Analysis and Reporting of QTc prolongation potential of new drugs using R tools, Expectations and General Guidance for Regulatory Submissions

Dhananjay Marathe

Steve Riley

Ana Ruiz

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2020 ACCP Annual Meeting
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Acknowledgments

- Moxifloxacin and placebo data made available by:
  - Borje Darpo, MD, PhD
    Chief Scientific Officer, Cardiac Safety, ERT
    https://www.ert.com/cardiac-safety/

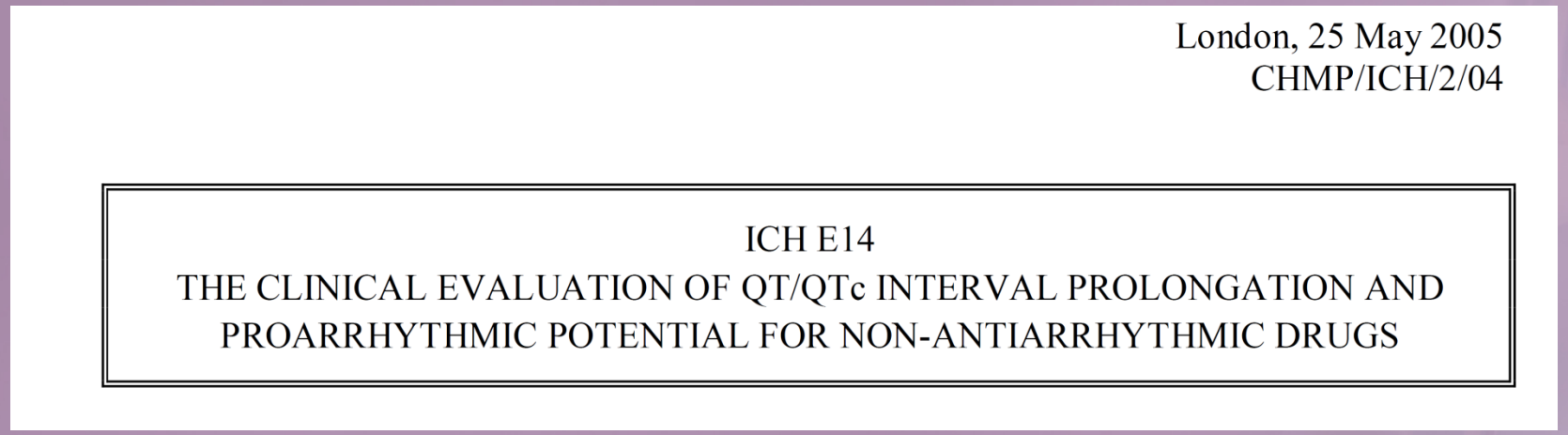
Agenda

- **ECG-PK Analysis Using R: History, Theory, and Demonstration**
  - *Steve Riley, PharmD, PhD, Senior Director, Clinical Pharmacology, Pfizer Inc*
- **Goodness of fit Diagnostics Using R and R Markdown Reporting Tool**
  - *Ana Ruiz-Garcia, PharmD, PhD, Senior Principal Scientist, Metrum Research Group*
- **Experience Regarding Expectations and General Guidance for Regulatory Submissions under ICH E14 Q&A (R3) for TQT Study Substitution Requests Based on Concentration-QTc Analysis**
  - *Dhananjay D. Marathe, PhD, Principal Scientist, Quantitative Pharmacology and Pharmacometrics, Merck & Co. Inc*

QT Interval Prolongation

- **QT interval prolongation predisposes to arrhythmia by prolonging repolarization**
- **Can lead to torsades de pointes, a fatal ventricular arrhythmia**
- **Can be congenital or drug-induced**

ICH E14



London, 25 May 2005
CHMP/ICH/2/04

ICH E14
THE CLINICAL EVALUATION OF QT/QTc INTERVAL PROLONGATION AND PROARRHYTHMIC POTENTIAL FOR NON-ANTIARRHYTHMIC DRUGS

- Essentially required all development programs to include a 'Thorough QT' (TQT) study prior to Phase 3
  - Incredibly successful; no drugs removed from market for QT liability since its release

ICH E14

- Areas described as, “under active investigation”
  - Alternatives to the TQT study
  - Use of exposure-response (ER) modeling to characterize the relationship between QTc and drug concentration
- ICH E14 Q&A (R2), March 2014
  - ER modeling, “can be evaluated in early phase studies and as part of the conventional QT study and may help inform further evaluation”, but not accepted as primary analysis

Shortcomings of the TQT Study

- TQT is the most costly Phase 1 study
- Exposes a relatively large number of healthy volunteers to investigational products
- Very conservative primary analysis (Intersection-Union Test) (IUT)
  - Known ~ 1-1.5 msec upward bias, potential for increased false positives
- A more cost- and time-efficient approach was needed

IQ-CSRC Consortium

- December 2012
  - Duke Cardiac Safety Research Consortium (CSRC) hosted 'Thinktank' meeting at FDA
  - Attendees: Industry, Academia, FDA, including Drs. Stockbridge, Throckmorton, and Temple, and EMA
  - Proposed the idea of replacing the TQT study with early Phase 1 data analysis
  - Innovation and Quality in Pharmaceutical Development (IQ)-CSRC Consortium was born!

