Interpretations based on Phase 1 ECG assessments and New Prospective Validation Study

Session IV: Phase 1 ECG assessment Under CiPA

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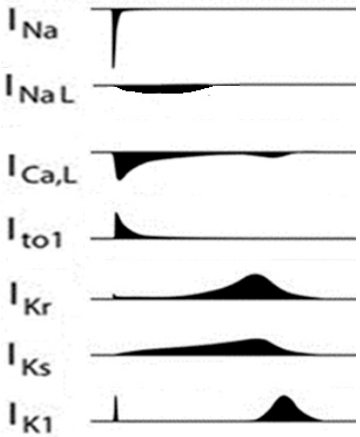
The opinions expressed in this presentation are mine and do not necessarily reflect the official views of the FDA

Comprehensive *in vitro* Proarrhythmia Assay: Four Components

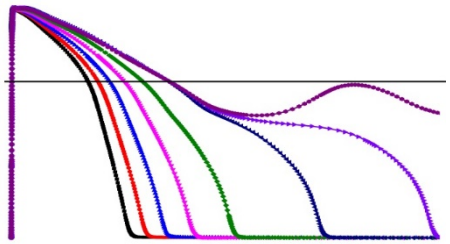
1. High Throughput Assessment of Effects on Multiple Ionic Currents



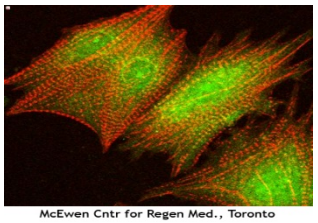
modified from Hoekstra et al., 2012

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

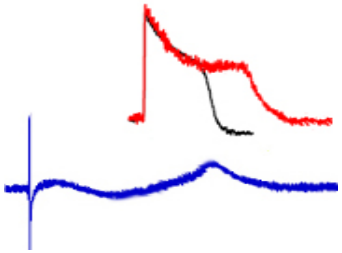
$$I_{stim} = C\frac{dV_m}{dt} + I_m$$



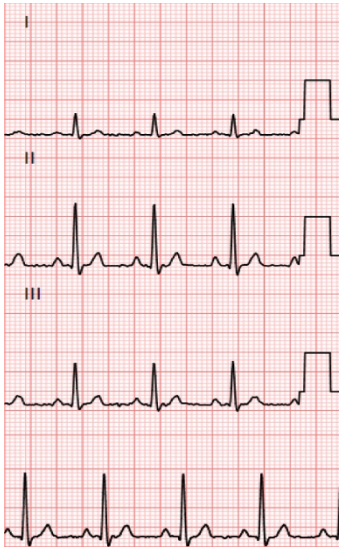
3. *In vitro* Effects on Human Stem-Cell Derived Ventricular Cardiomyocytes



McEwen Cntr for Regen Med., Toronto



4. Evaluation of Unanticipated Effects in Clinical Phase 1 Studies



Goal: Use human phase 1 ECG data to determine if there are unexpected ion channel effects compared to preclinical ion channel data

CiPA Phase 1 ECG Biomarker Assessment

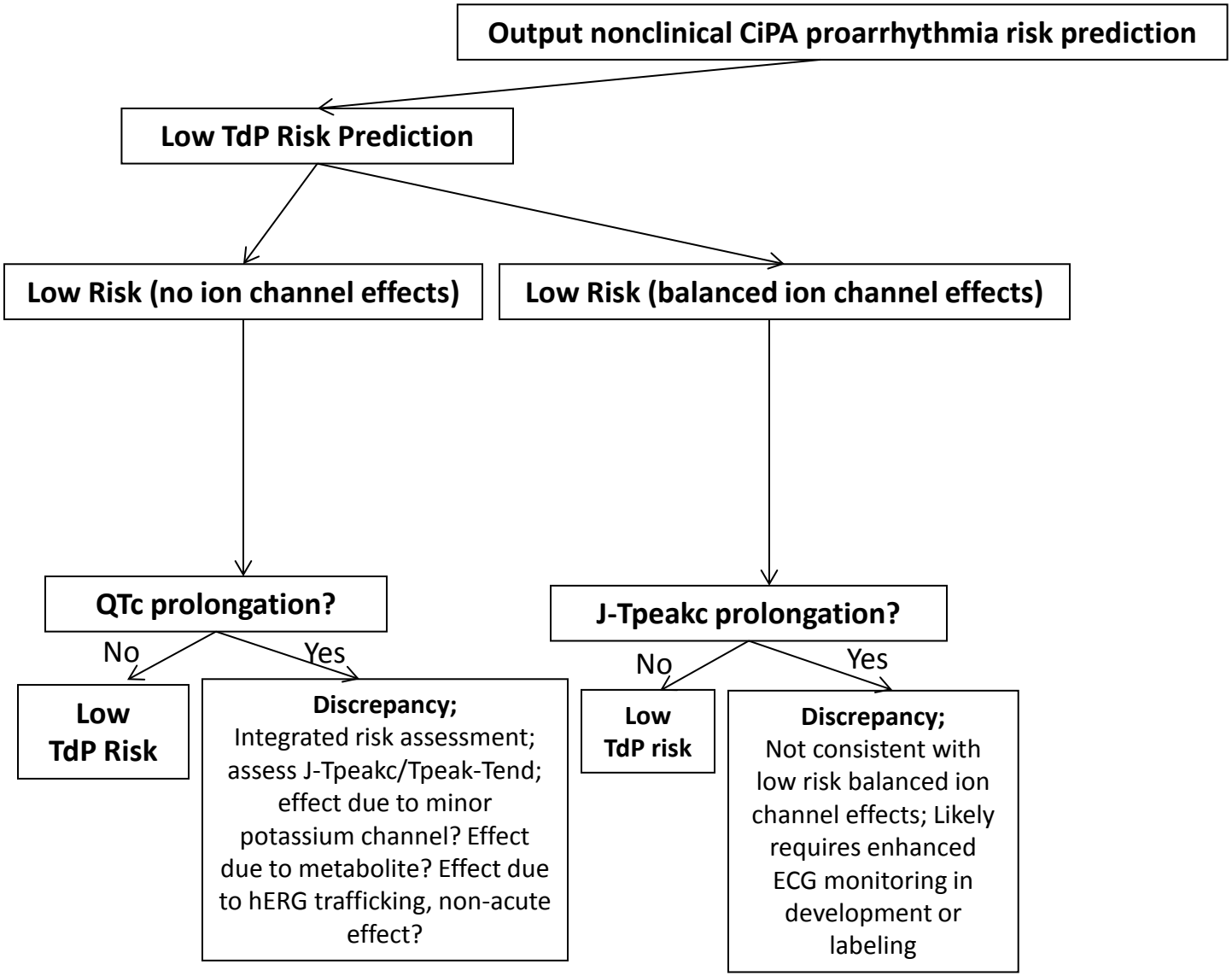
- Goal: Use human phase 1 ECG data to determine if there are unexpected ion channel effects compared to preclinical ion channel data
  - Human specific metabolite, protein binding
- New ECG biomarker(s) would need to add additional information beyond PR/QRS/QTc
  - Differentiate multi-ion channel effects 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 wide-spread use

