j, TRT_j is a binary variable where 0 = placebo and 1 = active drug (pooled dose levels), denoted by PTRTAN and PTRTA in ADCQT;
- C_{ijk} is the concentration for subject i in treatment j at time k;
- θ_2 is the population mean slope of the assumed linear association between concentration C_{ijk} and $\Delta QTcF_{ijk}$;
- $\eta_{2,i}$ is the random effect of subject i associated with the slope θ_2;
- θ_3 is the fixed effect associated with time;
- $QTcF_{ij0}$ is the baseline QTcF for individual subject, denoted by BASE when PARAMCD is QTCFAG in ADCQT;
- $\overline{QTcF_0}$ is the population mean baseline QTcF for all subjects;
- θ_4 is the fixed effect associated with centered baseline QTcF, i.e., $QTcF_{ij0} - \overline{QTcF_0}$, which is denoted by CBASE in ADCQT.

This model assumes the random effects are normally distributed with mean [0,0] and an unstructured covariance matrix **G**, whereas the residuals are normally distributed with mean 0 and variance **R**.

MODIFICATION ON THE PRE-SPECIFIED MODEL

The pre-specified model is generally recommended for use in most study designs involving healthy subjects (e.g., SAD, MAD, and TQT studies). This model provides a robust framework for analyzing data

under typical conditions. However, there are specific scenarios where modifications to the pre-specified model are necessary to better accommodate unique data structures. The white paper provides three scenarios below. There are summaries of the considerations for modifying the pre-specified model under these circumstances. These considerations ensure that the model remains flexible and applicable across different study designs and data structures, thereby maintaining the integrity and reliability of the statistical analysis.

1. The change from baseline in QTcF corrected for placebo ($\Delta\Delta QTcF$) as the dependent variable:
   - In studies with placebo group, $\Delta\Delta QTcF$ can be computed at every time point for each subject by subtracting the $\Delta QTcF$ for placebo from the $\Delta QTcF$ for each treatment arm;
   - $\Delta\Delta QTcF$ can be demoted by the variable CCOMPCHG in ADCQT. Display 1 is an example for how to calculate CCOMPCHG;
   - Since the placebo data have been calculated in $\Delta\Delta QTcF$ as the dependent variable, θ_1 and θ_3 terms in Equation 1 can be deleted.

     $$\Delta\Delta QTcF_{i1k} = (\theta_0 + \eta_{0,i}) + (\theta_2 + \eta_{2,i})C_{i1k} + \theta_4(QTcF_{i10} - \overline{QTcF_0})$$

USUBJID	TRTA	NRRLT	AVAL	BASE	CHG	ACOMPFL	COMP	COMPBASE	COMPCHG	CCOMPCHG	COMPTYPE
1001	Drug	0.5	390.333	390.333	0.000		388.889	391.111	-2.222	2.222	Placebo group at 0.5 h
1001	Drug	1	388.333	393.333	-5.000	average	390.111	393.389	-3.278	-1.722	Placebo group at 1 h
1001	Drug	4	387.333	381.000	6.333		388.222	389.556	-1.333	7.667	Placebo group at 4 h
1002	Placebo	0.5	374.000	372.333	1.667	Y	388.889	391.111	-2.222		Placebo group at 0.5 h
1002	Placebo	1	375.667	375.000	0.667	Y	390.111	393.389	-3.278		Placebo group at 1 h
1002	Placebo	4	371.000	372.667	-1.667	Y	388.222	389.556	-1.333		Placebo group at 4 h
1003	Placebo	0.5	393.667	402.333	-8.667	Y	388.889	391.111	-2.222		Placebo group at 0.5 h
1003	Placebo	1	397.333	401.333	-4.000	Y	390.111	393.389	-3.278		Placebo group at 1 h
1003	Placebo	4	396.667	406.667	-10.000	Y	388.222	389.556	-1.333		Placebo group at 4 h
1005	Placebo	0.5	401.667	392.333	9.333	Y	388.889	391.111	-2.222		Placebo group at 0.5 h
1005	Placebo	1	398.333	392.667	5.667	Y	390.111	393.389	-3.278		Placebo group at 1 h
1005	Placebo	4	399.333	390.333	9.000	Y	388.222	389.556	-1.333		Placebo group at 4 h
1007	Placebo	0.5	378.000	383.000	-5.000	Y	388.889	391.111	-2.222		Placebo group at 0.5 h
1007	Placebo	1	377.667	390.000	-12.333	Y	390.111	393.389	-3.278		Placebo group at 1 h
1007	Placebo	4	381.000	387.000	-6.000	Y	388.222	389.556	-1.333		Placebo group at 4 h
1008	Placebo	0.5	398.667	410.333	-11.667	Y	388.889	391.111	-2.222		Placebo group at 0.5 h
1008	Placebo	1	401.333	412.333	-11.000	Y	390.111	393.389	-3.278		Placebo group at 1 h
1008	Placebo	4	396.000	399.667	-3.667	Y	388.222	389.556	-1.333		Placebo group at 4 h
1010	Placebo	0.5	387.333	386.333	1.000	Y	388.889	391.111	-2.222		Placebo group at 0.5 h
1010	Placebo	1	390.333	389.000	1.333	Y	390.111	393.389	-3.278		Placebo group at 1 h
1010	Placebo	4	385.333	381.000	4.333	Y	388.222	389.556	-1.333		Placebo group at 4 h

Display 1. Example of CCOMPCHG ($\Delta\Delta QTcF$)

2. No placebo data
   - Although ICH E14 guidelines recommends that placebo data are included in the model to exclude small effects in the QTc interval, a concurrent placebo arm was not included due to design or ethical reasons;
3. Since there is no placebo data, θ_1 and θ_3 terms in Equation 1 can be deleted.

   $$\Delta QTcF_{i1k} = (\theta_0 + \eta_{0,i}) + (\theta_2 + \eta_{2,i})C_{i1k} + \theta_4(QTcF_{i10} - \overline{QTcF_0})$$

4. Data pooled from two or more studies
   - Pooled concentration and QTc data are used to increase the exposures and/or increase the number of subjects at higher dose levels;
   - It is proposed to apply LME model to individual studies;
   - When applying LME model to pooling data, it is proposed to include a study effect on key model parameters, such as intercept, slope, and residual error. And the heterogeneity (unequal variance) between studies should be evaluated.

EXAMPLE OF MODEL DESCRIPTION IN SAP

The following example is for a SAD/MAD phase 1 study involving health subjects and a placebo arm. The model described by Equation 1 is particularly suited to this design.

"The relationship between plasma concentrations of DURGX and ΔQTcF will be quantified using a linear mixed-effects modeling approach. The model will have ΔQTcF as the dependent variable, plasma concentrations of DURGX as the explanatory variate (0 for placebo), centered baseline QTcF (i.e., baseline QTcF for individual participant minus the population mean baseline QTcF for all participants) as an additional covariate, study treatment (active = 1 or placebo = 0) and time (i.e., post-dose time point: categorical) as fixed effects, and random effects on intercept and slope per participant. In all calculations, concentrations in participants who received placebo will be set to zero. DRUGX plasma concentrations below the quantifiable limit at pre-dose will be set to zero and after dosing will be set to 1/2 the lower limit of quantitation in the concentration-QTc analysis.

