Concentration‑QTc Assessment in Early Phase Trials

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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. With some example we try to further interpret the white paper.

INTRODUCTION

The 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.

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 meet the regulatory requirements of the ICH E14 guideline.

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.

FIRST MAIN TOPIC

DESIGN CONSIDERATIONS FOR C-QTC ANALYSIS

1. **Are sponsors expected to conduct thorough QT studies as part of the development of large proteins and monoclonal antibodies?**

   a) Large targeted proteins and monoclonal antibodies have a low likelihood of direct ion channel interactions and a thorough QT/QTc study is not necessary, unless the potential for proarrhythmic risk is suggested by mechanistic considerations or data from clinical or non-clinical studies.

   b) The recommendations contained in this document are generally applicable to new drugs having systemic bioavailability, but may not apply to products with highly localized distribution and those administered topically and not absorbed

2. **Gender**

   It is encouraged, but not mandatory, to include both men and women in the thorough QT study.

3. **Subject Enrollment**

   a) Until the effects of the drug on the QT/QTc interval have been characterized, the following exclusion criteria are suggested:

   b) A marked baseline prolongation of QT/QTc interval (e.g., repeated demonstration of a QTc interval >450 milliseconds (ms))

   c) A history of additional risk factors for TdP (e.g., heart failure, hypokalemia, family history of Long

QT Syndrome)

    d)   The use of concomitant medications that prolong the QT/QTc interval

4. Study Design

Commonly used designs are the sequential parallel group design and the alternating panel crossover design

5. Sample size

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

Stochastic PK/PD simulations have shown that the false negative rate 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

6. 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

7. Special Cases -- Where a placebo-controlled comparison using appropriate doses is not possible

Alternative study designs should incorporate as many of the usual "thorough QT/QTc" design features as possible, and the quality and extent of the pre-clinical evaluation is particularly critical. Other useful supplementary data might include intensive ECG data acquisition in early phase single or multiple ascending dose studies, utilisation of concentration-response analysis, and evaluation of exposures that are greater than are anticipated with the intended marketed dose.

8. Positive Control

    a)   Study's ability (its "assay sensitivity") to detect the study endpoint of interest.

    b)   The positive control should show a significant increase in QTc; i.e., the lower bound of the one-sided 95% Confidence Interval (CI) must be above 0 ms.

    c)   The study should be able to detect an effect of about 5 ms (the QTc threshold of regulatory concern) if it is present. Therefore, the size of the effect of the positive control is of particular relevance

    d)   Double-blinded positive control does not appear to be essential

9. The FDA's Interdisciplinary Review Team is recommending that exposures are at least twice the highest clinically relevant exposure without a separate positive control

10. Is it recommended that measurement of QT prolongation be performed on drug combinations?

    a)   In general, combinations of two or more drugs are unlikely to need a thorough QT/QTc study or intensive late stage monitoring, if the component drugs have been demonstrated to lack relevant effects in thorough QT/QTc studies as described in ICH E14.

    b)   If one or more of the component drugs have not been individually characterised for effects on the QT/QTc interval, they may be evaluated in combination or independently

11. 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

12. **Pooling Data**

    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，ECG measurement approaches be similar.

13. **Baseline**

    a) "time-matched" baseline (use the corresponding predose QTc measurements collected prior to drug administration on Day-1) and "pre-dose" baseline (taken shortly prior to dosing).

    b) For a parallel-group study a time-matched baseline allows the detection of differences in diurnal patterns between subjects. In a parallel study a "time-matched" baseline day, if performed, would ideally occur on the day before the start of the study.

    c) The "pre-dose" baseline is therefore usually adequate for cross-over studies.

    d) 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

14. **Is there now a reasonable approach to evaluating QTc in late stage clinical development in the case of a finding of QT prolongation prior to late phase studies?**

    a) If there is a large margin an intensive ECG might not be warranted.

    b) A negative result will almost always allow the collection of on therapy ECGs in accordance with the current practices in each therapeutic area to constitute sufficient evaluation during subsequent stages of drug development.

    c) A positive result will almost always call for an expanded ECG safety evaluation during later stages of drug development.

