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REVIEW PAPER

Scientific white paper on concentration-QTc modeling

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Abstract

The International Council for Harmonisation revised the E14 guideline through the questions and answers process to allow concentration-QTc (C-QTc) modeling to be used as the primary analysis for assessing the QTc interval prolongation risk of new drugs. A well-designed and conducted QTc assessment based on C-QTc modeling in early phase 1 studies can be an alternative approach to a thorough QT study for some drugs to reliably exclude clinically relevant QTc effects. This white paper provides recommendations on how to plan and conduct a definitive QTc assessment of a drug using C-QTc modeling in early phase clinical pharmacology and thorough QT studies. Topics included are: important study design features in a phase 1 study; modeling objectives and approach; exploratory plots; the pre-specified linear mixed effects model; general principles for model development and evaluation; and expectations for modeling analysis plans and reports. The recommendations are based on current best modeling practices, scientific literature and personal experiences of the authors. These recommendations are expected to evolve as their implementation during drug development provides additional data and with advances in analytical methodology.

Keywords Concentration-QTc model · ICH E14 · Thorough QT (TQT) study · Pharmacokinetics/pharmacodynamics

Abbreviations

AIC	Akaike information criteria
C	Concentration
CI	Confidence intervals
C_{max}	Maximum concentration
C-QTc	Concentration-QTc
ΔHR	Baseline-corrected heart rate
ΔQTc	Baseline-corrected QTc interval
ΔΔQTc	ΔQTc interval corrected for placebo
ECG	Electrocardiogram
E_{max}	Maximum effect
ER	Extended release
GOF	Goodness-of-fit
hERG	Human ether-a-go-go-related gene
HR	Heart rate
ICH	International Council for Harmonization
IR	Immediate-release
ms	Milliseconds
LME	Linear mixed effects
MAD	Multiple-ascending dose
MAP	Modeling analysis plan
MD	Multiple dose
PK	Pharmacokinetic
PD	Pharmacodynamics
QT	QT interval on ECG
QTc	QT interval corrected for heart rate
QTcF	Fridericia corrected QT interval

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SAD Single-ascending dose
SD Single dose
TQT Thorough QT/QTc

Introduction

The International Council for Harmonisation (ICH) E14 Questions and Answers document was revised in December 2015 to allow for concentration-QTc (C-QTc) modeling to be used as the primary analysis for assessing the QTc interval (hereafter referred to as QTc) prolongation risk of new drugs [1]. There are several important implications of this revision on the design and analysis of thorough QT/QTc (TQT) studies. Because the C-QTc modeling approach utilizes data from all doses and time points, a reliable assessment of QTc prolongation can be based on smaller-than-usual TQT trials or be obtained during trials in early development not specifically targeted at QT effects. Thus, sponsors of pharmaceutical products now can either perform smaller TQT studies or use C-QTc modeling with high quality electrocardiogram (ECG) measurements in single- and/or multiple- dose escalation (SAD/MAD) studies during early-phase clinical development as an alternative to the central tendency by time point approach to meet the regulatory requirements of the ICH E14 guideline [2]. When utilizing a modeling approach for regulatory purposes, it is particularly important that the quantitative methods used be clearly described to enable reproducibility. It is expected that data sources and modeling details, including the structural model, assumptions, criteria for assessment of model robustness and goodness-of-fit, be adequately described in a pre-specified modeling analysis plan (MAP), and reported in a standardized format [3].

The E14 implementation working group did not provide the technical details on how to perform and report C-QTc modeling to support regulatory submissions. The rationale for this approach is that specific analysis methodologies are expected to evolve over time as pharmaceutical and regulatory scientists implement this approach across drugs with diverse pharmacokinetic (PK) and pharmacodynamic (PD) attributes. The objective of this White Paper is to propose recommendations for designing studies to use C-QTc modeling as the primary analysis, conducting a C-QTc analysis, and reporting the results of the analysis to support regulatory submissions.

Study design considerations for C-QTc analysis

The TQT study is intended to determine whether the drug has a threshold pharmacologic effect on cardiac repolarization, as detected by QTc prolongation. The threshold level of regulatory concern is around 5 ms as evidenced by an upper bound of the 95% confidence interval around the mean effect on QTc of 10 ms [2]. 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. In some cases, a well-designed and conducted QTc assessment based on C-QTc analysis in early phase 1 studies can be an alternative approach to a TQT study to reliably exclude clinically relevant QTc effects. The appropriateness of these data will not be generally known until later in the development program when the therapeutic dose level has been identified and the intrinsic and extrinsic factors that increase exposures to drug and active metabolites are known. In this section, we discuss general study design features that should be considered when assessing whether the data can be used in a C-QTc analysis to substitute for a TQT study. It is anticipated that this approach will not be applicable to all drugs, such as for drugs with substantial heart rate effects, active metabolites that inhibit cardiac ion channels or formulations that have a narrow range of concentrations. Descriptions of these challenging drugs are presented in Table 1.

Study design

It is beyond the scope of this White Paper to provide all the study design features of early phase 1 clinical studies. SAD/MAD studies are generally acceptable for early QTc assessment. Commonly used designs are the sequential parallel group design (where the doses are gradually escalated, and after each dose administration and subsequent safety evaluation, a new cohort with new subjects is included and administered the next dose level) and the alternating panel crossover design (where dose escalation is alternated between 2 or more panels and each panel receives every other dose, and during the dosing of one cohort, the other cohort(s) are in washout). The choice of design is based on the study objectives, only one of which is the assessment of QTc prolongation. A placebo cohort should be used whenever possible to control for potential bias introduced by study procedures and to increase the power to exclude modest QTc effects in small-sized studies [4]. The general mechanisms to deal with potential bias and reduce study variability are discussed in the ICH E14 guidance for the TQT study and these are also applicable to