ECG Biomarker Analysis Summary

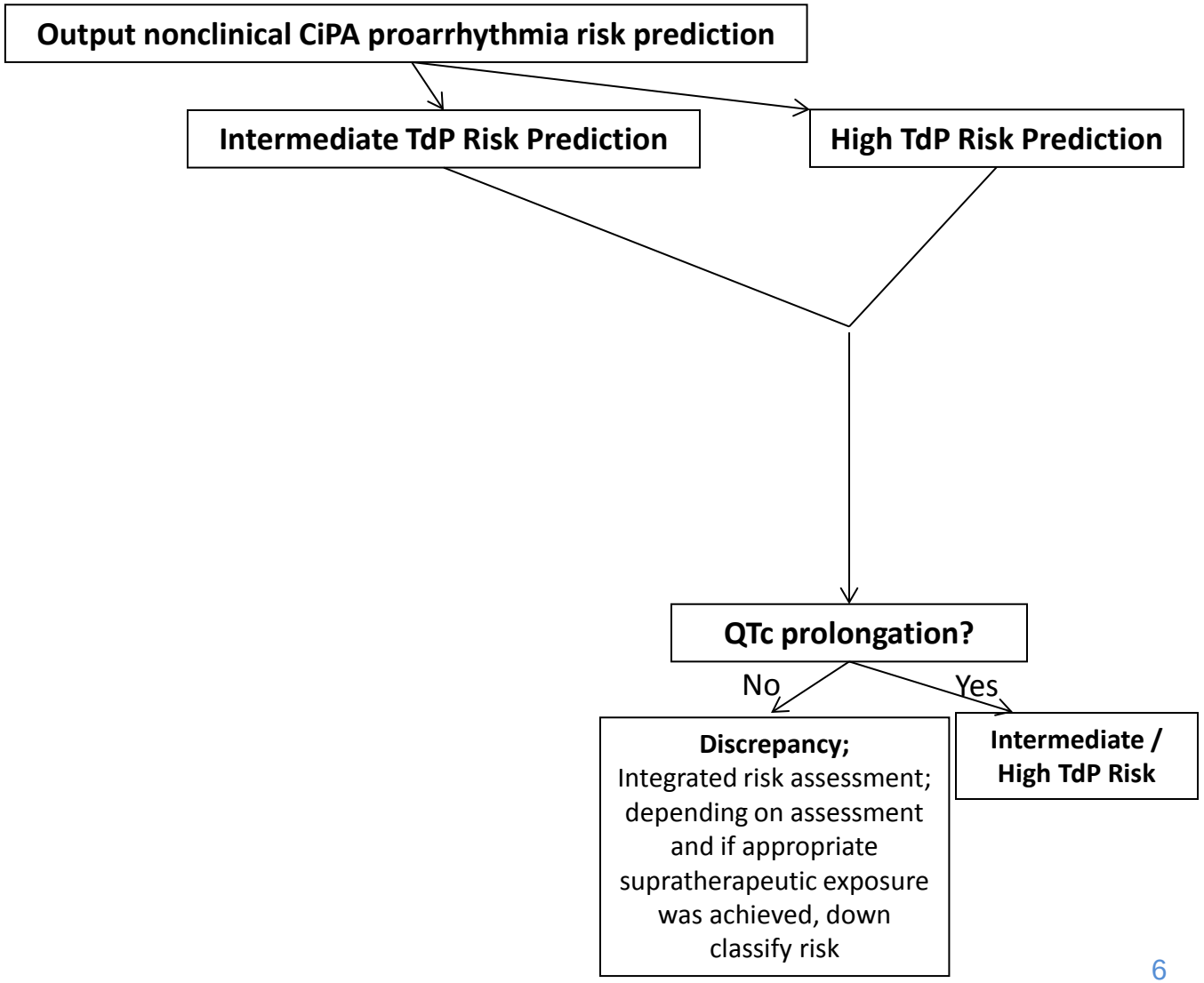
- Examined 12 potential ECG biomarkers and compared to ion channel data
  - 2 prospective FDA-sponsored clinical trials including 8 drugs and 3 drug combinations, some additional drugs
  - Comparison to 7 ion channel current data
- Multiple biomarkers can be applied in exposure-response analysis
- ROC-AUC 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

Johannesen et al. Clin Pharmacol Ther 2014;96:534; Clin Pharmacol Ther 2016;96:549 and Clin Pharmacol Ther 2016;99:214.
Vicente et al. J Am Heart Assoc 2015 pii: e001615;
Vicente et al. PLOS ONE 2016 (in press); Johannesen et al. PLOS ONE 2016 (in press).

