IMPLEMENTATION OF NOVEL ECG BIOMARKERS

CSRC CiPA meeting
May 21, 2018
Washington DC

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Chief Scientific Officer, Cardiac Safety, ERT
Disclosures

- I work as a consultant for ERT, a central ECG laboratory, and own shares in ERT.

- I represented EFPIA (European pharma industry) on the ICH E14 Expert and Implementation Working groups between 2001 and 2008.

- I also provide independent consultancy in relation to cardiac safety to pharmaceutical industry.
The role of JTpeak assessment

- **Hypothesis**: Lack of JTpeak prolongation supports 'balanced ion channel-block '(hERG = Ca or late Na) and supports reducing or eliminating late stage ECG monitoring, despite QT prolongation up to 20 ms
- Threshold of JTpeak prolongation < 10 ms has been proposed
The role of CiPA

FDA proposal

- 'Low' risk' CiPA compounds with a negative J-Tpeak evaluation will reduce or eliminate the required level of late stage ECG monitoring, despite QT↑ up to 20 ms

**Potential CiPA Assessment**

- Output nonclinical CiPA proarrhythmia risk prediction:
  - Low TdP Risk Prediction (Low Risk: no ion channel effects)
  - Intermediate TdP Risk Prediction
  - High TdP Risk Prediction (Low Risk: balanced ion channel effects)

- QTc prolongation?
  - No
  - Yes: Integrated risk assessment; assess J-Tpeak/Tpeak-Tend; effect due to minor potassium channel? Effect due to metabolite? Effect due to hERG trafficking, other non-acute effect?

- J-Tpeak prolongation?
  - No
  - Yes: Not consistent with low risk balanced ion channel effects; likely requires enhanced ECG monitoring in development or labeling

- QTc prolongation?
  - No
  - Intermediate / High TdP Risk

http://cipaproject.org

*: ‘Therefore, drugs that block hERG, but also have approximately equipotent late sodium or calcium channel blocking effects, are likely to have a low risk of TdP. These are referred to as balanced ion channel-blocking drugs.’

20 male and female healthy subjects; 3 treatment periods

9 subjects were to receive each drug, 6 on placebo
  ✓ Target to have at least 6 on active and 5 on placebo

Study drugs:
  ✓ 5 ‘QT-positive’ drugs: Ondansetron, quinine, dolasetron, moxifloxacin, dofetilide
  ✓ 1 QT negative: Levocetirizine
  ✓ 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

ECG methodology as in TQT studies

Primary analysis: Based on exposure response
## Non-clinical Testing

### Inhibitory potency in cardiac ion channels assays (IC$_{50}$, nM)

<table>
<thead>
<tr>
<th></th>
<th>hERG</th>
<th>Ca$^{2+}$</th>
<th>Late I$_{Na}$</th>
<th>Peak I$_{Na}$</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moxifloxacin</td>
<td>93,041</td>
<td>86,200</td>
<td>382,337</td>
<td>1,112,000</td>
<td>1, 2</td>
</tr>
<tr>
<td>Dolasetron</td>
<td>5,950</td>
<td>12,100</td>
<td>38,000</td>
<td>8,500</td>
<td>3, 3</td>
</tr>
<tr>
<td>Hydrodolasetron</td>
<td>NF</td>
<td>NF</td>
<td>NF</td>
<td>NF</td>
<td></td>
</tr>
<tr>
<td>Ondansetron</td>
<td>1,492</td>
<td>22,551</td>
<td>19,181</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Quinine</td>
<td>5,170</td>
<td>27,178</td>
<td>11,053</td>
<td>24,151</td>
<td>1</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>30</td>
<td>26700</td>
<td>162,000</td>
<td>753,160</td>
<td>2, 4</td>
</tr>
<tr>
<td>Levocetirizine</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