IQ-CSRC Consortium

- IQ-CSRC consortium formed to prospectively evaluate whether 'Early QT assessment' can be used to generate QT data with the same confidence as the TQT study
  - Contributors: 13 industry and FDA representatives, including Dr. Stockbridge
- Objective
  - Provide data in support of using routine clinical pharmacology studies to waive the requirement for a TQT study

TQT Waiver Concept

CARDIAC SAFETY

The IQ-CSRC Prospective Clinical Phase 1 Study: "Can Early QT Assessment Using Exposure Response Analysis Replace the Thorough QT Study?"

Borje Darpo, M.D., Ph.D.,[1,*] Nenad Sarapa, M.D.,[2,†] Christine Garnett, Pharm.D.,[3,*] Charles Benson, M.D., Ph.D.,[4,†] Corina Dota, M.D.,[5,*] Georg Ferber, Ph.D.,[6,‡] Venkateswar Jarugula, Ph.D.,[7,†] Lars Johannesen, M.Sc.,[8,9] James Keirns, Ph.D.,[10,†] Kevin Krudys, Ph.D.,[11] Catherine Ortemann-Renon, Pharm.D., Ph.D.,[12,*] Steve Riley, Pharm.D., Ph.D.,[13,‡] Danise Rogers-Subramaniam, Ph.D.,[4,†] and Norman Stockbridge, M.D., Ph.D.[14]

- Industry/FDA collaboration to demonstrate ability of ER analysis to identify a signal when one exists in small Phase 1 study setting

TQT Waiver Concept

Results From the IQ-CSRC Prospective Study Support Replacement of the Thorough QT Study by QT Assessment in the Early Clinical Phase

B Darpo[1,2*], C Benson[3†], C Dota[4*], G Ferber[5], C Garnett[6*], CL Green[7], V Jarugula[8†], L Johannesen[9], J Keirns[10†], K Krudys[11], J Liu[11], C Ortemann-Renon[12*], S Riley[13], N Sarapa[14†], B Smith[2], RR Stoltz[15], M Zhou[2] and N Stockbridge[16]

- Demonstrated signal in 5 “positive” controls and lack of signal in 1 “negative” control with small sample size
- FDA agreed that we did what they asked
- Data were sufficient to demonstrate ability of ER modeling to function as a primary endpoint

TQT Waiver Concept

- ICH E14 Q&A (R3), December 2015
  - IQ-CSRC Study results led to modification of Question 5 on ER modeling
- "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."

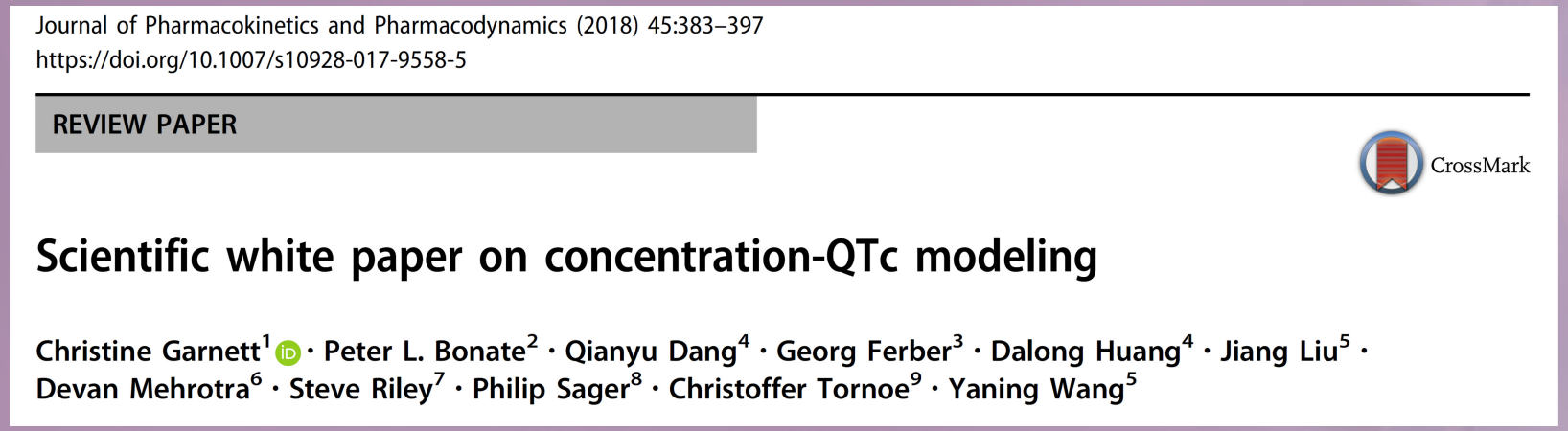
ICH E14 Q&A (R3)

