"Definitive" QTc Assessment in Early Phase Trials: Expectations from FDA's Interdisciplinary Review Team

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Disclosures

- The views expressed in this presentation are that of the author and do not reflect the official policy of the FDA. No official endorsement by the FDA is intended nor should be inferred.

- Data presented is publicly available

Outline

- Discuss the role of concentration-QTc analysis as the primary basis for decisions to classify the risk of a drug

- Points to consider when performing "definitive" QT assessment in early phase clinical trials
  - Study design and conduct
  - Data analysis

- Case study

Concentration-QTc as the Primary Analysis

- "Exposure-response information is at the heart of any determination of the safety and effectiveness of drugs*"

- ICH E14 Q&A (R3) (Dec 2015)
  - Concentration-response analysis, in which all available data across all doses are used to characterize the potential for a drug to influence QTc, can serve as an alternative to the by-timepoint analysis or intersection-union test as the **primary basis for decisions** to classify the risk of a drug.

  - When using a concentration-response analysis as the primary basis for decisions to classify the risk of a drug, the upper bound of the two-sided 90% confidence interval for the QTc effect of a drug treatment as estimated by exposure-response analysis should be <10 ms at **the highest clinically relevant exposure** …

Design Elements and Trial Conduct
- Expected for "Definitive" QT Assessment

Common to TQT Study and Early Phase QT Assessment

- **Standardized subject handling**
  - Minimize intrinsic variability by controlling food, postural changes
  - ECG recordings should be strictly matched for all dose cohorts
  - Record ECG prior to blood draws or PD assessments

- **Robust ECG acquisition**
  - Same model of ECG machine for each subject.
  - Replicate recordings at each time point
  - Readers of ECGs blinded to time, treatment and subject ID

- **Timing of ECGs**
  - Characterize the QTc effect of a drug throughout the dosing interval (around the T_{max} and ~ 24-hour for a single dose trial)
  - 6 to 8 timepoints

Study Design
- Expected for "Definitive" QT Assessment

- **SAD *vs*. MAD**
  - MAD: When significant PK accumulation of the parent or metabolite(s)
- **Placebo**: Control for potential bias introduced by study procedures
- **Baseline ECG**
  - Pre-dose baseline (e.g., the average of 3 measurements over 1 hour)
  - Time-matched assessments on the day before dosing if a placebo control is not feasible
- **Sample size**: 6 to 9 subjects per treatment (at least 6 placebo controls, can be pooled from different cohorts)
- **Dose range**
  - Cover the highest clinically relevant exposure
  - A sufficiently high multiple of the highest clinically relevant exposure if without a positive control for ECG assay sensitivity

Highest Clinically Relevant Exposure

- The expected highest exposure (for drug and metabolites) at the steady state (if not for single dose use) due to intrinsic (e.g., renal, hepatic, age) and extrinsic (e.g., metabolic inhibition, food effects) factors – "*worst case*" scenario

- Typically, determined at late phases of drug development

# Data Analysis
## - Expected for "Definitive" QT assessment

- Prospective specification of model characteristics to limit bias
- Exploratory analysis
  - Adequate correction for heart rate
  - Delayed drug effect
- Modeling
  - $\Delta QTc_{ijk} = Treatment_i + Time_k + \beta_j \times C_{ijk} + \varepsilon_{ijk}$
  - $\begin{pmatrix} int_i \\ \beta_i \end{pmatrix} \sim MVN \left(\begin{pmatrix} int \\ \beta \end{pmatrix}, (\Omega) \right)$ and $\varepsilon_{ijk} \sim N(0, \sigma^2)$
- Model selection and qualification
  - Goodness-of-fit: observed vs. predicted, Standardized residuals vs. concentrations/time, etc.
- Model prediction: at (highest) clinically relevant concentration

Case Study: Gilead's GS-4997 Waiver

- Retrospective QT analysis of FIH study
- Critical elements:
  - FIH study with doses 5-fold the highest clinical dose in phase 2/3 studies
    - SAD/MAD: 5 cohorts of 8 active, 2 placebo
  - Well characterized clinical pharmacology profile, with no effects on HR
  - Digital ECGs collected: -1 h to 12 h for SAD and days -1, 1 and 7 for MAD. Replicate ECGs extracted at time points coinciding with PK samples
  - Similar QTc and HR variability to legacy TQT studies

