A HESI Consortium Approach to Assess the Human Predictive Value of Non-Clinical Repolarization Assays

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HESI Pro-Arrhythmia
Disclaimer

• The views expressed are those of the presenter and do not necessarily reflect those of the FDA or other organizations
# Major Contributors

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Project Objectives

Stage 1. To assess the concordance between non-clinical repolarization assays and clinical measures of QT interval prolongation (retrospective analysis)

Stage 2. To investigate the mechanisms for any discrepancy identified between non-clinical and clinical results and to determine viable and successful alternative approaches to identify these compounds.

Stage 3. To assess the proarrhythmic potential of such compounds.
HESI ProA Stage 1 Goals

- Quantitative integrated risk assessment (concentration-response relationship) based on non-clinical and clinical repolarization assays.
- Establish the sensitivity, specificity and overall predictivity of each assay alone and in combination with respect to the clinical outcome.
- Identify compounds for which there is a lack of concordance between non-clinical and clinical assays.
Stage I Strategy

- Generate datasets containing non-clinical and clinical QT information.
- Public-private collaborative data collection.
- 4 approaches
  1. Data submitted to FDA (71 drugs).
  2. Additional data input from Pharma companies.
  3. Use of data from previous initiative (Hanson et al) (12 drugs).
  4. Data available from the literature (17 drugs).
FDA database

- FDA database designed to capture non-clinical and clinical QT data from submissions.
  - FDA personnel populating database

- Data entered
  - New Drug Applications (NDAs) and Investigational New Drug Applications (INDs) with a Thorough clinical QT (TQT) study
  - A TQT is a dedicated clinical study powered to detect a small QTc signal, upper bound >10 ms (ICH E14)
## FDA Database Contents

<table>
<thead>
<tr>
<th></th>
<th>TQT</th>
<th>hERG</th>
<th>APD</th>
<th>Non-Clinical ECG</th>
</tr>
</thead>
<tbody>
<tr>
<td># of drugs</td>
<td>71</td>
<td>64*</td>
<td>43*</td>
<td>49*</td>
</tr>
<tr>
<td>% Post-ICH57B</td>
<td>100%</td>
<td>34%</td>
<td>14%</td>
<td>18%</td>
</tr>
<tr>
<td></td>
<td>(n=22)</td>
<td>(n=6)</td>
<td>(n=9)</td>
<td></td>
</tr>
</tbody>
</table>

*The study dates for some non-clinical studies (10 hERG, 5 APD and 3 in vivo ECG study) are not available.

- Drugs with TQT studies: 71
- Drugs with all 3 non-clinical studies: 30
- Drugs with hERG and ECG studies: 43
- Clinical: 20 positive and 51 negative TQT studies
Brief Description of Nonclinical Studies

- **hERG**
  - whole voltage clamp, mammalian cell lines, GLP
- **APD**
  - APD90 at 1 Hz
  - Purkinje fibers: dog, rabbit, sheep
- **QTc**
  - Dog, primate
  - N = 4 (range, 2-16)
  - Anesthetized and conscious telemetry
  - Ascending and parallel dose

**Notes**
- Free drug concentrations tested were below TQT concentration for several drugs.
- Assay sensitivity (what effect size can be captured) was not addressed.
- Limited use of positive controls.
Study Metrics

• hERG, IC50
• APD, statistically significant
• QTc in vivo, statistically significant
  – Sponsor conclusions were utilized
• TQT, upper bound > 10 ms
  – FDA conclusions were utilized
Margins tested (first 22 drugs)
Several Drugs Tested Below Clinical (TQT) Concentration

hERG

APD

In vivo

ECG
Graphical template design

Results from each assay plotted on same y-axis

X-axis = log concentration (no values)

Ring around data point indicates significant effect as assigned by Sponsor

Clinical data - ring around data point indicates effect exceeding 10ms could not be excluded (based on E14)

APD = % from control; hRPT QTc = % QTc from baseline @ max effect (not Cmax); human QTc = delta QTcF
Concordance grid – Heat Map

TQT reference concentration (lowest positive conc. or highest non-positive conc.)

Margins below reference point

Margins above reference point

<table>
<thead>
<tr>
<th></th>
<th>F O L D B E L O W</th>
<th>REF</th>
<th>F O L D A B O V E</th>
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<tbody>
<tr>
<td></td>
<td>≤ 10000</td>
<td>≤ 3000</td>
<td>≤ 1000</td>
</tr>
<tr>
<td>TQT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>hERG</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>APD</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>QTc</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
</tbody>
</table>

NT = not tested at margin
+ = sig increase or IC50 at margin
- = no sig increase or IC50 at margin
(+) = not tested at this margin but significant effect at lower margins

NT - Assay Not Tested at this margin
+ = Significant increase or IC50 at this margin
- = No significant increase or IC50 at this margin
(+) = Not tested at this margin but significant effect at lower margin

concordant with TQT result
not concordant with TQT result
Concordant Positive Example