- Data need not come from a dedicated QT study, nor even a single study e.g., pooled SAD/MAD
- Must pre-specify modeling methods and assumptions, criteria for model selection, rationale for model components, and potential for pooling of data across studies be to limit bias
- Not applicable to every program – limitations exist

Scientific White Paper on Concentration-QTc Modeling

- E14 Working Group condition of satisfaction for the Q&A (R3) language was that a White Paper be created describing what an ER analysis package should look like
  - Target audience: Health Authorities without the pharmacometric expertise which resides within FDA

Scientific White Paper on Concentration-QTc Modeling



Journal of Pharmacokinetics and Pharmacodynamics (2018) 45:383–397
https://doi.org/10.1007/s10928-017-9558-5

REVIEW PAPER

CrossMark

Scientific white paper on concentration-QTc modeling

Christine Garnett[1] · Peter L. Bonate[2] · Qianyu Dang[4] · Georg Ferber[3] · Dalong Huang[4] · Jiang Liu[5] · Devan Mehrotra[6] · Steve Riley[7] · Philip Sager[8] · Christoffer Tornoe[9] · Yaning Wang[5]

- Provides current recommendations on planning, conduct, and ER analysis of early Phase 1 studies
- Recommendations expected to evolve with advances in knowledge and analytical methodology

Modeling Objectives

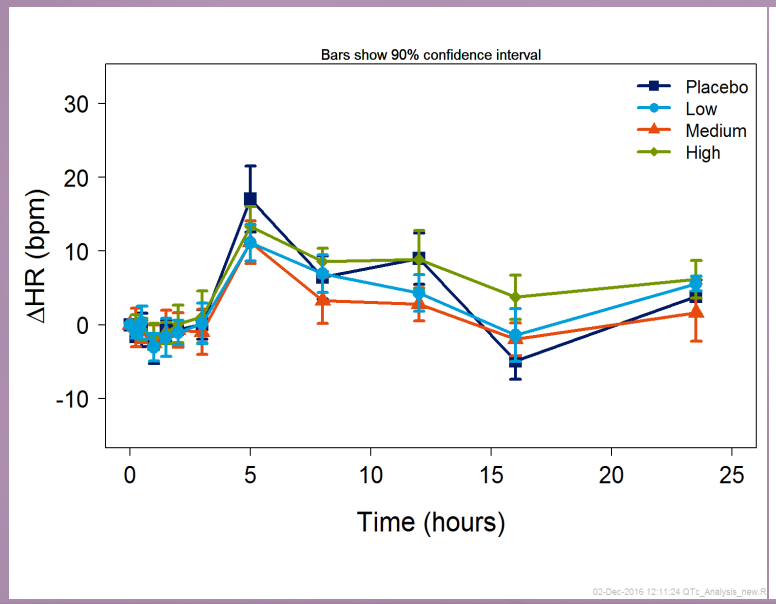
- Develop relationship between change from baseline heart-rate corrected QTc (ΔQTc) and drug concentration
- Compute the placebo-adjusted model-derived mean and 90% CI ΔQTc interval ($\Delta\Delta$QTc) at relevant drug concentration(s)
- Assess whether prolongation exceeds the 10 ms regulatory threshold described in the ICH E14 Guidance

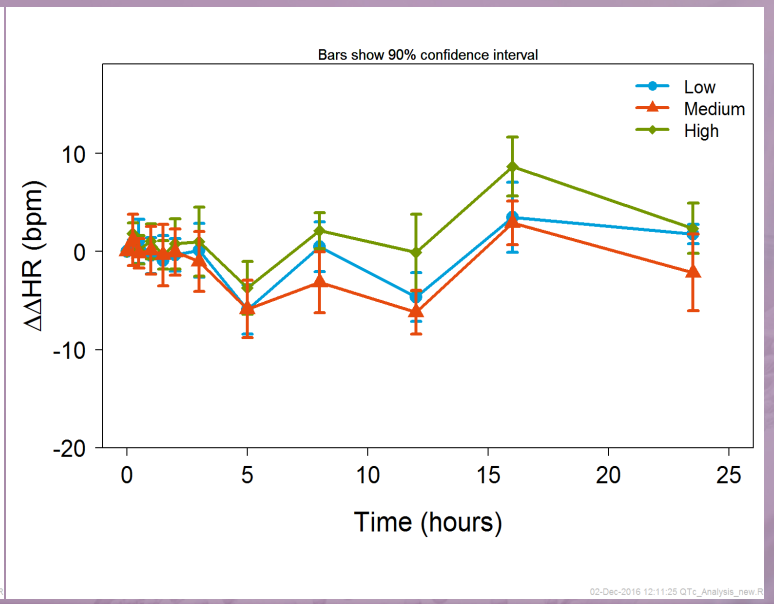
Evaluation of a Model-based Package – Modeling Analysis Plan (MAP)

