CSRC/FDA Meeting

The Role of Phase 1 ECG Assessment Under CIPA

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Agenda

- Potential Phase 1 ECG biomarker approaches that add information beyond standard approaches
  - 3 Talks
    - Panel discussion- Science and choice of the biomarkers to best fit needs of CiPA
- Practical considerations around implementation
  - 3 Talks and panel discussion
-

Meeting Overview

The focus on Phase 1 ECG's under CiPA has potential major implications

- **Robust discussion time**
  - Discussion is strongly encouraged!

Presenters have promised to stay within their allotted time limit ☺

Overview of CiPA and the Role of Phase 1 ECG Assessment Under CIPA

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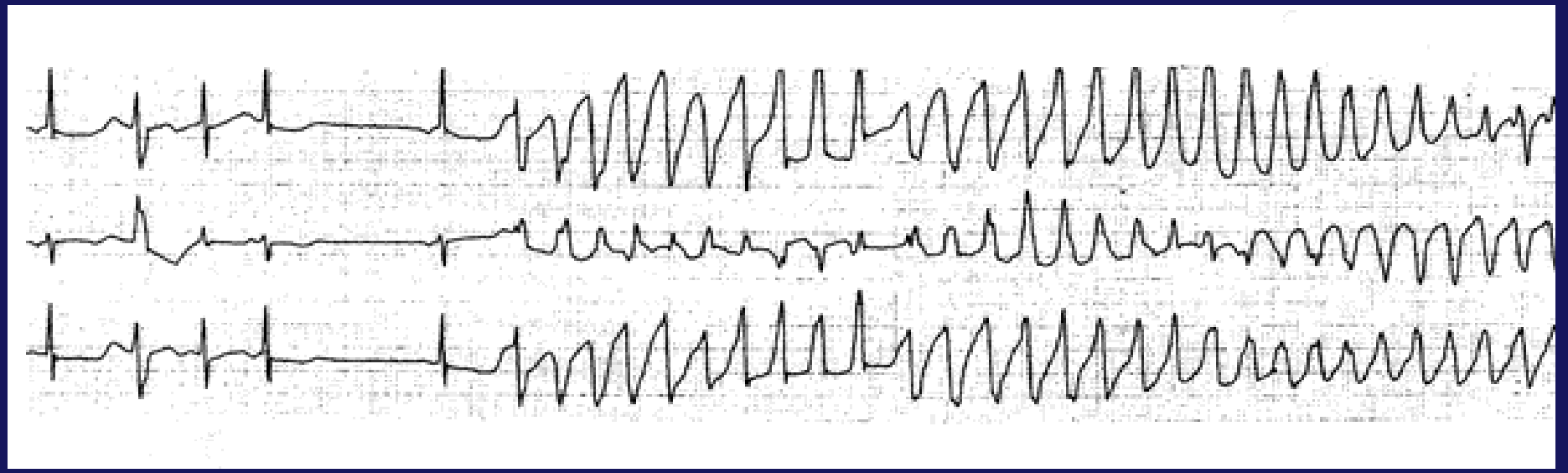

QT Prolongation/Drug-Induced Torsade

- 2002-2005 ICH Regulatory Discussions
- ICH E14/S7B
- Focus on surrogates- HERG and QTc testing
  - Both are sensitive but not very specific for predicting a drug's proclivity to cause proarrhythmia

QT Prolongation: Dissociation from TdP

- Sodium Pentobarbital
  - Prolongs QT but no TdP
  - Inhibits I_{kr}, I_{ks}, and late I_{Na}

- Amiodarone
  - TdP very rare
  - Inhibits I_{kr}, I_{ks}, late I_{Na}, and I_{ca}

- Verapamil
  - Inhibits I_{Kr} but also Ca influx

- Ranolazine
  - Prolongs QT but no TdP
  - Inhibits late I_{Na}, I_{kr}, and I_{NaCa}

