How Does the CIPA Initiative Relate to the IQ-CSRC Project?

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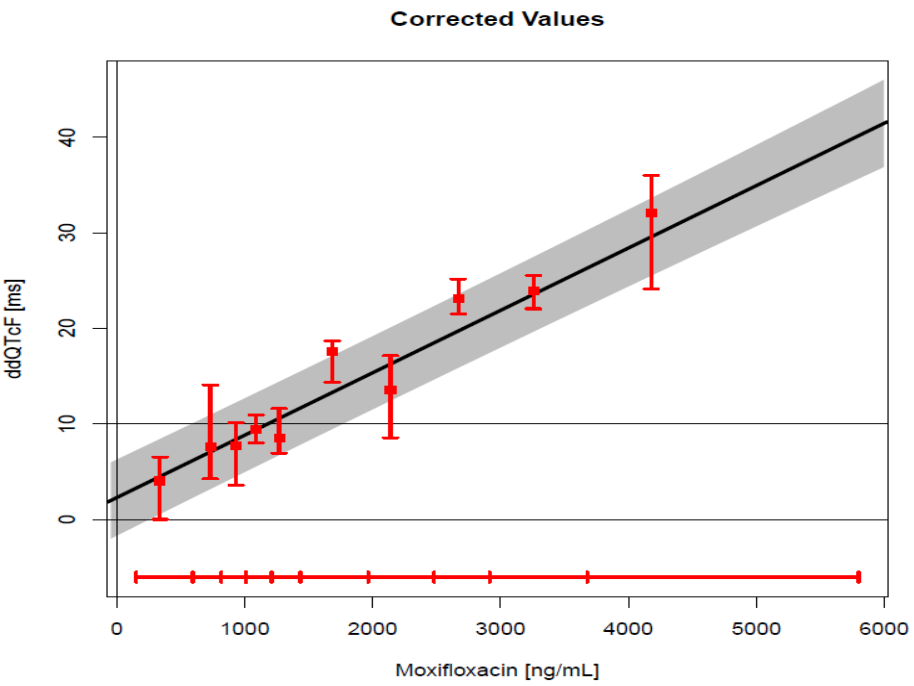
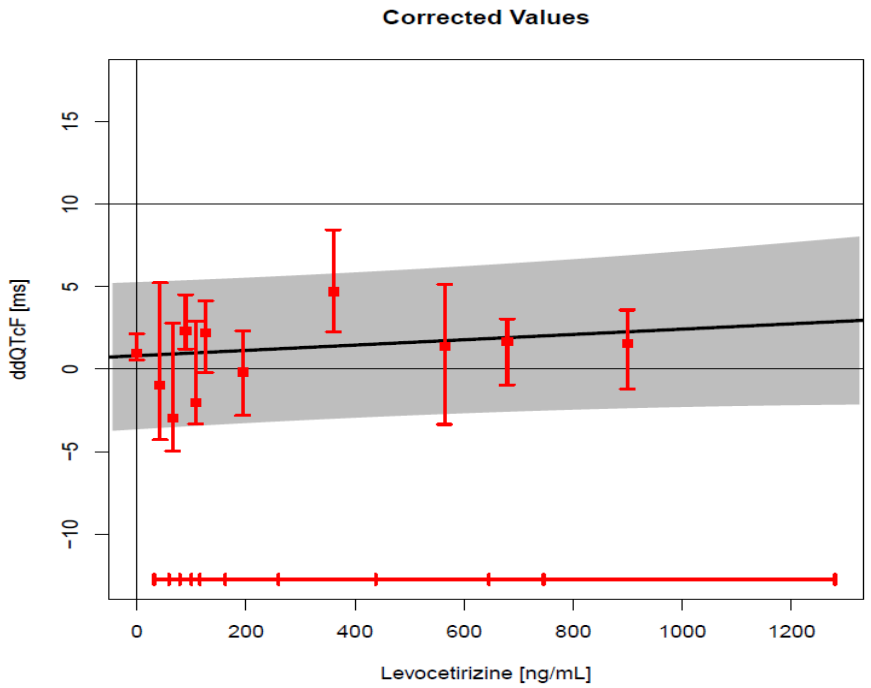
Industry Relationships