An unstructured covariance matrix will be specified for the random effects. If convergence cannot be achieved even after appropriate rescaling of the concentrations, the random effect on the slope and intercept will be dropped, in this order, until convergence is achieved. The degrees of freedom (df) estimates will be determined by the Kenward-Roger method. From the model, the slope (i.e., the regression parameter for the concentration) and the treatment effect-specific intercept (defined as the difference between active and placebo) will be estimated together with the 2-sided 90% CI. The estimates for the time effects will be reported with df and SE."

The following SAS codes can be used to conduct the LME model in the example:

```
proc mixed data=PKQTc method=reml;
  class USUBJID AVISTPT;
  model ΔQTcF=PTRTAN CONC1 AVISTPT CBASE / solution cl noint alpha=0.1
        alphap=0.1 covb ddfm=kr;
  random int CONC1 / type=un subject=USUBJID s;
run;

where PKQTc=PK/QTC analysis set, i.e., PKQTFL = 'Y' in ADCQT
```

Another example is for an oncology study without placebo data but with an active metabolite, it is crucial to characterize the effects of each analyte including parent drug and its metabolite, as well as any interactions between them. This characterization is challenging, especially when interpreting the contribution for each analyte to the overall effect.

"The relationship between ΔQTcF and plasma concentrations of DRUGX and METABOLITE will be quantified using a linear mixed-effects modeling approach. The model will have ΔQTcF as the dependent variable, plasma concentrations of DRUGX and METABOLITE as the explanatory variables, centered baseline QTcF (i.e., baseline QTcF for individual patient minus the population mean baseline QTcF for all patients) as an additional covariate, a fixed intercept (i.e., the population mean intercept), and random effects on intercept and slope for the concentration per patient. Plasma concentrations of DRUGX and METABOLITE below the limit of quantification (BLQ) will be set to zero for pre-dose time points after the initial dose and 1/2 of the lower limit of quantitation (LLOQ) for post-dose time points in the concentration-QTc analysis.

An unstructured covariance matrix will be specified for the random effects. If convergence cannot be achieved even after appropriate rescaling of the concentrations (i.e., multiplying or dividing by 10, 100, and 1000), the random effect on the slopes and intercept will be dropped, in this order, until convergence is achieved. The degrees of freedom estimates will be determined by the Kenward-Roger method. From the model, the slopes (i.e., the regression parameters for the concentrations of DRUGX and METABOLITE) and the fixed intercept will be estimated together with the 2-sided 90% CI.

The following 3 models will be explored: the full model with both analytes (DRUGX and METABOLITE), the individual model with DRUGX alone, and the individual model with METABOLITE alone. The model selection procedure will be conducted using the Akaike Information Criterion (AIC) and the t-value for the intercept estimator."

The following SAS codes can be used to conduct the LME model in the example:

```
proc mixed data=PKQTc method=reml;
```

```
  class USUBJID;
  model ΔQTcF=CONC1 CONC2 CBASE / solution cl alpha=0.1 alphap=0.1
        covb ddfm=kr;
  random int CONC1 CONC2 / type=un subject=USUBJID s;
run;

where PKQTC=PK/QTC analysis set, i.e., PKQTFL = 'Y' in ADCQT,
CONC1=concentration of DRUGX, CONC2=concentration of METABOLITE
```

ASSESSMENT OF MODEL-INDEPENDENT ASSUMPTIONS

Prior to proceeding with the concentration-QTc analysis, it's critical to validate assumptions using model-independent exploratory plots. Confirming these assumptions as outlined in the white paper is fundamental for a credible model. Four principal assumptions must be satisfied; otherwise, an adapted C-QTc model should be crafted.

Assumption 1: ***No drug effect on HR***. A key factor to examine is how a drug may substantially raise or lower heart rate (HR). While the exact impact on HR that might affect the QT/QTc evaluation isn't universally agreed upon, mean changes in HR greater than 10 beats per minute (bpm) are often seen as concerning. It's useful to assess the timing of average HR effects caused by a treatment. Typically, an analysis at each time point through statistical models will be carried out to assess the average HR changes as outlined subsequently:

"The by-time point analysis for HR will be based on a mixed model for repeated measurements (MMRM) with ΔHR as the dependent variable, time (i.e., post-baseline time point with at least 3 patients within treatment: categorical), treatment (Dose 1 to Dose X of DRUGX) and time-by-treatment interactions as fixed effects, and baseline HR as a covariate. From this analysis, the LS mean, SE, and 2-sided 90% CI of ΔHR will be calculated for each dose of DRUGX at each post-baseline time point, separately."

Or

"The by-time point analysis for HR on DRUGX versus placebo will be based on a mixed model for repeated measures (MMRM) with ΔHR as the dependent variable, time (i.e., post-dose time point: categorical), treatment (Dose 1 to Dose X of DRUGX, and placebo) and time-by-treatment interaction as fixed effects, and baseline HR as a covariate. From this analysis, the LS mean, SE, and 2 sided 90% CI will be calculated for the contrast 'DRUGX versus placebo' (ΔΔHR) for each dose of DRUGX at each post-dose time point, separately."

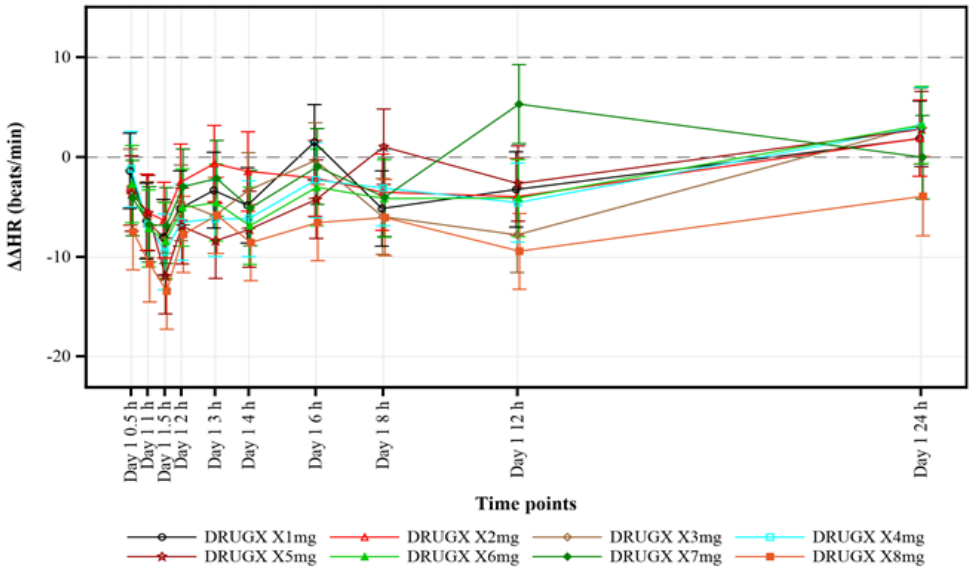

Figure 1. ΔΔHR across time points with statistical modeling

Figure 1 shows the exploratory plots for this assumption. The LS mean ΔΔHR is below 10 bpm for all dose levels of DRUGX across all post-baseline time points, indicating that DRUGX has no clinically relevant effect on HR. The plots also show the 90% confidence intervals for the LS mean ΔΔHR, which are narrow and symmetric around the mean. The p-values for the time-by-treatment interaction, if above 0.05, would suggest no significant difference between the DRUGX doses and placebo in terms of HR change over time.