- To limit potential biases, critical analysis features should be pre-specified in a MAP
  - Data sources
  - Baseline correction method (pre-dose vs time-matched)
  - Heart rate correction
  - Model and methods for evaluation/selection
  - QTc risk decision criterion
  - Rationale for choosing concentration of interest
- MAP should describe strategy for moving through the analysis

Exploratory Plots Evaluate Model Assumptions

- **Assumption 1: No drug effect on heart rate**
  - Look for consistency of change from baseline HR (ΔHR) with time, dose, and treatment

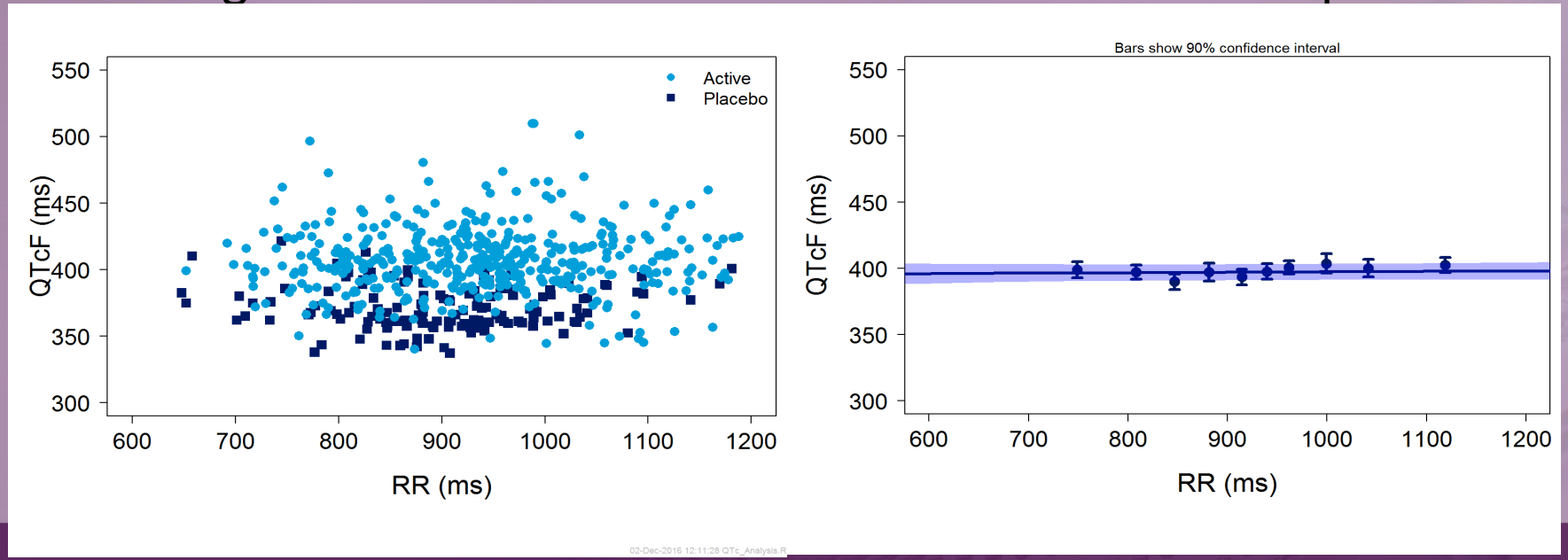




ΔHR: change from baseline heart rate (HR);
ΔΔHR: placebo-corrected change from baseline HR

