CSRC/FDA Workshop: The Proarrhythmic Assessment of New Chemical Entities

Exposure Response Analysis in FIH Studies as a Replacement for the Thorough QT study and Novel ECG Biomarkers Proposed to be Used Under CIPA (The Comprehensive In Vitro Proarrhythmia Assay)

ACC Heart House
Washington, D.C.
Wednesday, April 6, 2016

Description: The ICH E14 clinical guidance has been revised (December 2015) and now enables the use of exposure response (ER) analysis applied to early phase clinical data to provide definitive evidence of the lack of a QT effect of a drug in development. ER analysis has evolved as an increasingly important method to assess a drug's ECG effects; most drugs that cause concerning QT prolongation do this in direct relation to increasing plasma concentrations. Since the power of ER analysis to exclude small ECG effects is greater than the 'by timepoint' analysis, it can be used in early clinical phase studies to provide ECG data with the same level of confidence as from the TQT study. A remaining concern with this approach may however be the lack of a positive control. In TQT studies, the positive control demonstrates that a small QT effect can be detected and thereby provides protection against a false negative result.

7:45am-8:00am Breakfast

8:00am-8:05am: Welcome and introduction - Borje Darpo-MD, PhD (iCardiac Technologies)(5min)
- Co-Chairs:
  - Christine Garnett- PharmD, (FDA)
  - Borje Darpo- MD, PhD (iCardiac Technologies)

8:05am-8:25am Session I: This session will discuss ER analysis applied to early phase clinical data with emphasis on whether a positive control is needed and alternative methods to establish the study's sensitivity in lieu of a pharmacological positive control. (20min)
- How can exposure response analysis of ECG data from early phase clinical studies be used to detect or exclude clinically relevant effects of a new chemical entity?
- How can protection against false negative result be provided in lieu of a positive control?
- Which data do regulators expect to grant a TQT study waiver?

8:25am-8:45am Session II: Exposure response analysis to evaluate a drug's effect on ECG parameters. Christine Garnett- PharmD (FDA) (20min)
- Role in regulatory decision making
- Proposed criteria for a negative QT assessment using ER analysis applied to early clinical study data

- How should a clinician without in-depth insight into exposure response modeling evaluate whether the results from the analysis provides an acceptable estimate of the drug's QT effect

8:45am-8:55am Q&A (10min)

8:55am-9:15am Session III: Which type of data does FDA's Interdisciplinary Review Team expect to waive a TQT study? Jiang Liu- MD, (FDA)(15 min)
- Points to consider when performing definitive QT assessment in early stage clinical studies
- In which scenarios is it better to perform definitive QT assessment in a MAD study?
- Key parameters impacting the power of small studies to exclude a QT effect using ER analysis

9:15am-9:17am Q&A (5min)

9:15am-9:35am Session IV: Proposed Methods to Replace the Positive Control in QT Studies Introduction to the topic: What is the role of the positive control? Norman Stockbridge- MD, PhD (FDA)(5min)
- Industry Perspective- Boaz Mendzelevski, MD (BioClinica)
- The pharmacological positive control can be replaced by a meal. Jorg Taubel- MD (Richmond Pharmacology)(15 min)
  - How to implement the food procedure into a standard SAD or MAD trial
  - Proposed criteria for assay sensitivity for the food effect

9:35am-9:40am Q&A (5min)

- Quality metrics applied to ECG data as a replacement for the positive control. Marek Malik-MD (St. Paul's Cardiac Electrophysiology)(15 min)
  - Which quality metrics can be applied to data from early phase clinical studies?
  - How would quality assurance provide protection against false negative results?

9:40am-9:45am Q&A (5min)

- Using moxifloxacin to establish assay sensitivity in early phase clinical studies. Robert Kleiman- MD (ERT)(15min)
Based on the preclinical data, the drug's effects in humans are similar to what would be expected. The QT interval prolongation is not always proarrhythmic, as part of GIPA, it will be important to determine if a drug's effects in humans is similar to what would be expected based on the preclinical ion channel data.