Assumption 2: *QTc interval is independent of HR.* For drugs that do not have a significant effect on HR, QTcF is usually a sufficient correction method, and there is no need to evaluate the appropriateness of this correction method. If an individualized HR correction method is used, the drug-free data should be used to evaluate the rationality of the selected method, to determine whether QTc is independent of HR.

To evaluate this hypothesis, scatter plots of QTcF and RR interval for each DRUGX dose level (Figure 2) can be generated, and a simple linear regression line can be fitted to all QTcF-RR pairs of all patients. In addition, quantile plots of QTcF and RR interval can be drawn (Figure 3) and compared with a mean fitted regression line (90% CI) that comes from a linear mixed-effects model. The quantile plots reflect the distribution of the observed data, while the fitted regression line reflects the predictive ability of the model on the data.

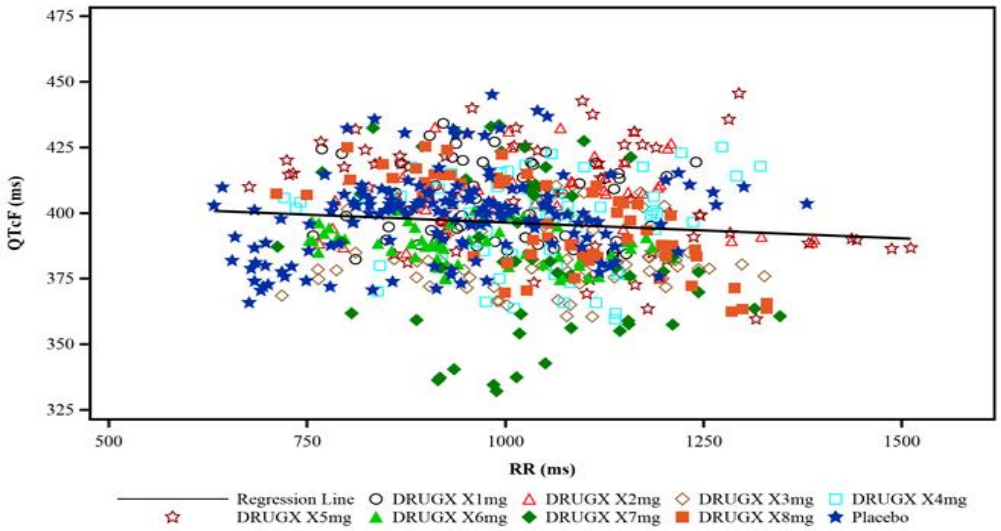

Figure 2. A scatter plot of QTcF and RR intervals

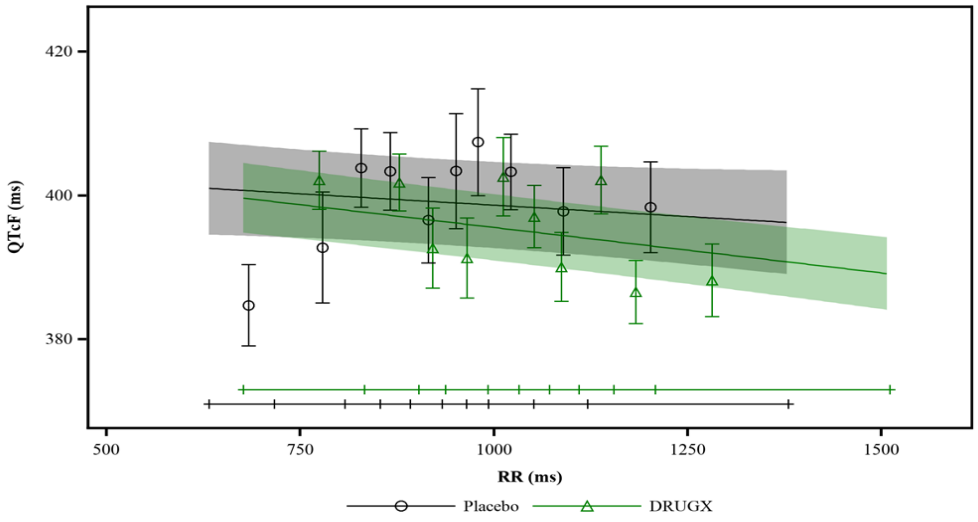

Figure 3. A decile plot of QTcF and RR intervals

From Figure 2 and Figure 3, it can be seen that there is no obvious linear relationship between QTcF and RR interval, indicating that QTcF is effective in correcting for HR. If an individualized HR correction method is used, a similar graphical method can be used to evaluate its suitability.

Assumption 3: ***No time delay (hysteresis) between drug concentrations and ΔQTc Concordance, or lack thereof.*** The hysteresis can be assessed by a graphical method based on LS mean ΔQTcF and geometric mean concentration at each post-baseline time point, where LS mean ΔQTcF comes from the by-time point analysis using statistical modeling as described in assumption 1. In addition, a hysteresis plot should be provided, which connects the LS mean ΔQTcF and the mean concentration at the same time point by dose in temporal order. Under the above specification, a counterclockwise loop in the lag plot may indicate the presence of a time lag.

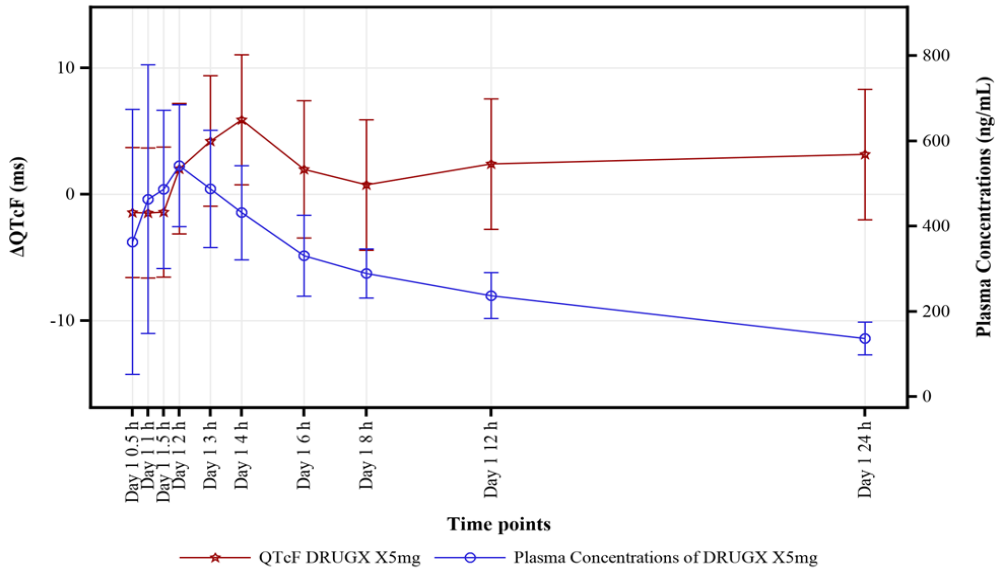

Figure 4. Joint plot of DRUGX plasma concentrations and ΔQTcF over time for X5 mg

