QTc Exposure-Response Modeling Workshop: What is Required?

Cardiac Safety Research Consortium Think Tank
December 6-7, 2016 | Washington, DC
Agenda

• Session I: Historical overview of the ICH E14 guidelines and the evolution to including C-QTc modeling. Christine Garnett, PharmD
• Session II: The non-modelers version of expectations around the statistical analysis plan, report, and model(s). Steve Riley, PharmD, PhD
• Session III: Regulatory perspective for using C-QTc as the primary analysis: trial design, ECG quality evaluation, evaluation of modeling/simulation results, and decision making. Dhananjay Marathe, PhD
• Session IV: Clinical parameters of interest for concentration-QTc analysis of small studies. Borje Darpo, MD
• Discussion: All speakers plus Lars Johannesen, PhD and Georg Ferber, PhD
Historical overview of the ICH E14 guidelines and the evolution to including C-QTc modeling

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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.
C-QTc Pivotal for Interpretation of TQT Study Results

<table>
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<tr>
<th>Therapeutic dose</th>
<th>4 (UCL=8) ms</th>
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<tr>
<td>Supra-therapeutic dose</td>
<td>15 (UCL = 18) ms</td>
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$\Delta \Delta \text{QTc}$, change from baseline QTc placebo corrected; $C_{\text{max}}$, maximum concentration; ms, milliseconds
Milestones for Using C-QTc Analysis

ICH E14: C-QTc use is “under active investigation”

2005

FDA IRT: C-QTc analysis conducted for all TQT studies

2006

FDA publication on role of C-QTc in regulatory decision-making

2008

FDA agreement of the design of IQ/CSRC Study and impact of positive results

2012

ICH E14 (R2): Role of C-QTc analysis

2014

Results of the IQ/CSRC Study to evaluate C-QTc in Phase 1 study

2015

ICH E14 (R3): Use of C-QTc analysis as primary analysis

2015
Key Changes made by ICH E14(R3)

1. When using a concentration-response analysis as the primary basis for decisions to classify the risk of a drug, the upper bound of the two-sided 90% confidence interval for the QTc effect of a drug treatment as estimated by exposure-response analysis should be <10ms at the highest clinically relevant exposure to conclude that an expanded ECG safety evaluation during later stages of drug development is not needed. (See E14, Section 2.2.4 and Q&A #7)
Key Changes made by ICH E14(R3)

2. Concentration-response data need not come from a dedicated QT study
   – Data can be acquired from first-in-human studies, multiple-ascending dose studies, or other studies. Test for heterogeneity.
   – Robust, high-quality ECG recording and analysis sufficient to support a valid assay for ECG intervals

3. If there are data characterizing the response at a sufficiently high multiple of the clinically relevant exposure a separate positive control would not be necessary.

Study Design
- Key elements
- Pooling data
- Challenging drugs

Model Approach
- Exploratory plots
- Pre-specified model
- Model development
- Model evaluation
- Model predictions

Reporting Results
- Modeling analysis plan
- Modeling report

Examples
- Linear C-QTc model
- Detection of poor model fit
Using Phase 1 Data as Definitive Assessment to Exclude QTc Prolongation

**Nonclinical**
- In vitro and in vivo assays per ICH S7b

**Phase 1**
- High quality ECGs in SAD/MAD studies

**Phase 2**
- Intrinsic and extrinsic factors affecting PK
- Clinical doses

**Phase 3**

**FDA Filing**

**KEY DECISIONS**
- High quality ECGs?
- Adequate exposure margin?
- QTc data adequately characterized using C-QTc analysis?
- Assay sensitivity?

**No**
- Dedicated QT assessment (TQT)
- Include additional QTc at high exposure

**Yes**
- Use Phase 1 data as definitive assessment

*SAD/MAD,* single/multiple ascending dose study; *PK,* pharmacokinetic
ICH E14(R3) Implementation Challenges

• Technical details of C-QTc analysis
• Timing and components of regulatory submission to justify using Phase 1 study data as a substitute for a TQT study
• Exposure margin needed to obviate the positive control in a phase 1 study
• Pooling data from multiple studies
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