Cara H. Nelson et al. A Quantitative Framework to Evaluate Proarrhythmic Risk in a First-in-Human Study to Support Waiver of a Thorough QT Study. CPT 2015

Hysteresis Assessment
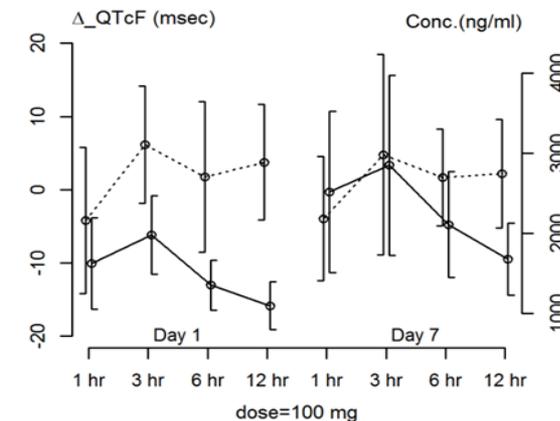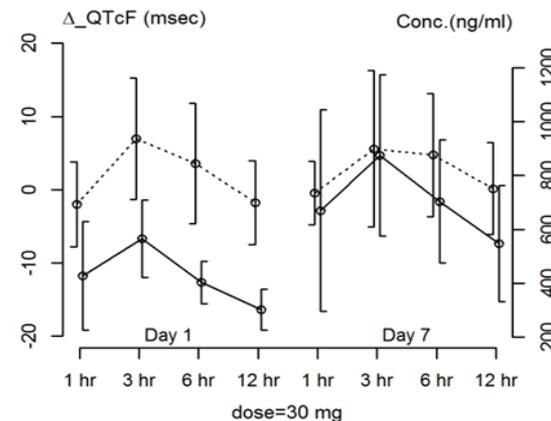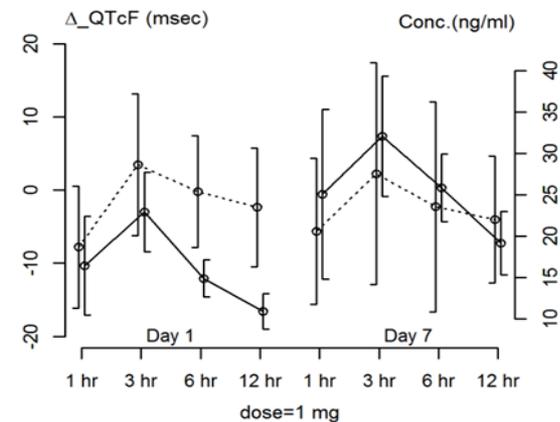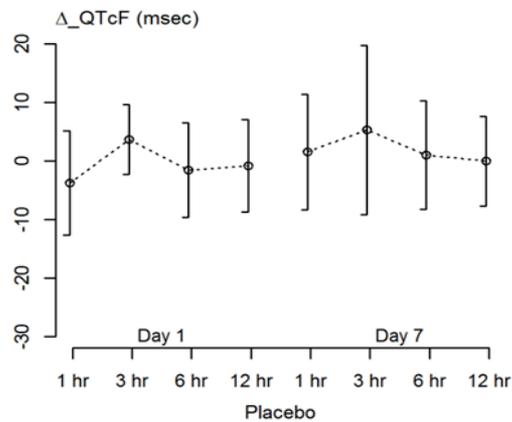
Key Results:
Meets Requirements for a Negative Effect

Predicted ΔΔQTcF and 2-side 90% confidence Intervals at Cmax

Analyte	Dose of GS-4997	Concentration (ng/ml)	Predicted ΔΔQTcF (msec)	90% Confidence Interval (msec)
GS-4997	18 mg, once daily (Therapeutic)	575[a]	1.14	(-2.22, 4.63)
	100 mg, once daily (Supratherapeutic)	2717[b]	3.05	(-1.85, 7.92)
Metabolite A	18 mg, once daily (Therapeutic)	2300[a]	1.36	(-2.14, 4.94)
	100 mg, once daily (Supratherapeutic)	8308[b]	2.37	(-3.01, 7.36)

