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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Disclaimer

- The views expressed in this presentation are that of the author and do not reflect the official policy of the FDA. No official endorsement by the FDA is intended nor should be inferred.

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 QTcI, 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)

[2]Borje Darpo, *CSRC-FDA workshop 2016*; [3]Ferber G. et al, *JCP*, June 2016

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_{max}) with ΔQTc as dependent variable and appropriate fixed/random effects
  - Goodness of fit
  - Appropriate ΔΔQTc calculation (treatment-placebo contrast)

Study Design	❑ SAD/MAD ❑ Placebo control ❑ Baseline ECG ❑ Post-dose ECG/PK
ECG Quality	❑ Data acquisition ❑ Design/Trial Conduct ❑ Data pooling considerations
Dose Range	❑ Wide exposure range ❑ Therapeutic dose ❑ highest clinically relevant exposure (*Supratherapeutic*) ❑ High multiples (at least 2-fold) of *supratherapeutic*
Sample size	❑ Subjects per treatment ❑ Treatment cohorts ❑ Subjects with placebo
Assay Sensitivity (positive control)	❑ Meets criteria for waiving requirement
C-QTc Analysis	❑ Pre-specified analysis plan ❑ Exploratory plots ❑ LME model (or alternative) ❑ Goodness of fit ❑ Appropriate ΔΔQTc calculation

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ECG Quality	❑ Data acquisition ❑ Design/Trial Conduct ❑ **Data pooling considerations**
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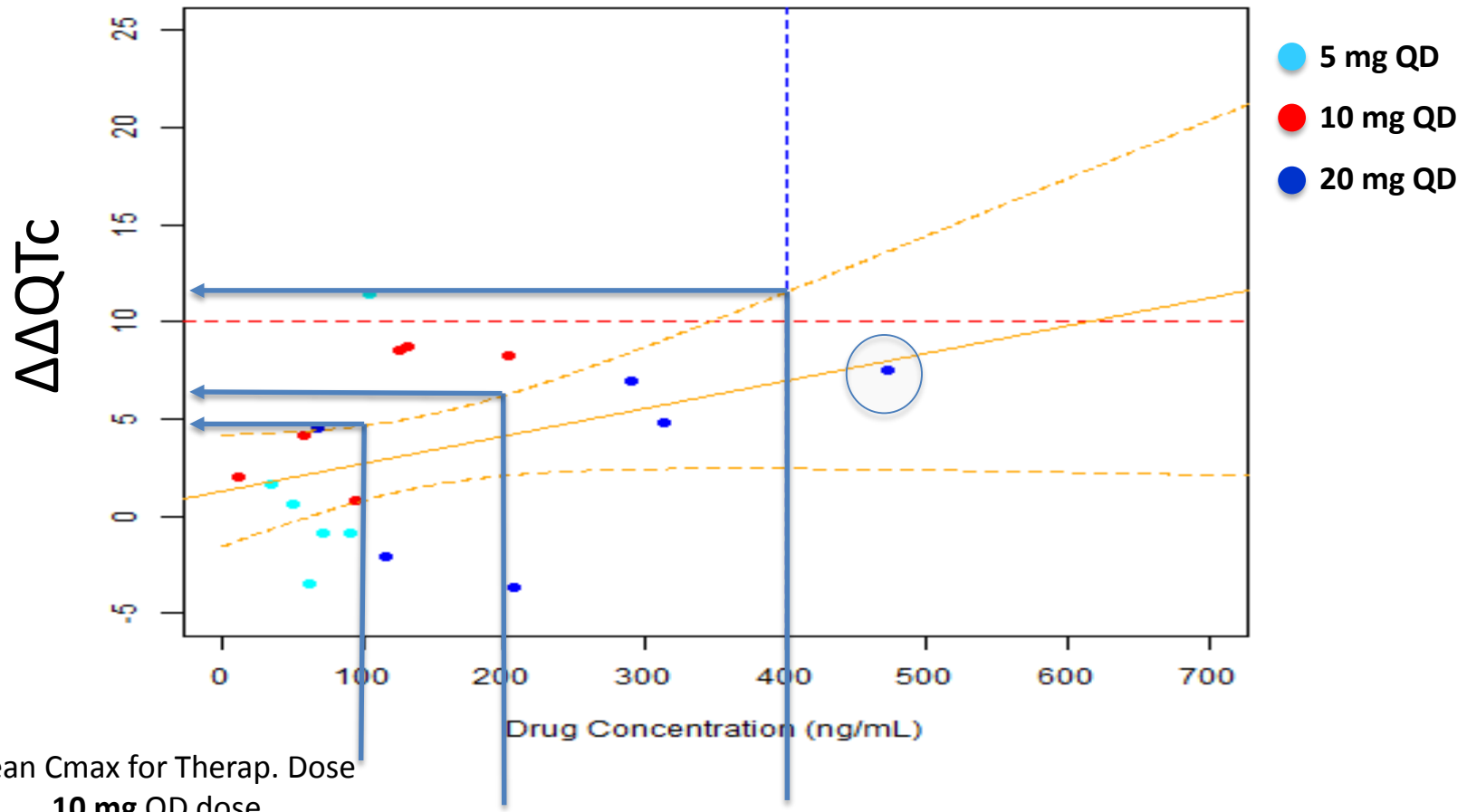
Exposure margin and dosing to satisfy requirement for waiving positive control