MODELING APPROACH

1. **C-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**

2. **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 ∆∆QTc should be <10 ms at the highest clinically relevant exposure to conclude that an expanded ECG safety evaluation during later stages of drug development is not needed**

3. **A pre-specified linear mixed effects model is recommended as the primary analysis to exclude a 10-ms QTc prolongation effect**

4. $\Delta QTc_{ijk} = (\theta_0 + \eta_{0,i}) + \theta_1 TRT_j + (\theta_2 + \eta_{2,i})C_{ijk} + \theta_3 TIME_k + \theta_4(QTc_{ijk=0} - \overline{QTc_0}) + \varepsilon_{ijk}$

    a) ΔQTc_{ijk} **is the change from baseline in QTc for subject i in treatment j at time k**

    b) θ_0 **is the population mean intercept in the absence of a treatment effect**

    c) $\eta_{0,i}$ **is the random effect associated with the intercept term θ_0**

    d) θ_1 **is the fixed effect associated with treatment TRT_j (0 = placebo, 1 = active drug)**

    e) θ_2**is the population mean slope of the assumed linear association between concentration**

and ΔQTc_{ijk};

f) $\eta_{2,i}$ is the random effect associated with the slope θ_2

g) C_{ijk} is the concentration for subject i in treatment j and time k

h) θ_3 is the fixed effect associated with time

i) θ_4 is the fixed effect associated with baseline $QTc_{ijk=0}$, $\overline{QTc_0}$ is overall mean of QTc_{ij0}, i.e., the mean of all the baseline(= time 0) QTc values

5. SAS code

```
ods listing close;
ods output estimates = EST solutionf = SOL CovParms = COV covb = pp
           coef = ppp CovParms  = o solutionf = fixed solutionr = random;
PROC MIXED DATA = DATA METHOD = REML ORDER = DATA;
    CLASS SUBJID TRTA ATPT;
    MODEL CHG = TRTA ATPT BASEADJ CONC/DDFM = KR NOINT SOLUTION OUTP = PRED;
    RANDOM INTERCEPT CONC/TYPE = UN SUBJECT = SUBJID;
RUN;
ods output close;
ods listing;
```

Figure 1. SAS code for mixed model

Note: The SAP should specify approaches to handle non-convergence of the model, including any transformations of concentration data

6. Note

To avoid unnecessary model-building steps, removing non-significant parameters from the model is generally not recommended.

Variations to the pre-specified linear fixed effects C-QTc model.

Variation	Rationale	Impact on model parameters
$\Delta\Delta$QTc as the dependent variable	In crossover TQT studies with William's square design, $\Delta\Delta$QTc 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 $\Delta\Delta$QTc 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

Figure 2. Variations to the pre-specified linear fixed effects C-QTc model

MODELING INDEPENDENT CHECKS OF ASSUMPTIONS USING EXPLORATORY PLOTS

1. Assumption 1：No drug effect on 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
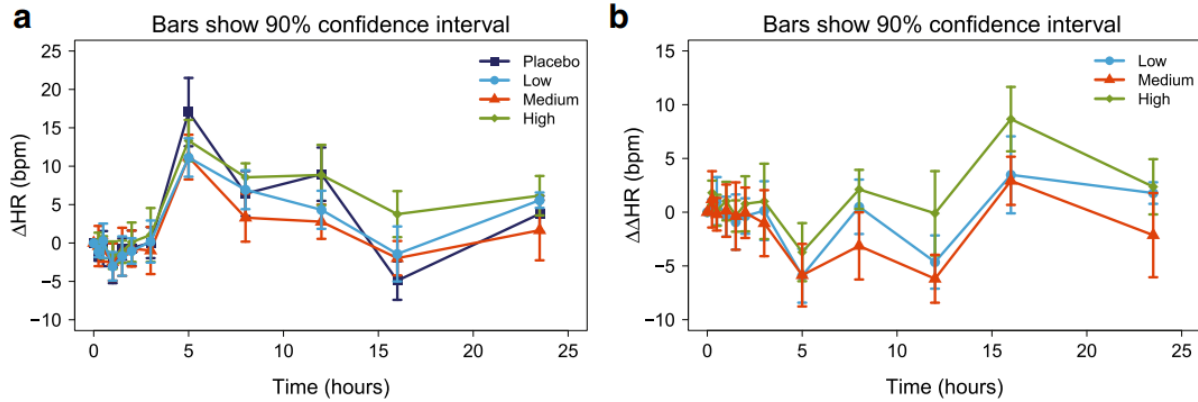