10:00am-10:05am Q&A (5min)
- Bias evaluation provides protection against false negative results and can replace the positive control.
  - Borje Darpo- MD, PhD (iCardiac Technologies)(15min)
  - Evaluation of reported QTc values vs. a fully automated background to detect insensitive methods
  - Proposed criteria for bias evaluation

10:20am-10:25am Q&A (5min)

10:25am-11:20am Session V: Panel Discussion - How can we confidently replace the TQT study? (55min)
**Moderators:** Christine Garnett- PharmD and Borje Darpo- MD, PhD
- Krishna Prasad- MD (EMA)
- Kaori Shinagawa - MD (PMDA)
- ICH E14 Implementation Working Group members

11:20am-11:25am Q&A (5min)

11:25am-11:30am Summary and Proposed Steps.
Christine Garnett- PharmD (FDA)(5min)

11:30am-12:30pm Lunch

**Background:** It is well established that drug-induced QT interval prolongation is not always proarrhythmic when multiple ion channels are affected. The Comprehensive In Vitro Proarrhythmia Assay (CiPA) is being developed to use non-clinical cardiac safety evaluations to directly determine a drug’s proarrhythmic potential, irrespective of effects on the QT interval. As part of GIPA, it will be important to determine if a drug’s effects in humans is similar to what would be expected based on the preclinical ion channel data.

12:30pm-12:35pm: Purpose of the meeting and logistics– Philip Sager- MD (Consultant, Stanford University)(5 min)

12:35pm-12:50pm Overview of CiPA and the Role of Phase 1 ECG Assessment Under CiPA – Philip Sager- MD (Stanford University)(15 min)

12:50am-1:40pm Potential ECG biomarker approaches
(50 min) Moderator David Strauss- MD, PhD (FDA)
- Theoretical underpinnings of the GEC and additional insights beyond the PR, QRS, and QTc - Fabio Badilini (AMPS) (10 min)
- Novel GEC biomarkers – Joel Xue (GE) (10 min)
- J-Tpeak-Tend and Tpeak-Tend, including exposure response analysis, methodology and open source software – Lars Johannesen- PhD (FDA)(15 min)
- Analysis comparing different approaches – Jose Vicente- MS (FDA) (15 min)

1:40pm-2:25pm Panel Discussion: Science and choice of the biomarkers to best fit needs of CiPA (45 min)
**Facilitator:** David Strauss- MD, PhD (FDA)
- Joel Xue- PhD (GE Healthcare)
- Fabio Badilini- PhD (AMPS)
- Jean-Philippe Couderc- PhD, MBA (University of Rochester)
- Jose Vicente- MS (FDA)
- Lars Johannesen- PhD (FDA)
- Philip Sager- MD (Consultant, Stanford University)
- Jeremy Ruskin- MD (Massachusetts General Hospital)
- Robert Kleiman- MD (ERT)

2:25pm-2:45pm Break (20min)

2:45pm-3:15pm Practical considerations around implementation (30 min) Moderator: Philip Sager (Stanford University)
- Practical approaches to evaluating ECG biomarker results and regulatory perspective – David Strauss, MD, PhD (FDA)(15 min)
- How core labs could implement new ECG biomarker approaches – Robert Kleiman, MD (ERT) (15 min)
- How sponsors could implement new ECG biomarker approaches – Jonas Pettersson, MD, PhD (Novo Nordisk) (10 min)
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3:15pm-4:15pm Panel Discussion: Practical considerations around implementation (60 min)
Facilitator: Philip Sager
- Jonas Petterson- MD, PhD (Novo Nordisk)
- Robert Kleiman- MD (ERT)
- David Strauss- MD, PhD (FDA)
- Norman Stockbridge- MD, PhD (FDA)
- Jay Mason- MD (University of Utah),
- Corina Dota- MD (AstraZeneca)
- Peter Kowey- MD (Main Line Health)
- Borje Darpo- MD PhD (iCardiac Technologies)

4:15pm-4:25pm Summary and proposed next steps (10min)
- Philip Sager- MD (Stanford University)
- David Strauss- MD, PhD (FDA)
- Robert Kleiman- MD (ERT)
- Jose Vicente- MS (FDA)