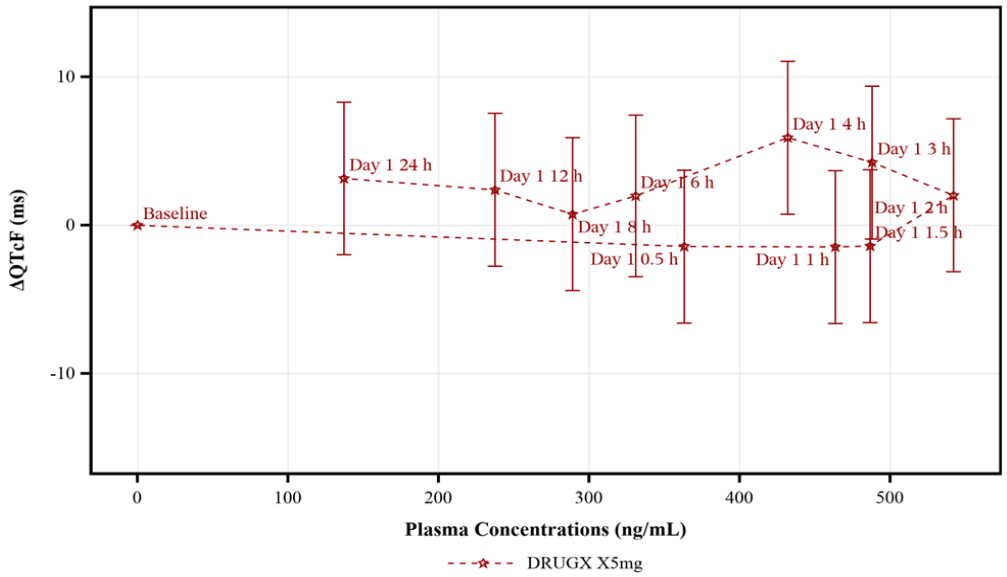

Figure 5. Plot of DRUGX plasma concentration and ΔQTcF connected in temporal order

From Figure 4, it can be seen that the peak concentration of DRUGX is reached around 2 hours after dosing, and the peak ΔQTcF is reached around 4 hours after dosing, suggesting a possible time lag between the two variables. However, the magnitude of ΔQTcF is small and within the normal range,

indicating that the effect of DRUGX on QTc is minimal. Figure 5 confirms that there is a counterclockwise loop in the lag plot, which means that the drug concentration and ΔQTcF are not synchronized. However, the loop is not very pronounced, and the relationship between drug concentration and ΔQTcF is weak and not clinically relevant.

Assumption 4: *Linear concentration-QTc relationship*. A scatter plot of observed ΔQTcF and concentration with a locally weighted scatter plot smoothing (i.e., LOESS) line and 95% CI with optimal smoothing parameters selected by the AIC with correction. A simple linear regression line can be provided to check the assumption of a linear concentration-QTc relationship. The LOESS line can help to visualize the shape of the concentration-QTc relationship and identify any deviations from linearity. The LOESS line should be close to the linear regression line if the linear assumption is valid. If data are pooled from multiple studies, the regression lines are to be displayed for each study and pooled across studies.

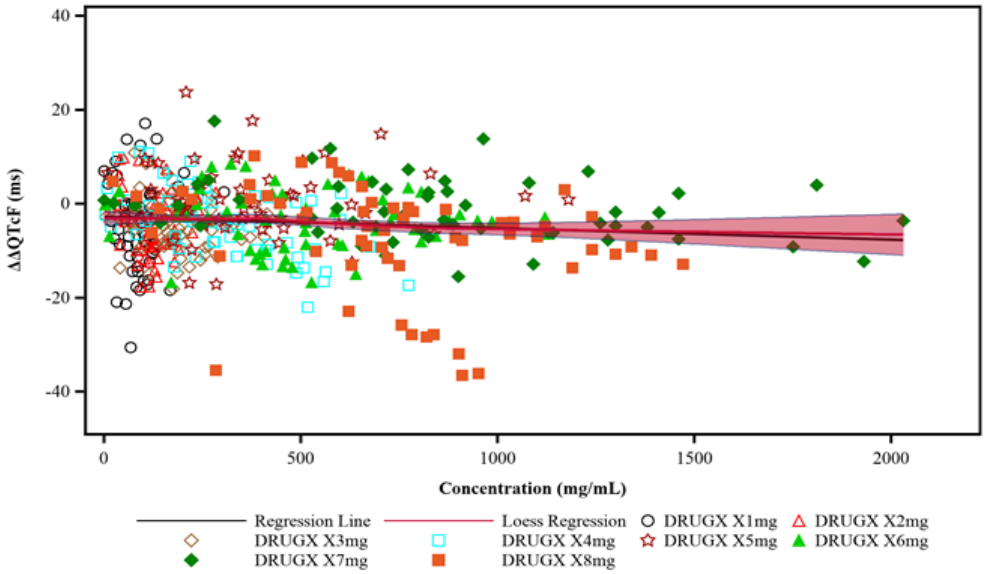

Figure 6. Scatter plot of observed DRUGX plasma concentrations and ΔΔQTcF with simple linear regression and LOESS regression

For concentration-QT analysis involving multiple studies, the following assumption is added:

Assumption 5: *Homogeneity (Equal Variances)*. This assumption states that the variance of the QTc response is the same across different studies and different concentrations of the drug. The concentration-QTc analysis method will be assessed to account for heterogeneity (unequal variance) when pooling data from multiple studies. Both the plots of the standardized residuals versus model-predicted ΔQTcF and versus studies based on the performed concentration-QTc model, and Levene's test at 5% significance level for assessing the assumption of equal variances between the studies can be provided to support the assumption.

The SAS code for the Levene's test is as follows:

```
PROC GLM DATA=PKQTc;
      class STUDYID;
      model CHG= STUDYID;
      means STUDYID / hovtest = LEVENE;
RUN;
```

Where PKQTc = PK/QTc analysis set, CHG = ΔQTcF, STUDYID = Study Identifier.