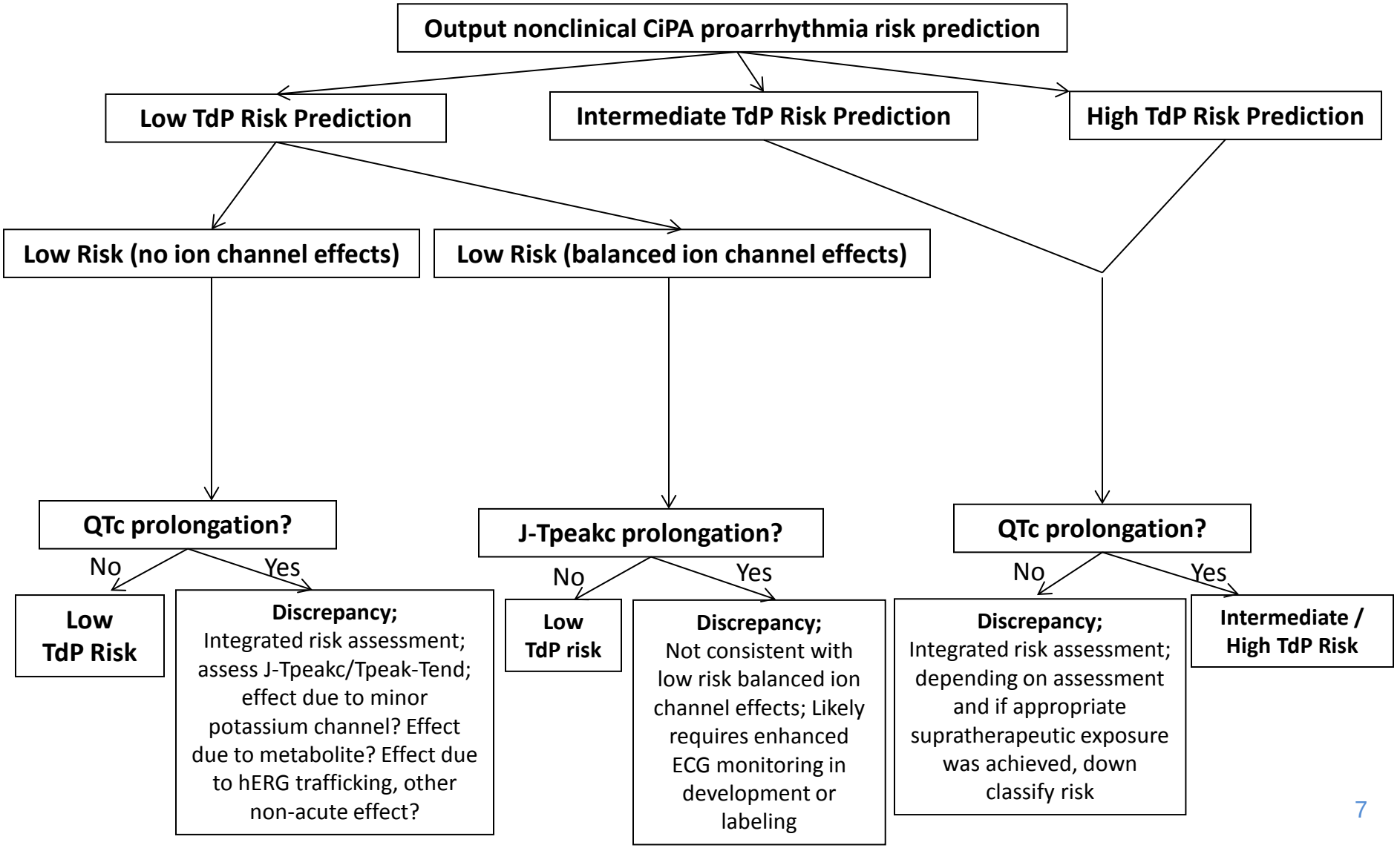
Potential **CiPA Assessment (Low TdP Risk)**



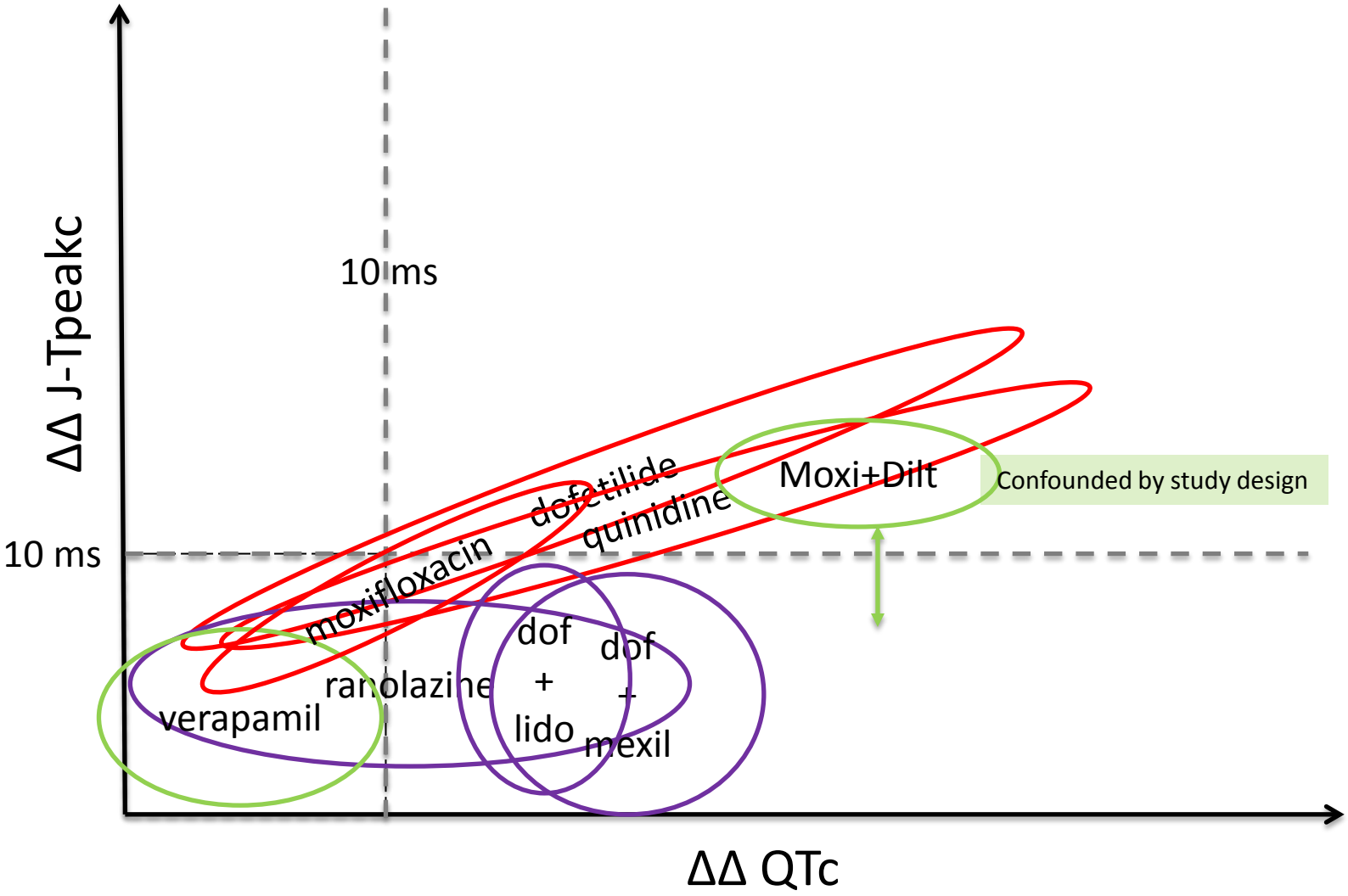
Potential CiPA Assessment (TdP Risk)



