Regulatory perspective for using C-QTc as the primary analysis: trial design, ECG quality evaluation, evaluation of modeling/simulation results and decision-making

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Outline

• Expectations for C-QT regulatory submissions under ICH E14 Q&A (R3)
• Exposure margin and dosing to satisfy requirement for waiving positive control
• Considerations for data pooling from multiple studies
• QT-IRT statistics for C-QT submissions
• Common issues across multiple submissions
• Tutorial—Implementation of white paper at FDA
Expectations for C-QT regulatory submissions under ICH E14 Q&A (R3)

- Study Design
- ECG Quality
- Dose range
- Sample size
- Assay Sensitivity
- C-QTc analysis
Expectations for C-QT regulatory submissions under ICH E14 Q&A (R3)

➢ Study Design

• SAD vs. MAD
  – MAD necessary if significant PK accumulation of the parent and/or relevant metabolite(s)

• Placebo control
  – Control for potential bias introduced by study procedures and diurnal variations
Expectations for C-QT regulatory submissions under ICH E14 Q&A (R3)

• Baseline ECG
  – Pre-dose baseline (e.g. average of 3 time points over 1 hour)
  – Full day baseline to compute QTcl, if needed for drugs with heart rate effects

• Post-dose ECG/PK
  – Covers Tmax of parent/metabolite;
  – Any delayed effects over 24 hours for single dose trial
Expectations for C-QT regulatory submissions under ICH E14 Q&A (R3)

- **ECG Quality**
  - Data acquisition
    - Replicates
    - Blinded readers
    - Same reader for all ECGs in a subject
    - Acquisition at similar facility
  - Design/Trial conduct
    - Prior to PK sampling
    - Standardized meal timing
    - Supine etc.
  - Data pooling considerations (detailed later)
Expectations for C-QT regulatory submissions under ICH E14 Q&A (R3)

- **Dose range**
  - Cover wide exposure range
  - Therapeutic dose (e.g. 10 mg QD)
  - **highest clinically relevant exposure** (e.g. 20 mg QD or higher as supratherapeutic dose)

*Highest exposure for drug and/or metabolites (mean $C_{max}$) after the single dose or at the steady state due to intrinsic (renal/hepatic impairment, age/race/gender, disease status) or extrinsic factors (metabolic inhibition, food effects) e.g. 2-fold exposure for same therapeutic dose with CYP3 inhibition
Expectations for C-QT regulatory submissions under ICH E14 Q&A (R3)

- **Dose range**
  - Cover wide exposure range
  - Therapeutic dose (e.g. 10 mg QD)
  - **highest clinically relevant exposure** (e.g. 20 mg QD or higher as supratherapeutic dose)
  - Sufficiently high multiples of the **highest clinically relevant exposure** without a positive control for ECG assay sensitivity (e.g. ≥2-fold of exposure with CYP3 inhibition i.e. ≥40 mg QD)
Expectations for C-QT regulatory submissions under ICH E14 Q&A (R3)

- **Sample size**
  - Subjects per treatment
    - 6-9 subjects per treatment cohort
  - Treatment cohorts
    - wide exposure range
  - Subjects with placebo
    - at least 6 placebo controls; these can be pooled from different cohorts
Expectations for C-QT regulatory submissions under ICH E14 Q&A (R3)

- **Assay Sensitivity** (positive control)
  - Meets criteria for waiving requirement
    - Evaluation of *sufficiently high multiples* (at least 2-fold) of highest clinically relevant exposures (e.g. ≥40 mg QD dose in example described earlier)
    - Non-pharmacological approaches under investigation (e.g. bias evaluation\(^2,3\)) may provide an alternative to requirement for multiple fold exposure, upon validation in future
    - If a sufficiently high exposure has not been evaluated, a traditional or alternative TQT study necessary, with *positive control* (moxifloxacin)

Expectations for C-QT regulatory submissions under ICH E14 Q&A (R3)

- **C-QTc analysis**: Adequate characterization of QTc data
  - Pre-specified analysis plan
  - Exploratory plots to test model assumptions
  - LME model (or alternative models, e.g., $E_{\text{max}}$) with $\Delta$QTc as dependent variable and appropriate fixed/random effects
  - Goodness of fit
  - Appropriate $\Delta\Delta$QTc calculation (treatment-placebo contrast)
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<tbody>
<tr>
<td></td>
<td>□ Placebo control</td>
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<td></td>
<td>□ Baseline ECG</td>
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<td>□ Post-dose ECG/PK</td>
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<td>ECG Quality</td>
<td>□ Data acquisition</td>
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<td>□ Design/Trial Conduct</td>
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<td>□ Data pooling considerations</td>
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<td>□ Meets criteria for waiving requirement</td>
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<tr>
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<td>□ Pre-specified analysis plan</td>
</tr>
<tr>
<td></td>
<td>□ Exploratory plots</td>
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|                      | • Appropriate ΔΔQTc calculation  

Exposure margin and dosing to satisfy requirement for waiving positive control

- Mean Cmax for Therap. Dose
  - 10 mg QD dose
- Mean Cmax for highest clinically relevant exposure (DDI/Organ impairment)
  - 20 mg QD dose
- 2-fold the highest clinically relevant exposure
  - 40 mg QD dose
Exposure margin and dosing to satisfy requirement for waiving positive control