Table 1 Challenging drugs and study designs when using C-QT analysis

Challenge	Considerations
Combination drugs or active metabolites	When modeling the QT effect of a combination drug or a drug with active metabolites, it is important to characterize the effect of each analyte (i.e., individual drug parent and/or metabolite concentrations), as well as any interaction between analytes. Careful design of the sampling time points is needed to ensure that C_{max} is captured for all analytes. Each analyte should not be analyzed as a series of univariate analyses, but rather analyzed using separate slopes for each analyte and with corresponding interaction [29, 30]. Careful interpretation is needed to understand the contribution of each analyte to the total effect. PD models may not necessarily be the same for both analytes, e.g., one analyte may be linear and the other nonlinear in nature [31, 32]. For combination drugs, the study design should consider including each drug administered alone and in combination at the highest safe dose
Cytotoxic oncology drugs	Assessing the QT effect of cytotoxic oncology drugs have many challenges and it is beyond the scope of this paper to detail them [33]. Challenges that could impact a MAP are (1) patients may be on multiple drugs in addition to the drug of interest and it is not possible to measure the drug concentration for every drug they are taking; (2) patients have wider between-patient variability than seen in healthy volunteer studies; (3) it may not be ethical to have a placebo and/or positive control groups; and (4) it may not be feasible to obtain exposures higher than the therapeutic exposures. In such cases, there is a reluctance to draw conclusions of a lack of an effect and the MAP should be designed to exclude mean effects as large as 20 ms (ICH E14 Q&A 6.1) [1]
Drug-induced changes in heart rate	There is little experience with applying C-QTcF models to drugs that significantly increase or decrease heart rate (e.g., mean change > 10 bpm). Using subject-specific heart rate correction method based on wide range of HR collected at baseline could be one approach to account for heart rate effects, but other approaches may also be applied [5]
Extended Release products	Careful design of the sampling points is needed to ensure that C_{max} is captured and a wide range of concentrations and corresponding QTc are obtained. It is not necessary to study the extended release (ER) formulation as an immediate release (IR) formulation can be used instead, but care must be taken to ensure exposures to parent and active metabolite with the IR formulation meet or exceed exposures expected with the ER formulation
PK/PD hysteresis	If a delay of the QTc effect cannot be explained by the concentration of the drug's metabolites, a PK/PD model with a separate effect compartment may be helpful if there are frequent QT measurements around the time of the expected maximal effect [25, 34]
Non-HERG changes in QTc	Blockade of hERG potassium channel causes QT interval prolongation, but drugs can also affect other cardiac ion channels leading to concentration-effect relationships for PR, QRS or $J - T_{peak}$ [35, 36]
Drug interaction studies	It is important to characterize the effect of the test drug and interacting drug as the interacting drug could prolong the QT interval (e.g., ketoconazole) similar to combination drugs described above
Food effect studies	Food affects the QT interval [16, 37]. Consideration should be given to standardize meals across periods, preferably at time points removed from T_{max}. Special care is needed for drugs that affect gastric emptying, glucose uptake or metabolism, since both glucose and C-peptide have been shown to influence QTc [38]

the early phase 1 studies for QTc assessment (Supplemental Material, Table S1).

Baseline ECGs

Regardless of study design, time-matched baseline ECG recordings are generally not required in early phase 1 parallel studies because the inclusion of the placebo data allows for the detection of diurnal patterns in the QTc data. PK/PD simulations have shown that accounting for diurnal variability increases the power of the C-QTc analysis to exclude small mean QTc effects [4]. The collection of baseline ECG data over a wide range of heart rates on the day before dosing is recommended for drugs that meaningfully affect heart rate [5]. Although there is no consensus on the best approach to characterize the QT/QTc interval for these drugs, it is common to compute a subject-specific heart-rate-corrected QT interval derived from QT/RR pairs collected from baseline ECG recordings [6].

Sample size

Early phase 1 studies will not be specifically powered for the QTc assessment and will generally be under-powered for using the intersection union test by dose cohort [7, 8]. In general, typical SAD/MAD studies contain at least four dose cohorts, with each cohort having 4–8 subjects on drug and 2–4 subjects on placebo; and these are likely to be sufficient for early QTc assessment based on C-QTc analysis if the study is well conducted per Supplemental Material, Table S1 [9, 10]. Stochastic PK/PD simulations have shown that the false negative rate (i.e., falsely

concluding no QTc prolongation) of C-QTc analyses is controlled at around 5% when the true effect is 10 ms in small-sized studies of 6–12 subjects with multiple measurements per subject [4, 11–13]. When simulations were performed using the same sample sizes and assuming no underlying QTc effect (placebo), the fraction of studies in which an effect above 10 ms could be excluded was above 85% [12, 13]. Power to exclude a 10-ms effect will be less for a drug with small true mean QTc effects (i.e., 3–5 ms) and will be influenced by variability in the QTc measurements.

Exposure margin

To ensure adequate QTc assessment, the exposure in early phase studies should be well above the maximum therapeutic exposure to cover the potential impact of intrinsic and extrinsic factors, including unanticipated factors, on drug exposure. There are several circumstances where C-QTc analysis of data from repeat doses of drug is recommended: for drugs that have significant PK accumulation of the parent or potentially clinically significant metabolite(s) in plasma on repeat dosing to steady state; if the exposure to the parent drug or metabolites(s) at the maximum tolerated single dose does not match or exceed the supratherapeutic exposure at steady state.

Positive control

A limitation of performing QTc assessment in early phase 1 studies is the lack of a positive control to demonstrate ECG assay sensitivity [14]. Without a separate positive control and thus a direct measure of assay sensitivity, the QTc response should be characterized at a sufficiently high multiple of the clinically relevant exposure [1]. The FDA's Interdisciplinary Review Team is recommending that exposures are at least twice the highest clinically relevant exposure (i.e., the highest dose should give a mean C_{max} that is twice the $C_{max,ss}$ obtained during metabolic inhibition with a concomitant drug or with renal or hepatic dysfunction) to obviate the positive control. If this exposure margin cannot be achieved in the early phase studies, a dedicated TQT study that includes a positive control may still be needed until a non-pharmacological approach for assay sensitivity has been validated [15–17].

Pooling data

Pooling data from multiple studies is not recommended in cases where differences in the study conditions may cause bias in results: (1) the study control procedures (e.g., placebo, food control) are different; (2) ECG acquisition and ECG measurement at baseline and during the treatment are different; or (3) study subjects are taking concomitant medications or with comorbid conditions that increase the variability in the QTc interval in one study but not the other. If there is a need to pool data from multiple studies to cover a wide range of doses/exposures or to increase the number of subjects exposed to drug at higher doses, it is important that similar clinical conduct and subject handling be performed in each study and that the ECG acquisition and ECG measurement approaches be similar (Supplemental Material, Table S1), as well as the bioanalytical assay. It is preferred that the concentration–response data come from related study protocols (e.g., SAD/MAD) to ensure that study procedures and timing of ECG measurements are similar across dose levels and placebo arms.

