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

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

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

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
  o 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

Vicente et al. J Am Heart Assoc 2015 pii: e001615;
**Potential CiPA Assessment (Low TdP Risk)**

Output nonclinical CiPA proarrhythmia risk prediction

Low TdP Risk Prediction

- Low Risk (no ion channel effects)
- Low Risk (balanced ion channel effects)

**QTc prolongation?**

- No: Low TdP Risk
- Yes: Discrepancy; Integrated risk assessment; assess J-Tpeakc/Tpeak-Tend; effect due to minor potassium channel? Effect due to metabolite? Effect due to hERG trafficking, non-acute effect?

**J-Tpeakc prolongation?**

- No: Low TdP Risk
- Yes: Discrepancy; Not consistent with low risk balanced ion channel effects; Likely requires enhanced ECG monitoring in development or labeling
**Potential CiPA Assessment (TdP Risk)**

Output nonclinical CiPA proarrhythmia risk prediction

Intermediate TdP Risk Prediction  High TdP Risk Prediction

QTc prolongation?

- No
- Yes

- Discrepancy; Integrated risk assessment; depending on assessment and if appropriate supratherapeutic exposure was achieved, down classify risk
- Intermediate / High TdP Risk
**Potential CiPA Assessment**

Output nonclinical CiPA proarrhythmia risk prediction

- **Low TdP Risk Prediction**
  - Low Risk (no ion channel effects)
    - QTc prolongation?
      - No: Low TdP Risk
      - Yes: Discrepancy; Integrated risk assessment; assess J-Tpeakc/Tpeak-Tend; effect due to minor potassium channel? Effect due to metabolite? Effect due to hERG trafficking, other non-acute effect?
  - Low Risk (balanced ion channel effects)
    - J-Tpeakc prolongation?
      - No: Low TdP risk
      - Yes: Discrepancy; Not consistent with low risk balanced ion channel effects; Likely requires enhanced ECG monitoring in development or labeling

- **Intermediate TdP Risk Prediction**
  - Discrepancy; Integrated risk assessment; depending on assessment and if appropriate supratherapeutic exposure was achieved, down classify risk

- **High TdP Risk Prediction**
  - QTc prolongation?
    - No: Intermediate / High TdP Risk
    - Yes: Discrepancy; Integrated risk assessment; dependent on assessment and if appropriate supratherapeutic exposure was achieved, down classify risk
Clinical Study Data To Date

ΔΔ J-Tpeakc

- 10 ms

ΔΔ QTc

- Confounded by study design

- Vicente et al. J Am Heart Assoc 2015 pii: e001615;
Clinical Study Data To Date

ΔΔ J-Tpeakc

10 ms

ΔΔ QTc

10 ms

hERG

hERG + late sodium & hERG + calcium + late sodium
New Prospective Clinical Study

To show that a combined assessment of QTc and J-$\text{T}_{\text{peak}}$ 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

~clinical concentration

**Ranolazine**
hERG ≈ late sodium block

Ion Channel Effects

Verapamil
hERG ≈ calcium block

Lopinavir/Ritonavir
hERG ≈ late sodium ≈ calcium block

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

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 $\geq 10$ 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

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

ΔΔ J-Tpeakc

ΔΔ QTc

10 ms

- dofetilide
- chloroquine
- dof + diltiazem
- ranolazine
- verapamil
- Lopinavir/ritonavir
Clinical Study Data To Date

hERG

hERG + late sodium and/or calcium
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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Potential CiPA Assessment

Output in silico proarrhythmia risk

Low TdP Risk Prediction

Intermediate TdP Risk Prediction

High TdP Risk Prediction

Low Risk (no ion channel effects)

iPSC-CM repolarization effects?

No

CiPA Low Risk

Yes

Discrepancy

Low TdP Risk

QTc prolongation?

No

Yes

Discrepancy; Investigate mechanism

Low TdP Risk

Intermediate / High TdP Risk

Intermediate TdP Risk Prediction

Low Risk (balanced ion channel effects)

iPSC-CM repolarization effects?

No

Yes

(iexact role pending validation data)

Low TdP Risk

Discrepancy; Not consistent with low risk balanced ion channel effects; Likely requires enhanced ECG monitoring in development or labeling

QTc prolongation?

No

Yes

Investigate mechanism

Discrepancy; Investigated risk assessment; depending on assessment and if appropriate supratherapeutic exposure was achieved, down classify risk

J-Tpeakc prolongation?

No

Yes

Low TdP risk

Discrepancy; Not consistent with low risk balanced ion channel effects; Likely requires enhanced ECG monitoring in development or labeling

High TdP Risk Prediction

Low TdP Risk

Discrepancy; Investigate mechanism

Low TdP Risk