Member of DSMB, Adjudication Committee, or Consultant

- Genentech
- Abbvie
- Aerpio
- Akebia
- Balance
- Medtronic
- Biomedical Systems
- ICardiac
- Heart Metabolics
- Milestone
- Theravance
- Lilly
- Viamet
- Shire
- Helsinn
- Celgene
- SNBL
- Pharmacyclics
- Anthera

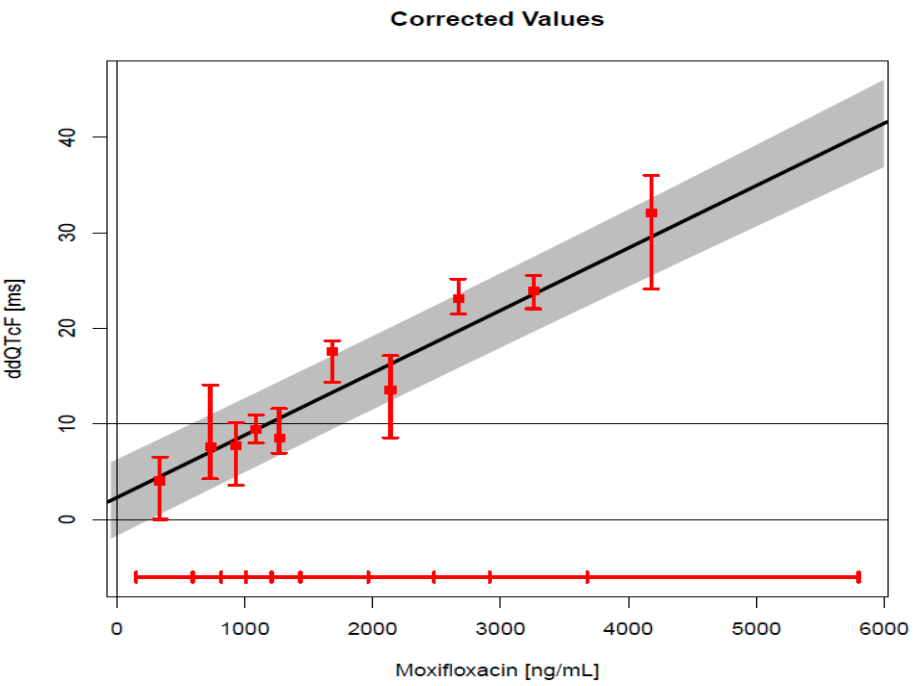
IQ-CSRC Clinical Study

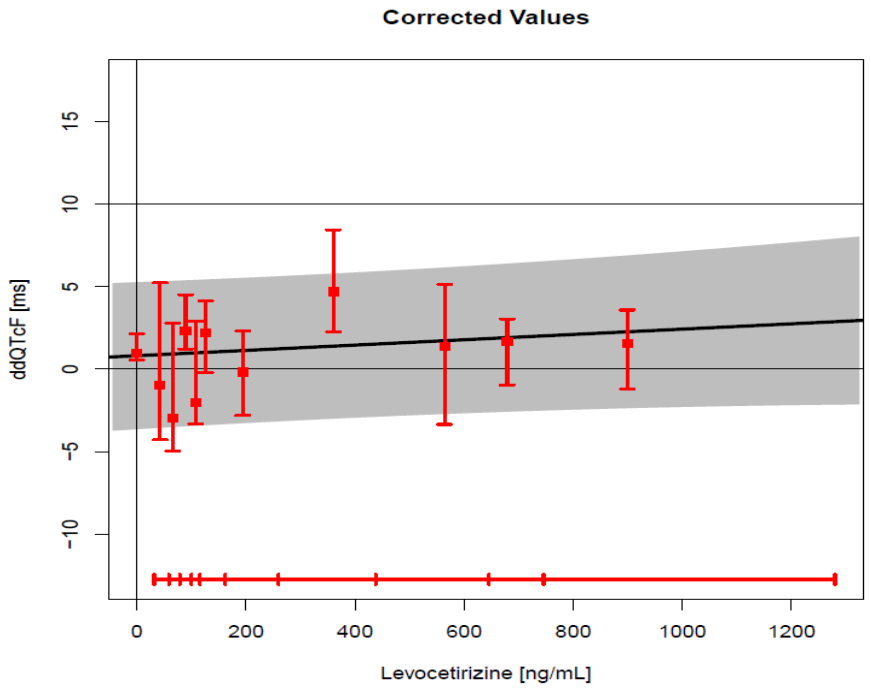




- Demonstrates a sufficiently high level of sensitivity to be considered in lieu of the TQT Study
- Demonstrates the value of PK/PD modeling

IQ-CSRC Clinical Study





- Demonstrates a sufficiently high level of sensitivity to use in lieu of the TQT Study
- **Demonstrates the value of PK/PD modeling**

Achievements/Issues With Current Approach

- ICH E14/S7B have resulted in no drugs with unrecognized risk being approved
- QT prolongation ≠ Proarrhythmia
- HERG block ≠ Proarrhythmia
- Negative impact on drug development
- New paradigm

CIPA

- CIPA is clearly a different paradigm from the current approach
- Focused on the potential of a drug to have a meaningful risk of causing TdP, not on the QTc
- It is not primarily focused on other electrophysiologic effects, such as conduction block
  - Assessment of multiple ion channels should be informative

CiPA: Three Component Proposal

Ionic Currents / In Silico Based Approach

Effects on Multiple Cardiac Currents (Voltage Clamp Studies)

+

Reconstruction of Cellular Electrophysiology (*In Silico* Studies)

Myocyte-Based Approach

Effects on Human Ventricular Myocytes (*In Vitro* Studies)

Human Phase 1 ECG's

Effects on Human ECG morphology/waveforms

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Human Phase 1 ECG's Under CIPA