Figure 3. Mean $\pm$SD for ΔHR and $\Delta\Delta$HR for each dose and timepoint

2. Assumption 2：QTc interval is independent of HR

    a) **QTcF is usually a sufficient correction method for drugs with insignificant effects on HR**

and evaluation of this correction method is not needed
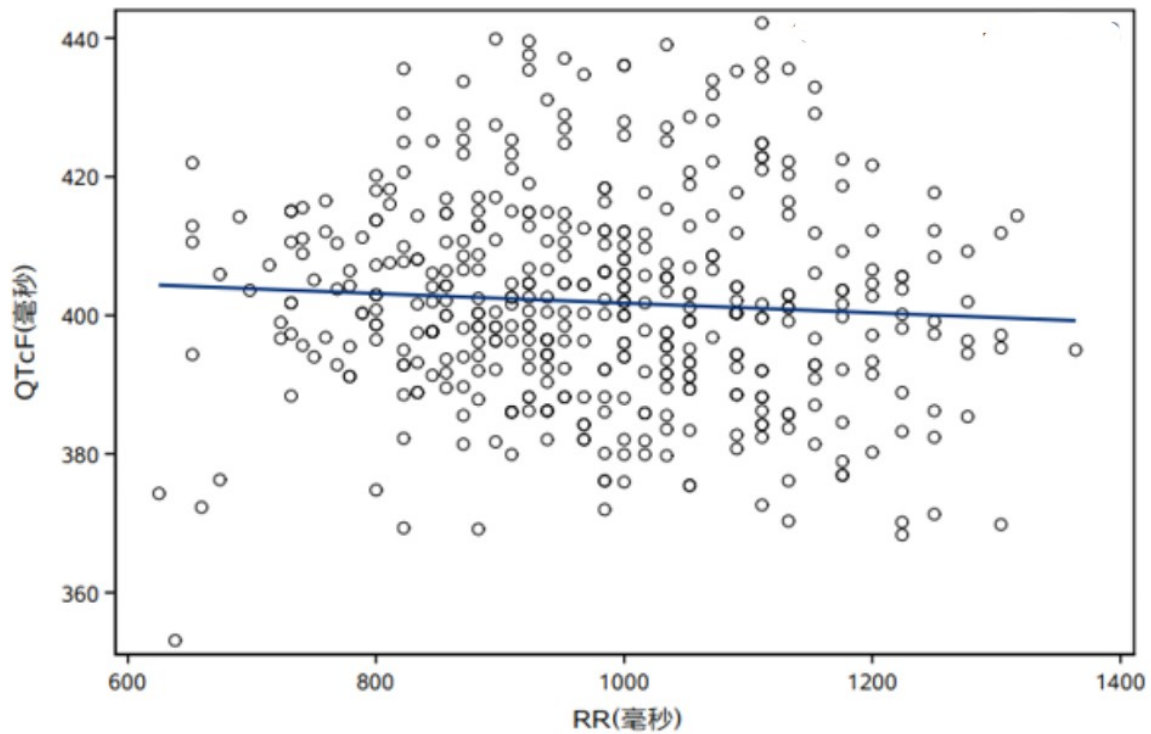
b)   Slope for QTcF-RR<|0.045|

