How Does the CIPA Initiative Relate to the IQ-CSRC Project?

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Industry Relationships

Member of DSMB, Adjudication Committee, or Consultant

- Genentech
- Abbvie
- Aerpio
- Akebia
- Balance
- Medtronic
- Biomedical Systems
- ICardiac
- Heart Metabolics
- Milestone
- Theravance
- Lilly
- Viamet
- Shire
- Helsinn
- Celgene
- SNBL
- Pharmacyclics
- Anthera
IQ-CSRC Clinical Study

- Demonstrates a sufficiently high level of sensitivity to be considered in lieu of the TQT Study
- Demonstrates the value of PK/PD modeling
IQ-CSRC Clinical Study

- Demonstrates a sufficiently high level of sensitivity to use in lieu of the TQT Study
- Demonstrates the value of PK/PD modeling
Achievements/Issues
With Current Approach

• ICH E14/S7B have resulted in no drugs with unrecognized risk being approved

• QT prolongation ≠ Proarrhythmia

• HERG block ≠ Proarrhythmia

• Negative impact on drug development

• New paradigm
CIPA

- CIPA is clearly a different paradigm from the current approach

- Focused on the potential of a drug to have a meaningful risk of causing TdP, not on the QTc

- It is not primarily focused on other electrophysiologic effects, such as conduction block
  - Assessment of multiple ion channels should be informative
CiPA: Three Component Proposal

Ionic Currents / In Silico Based Approach

Effects on Multiple Cardiac Currents (Voltage Clamp Studies) + Reconstruction of Cellular Electrophysiology (In Silico Studies)

Myocyte-Based Approach

Effects on Human Ventricular Myocytes (In Vitro Studies)

Human Phase 1 ECG’s

Effects on Human ECG morphology/waveforms
CiPA: Three Component Proposal

**Ionic Currents / In Silico Based Approach**
- Effects on Multiple Cardiac Currents (Voltage Clamp Studies)
- Reconstruction of Cellular Electrophysiology (*In Silico* Studies)

**Myocyte-Based Approach**
- Effects on Human Ventricular Myocytes (*In Vitro* Studies)
- Human Phase 1 ECG’s
- Effects on Human ECG morphology/waveforms
Human Phase 1 ECG’s Under CIPA

- To confirm that there are not unanticipated drug-induced electrophysiologic/ECG effects based on the preclinical assessments
- Identify preclinical false negatives
  - Untested ion channels
  - Human-specific metabolites
- Unanticipated findings, if of possible clinical significance, might indicate a need for additional analysis
  - Scenario 1- CIPA identifies a compound as being very low risk for TdP and, as expected there is QT prolongation- no further evaluation needed
  - Scenario 2- CIPA identifies a compound as being very low risk for TdP and, there is unexpected QT prolongation- further evaluation may be needed
- Also of interest are other channel effects- Na, Ca, etc.
Human Phase 1 ECG’s

- Also critical for effects on ventricular and AV conduction

- Requires careful ECG interval and waveform assessments

- $Q_{T_C}$ PK/PD modeling clearly increases sensitivity and adds value

- Are other novel intervals useful to evaluate?
  - For example, $J-T_{peak}$, $T_{peak}-T_{end}$

- Working group will be focusing on this for CIPA
Going Beyond QT to Differentiate Multi-Channel Effects

QRS

J-Tpeak

Tpeak-Tend

ECG

Calcium, late sodium

Sodium

Ventricular action potentials

hERG potassium

ECG Signature Dependent on Ion Channel Effects

Table 1  Impact of “pure” and mixed hERG channel blockers on electrocardiographic intervals

<table>
<thead>
<tr>
<th>ECG interval</th>
<th>“Pure” hERG block (dofetilide)</th>
<th>hERG block + ICa block (verapamil)</th>
<th>hERG block + peak INa (quinidine)</th>
<th>hERG block + late INa (ranolazine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>No Δ</td>
<td>↑</td>
<td>No Δ</td>
<td>No Δ</td>
</tr>
<tr>
<td>QRS</td>
<td>No Δ</td>
<td>No Δ</td>
<td>↑</td>
<td>No Δ</td>
</tr>
<tr>
<td>QTc</td>
<td>↑</td>
<td>No Δ</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>J-T_{peak}</td>
<td>↑</td>
<td>No Δ</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>T_{peak}-T_{end}</td>
<td>↑</td>
<td>No Δ</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

PR interval data may be difficult to interpret due to heart rate and autonomic effects
Pure hERG Block (Dofetilide) vs. hERG>Calcium>Sodium Block (Quinidine)

- Pure hERG block equally prolonged J-Tpeak and Tpeak-Tend
- hERG block with additional Ca & Na block prolonged Tpeak-Tend > J-Tpeak

Phase 1 ECG Assessment Under CIPA

- PK/PD modeling of QTc seems appropriate, given higher sensitivity
- Other intervals may provide insight into multi-channel effects
  - QRS, J-$T_{\text{peak}}$, $T_{\text{peak}}$-$T_{\text{end}}$
  - ? Other indices
- Appropriate methodologies need to be defined
  - ECG analysis approach- single lead, composite, vector
- Working group commencing in early 2015
Thank you

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