ΔΔQTc

Mean Cmax for Therap. Dose
10 mg QD dose

Mean Cmax for highest clinically relevant exposure (DDI/Organ impairment)
20 mg QD dose

2-fold the highest clinically relevant exposure
40 mg QD dose
Considerations for data pooling from multiple studies

• Preferable that C-QT analysis data come from a single study to minimize between-study variability
  – Single study could be SAD/MAD under same protocol or conducted at same clinical site

• When pooling from multiple studies is necessary (e.g., to cover a wide range of dose/exposure or increase number of subjects exposed to drug)
  – Similar design control procedures (e.g., placebo, food)
  – Same robust clinical conduct and subject handling performed in each study
  – Similar ECG acquisition/measurement approaches at baseline and during the treatment
Considerations for data pooling from multiple studies

• When pooling HV and patient studies, be mindful that patients taking concomitant medications or with comorbid conditions could influence the C-QT relationship
  – C-QT analysis using patient data can be valuable for drugs that prolong the QTc interval: may characterize the effect in patients and evaluate covariates that increase a patient’s risk
QT-IRT statistics for C-QT submissions under ICH E14 Q&A (R3)

- 25 proposals (Dec 2015 to Nov 2016)
  - 11 agreements, 14 disagreements
  - 2 alternative TQT studies with C-QTc as primary analysis (Moxifloxacin C-QTc for assay sensitivity)
  - 23 non-TQT early phase studies
    - 8 SAD/MAD studies
    - 5 SAD studies
    - 5 Pooled studies
    - 5 Other designs (phase 1, DDI, phase 2)

- Lack of assay sensitivity or adequate exposure margin is the predominant reason for not agreeing with the proposal
Some common issues across multiple submissions: Design Issues

• Expectation of exposure margin to waive the requirement for the inclusion of a positive control is not achieved
  – If it is not feasible to achieve requisite higher exposures due to design issues (tolerability, pill-burden, saturable absorption etc.)

• Use of concomitant drugs that may confound the assessment of QT effects of the product in the study and make it difficult to support a claim of absence of QTc prolongation
  – Drugs that can blunt the QT prolongation effect of investigational drug
  – CYP3 inhibitors (keto/itraconazole) which themselves cause QT prolongation
Some common issues across multiple submissions: Design Issues

- ECG analysis is a part of a food effect study, and adequate control for food for different dose levels is not in place to avoid bias and interpretation.
- ECG sampling near Tmax of parent drug is proposed but not at/near Tmax of potentially relevant metabolite.
- In single dose trial, ECG sampling is not for sufficient duration (at least 24 hours) to evaluate potential delayed effect.
- Pooling of studies may not be appropriate: Single vs. replicate measurements, placebo control absent in some, holter vs. standard 12-lead ECG, Healthy vs. patients.
Some common issues across multiple submissions: Analysis Issues

• Baseline QTc is not proposed as a covariate for C-QTc model
• ΔΔQTc is calculated by subtracting averaged or time matched mean ΔQTc for placebo from ΔQTc for the active treatment for each time point.
  – This is reasonable for exploratory evaluation
  – But final predictions of effect should be based on contrast of ΔQTc for treatment vs. placebo.

• Random effect (subject) is only specified for intercept and not slope
  – Random effect on slope may cause non-convergence, but often can be resolved by rescaling the concentration so that the range in observed concentrations is in the same magnitude as the QT measurements
  – If not, the model can be simplified by eliminating random effect on slope
Implementation of white paper at FDA

• White paper on best practices in concentration-QTc modeling provides:
  – the scientific rationale for using C-QTc as primary analysis
  – the mathematical description of the predefined C-QTc model
  – assumptions of the model and how these are verified

• A hands-on tutorial, under development, that will provide an “example analysis” using a publicly available dataset/design\(^4\)
  – Dofetilide and placebo for positive analysis
  – Verapamil and placebo for analysis with no C-QTc signal

\(^4\)Johannesen L et. al., *CPT*, 2014, Jul 23
Implementation of white paper at FDA

• Tutorial will follow workflow recommended in white paper:
  – Brief summary of the clinical study used in the example
  – Preparation of an analysis ready dataset including derivation of ECG variables.
  – Preliminary examination of the data as well as assessing the presence of a hysteresis.
  – Modeling with pre-specified LME model
  – Evaluation of model performance
  – Estimation of mean and 90% CI at clinically relevant conc.
Implementation of white paper at FDA

• Tutorial will provide relevant codes and description:
  – Code to generate an analysis ready data set
  – Generate exploratory graphics
  – Model fitting
  – Contrast to generate ΔΔQTc
  – P-values (various approaches)
  – Prediction with confidence intervals
  – Example of model discrimination
  – Implementation of alternative models (log-linear, quadratic)
  – Diagnostic plots
Summary

• Understanding key concepts of appropriate highest exposure margin and (in some cases) data pooling is essential towards adequate characterization of QT risk in early phase studies with C-QT, without the need for a TQT.

• Outlined common issues related to design and analysis found across submissions that often result in non-agreements for the C-QT proposals. These might inform design and analysis decisions in future C-QT based proposals.

• The forthcoming tutorial to C-QT white paper acts as a training aid by providing an example analysis which may be helpful for conducting concerted C-QT analyses and visualization within and outside the Agency.