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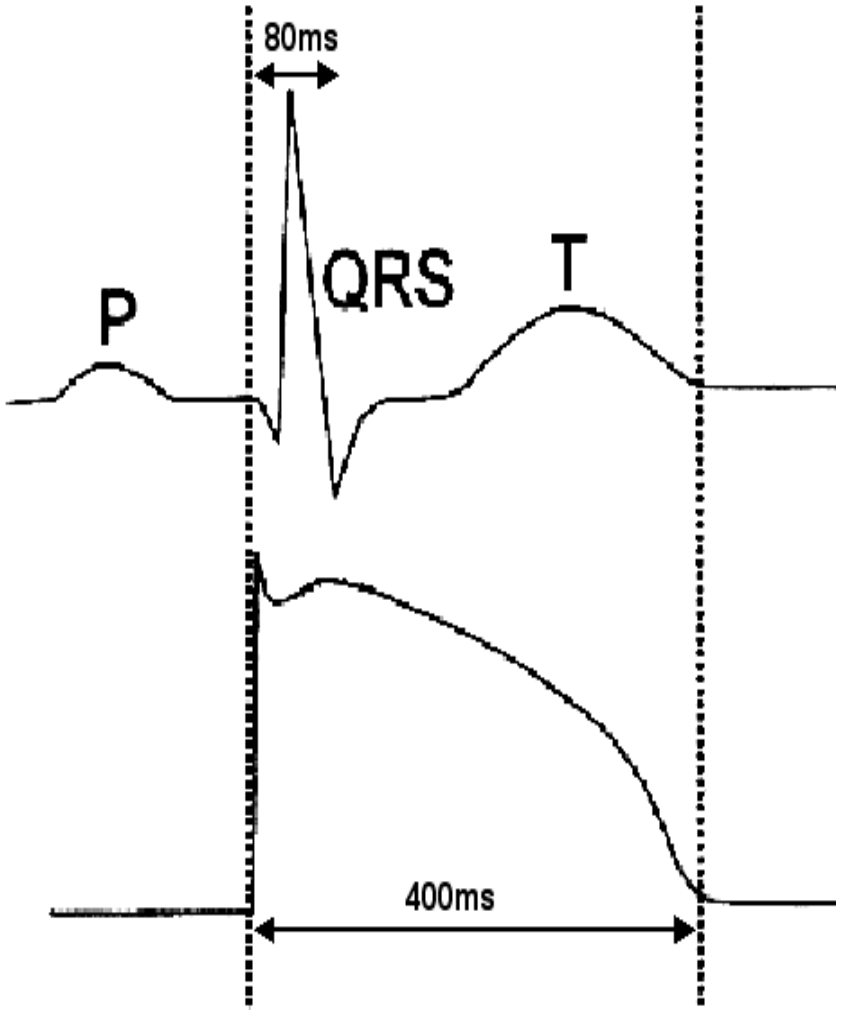
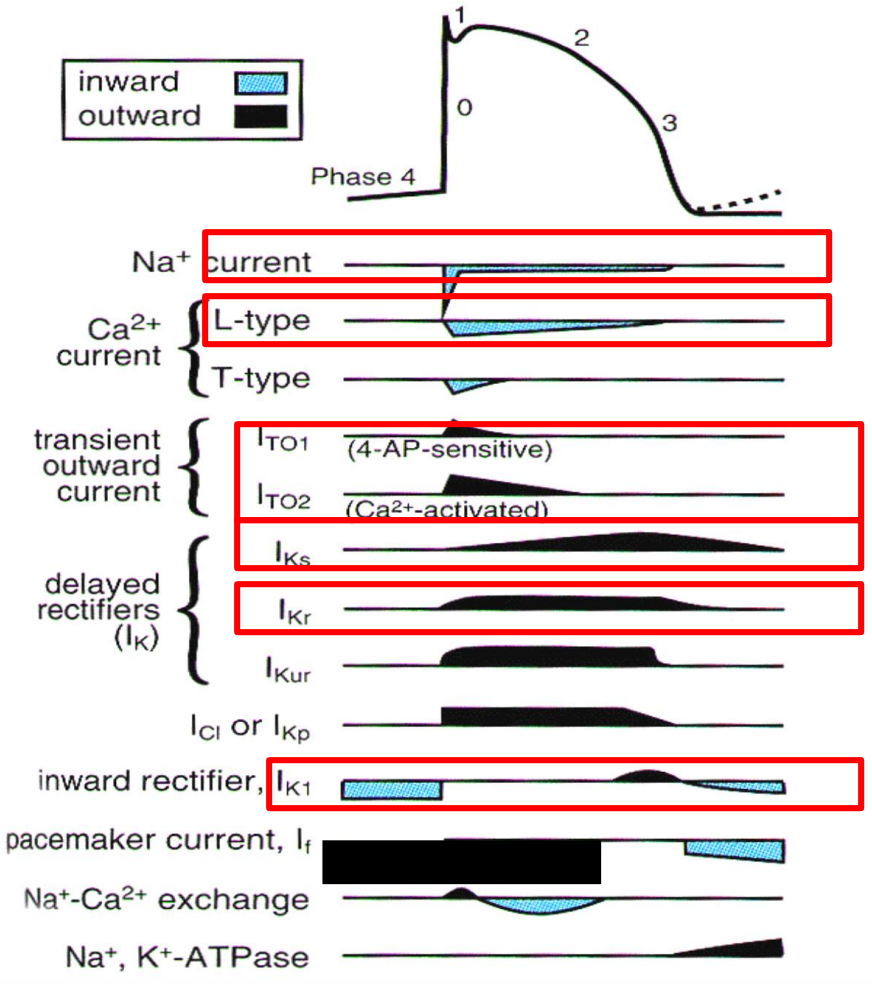
  - No EAD's, reduces dispersion
- Verapamil
  - Inhibits I_{Kr} but also Ca influx
  - No QT prolongation or TdP
- Ranolazine
  - Prolongs QT but no TdP
  - Inhibits late I_{Na}, I_{kr}, and I_{NaCa}
  - No EAD's, reduces dispersion;
  - Suppresses E4031 induced TdP

