EXPOSURE RESPONSE ANALYSIS TO EVALUATE A DRUG'S EFFECT ON ECG PARAMETERS

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Disclosures

- 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.

- The data presented are publicly available
## 10-year Experience with Regulatory Decision-Making

<table>
<thead>
<tr>
<th>Year</th>
<th>Events</th>
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| 2005 | • ICH E14  
      • Analysis of the relationship between drug concentration and QT/QTc interval changes is under active investigation |
| 2008 | • FDA publication on role of C-QTc in regulatory decision-making  
      • Waive TQT for QT prolonging drugs; predict QT effects at doses not studied in TQT study; evaluate assay sensitivity of positive control; and perform dose adjustments in special populations |
| 2014 | • ICH E14 Q&A (R2)  
      • Importance of model pre-specification; provide insight into regimens not studied directly; predict QTc effects of intrinsic & extrinsic factors that affect PK; inform dose selection; clarify ambiguous results |
| 2015 | • ICH E14 Q&A (R3)  
      • Used as an alternative method to the IUT to serve as primary basis for decisions to classify the risk of a drug; data can come from other clinical pharmacology studies than TQT study |
Outline

• C-QTc analysis for regulatory decisions

• ICH E14 Q&A (R3) key changes to design and analysis of QT data

• Implementation of ICH E14 Q&A (R3)
  – Analysis expectations
  – Assay sensitivity
  – Difficult drugs
C-QTc Provides Clinically Relevant Perspectives of TQT Results

- Doses not directly studied
- Specific populations
- Formulation changes
- Ambiguous results using IUT

## Examples where C-QTc Modeling had Impact on Regulatory Decisions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Impact</th>
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<tbody>
<tr>
<td>Anzemet (dolansetron)</td>
<td>• Project the QTc prolongation in elderly and renally impaired patients in the product label.</td>
</tr>
<tr>
<td>Zofran (ondansetron)</td>
<td>• No single intravenous dose of ondansetron to exceed 16 mg due to the risk of QT prolongation.</td>
</tr>
<tr>
<td>Celexa (citalopram)</td>
<td>• Project the QTc prolongation at the 40-mg dose, which was not directly evaluated in the TQT study.</td>
</tr>
<tr>
<td>Caprelsa (vandetanib)</td>
<td>• Characterize QTc prolongation in patients from ECGs obtained in phase 3 trials for the product label.</td>
</tr>
<tr>
<td>Ranexa (ranolazine)</td>
<td>• Characterize QTc prolongation in patients with highly variable pharmacokinetics. Project QTc prolongation in patients with hepatic impairment.</td>
</tr>
<tr>
<td>Edurant (rilpivirine)</td>
<td>• Supported no precautionary labeling statements</td>
</tr>
<tr>
<td>Saphris (asenapine)</td>
<td>• QTc prolongation (2-5 ms) is predicted by CEM and not the mean values reported from the IUT analysis (5-10.5 ms)</td>
</tr>
<tr>
<td>Sertindole</td>
<td>• Project QTc prolongation in patients who are CYP2D6 poor metabolizers for benefit-risk assessment.</td>
</tr>
</tbody>
</table>

Drug information publicly available from FDA website
Good Concordance Between C-QTc and IUT in TQT Studies

**Hypothesis:**

\[ H_0: \beta \leq 0 \]

\[ H_1: \beta > 0 \]

**TQT Studies (N=204)**

<table>
<thead>
<tr>
<th>Slope from C-QTc relationship</th>
<th>( \beta \leq 0 )</th>
<th>( \beta &gt; 0 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>E14 negative (n=165)</td>
<td>86%</td>
<td>14% (Discrepant)</td>
</tr>
<tr>
<td>E14 positive (n=39)</td>
<td>8% (Discrepant)</td>
<td>92%</td>
</tr>
</tbody>
</table>

**Considerations:**

- **Slope alone does not give full assessment of QTc prolongation risk**
- **Drugs can have a positive slope but no clinically meaningful QTc prolongation**

Zhang et al. Therapeutic Innovation & Regulatory Science 2015, Vol. 49(3) 392-397

Linear C-QTc models have adequate sensitivity and specificity

IQ/CSRC Study: Phase 1 data to replace the TQT study

- The goal of the study was to demonstrate that a small dose-escalation study could detect the QT effects of drugs known to prolong the QTc interval around the regulatory threshold.

- The drugs and doses for this study were selected by the FDA with an understanding that successful detection of the drugs would form the basis for the use of C-QTc approach in FIH studies.

Each drug was given to nine subjects (six for placebo) in two dose levels.