Table 2 summarizes the study design features that influence the decision to use C-QTc analysis of data collected in a phase 1 study to replace a TQT study. It is important that ECG quality, dose/exposure margin, sample size, timing of PK sample and ECG recordings and effects on HR are considered when planning to use C-QTc analysis in a phase 1 study (or pooled studies) that is intended to substitute for a TQT study.

Modeling approach

Objectives

Concentration-QTc analysis can serve as an alternative to the by-timepoint analysis or intersection–union test as the primary basis for decisions to classify the risk of a drug [1]. When C-QTc analysis is utilized as the primary basis for decisions to classify the risk of a drug, the upper bound of the two-sided 90% confidence interval for model-derived $\Delta\Delta$QTc should be < 10 ms at the highest clinically relevant exposure (see [2, E14 Sect. 2.2.2]) to conclude that an expanded ECG safety evaluation during later stages of drug development is not needed [1]. A pre-specified linear mixed effects model is recommended as the primary analysis to exclude a 10-ms QTc prolongation effect. For drugs that prolong the QTc interval, however, the objectives of the C-QTc analysis are more exploratory and the pre-specified model may not be appropriate in this setting.

Baseline-adjusted QTc interval

For the pre-specified model, the preferred dependent variable in the model is the baseline-adjusted and Fridericia heart-rate-corrected QT interval (ΔQTcF) [13]. Unless drug-free QT data are collected in all subjects over a range of heart rates like the range of heart rates observed during treatment, the use of subject- and study-specific corrections is not generally recommended. The choice of which

Table 2 Design features to consider when using C-QTc analysis in a phase 1 study as a substitute for a TQT study

Category	Adequacy of study design feature	Consideration	Impact on design and/or analysis
ECG quality	Is the quality of the ECG recordings and analysis sufficient to support a valid assay for ECG intervals?	Supplemental Material, Table S1	Study design to include high-quality, robust ECG recordings and analysis
Dose	Is the highest dose expected to cover clinical relevant exposures?	– Pre-specify pooling strategy and ensure between-study variability is minimized by similar procedures, or – Use C-QTc only in the trial where the highest exposure can be expected	Analysis method to account for heterogeneity when pooling data from multiple studies
	Is exposure safety margin of twofold maximal clinical exposure not possible?	Assay sensitivity	Study design to include positive control [39] or use other methods for assay sensitivity [15, 16]
Sample size	Is the number of subjects in the placebo and treatment arms sufficient to exclude a 10-ms mean QTc effect?	– Pool studies, or – Increase sample size, or – Use crossover design	Analysis methods need to account for heterogeneity when pooling data from multiple studies
Time-matched PK samples and ECG recordings	Is the timing of matched PK and ECG recordings sufficient to capture direct and/or delayed effects?	Supplemental Material, Table S1	Study design to include additional time points
Heart rate	Is the mean increase or decrease from baseline HR > 10 bpm [5]?	Include baseline day and ensure wide range of RR values to estimate a subject-specific QT correction or use of other methods to assess QT/QTc interval	Study design to include drug-free baseline day

baseline correction method (predose versus time-matched) to use will depend on study design and should be pre-specified in the MAP. Predose baseline adjustment uses the average of QTc measurements obtained immediately prior to dosing as the baseline of each treatment period. Time-matched baseline adjustments use the corresponding pre-dose QTc measurements collected prior to drug administration on Day-1. A time-matched baseline adjustment may be used when placebo data are not available to minimize the effect of diurnal variation in QTc [18].

Although the focus of this white paper is on the QTc interval, the same methodology can be applied to other ECG parameters such as heart rate (HR), PR interval, QRS complex, JTc interval, $J - T_{peak}c$ and $T_{peak} - T_{end}$.

Pre-specified linear mixed effects model

The pre-specified linear mixed effect (LME) C-QTc model is used as the primary analysis. This model, while over-parameterized (i.e., a model that contains parameters that may not influence the prediction), appropriately addresses the overall modeling objective. The default dependent variable is ΔQTcF; hereafter the dependent variable is referred to more generically as ΔQTc. The fixed effect parameters are intercept, slope, influence of baseline on intercept, treatment (active = 1 or placebo = 0) and nominal time from first dose (Table 3). Subject is included as an additive random effect on both intercept and slope terms.

$$\Delta QTc_{ijk+} = \left(\theta_0 + \eta_{0,i}\right) + \theta_1 TRT_j \left(\theta_2 + \eta_{2,i}\right) C_{ijk} + \theta_3 TIME_j + \theta_4 \left(QTc_{i,j=0} - \overline{QTc_0}\right) \quad (1)$$

In Eq. 1, ΔQTc_{ijk} is the change from baseline in QTc for subject i in treatment j at time k; θ_0 is the population mean intercept in the absence of a treatment effect; $\eta_{0,i}$ is the random effect associated with the intercept term θ_0; θ_1 is the fixed effect associated with treatment TRT_j (0 = placebo, 1 = active drug); θ_2 is the population mean slope of the assumed linear association between concentration and ΔQTc_{ijk}; $\eta_{2,i}$ is the random effect associated with the slope θ_2; C_{ijk} is the concentration for subject i in treatment j and time k; θ_3 is the fixed effect associated with time; and θ_4 is the fixed effect associated with baseline $QTc_{i,j=0}$; $\overline{QTc_0}$ is overall mean of QTc_{ij0}, i.e., the mean of all the baseline (= time 0) QTc values. It is assumed 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.

