Role of ECG Assessment during Clinical Development under CIPA and Experimental Findings:

FDA Clinical & Stem Cell Studies

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FDA Research Overview

• Background
  – Importance of multi-channel block
  – Analysis of 34 Thorough QT studies

• Overview of results from two FDA-sponsored clinical trials
  – 8 drugs with known electrophysiological effects
  – 3 drug combinations

• Overview of results from stem cell derived cardiomyocyte experiments
  – Voltage sensitive dye and microelectrode arrays
  – 26 drugs, 3 drug combinations, 2 stem cell vendors
Importance of Multi-Channel Block

- Almost all drugs that cause torsade block hERG and prolong QT
  - hERG & QT are sensitive markers for torsade risk
- However, some drugs block hERG and prolong QT, but do not cause torsade
  - Not specific markers for torsade risk
  - Focus on hERG and QT has likely prevented some effective drugs from reaching the market
- Drugs that block hERG and prolong QT, but do not cause torsade also block late sodium or calcium channels
  - Examples: ranolazine, verapamil, amiodarone
  - Late sodium & calcium block can shorten APD and prevent early after depolarizations (triggers for torsade)
Going Beyond QT to Differentiate Multi-Channel Effects

ECG

QRS

J-Tpeak

Tpeak-Tend

J

Calculus, late sodium

Tpeak

Tend

Sodium

Ventricular action potentials

hERG potassium
Analysis of 34 Thorough QT Studies

- hERG block prolongs J-Tpeak and Tpeak-Tend
- Additional late sodium or calcium channel block shortens J-Tpeak
- Limitation:
  - Incomplete ion channel data beyond hERG on many drugs

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

I. 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

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

L Johannsen¹,², 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

Approximate percent channel block at Cmax in clinical study

<table>
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<tr>
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<th>hERG Block</th>
<th>Late Sodium Block</th>
<th>Calcium Block</th>
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<tr>
<td>Dofetilide</td>
<td>+++</td>
<td></td>
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<tr>
<td>Quinidene</td>
<td>++++++</td>
<td>+</td>
<td>++</td>
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<tr>
<td>Ranolazine</td>
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+ = weak channel block  ++++++ = strong channel block

Study design, ECG and data analysis at FDA
Clinical study at Spaulding Clinical Research
Pharmacokinetic analysis at Frontage Laboratories
Ion channel data at Zenas
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
Strong Late Sodium and hERG Block (Ranolazine)

- Ranolazine prolonged Tpeak-Tend, but not J-Tpeak.
- Consistent with late sodium current block shortening J-Tpeak.

\[\Delta \Delta \text{Mean} \pm 95\% \text{ CI (ms)}\]

**Ranolazine**

- QTc
- Tpeak-Tend
- J-Tpeakc

**Dofetilide**

- QTc
- J-Tpeakc
- Tpeak-Tend

\[\text{Ranolazine concentration (nM)}\]

\[\text{Dofetilide concentration (nM)}\]
Clinical Trial 2

- Can we re-create the ECG signature of ranolazine by combining a pure hERG blocking drug with late sodium current blocking drugs?
  - Dofetilide + mexiletine = ranolazine?
  - Dofetilide + lidocaine = ranolazine?

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+ = weak channel block       ++++ = strong channel block

Study design, ECG and data analysis at FDA
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Ion channel data at Zenas
Multiple doses resulted in increasing concentrations of dofetilide and mexiletine.
Dofetilide + Mexiletine

Late sodium current block with mexiletine shortens QT prolongation from dofetilide.
Late sodium current block with lidocaine shortens QT prolongation from dofetilide
Late sodium current block shortens J-Tpeak, not Tpeak-Tend.

Late sodium current block shortens QT.

Late sodium current block shortens J-Tpeak.

Late sodium current block has no effect on Tpeak-Tend.
Note flat and asymmetric T-waves with dofetilide that normalize when mexiletine is co-administered.

