New ECG Biomarkers and their Potential Role in CiPA: Results and Implications

HESI – CSRC – CiPA Meeting
Washington, DC - May 21, 2018

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for the ECG Biomarker Working Group

Division of Cardiovascular and Renal Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA’s views or policies.
Role of Phase I ECG Data Under CiPA

1. In vitro Assessment of Drug Effects in Multiple Ionic Currents
   - Sodium
   - Calcium
   - hERG Potassium

2. In silico Computer Modeling to Predict Risk
   - $I_{stim} = C \frac{dV_m}{dt} + I_m$

3. In vitro effects on Human Stem Cell Derived Ventricular Cardiomyocytes

4. In vivo ECG Biomarker in Phase 1 Clinical Trials
   - ECG
   - baseline
   - on drug

To determine if there are unexpected ion channel effects compared to preclinical ion channel data

ECG biomarker(s) for CiPA

Can the ECG differentiate predominant hERG block vs. balanced ion channel block?

Observation (2012)
• J-Tpeakc identified as ECG biomarker to detect inward current block in retrospective analysis of 34 drug-safety clinical studies

Confirmation (2013)
• Prospective clinical study (Study 1)

Verification of mechanism of action (2014)
• Prospective clinical study (Study 2)

Validation (2017-2018)
• Prospective CiPA validation clinical study (Study 3)
ECG biomarker(s) for CiPA

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Analysis of 34 ‘Thorough QT’ Clinical Studies

Improving the Assessment of Heart Toxicity for All New Drugs Through Translational Regulatory Science

L Johannesen¹,²,³, J Vicente²,⁴, RA Gray², L Galeotti², Z Loring², CE Garnett¹,⁵, J Florian¹, M Ugander²,³, N Stockbridge⁶ and DG Strauss²


- Analysis of 500,000 digital ECGs from 34 clinical studies
- Identified ECG biomarker (J-Tpeak) that could differentiate predominant hERG blocking drugs from balanced ion channel blockers
ECG Biomarkers to Differentiate hERG vs. Balanced Ion Channel Block

Retrospective Analysis of TQT Studies

Retrospective analysis of 34 thorough QT studies revealed patterns of QTc prolongation

Predominant hERG block
- Prolongs QTc, J-Tpeakc and Tpeak-Tend

hERG + late sodium and/or calcium block
- Prolongs QTc and Tpeak-Tend, while shortening or having no effect on J-Tpeakc

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- J-Tpeakc identified as ECG biomarker to detect inward current block in retrospective analysis of 34 drug-safety clinical studies

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Prospective Clinical Study 1

Differentiating Drug-Induced Multichannel Block on the Electrocardiogram: Randomized Study of Dofetilide, Quinidine, Ranolazine, and Verapamil

L Johannesen¹,², J Vicente¹,³, JW Mason⁴, C Sanabria⁴, K Waite-Labott⁴, M Hong⁵, P Guo⁵, J Lin⁵, JS Sørensen⁶, L Galeotti¹, J Florian⁶, M Ugander¹,², N Stockbridge⁷ and DG Strauss¹,²


**Goal:** To confirm ECG signatures of predominant hERG vs. balanced ion channel block observed in retrospective analysis of 34 thorough QT studies
Clinical Study 1 – Drugs & Channel Block

<table>
<thead>
<tr>
<th></th>
<th>hERG Block</th>
<th>Late Sodium Block</th>
<th>Calcium Block</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dofetilide</td>
<td>++++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinidine</td>
<td>+++++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Ranolazine</td>
<td>+++</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td>+++</td>
<td></td>
<td>+++</td>
</tr>
</tbody>
</table>

+ = weak channel block
+++++ = strong channel block
hERG vs. balanced ion channel block

Dofetilide (predominant hERG block)

- hERG block prolonged QTc by prolonging J-Tpeakc and Tpeak-Tend
- Balanced ion channel block prolonged QTc by prolonging Tpeak-Tend with no effect on J-Tpeakc

Ranolazine (hERG + late sodium)

ECG biomarker(s) for CiPA

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Confirmation (2013)
- Prospective clinical study (Study 1)

Verification of mechanism of action (2014)
- Prospective clinical study (Study 2)

Validation (2017-2018)
- Prospective CiPA validation clinical study (Study 3)
Late Sodium Current Block for Drug-Induced Long QT Syndrome: Results From a Prospective Clinical Trial

L Johannesen¹,², J Vicente¹,³,⁴, JW Mason⁵,⁶, C Erato⁵, C Sanabria⁵, K Waite-Labott⁵, M Hong⁷, J Lin⁷, P Guo⁷, A Mutlib⁷, J Wang⁷, WJ Crumb⁸, K Blinova¹, D Chan¹, J Stohlman¹, J Florian³, M Ugander¹,², N Stockbridge³ and DG Strauss¹,²


**Goal:** To confirm mechanism of ECG signatures of predominant hERG vs. balanced ion channel block (hERG + late sodium)
Clinical Study 2: hERG+late sodium Design

• Can we re-create the ECG ‘signature’ of ranolazine by combining a predominant hERG blocking drug with late sodium current blocker?
  – Dofetilide + mexiletine = ranolazine?
  – Dofetilide + lidocaine = ranolazine?

