Session I: Role of Concentration Effect Modeling in Assessing a Drug’s Effect on the QTc Interval
Applications of C-QT Modeling

• Predict the QTc effects of lower doses, dosing regimens, routes of administration, or formulations not evaluated in TQT study

• Predict the QTc effects of intrinsic and extrinsic factors that affect PK to support dose adjustments

• Clarify ambiguous results in TQT study

• Obviate the TQT study for drugs with QT prolongation or shortening in phase 1 studies
TQT Study Decision Tree

Nonclinical Assessments

Early-Phase QT Assessments

Option to waive TQT Study

Expanded Phase 2/3 ECG Monitoring

TQT Study

Expanded Phase 2/3 ECG Monitoring

Routine ECG Monitoring

Prior Knowledge of Similar Products
Challenges with Early Phase 1 QT Assessment

• Lack of assay sensitivity
• Lack of standardized ECG collection
• Limited clinical pharmacology profile
• Small trials
  – Reduced power to exclude small increases in QTc using E14 statistical method
Challenges Using C-QT Analysis to Exclude Small QTc Effects

• Evidence to support the lack of C-QT relationship

• Lack of pre-specification of model structure and modeling methods

• Impact of model misspecification
Session 1 Agenda

- FDA statistical perspective
  - Joanne Zhang, Ph.D.
- Statistical framework of C-QT model
  - Günter Heimann, Ph.D.
- Power of detecting moxifloxacin response in small clinical trials using C-QT model
  - Georg Ferber, Ph.D.
- Industry experience of applying C-QT analysis in phase 1 studies
  - Pfizer Experience, Steve Riley, Pharm.D., Ph.D.
  - AstraZeneca Experience, Corina Dota, M.D.
- Round table discussion
Breakout Session 1

• Moderators: Christine Garnett, Steve Riley
• Key Question:
  – What work remains to be done to convincingly demonstrate that C-QT modeling applied to early clinical data can exclude mild QTc prolongation with the same level of confidence as the E14 ‘time-matched QTc analysis’?