Figure 4. Scatter plot and regression line plot for QTcF vs RR

3.   Assumption 3：No time delay between drug concentrations and ΔQTc Concordance (PK/PD hysteresis)

If the Tmax versus Umax differ by more than 60 minutes using a 1-sided 1-sample Wilcoxon test, the presence of hysteresis will be further assessed
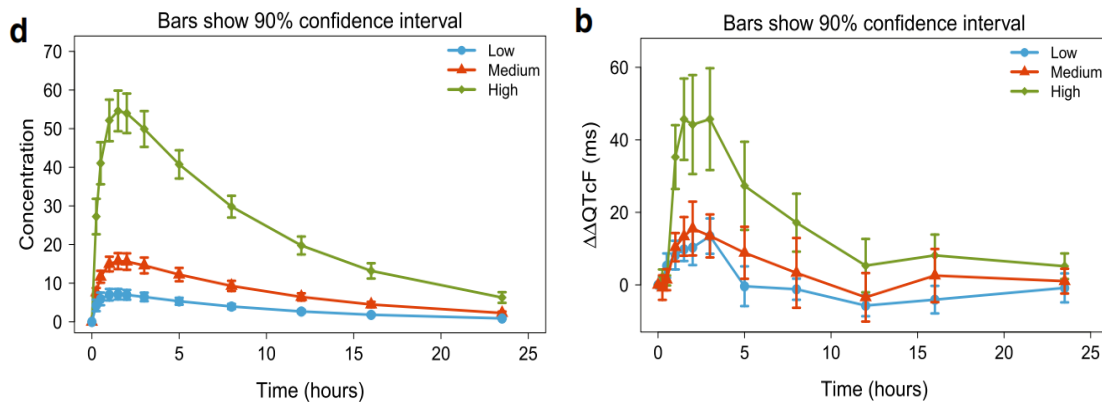

Figure 5. Concentration and $\Delta\Delta QTcF$ vs. Time plot for each dose for each timepoint

4.   Assumption 4：Linear C-QTc relationship

Is used to detect drug effect, and when a drug effect is detected, whether there are major violations to the
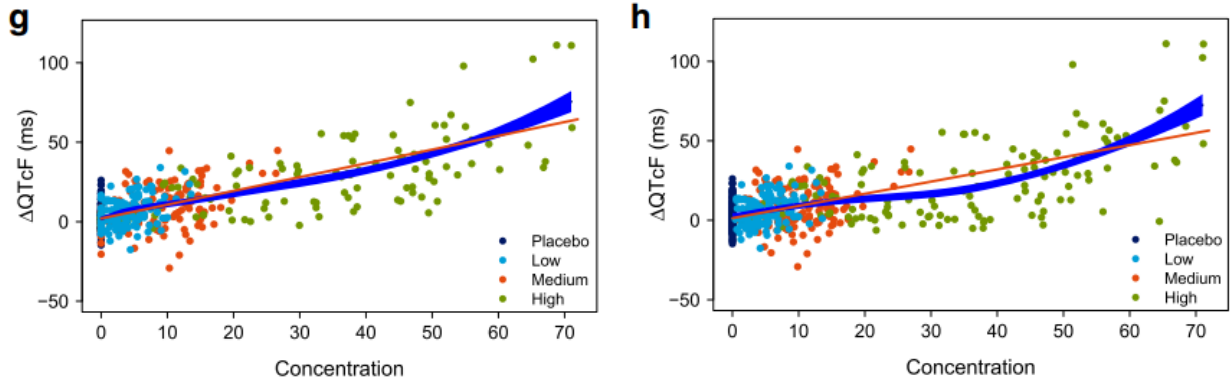
6

linear assumption.