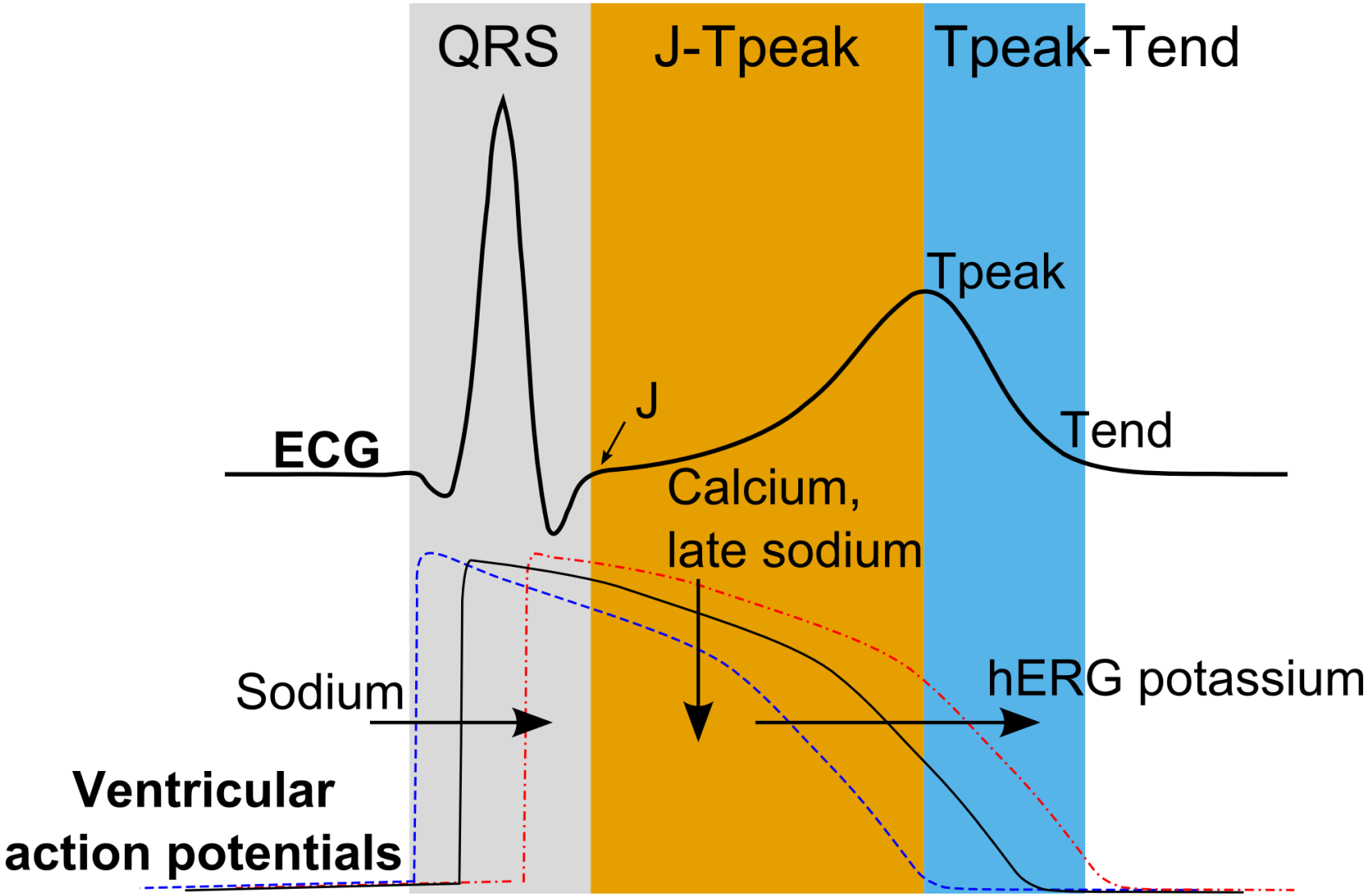
- To confirm that there are not unanticipated drug-induced electrophysiologic/ECG effects based on the preclinical assessments
- Identify preclinical false negatives
    - Untested ion channels
    - Human-specific metabolites
- Unanticipated findings, if of possible clinical significance, might indicate a need for additional analysis
    - Scenario 1- CIPA identifies a compound as being very low risk for TdP and, as expected there is QT prolongation- no further evaluation needed
    - Scenario 2- CIPA identifies a compound as being very low risk for TdP and, there is unexpected QT prolongation- further evaluation may be needed
- Also of interest are other channel effects- Na, Ca ,etc.

Human Phase 1 ECG's

- Also critical for effects on ventricular and AV conduction

- Requires careful ECG interval and waveform assessments
- QT_C PK/PD modeling clearly increases sensitivity and adds value
- Are other novel intervals useful to evaluate?
  - For example, J-T_{peak}, T_{peak}-T_{end}
- Working group will be focusing on this for CIPA

Going Beyond QT to Differentiate Multi-Channel Effects



Johannesen…Strauss. *Clin Pharmacol Ther* 2014;96:549-58.