Exploratory Plots Evaluate Model Assumptions

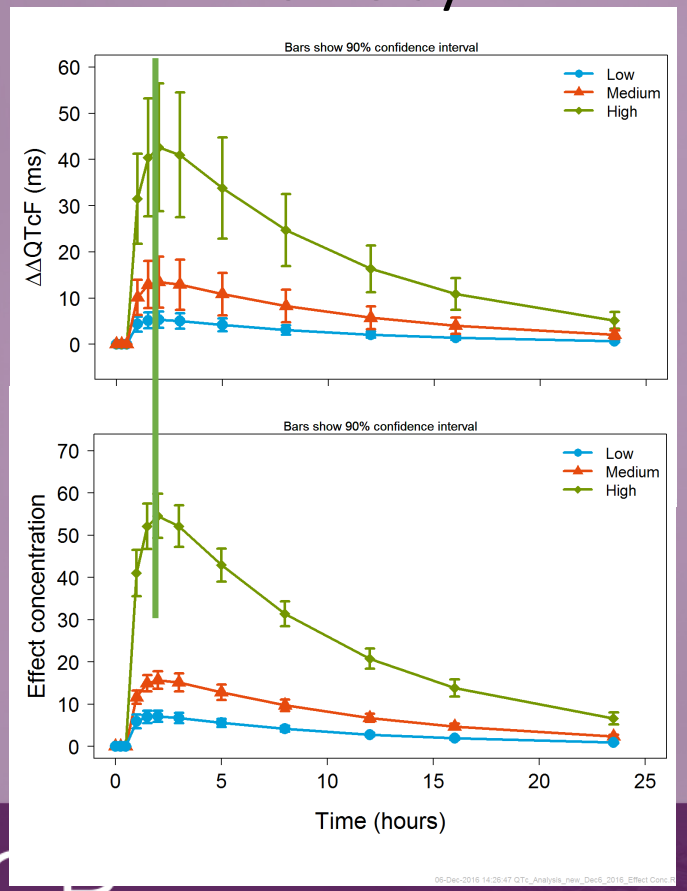
- **Assumption 2: QTc interval is independent of heart rate**
  - Range of HR are similar off- and on-drug
  - Linear regression line should show the lack of relationship between QTc and



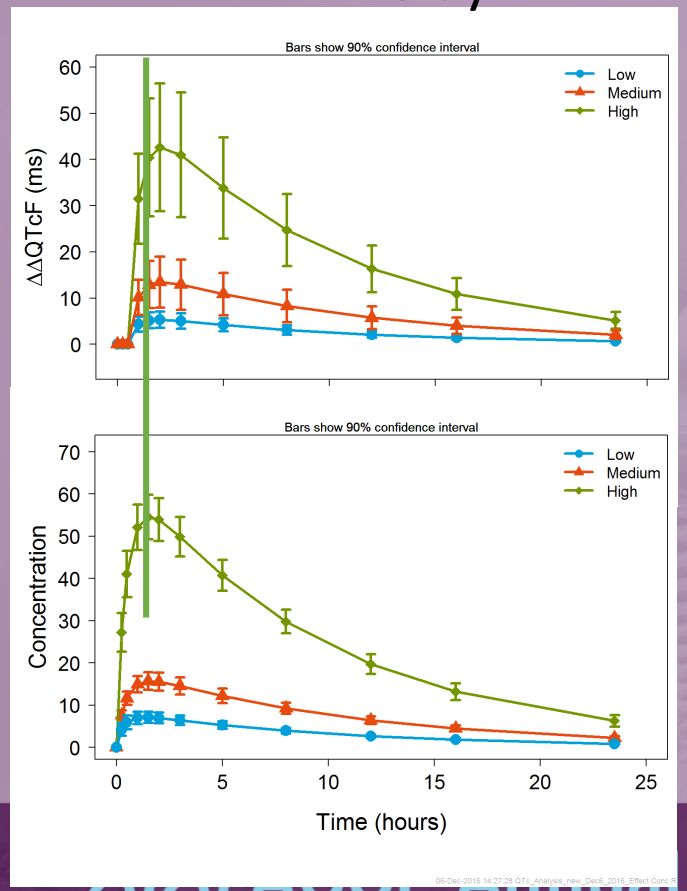
Exploratory Plots Evaluate Model Assumptions

