A Proposal to Review The TQT Study

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Early Phase QT Data to Replace the TQT Study

- Exposure Response (ER) analysis provides enhanced power to exclude a QT effect of regulatory concern with lower sample size, in Phase 1 studies.
- This promotes the use of routine Phase 1 studies, augmented with intensive ECG and PK sampling, to replace the TQT study for assessing cardiac safety.
- Intensive QT (IQT) studies are increasingly accepted by regulators in lieu of the ICH-E14 mandated TQT studies, potentially saving cost and resources.
- However, there are no published guidelines or recommendations for the design and analysis of IQT studies, including the ER modelling approach.
- Likewise, it is not yet clear whether a single IQT study, similar to the TQT study, will satisfy all regulatory authorities for all indications and circumstances.
- It is also to be seen what will be the impact of conducting routine SAD/MAD IQT studies in ‘non-specialized’ Phase 1 units on the QT data and outcome.
- TQT studies may still be required if a routine SAD/MAD design may not be suitable, based on drug characteristics (e.g., long T1/2, delayed effects, etc.).
IQ/CSRC IQT Study: Model Limitations

• Study drugs were selected based on their pronounced QTc effect.
• Drugs with long half lives, active metabolites, autonomic and HR effects were excluded.
• Consequently, the study could not answer the question of how well will the model perform in drugs with borderline QT effect.
• The model assumes that false negative and false positive rates would be minimal, but, the (IQ/CSRC) study was not designed to test this.
• Concerns regarding period & sequence (ie, un-blinding) effects in ascending dose studies remain
• Also, ER Models are operator dependent and there’s currently no universally established model
Potential IQT Drug Exclusion Check List

• Drugs with long T1/2
• Drugs with delayed effects
• Drugs requiring up-titration
• Drugs with active metabolites
• Drugs with known autonomic effects
• Drugs associated with QT:RR hysteresis

All of the above (and other) drug characteristics may suggest a different study design or a TQT study.
# The Case of Pitolisant TQT and IQT (SAD) Studies

## TQT Study (P09-11) 25 Males

<table>
<thead>
<tr>
<th>Slope*</th>
<th>90 % CI</th>
<th>Dose</th>
<th>Concentration</th>
<th>ΔΔQTcF (ms)</th>
<th>90% CI</th>
<th>Width of 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.027</td>
<td>0.013; 0.040</td>
<td>40 mg</td>
<td>46 ng/mL</td>
<td>1.67</td>
<td>0.74; 3.30</td>
<td>2.56</td>
</tr>
<tr>
<td></td>
<td></td>
<td>120 mg</td>
<td>156 ng/mL</td>
<td>4.97</td>
<td>3.42; 8.19</td>
<td>4.77</td>
</tr>
</tbody>
</table>

*The female population slope in the TQT study was 0.054 ms/ng/mL

## SAD Study (P14-05) 18 Males

<table>
<thead>
<tr>
<th>Slope</th>
<th>90 % CI</th>
<th>Dose</th>
<th>Concentration</th>
<th>ΔΔQTcF (ms)</th>
<th>90% CI</th>
<th>Width of 90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.031</td>
<td>0.021; 0.041</td>
<td>160 mg</td>
<td>172 ng/mL</td>
<td>5.9</td>
<td>1.90; 9.98</td>
<td>8.08</td>
</tr>
<tr>
<td></td>
<td></td>
<td>200 mg</td>
<td>223 ng/mL</td>
<td>7.5</td>
<td>3.42; 11.90</td>
<td>8.48</td>
</tr>
<tr>
<td></td>
<td></td>
<td>240 mg</td>
<td>279 ng/mL</td>
<td>9.23</td>
<td>4.68; 14.4</td>
<td>9.72</td>
</tr>
</tbody>
</table>

ICH-E14 Q&A R3, released December 2015, states:

“Concentration-response analysis, in which all available data across all doses are used to characterize the potential for a drug to influence QTc, can serve as an alternative to the by-time point analysis or intersection-union test as the primary basis for decisions to classify the risk of a drug.”
My Proposal

• Since:
  – ER Modelling is a more statistically robust method than the E14 IUT
  – Regulators appear amendable to relinquish positive control for IQT studies

• Consider:
  – Replacing the IUT approach with ERM as the TQT primary analysis, and
  – Relinquishing the requirement for positive control in TQT studies
  – This would make TQT studies more cost effective, therefore, possibly reducing the need to compromise on study design when SAD/MAD IQT studies may not be the best option for assessing cardiac safety (based on drug property considerations, as discussed earlier)
Back-up Slides
Rate of false negatives based on simulated small studies

Panel A: rate of false negatives with drug data
Panel B: Rate of false positives using placebo data and time-matched PK data (no QT effect)

- 15,000 small studies with 6 – 18 subjects on active and 6 on placebo simulated on TQT study data
- Rate of a false negative results is around 5% with 6 on active when a drug like moxifloxacin is tested.
- With a sample size of 9 on drug and 6 on placebo, the fraction of negative studies is above 90% for 3 of the studies and above 85% for the remaining 2.
- The fraction of non-negative studies (1–fraction of negatives) in the no-effect scenario corresponds to the rate of false positives.

TQT vs IQT Studies

- **TQT and IQT studies may produce somewhat different results for same IP**
  - *TQT studies may produce a slightly higher ddQTc effect*
- **QT study design (XO/PG) may account for some variations in the outcome**
  - Parallel group studies may produce steeper C:QT slopes (higher QTc effect)
- **Gender differences are major contributors for QT differences**
  - Female subjects exhibit a more pronounced QTc effect
  - Many routine SAD/MAD studies exclude female subjects
- **Smaller sample size may lead to higher variability (wider CIs)**
  - IQT may produce up to 40% higher variability compared with TQT study
Do We Need Positive Controls in IQT Studies?

• Pros:
  – Better scientific rigor
  – Assurance against false negative
  – Regulatory and clinical confidence

• Cons:
  – Adds extra logistics and increases cost of clinical research
  – Does not contribute directly to the clinical investigation itself
  – Is not the most cost effective method for demo assay sensitivity
This study was presented to the FDA and EMA and was accepted by both agencies as adequate for assessment of the pro-arrhythmic risk of GS-4997.
Pitolisant TQT and IQT (SAD) Studies: Comparison of the Moxi Effects

- **Mean Maximum ΔΔQTcF values**
  - SAD study: 10.7 (6.5; 14.9) ms
  - TQT study: 9.09 (6.20; 11.98) ms

- **Time-averaged mean ΔΔQTcF values of**
  - SAD study: 7.03 ms
  - TQT study: 7.60 ms

- **90 % CI mean widths for ΔΔQTcF 8.40 vs. 5.99 ms (time averaged)**
  - As expected from the differences in sample sizes width of 90 % CI in the SAD study greater by 40 % compared with the TQT study.
  - The greater width of CI for the slopes in early phase clinical studies may adversely affect the accuracy of interpretation of QT liability of the IP.