How CiPA might be implemented in clinical development and regulatory approaches

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QTc Evaluation in Drug Development

- Nonclinical
  - In vitro and in vivo assays per ICH S7b

- Phase 1
  - Thorough QT evaluation (TQT study or substitute)

- Phase 2
- Phase 3
  - ECG monitoring in patients
  - Labeling and risk mitigation strategies

E14/QTc Prolongation
Proarrhythmic Risk Evaluation in Drug Development

Nonclinical • In vitro and in vivo assays per ICH S7b

Phase 1 Thorough ECG evaluation (TQT study or substitute)

Phase 2

Phase 3 • ECG monitoring in patients

FDA Filing • Labeling and risk mitigation strategies

Low TdP Risk

E14/QTc Prolongation

+ hERG Inhibition

Nonclinical CiPA

Confirm low TdP Risk with ECG Profile

Y

N
Clinical Questions with CiPA Implementation

ECG study design, analysis and interpretation for a drug that inhibits multiple cardiac ion channels

- Can the SAD study provide sufficient data to characterize the ECG profile for drugs with nonlinear exposure-response relationships?
- How to confirm a “low proarrhythmic risk” drug using the ECG profile?
- How to detect “unanticipated effects” in the clinical ECGs?
Clinical Questions with CiPA Implementation

Need for late phase ECG monitoring

- Is ECG monitoring needed for “low risk” drugs that moderately prolong the QTc interval at clinical exposures?
- Does the drug affect other ECG intervals?
Clinical Questions with CiPA Implementation

Communicating Risk in Product Label

- Low risk: What is the proarrhythmic risk when used with other QT-prolonging drugs?
- Low risk: What is the proarrhythmic risk when used in high risk patients (i.e., those with congenital long QT, electrolyte imbalances, structural heart disease)?
- Intermediate vs. high risk: is there a difference in product labels?
CiPA Use in Clinical Development

**Current scenarios***

- Replacing an uninterpretable TQT study for a drug with large heart rate increases (>20 bpm) at therapeutic doses
- Supporting late phase ECGs when a TQT study can not be conducted because of safety concerns with healthy volunteers and feasibility concerns in patients.

**Possible future scenarios**

- Supplementing Phase 1 ECG evaluation when exposure margin is not large enough to waive positive control
- Oncology safety evaluation
- Influencing the intensity of ECG monitoring in late phase trials
- Aligning product labels with proarrhythmic potential

*FDA has requested CiPA with these scenarios*
Oncology Drugs: A Good Place to Implement CiPA?

Problem:
- Without placebo controls and large exposure margins, QTc assessments are designed to exclude large increases (>20 ms)
- QTc outliers in late phase clinical studies are difficult to interpret with confounding QT prolonging drugs and co-morbid conditions of patient

<table>
<thead>
<tr>
<th>Example Drugs</th>
<th>QTc prolongation magnitude (12.2)</th>
<th>C-QTc Relationship? cited in labeling?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib</td>
<td>No large changes in the mean QTc interval (&gt;20 ms)</td>
<td>No</td>
</tr>
<tr>
<td>Eribulin</td>
<td>11 ms (UCL: 19.5 ms)</td>
<td>No</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>No large changes in the mean QTc interval (&gt;20 ms)</td>
<td>No</td>
</tr>
</tbody>
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Example Clinical Implementation

Example 1

- Drug found to be multi-ion channel blocker with low TdP risk in CIPA conducted prior to FIH study
- What to do?
  - Collect intensive ECGs in the SAD & MAD studies. Evaluate ECG biomarkers using dose- and concentration-ECG analyses.
  - At highest clinical exposure scenario, evaluate drug’s effect on QTc, J-T\text{peak}, and T\text{peak,end}.
  - Confirm \textit{in silico} Low TdP Risk score and there are no unanticipated effects
  - Continue with clinical development with modified ECG monitoring (if applicable)

Example 2

- Drug was found not to inhibit hERG and CIPA was not conducted prior to FIH study; however, concentration-dependent QTc prolongation was observed in FIH study.
- What to do?
  - Continue clinical development with ECG monitoring according to E14 Q&A 7.1
  - Perform CIPA, test for off-target QTc effects, test for active metabolites
Conclusion

• FDA’s interdisciplinary review team (IRT) has requested a CiPA approach to support clinical ECGs when a TQT study was not feasible or interpretable.
• Identify clinical scenarios where CiPA can be implemented to gain experience with the approach and to answer outstanding questions.
• If a sponsor would like to use a CIPA approach in their drug development program, contact the IRT via the Clinical Division.
TQT Study
SAD/MAD
CiPA