GOODNESS-OF-FIT EVALUATION

Goodness-of-fit (GOF) evaluation should be presented for the final C-QTc model, and when relevant for key stages during model development. A C-QTc quantile plot of observed data overlaid with the model predictions (Figure 7) is a visual assessment of how well the model fits the data. The plot shows the mean placebo-adjusted ΔΔQTcF (90% CI) within each concentration decile and the model-predicted mean ΔΔQTcF with 90% CI. The solid black line with gray shaded area represents the model-predicted relationship between ΔΔQTcF and plasma concentration, which is calculated from a linear equation (see Equation 3). The red filled circles with vertical bars show the mean placebo-adjusted ΔΔQTcF with 90% CI displayed at the associated median plasma concentration within each decile for the drug. The term placebo-adjusted ΔΔQTcF can be used to illustrate the underlying data on subject level, representing the observational data. It can be defined as the observed ΔQTcF for each subject minus the estimated time effect (i.e., the model-predicted mean ΔQTcF in the placebo group). The horizontal red line with notches indicates the range of concentrations divided into deciles for the drug. The area between each decile represents the point at which 10% of the data are present; the first notch to second notch denotes the first 10% of the data, the second notch to third notch denotes the 10-20% of the data and so on. The plot provides a visual comparison of the observed and predicted ΔΔQTcF values across the range of concentrations and evaluates the fit of a linear model and the concentration-response relationship. From this plot, it can be seen that the predicted ΔΔQTcF values are close to the observed ΔΔQTcF across all plasma concentrations, indicating a good fit of the model to the data.

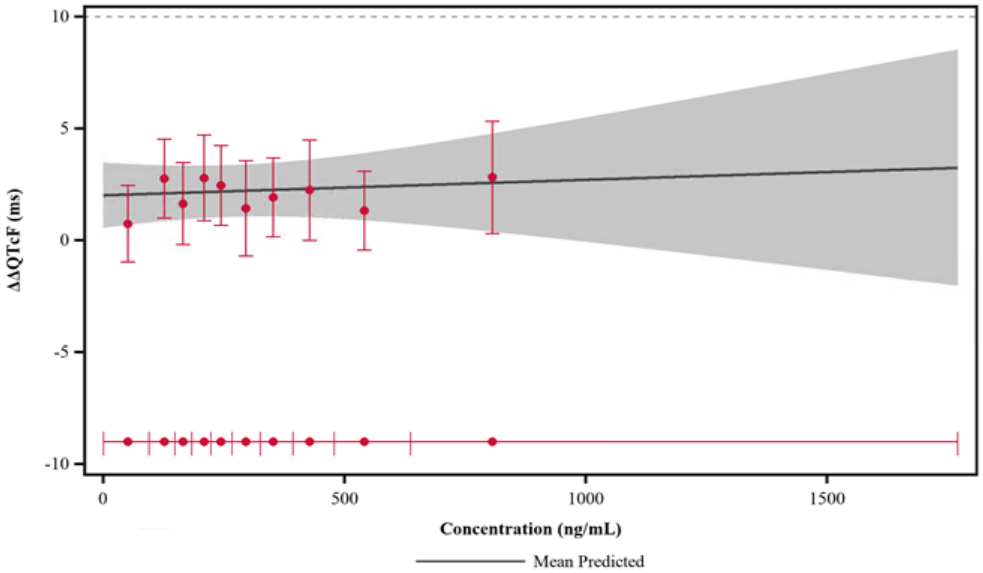

Figure 7. Model-predicted ΔΔQTcF (mean and 90% CI) and observed ΔΔQTcF (mean and 90% CI) across deciles of plasma concentrations

The model-predicted mean ΔΔQTcF is defined as the difference between the model-predicted ΔQTcF at concentration of interest and model-predicted ΔQTcF for placebo (concentration = 0), as denoted by Equation 2.

$$Mean\ \Delta\Delta QTcF = Mean\left(\Delta QTcF_{ijk} | j = 1, C_{ijk} = C\right) - Mean\left(\Delta QTcF_{ijk} | j = 0, C_{ijk} = 0\right) \quad (2)$$

The estimated ΔΔQTcF at concentration of interest (Equation 3) and corresponding 90% CI (Equation 4-5) can be calculated by plugging in $Mean\left(\Delta QTcF_{ijk} | j = 1, C_{ijk} = C\right)$ and $Mean\left(\Delta QTcF_{ijk} | j = 0, C_{ijk} = 0\right)$ into Equation 1.

$$Estimated\ Mean\ \Delta\Delta QTcF(C) = \theta_{1,Est} + C\theta_{2,Est} \quad (3)$$

$$Estimated\ SE = \sqrt{var\left(\theta_{1,Est}\right) + C^2 var\left(\theta_{2,Est}\right) + 2C\left(cov\left(\theta_{1,Est}\theta_{2,Est}\right)\right)} \quad (4)$$

$$90\%\ CI = Estimated\ Mean\ \Delta\Delta QTcF(C) \pm t(0.95, DF) \times Estimated\ SE \quad (5)$$

In the equations, 'Est' refers to an estimate of the true parameter from the model fit, and $\theta_{1,Est}$ is the estimated treatment-specific intercept; $\theta_{2,Est}$ is the estimated slope, $var(\theta_{1,Est})$ is the variance of the treatment-specific intercept; $var(\theta_{2,Est})$ is the variance of the slope; $cov(\theta_{1,Est}\theta_{2,Est})$ is the covariance of the intercept and slope; t is the critical value determined from the t-distribution; DF is the degrees of freedom; C is the concentration of interest.

Evaluating the suitability of the linear mixed-effects model will require generating normal quantile-quantile (Q-Q) plots for the standardized residuals and random effects, as well as scatter plots of standardized residuals against concentration, predicted change in QTcF (ΔQTcF), and centered baseline QTcF. This evaluation also includes creating a plot of predicted ΔQTcF against observed ΔQTcF, alongside the previously mentioned decile plot. The scatter plots related to concentration and centered baseline QTcF will incorporate LOESS lines with smoothing parameters optimized by the Akaike information criterion with a correction. Should evidence suggest that a linear model is not suitable, alternative models, such as an Emax model, may be considered. Following this, the concentration-QTc analysis will be performed anew using the model that best accounts for the observed nonlinearity.

C-QT ANALYSIS MODEL RESULTS

In this section, the example results of the C-QT analysis model are presented, including the model parameter estimates, the model-predicted ΔΔQTcF at concentration of interest, e.g., Cmax of each dose level, and the threshold concentration that causes the upper bound of the two-sided 90% CI of the model-predicted ΔΔQTcF of 10 ms.

MODEL PARAMETER ESTIMATES

Table 2 shows the model parameter estimates for the intercept, slope, and time effect of the linear mixed-effects model, as well as their standard errors, 90% confidence intervals, and p-values. The slope represents the change in mean placebo-adjusted ΔΔQTcF per unit increase in plasma concentration (Equation 3). The positive significant slope indicates a positive concentration-response relationship. A statistically significant treatment effect-specific intercept is not biologically plausible and therefore may be indicative of hysteresis or model misspecification.