In the above model, an unstructured covariance matrix is the preferred random effects covariance matrix because it does not impose constraints on the variances. Other random

Table 3 Fixed effect parameters in the Pre-specified linear mixed effects C-QTc model

Parameter/Variable	Assumptions and rationale	Specification
Treatment-specific intercept, θ_1	Although a treatment-specific intercept is not physiologically justified, it allows the relationship on drug to differ from that on placebo even at lowest concentrations, this effect gives the model flexibility under the scenario of model misspecification [13]	Categorical factor, where 1 = drug (pooled dose levels) 0 = placebo
Slope of Concentration, θ_2	Assumes there is no delay between plasma drug concentrations and QTc interval prolongation. This assumption should be evaluated (see "Model independent checks of assumptions using exploratory plots")	Continuous covariate Parent or metabolite concentrations
Mean QTc change from baseline at time k for placebo, θ_3	Assumes the time course of ΔQTc is the same in the placebo and drug arms Accounts for diurnal variation in ΔQTc in the LME model Avoids use of complex, nonlinear models to describe diurnal variation [40]	Categorical factor, with time starting after the first dosing event If QTc measurements are collected over multiple days, the Time parameter could be reduced to time after dose on same day and DAY is included in model as a factor. The inclusion of an interaction term should be investigated as part of a more detailed modeling procedure
Baseline QTc, θ_4	Allows for imbalances in baseline values in placebo and drug arms Shown to increase precision in parameter estimates [19]	Continuous covariate For each subject, the average pre-dose QTc measurements are obtained and centered on the mean of the population for each period

effect models based on the specific study design are also acceptable (e.g., with crossover designs [19]); however, over-parameterized random effects models may not converge and may need to be simplified for convergence to occur. Although this model is technically an error-in-variables problem, measurement error in C does not affect the estimation of the concentration slope unless the measurement error exceeds 30% [20].

Model parameters are to be estimated using maximum likelihood or restricted maximum likelihood approaches. There is no recommendation for preferred software. The MAP should specify approaches to handle non-convergence of the model, including any transformations of concentration data. To avoid unnecessary model-building steps, removing non-significant parameters from the model is generally not recommended [21]. It is not expected that the slope estimate will be materially influenced by an overparameterized model if there are sufficient data in the placebo group (see Supplemental Material, Effect of Model Overparameterization in QT Analyses).

The pre-specified model is recommended because it can be used for most study designs in healthy subjects (e.g., SAD, MAD and TQT studies). There are, however, situations when changes to the pre-specified model are needed to accommodate different data structures, such as when ΔΔQTc is used as the dependent variable in the model, placebo data are not available, or when the data are pooled from multiple studies. Considerations for changes to the pre-specified model under these scenarios are summarized in Table 4.

Model independent checks of assumptions using exploratory plots

Basic assumptions made in the modeling process can efficiently be evaluated using simple graphics as summarized below with details provided in Table 5. If the following modeling assumptions are not supported by the data, the model development for adapted C-QTc model is recommended.

- *Assumption 1: No drug effect on HR* One consideration is the potential of a drug to significantly increase or decrease HR. Although there is no consensus on the specific threshold effect on HR that could influence QT/QTc assessment, mean increases or decrease > 10 bpm have been considered problematic [5]. The time course of mean ΔHR/ΔΔHR effects by treatment is a useful evaluation (Fig. 1).
- *Assumption 2: QTc interval is independent of HR* QTcF is usually a sufficient correction method for drugs with insignificant effects on HR and evaluation of this correction method is not needed. If an individualized heart rate correction method is used, the appropriateness of the selected method should be assessed to determine if QTc is independent of HR using drug-free data (Fig. 2).

Table 4 Variations to the pre-specified linear mixed effects C-QTc model

Variation	Rationale	Impact on model parameters
ΔΔQTc as the dependent variable	In crossover TQT studies with William's square design, ΔΔQTc can be computed at every time point for each subject by subtracting the ΔQTcF for placebo from the ΔQTcF for each treatment arm	θ_1 and θ_3 terms are not needed in the model
No placebo data[a]	Either by design or ethical reasons, a concurrent placebo arm was not included	θ_1 and θ_3 terms are not needed in the model Model-derived ΔΔQTc is not generated
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	Apply LME model to individual studies Between study differences and potential bias when pooling studies need to be evaluated. There is not much experience analyzing pooled data using the pre-specified model, but analysts could consider including a study effect on key model parameters, such as intercept, slope and residual error

[a]It is recommended that placebo data are included in the model to exclude small effects in the QTc interval as described in ICH E14 guidelines

- *Assumption 3: No time delay between drug concentrations and ΔQTc* Concordance, or lack thereof, in the time course of drug concentrations and ΔΔQTc − ΔQTc corrected for spontaneous diurnal variation as seen in a placebo group—can be evaluated by examining the mean concentration and QTc profiles by dose level and time (Fig. 3a–f). If the time course of ΔΔQTc is concordant with the PK profile, the default model assumption of a direct temporal relationship between drug concentration and QTc effect can be supported (Fig. 3, left panels). If, however, there is a delay between peak concentration and peak QTc or QTc effect (Fig. 3, right panels), the analyst must consider the possibility of a delayed temporal effect and the model applied should account for this delay (see "Model development for adapted C-QTc models"). An isolated outlying mean value of ΔΔQTcF, e.g., in the late elimination phase of the drug, need not be an indication for a systematic delay between concentration and effect.
- *Assumption 4: Linear C-QTc relationship* The adequacy of using a linear model can be assessed by the concentration-ΔQTc plot incorporating a trend line (e.g., loess smooth or linear regression, Fig. 3g, h). The trend line does not reflect a model fit of data, but rather is used to detect drug effect, and when a drug effect is detected, whether there are major violations to the linear assumption. If data are pooled from multiple studies, trend lines are to be displayed for each study and pooled across studies.

C-QTc quantile plots are an effective format for displaying relationships that may be difficult to identify in the presence of highly variable data and a low signal-to-noise ratio [22]. The C-QTc quantile plots used in the examples are generated by binning the independent variable (e.g., concentrations) into quantiles (bins with equal number of observations, typically deciles) and plotting the local median or midpoint of the observations in each of the independent variable bins against the corresponding local mean dependent variable (e.g., ΔQTc or ΔΔQTc and associated 90% confidence).

Model development for adapted C-QTc models

If the exploratory plots indicate the modeling assumptions are not met, additional modeling steps are recommended to determine objectively the appropriate C-QTc model. When apparent differences in the time course and/or distribution of HR between on- and off-drug conditions are observed in exploratory plots, other approaches to evaluate QT/QTc should to be considered as summarized in [5].