- **Assumption 3: No time delay between drug concentrations and Δ Δ QTc**

No Delay



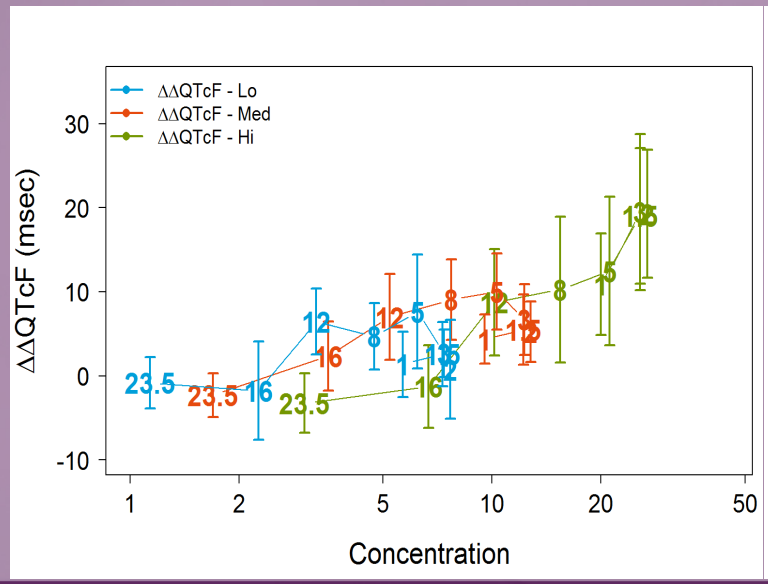
1 hr Delay



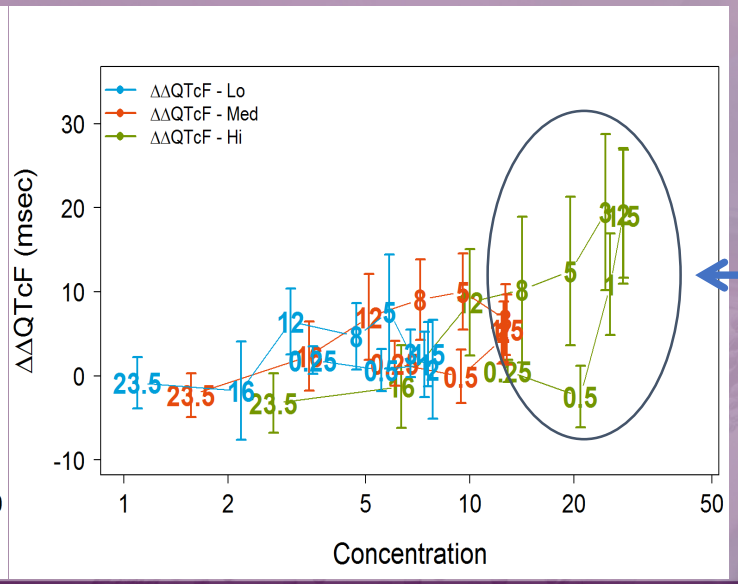
Exploratory Plots Evaluate Model Assumptions

- **Assumption 3: No time delay between drug concentrations and Δ Δ QTc (cont)**
  - Evaluate for presence of hysteresis loop

No Delay



1 hr Delay

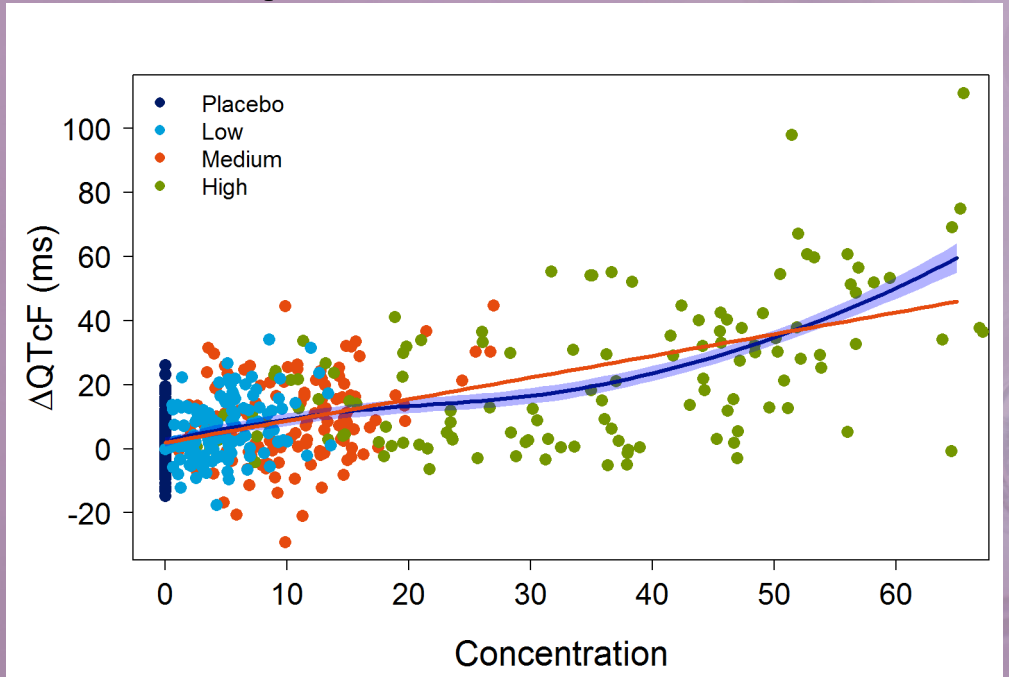


Suggestion of hysteresis at high dose

ΔΔQTc: placebo-corrected change from baseline QTc

Exploratory Plots Evaluate Model Assumptions

- **Assumption 4: Linear C-QTc relationship**
- Consider shape of C-QTc relationship
- Magnitude of ΔQTc over observed concentration range
- Concentration range covers worst-case clinical exposure scenario