Figure 6. ΔQTcF vs. Concentration plot for each dose

MODEL EVALUATION

1.   Goodness-of-fit plots should be presented for the final C-QTc model

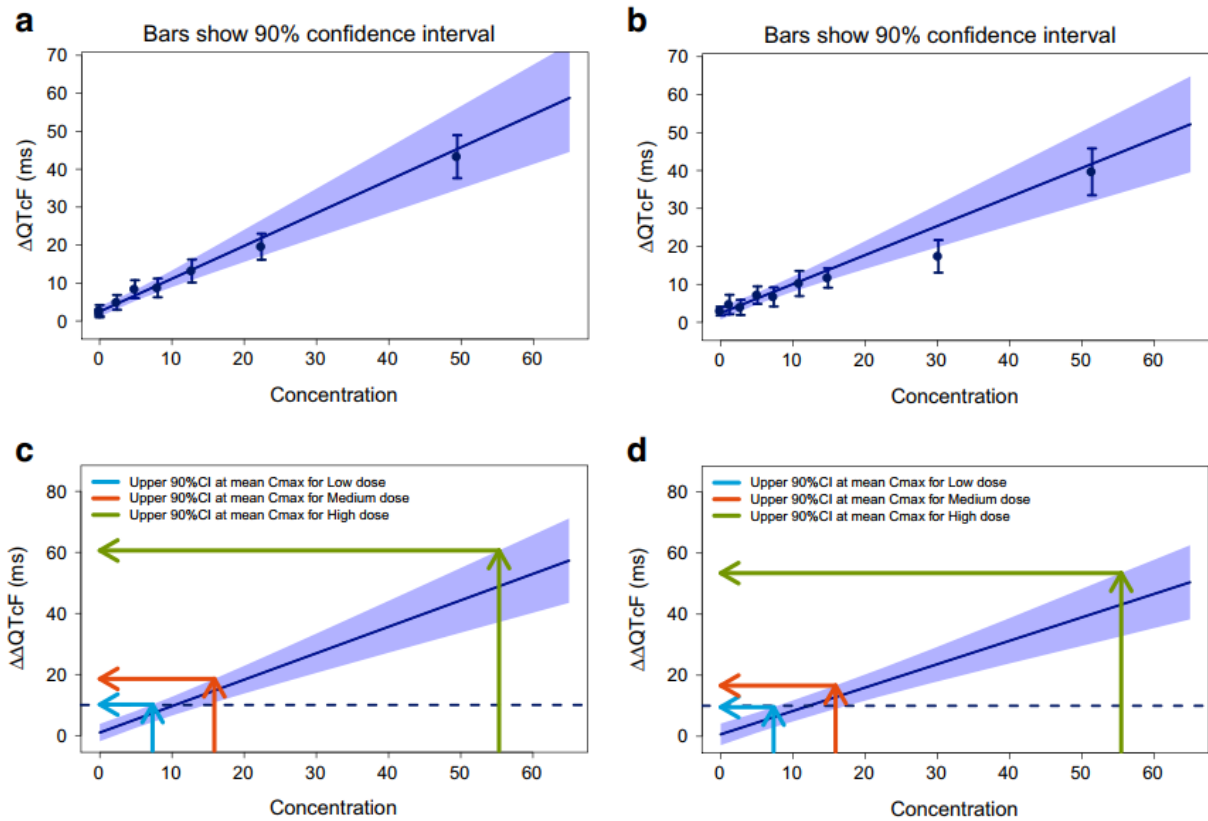

Figure 7. Supratherapeutic exposure for ΔΔQTcF vs Concentration plot

2. **Model parameters are to be presented in tabular format showing the estimate, standard error of the estimate, p value and 95% confidence interval**

Parameter	Estimate(SE)	90%CI	P value
Intercept (θ_0)	xx.x(xx.xx)	(xx.xx, xx.xx)	x.xxx
Concentration (θ_2)	xx.x(xx.xx)	(xx.xx, xx.xx)	x.xxx
Treatment (θ_1)	xx.x(xx.xx)	(xx.xx, xx.xx)	x.xxx
Timepoint (θ_3)			
1h	xx.x(xx.xx)	(xx.xx, xx.xx)	x.xxx
2h	xx.x(xx.xx)	(xx.xx, xx.xx)	x.xxx
...	xx.x(xx.xx)	(xx.xx, xx.xx)	x.xxx
Baseline QTc (θ_4)	xx.x(xx.xx)	(xx.xx, xx.xx)	x.xxx

Figure 8. Model parameters to be presented in tabular format

3. **Model development for adapted C-QTc model**

    a) Other approaches to evaluate QT/QTc should to be considered[1]

    b) The drug effect models routinely tested are the linear and Emax families of models; however, other types of PD models can be explored to optimize the model fit

    c) The model and methods for model evaluation and selection need to be pre-specified in a SAP to limit bias.

    d) Model selection should be based on the pre-specified objective criteria (e.g., objective function value, (AIC), level of statistical significance, goodness of fit plots, standard error in model parameters)