Summary – Clinical Studies

• QT interval is a balance of inward (sodium, calcium) and outward (potassium) ion channel currents
  – hERG block prolongs J-Tpeak and Tpeak-Tend
  – Late sodium current block shortens J-Tpeak

• Blocking the late sodium current can have a significant effect on QT
Stem Cell Cardiomyocyte Studies

- Experiments performed at FDA led by Ksenia Blinova
- Voltage sensitive dyes (VSD) and microelectrode arrays (MEA)
  - Clyde Biosciences
  - Axion Biosystems
- 2 different commercially available cells
  - Cellular Dynamics International (CDI)
  - Axiogenesis
- 26 drugs + 3 drug combinations
  - Sequential dosing (multiple doses per well)
  - Positive controls on every plate
- 7 drugs – single dose per well, chronic recordings up to 72 hours
- Will present limited highlight of results
Voltage Sensitive Dye (VSD) Methods

Full recording ➔ Median beat

- 15 seconds recordings
- APD90 rate on median beat rate corrected with Friderica (same as clinical QT data)

15 seconds traces for arrhythmia analysis
Microelectrode Array (MEA) Methods

- 25 minute recordings
- Irregular beating for arrhythmias
- 30 most stable beats average beat

Field potential duration (FPD) on average beat
- Fridericia’s rate correction
hERG block from dofetilide causes dose dependent increase in APD and arrhythmias
Dofetilide – 2 Platforms

hERG block from dofetilide causes dose dependent increase in FPD and arrhythmias

Similar result between FPD and APD

Arrhythmias
hERG block from ranolazine causes dose dependent increase in APD, but no arrhythmias in this dose range
Ranolazine – 2 Platforms

hERG block from ranolazine causes dose dependent increase in FPD, but no arrhythmias in this dose range.

Similar result between FPD and APD.
Dofetilide vs. Ranolazine at ~50% hERG Block

At comparable amounts of hERG block ranolazine has less APD prolongation suggesting the ability of late sodium block to “rescue” extreme hERG block.
Dofetilide vs. Ranolazine at ~50% hERG Block

At comparable amounts of hERG block ranolazine has less APD prolongation suggesting the ability of late sodium block to “rescue” extreme hERG block.
Lidocaine Eliminates Arrhythmias from Dofetilide

Axiogenesis

Baseline

Dofetilide 3 nM

Dofetilide 3 nM + Lidocaine 5000 nM

CDI

Baseline

Dofetilide 6 nM

Dofetilide 6 nM + Lidocaine 5000 nM
Ability for Chronic Recordings with Stem Cells

Chronic recordings detect FPD increase from pentamidine blocking hERG trafficking
Summary – Stem Cell Studies

• Concentration dependent APD & FPD prolongation from hERG block in both cell types
  – Stronger effect than clinical QT response
• Late sodium current block may be able to “rescue” extreme hERG block
• Ability to detect drug-induced arrhythmias and chronic drug effects
• More results to come on all 26 drugs
Potential Role of ECG Assessment during Clinical Development under CIPA

• Mechanistic evaluation of the ECG can confirm ion channel predictions from \textit{in silico} models / stem cell cardiomyocytes

• Advantages of ECG assessment methodology
  – Correct combination/ expression of ion channels
  – Take protein binding and metabolites into account
Thank You to All Collaborators and Contributors!

**FDA**
- Lars Johannesen
- Jose Vicente
- Ksenia Blinova
- Norman Stockbridge
- Jayna Stohlman
- Dulciana Chan
- Jeffry Florian
- Loriano Galeotti
- Martin Ugander
- Jens Sorensen
- Meisam Hosseini
- Tom Colatsky
- Zhihua Li

**Spaulding Clinical Research**
- Jay Mason
- Carlos Sanabria
- Kristin Waite-Labott
- Cassandra Erato

**Frontage Laboratories**
- Mira Hong
- Ping Gou
- John Lin

**Axion Biosystems**
- James Ross
- Matt Brock
- Daniel Millard
- Stacie Chvatral
- Tom O'Brien

**Clyde Biosciences**
- Godfrey Smith
- Maria Hortigon
- Victor Zamora Rodriguez
- Margaret Craig

**Cellular Dynamics**
- Blake Anson
- Kyle Kolaja

**Axiogenesis**
- Greg Luerman
- Brian Murphy

**Zenas Technologies**
- William Crumb

**GE Healthcare**
- Joel Xue

**Funding Support**
- FDA Critical Path Initiative Grant
- FDA Chief Scientist Challenge Grant
- FDA Office of Women’s Health Grant
- FDA CDRH
- FDA CDER