<table>
<thead>
<tr>
<th></th>
<th>hERG Block</th>
<th>Late Sodium Block</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranolazine</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>++++</td>
<td></td>
</tr>
<tr>
<td>Mexiletine</td>
<td></td>
<td>+++</td>
</tr>
<tr>
<td>Lidocaine</td>
<td></td>
<td>+++</td>
</tr>
</tbody>
</table>
Clinical Study 2: ECG Effect of hERG + Late Sodium Block

Late sodium current block shortens QTc

Late sodium current block shortens J-T_{peakc}

Late sodium current block has no effect on T_{peak}-T_{end}

J-Tpeakc, QTc and other ECG biomarkers
hERG vs. Balanced Ion Channel Block

• ROC-AUC analysis for the ability of each biomarker to discriminate individual ECGs from
  • Balanced ion channel block vs.
  • Predominant hERG block
• J-T_{peakc} is the best discriminator for the presence of late sodium current block
  • ΔΔJ-T_{peakc} < 9ms → Late Na

ECG biomarker(s) for CiPA

Observation (2012)
• J-Tpeakc identified as ECG biomarker to detect inward current block in retrospective analysis of 34 drug-safety clinical studies

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Validation (2017-2018)
• Prospective CiPA validation clinical study (Study 3)
Prospective Clinical Study 3

Mechanistic Model-Informed Proarrhythmic Risk Assessment of Drugs: Review of the “CiPA” Initiative and Design of a Prospective Clinical Validation Study

Jose Vicente¹, Robbert Zusterzeel², Lars Johannesen², Jay Mason³,⁴, Philip Sager⁵, Vikram Patel², Murali K. Matta², Zhihua Li², Jiang Liu², Christine Garnett¹, Norman Stockbridge¹, Issam Zineh² and David G. Strauss²


• To validate the proposed role of phase I ECG assessment under CiPA (differentiate ECG signature of predominant hERG vs. balanced ion channel block)
• To assess whether calcium block shortens hERG block induced QTc prolongation by shortening J-Tpeakc
Clinical Study 3 Part 1: Design and Hypotheses

- 10 subjects per treatment arm
- Balanced ion channel blockers do not prolong J-Tpeakc at Cmax on Day 3 (high exposure)
- Predominant hERG blocker prolongs QTc at Cmax on Day 1 (low exposure)

Ion channel data: Crumb et al. J Pharmacol Toxicol Methods 2016; Study design: Vicente et al. Clin Pharm Ther 2018
Study Design

![Graph showing chloroquine and ranolazine levels over days 1, 2, and 3.](image)
Part 1 results: Ranolazine (hERG + late sodium)

- Concentration-QTc prolongation
- Flat J-Tpeakc slope, upper bound 12 ms
Part 1 results: Verapamil (hERG + calcium)

- Concentration-QTc prolongation
- No J-Tpeakc prolongation (upper bound < 10 ms)
Part 1 results: Lopinavir/ritonavir (hERG+calcium+late sodium)

- QTc prolongation (nonlinear)
- No J-Tpeakc prolongation (upper bound < 10 ms)

**Table: ΔΔQTcF and ΔΔJ-Tpeakc**

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔΔQTcF (ms)</td>
<td>13.3 [7.9 to 18.7]*</td>
<td>31.5 [20.2 to 42.9]*</td>
</tr>
<tr>
<td>ΔΔJ-Tpeakc (ms)</td>
<td>3.6 [-2.4 to 9.7]</td>
<td>-2.6 [-11.4 to 6.1]</td>
</tr>
</tbody>
</table>

* Poor model fit, so QTc estimates should be interpreted with caution.
Part 1 results: Chloroquine (hERG)

- QTc prolongation
- J-Tpeakc prolongation (large intercept with flat slope)

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔΔQTcF (ms)</td>
<td>30.7 [22.6 to 38.9]</td>
<td>50.5 [38.5 to 62.5]</td>
</tr>
<tr>
<td>ΔΔJ-Tpeakc (ms)</td>
<td>12.1 [6.1 to 18.2]*</td>
<td>14.9 [3.7 to 26.0]*</td>
</tr>
</tbody>
</table>

