Cardiac Safety Research Consortium
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Thinktank Meeting Agenda
QT Assessment in Early Clinical Development -
Can the Predictive Value be Enhanced to be Similar to That of a TQT study?

White Oak Facility, FDA Headquarters • Silver Spring, MD • February 2, 2011

7:30-8:00 AM
Registration and Continental Breakfast

8:00-8:30 AM
Welcome: *Philip Sager* (5 min)
Welcome and Setting the Stage: Meeting Co-Chair *Borje Darpo* (10 min)
Regulatory Perspective: *Doug Throckmorton* (15 min)

8:30-10:00 AM
Session I: Role of Concentration Effect Modeling in Assessing a Drug's Effect on the QTc Interval
Session Chair and Moderator: Christine Garnett

- FDA Perspective on using concentration-QTc relationship in regulatory decisions: *Christine Garnett, FDA* (5 min)
- FDA Statistical Perspective*: Joanne Zhang* (15 min)
- Industry experience of the concentration-QTc relationship in phase 1 studies:
    - Pfizer Experience: *Steve Riley* (10 min)
    - AstraZeneca Experience: *Corina Dota* (10 min)
- Statistical properties (type 1 error, power) of concentration-QTc analysis: *Gunter Heimann* (10 min)
- Data-based simulation studies to assess the power of detecting moxifloxacin QTc response using concentration-QTc in small phase-1 studies: *Georg Ferber* (10 min)
- Round Table Discussion: Chair, speakers and *Krishna Prasad* (30 min)

10:00-10:10 AM Break

10:10-11:20 AM
Session II: How Can Assay Sensitivity be Established in Early Clinical Trials without the use of Moxifloxacin?
Session Chair and Moderator: Charles Benson

- FDA View: What is needed to demonstrate that a QT Study is sufficiently sensitive to detect a small change in QT without the use of a positive control: *Norman Stockbridge* (10 min)
- Quality criteria as evidence of assay sensitivity for studies assessing QT effects: *Marek Malik* (10 min)
- Autonomic maneuvers and food effect as examples of alternative approaches to demonstrate assay sensitivity: *Anthony Fossa* (10 min)
- Statistical Approaches to assay sensitivity: *Stanley Young*(10 min)
- Round Table Discussion: Chair, speakers, *Philip Sager*, and *Colette Strnadova* (30 min)

11:20-12:20 PM
Session III: Can an approach integrating non-clinical and early clinical QT assessment replace the thorough QT Study?
Session Chair and Moderator: Borje Darpo

- How can early phase studies produce QT data with the same validity of a TQT study? Design considerations and measurement techniques of early studies: *Borje Darpo* (10 min)
- The role of non-clinical assays in determining the level of clinical QT assessment: *Rob Wallis* (10 min)
- What aspects of the non-clinical data increase confidence in this data in an integrated approach of QT data?: *John Koerner* (10 min)
- Round Table Discussion: Chair, speakers and *Christine Garnett* (30 min)

12:20- 12: 50 PM Lunch

12:50-1:40 PM
Session IV: What will it take to convince a regulator?
Session Chair and Moderator: Krishna Prasad

- Industry View: Integration of non-clinical and clinical data to Replace the TQT Study: *Charles Benson* (10 min)
- What will it take to convince a regulator that the TQT study can be replaced by combining non-clinical and early clinical data: **Personal View from Regulators:**
    - FDA: *Robert Temple* (10min)
    - EMA: *Krishna Prasad* (10min)
    - Health Canada: *Colette Strnadova* (10min)
- Round Table Discussion: Chair, speakers and *Borje Darpo* (10 min)

1:40- 1:50 PM
Introduction to Break-Out Sessions: *Philip Sager, MD*

1:50-3:00 Break-out Sessions
Effort #1: Effort #2: Effort #3:

3:00-5:00 PM
Roundtable Discussion & Reports from Break-out Sessions
Facilitators: *Borje Darpo, Christine Garnett and Philip Sager.*

5:00-5:30 PM
Meeting Summary and Wrap-up
Wrap-up and Future Directions: Meeting Co-Chair: *Christine Garnett* (20 min)
Conclusions and Meeting Outcome: *Philip Sager* (10 min)

Objectives and Expected Outcome

Objective of Meeting

The objective of the meeting is to identify key knowledge gaps and propose research areas in regard to future replacement of the ICH E14 'thorough QT/QTc study' with QT assessment in early clinical trials using alternative analysis techniques and refined methodologies. While improved non-clinical assessment of proarrhythmic risk may constitute an important part of this strategy, the meeting will focus on clinical QT assessment.