Parameter	Estimate	SE	t-Value	p-value	90% CI
Treatment Effect (ms)	1.95	0.8814	0.06	0.953	0.4953, 3.4101
DRUGX Slope (ms per ng/mL)	0.002	0.0021	0.91	0.0956	-0.0015, 0.0052
Centered Baseline Effect (ms)	-0.049	0.0414	-1.18	0.2485	-0.1200, 0.0219
Day 1 0.5 h Post-dose Effect (ms)	-4.57	1.5796	-2.89	0.0057	-7.218, -1.919
Day 1 1 h Post-dose Effect (ms)	-4.18	1.5511	-2.69	0.0098	-6.784, -1.575
Day 1 1.5 h Post-dose Effect (ms)	-3.15	1.5302	-2.06	0.0456	-5.722, -0.577
Day 1 2 h Post-dose Effect (ms)	-3.6	1.5237	-2.36	0.0228	-6.163, -1.039
Day 1 3 h Post-dose Effect (ms)	-3.13	1.5112	-2.07	0.0449	-5.668, -0.582
Day 1 4 h Post-dose Effect (ms)	-2.72	1.5076	-1.8	0.079	-5.253, -0.178
…					

Table 2: Example of the C-QT model parameter estimates

MODEL-PREDICTED ΔΔQTCF AT CONCENTRATION OF INTEREST

Table 3 shows the predicted ΔΔQTcF at Cmax for DRUGX X1mg and X2mg on Day 1 and Day 8 separately. The Cmax values were obtained from the PK/QTc analysis set. The model-predicted ΔΔQTcF at Cmax was calculated by plugging in the Cmax value into Equation 3, using the model parameter estimates from Table 2.

Treatment	Visit	Geometric mean Cmax of DRUGX (ng/mL)	Model-Predicted ΔΔQTcF (ms) (90% CI)
DRUGX X1mg	Day 1	150.32	2.26 (1.05, 3.48)
	Day 8	344.26	2.61 (1.41, 3.81)
DRUGX X2mg	Day 1	450.35	2.79 (1.46, 4.13)
	Day 8	749.23	3.32 (1.29, 5.36)
10 ms Threshold		1694	4.99 (-0.02, 10.00)

Table 3: Example of the model-predicted ΔΔQTcF at concentration of interest

PREDICTED ΔΔQTCF INTERVAL AT GEOMETRIC MEAN PEAK DRUGX CONCENTRATIONS

Figure 8 shows the relationship between the model-predicted ΔΔQTcF and plasma concentration for DRUGX, along with their 90% CI. The dashed horizontal line indicates the regulatory threshold of 10 ms for ΔΔQTcF. The upper bound of the 2-sided 90% CI of the model-predicted ΔΔQTcF is below 10 ms at clinically relevant exposure, it can be concluded that DRUGX does not cause clinically concerning QTc prolongation within the observed plasma concentration range.

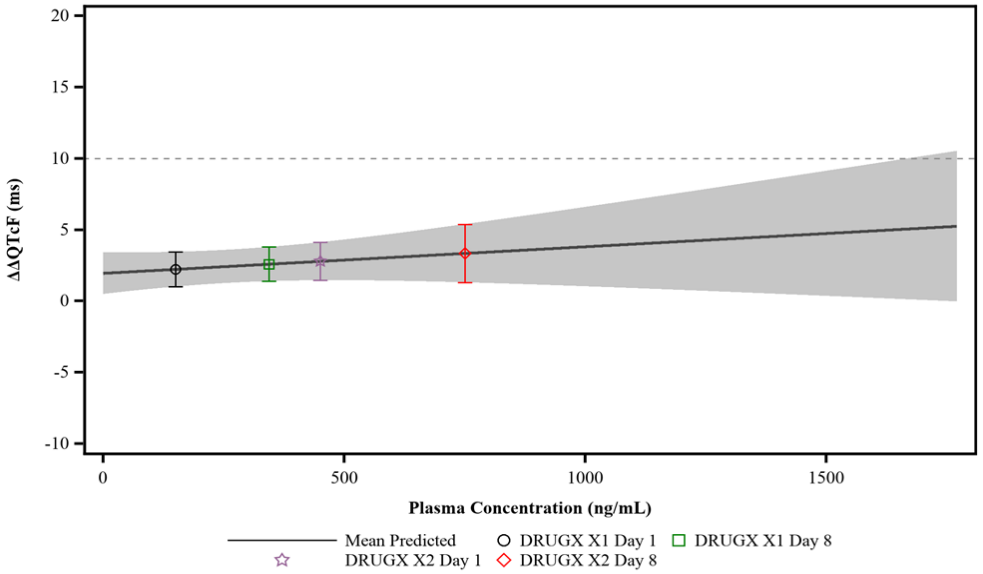

Figure 8. Predicted ΔΔQTcF interval at geometric mean peak DRUGX concentrations

All outcomes are obtainable using SAS, as outlined below.

```
proc mixed data=PKQTc method=reml;
  class USUBJID AVISTPT;
  model ΔQTcF=PTRTAN CONC1 AVISTPT CBASE / solution cl noint alpha=0.1
        alphap=0.1 covb ddfm=kr;
  random int CONC1 / type=un subject=USUBJID s;
  estimate 'Predicted Δ Δ QTcF at Geomean of Cmax on Day 1 for DRUGX X1mg'
           PTRTAN 1 CONC1 150.32 / cl alpha = 0.1 ;
  estimate 'Predicted Δ Δ QTcF at Geomean of Cmax on Day 8 for DRUGX X1mg'
           PTRTAN 1 CONC1 344.26 / cl alpha = 0.1 ;
  estimate 'Predicted Δ Δ QTcF at Geomean of Cmax on Day 1 for DRUGX X2mg'
           PTRTAN 1 CONC1 450.35 / cl alpha = 0.1 ;
  estimate 'Predicted Δ Δ QTcF at Geomean of Cmax on Day 8 for DRUGX X2mg'
           PTRTAN 1 CONC1 749.23 / cl alpha = 0.1 ;
```

```
run;
```

E-SUBMISSION PACKAGES

The preparation of e-submission packages, including define files, reviewer guides, and programs, does not differ significantly from the regular process. According to the FDA guideline Submitting Clinical Trial Datasets for Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential of Drugs, it is recommended to submit both ADCQT and ADPC datasets. The variables in ADCQT and ADPC should be coded consistently to ensure proper mapping of time-matched PK and ECG rows.

Since the Subject Level Analysis Dataset (ADSL) is included in the single or integrated analysis packages, it is permissible to omit ADSL from the C-QTc analysis packages if there are no changes to ADSL. However, it is important to note in reviewer guides that ADSL was included in the single or integrated analysis packages. Furthermore, to facilitate the reviewers to view and reproduce the analysis results, the relevant program codes should also be provided.

REFERENCES

Garnett C, Bonate PL, Dang Q, et al. Scientific white paper on concentration-QTc modeling. [Published correction appears in J Pharmacokinet Pharmacodyn. 2018;45(3):399]. J Pharmacokinet Pharmacodyn. 2018;45(3):383-397.