It is important that the drug effect model adequately describe the observed concentration and ΔQTc relationship to obtain reliable estimation of the degree of prolongation at doses/concentrations of interest. The drug effect models routinely tested are the linear and E_{max} families of models; however, other types of PD models can be explored to optimize the model fit. Simpler models are preferred over more complex models when statistically justified. Logarithmic transformation of the concentration data is not recommended because the proposed modeling approach uses placebo concentrations that are set to zero. Because the results of the analysis will be critical to assessment of risk, the model and methods for model evaluation and selection need to be pre-specified in a MAP to limit bias. Model selection should be based on the pre-specified objective criteria (e.g., objective function value, Akaike information criteria (AIC), level of statistical significance, goodness of fit plots, standard error in model parameters)

Table 5 Description of exploratory and goodness-of-fit plots

Plot	Model assumption tested	What to evaluate	Model impact
Exploratory plots			
Time course of HR stratified by dose	No drug effect on HR	Consistency of change from baseline HR (ΔHR) with time, dose and treatment	If dose- or concentration-dependent effects on HR are observed, the relationship between QT and RR may differ between on- and off-treatment, impacting the QT correction differently between the two conditions This could potentially violate the assumption that the applied QTc correction is an adequate heart rate correction method
QTc versus RR intervals	QTc is independent of HR for drug-free and/or placebo treatments	Linear regression line should show the lack of relationship between QTc and RR intervals Range of HR are similar off- and on-drug	Individual correction factor is potentially poorly estimated due to narrow range of RR intervals within each subject which could bias the C-QTc model
Time course of mean concentrations and mean ΔQTc, ΔΔQTc intervals	Explore direct effect assumption Evaluate PK/PD hysteresis	Shape of PK- and QTc-time profiles, e.g., time course of effect, time of peak, return to baseline Magnitude of variability in PK and QTc	High inter-subject variability in ΔQTc can mask signal in mean curves—this is important in small-sized studies
C-ΔQTc	Evaluate linearity and heterogeneity assumptions between exposure and QTc across doses and studies	Shape of C-QTc relationship Magnitude of ΔQTc over observed concentration range Concentration range covers worse case clinical exposure scenario	Model-independent observations are not corrected for covariates and might therefore not appear to match model prediction Confounding factors not accounted for Heterogeneity between doses/trials
Goodness of fit plots			
Model predicted versus observed ΔQTc	Model specification is adequate.	Model and observed values should fall around the line of unity without evidence of systematic bias. Loess smooth line with 95% CI should include the unity line over range of values	Systematic bias indicates model misspecification. For example, model predictions will be negatively biased at high values when PK/PD hysteresis is ignored and model predictions will be positively biased at high values when a linear model is applied to nonlinear data
Quantile–Quantile plot of residuals	Residuals follow normal distribution with mean of zero	Residuals should fall on the line of unity	Heavy tails indicate model misspecification. The plot does not indicate source of misspecification
Concentrations versus residuals Baseline QTc versus residuals Time versus residuals Active treatment versus residuals	Model covariates are adequate	Residuals should be randomly scattered around zero The 95% CI of the loess line should include zero	Bias in residuals indicates model misspecification. A residual plot should be made for each model parameter
Quantiles of concentrations and ΔQTc overlaid with slope of final model	Drug effect model is adequate	The concentration-QTc relationship obtained from final model should describe the observed data	Any systematic differences between the modeled versus observed data indicates model misspecification

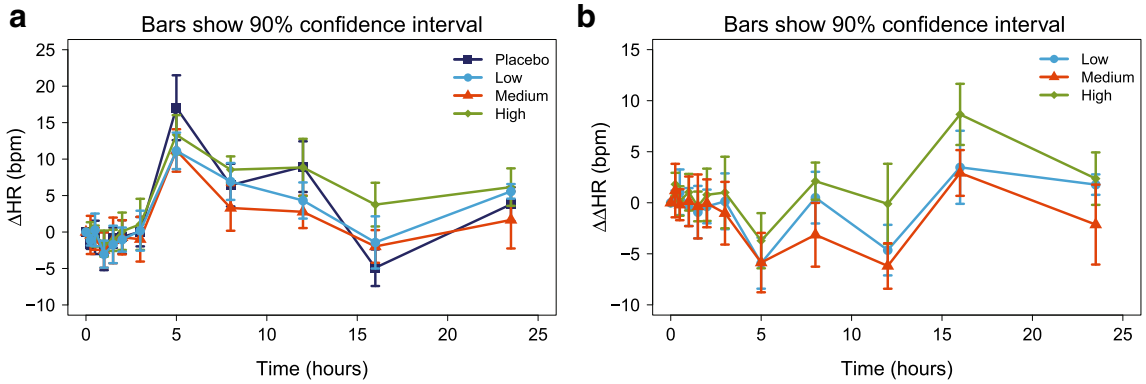

Fig. 1 Evaluation of drug induced effect on heart rate by dose: **a** time course of the mean change from baseline in heart rate and **b** the mean change from baseline placebo-adjusted heart rate

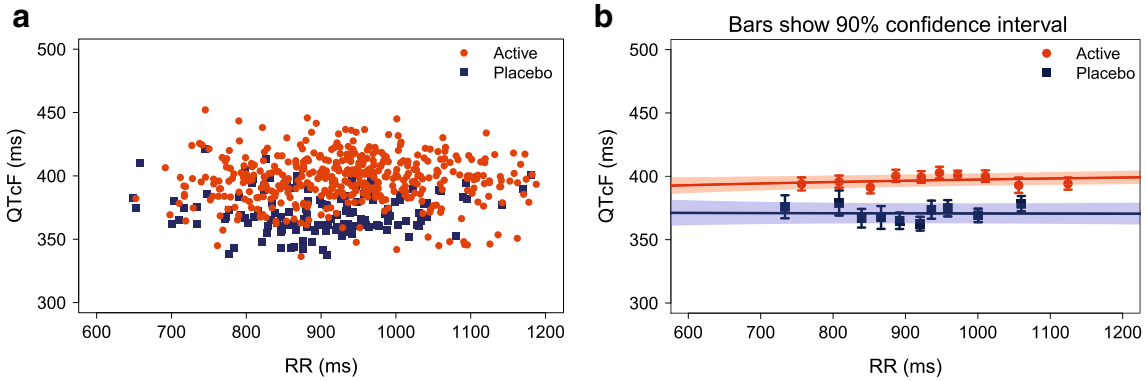

Fig. 2 Evaluation of the heart rate corrected QT interval: **a** scatterplot of QTcF and RR intervals by treatment and **b** QTcF-RR quantile plot (with quintiles) with linear mixed effects line and 95% confidence interval

and follow standard modeling practices including sensitivity analyses and model qualification [3, 23].