* Poor model fit, so J-Tpeakc estimates should be interpreted with caution
Clinical Study Part 1 Summary

• Concentration-dependent $\Delta \Delta QTc$ prolongation was observed for all the drugs in Part 1

• Balanced ion channel blockers had flat or negative $\Delta \Delta J$-$\text{Tpeakc}$ slope
  – Verapamil and Lopinavir/ritonavir upper bound < 10 ms
  – Ranolazine upper bound 2 ms above threshold

• Predominant hERG block (chloroquine) prolonged both $\Delta \Delta QTc$ and $\Delta \Delta J$-$\text{Tpeakc}$
Clinical Study 3 Part 2: Design and Hypotheses

2 Period crossover design with 10 subjects

<table>
<thead>
<tr>
<th>Period 1</th>
<th>Day 1: low exposure</th>
<th>Day 2</th>
<th>Day 3: high exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dofetilide hERG</td>
<td>Placebo</td>
<td>Dofetilide hERG</td>
<td></td>
</tr>
<tr>
<td>Diltiazem Calcium</td>
<td>Diltiazem Calcium</td>
<td>Diltiazem + Dofetilide Calcium + hERG</td>
<td></td>
</tr>
</tbody>
</table>

Placebo (from Part 1)

- Diltiazem shortens dofetilide-induced QTc prolongation by shortening J-Tpeakc
  - \( H_0: \Delta QTc \text{ (Dof Cmax, Dilt=0)} \leq \Delta QTc \text{ (Dof Cmax, Dilt Cmax)} \)
    - Dof Cmax from Dilt+Dof day 3
- If success for QTc, then test for J-Tpeakc
Study Design and PK profile

Period 1
Day 1
Day 2
Day 3

**Dofetilide**

Period 2
Day 1
Day 2
Day 3

**Diltiazem**

**Placebo**

**Dofetilide**

**Dofetilide**

**Time (hours after first dose)**

**Dofetilide (pg/mL)**

**Diltiazem (ng/mL)**
Study 3 - Part 2 results: dofetilide (hERG) vs. diltiazem + dofetilide (calcium + hERG)

- Diltiazem (calcium block)
  - Did not reduce ΔΔQTc prolongation by dofetilide
  - Shortened dofetilide-induced prolongation of ΔΔJ-Tpeakc in the exploratory analysis
  - Further prolonged ΔΔTpeak-Tend
Study 3 - Part 2 Summary

• Diltiazem (calcium block) did not reduce ΔQTc prolongation by dofetilide (hERG block)
• Diltiazem reduced ΔJ-Tpeakc prolongation caused by dofetilide
• The reason for the lack of QT shortening with diltiazem is unclear, however may be due to indirect effects
  – e.g. autonomic response from decreased blood pressure or increased ventricular loading from prolonged PR
• Of note, verapamil and lopinavir/ritonavir (which have hERG and calcium block) prolonged QTc without prolonging J-Tpeakc in Part 1
Challenges

- Nonlinear concentration-response relationships

- Diltiazem (calcium block) did not shorten QTc prolongation by dofetilide (hERG block)

- Better J-Tpeak/RR characterization may help to reduce variability of J-Tpeakc measures
Reproducibility of Results

• Previous Clinical Study 1 results for J-Tpeak measures have been reproduced using alternative ECG methods

• Special issue of J Electrocardiol with results of ISCE’s 2017 J-Tpeak initiative
  – Couderc et al.; Badilini et al.; Chien et al.; Chiu et al.; and Vicente et al.

• Also, Brockway et al. Clin Pham Ther 2017
Summary of ECG Findings

• Balanced ion channel blockers that prolonged QTc had a flat or negative J-Tpeakc slope

• Predominant hERG blockers prolonged both QTc and J-Tpeakc

• Exposure-response analysis of QTc and J-Tpeakc could differentiate hERG vs. balanced ion channel block in small sample sized study
hERG vs. balanced ion channel block

Dofetilide (predominant hERG block)

- hERG block prolonged QTc by prolonging J-T_{peakc} and T_{peak}-T_{end}

Ranolazine (hERG + late sodium)

- Balanced ion channel block prolonged QTc by prolonging T_{peak}-T_{end} with no effect on J-T_{peakc}

Potential impact of CiPA

- Can CiPA nonclinical proarrhythmia assessment combined with clinical ECG assessment better inform ECG monitoring (e.g., in specific populations and in the range of 10-20ms mean ΔΔQTc prolongation)?
Acknowledgements

