FDA's Analysis and Interpretation of the IQ/CSRC Clinical Study

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Disclaimer: My remarks today do not necessarily reflect the official views of the FDA
Outline

• FDA’s review of the IQ/CSRC study
• Comparison between C-QT and Central Tendency Test (IUT)
• Concerns regarding IQ/CSRC project
• Current regulatory application and moving forward
• Summary
Review of the IQ/CSRC Study

Independently confirmed the study results

<table>
<thead>
<tr>
<th>Treatment</th>
<th>slope Estimate</th>
<th>LB</th>
<th>UB</th>
<th>Day1</th>
<th>Day2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cmax</td>
<td>Cmax</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ΔΔQTc M</td>
<td>ΔΔQTc LB</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>0.0364</td>
<td>0.025</td>
<td>0.0479</td>
<td>284</td>
<td>10.1</td>
</tr>
<tr>
<td>Quinine</td>
<td>0.0041</td>
<td>0.0031</td>
<td>0.005</td>
<td>4468</td>
<td>15</td>
</tr>
<tr>
<td>Dolasetron</td>
<td>0.0203</td>
<td>0.0083</td>
<td>0.0323</td>
<td>211</td>
<td>7.3</td>
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<tr>
<td>Moxifloxacin</td>
<td>0.0063</td>
<td>0.0055</td>
<td>0.0071</td>
<td>1862</td>
<td>14.5</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>19.6</td>
<td>15.2</td>
<td>24</td>
<td>0.42</td>
<td>10.5</td>
</tr>
<tr>
<td>Levocetirizine</td>
<td>0.0007</td>
<td>-0.0027</td>
<td>0.0042</td>
<td>157</td>
<td>0.8</td>
</tr>
</tbody>
</table>

C-QT is the primary

CSRC/IQ
Outline

• FDA’s review of the IQ/CSRC study
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Generally Good Concordance Between C-QTc and E14 in TQT Studies

Moxifloxacin in 5 TQT studies

13 different positive TQT studies
Two Analysis Methods

Primary method (E14) (intersection-union test)
- Easy to implement
- Fewer model assumptions
- Focus on single time point:
  - Sponsor might be punished for adding a time point

Exposure-response method (C-QT modeling)
- Concentration data used
- Used all time points, can reduce sample size
- Robust to outliers
- Applicable for alternative designs
- More model assumptions
- Intensive analysis
- Result interpretation
## Positive Bias for E14 Method

<table>
<thead>
<tr>
<th>Profile of Means</th>
<th>$\rho$</th>
<th>N=20</th>
<th>N=40</th>
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</thead>
<tbody>
<tr>
<td>$(0, 0, 0, 0, 0, 0, 0, 0)$</td>
<td>0</td>
<td>4.50</td>
<td>3.18</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>3.18</td>
<td>2.25</td>
</tr>
<tr>
<td>$(5, 5, 5, 5, 5, 5, 5, 5)$</td>
<td>0</td>
<td>4.50</td>
<td>3.18</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>3.18</td>
<td>2.25</td>
</tr>
<tr>
<td>$(0, 0, 5, 5, 5, 5, 0, 0)$</td>
<td>0</td>
<td>3.33</td>
<td>2.31</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>2.31</td>
<td>1.63</td>
</tr>
<tr>
<td>$(1, 2, 3, 4, 5, 4, 3, 2)$</td>
<td>0</td>
<td>2.87</td>
<td>1.69</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>1.69</td>
<td>0.93</td>
</tr>
<tr>
<td>$(0, 0, 0, 5, 5, 0, 0, 0)$</td>
<td>0</td>
<td>2.16</td>
<td>1.34</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>1.34</td>
<td>0.90</td>
</tr>
<tr>
<td>$(0, 0, 0, 0, 5, 0, 0, 0)$</td>
<td>0</td>
<td>1.16</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>0.35</td>
<td>0.05</td>
</tr>
</tbody>
</table>

**Note:** Power = $P(90\% UB < 10)$, sd=10 ms.

**C-QTc Analysis Seems Less Biased**

\[
T_{\text{max}} = 1.5 \text{ h} \\
\text{ddQTc}_{\text{max}} = 10 \text{ ms}
\]

- **PK-ddQTc** (linear, no delay)
  - Between and within subject variability
- **Sampling time** (n=11)
  - 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h

**SD=10 ms**

- **N=60**

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**Graphs:**

- **Time(h)**
  - \(Cp(\text{mg/L})\)
  - \(ddQTc\)
  - \(T_{\text{max}} = 1.5 \text{ h}\)
  - \(ddQTc_{\text{max}} = 10 \text{ ms}\)

- **Sampling time (n=11)**
  - 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h
C-QTc Analysis Can Provide Optimal Estimation with Smaller Sample Size

Use all time points

Power (%) (N=10,000)

3ms Scenario

5ms Scenario

Number of Subjects

Power (%) (N=10,000)

Small Drug Effect (5ms) Crossover Model

Small Drug Effect (3ms) Crossover Model

Power: % Replicates where UCL <10 ms
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Concerns Brought Up