If exploratory plots indicate a delay between drug concentration and the effect on QTc (Fig. 3, right panels), the presence of active metabolites should be considered and models including the concentration of these metabolites explored. For example, QT, QRS, and PR interval prolongations with Anzemet appear to be associated with higher concentrations of its active metabolite, hydrodolasetron [24]. If metabolites do not explain the delay between QTc-effect and the concentration of the parent drug, a PK/PD model with a separate effect compartment may, at times, be helpful [25]. There are some investigations in the use of metrics or tests for the absence of hysteresis between PK and QTc, but there is little experience on their applicability in practice [26, 27].

In most cases, covariate analysis (e.g., effect of sex, weight) will not be routinely performed with C-QTc models based on data from healthy volunteers. There may be, however, instances where covariate identification is of interest. The method for covariate selection should be prespecified in the MAP, including methods for handling highly correlated covariates, such as baseline QTc and sex.

Model evaluation

Goodness-of-fit (GOF) plots, as described in Table 5, should be presented for the final C-QTc model, and when relevant for key stages during model development (see Supplemental Material, Case Study of a Misspecified Model). It is recommended to choose GOF plots appropriate for the analysis, as the value of different GOF plots may be dependent on the situation. Both scatterplots and quantile plots are useful representations of the residuals for continuous model parameters (e.g., concentrations, baseline QTc) and boxplots are useful for categorical parameters (e.g., time, treatment). A C-QTc quantile plot of observed data overlaid with the model predictions (Fig. 4a, b) is another visual assessment of how well the model fits the data.

Model parameters are to be presented in tabular format showing the estimate, standard error of the estimate, p value and 95% confidence interval. Model parameters that are not supported by the observed data will be poorly estimated and their 95% confidence intervals will include zero. Because an over-parameterized model may at times

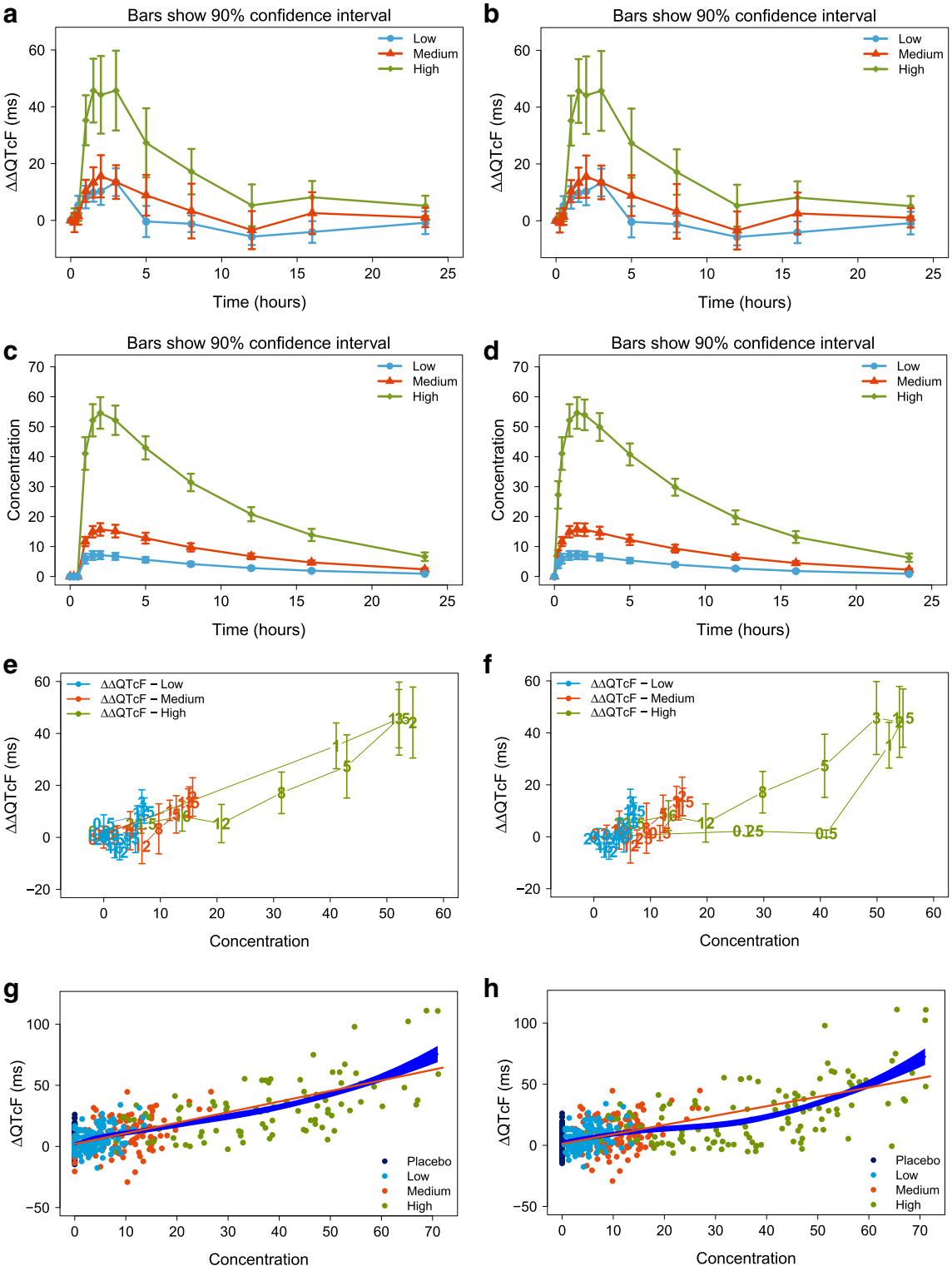

Fig. 3 Evaluation of PK/PD hysteresis using exploratory plots with examples of a direct effect in left panels and a 1-h delayed-effect in right panels: **a**, **b** time course of mean and 90% CI ΔΔQTcF and **c**, **d** drug concentration; **e**, **f** mean ΔΔQTc and concentration connected in temporal order by dose; **f**, **g** scatter plot of paired ΔQTc and concentration data with loess smooth line and 95% confidence intervals (shading) and linear regression line (solid line) (Color figure online)

have lower AIC values compared to a simpler model, it is important that the MAP describes specific criteria for choosing the appropriate model. Parameter estimates should also be evaluated for evidence of model

