Breakout #4 – Phase 1 ECG:

Potential Role of ECG under CiPA

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Role of Phase I ECG Data Under CiPA

To determine if there are unexpected ion channel effects compared to preclinical ion channel data

Can CiPA nonclinical proarrhythmia assessment combined with clinical ECG assessment better inform ECG monitoring (e.g., in specific populations and in the range of 10-20ms mean ΔΔQTc prolongation)?
Discussion Items

• Summary of results supporting J-Tpeakc use to inform multi-ion channel effects

• Role of ECG in a potential implementation of CiPA
  – Integrated risk assessment, context of use and potential thresholds
  – How to handle discrepancies
  – Limitations/Challenges

• Challenges in concentration-ECG-response models
  – Identifying nonlinear relationships in small sized trials
  – Impact on interpretation of results

• Heart rate dependency of J-Tpeak interval
  – J-Tpeak/RR adaptation and hysteresis
  – Population vs. subject-specific corrections

• Are we ready?
ECG Biomarkers to Differentiate hERG vs. Balanced Ion Channel Block

hERG vs. balanced ion channel block

- Dofetilide (predominant hERG block)
  - Prolongs QTc by prolonging J-Tpeakc and Tpeak-Tend

- Ranolazine (hERG + late sodium)
  - Prolongs QTc with no effect on J-Tpeakc

Challenges

• Nonlinear concentration-response relationships

• Diltiazem (calcium block) did not shorten QTc prolongation by dofetilide (hERG block)

• Better J-Tpeak/RR characterization may help to reduce variability of J-Tpeakc measures
Potential Role of ECG under CiPA
Challenges in concentration-ECG-response

- Can the SAD study provide sufficient data to characterize the ECG profile for drugs with nonlinear exposure-response relationships?
- Phase 1 vs. larger studies?
- ECG signatures
  - Proarrhythmic risk vs. ion channel effects
  - “balanced ion channel block” vs. proarrhythmic risk
- Use of other intervals (e.g., PR, QRS) as indicators of ion channel effects (e.g., calcium, peak sodium)?
- When to default back to TQT or C-QT?
Different hERG + Calcium ECG signatures

- Diltiazem (calcium block) did not shorten QTc prolongation by dofetilide (hERG block)
- However, verapamil (hERG + calcium) prolonged QTc without prolonging J-Tpeakc
- Thus, ECG signature of hERG + calcium is unclear
  - Although verapamil QTc and J-Tpeakc signature is similar to ranolazine (hERG + late sodium)
- Calcium block has been shown to prevent EADs in nonclinical assays
- No TdP with verapamil
Heart rate correction (J-Tpeak)

• Like QT, J-Tpeak is heart rate dependent
  – Population (n=431 subjects) correction available
    • $J\text{-Tpeak}_c = J\text{-Tpeak}/RR^{0.58}$
  – Adaptation to HR is not instantaneous
    • $J\text{-Tpeak}/RR$ hysteresis not characterized yet
• Characterization of HR dependency and adaptation in a larger population is ongoing
• Feasibility of individual/study-specific correction in Phase 1 studies?

CHALLENGES IN CONCENTRATION-ECG-RESPONSE
Nonlinear concentration-response (I)

- Nonlinearity vs. limited number of subjects informing high concentrations?
Nonlinear concentration-response: Delayed effects ("Hockey stick")?

- Delayed effects vs. different ion channel effects at different (higher) concentrations?
Nonlinear concentration-response: large intercepts with flat slope

Flat, linear or Emax concentration-J-Tpeakc relationship?
- Not enough data at low concentrations?
- Not large enough sample size?
HERG + LATE SODIUM VS.
HERG + CALCIUM
hERG+Calcium vs. hERG+late sodium with different Drugs

Verapamil (hERG + Calcium)  Ranolazine (hERG + late sodium)

ΔΔ ± 90% CI

QTc

J-Tpeakc

Verapamil (ng/mL)  Ranolazine (ng/mL)
hERG+Calcium vs. hERG+late sodium with Drug Combinations

- ΔQTc (ms)
- ΔJ - Tpeakc (ms)
- ΔTpeak - Tend (ms)

Dofetilide (ng/mL)

Dofetilide + Calcium
Dofetilide + Diltiazem + Dofetilide
Dofetilide + Mexiletine + Dofetilide

- hERG
- hERG + Calcium
- hERG + late sodium
HEART RATE DEPENDENCY OF J-TPEAK
Heart rate correction (QT)

• Heart rate correction of QT approaches described in ICH/E14

   - Adaptation to new HR is not instantaneous (QT/RR hysteresis effect)
Heart rate correction (J-Tpeak)

• J-Tpeak is also heart rate dependent
  – Population (n=431 subjects) correction available\(^1\)
    • J-Tpeak\(_c\) = J-Tpeak/RR\(^{0.58}\)
  – Like for QT, adaptation to HR is not instantaneous
    • J-Tpeak/RR hysteresis not characterized yet

• Characterization of HR dependency and adaptation in a larger population is ongoing

• Feasibility of individual/study-specific correction in Phase 1 studies?

QT and J-Tpeak Heart Rate Dependency

Biomarker-RR relationship for two different subjects (red vs. blue) at baseline

\[ J - T_{peakc} = \frac{J - T_{peak}}{RR^{0.58}} \]

- Ongoing collaboration with Dr. Malik to characterize J-Tpeakc/RR hysteresis

<table>
<thead>
<tr>
<th>For 22 Subjects</th>
<th>QT</th>
<th>J-Tpeak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Slope</td>
<td>0.29</td>
<td>0.53</td>
</tr>
<tr>
<td>SD of Slope</td>
<td>0.07</td>
<td>0.12</td>
</tr>
<tr>
<td>SD/Mean (%)</td>
<td>24%</td>
<td>23%</td>
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</tbody>
</table>
Sources of J-Tpeakc variability (I)

- Ranolazine: heart rate increase in 2 time-points in 2 subjects (i.e., 6 ECGs) drive wider CIs ~Cmax