ΔQTc: change from baseline QTc

Linear C-QTc Relationship

- A pre-specified linear mixed effect model (LME) is considered scientifically plausible and appropriately addresses the overall modeling objective
  - Dependent variable: ΔQTcF
  - Fixed effects: Treatment-specific intercept, nominal time post-first dose, slope, and baseline QTc
  - Random effects: Intercept and slope

Linear C-QTc Relationship

- Pre-specified LME recommended as it can be applied to most common study designs in healthy volunteers, e.g., SAD/MAD, TQT
  - Applied if basic assumptions satisfied in exploratory graphics
- Anticipated deviations from the recommended model should be documented in MAP
  - Recommended changes based on certain scenarios provided in White Paper, e.g., when pooling data across studies

Linear C-QTc Relationship

- If ***no drug effect*** detected from exploratory plots and LME model at the highest clinically relevant exposure:
  - Sponsor has adequately addressed QTc prolongation risk
  - Sponsor can conclude that an expanded ECG safety evaluation during later stages of drug development is not needed
- Above conclusions assume that model fit adequately describes data

Model Development

- If ***drug effect*** detected from exploratory plots and LME model at the highest clinically relevant exposure:
  - Additional model development recommended to objectively determine the appropriate drug model
  - Model must adequately describe observed concentration-ΔQTc relationship to ensure reliable estimate of QTc prolongation
  - Simpler models are preferred over more complex models when statistically justified

Model Development

- Model selection criteria pre-specified in MAP and follow standard modeling practices*
- Based on objective and subjective criteria, e.g.,
  - Akaike Information Criteria (AIC)
  - Statistical significance and standard error (SE) of estimates
  - Goodness-of-fit (GOF) plots

* FDA: https://www.fda.gov/media/128793/download
EMA: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-reporting-results-population-pharmacokinetic-analyses_en.pdf

Model Evaluation

- GOF plots should be presented for final model and any key steps in model development
- Scatterplots and quantile plots useful for evaluating residuals (differences between observed and predicted values) for continuous covariates, e.g., concentration, baseline QTc
- Boxplots useful for evaluating residuals against categorical covariates, e.g., time, treatment
- Tabular display of parameter estimates, SEs, p-values, confidence intervals (CIs) required to evaluate quality of fit

Estimation of Model-derived ΔΔQTcF

- Use final C-QTc model
- Compute mean and 90% CI model-derived ΔΔQTcF at the highest clinically relevant concentration
- ***Strongly recommended*** that the model not be extrapolated to concentrations outside the observed concentration range used to derive the parameter estimates

Reporting

- Stand-alone or integrated into study report
- Recommended content based upon EFPIA MID3 Working Group output*
- Should include clinical relevance of results and describe patients at increase risk of QTc prolongation

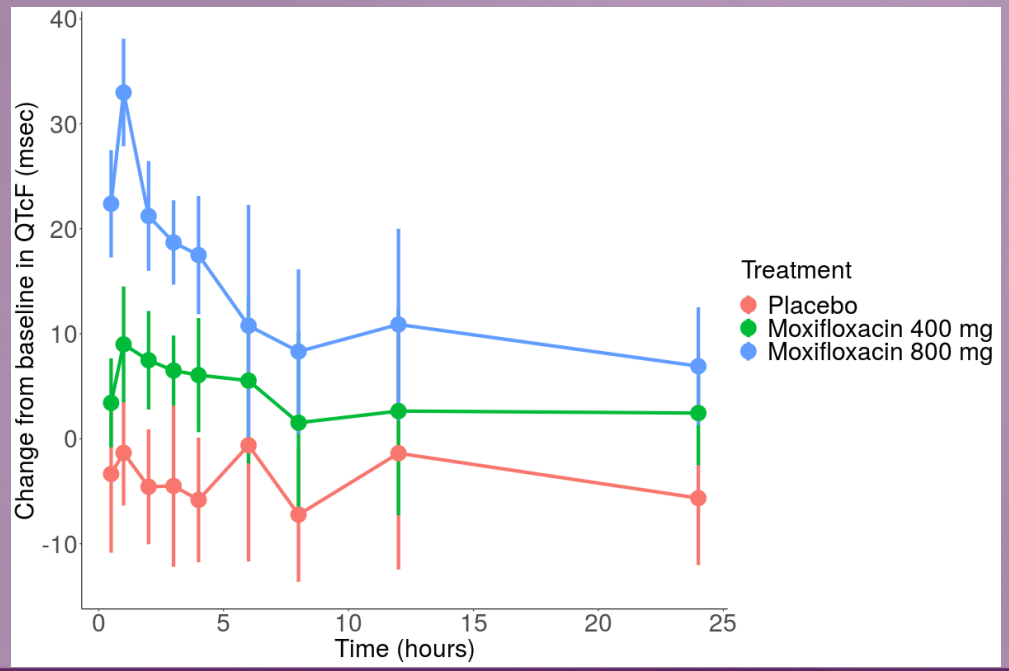
* Marshall, SF, et.al., Good Practices in Model-Informed Drug Discovery and Development: Practice, Application, and Documentation. CPT-PSP. 2016:5, 93-122. http://onlinelibrary.wiley.com.proxy1.athensams.net/doi/10.1002/psp4.12049/epdf