Thus QTc Prolongation need not cause TdP and Late I_{Na} and I_{Ca} appear protective


80ms
P
QRS
T
400ms


inward
outward
Phase 4
0
1
2
3
Na+ current
Ca2+ current
L-type
T-type
transient outward current
ITO1 (4-AP-sensitive)
ITO2 (Ca2+-activated)
delayed rectifiers (IK)
IKs
IKr
IKur
ICl or IKp
inward rectifier, IK1
pacemaker current, If
Na+-Ca2+ exchange
Na+, K+-ATPase

Consequences: Compound with QT effect

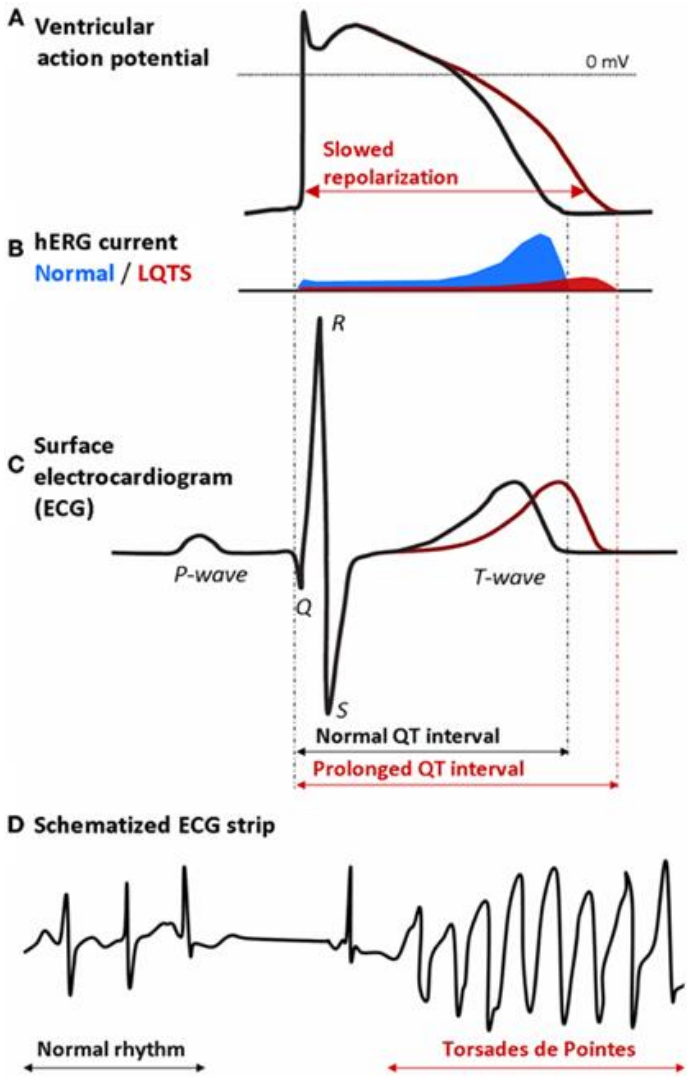
Consequences of developing a compound with QT effect