1. Limited number of drugs tested
2. Small sample size: large impact from outliers
3. Need for placebo control
4. Modeling
   - Time/Treatment effect and other covariates?
5. C-QT data issue: nonlinearity and hysteresis
6. No positive control for assay sensitivity
7. Interpretation: clinically relevant exposure
8. Decision criteria and timing
Pfizer’s Retrospective Study

Time-specific intercept, variability from circadian rhythm

Riley S.P. et al., ACoP 2013
Subsampling from Archived TQT Studies

- Repeat subsampling from 15 positive and 10 negative studies to mimic an early phase study with 6 or 9 subjects on drug and 4 or 6 on placebo
- Results are supportive:
  - False positive rates are low (depends on QT effect size)
  - For drugs with a QTc effect of 12 ms or above according to TQTs, the false negative rates are below 5%
  - **Grey zone:** drugs with a QTc effect of around 7 to 12 ms according to TQTs => ? *clinically relevant QT prolongation*
Grey Zone: Positive TQT with Marginal Signal
(Is it really ‘positive’ at the relevant dose?)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Central tendency test from TQT</th>
<th>Subsampling with 9 subjects on drug and 6 on placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time (min)</td>
<td>∆∆ QTcF (ms)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Negative rate (UB &lt; 10 ms)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Positive rate (UB &gt; 10 ms &amp; slope significantly positive)</td>
</tr>
<tr>
<td>0.1</td>
<td>180</td>
<td>2.6 (-1.4, 6.6)</td>
</tr>
<tr>
<td>0.3 (relevant)</td>
<td>5</td>
<td>7.4 (3.9, 11.0)</td>
</tr>
<tr>
<td>0.5 (pseudo-relevant)</td>
<td>5</td>
<td>8.4 (4.8, 11.9)</td>
</tr>
</tbody>
</table>

Concentration vs. ∆∆ QTcF (ms) graphs are shown for different doses, with concentration units in parts per million (ppm).
False Negative Rate Based on Simulation

Based on UB < 10 ms when true drug effect is 10 ms at Cmax
Placebo Time-Course Should be Considered in the ΔQTc Modeling

Placebo Time-Course of ΔQTcF

Different Answers?
Ignoring Hysteresis May Increase FNR

ΔQTc3 Model

Slope

True Slope = 0.73

% False Negative

Slope Estimate

Time Delay (minutes)

Time Delay (minutes)
Assay Sensitivity in QT-IRT Database

Total 310 TQT studies (2005 – Nov, 2014)

• 13 (4.2%) had an issue of assay sensitivity:
  • Grade 1 (+): 3 (missing the rising phase)
  • Grade 2 (++): 4 (no expected time course)
  • Grade 3 (+++): 3 (LB < 5 ms)
  • Grade 4 (++++): 3 (Point estimates around 5 ms & flat time course)

Low failure rates in TQT do NOT mean a positive control is not important.
Assay Sensitivity for Early Assessment

• Based on the assay sensitivity survey and the resampling results:
  – We have the capability to ensure the operation sensitivity if we care.
  – Population sensitivity is not a common issue.

• In general, excess noise results in inconclusive or false ‘positive’ findings

• Alternative ways for operation sensitivity should be in place (e.g., review of QT-RR relationships, data throughout the nominal time window, QT-RR hysteresis)
Concerns & Potential Solutions

1. Limited number of drugs tested
2. Small sample size: **effect size seems more important**
3. Need for placebo control: **Yes, at this moment**
4. Modeling - **Time/Treatment** effect
5. C-QT data issue: nonlinearity and **hysteresis**
6. No positive control for assay sensitivity: **Alternative ways for ECG quality**
7. Interpretation: **clinically relevant exposure**
8. Decision criteria and timing: **Continuous Assessment**
   - **Dose range**
   - **Profile of the concentration-QTc relationship**
   - **Integrated preclinical knowledge**
   - **Two-stage review: Early phase & Pre-NDA/NDA**
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Already Happening in Waiving TQT

• Significant QT prolongation and a slope
• Significant negative slope that demonstrate QT shortening
• No effect at supratherapeutic exposure multiple times higher than therapeutic exposure with reliable placebo control and ECG quality
Criteria for Negative QT assessment?

The upper bound of the 2-sided 90% confidence interval (CI) of the predicted placebo-corrected ΔQTcF is below 10 ms at the highest clinically relevant plasma concentrations of the drug:

- Generally unknown at the early phase assessment
- Should target ‘worst PK scenario’ as in a TQT
- Should be covered by the early phase ECG assessment

• Interpretation & Decision: Continuous Assessment
  - Dose range
  - Profile of the concentration-QTc relationship
  - Integrated preclinical knowledge
  - Multiple-stage review: Early phase – EOP2 – Pre-NDA/NDA
Summary

• FDA independently confirmed the results of IQ-CSRC prospective study
• C-QT uses all time points and is less biased. Therefore, sample size can be reduced.
• Utility of C-QTc relationship from early clinical studies for the QT assessment is promising
• Some concerns regarding the details of trial design, modeling and validation, criteria for industry/regulatory decision, regulatory review standard and procedures need further clarification
Acknowledgment

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• Kevin Krudys
• Colleagues in the Division of Pharmacometrics
Thank You!

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