• FDA Team
  – Lars Johannesen
  – Robbert Zusterzeel
  – Roberto Ochoa-Jimenez
  – Meisam Hosseini
  – Murali Matta
  – Vikram Patel
  – Christine Garnett
  – Jeff Florian
  – Jiang Liu
  – Norman Stockbridge
  – David Strauss

• Additional CiPA Phase 1 ECG Team
  – Philip Sager
  – Joel Xue
  – Fabio Badilini
  – Jean-Philippe Couderc
  – Robert Kleiman
  – Jay W. Mason
  – Jeremy Ruskin
  – Catherine Ortemann-Renon
  – Corina-Dana Dorta
  – Jorg Taubel
  – Boaz Mendzelevski
  – Colette Strnad
  – Jennifer Pierson
Role of Phase I ECG Data Under CiPA

To determine if there are unexpected ion channel effects compared to preclinical ion channel data

Publicly available resources

- **FDA Study 3**: release planned after primary results manuscript

- Automated algorithm for J-\(T_{\text{peak}}\) and \(T_{\text{peak}}-T_{\text{end}}\)
  - **Open source code** available at: https://github.com/FDA/ecglib

- ECG signals and clinical data from 2 FDA-sponsored clinical trials
  - **FDA Study 1** (NCT01873950) data are available at PhysioNet's PhysioBank https://physionet.org/physiobank/database/ecgrdvq/ (doi:10.13026/C2HP45) as well as at the Telemetric and Holter ECG Warehouse http://thew-project.org/Database/E-OTH-12-5232-020.html
    - Vicente et al. J Am Heart Assoc. 2015. doi: 10.1161/JAHA.114.001615

  - **FDA Study 2** (NCT02308748) data are available at PhysioNet's PhysioBank https://physionet.org/physiobank/database/ecgdmmld/ (doi:10.13026/C2D016)
Ion Channel Effects

Chloroquine

Ranolazine

Verapamil

Lopinavir

Ritonavir

Quinidine

Dofetilide

Diltiazem

Vicente et. al JAHA 2015
## Summary of ECG effects

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low concentration Day 1</th>
<th>High concentration Day 3</th>
<th>CiPA risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>QTc (ms)</td>
<td>J-Tpeakc (ms)</td>
<td>J-Tpeakc (ms)</td>
</tr>
<tr>
<td>Ranolazine</td>
<td>14.1 [7.5 to 20.8]</td>
<td>2.2 [-4.3 to 8.7]</td>
<td>1.2 [-9.5 to 12.0]</td>
</tr>
<tr>
<td>Verapamil</td>
<td>13.9 [10.0 to 17.8]</td>
<td>3.6 [-2.4 to 9.7]</td>
<td>-2.6 [-11.4 to 6.1]</td>
</tr>
<tr>
<td>Lopinavir + Ritonavir</td>
<td>13.3 [7.9 to 18.7]*</td>
<td>1.2 [-5.4 to 7.8]</td>
<td>-2.9 [-14.6 to 8.8]</td>
</tr>
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<td>Chloroquine</td>
<td>30.7 [22.6 to 38.9]</td>
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<td>14.9 [3.7 to 26.0]*</td>
</tr>
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</table>

Values reported as mean predictions and 90% confidence intervals at Cmax on days 1 and 3

*: Fit of exposure-response lopinavir-QTc and chloroquine-J-Tpeakc models were poor and therefore estimates should be interpreted with caution
ICH S7B Non-Clinical Testing Strategy (with CiPA?)

CiPA Assessment

Non-clinical Testing Strategy

- In Vitro $I_{Kr}$ Assay
- In Vivo QT Assay

IKr or QT positive?

Follow-up Studies

Integrated Risk Assessment

Evidence of Risk

Chemical/Pharmacological Class

Relevant Non-clinical and Clinical Information
J-T Peak c separates predominant hERG block from balanced ion channel block

- J-T Peak c 10 ms cut off separates predominant hERG block from balanced ion channel block (hERG + late sodium)
- Other measurement methods (e.g. from other leads) may result in different thresholds
QT and J-Tpeak Heart Rate Dependency

Biomarker-RR relationship for two different subjects (red vs. blue) at baseline

\[ J - T_{peak} = \frac{J - T_{peak}}{RR^{0.58}} \]