Potential **CiPA Assessment**



Clinical Study Data To Date



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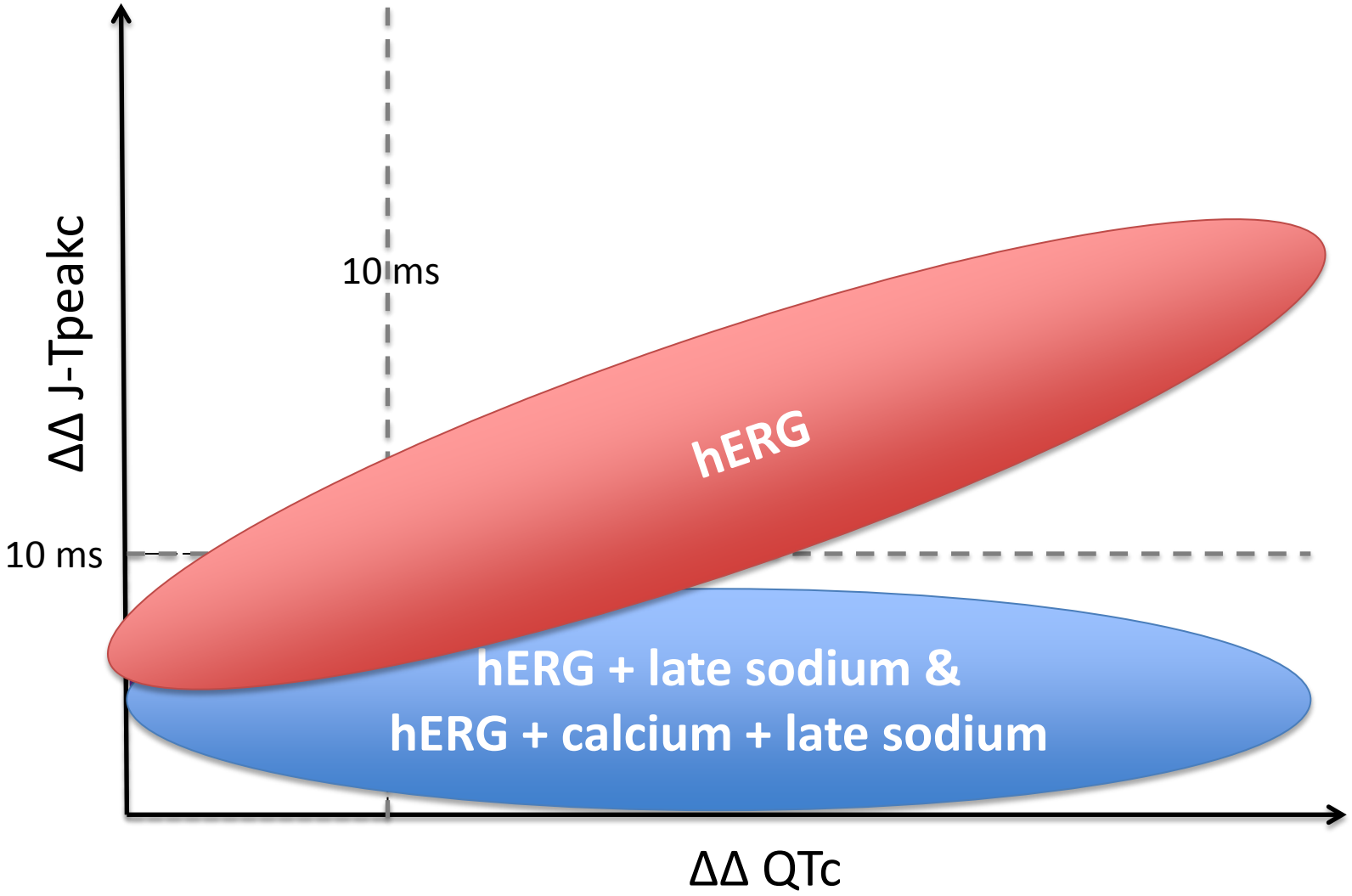


New Prospective Clinical Study

To show that a combined assessment of QTc and J-T_{peak}c can differentiate between drugs that

1. are selective/predominant hERG channel blockers
2. have balanced block of hERG and late sodium and/or calcium

using exposure-response analysis in small sample size Phase 1 clinical study

Two parts:

- Part 1: 50-subject parallel study (4 drugs and placebo)
  - 10 subjects receiving each drug or placebo
- Part 2: 10-subject crossover study

Part 1: Parallel Study – 4 Drugs

TdP risk:

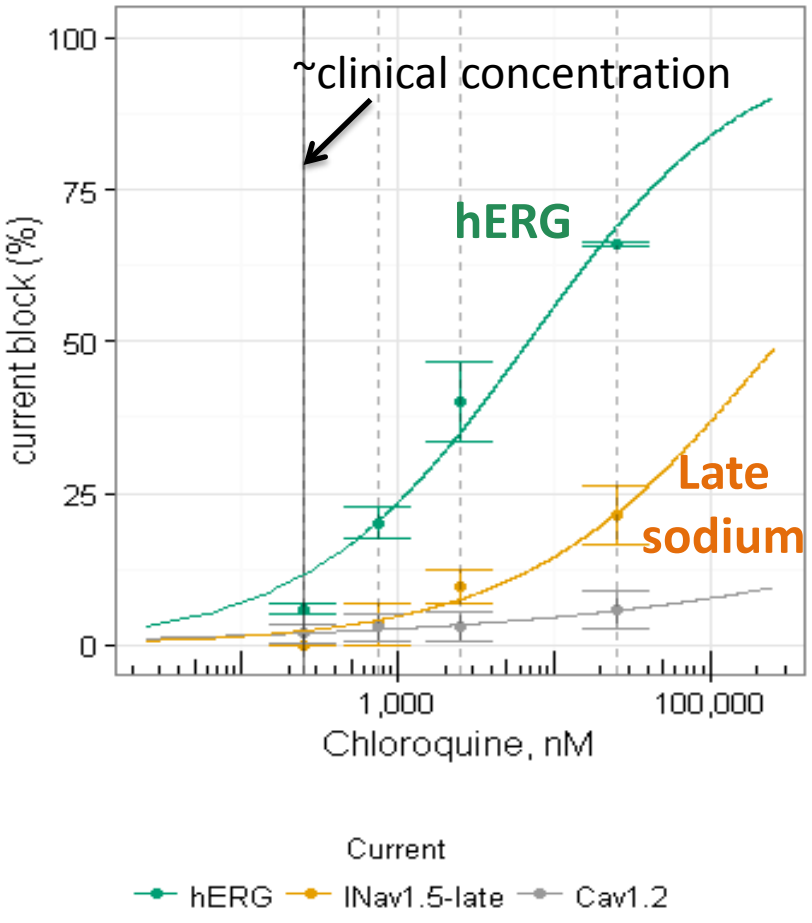
- Chloroquine – Predominant hERG block

Low TdP risk (Balanced ion channel effects):

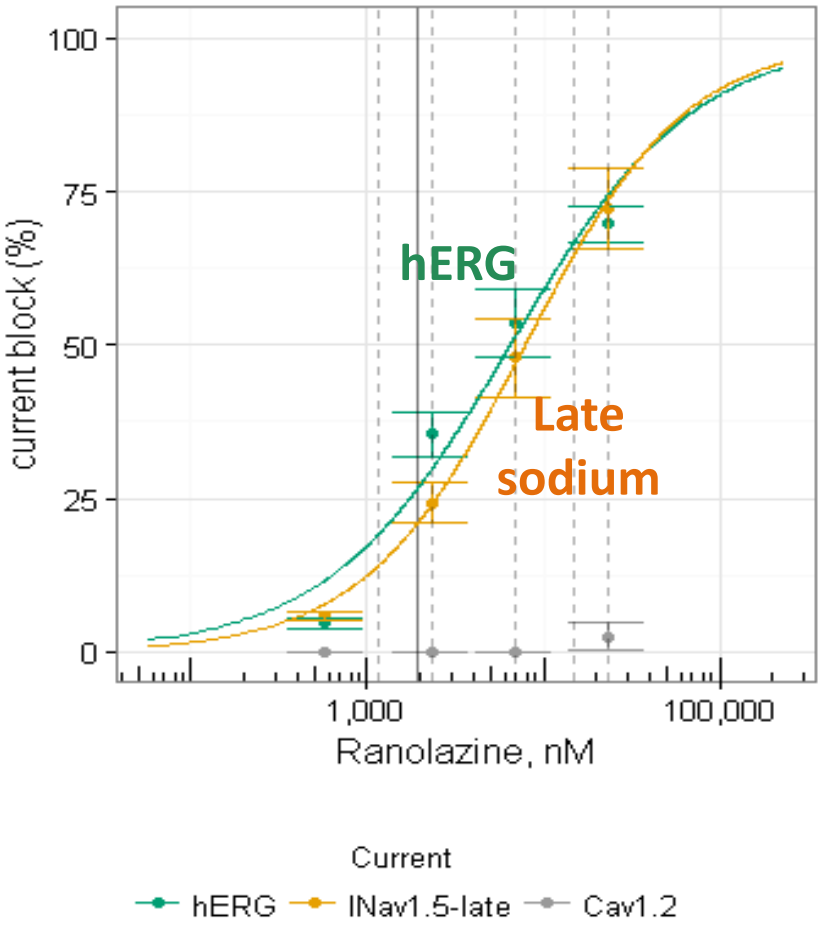
- Ranolazine – Late sodium ≈ hERG block
- Verapamil – Calcium ≈ hERG block
- Lopinavir/ritonavir – Late sodium ≈ calcium ≈ hERG block

Ion Channel Effects

Chloroquine
Predominant hERG block



Ranolazine
hERG ≈ late sodium block

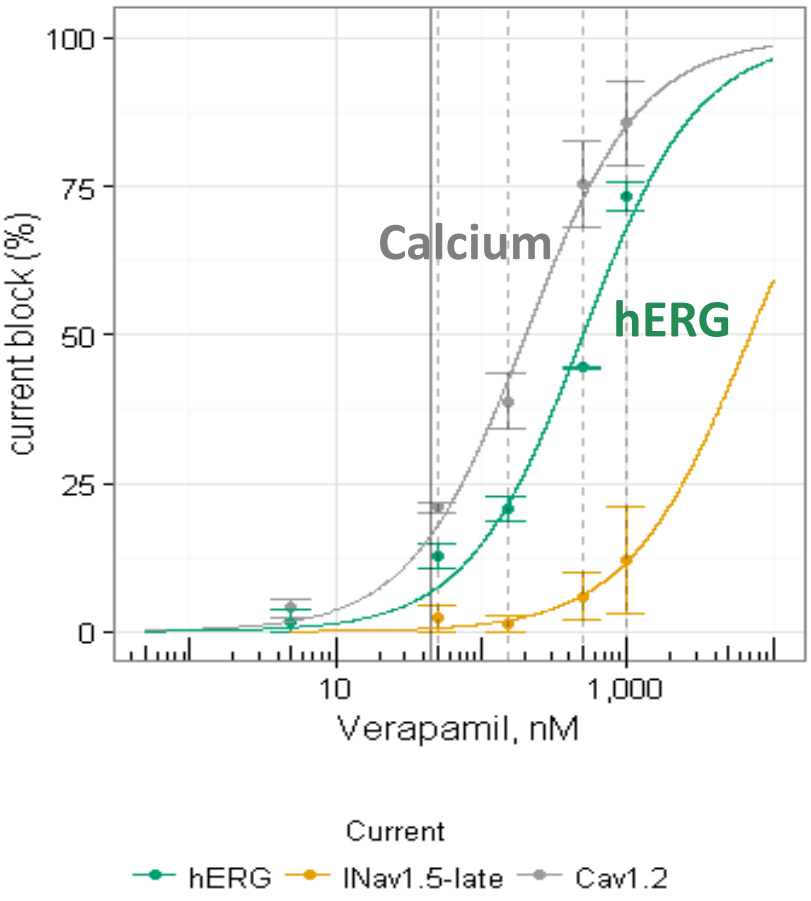


Crumb et al. J Pharm Toxicol Methods 2016;81:251.