- Significant development burden
- Increased perceived risk = increased burden to demonstrate benefit
- Increased costs
- Delays in filing and/or approval
- Label warnings and competitive implications
- Licensing/partnering issues
- **Often leads to termination of development**

Current Proarrhythmia Evaluation

- ICH E14/S7B have resulted in no drugs with unrecognized risk being approved or removed from the market
- Negative impact on drug development
  - Premature discontinuation due to hERG or QT “signal”
    - (Inaccurate) perception of risk leading to drug discontinuation
      - Estimates of up to 60%
    - Concerns regarding development burden, costs, labeling
    - Many potentially good compounds never get evaluated in humans due to a hERG effect
  - Drug development in specific areas- CNS
  - Many drugs with QT labeling are unlikely to be proarrhythmic
  - Engineering-out hERG- applicability/other effects

CiPA:
Comprehensive In Vitro Proarrhythmia Assay



Goal: Develop a new *in vitro* paradigm for cardiac safety evaluations of new drugs that provides a more accurate and comprehensive **mechanistic-based** assessment of proarrhythmic potential

Focus: On proarrhythmia (not QT prolongation)

We understand the mechanism of TdP- reduced repolarization reserve, early afterdepolarizations (EAD's), resulting transmural reentry

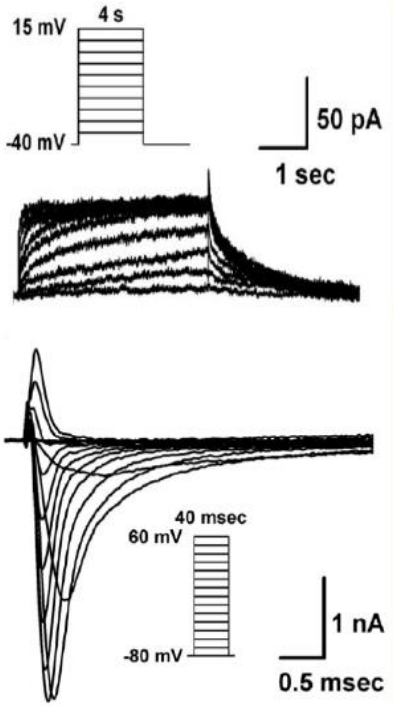
New Paradigm: Focus on Proarrhythmia

- QT prolongation ≠ Proarrhythmia
- HERG block ≠ Proarrhythmia

- Reduce the premature termination of drugs with favourable benefit:risk profiles
  - Permit straightforward clinical dev. and clean labelling of drugs with a low proarrhythmic risk, despite QT prolongation
- Make drug development more efficient
  - Move the bulk of proarrhythmic assessment to the discovery phase; simplify clinical development
  - Earlier removal of regulatory uncertainty
  - Use the assays to potentially guide candidate selection
  - Obviate the TQT study
- Enhance the accuracy with which existing and/or new drugs are labelled relative to actual proarrhythmic risks