Expected Outcome

The expected outcome is the formation of collaborative CSRC research groups with members from regulators, sponsors and academia with the goal to perform, promote and compile research in areas addressing identified key knowledge gaps.

Session 1: Role of concentration effect modeling in assessing a drug's effect on the QTc interval

Replicate ECG collection with concurrent plasma drug concentrations measured in early clinical development (i.e., single- and multiple dose ascending studies) provide a unique opportunity to evaluate potential drug-induced QT effects over a broad range of doses and concentrations that might not be evaluated again during the drug development process. Pooling QT and drug concentration data across doses, time, subjects, and studies can yield large data sets to which PK-PD models can be applied to predict concentrations at which QT prolongation could be clinically relevant. The purpose of this session is to discuss how the concentration response analyses can be implemented in early phase studies to characterize small effects on QTc.

Session 2: How can assay sensitivity be established in early clinical trials without the use of moxifloxacin?

A mandated element of the TQT study is the use of a positive control with a consistent and well characterized effect on the QTc interval. The role of the positive control is to establish assay sensitivity, i.e., to demonstrate the study's ability to detect small QTc changes. The use of a positive control in a TQT study provides reassurance that the multiple components, which may influence precision and accuracy of the measurements result in an expected QTc effect. The measured effect by the positive control is thereby an evaluation of the total experimental conditions for the study (including measurement techniques, ECG platforms and experimental conditions at the clinical site). The requirement for a positive control is somewhat unusual for studies in healthy volunteers but has been successful in providing confidence for the most important feature of TQT studies: the ability to detect small QTc changes.

Based on its reproducible pharmacokinetic profile and consistent QTc effect, the fluoroquinolone antibiotic moxifloxacin has been used as the positive control in the vast majority of TQT studies. It seems however unlikely that it will be feasible to include a pharmacological agent as a positive control in most early clinical trials and alternative approaches should therefore be sought to demonstrate assay sensitivity. The purpose of this session is to outline such alternative methods, which may include autonomic maneuvers, physiological response (e.g., postprandial QTc prolongation) and other non-pharmacological measures. The session should also address whether improving quality measures of the ECG analysis will obviate the need for positive control in a TQT study.

Session 3: Design and methodology for QT assessment in early clinical trials

TQT studies are in most cases powered to exclude a QTc effect exceeding 10 ms and a typical sample size of these studies currently range from around 30 subjects to more than 60 per treatment group/arm. Clearly, most early clinical trials of standard design, e.g., the First-dose-in-Man, single- and multiple dose ascending study (SAD/MAD) will not have the same power to detect or exclude small QTc changes if the precision of methodologies are not substantially improved and/or alternative analyses are explored. There are a number of ways by which the precision of the QT measurement can be improved, ranging from strict standardization of measurement conditions to highly or fully automated techniques. While ECGs in many TQT studies are captured with continuous recordings using Holter monitors, only a small fraction of the captured data are analyzed. Emerging new techniques with improved precision, exploration of methods that analyze more ECG data and novel designs may represent opportunities to substantially increase the power of early clinical QT assessment.

Session 4: Identification of research topics including expectations of an integrated QT assessment

Session Note: This session needs to be further discussed and refined by the planning committee. The intention is to:

- *Discuss whether the results of non-clinical assays can play a role in identifying projects for which a thorough QT study can be replaced with refined early QT assessment, provided identified research supports this approach;*
- *Based on the previous session, identify well circumscribed research areas expected to generate data to support or refute that early QT assessment can replace the 'thorough QT/QTc study'.*

The focus of this session should be to deliver CSRC research topics that can deliver tangible results within a time frame of 1 or 2 years and to promote the interest of participants to take part in these. We do not expect that CSRC will undertake yet another concordance project between non-clinical and clinical QT assessment and the non-clinical presentations are included, as a preliminary proposal, to form a background for the discussion; as an example, there may be non-clinical outcomes that in the near-term future will <u>not</u> allow replacement of the TQT study by novel approaches and other scenarios where such approaches may seem more acceptable.

Participating regulators will present on their personal views, based on their own experience.