New Advances in the Assessment of Drug-Induced Arrhythmias and the Comprehensive In Vitro Proarrhythmia Assay (CiPA)

Kellogg Center at Gallaudet University
800 Florida Ave NE
Washington, DC 20002
May 21st -22nd , 2018

May 21st Day 1

8:00am – Continental Breakfast
Welcome and Introduction Philip Sager, MD (Stanford University)(15 min)

8:15am-9:45am Session I: Overview
Moderator: Gary Gintant, PhD *(AbbVie)*

- TdP mechanisms and insights- scientific rationale for CiPA **Gary Gintant, PhD** (Abbvie)(15 min)
- The need for a new approach to assessing the proarrhythmic potential of drugs and overview of CiPA **Philip Sager, MD** (Stanford University)(15 min)
- The potential role of CIPA on drug discovery, development, and regulatory pathways **David Strauss, MD, PhD** (US FDA)(20 min)

Q&A / Panel Discussion (40 min) Speakers and
- **Krishna Prasad, MD** (EMA)
- **Corina Dota, MD, PhD** (AstraZeneca)
- **Peter Kowey, MD** (Jefferson Univ)

9:45am-10:00am Break

10:00am-12:00pm Session II: In Silico Modeling and Ion Channel Approaches
Moderator: Gary Mirams, PhD *(University of Nottingham)*

- In Silico modeling- state of the art **Gary Mirams, PhD** (University of Nottingham)(15 min)
- **S**ummary of In Silico model approach and validation study; In Silico Results **Zhihua Li, PhD** (US FDA)(30 min)
- Ion Channel Assays and Data – lessons learned and data quality criteria **Wendy Wu, PhD** (US FDA)(30 min)

Q&A / Panel Discussion (45 min) Speakers and
Najah Abi Gerges, PhD (AnaBios)
Jim Kramer, PhD (Charles River)
Takashi Yoshinaga, PhD (Eisai)

12:00pm-12:30pm Working Lunch

12:30pm-2:30pm Session III: IPS-Stem Cells and Phase 1 ECG
Moderators: David Strauss, MD, PhD *(US FDA)*

- IPS-Stem Cells: Summary of approach, Detailed results and implications **Ksenia Blinova, PhD** (US FDA)(30 min)
- New ECG biomarkers and their potential role in CiPA; Results and implications **Jose Vicente Ruiz, PhD** (US FDA)(30 min)
- Implementation of ECG biomarkers **Borje Darpo, MD, PhD** (ERT) (10 min)

Q&A / Panel Discussion (50 min) Speakers and
- ***Gary Gintant, PhD*** *(Abbvie)*
- **Yasunari Kanda, PhD** (Japan NIHS)
- **Charles Benson, MD, PhD** (Eli Lilly)

2:30pm-2:45pm Break

2:45pm-4:50pm Session IV: Regulatory Evaluation and Potential Implementation
Moderator: Philip Sager, MD *(Stanford University)*

- Data summary overview ***David Strauss, MD, PhD*** *(US FDA)* (15 min)
- How CiPA might impact pre-clinical safety testing and S7B **Derek Leishman, PhD** (Eli Lilly)(20 min)
- How CiPA might be implemented in clinical development and regulatory decision making **Christine Garnett, PhD** (US FDA)(20 min)
- Regulatory considerations and next steps **Krishna Prasad, MD** (MHRA)(10 min)

Q&A/Panel discussion (60 min) Speakers and
- **Colette Strnadova, PhD** (Health Canada)
- **Kaori Shinagawa, MD, PhD** (PMDA)
- **Jean-Pierre Valentin, PhD** (UCB, EFPIA)
- **Maki Ito MD, PhD** (JPMA, Merck)

5:00pm Adjourn

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May 22nd Day 2

7:30am-8:00am Continental Breakfast

8:00am-8:10am General Instructions

8:10am–10:30am Work Stream Breakouts

Breakout 1 – In Silico
Leaders: Zhihua Li, PhD *(US FDA);* ***Gary Mirams, PhD*** *(University of Nottingham);* ***Takashi Yoshinaga, PhD*** *(Eisai)*

The In Silico Breakout Session discussion will focus the on:

- Considerations of implementing the proposed CiPA model and qNet metric
- General principles to qualify any new models and metrics to be used under the CiPA paradigm

Breakout 2 – Ion Channel
Leaders: Wendy Wu, PhD (US FDA); **Jim Kramer, PhD** (Charles River); **Najah Abi Gerges, PhD** (AnaBios)

The Ion Channel Breakout Session discussion will focus the on:

- Data quality standards (for consideration of cell integrity and recording quality)
- Current run-up, run-down, steady state
- Unified experimental protocol for CiPA
- Temperature for hERG channel recording
- Agonist for late NaV1.5 current
- Charge carrier for CaV1.2 current
- Where and how drug effects are measured during the voltage protocols

Breakout 3 – Myocyte
Leaders: Gary Gintant, PhD *(Abbvie);* ***Ksenia Blinova, PhD*** *(US FDA);* ***Yasunari Kanda, PhD*** *(Japan NIHS)*

The Myocyte Breakout Session discussion will focus the on:

- Brief review of Validation Study results
- Findings of JiCSA study results
- Comparison of JiCSA and Validation study results (points of concordance, discordance, models)
- Comparison of sensitivity of different cell lines (non-core sites study)
- Setting best practices and calibration standards
- Roles of myocytes (internal decision-making vs. regulatory perspectives, flow chart examples, benefits vs. current regulatory paradigm)

Breakout 4 – Phase 1 ECG
Leaders: **Jose Vicente Ruiz, PhD** (US FDA); **Christine Garnett, PhD** (US FDA)

The ECG Breakout Session will focus on:

- Summary of results supporting J-Tpeak 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?

10:30am-11:00am Break

11:00am-12:00pm Reports from Work Stream Breakouts

12:00pm-12:30pm Working Lunch

12:30pm-2:30pm Advances in Clinical QTc Assessments and Updates from the FDA QT Interdisciplinary Review Team (IRT)
Moderator: Philip Sager, MD *(Stanford University)*

- Recent insights from the FDA QT IRT on Concentration-QTc analysis and requirements for obtaining a 'TQT study waiver' **Dhananjay Marathe, PhD** (US FDA) (15 min)
- Application of bias metrics during IRT review **Lars Johannesen, PhD** (US FDA)(10 min)
- Issues with exposure-response analysis, how we can close the gap **Georg Ferber, PhD** (Consultant)(20 min)
- QTc evaluation for drugs with a substantial heart rate effect **Marek Malik, MD, PhD** (University of London) (15 min)
- Q&A / Panel Discussion (60 min)
    - **Christine Garnett, PhD** (US FDA)
    - **Borje Darpo, MD, PhD** (ERT)
    - **Dalong Huang, PhD** (US FDA)

2:30 pm Adjourn