Practical approaches to evaluating ECG biomarker results and regulatory perspective

April 6, 2016

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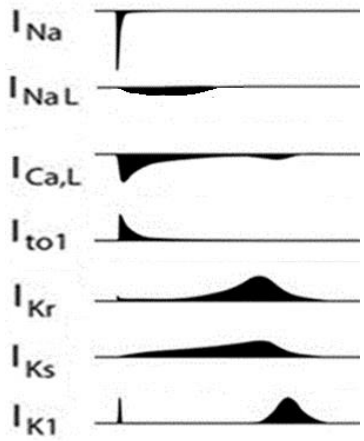
Disclaimer

The opinions expressed in this presentation are mine and do not necessarily reflect the official views of the U.S. Food and Drug Administration (FDA)

Comprehensive *in vitro* Proarrhythmia Assay: Four Components

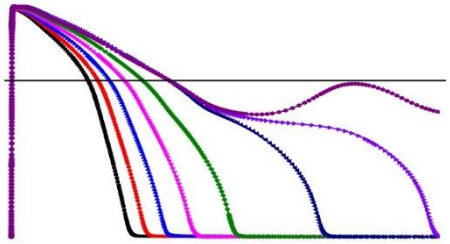
1. High Throughput Assessment of Effects on Multiple Ionic Currents



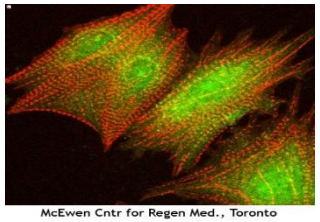
modified from Hoekstra et al., 2012

2. *In silico* Reconstruction of Human Ventricular Cardiomyocyte Electrophysiology

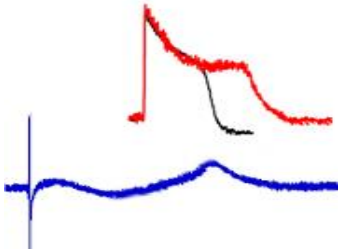
$$I_{stim} = C\frac{dV_m}{dt} + I_m$$



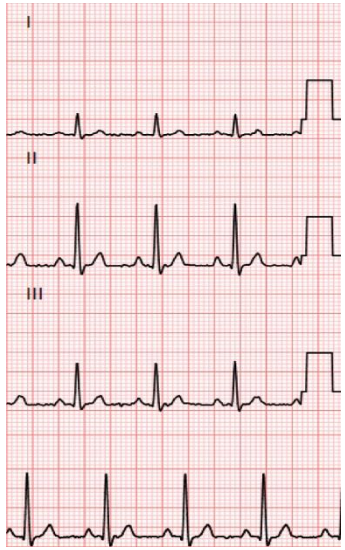
3. *In vitro* Effects on Human Stem-Cell Derived Ventricular Cardiomyocytes



McEwen Cntr for Regen Med., Toronto



4. Evaluation of Unanticipated Effects in Clinical Phase 1 Studies



Goal: Develop a new *in vitro* paradigm for cardiac safety evaluation of new drugs that provides a more accurate and comprehensive mechanistic-based assessment of proarrhythmic potential

CiPA Phase 1 ECG Biomarker Assessment

- Goal: Use human phase 1 ECG data to determine if there are unexpected ion channel effects compared to preclinical ion channel data
  - Human specific metabolite, protein binding
- New ECG biomarker(s) would need to add additional information beyond PR/QRS/QTc
  - Differentiate multi-ion channel effects during repolarization
  - Can be corrected for heart rate (if needed)
  - Sufficient power to detect changes in small sample sizes with exposure-response analysis
  - Available for unrestricted wide-spread use

Biomarker Analysis Summary

- Examined 12 potential ECG biomarkers and compared to ion channel data
  - 2 prospective FDA-sponsored clinical trials including 8 drugs and 3 drug combinations, some additional drugs
  - Comparison to 7 ion channel current data
- Multiple biomarkers can be applied in exposure-response analysis
- ROC-AUC analysis showed that J-Tpeakc is the strongest predictor of inward current block in the presence of hERG block
- J-Tpeak has similar inter/intra-subject variability and heart rate relationship as QT; T-wave flatness has variable heart rate relationship
- J-Tpeak/Tpeak-Tend FDA algorithm being released as open-source software

Potential Statistical Framework

CiPA Preclinical Assessment = Low Risk

No hERG block at expected clinical concentrations or hERG block with offsetting late sodium and/or calcium block (possible QTc prolongation expected)

QTc upper bound < 10 ms
(at supratherapeutic concentration; exposure response in early phase 1 study)

No

JTpeakc upper bound < 10 ms (at supratheraputic concentration; exposure response in early phase 1 study)

Yes

No

Consistent with CiPA low risk

- Do not need expanded ECG analysis in development

Potential discrepancy between preclinical testing and phase 1 results

- Investigate mechanism (e.g. free concentration higher than expected, human specific metabolite), consider amount of QTc prolongation

Potential Statistical Framework

CiPA Preclinical Assessment = TdP Risk

Intermediate or High TdP Risk

Likely selective or predominant hERG block at predicted clinical concentrations

QTc upper bound < 10 ms

(at supratherapeutic concentration; exposure response in early phase 1 study)

Yes

No

Potential discrepancy between preclinical testing and phase 1 results

- Investigate mechanism (e.g. free concentration less than expected, human specific metabolite, multichannel effects, confounding heart rate effects), consider amount of QTc and J-Tpeakc prolongation
- Depending upon additional investigation, consider down classification (e.g. high→ intermediate or intermediate → low)

Consistent with CiPA intermediate/high TdP risk

Further steps toward ICH/regulatory acceptance

- Further testing of statistical framework for exposure-response analysis in small sample sizes
  - Resampling data from prior TQT studies
  - New prospective study with design similar to IQ-CSRC study
- J-Tpeak open source software released
  - Multi-site reproducibility study among ECG core labs
  - Implemented in automated fashion in ECG Warehouse

Summary

- Identified best biomarker for differentiating selective hERG blockers from hERG + late sodium/calcium blockers
- Statistical framework for application in small sample sizes similar to QTc
- Need additional test drugs
  - Plan to characterize additional drugs for TdP risk and analyze data from the ECG warehouse
  - Potential confirmatory prospective clinical study to be completed in 2017
- Timeline – CiPA validation/qualification package (for all preclinical components and phase 1 ECG) to ICH E14/S7B discussion group by December 2017

Acknowledgements

FDA

- Lars Johannesen
- Jose Vicente
- Norman Stockbridge
- Meisam Hosseini
- Christine Garnett
- Jeffry Florian
- Jiang Liu
- Qianyu Dang

Additional CiPA Phase 1 ECG Team

- Phillip Sager
- Joel Xue
- Fabio Badilini
- Jean-Philippe Couderc
- Robert Kleiman
- Jay Mason
- Jeremy Ruskin
- Catherine Ortemann-Renon
- Corina-Dana Dorta
- Jorg Taubel
- Boaz Mendzelevski
- Colette Strnad

CiPA Steering Committee and Leads

- Jennifer Pierson (HESI)
- Norman Stockbridge

- Ion Channel working group
  - Bernard Fermini
- In silico working group
  - Thomas Colatsky
- Cardiomyocyte group
  - Gary Gintant
- Clinical
  - Philip Sager

- All contributors to CiPA

Thank you