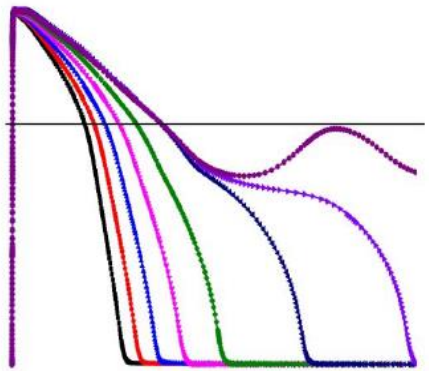
Components of CiPA

Drug Effects on Multiple Human Cardiac Currents

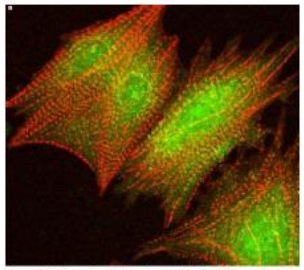


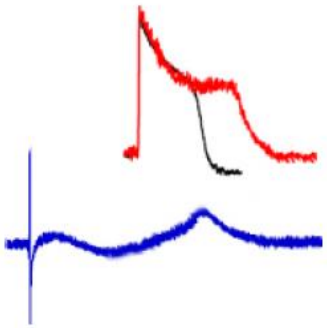
In Silico Reconstruction Cellular Human Ventricular Electrophysiology