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ICH Expert Working Group. “THE CLINICAL EVALUATION OF QT/QTC INTERVAL PROLONGATION AND PROARRHYTHMIC POTENTIAL FOR NONANTIARRHYTHMIC DRUGS E14” Released on 12 May 2005.
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ICH E14 Implementation Working Group. “ICH E14 Guideline: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs - Questions & Answers (R3)” Released on 10 December 2015.
https://database.ich.org/sites/default/files/E14_Q%26As_R3_Q%26As.pdf

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CONTACT INFORMATION

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Enterprise: Dizal
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APPENDIX 1: VARIABLES IN ADCQT

Variable Name	Variable Label	Type	Code List / Controlled Term	Comments
STUDYID	Study Identifier	Char		
USUBJID	Unique Subject Identifier	Char		
QTFL	QT/QTc Analysis Set	Char	NY	Patient-level analysis populations for by timepoint relevant analysis, e.g., the statistical modeling in assumption 1. Example of definition: all patients who received at least 1 dose of study drug and had cardiodynamic ECG measurements at baseline as well as on-treatment with at least 1 post-baseline time point with a valid change-from-baseline value for at least 1 ECG parameter QTcF.
PKQTFL	PK/QTc Analysis Set	Char	NY	Patient-level analysis populations for C-QTc modeling analysis, e.g., all patients in the QT/QTc population who had at least 1 post-dose value of plasma concentration of study drug with at least 1 pair of post-dose PK concentration and ΔQTcF data from the same scheduled time point.
TRTP	Planned Treatment	Char		ADEG.TRTP
TRTPN	Planned Treatment (N)	Num		ADEG.TRTPN
TRTA	Actual Treatment	Char		ADEG.TRTA
TRTAN	Actual Treatment (N)	Num		ADEG.TRTAN
PTRTA	Pooled Actual Treatment	Char		If ADCQT.TRTA='Placebo' then ADCQT.PTRTA='Placebo'; else if ADCQT.TRTA is not missing then ADCQT.PTRTA='DRUGX', i.e., active treatment
PTRTAN	Pooled Actual Treatment (N)	Num		The numeric value for ADCQT.PTRTA
APERIOD	Period	Num		ADEG.APERIOD
APERIODC	Period (C)	Char		ADEG.APERIODC
AVISIT	Analysis Visit	Char		ADEG.AVISIT
AVISITN	Analysis Visit (N)	Num		ADEG.AVISITN
ATPT	Analysis Timepoint	Char		ADEG.ATPT
ATPTN	Analysis Timepoint (N)	Num		ADEG.ATPTN
AVISTPT	Analysis Visit and Timepoint	Char		Concatenate the ADEG.AVISIT and ADEG.ATPT if there are multiple visits involved in C-QT analysis
AVISTPTN	Analysis Visit and Timepoint (N)	Num		The numeric value for ADCQT.AVISTPT
ATPTREF	Analysis Reference Time Point	Char		ADEG.EGTPTREF
ARDTM	Date/Time of Reference	Num		ADEG.ARDTM
AARDTM	Actual Date/Time of Reference	Num		ADEG.AARDTM
ARRLT	Actual Relative Time from Reference TPT	Num		ADEG.ARRLT
NRRLT	Nominal Relative Time from Ref TPT	Num		ADEG.NRRLT
RRLTU	Relative Time from Reference TPT Units	Char		ADEG.RRLTU
ADTM	Analysis Datetime	Num		ADEG.ADTM
ADT	Analysis Date	Num		ADEG.ADT
ATM	Analysis Time	Num		ADEG.ATM
ADY	Analysis Relative Day	Num		ADEG.ADY

Variable Name	Variable Label	Type	Code List / Controlled Term	Comments
AVISDY	Analysis Visit Day	Num		Populate from ADEG.AVISIT
APERDAY	Analysis Nominal Period Day	Num		Populate with the numeric relative day within the Period based on AVISITN. For example, “Period 2 Day 1” is APERDAY=1. ADEG.APERDAY and ADPC.APERDAY should be coded consistently so mapping of time-matched measures can be performed.
PARAM	Parameter	Char		ADEG.PARAM
PARAMCD	Parameter Code	Char		ADEG.PARAMCD
PARAMN	Parameter (N)	Num		ADEG.PARAMN
PARCAT1	Parameter Category 1	Char		ADEG.PARCAT1
PARCAT1N	Parameter Category 1 (N)	Num		ADEG.PARCAT1N
AVAL	Analysis Value	Num		ADEG.AVAL
AVALC	Analysis Value (C)	Char		ADEG.AVALC
AVALU	Analysis Value Units	Char		ADEG.AVALU
AVALCAT1	Analysis Value Category 1	Char		ADEG.AVALCAT1
AVALCA1N	Analysis Value Category 1 (N)	Num		ADEG.AVALCAT1N
ABLFL	Baseline Record Flag	Char	Y_NULL	ADEG.ABLFL
AEGBLFL	Records used to Derive the Baseline Flag	Char	Y_NULL	ADEG.AEGBLFL
BASE	Baseline Value	Num		ADEG.BASE
BASEC	Baseline Value (C)	Char		ADEG.BASEC
BASETYPE	Baseline Type	Char		ADEG.BASETYPE
CHG	Change from Baseline	Num		ADEG.CHG
PCHG	Percent Change from Baseline	Num		ADEG.PCHG
CHGCAT1	Change from Baseline Category 1	Char		ADEG.CHGCAT1
CHGCAT1N	Change from Baseline Category 1 (N)	Num		ADEG.CHGCAT1N
DTYPE	Derivation Type	Char	DTYPE	ADEG.DTYPE
ONTRTFL	On Treatment Record Flag	Char	Y_NULL	ADEG.ONTRTFL
EVLEGFL	Evaluable ECG Flag	Char	Y_NULL	ADEG.EVLEGFL
ANCSIND	Analysis Clinical Significance Indicator	Char		ADEG.ANCSIND
BNCSIND	Baseline Clinical Significance Indicator	Char		ADEG.BNCSIND
CRITx	Analysis Criterion x	Char		ADEG.CRITx. A text string identifying a pre-specified criterion within a parameter, for example QTcF $\geqslant$ 500. Required if CRITyFL exists (see ADaM IG).
CRITxFL	Criterion x Evaluation Result Flag	Char	NY	ADEG.CRITxFL. Character flag variable indicating whether the criterion defined in CRITy was met by the data on record. See CRITy for more information regarding how to use CRITy and CRITyFL to indicate whether a criterion is met (see ADaM IG).
ACOMPFL	Comparator Record Flag	Char	Y_NULL	If record is part of the comparator treatment (e.g., placebo) then ACOMPFL=”Y” else ACOMPFL is null, e.g., if ADCQT.TRTA='Placebo' then ADCQT.ACOMPFL=”Y” else ADCQT.ACOMPFL is null.