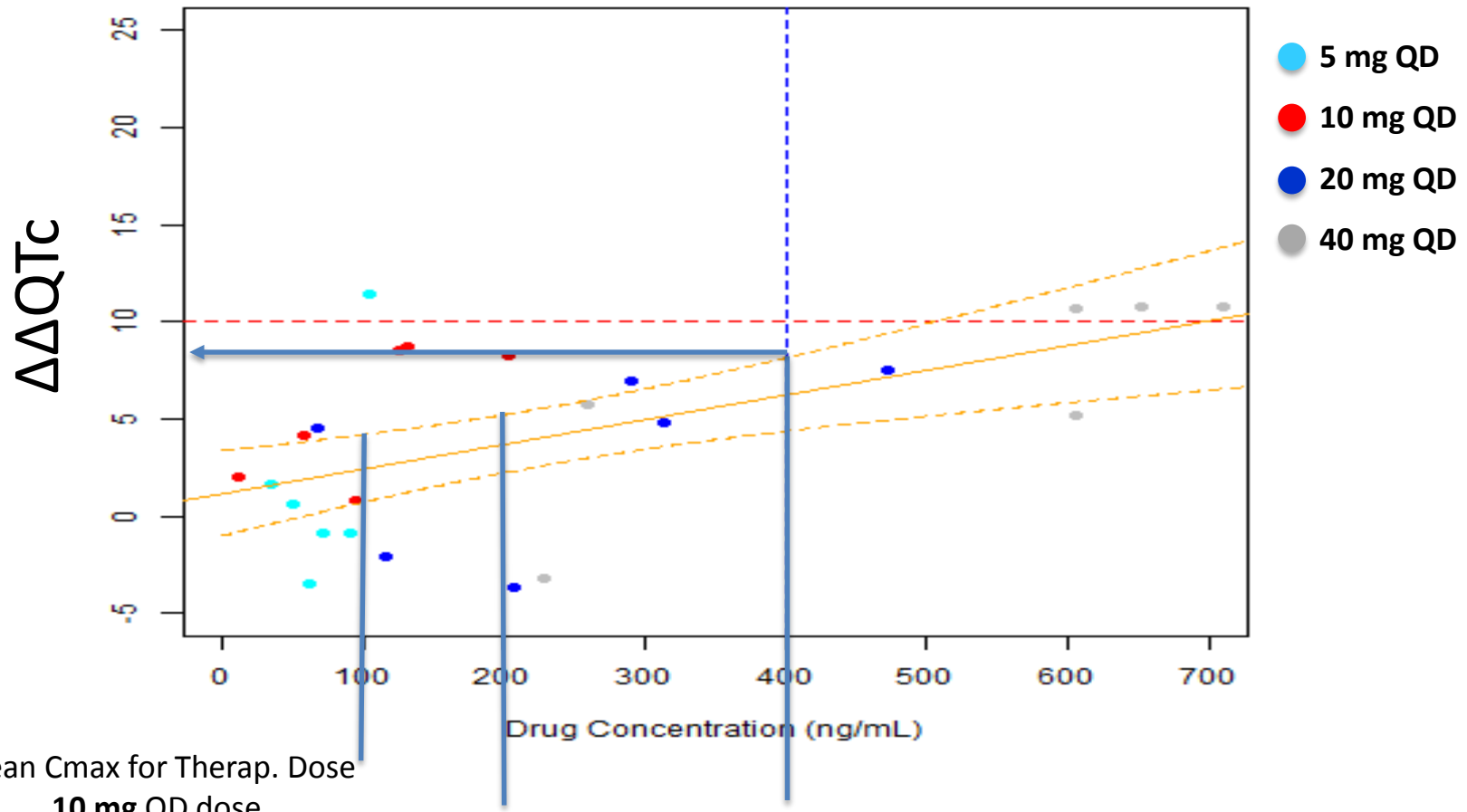


Mean Cmax for Therap. Dose
10 mg QD dose

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



Mean Cmax for Therap. Dose
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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.


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