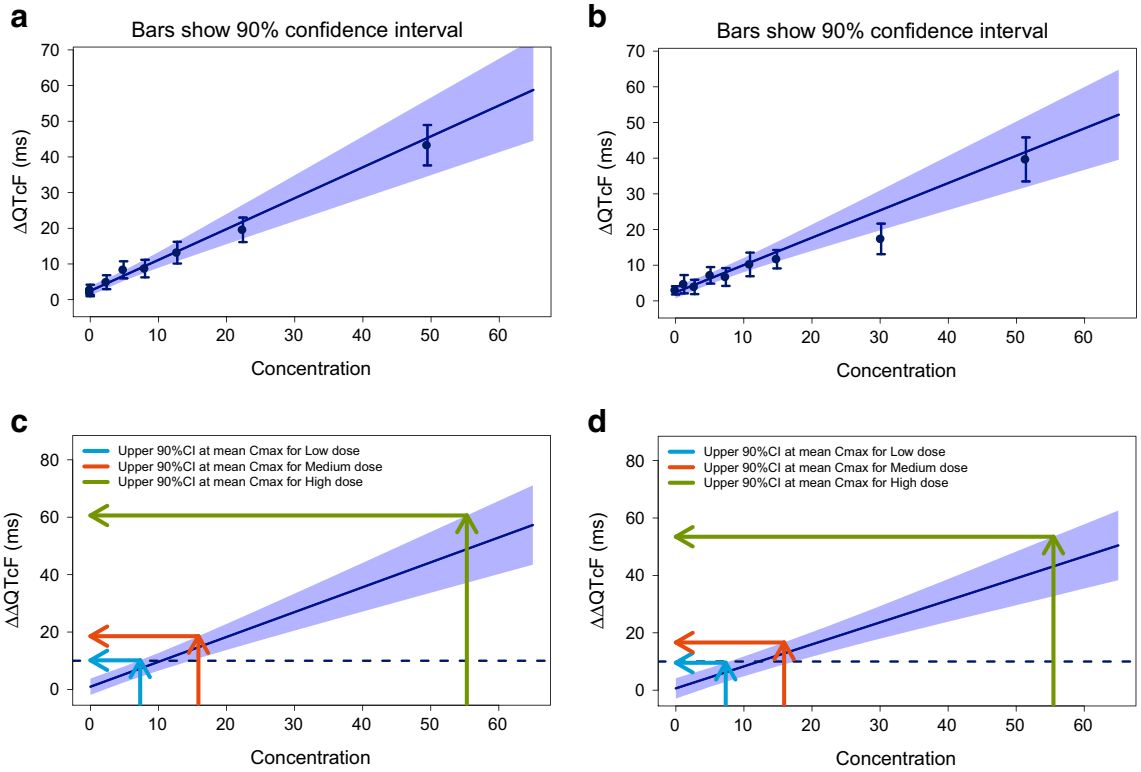

Fig. 4 Evaluation of the final model for correctly specified model (left panels) and misspecifed model (right panels): **a**, **b** ΔQTc versus drug concentration quantile plot with model slope and 90% CI; and **c**, **d** ΔΔQTc versus concentration with associated predictions shown by arrows at mean C_{max} by dose. In the C-QTc quantile plot, it should be noted that with a model including time as factor, the regression line $y = \Theta x + t$ with slope Θ and treatment effect t will not fit the observed data if the average time effect is not zero. To obtain a visual fit, either the regression line or the observed data (ΔQTc) need to be adjusted for the time effect (Color figure online)

misspecification (Supplemental Material, Table S2). Similarly, a large significant treatment effect may indicate a misspecified model as illustrated in the Supplemental Material, Case Study of a Misspecified Model, and shown by PK/PD simulations [13].

Estimation of model-derived ΔΔQTc at concentration(s) of interest

The final C-QTc model should be used to compute the ΔΔQTc at concentrations of interest, such as concentrations representing a therapeutic dose in a patient population and the expected increased concentrations associated with drug interactions, impaired hepatic or renal function, and in patients with polymorphisms in CYP enzymes. Because the C-QTc models are data-driven and empirical PD models are used to describe the observed data, it is strongly recommended that the model not be extrapolated to concentrations that fall outside the range of observed concentrations used to generate the model. For decision making, the concentration of interest will be derived from the drug development program and, therefore, can be treated as a prediction variable without concerns of uncertainty.

For the pre-specified C-QTc model, the change from baseline QTc adjusted for placebo (ΔΔQTc) is the difference between the model-derived ΔQTc at concentration of interest and model-derived ΔQTc for placebo (concentration = 0).

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

where $\Delta QTc_{(C,trt=active)}$ is the ΔQTc at concentration from the final C-QTc model using ΔQTc as the dependent variable, C is the concentration of interest.

In the simplest case and when using the pre-specified linear model, the mean and two-sided 90% CI for ΔΔQTc at concentrations of interest (i.e., C_{max} at specific dose level) are computed from Eqs. 3–5, where "Est" refers to an estimate of the true parameter from the model fit.

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

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

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

where $\theta_{1,Est}$ 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; SE is the standard error; and CI is the confidence interval.

For adapted C-QTc models that have different structures (e.g., nonlinear models or linear models with interaction terms), the mean and 90% CI for ΔΔQTc can be computed by non-parametric bootstrap methods with subject identifier used as the unit for resampling. Resampling should be stratified by dose level within the active treatment and the placebo subjects. Model parameters and ΔΔQTc (Eq. 2) are determined from each of the replicate bootstrapped datasets. Two-sided 90% CIs are computed from the 5th and 95th percentile of the rank-ordered ΔΔQTc values from all replicates and bias correction may be applied.