NF: Not found

1: Crumb et al. Journal of Pharmacological and Toxicological Methods 2016; 81: 251–262
4: Li et al. Circ Arrhythm Electrophysiol 2017; 10: 1-12
## 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
<table>
<thead>
<tr>
<th>Drug</th>
<th>Tmax</th>
<th>Largest ΔΔPR</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 2</td>
<td>Mean (ms)</td>
<td>90% CI (ms)</td>
<td>Time (hour)</td>
<td>Mean (ms)</td>
<td>Cmax ng/mL#</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>2/0.5</td>
<td>2.5</td>
<td>90% CI -5.0 to 10.0</td>
<td>Time 12</td>
<td>5.9</td>
<td>236</td>
<td>0.4 to 11.5</td>
</tr>
<tr>
<td>Quinine*</td>
<td>2-3/1</td>
<td>8.9</td>
<td>4.3 to 13.5</td>
<td>2</td>
<td>16.0</td>
<td>5,827</td>
<td>7.1 to 24.9</td>
</tr>
<tr>
<td>Dolasetron</td>
<td>1/0.5</td>
<td>4.1</td>
<td>-0.1 to 8.3</td>
<td>2</td>
<td>16.3</td>
<td>403</td>
<td>10.3 to 22.2</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>2/1</td>
<td>0.8</td>
<td>-7.2 to 8.9</td>
<td>12</td>
<td>1.3</td>
<td>4,663</td>
<td>-3.8 to 6.3</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>2-3/2-3</td>
<td>5.7</td>
<td>-1.3 to 12.6</td>
<td>12</td>
<td>3.0</td>
<td>0.92</td>
<td>-4.1 to 10.0</td>
</tr>
<tr>
<td>Levocetirizine</td>
<td>1/2</td>
<td>4.2</td>
<td>-5.2 to 13.6</td>
<td>6</td>
<td>2.3</td>
<td>1004</td>
<td>-2.6 to 7.3</td>
</tr>
</tbody>
</table>

*: During the first 8 hours on Day 1; #: Geometric mean

Mean values above 10 ms are shown in bold italics

Known effects on PR and QRS intervals by quinine and dolasetron confirmed
### Effect on QRS interval

<table>
<thead>
<tr>
<th></th>
<th>Tmax Day 1/2</th>
<th>Day 1</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean (ms)</td>
<td>90% CI (ms)</td>
<td>Time (hour)</td>
<td>Mean (ms)</td>
<td>Cmax ng/mL#</td>
<td>90% CI (ms)</td>
<td>Time (hour)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ondansetron</td>
<td>2/0.5</td>
<td>0.7</td>
<td>-0.5 to 1.9</td>
<td>6</td>
<td>2.1</td>
<td>236</td>
<td>0.2 to 4.0</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinine</td>
<td>2-3/1</td>
<td>4.0</td>
<td>2.4 to 5.7</td>
<td>2</td>
<td>7.7</td>
<td>5,827</td>
<td>3.7 to 11.6</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dolasetron</td>
<td>1/0.5</td>
<td>2.1</td>
<td>0.9 to 3.2</td>
<td>2</td>
<td>5.2</td>
<td>403</td>
<td>2.9 to 7.4</td>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>2/1</td>
<td>1.0</td>
<td>-0.1 to 2.2</td>
<td>2</td>
<td>2.0</td>
<td>4,663</td>
<td>-1.2 to 5.1</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dofetilide</td>
<td>2-3/2-3</td>
<td>0.2</td>
<td>-0.9 to 1.3</td>
<td>2</td>
<td>0.6</td>
<td>0.92</td>
<td>-1.4 to 2.7</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levocetirizine</td>
<td>1/2</td>
<td>0.3</td>
<td>-0.8 to 1.5</td>
<td>12</td>
<td>-1.7</td>
<td>1004</td>
<td>-4.7 to 1.3</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*: During the first 8 hours on Day 1; #: Geometric mean

_Mean values above 5 ms are shown in bold italics_

**Known effects on PR and QRS intervals with quinine and dolasetron confirmed**
J-Tpeak methodology

• FDA approach adopted for JTpeak measurements:
  ✓ Vector magnitude (VM) lead
  ✓ Median beat computed in each 10-second replicate