APD = deltaAPD90 from control; in vivo QTc = delta(delta)QTc @ max effect; human QTc = deltaQTcF

<table>
<thead>
<tr>
<th></th>
<th>≤10000</th>
<th>≤3000</th>
<th>≤1000</th>
<th>≤300</th>
<th>≤100</th>
<th>≤30</th>
<th>≤10</th>
<th>≤3</th>
<th>≤30</th>
<th>≤100</th>
<th>≤300</th>
<th>≤1000</th>
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<td>TQT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
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<td>NT</td>
<td>NT</td>
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<td>NT</td>
</tr>
<tr>
<td>hERG</td>
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<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>-</td>
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<tr>
<td>QTc</td>
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<td>NT</td>
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<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
</tbody>
</table>

double/open symbol = significant change

Free Concentration

% hERG inhibition; change APD or QT (% or msec)

hERG #1
hERG #2
in vitro APD
in vivo QTc
human QTc
TQT reference for concordance
Exposure +/- 3x TQT reference
Exposure +/- 10x TQT reference
Exposure +/- 30x TQT reference
Exposure +/- 100x TQT reference
hERG IC50
Concordant Negative Example

% hERG inhibition; change APD or QT (% or msec)

Double/open symbol = significant change
APD = deltaAPD90 from control; in vivo QTc = delta(delta)QTc @ max effect; human QTc = deltaQTcF
Definitions

- **Sensitivity** - Proportion of non-clinical results that correctly identify delayed repolarization clinically (gold standard).

- **Specificity** - Proportion of non-clinical results that correctly identify absence of delayed repolarization clinically.

- **Concordance** - Proportion of non-clinical results that correctly identify clinical effect.
  - Evaluated per assay, e.g., by hERG
  - Integrated analysis - A positive non-clinical assay result in ANY assay = Overall positive non-clinical result.
### Concordance Summary (71 Drugs)

<table>
<thead>
<tr>
<th></th>
<th>1X (n=16)</th>
<th>3X (n=22)</th>
<th>10X (n=33)</th>
<th>30X (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>hERG</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total = 64</td>
<td>Sensitivity</td>
<td>0.0</td>
<td>0.25</td>
<td>0.20</td>
</tr>
<tr>
<td>TQT (-) = 46</td>
<td>Specificity</td>
<td>0.91</td>
<td>0.79</td>
<td>0.83</td>
</tr>
<tr>
<td>TQT (+) = 18</td>
<td>Concordance</td>
<td>0.63</td>
<td>0.59</td>
<td>0.64</td>
</tr>
<tr>
<td><strong>APD</strong></td>
<td>1X (n=16)</td>
<td>3X (n=22)</td>
<td>10X (n=26)</td>
<td>30X (n=27)</td>
</tr>
<tr>
<td>Total = 43</td>
<td>Sensitivity</td>
<td>0.0</td>
<td>0.0</td>
<td>0.22</td>
</tr>
<tr>
<td>TQT (-) = 29</td>
<td>Specificity</td>
<td>0.90</td>
<td>0.93</td>
<td>0.82</td>
</tr>
<tr>
<td>TQT (+) = 14</td>
<td>Concordance</td>
<td>0.56</td>
<td>0.64</td>
<td>0.62</td>
</tr>
<tr>
<td><strong>QTc</strong></td>
<td>1X (n=13)</td>
<td>3X (n=24)</td>
<td>10X (n=27)</td>
<td>30X (n=18)</td>
</tr>
<tr>
<td>Total = 49</td>
<td>Sensitivity</td>
<td>0.25</td>
<td>0.29</td>
<td>0.25</td>
</tr>
<tr>
<td>TQT (-) = 35</td>
<td>Specificity</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
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<tr>
<td>TQT (+) = 14</td>
<td>Concordance</td>
<td>0.77</td>
<td>0.79</td>
<td>0.78</td>
</tr>
<tr>
<td><strong>Integrated</strong></td>
<td>1X (n=30)</td>
<td>3X (n=46)</td>
<td>10X (n=53)</td>
<td>30X (n=55)</td>
</tr>
<tr>
<td>Total = 71</td>
<td>Sensitivity</td>
<td>0.11</td>
<td>0.31</td>
<td>0.31</td>
</tr>
<tr>
<td>TQT (-) = 51</td>
<td>Specificity</td>
<td>0.90</td>
<td>0.88</td>
<td>0.81</td>
</tr>
<tr>
<td>TQT (+) = 20</td>
<td>Concordance</td>
<td>0.67</td>
<td>0.72</td>
<td>0.66</td>
</tr>
</tbody>
</table>

*Integrated approach: A positive in any nonclinical study is considered a positive overall nonclinical finding.
Additional Analyses - Stratification

• Study Date
  – Pre vs Post ICH S7B

• In vivo ECG data
  – Crossover vs parallel design
  – Telemetry vs non-telemetry
  – Plasma drug levels: concurrent vs extrapolated