Alternative pathway to assess QT effects of new drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Slope, mean ms per ng/mL</th>
<th>LB 90% CI</th>
<th>UB 90% CI</th>
<th>Treatment effect ms</th>
<th>Cmax Day 1, ng/mL</th>
<th>Projected QTc effect mean, ms</th>
<th>LB 90% CI*</th>
<th>UB 90% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive drugs (Day 1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ondansetron</td>
<td>0.033</td>
<td>0.025</td>
<td>0.042</td>
<td>0.2</td>
<td>284</td>
<td>9.7</td>
<td>6.2</td>
<td>12.8</td>
</tr>
<tr>
<td>Quinine</td>
<td>0.004</td>
<td>0.0034</td>
<td>0.0047</td>
<td>-3.0</td>
<td>3623</td>
<td>11.6</td>
<td>6.8</td>
<td>17.1</td>
</tr>
<tr>
<td>Dolasetron</td>
<td>0.021</td>
<td>0.013</td>
<td>0.028</td>
<td>3.1</td>
<td>211</td>
<td>7.4</td>
<td>3.0</td>
<td>11.0</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>0.0065</td>
<td>0.0059</td>
<td>0.0072</td>
<td>2.3</td>
<td>1862</td>
<td>14.5</td>
<td>10.5</td>
<td>17.7</td>
</tr>
<tr>
<td>Dofetilide*</td>
<td>22.2</td>
<td>18.9</td>
<td>25.6</td>
<td>1.1</td>
<td>0.42</td>
<td>10.5</td>
<td>6.3</td>
<td>14.9</td>
</tr>
<tr>
<td>Negative drug (Day 2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levocetirizine</td>
<td>0.0014</td>
<td>-0.0013</td>
<td>0.0041</td>
<td>0.7</td>
<td>1005</td>
<td>2.1</td>
<td>-2.3</td>
<td>6.1</td>
</tr>
</tbody>
</table>

*: Slope from linear model for comparison.

Predicted effect for dofetilide using Emax model: 11.6 ms; 90% CI 7.0 to 16.0

C-QTc Relationship as Primary Analysis

• 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 <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. (See E14, Section 2.2.4 and Q&A #7)

ICH E14 Q&A (R3)
Sources of Data for C-QTc Analysis

• 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
  – 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.
Using Phase 1 Data as Definitive Assessment to Exclude QTc Prolongation

**KEY DECISIONS**

- High quality ECGs?
- Adequate exposure margin?
- QTc data adequately characterized using ER?
- Assay sensitivity?

**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**

- Dedicated QT assessment (TQT)
- Include additional QTc at high exposure
- Use Phase 1 data as definitive assessment
Assay Sensitivity

• 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.
  – C-QTc relationship over large exposure range can substitute for assay sensitivity (*no further evaluation*)
  – Exposure margin is drug dependent, e.g.,
    • 3-5-fold higher then exposures observed in patients with renal impairment or taking metabolic inhibitor
  – Challenging for poorly tolerated drugs and drugs with nonlinear PK
• Moxifloxacin positive control in TQT study
• Non-pharmacological evaluations??
Concentration-QTc Model

- Best practices document is currently being written
- Pre-specified modeling and analysis plan
- Adequate model fit will have:
  - Goodness-of-fit plots show minimal bias with respect to concentrations, studies, time/day, doses
  - Good parameter precision
Potentially Difficult Drugs to Assess Using C-QTc in Phase 1 Study

- Drugs with heart rate effects
  - Inadequate heart rate correction; potential for QT/RR hysteresis

- Drugs with multiple moieties (parent and metabolites) that inhibit hERG channel
  - Single dose studies might not capture effects; C-QTc modeling of multiple variables is challenging; interpretation of model can be difficult.

- Extended-release formulations
  - C-QTc modeling of narrow concentration range can give incorrect results.

- Drugs with PK/PD hysteresis
  - Timing of ECG/PK samples is important for model; PK model needed.
Key Messages

• Concentration-QTc analysis can be used as primary analysis in TQT or Phase 1 studies. This change is based on:
  – 10-years experience in applying these analysis to TQT studies
  – Good concordance between the results of IUT and concentration-QTc analysis even though the two approaches do not test the same hypothesis
  – Simulations studies (internal and external) evaluating the statistical properties of concentration-QTc analysis
  – Positive IQ/CSRC study results

• C-QTc analysis of Phase 1 data can substitute for a TQT study. Important considerations include ECG quality, exposure margin, C-QTc model and assay sensitivity.
• C-QTc relationship over large exposure range can substitute for assay sensitivity (no further evaluation)
• Not all drugs are good candidates for Phase 1 paradigm. Some drugs will require special considerations to the study design and/or analysis.