- Ongoing collaboration with Dr. Malik to characterize J-Tpeakc/RR hysteresis

<table>
<thead>
<tr>
<th>For 22 Subjects</th>
<th>QT</th>
<th>J-Tpeak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Slope</td>
<td>0.29</td>
<td>0.53</td>
</tr>
<tr>
<td>SD of Slope</td>
<td>0.07</td>
<td>0.12</td>
</tr>
<tr>
<td>SD/Mean (%)</td>
<td>24%</td>
<td>23%</td>
</tr>
</tbody>
</table>
Methods – Part 1

• Linear mixed effects model
  QTc (or J-Tpeakc) ∼ TIME + ACTIVE + CONC + (1 + CONC|USUBJID)
  – TIME and ACTIVE categorical
  – CONC set to 0 for placebo

• If model fit ok, test predicted upper bound
  – ΔΔQTc > 10 ms on day 1 for hERG block
  – ΔΔJ-Tpeakc < 10 ms on day 3 for multichannel block
ECG methods

10-s 12-lead ECG (Mason-Likar)

Median beat

ML to vectorcardiogram¹

Vector magnitude
Lead

\[ \sqrt{X^2 + Y^2 + Z^2} \]

Figure adapted from Johannesen et al. Clin Pharm Ther 2014

¹ Median beat

ML to vectorcardiogram

Vector magnitude
Lead
ECG adjudication process example

• QRS onset and offset adjudicated on vcgmag
• Tpeak and Tend on vcgmag
ECG semi-automatic adjudication process

- Reviewers blinded to treatment and time
- ECGs from 1 subject in 1 sitting
- Discrepancies > 5 ms reassessed
- Remaining discrepancies with tie break team (round 3)
Sources of J-Tpeakc variability (I)

- Ranolazine: heart rate increase in 2 time-points in 2 subjects (i.e., 6 ECGs) drive wider CIs ~Cmax
Sources of variability (II)

• Lopinavir: Wide confidence intervals explained by 9 ECGs (3 timepoints) of one of the 10 subjects
  – T-P wave merging (QT?)
  – Notched T-wave (Tpeak “jumps”)

QTc

J-Tpeakc
Study 3 Results: Time-profiles

Ranolazine (hERG + late sodium)

Verapamil (hERG + calcium)

Lopinavir/Ritonavir (hERG + calcium + late sodium)

Chloroquine (predominant hERG)
Study 3 - Part 2: PD profiles on Day 3

- Diltiazem did not reduce ΔQTc prolongation by dofetilide
- Potential ΔJ-Tpeak shortening confounded by lower dofetilide concentrations on Day 3
hERG+Calcium vs. hERG+late sodium

Dofetilide & Diltiazem
- Dofetilide + Diltiazem
- Dofetilide alone

Dofetilide & Mexiletine
- Dofetilide alone
- Dofetilide + Mexiletine
hERG + Calcium vs. hERG + late sodium

- ΔQTc (ms)
- ΔJ - Tpeakc (ms)
- ΔTpeak - Tend (ms)

Dofetilide (ng/mL)

Dofetilide vs. Diltiazem + Dofetilide

Dofetilide vs. Mexiletine + Dofetilide

- hERG + calcium
- hERG + late sodium

ΔQTc (ms)

0.0 0.5 1.0 1.5 2.0 2.5

0 20 40

-10 ms

-20 ms

+12 ms
Clinical Study 2: ECG Effect of hERG + Calcium Block

• Despite prolonging PR, calcium block (diltiazem) did not shorten QTc prolongation induced by hERG block (moxifloxacin)

• Not clear if due to mechanism or study design limitations

Example of “ECG signature” method: QTc vs. T-wave amplitude changes
Summary of “ECG signatures”

Predominant hERG block prolongs QTc and J-Tpeakc

Balanced ion channel block prolongs QTc but not J-Tpeakc

* Chloroquine and lopinavir not shown because poor fit of concentration-response models did not allow for accurately predict ΔΔJ-Tpeakc (chloroquine) and ΔΔQTc (lopinavir) in a concentration-dependent fashion.
Analysis of 84 drugs from TQT studies

- Drug-induced ΔΔQTc vs. ΔΔJ-Tpeakc map shows different regions for different ion channel effect profiles

Hosseini et al. ISCE 2017
Upcoming Breakout Session (5/22/2018): Discussion Items

- Summary of results supporting J-Tpeakc use to inform multi-ion channel effects
- Heart rate dependency of J-Tpeak interval
  - J-Tpeak/RR adaptation and hysteresis
  - Population vs. subject-specific corrections
- Challenges in concentration-ECG-response models
  - Identifying nonlinear relationships in small sized trials
  - Impact on interpretation of results
- Role of ECG in a potential implementation of CiPA
  - Integrated risk assessment, context of use and potential thresholds
  - How to handle discrepancies
  - Limitations
- Are we ready?