• Clinical TQT signal magnitude
## Concordance Summary
(Stratification by TQT magnitude)

<table>
<thead>
<tr>
<th>Integrated</th>
<th>1X (n=30)</th>
<th>3X (n=46)</th>
<th>10X (n=53)</th>
<th>30x (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total = 71</td>
<td>Sensitivity</td>
<td>0.11</td>
<td>0.31</td>
<td>0.31</td>
</tr>
<tr>
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<td>Specificity</td>
<td>0.90</td>
<td>0.88</td>
<td>0.81</td>
</tr>
<tr>
<td>TQT (+) = 20</td>
<td>Concordance</td>
<td>0.67</td>
<td>0.72</td>
<td>0.66</td>
</tr>
<tr>
<td>ddQTC &lt;5</td>
<td>1X (n=17)</td>
<td>3X (n=28)</td>
<td>10X (n=30)</td>
<td>30x (n=30)</td>
</tr>
<tr>
<td>Total = 42</td>
<td>Sensitivity</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>TQT (-) = 42</td>
<td>Specificity</td>
<td>0.88</td>
<td>0.89</td>
<td>0.80</td>
</tr>
<tr>
<td>TQT (+) = 0</td>
<td>Concordance</td>
<td>0.88</td>
<td>0.89</td>
<td>0.80</td>
</tr>
<tr>
<td>5 ≤ ddQTC &lt;10</td>
<td>1X (n=7)</td>
<td>3X (n=11)</td>
<td>10X (n=15)</td>
<td>30x (n=15)</td>
</tr>
<tr>
<td>Total = 18</td>
<td>Sensitivity</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TQT (-) = 9</td>
<td>Specificity</td>
<td>1.00</td>
<td>0.80</td>
<td>0.86</td>
</tr>
<tr>
<td>TQT (+) = 9</td>
<td>Concordance</td>
<td>0.57</td>
<td>0.36</td>
<td>0.40</td>
</tr>
<tr>
<td>10 ≤ ddQTC &lt;20</td>
<td>1X (n=3)</td>
<td>3X (n=4)</td>
<td>10X (n=5)</td>
<td>30x (n=7)</td>
</tr>
<tr>
<td>Total = 8</td>
<td>Sensitivity</td>
<td>0</td>
<td>0.50</td>
<td>0.60</td>
</tr>
<tr>
<td>TQT (-) = 0</td>
<td>Specificity</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>TQT (+) = 8</td>
<td>Concordance</td>
<td>0</td>
<td>0.50</td>
<td>0.60</td>
</tr>
<tr>
<td>ddQTC ≥ 20</td>
<td>1X (n=3)</td>
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<td>10X (n=3)</td>
<td>30x (n=3)</td>
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<tr>
<td>Total = 3</td>
<td>Sensitivity</td>
<td>0.33</td>
<td>0.67</td>
<td>0.67</td>
</tr>
<tr>
<td>TQT (-) = 0</td>
<td>Specificity</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>TQT (+) = 3</td>
<td>Concordance</td>
<td>0.33</td>
<td>0.67</td>
<td>0.67</td>
</tr>
</tbody>
</table>
Summary

• We retrospectively evaluated the translation of nonclinical data submitted to the FDA to clinical TQT data (gold standard)
• 71 drugs were evaluated
• Concordance was evaluated quantitatively at multiples of the clinical exposure
Summary

- Concordance varied with clinical exposure multiples, with sensitivity increasing, and specificity decreasing at higher multiples up to 30 fold.
- Concordance was moderate at best.
- Sensitivity was lower than specificity at most multiples.
- Concordance and sensitivity increased with larger TQT signals, with caveat that sample size was extremely small.
Considerations

• Study Limitations
  – Test doses or concentrations evaluated in non-clinical studies was lower than clinical exposure in many cases
  – Experimental design and data analysis
  – Reliance on inferred plasma drug levels in vivo
  – Unknown assay sensitivity and inadequate use of positive controls.
  – Small sample sizes, particularly when data was stratified

• We could likely achieve greater concordance by addressing limitations noted above.
Thank You

• We would like to thank the HESI ProArrhythmia Committee members
HESI ProArrhythmia Committee Representation

Abbott Laboratories
Amgen, Inc.
AstraZeneca
Bristol-Myers Squibb
Data Sciences International
Eli Lilly and Company
European Medicines Agency
GlaxoSmithKline
Hoffman-La Roche, Inc.
Johnson & Johnson
Karolinska Institute
Merck

Medicines and Healthcare Products Regulatory Agency (UK)
Novartis Pharmaceuticals
Pfizer Inc.
Pharmaceuticals & Medical Devices Agency
Sanofi-Aventis
Takeda Pharmaceutical Company Limited
The Ohio State University
Uniformed Services University of the Health Sciences, School of Medicine
University of Wisconsin-Madison
US FDA