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

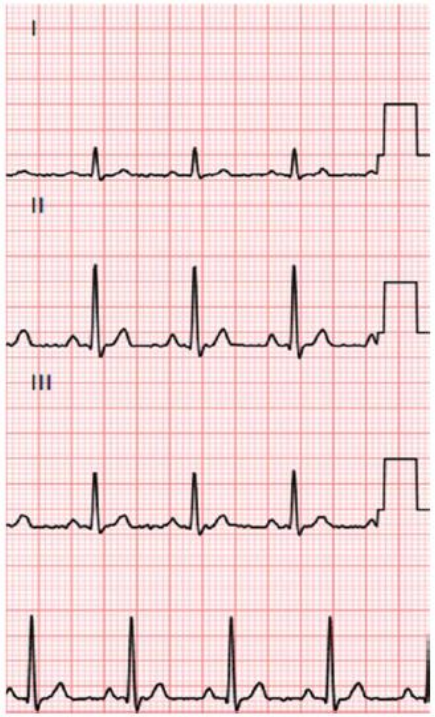


In Vitro Effects Human Stem-Cell Derived Ventricular Myocytes





Clinical Evaluation Unanticipated Electrophysiology



Proarrhythmia Risk Score

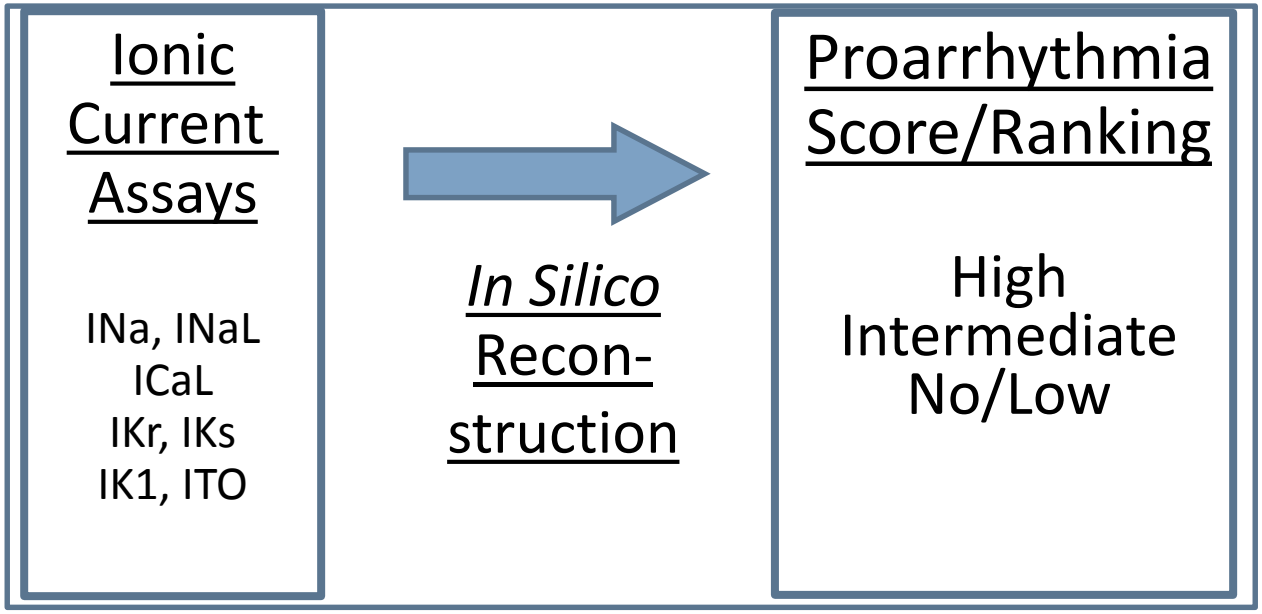
Ion Channel Working Group

- Ion Channel selection
  - Fundamental role in defining human action potential duration and playing a role in TdP development
    - I_{Na}, I_{Kr}, I_{Ks}, I_{CA}, I_{K1}, I_{To}
  - Standardized ion channel assay development
    - Physiologic temperature
    - IC_{50} and exposure-response
    - Information on kinetics-, voltage- and use-dependence
    - High throughput

In Silico Working Group

- To develop a computer model of the adult human ventricular myocyte that can be used to predict TdP risk
- Results from a cardiac modeling experts meeting held by the identified the O'Hara-Rudy model as the "gold standard"
  - Being modified
  - Built using experimental data from human hearts
- Key requirements for model development:
  - Preserve an immediate and direct relationship to experimentally derived and verifiable data sets
  - Make the model and supporting data sets available as a community resource

CiPA Non-Clinical Testing Schema



hSC-Myocytes (2015)

Detect / Confirm Effects on Currents

- **Integrated "Signature" Responses**
  - **Field Potentials (MEA)**
  - **Action Potentials (VSO)**
  - **fAPD↑ , Spike amplitude**

hSC-Myocytes (Future)

Confirm Proarrhythmic Score

- **Integrated Responses**
  - **Field Potentials (MEA)**
  - **Action Potentials (VSO)**
  - **fAPD↑ , Spike amplitude**
  - **EAD incidence,**
  - **Tachyarrhythmias**

Human Phase 1 ECG's Under CIPA

To confirm that there is no discordance between the preclinical data and the observed human ECG effects

- Identify preclinical false negatives
  - Human-specific metabolites, differences in protein binding
  - Untested ion channels
- Lack of concordance, might indicate a need for additional analysis

<u>Current Measurements</u>

- PR- Fast I_{Na}, $I_{CA,}$ Autonomic factors, Heart Rate
- QRS- Fast I_{Na}
- QTc- Multiple currents (I_{Na}, I_{kr}, I_{ks}, I_{CA}, I_{K1}, I_{to})

- Not useful for assessing multi-channel block
  - Late I_{Na} or I_{CA}

New Human ECG Biomarkers

- Needed 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

Collaborators

- Phase 1 ECG Working Group
  - David Strauss,Fabio Badilini, Jean-Philippe Couderc, Robert Kleinman, Lars Johannesen, Jose Vicente, Jay W. Mason, Jeremy Ruskin, Catherine Ortemann-Renon, Corina-Dana Dora, Jorg Taubel, Boaz Mendzelevski, Colette Strnad, Jennifer Pierson, Norman Stockbridge
- CiPA Steering Comm.
  - Drs. Stockbridge, Gintant, Petit, Colatsky, Strnadova, Garnett, Strauss, Fermini, Leishman, Valentin, Pierson, Zhang, Shinagawa, Kolaja, Prasad, Trayanova, Sekino, Sager
- FDA, EMA, PMDA, JiCSA, Health Canada
- CSRC
- HESI
- SPS
- In Silico Modelers
- Pharmaceutical and Device Companies
- CRO’s
- Numerous Academic Groups

Thank you

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