• iCOMPAS (iCardiac) for all intervals and fiducials
  ✓ RR, QRS onset, J-point, Tpeak, Tend

• Semi-automated method with over-read by central ECG laboratory of 3 replicates
  ✓ Over-read by technician after dedicated training
  ✓ Extensive secondary overview of cardiologist (WZ) to ensure consistency across technicians (n= 3)
Computations of the median VM beat

Standard Lead configuration (Mason-Likar)

Orthogonal Leads (XYZ)

Guldenring Transformation (1)

Median Beat From VM lead

*: RMS: Root mean square

Concentration – QTc/JTpeak_c analysis

Mean JTpeak_c 10 ms ~ mean QTcF 12.5 ms
Concentration – QTc/JTpeak\_c analysis

<table>
<thead>
<tr>
<th></th>
<th>Slope ms per ng/mL</th>
<th>90% CI ms per ng/mL</th>
<th>Intercept ms</th>
<th>90% CI ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-QTc</td>
<td>0.019</td>
<td>0.006 to 0.031</td>
<td>-0.4</td>
<td>NS</td>
</tr>
<tr>
<td>C-JTpeak_c</td>
<td>-0.013</td>
<td>-0.023 to -0.003</td>
<td>-2.0</td>
<td>NS</td>
</tr>
</tbody>
</table>

Mean JTpeak\_c 10 ms ~ mean QTcF: Not applicable
## Dofetilide

### Concentration – QTc/JTpeak_c analysis

![Graph showing concentration vs. placebo-corrected change-from-baseline](image)

### Table: Concentration Analysis

<table>
<thead>
<tr>
<th></th>
<th>Slope</th>
<th>90% CI</th>
<th>Intercept</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-QTc</td>
<td>15.9</td>
<td>10.51 to 21.33</td>
<td>3.7</td>
<td>NS</td>
</tr>
<tr>
<td>C-JTpeak_c</td>
<td>5.6</td>
<td>-3.1 to 14.2</td>
<td>3.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

Mean JTpeak_c 10 ms ~ mean QTcF 22.5 ms
Concentration – QTc/JTpeak_c analysis

Quinine concentration (ng/ml)

Placebo-corrected Change-from-baseline

Slope
ms per ng/mL
90% CI
ms per ng/mL
Intercept
ms
90% CI
ms

C-QTc 0.003 0.0017 to 0.0036 0.6 NS
C-JTpeak_c -0.0004 -0.0015 to 0.0008 -6.1 NS

Mean JTpeak_c 10 ms ~ mean QTcF: Not applicable
In this dataset, JTpeak prolongation was observed for ‘pure’ hERG blockers, but not for dolasetron and quinine
  - Both dolasetron (hydrodolasetron and quinine) exhibit multi-channel block, including inhibition of peak sodium current

Clinical experience with JTpeak outside the DARS division is largely lacking

Substantial, prospective validation outside the CiPA project is needed:
  - JTpeak/QTc relationship and dynamics for drugs with multi-channel block, e.g. peak Na, are not well characterized
  - Dynamics of JTpeak ↑ vs. QTc↑ within the range of mild QTc↑ (e.g., 10 to 20 ms) are not sufficiently studied
  - Role and added value to standard ECG parameters (including PR and QRS) in terms of determining whether late stage ECG monitoring can be reduced or eliminated despite QT↑ up to 20 ms are untested
  - Variability of JTpeak measurements when implemented by different ECG vendors is largely unknown

In our experience to-date, automated JTpeak algorithms are not sufficiently precise or consistent to rely on for important safety decisions, esp. for drugs that alter T-wave morphology
In my view, JTpeak evaluation as part of important safety decisions in terms of cardiac safety:
✓ Is not based on scientific consensus on the underlying electrophysiology of this interval
✓ Is not supported by clinical experience
✓ Will require substantial prospective validation outside the CiPA project
Acknowledgments

Software:
Jean-Philippe Couderc, PhD, MBA, Chief Technology Officer, ERT
Thuan Pham – Director of Software Development
Vuong Le – Senior Software Developer

