ECG ASSESSMENT IN EARLY CLINICAL TRIALS
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THE SCENE HAS CHANGED

The ICH E14 Q&A document was revised and endorsed in all regions on December 10, 2015

- The revision of E14 is a consequence of activities that have been ongoing for several years
- Extensive experience has been gained by the FDA from applying exposure response (ER) analysis on data from TQT studies and patient data
- Enabled through the centralized (IRT) review of QT studies
- The IQ-CSRC prospective study with the objective to validate the approach of applying exposure response analysis on data from standard clinical pharmacology studies
TQT STUDY EXAMPLES: ALBIGLUTIDE

85 subjects, 4 treatment, parallel with nested XO study, 39 days of dosing

Precision: Mean SD of ΔQTcl = 6.1 ms

ER slope: -0.0003 ms per ng/mL
(90% CI: -0.0004 to -0.0001)
SAD FIH study with 8 dose groups (6+2)
- Linear model with an intercept captures the data nicely
- Variability in highest dose group handled
- QT effect ($\Delta \Delta QTcF > 10$ msec can be excluded within observed PK range.
EXPOSURE-RESPONSE ANALYSIS: MAD STUDY

Linear model with intercept:

- Intercept: 3.9 ms (90% CI: 1.0 to 6.8 ms)
- Slope 0.016 ms per ng/ml (0.011 to 0.021 ms)
OBJECTIVES OF THE IQ-CSRC PROSPECTIVE STUDY

The objective of the initiative was to evaluate whether QT assessment in early phase clinical studies can replace or serve as an alternative the TQT study.

Therefore, a prospective clinical study was conducted in healthy subjects with design similarities with a standard FIH study.

The underlying idea was to apply exposure response (ER) analysis on robust ECG data from early phase clinical studies without change in standard design.

Collaborative project between the IQ-consortium, CSRC and FDA.

Design of study, selection of drugs and doses and statistical analysis discussed and agreed upon with FDA.
IQ-CSRC STUDY DESIGN

**Patients and treatment**
- 20 male and female healthy subjects
- Three treatment periods
- Nine subjects were to receive each drug, 6 on placebo
- Target to have at least 6 on active and 5 on placebo

**Study drugs and dosing**
- Study drugs: Five ‘QT-positive’ drugs, well characterized from previous studies
- One QT negative, Placebo
- Dosing on 2 days:
  - Day 1: Dose intended to give app. 10 to 12 ms QTc effect.
  - Day 2: Dose intended to give app. 15 to 20 ms effect

**Methodologies**
- ECG methodology as in TQT studies (iCardiac’s High Precision QT technique)
- Primary analysis: Based on exposure response
The positive slope is statistically significant. QTc effect above 10 ms at the Cmax of Day 1 cannot be excluded.
HYDRODOLASETRON EXPOSURE-RESPONSE ANALYSIS

<table>
<thead>
<tr>
<th>Slope, mean ms per ng/mL</th>
<th>LB 90% CI</th>
<th>UB 90% CI</th>
<th>Treatment effect (intercept) 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>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.021</td>
<td>0.014*</td>
<td>0.029</td>
<td>3.2</td>
<td>211</td>
<td>7.7</td>
<td>3.7</td>
<td>11.6**</td>
<td>Met</td>
</tr>
</tbody>
</table>
LEVOCETIRIZINE EXPOSURE-RESPONSE ANALYSIS

* QTc effect above 10 ms can be excluded at the geometric mean Cmax on Day 2.
## RESULTS: PRIMARY ANALYSIS

<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><strong>Positive drugs (Day 1)</strong></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><strong>0.025</strong></td>
<td>0.042</td>
<td>0.2</td>
<td>284</td>
<td>9.7</td>
<td>6.2</td>
<td><strong>12.8</strong></td>
</tr>
<tr>
<td>Quinine</td>
<td>0.004</td>
<td><strong>0.0034</strong></td>
<td>0.0047</td>
<td>-3.0</td>
<td>3623</td>
<td>11.6</td>
<td>6.8</td>
<td><strong>17.1</strong></td>
</tr>
<tr>
<td>Dolasetron</td>
<td>0.021</td>
<td><strong>0.013</strong></td>
<td>0.028</td>
<td>3.1</td>
<td>211</td>
<td>7.4</td>
<td>3.0</td>
<td><strong>11.0</strong></td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>0.0065</td>
<td><strong>0.0059</strong></td>
<td>0.0072</td>
<td>2.3</td>
<td>1862</td>
<td>14.5</td>
<td>10.5</td>
<td><strong>17.7</strong></td>
</tr>
<tr>
<td>Dofetilide*</td>
<td>22.2</td>
<td><strong>18.9</strong></td>
<td>25.6</td>
<td>1.1</td>
<td>0.42</td>
<td>10.5</td>
<td>6.3</td>
<td><strong>14.9</strong></td>
</tr>
<tr>
<td><strong>Negative drug (Day 2)</strong></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><strong>-0.0013</strong></td>
<td><strong>0.0041</strong></td>
<td>0.7</td>
<td>1005</td>
<td>2.1</td>
<td>-2.3</td>
<td><strong>6.1</strong></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
Question 5 (revised)
Important Considerations

› If there are data characterizing the response at a sufficiently high multiple of the clinically relevant exposure (see E14 Section 2.2.2), a separate positive control would not be necessary.

Decision-making

› Both the intersection-union test and the concentration-response analysis can estimate the maximum effect of a drug treatment on the QTc interval, ....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).
DOES PRECISION OF THE QT MEASUREMENT MATTER?