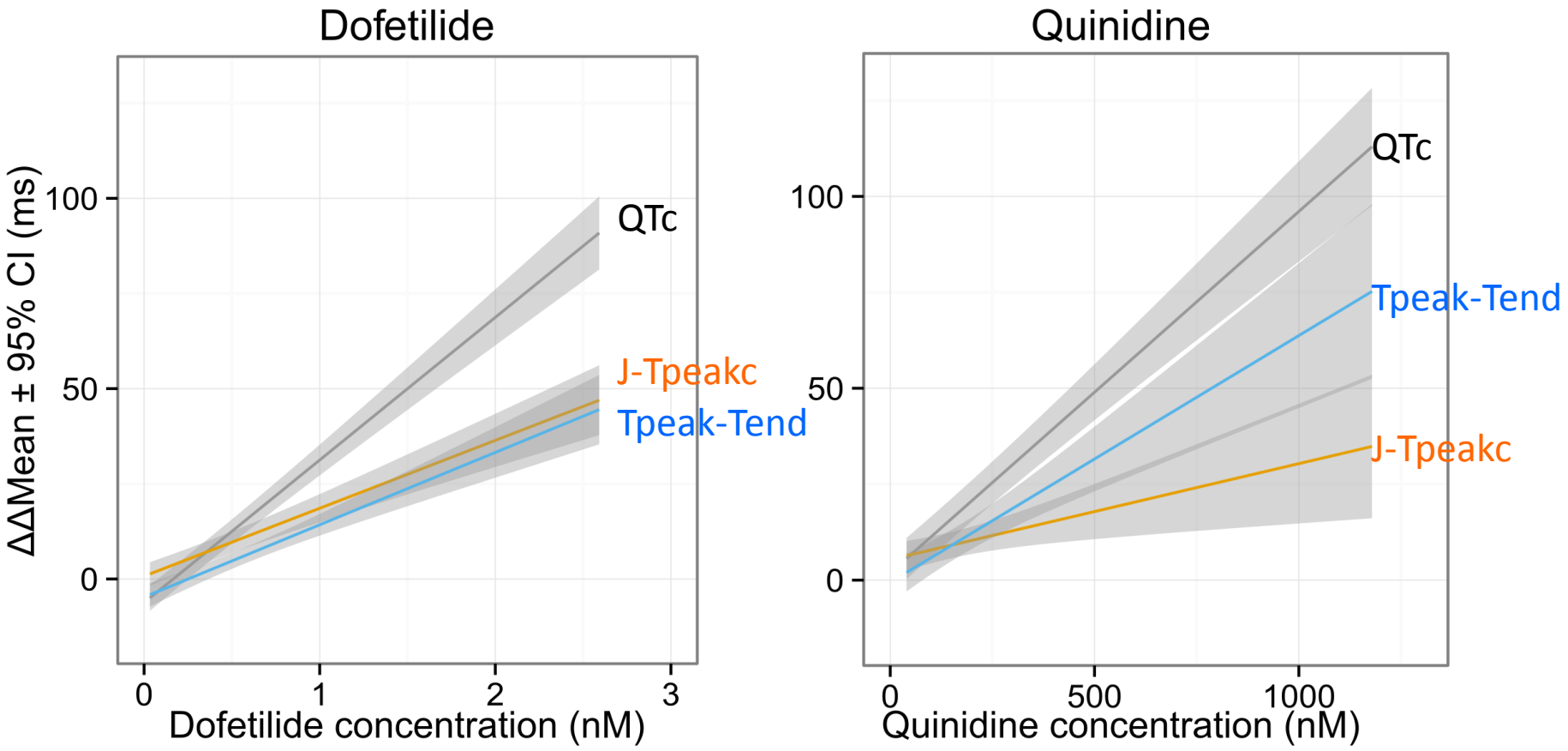
ECG Signature
Dependent on Ion Channel Effects

Table 1 Impact of "pure" and mixed hERG channel blockers on electrocardiographic intervals

ECG interval	"Pure" hERG block (dofetilide)	hERG block + ICa block (verapamil)	hERG block + peak INa (quinidine)	hERG block + late INa (ranolazine)
PR	No Δ	↑	No Δ	No Δ
QRS	No Δ	No Δ	↑	No Δ
QTc	↑	No Δ	↑	↑
$J–T_{peak}$	↑	No Δ	↓	↓
$T_{peak}–T_{end}$	↑	No Δ	↑	↑

PR interval data may be difficult to interpret due to heart rate and autonomic effects

Pure hERG Block (Dofetilide) vs. hERG>Calcium>Sodium Block (Quinidine)



- Pure hERG block equally prolonged J-Tpeak and Tpeak-Tend
- hERG block with additional Ca & Na block prolonged Tpeak-Tend > J-Tpeak

Johannesen…Strauss. *Clin Pharmacol Ther* 2014;96:549-58.

Phase 1 ECG Assessment Under CIPA

- PK/PD modeling of QTc seems appropriate, given higher sensitivity
- Other intervals may provide insight into multi-channel effects
    - QRS, J-T_{peak}, T_{peak}-T_{end}
    - ? Other indices
- Appropriate methodologies need to be defined
    - ECG analysis approach- single lead, composite, vector
- Working group commencing in early 2015

Thank you

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