a   Projected mean steady-state C_{max} following once daily oral dosing of 18 mg GS-4997 simulated using semi-compartmental modeling
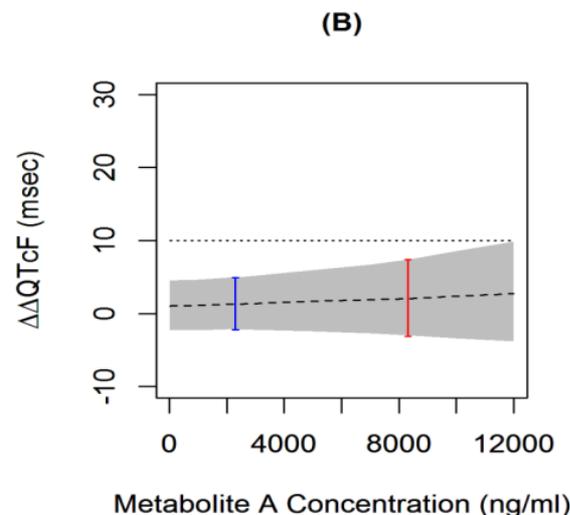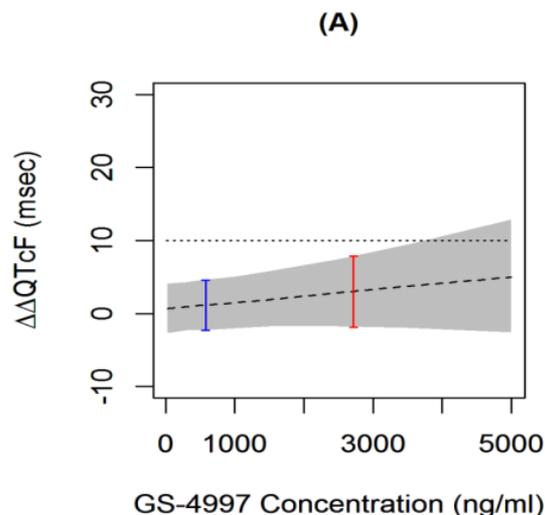
b   Observed geometric mean C_{max} following once daily oral dosing of 100 mg GS-4997 for 7 days

No statistically significant slope

GS-4997 Waiver Based on C-QTc

- **FDA's rationale for adequate QT assessment**
  - Good ECGs quality
  - Experience with exposure considerably higher than the highest clinically relevant exposure
  - C-QTc analyses

ECG Assay Sensitivity
 - Expected for "Definitive" QT assessment

- A sufficiently high multiple of the highest clinically relevant exposure

- Positive control (moxifloxacin 400 mg with QTc effect ~ 10 ms)
    - By-time analysis
    - Concentration-QTc relationship

Concentration-QTc as the primary for a more efficient TQT study

- A positive control for ECG assay sensitivity is required when a sufficiently high multiple of the highest clinically relevant exposure is not feasible

- Assay sensitivity based on C-QTc for the positive control (e.g., 400 mg moxifloxacin single dose)
  - Significantly positive slope
  - the lower bound of the 2-sided 90% confidence interval of the placebo-corrected QTc change from baseline at the observed Cmax of the 400 mg moxi dose exceeds 5 ms

- Sample size: ~20 subjects per arm *? (still under evaluation)*

Typical Regulatory Process

- Plan for QT-assessment during the PIND meeting
  - QT-IRT will response to the QT-related question
- FIH study protocol with QT-assessment as a potential objective
  - Study design including ECG monitoring details
  - Dose/exposure range
  - General concentration-QTc analysis plan following the guidance
- Pre-specification of modeling characteristics, analysis and report back to QT-IRT to gain consensus on interpretation of results
  - Internal decision and ECG monitoring plan for future trials
- Regulatory decision on adequacy of QT-assessment
  - Generally at EOP2

Key Points

- Concentration-QTc as the primary basis for decisions:

   1. High ECGs quality and good conduct of trials

   2. Adequate exposure margin*
      - Cover the highest clinical exposure
      - Sufficiently high multiple of the highest clinically relevant exposure without a method for ECG assay sensitivity

   3. Prospectively specified and well conducted exposure-response analysis