Ion Channel Effects

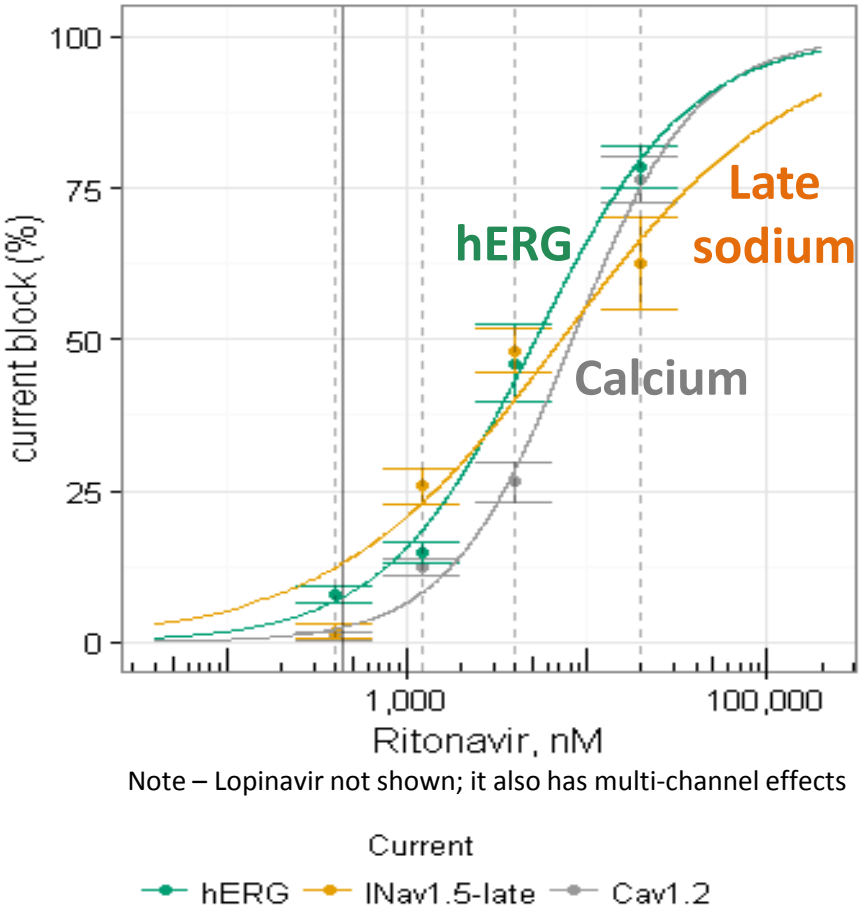
Verapamil

hERG ≈ calcium block



Lopinavir/Ritonavir

hERG ≈ late sodium ≈ calcium block



Note – Lopinavir not shown; it also has multi-channel effects

Crumb et al. J Pharm Toxicol Methods 2016;81:251.

Part 1: Parallel Study Design

- 50 healthy subjects will be enrolled and randomized to one treatment
- Multiple doses of each drug will be given on 3 consecutive days to achieve low exposure on Day 1 and high exposure on Day 3
- Doses have been selected such that
  - Chloroquine, ranolazine and lopinavir/ritonavir are expected to have ~10 ms mean QTc prolongation on Day 1 and ~20 ms QTc prolongation on Day 3
  - Verapamil QTc upper bound likely >10 ms on Day 3
- Data will be analyzed using linear mixed-effects exposure-response models

Part 1: Primary Endpoints

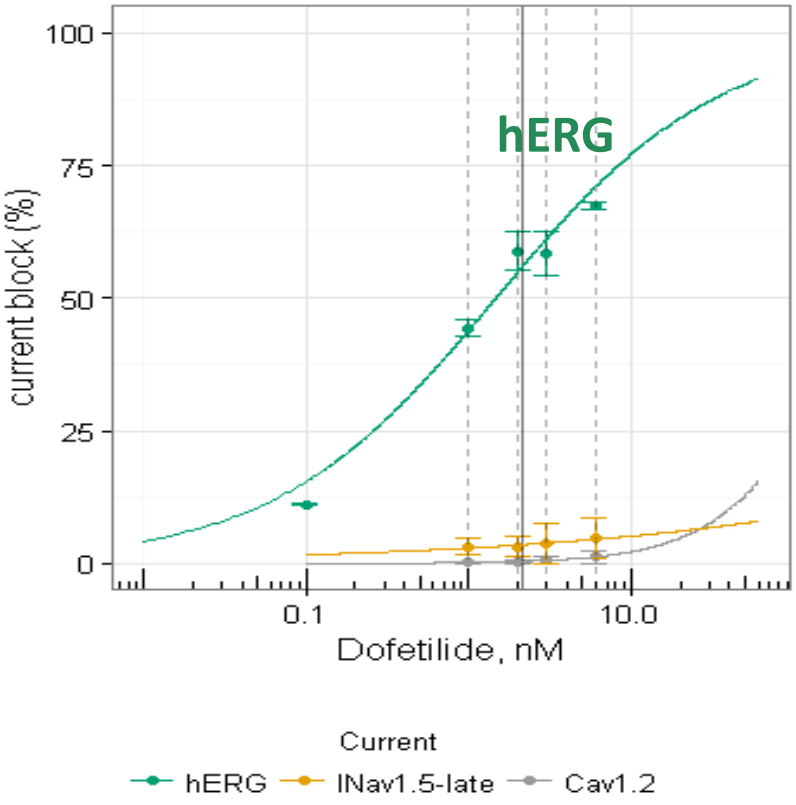
- Predominant hERG block (chloroquine)
  - Upper bound of the 2–sided 90% CI ≥10 ms for the projected QTc effect at the peak plasma level on Day 1 (concentration expected to cause 10 ms QTc prolongation)