Variable Name	Variable Label	Type	Code List / Controlled Term	Comments
COMP	Comparator Value	Num		If DTYPE ne “AVERAGE” then null else if ACOMPFL eq ”Y” then COMP=AVAL; else COMP value is based on the corresponding COMPTYPE (similar as BASETYPE).
COMPBASE	Baseline Value of the Comparator	Num		If DTYPE ne “AVERAGE” then null else if ACOMPFL eq “Y” then COMPBASE=BASE; else COMPBASE value is based on the corresponding COMPTYPE.
COMPCHG	Change from Baseline in the Comparator	Num		If DTYPE ne “AVERAGE” then null else if ACOMPFL eq “Y” then COMPCHG=CHG else COMPCHG value is based on the corresponding COMPTYPE.
CCOMPCHG	Comparator corrected change from BL	Num		If DTYPE ne “AVERAGE” then null else if ACOMPFL ne “Y” then CCOMPCHG=CHG – COMPCHG else null.
COMPTYPE	Comparator Type	Char		Encodes the key that allows for identifying comparator treatment (e.g., placebo) rows used to compute the comparator and baseline corrected changes (i.e., double deltas) from each DTYPE = ”AVERAGE” and ACOMPFL ne “Y”. This is like BASETYPE. Example values as 'Placebo group at 0.5 h', 'Placebo group at 2 h', etc.
CBASE	Centralized Baseline	Num		For ADCQT.DTYPE='AVERAGE' and ADCQT.PARAMCD='QTCF', ADCQT.CBASE is mapped for individual participant. ADCQT.CBASE=ADCQT.BASE minus the population mean baseline QTcF for all participants in PK/QTc population.
ANALY1	Analyte 1	Char		The analyte in ADPC.PARAMCD that corresponding to ADCQT.CONC1, i.e. study treatment 'DRUGX'
A1DTM	Analyte 1 Analysis Datetime	Num		Fetch the datetime (ADPC.ADTM) of the time-matched PK samples corresponding to ADCQT.CONC1
A1RRLT	Relative Time from Analyte 1 Datetime	Num		Relative Time of ECG collection datetime to time-match PK sampling datetime, e.g., ADCQT.A1RRLT=(ADCQT.ADTM - ADCQT.A1DTM) / 3600
A1RRLTU	Relative Time from Analyte 1 DT Units	Char	UNIT	
A1OUTWFL	Analyte 1 Out of Window Flag	Char	Y_NULL	Define the window of ECG collection datetime and PK sampling datetime through SAP, e.g., 1 hour, if ADCQT.A1RRLT > 1, then ADCQT.A1OUTWFL = 'Y'. The out-of-window records should be excluded from C-QTc analysis.
CONC1	Concentration of Investigator Production	Num		Fetch the time-matched concentration of investigator production (ADPC.AVAL for investigator production). Example of definition: Map for ADCQT.PARAMCD='QTCF' and ADCQT.ECGPKFL='Y', get the corresponding timepoint investigator production concentration from ADPC; if ADCQT.TRTA='Placebo', then ADCQT.CONC1=0; if the pre-dose concentration is below the quantifiable limit, set ADCQT.CONC1=0; if the post-dose concentration is below the quantifiable limit, set ADCQT.CONC1=quantifiable limit/2
CONC1U	Conc. of Investigator Production Units	Char		ADPC.AVALU for investigator production

Variable Name	Variable Label	Type	Code List / Controlled Term	Comments
ANALY2	Analyte 2	Char		Same as ADCQT.ANALY2 but for metabolites of investigator production
A2DTM	Analyte 2 Analysis Datetime	Num		Same as ADCQT.A2DTM but for metabolites of investigator production
A2RRLT	Relative Time from Analyte 2 Datetime	Num		Same as ADCQT.A2RRLT but for metabolites of investigator production
A2RRLTU	Relative Time from Analyte 2 DT Units	Char		Same as ADCQT.A2RRLTU but for metabolites of investigator production
A2OUTWFL	Analyte 2 Out of Window Flag	Char	Y_NULL	Same as ADCQT.A2OUTWFL but for metabolites of investigator production
CONC2	Concentration of <Metabolite 1>	Num		Same as ADCQT.CONC2 but for metabolites of investigator production
CONC2U	Concentration of <Metabolite 1> Units	Char		Same as ADCQT.CONC2U but for metabolites of investigator production
ECGPCFL	ECG Matching PK Flag	Char	Y_NULL	Populate with "Y" if there is a matching nominal PK sample time point for the nominal ECG time point (i.e., if there are time-matched PK measures in ADPC for this ECG).
IUTANLFL	Intersection Union Test Analysis Flag	Char	Y_NULL	Record-level analysis flag. Set to "Y" if the record is used in the intersection union test (i.e., by-time in assumption 1) analysis or null otherwise.
CATANLFL	Categorical Analysis Flag	Char	Y_NULL	Record-level analysis flag. Set to "Y" if the record is used in the categorical analysis or null otherwise.
CQTANLFL	Concentration QT Analysis Flag	Char	Y_NULL	Record-level analysis flag. Set to "Y" if the record is used in the concentration (investigator production)-QT analysis or null otherwise.
M1QTANFL	<Metabolite 1> Conc. QT Analysis Flag	Char	Y_NULL	Record-level analysis flag. Set to "Y" if the record is used in the concentration (metabolite of investigator production)-QT analysis or null otherwise.
CMQTANFL	IP and Metabolite Conc. QT Analysis Flag	Char	Y_NULL	Record-level analysis flag. Set to "Y" if the record is used in the concentration (both parent and metabolite of investigator production included)-QT analysis or null otherwise.
ANL01	Analysis 01	Char		A text string describing analysis number 01, which is reserved for the primary analysis (e.g., assessment of investigational drug treatment QT effects).
ANL01FL	Analysis Flag 01	Char	Y_NULL	Selection variable to identify the exact set of records used in the analysis number 01 corresponding to ANL01.
ANL02	Analysis 02	Char		A text string describing the analysis flag number 02, which is reserved for the assay sensitivity analysis (e.g., assessment of positive control QT effects).
ANL02FL	Analysis Flag 02	Char	Y_NULL	Selection variable to identify the exact set of records used in the analysis number 02 corresponding to ANL02.
EGSEQ	Sequence Number	Num		ADEG.EGSEQ
VISIT	Visit Name	Char		ADEG.VISIT
VISITNUM	Visit Number	Num		ADEG.VISITNUM
EGTPT	Planned Time Point Name	Char		ADEG.EGTPT
EGTPTNUM	Planned Time Point Number	Num		ADEG.EGTPTNUM
EGTESTCD	ECG Test or Examination Short Name	Char		ADEG.EGTESTCD

Variable Name	Variable Label	Type	Code List / Controlled Term	Comments
EGTEST	ECG Test or Examination Name	Char		ADEG.EGTEST
EGREPNUM	ECG Replicate Number	Char		ADEG.EGREPNUM
EGDTC	Date/Time of Specimen Collection	Char		ADEG.EGDTC
EGSTRESN	Numeric Result/Finding in Standard Units	Num		ADEG.EGSTRESN
EGSTRESC	Character Result/Finding in Std Format	Char		ADEG.EGSTRESC