Statistics:
Randy Brown, Head DM and Statistics
Kalvin Connor – Associate Statistician
Hongqi Xue, PhD – Senior Statistician

ECG Over Reading:
Helen Zapesochny – Core Lab Manager/Senior ECG Analyst
Jodie Palma – Senior ECG Analyst
Yulia Slepynina – Senior ECG Analyst
Wojciech Zareba, MD, PhD, FACC, FESC
Professor of Medicine/Cardiology, University of Rochester Medical Center and iCardiac/ERT

Project Management:
Mark Ticktin – Director of Research Projects
• Fiducials from Median VM beat: adjudication tools
Statistical analysis of QTcF and JTpeak\textsubscript{c}

- A separate analysis was performed for each of the 6 active drugs against the pooled placebo subjects.
- QTcF and JTpeak\textsubscript{c} were assessed separately using both exposure response analysis and by timepoint analysis.
- Pre-specified model from exposure response white paper was used in place of mixed effects model used in IQ-CSRC prospective study. (1)
- Only pre-specified model was fit at this time, additional modeling still to be explored.
- JTpeak was corrected for heart rate using the JTpeak and RR value from each replicate and correction factor of 0.58 (2)

\[ JTpeak\textsubscript{c} = \frac{JTpeak}{RR^{0.58}} \]

2. Johannesen, L. et al. Improving the assessment of heart toxicity for all new drugs through translational regulatory science. CPT 95; 501–508, 2014
Exposure response analysis

Analysis was performed using a linear mixed-effects model with change-from-baseline QTcF (or JTpeak_c) as the dependent variable. The model used for analysis was:

$$\Delta QTcF \ (or \ JTpeak_c) \sim Treatment + Time + Concentration$$

+ Centered Baseline

- Treatment (active or placebo) and time as categorical factors
- Plasma concentration as a continuous covariate (i.e., 0 for placebo)
- Centered baseline as an additional covariate
- Random intercept per subject
- Analysis was repeated using data from Day 1 only.
By timepoint analysis

Analysis was performed using a linear mixed-effects model with change-from-baseline QTcF (or JTpeak\_c) as the dependent variable. The model used for analysis was:

\[ \Delta QTcF \text{ (or JTpeak\_c)} \sim \text{Treatment} + \text{Time} + \text{Treatment} \times \text{Time} + \text{Baseline} \]

- Treatment, time, and time-by-treatment interaction as categorical fixed effects
- Baseline as a continuous covariate
- An compound symmetry covariance structure was specified for the repeated measures at post-dose timepoints for each subject.
## Reported ADRs (for what it’s worth…)*

<table>
<thead>
<tr>
<th>Drug</th>
<th># Reported TdP*</th>
<th># of cardiac ADRs</th>
<th>% of cardiac ADRs</th>
<th># of all ADRs</th>
<th>% of all ADRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moxifloxacin</td>
<td>145</td>
<td>2,558</td>
<td>5.7%</td>
<td>31,678</td>
<td>0.5%</td>
</tr>
<tr>
<td>Dolasetron</td>
<td>2</td>
<td>104</td>
<td>1.9%</td>
<td>562</td>
<td>0.4%</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>134</td>
<td>2,033</td>
<td>6.6%</td>
<td>6,237</td>
<td>2.2%</td>
</tr>
<tr>
<td>Quinine</td>
<td>13</td>
<td>285</td>
<td>4.6%</td>
<td>5,278</td>
<td>0.3%</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>89</td>
<td>1,468</td>
<td>6.9%</td>
<td>15,012</td>
<td>0.7%</td>
</tr>
<tr>
<td>Ranolazine**</td>
<td>33</td>
<td>1,453</td>
<td>2.3%</td>
<td>7,085</td>
<td>0.5%</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>534</td>
<td>5,506</td>
<td>9.7%</td>
<td>34,659</td>
<td>1.5%</td>
</tr>
</tbody>
</table>

* Unknown denominator and causality

** Example of safe drugs according to the CiPA paradigm

Source: WHO’s Vigiaccess; March 12, 2018