- Balanced ion channel drugs (ranolazine, verapamil, lopinavir/ritonavir)
  - Upper bound of the 2–sided 90% CI <10 ms for the projected J-T_{peakC} effect at the peak plasma level on Day 3

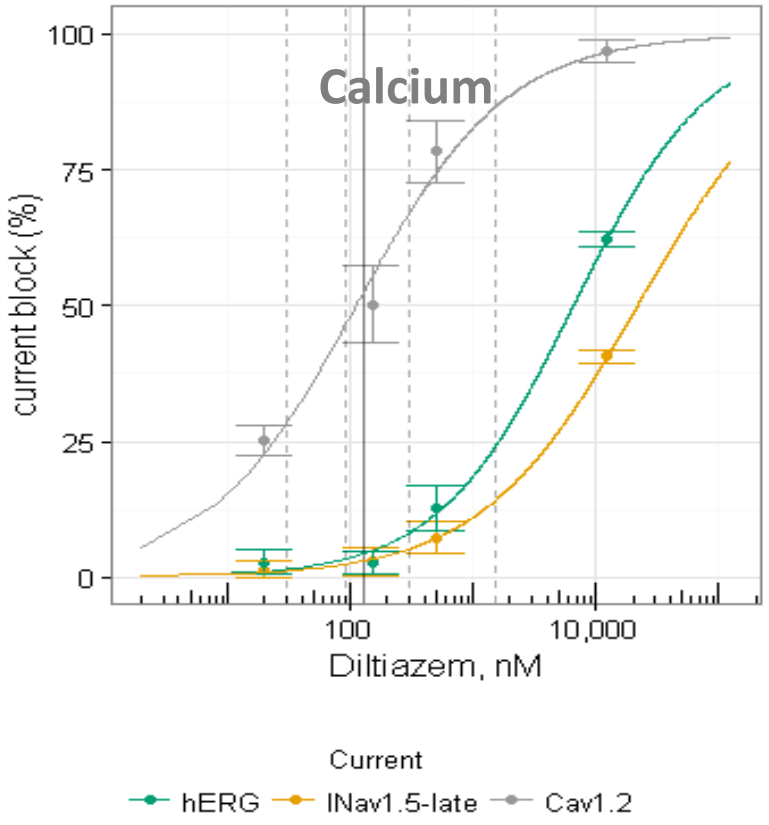
Part 2: Crossover Study Drugs

Period 1 – Dofetilide; Period 2 – Diltiazem/dofetilide

Dofetilide
hERG block



Diltiazem
Calcium block



Crumb et al. J Pharm Toxicol Methods 2016;81:251.

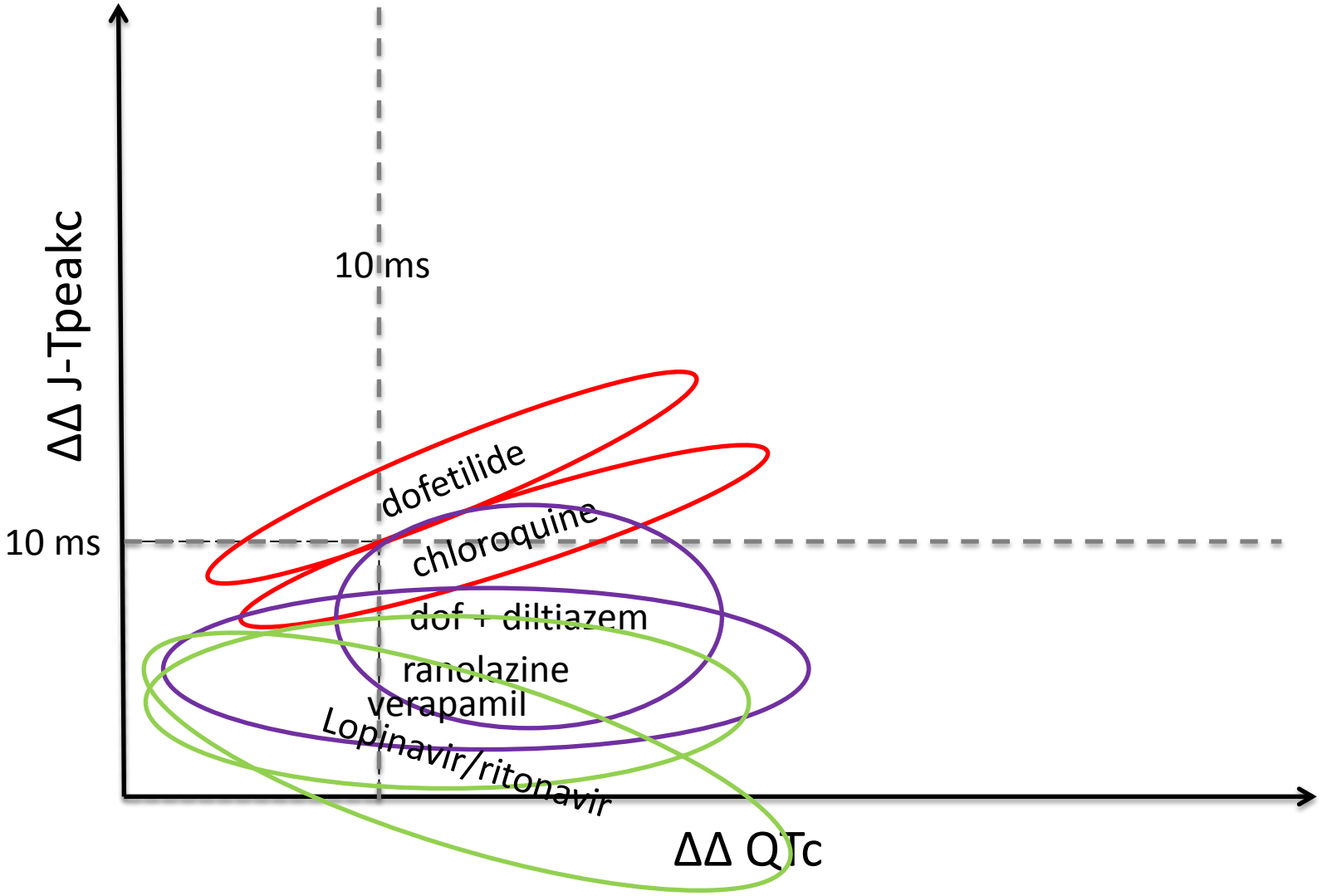
Part 2: Crossover Study Design

- **Objective**: To determine if calcium channel block can reduce the QTc prolongation from hERG by shortening J-Tpeakc

