Implementation of CIPA during Drug Development: Practical Considerations

Hugo M. Vargas, PhD, DSP

Scientific Director
Integrated Discovery & Safety Pharmacology
Comparative Biology & Safety Sciences
Amgen, Inc
CIPA Must Identify Different Phenotypes

CIPA Assays Must Differentiate:

- hERG blockers with substantial QTc Prolongation & associated with TdP (1)
- hERG blockers with substantial QTc Prolongation & NOT associated with TdP (2)
- Drugs with no-direct ion channel effects with modest QTc Prolongation (3)

Slide courtesy of D. Leishman (Lilly; modified with permission)
Impact of CIPA on Pharma: The Upside

- **Positive impact on drug development → no TQT**
  - Prevent ‘inappropriate’ attrition of beneficial candidates
  - Improve probability of success of new drug candidates
  - Benefits Many:
    - Large-sized & Smaller-sized sponsors (emerging)
    - Patients

- **Leverage nonclinical pro-arrhythmia assays**
  - Opportunity for cost-effective drug development
  - Potential to advance drugs with “safe” QTc prolongation
Implementation of CIPA: Challenges

- **CIPA: unproven for predicting proarrhythmic risk**
  - Multi-channel assays: what protocol & parameters (e.g., kinetics)
  - In silico Action Potential evaluation (isAP)
  - Human stem cell-derived cardiomyocytes (hSC-CM)

- **Confidence in Assays: Integrating new risk signals**
  - S7B paradigm: hERG risk $\rightarrow$ QTc prolong. $\rightarrow$ TdP risk
  - CIPA paradigm: [7 channels + isAP + hSC-CM] risk $\rightarrow$ TdP risk

- **Resource impact**
  - Apply all CIPA assays to all chemical leads or “the one that matters”?
  - Front-loaded approach (candidate selection stage; pre-IND)
    - Concentrations to test?
  - Staged (tiered) approach (do some pre-IND; do some post-FIH)
    - Identify test concentrations based on actual exposure
Implementation of CIPA: Challenges

- Integration of Multiple Signals of Risk
  - Interpretation of signals using the CIPA paradigm
    - What does low pro-arrhythmic risk look like?
      - E.g., compounds in the 2 & 3 space
    - What endpoints define pro-arrhythmic risk?
      - E.g., need to be able to identify “torsadogens” with confidence (1)
  - Conflicting data signals → how to progress drug candidates?
    - hERG vs multi-channel blockade (what is right balance)
    - in vitro evidence (positive) vs in vivo QTc findings (negative); vice-versa
    - pro-arrhythmic signals at high margins
    - managing multi-channel blockade in vivo
      - Hemodynamic consequences
      - Cardiac electrical consequences (conduction defects, etc)
      - Arrhythmic consequences
Progressing New Drug Candidates: Implementing the CIPA Paradigm

<table>
<thead>
<tr>
<th>AMG #</th>
<th>hERG (IC50, μM)</th>
<th>[Cmax]_{free} (FIH-MTD, μM)</th>
<th>hERG / [Cmax]_{free}</th>
<th>QTc Signal (FIH) (≥20 msec)</th>
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<tbody>
<tr>
<td>1</td>
<td>126</td>
<td>0.496</td>
<td>253</td>
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<tr>
<td>2</td>
<td>&gt;89</td>
<td>0.538</td>
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<td>5</td>
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<td>&gt;780</td>
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<tr>
<td>6</td>
<td>&gt;30</td>
<td>0.44</td>
<td>&gt;68</td>
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</table>

- **CIPA implementation challenge:**
  - Would pro-arrhythmia risk assessment change for #1-5?
  - What additional CIPA assay information would help #6?
AMG 6: QTc/hERG vs FIH-SAD Exposure

C\textsubscript{max} Range

5/6 cohorts: ↑QTc Interval

QTc Prolongation - Indirect:
- ↓ Body temp
- Bradycardia
- Autonomic effects

\[\text{Effect (\% Inh or \%Prolongation)}\]

\[\text{[AMG 6] (free, uM)}\]
In Vitro Safety Pharmacology: Summary

- **Secondary Pharmacology Profile:**
  - hERG: $IC_{50} > 30 \mu M$
    - Inhibition: 3 $\mu M$ (10%); 10 $\mu M$ (15%); 30 $\mu M$ (30%)
  - IKs: $IC_{50} > 300 \mu M$
    - Inhibition: 100 $\mu M$ (0%); 300 $\mu M$ (13%)
  - NaV1.5: $IC_{50} = 146 \mu M$
  - CaV1.2: $IC_{50} = 98 \mu M$

- **APD, human Purkinje fiber (1 Hz): 1-30 $\mu M**
  - NOEL: 1 $\mu M$
  - APD90 prolonged:
    - 3 $\mu M$ (13%)
    - 10 $\mu M$ (28%)
    - 30 $\mu M$ (48%)
Take Home Messages

- **CIPA Assays: Confidence in models to be determined**
  - Translational performance needs to be understood → drive use

- **Clarity on Issues: Pending**
  - Definition of low TdP risk (“safe QTc prolongation”)
  - Managing conflicting data signals → what is minimal data set?
  - Regulatory Consensus on TQT waiver

- **Staged-Assays: A Consideration for Resourcing**
  - A practical alternative
  - Enable “case-by-case” solutions vs “one-size fits all” screening
    - Focuses testing on “the one drug that matters”
Acknowledgments

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- ChanTest
- SCAP Test (*in silico* modeling)
APD in human models: human Purkinje fibers vs In Silico

![Graph showing APD prolongation or inhibition](image)