› Not much in the case of a large effect.


ER slope: 0.0163 ms per ng/mL
(90% CI: 0.0150 to 0.0175)
Criteria for negative QT assessment:
The upper bound of the 2-sided 90% confidence interval (CI) of the predicted placebo-adjusted ΔQTcF is below 10 ms at clinically relevant plasma levels of the drug.

EXPERT PRECISION QT

Incoming Data

Minimize for periods of HR variability, noise and signal artifacts within timepoints

10 ECGs

Manual Adjudication

Adjudicate all “problem” beats (pass-fail), no re-measurement
In 3 of 10 ECGs manually assess all parameters, including for QC
Final QC by cardiologist

Flag for review all low-confidence beats
Use measurements from high-confidence beats

Median of 100-120 QT-RR values/timepoint

ERT EPQT Process

02743918 6825709269 51753896014 4782309126 267542471

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THE ROLE OF PRECISION FOR EARLY QT ASSESSMENT

- Sample size to exclude a QTc effect > 10 ms using ER analysis in SAD Study

<table>
<thead>
<tr>
<th>Assumed underlying effect</th>
<th>SD of ΔQTcF</th>
<th>Number/cohort needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 ms</td>
<td>6 ms</td>
<td>9</td>
</tr>
<tr>
<td>3 ms</td>
<td>10 ms</td>
<td>21</td>
</tr>
</tbody>
</table>

- Early QT assessment with conventional semi-auto analysis will be much less likely to exclude a small effect with a negative drug.
LEMBOREXANT – CASE STUDY

- FIH MAD study with 6 cohorts (6+2), dosing for 14 days
- Full baseline on Day -1
- Targeted indication: Insomnia
- Drug dosed in evening

LEMBOREXANT – CASE STUDY (3)

- Data pooled with Japanese 14-day MAD bridging study
- 4 dose cohorts (6+2) with 2.5, 10 and 25 mg OD to Japanese subjects and 10 mg to White
- Full baseline on Day -1; same ECG technique
- Race tested as fixed effect in model; not significant, dropped from model

QT ASSESSMENT IN SAD OR MAD?

SAD:
› Achieved plasma levels are often higher in SAD as compared to MAD studies
› Short duration between baseline and ECG day
› Sufficient number of placebo subjects (8 or more)

MAD:
› With substantial accumulation of parent of major metabolites
› When dose titration is needed to reach high levels
THE REMAINING ROLE OF THE TQT STUDY

› The sponsor’s choice.
  ▪ Some sponsors may choose to conduct a TQT study for drugs that make it beyond Phase II only.
› When a sufficient exposure margin cannot be (or were not) achieved in healthy subjects.
  ▪ May call for the use of a positive control.
› To confirm or more precisely characterize the QT effect for a drug with a ‘non-negative’ Early QT assessment.
  ▪ Can be done in a TQT study or in patients.
TQT study using ER analysis as primary statistical method

- 4-way crossover - drug, placebo, and moxifloxacin
- n = 24
- Predicted effect of moxifloxacin @ 1900 ng/mL: 15.0 ms (90% CI: 12.9 to 17.1)
CONCLUSIONS

- Early QT assessment is now an accepted way to confidently exclude that a new drug has a clinically relevant effect on the QT interval.
- The TQT study will not completely disappear as a viable option in select cases.
- Overall, QT assessment will be done more effectively:
  - Potential ECG effects of an NCE will be known earlier.
  - ECG assessment can be performed as part of routine SAD/MAD studies or in small tailored studies.
# Variability in Recent Crossover Studies by iCardiac*

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Endpoint</th>
<th>SD of ΔQTc (ms)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TQT, 3-way XO</td>
<td>QTcF</td>
<td><strong>6.0</strong></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>TQT, 3-way XO</td>
<td>QTcF</td>
<td><strong>5.7</strong></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>TQT, 3-way XO</td>
<td>QTcF</td>
<td><strong>6.1</strong></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>TQT, 3-way XO</td>
<td>QTcF</td>
<td><strong>6.9</strong></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>TQT, 4-way XO</td>
<td>QTcF</td>
<td><strong>5.8</strong></td>
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<tr>
<td>6</td>
<td>TQT, 4-way XO</td>
<td>QTcI</td>
<td><strong>6.0</strong></td>
<td>HR effect</td>
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<tr>
<td>7</td>
<td>TQT, 4-way XO</td>
<td>QTcF</td>
<td><strong>5.6</strong></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>TQT, 4-way XO</td>
<td>QTcF</td>
<td><strong>5.5</strong></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>TQT, 4-way XO</td>
<td>QTcF</td>
<td><strong>5.4</strong></td>
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<tr>
<td>10</td>
<td>TQT, 4-way XO</td>
<td>QTcF</td>
<td><strong>5.3</strong></td>
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<tr>
<td>11</td>
<td>TQT, 5-way XO</td>
<td>QTcF</td>
<td><strong>6.1</strong></td>
<td>Tested vs. QTcI</td>
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<tr>
<td>12</td>
<td>TQT, 5-way XO</td>
<td>QTcI</td>
<td><strong>6.4</strong></td>
<td>HR effect</td>
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<tr>
<td>13</td>
<td>TQT, 5-way</td>
<td>QTcI</td>
<td><strong>6.5</strong></td>
<td>Tested vs. QTcF</td>
</tr>
</tbody>
</table>

*iCardiac was acquired by ERT in December 2017*