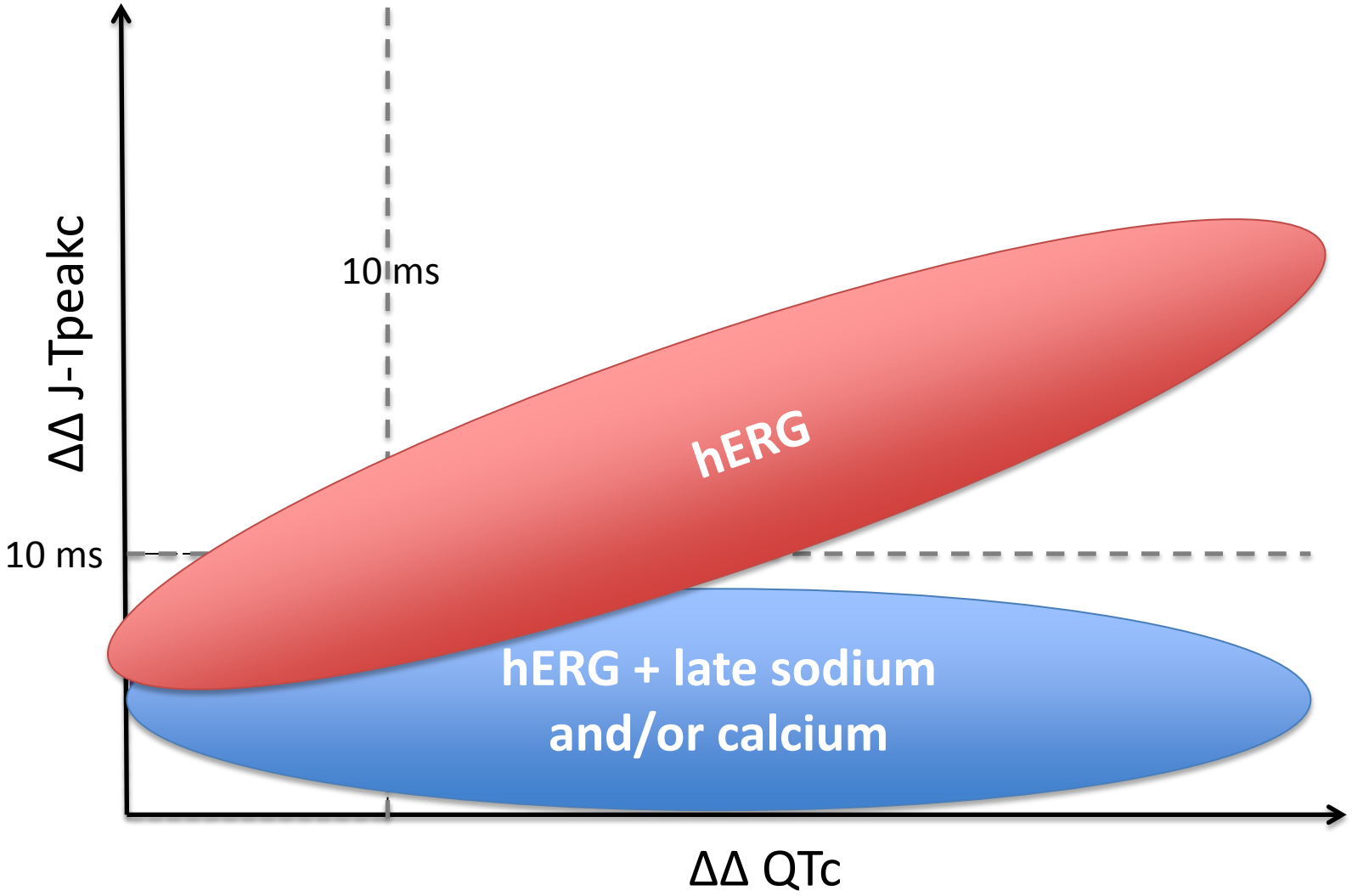
- **Design**: 10 healthy subjects will be randomized to undergo two treatment periods
  - Period 1 – Dofetilide alone
    - Day 1 – Dofetilide dose for ~10 ms QTc prolongation
    - Day 3 – Dofetilide dose for >20 ms QTc prolongation
  - Period 2 – Diltiazem + dofetilide
    - Day 1 and 2 – Diltiazem alone
    - Day 3 – Diltiazem + dofetilide

- **Primary Endpoint**: The criterion for calcium block (diltiazem) effects on the J-Tpeakc prolongation from hERG block (dofetilide) will be
  - whether the significance level of the diltiazem concentration covariate is statistically significant (i.e. $p < 0.05$) with data from both periods pooled using a linear mixed effects model
  - If diltiazem concentration covariate is statistically significant, the same test will be performed to assess calcium block (diltiazem) effects on J-Tpeakc

New Clinical Study Drugs



Clinical Study Data To Date



Summary and Planned CiPA Confirmation Package for December 2017

- Analysis of 12 ECG biomarkers from multiple prior clinical studies demonstrating J-Tpeakc as the best biomarker to differentiate QTc prolonging drugs with selective hERG block from QTc prolonging drugs with hERG and late sodium or calcium block
- Statistical framework for combined analysis of QTc and J-Tpeakc for use in small sample size, early phase 1 clinical studies using exposure-response analysis
- Prospective clinical study to verify this approach including drugs with
  - selective/predominant hERG block (dofetilide, chloroquine)
  - hERG + late sodium block (ranolazine)
  - hERG + calcium block (verapamil, dofetilide+diltiazem)
  - hERG + late sodium + calcium block (lopinavir/ritonavir)
- Analysis of QTc and J-Tpeakc in a large number of prior TQT studies with matching hERG, calcium and late sodium ion channel data
- Freely-available open-source software for J-Tpeakc assessment along with comparison to other commercial software

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Additional CiPA Phase 1 ECG Team

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


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ADMINISTRATION

Potential CiPA Assessment