MODEL-DERIVED ΔΔQTC AT CONCENTRATION(S) OF INTEREST

1. **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**

    a) Method 1:

```
ods listing close;
ods output estimates = EST solutionf = SOL CovParms = COV covb = pp
           coef = ppp CovParms  = o solutionf = fixed solutionr = random;
PROC MIXED DATA = DATA METHOD = REML ORDER = DATA;
    CLASS SUBJID TRTA ATPT;
    MODEL CHG = TRTA ATPT BASEADJ CONC/DDFM = KR NOINT SOLUTION OUTP = PRED;
    RANDOM INTERCEPT CONC/TYPE = UN SUBJECT = SUBJID;
    ESTIMATE 'Δ ΔECG at Cmax for T vs R' CONC xx.x TRTA 1-1/CL ALPHA = 0.1;
RUN;
ods output close;
ods listing;
```

Figure 9. SAS code for the MODEL-DERIVED ΔΔQTC

    b) Method 2: For adapted C-QTc models (e.g., nonlinear models or linear models with interaction terms), the mean ΔΔQTc and 90% CI for QTc can be computed by non-parametric bootstrap

methods

OTHERS

Evaluation of the effects of a drug on the standard ECG intervals and waveforms is considered a fundamental component of the safety database of any new drug application.

Regardless of the outcome of the "TQT study," ECG changes recorded as adverse events should be pooled from all studies for analysis. ECG interval data from the "TQT study" should only be pooled with subsequent trials of similar rigor with regard to ECG data collection and analysis.
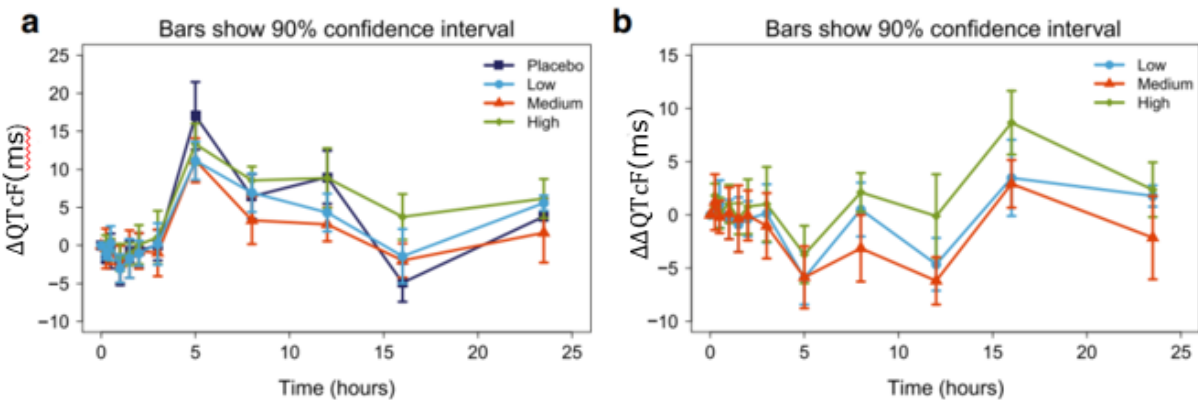
Analyses of Central Tendency

Figure 10. Analyses of Central Tendency for ∆∆QTC

Categorical Analyses

Absolute QTc interval prolongation: (QTc interval > 450、QTc interval > 480、QTc interval > 500

Change from baseline in QTc interval: (QTc interval increases from baseline >30、QTc interval increases from baseline >60）

CONCLUSION

We have introduced the Concentration-QTc assessment in the early phase trials from background, design, modeling approach, modeling assumptions check, model evaluation ant others perspectives. These introductions would help sponsors to design and analysis data to meet requirements from ICH E14.

REFERENCES

1. https://www.cde.org.cn/ichWeb/guideIch/toGuideIch/3/0

2. E14 Implementation Working Group ICH E14 Guideline: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for NonAntiarrhythmic Drugs Questions & Answers (R3). 10 December 2015 Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E14/E14_Q_As_R3_Step4.pdf

3. Garnett C, Bonate PL, Dang Q, Ferber G, Huang D, Liu J, Mehrotra D, Riley S, Sager P, Tornoe C, Wang Y. Scientific white paper on concentration-QTc modeling. J Pharmacokinet Pharmacodyn. 2018 Jun;45(3):383-397.