Reporting of C-QTc modeling results

Modeling analysis plan

A detailed plan should be prospectively written for the C-QTc analysis. The plan should include the following:

- The objective(s) of the analysis.
- A brief description of the study (or studies) from which the data originate and, if pooling data, the rationale for pooling data and a discussion of the similarities with respect to clinical conduct, subject handling and ECG acquisition, ECG measurement approaches, and bioanalytical assay.
- The key features of the data to be analyzed (e.g., how many studies, subjects, dose levels, time-matched PK/ECG samples).
- A brief description of ECG acquisition and measurement, including the use of core ECG laboratory, analysis approach, and blinding procedures of ECG readers.
- The procedures for data transformations, handling missing data, outlying data and concentration data below the limitation of quantification.
- The general modeling aspects (e.g., software, estimation methods).
- The graphical data exploration of model assumptions (as described in Table 5).
- The dependent variable including methods for heart rate correction and baseline-correction.
- The C-QTc models to be tested, including alternative models to be used in cases of non-convergence, PK/PD hysteresis, nonlinearity, et cetera.
- If pooling data, the objective criteria for testing heterogeneity.
- The covariate models to be tested together with a rationale for including these covariates.
- The criteria to be used for selection of models during model building and inclusion of covariates (e.g., objective function value, AIC, level of statistical significance, GOF plots, standard error in model parameter, inter-individual variability, clinical relevance).
- The methods to be used for model-based predictions and the rationale for choosing the exposure of interest.

There may be cases where the selection of a specific model can only be made once data are available. The principles governing this selection are clearly pre-specified. The MAP can be a stand-alone document or incorporated into the statistical analysis sections of the protocol.

Modeling results

Recommendations for information to be reported are summarized in Table 6 and are based on European Medicines Agency's Guideline on reporting the results of population pharmacokinetic analyses [28] and recommendations by European Federation of Pharmaceutical Industries and Associations' working group on Model-Informed Drug Discovery and Development [3]. The modeling output can be documented in a stand-alone report or within specific report sections in the cardiac safety report or clinical study report.

Summary

This White Paper provides recommendations on how to plan and conduct definitive QTc assessment of a drug using C-QTc modeling in early phase clinical pharmacology and TQT studies. The recommendations are based on current best modeling practices, examples in scientific literature, and personal experiences of the authors. These recommendations are expected to evolve as their implementation during drug development provides additional data and with advances in analytical methodology.

A critical recommendation is a pre-specified LME model as the primary analysis to exclude a 10-ms QTc

Table 6 Reporting of C-QTc modeling results

Report section	Important elements
Synopsis	Concise summary of objectives, methods, key results and conclusions
Introduction	Summary of clinical pharmacology of drug and preclinical/clinical cardiac safety
	Description of therapeutic and high clinical exposure scenario due to intrinsic or extrinsic factors
	Clinical relevance of the concentration used for model predictions
Objectives	Concise statement of modeling objectives
Data	Description of clinical study(ies) design, doses and dose administration, subjects, timing PK/ECG measurements
	If pooling studies, highlight any differences between studies in subject handling as well as ECG acquisition and measurements and bioanalytical assay. Specify heterogeneity assessment.
Methods	Refer to MAP in appendix
	Changes to MAP
Results	Summary of dataset, including subjects, observations, data transformations, missing data and outliers
	Graphical exploratory analysis to evaluate model assumptions of no HR effect, linear relationship and lack of PK/PD hysteresis
	Description of model and model development results
	Description of final model results with GOF plots and parameter table
	Description of model predictions
Discussion	Explain clinical relevance of results
	Discuss adequacy of data (e.g., exposure range, assay sensitivity, model assumptions)
	If drug prolongs QTc interval, describe patients at increased risk of QTc prolongation based on their intrinsic or extrinsic factors.
Conclusions	Discuss clinical relevance of findings in the context of ICH E14
Appendices	Modeling analysis plan
	Dataset specifications
	Model scripts/codes/output
	Clinical pharmacology table

prolongation effect. A pre-specified model minimizes bias, as subjectivity in model selection could favor a model that inflates the type I error. Pre-specification allows for standardization of the analysis across industry and regulatory regions and offers several additional benefits, including providing transparency in modeling expectations, increasing the reproducibility of results, and streamlining the review process. It is expected that the pre-specified LME model will be suitable for most the drugs evaluated, with potential exceptions described in Table 1. The intention of the recommended modeling approach is to simplify and increase the objectivity of traditional PK/PD modeling process by utilizing the pre-specified model and, if drug effect is detected, optimizing the drug-effect model using PK/PD modeling principles. In this scenario, it is extremely important that the model qualification and selection process follows the MAP to avoid bias. It is possible that the model-derived ΔΔQTc of the final model will be lower than one derived from the pre-specified model. To minimize inconsistent interpretation, the reporting of these results should focus on (1) the final model selection process and how well the final model describes the data; (2) the difference between models in the model-derived ΔΔQTc at exposure of interest; and (3) whether the exposure of interest is therapeutic or supratherapeutic.

To use the C-QTc modeling analysis of data from a phase 1 study as an alternative to a TQT study, a critical element is that the QT response be evaluated at a sufficiently high multiple of the clinically relevant exposure to waive the need for assessing assay sensitivity with an active control. A large exposure margin provides confidence that small QTc effects at clinically relevant exposures have not been missed in the evaluation. Other important design elements that are common to TQT studies should be included in the phase 1 design. Careful subject handling and robust ECG acquisition and blinded measurement are necessary to minimize bias and variability. Time-matched PK samples and ECG measurements should cover the inter-dosing interval and include time of peak concentrations of parent and metabolites and be collected for at least 24 h following a single dose. For a drug with a long half-life of parent or active metabolites, there needs to be ECG measurements taken when peak concentrations are achieved or at earlier times at higher doses that give the maximum concentrations achieved over time. The number of subjects on placebo and pooled doses should provide

sufficient power to exclude a 10-ms QTc prolongation effect using C-QTc analysis.

Overall, the recommendations within the White Paper provide opportunities for increasing efficiencies in this safety evaluation. Given the decade of experience using C-QTc model in drug development and regulatory decisions, the recommended modeling approach is not anticipated to compromise detection of drugs with QT liability.

Disclaimer The views presented in this article are the personal opinions of the authors and do not reflect the official views of their respective organizations.

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