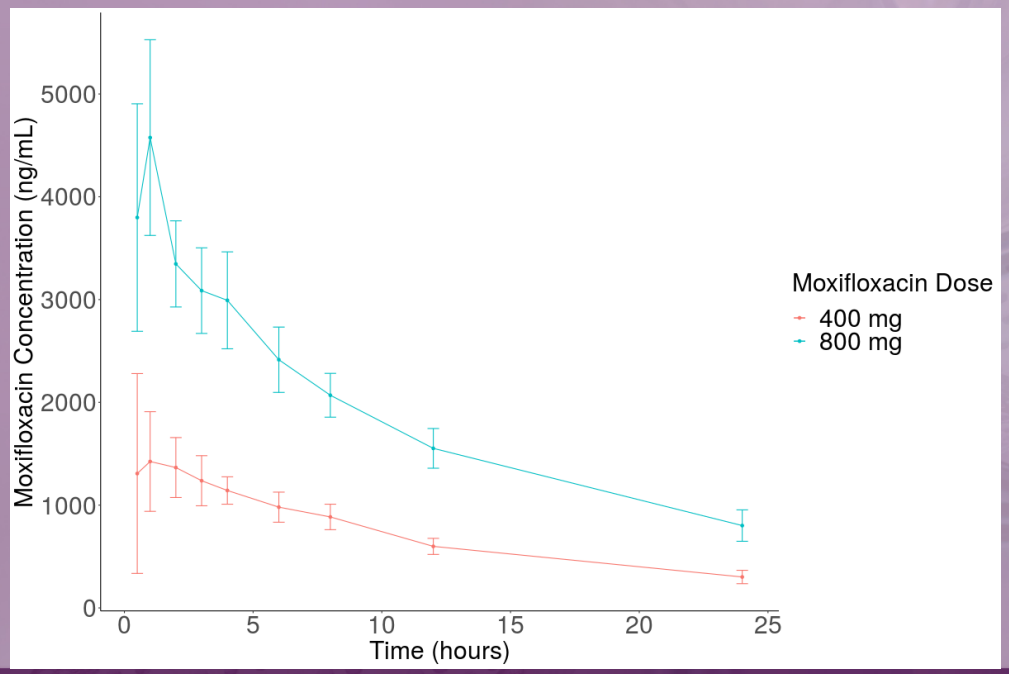
Potentially Difficult Drugs to Assess Using C-QTc in Phase 1 Study

- Heart rate effects
  - Inadequate heart rate correction; potential for QT/RR hysteresis
- Multiple hERG-inhibiting moieties (parent and metabolites)
  - Single dose studies may not capture effects; modeling of multiple variables challenging, but may be possible; interpretation can be difficult
- Extended-release formulations
  - C-QTc modeling of narrow concentration range can give incorrect results
- PK/PD hysteresis
  - ECG/PK sample timing is important for model; PK model needed
- Inhaled products
  - Relevance of systemic drug concentrations for C-QTc analysis for locally-acting inhaled therapeutics is debatable; depends on systemic exposure

Demonstration

- Dataset from moxifloxacin and placebo treatments in IQ-CSRC study
- Moxi 400 mg PO (therapeutic dose) on Day 1; 800 mg IV (supratherapeutic dose) on Day 2 (moxi.csv)
- Serial PK and ECG collection adequate to capture Cmax





Demonstration

- Objective is to characterize the relationship between moxifloxacin concentrations and QTcF interval
- Data summarization, modeling, and reporting all done in R

Demonstration

- Prespecified linear model

$$\Delta QTcF = (\theta_0 + \eta_{0,i}) + \theta_1 TRT_j + (\theta_2 + \eta_{2,i}) C_{ijk} + \theta_3 Time_k + \theta_4 (QTc_{i,j=0} - \overline{QTc_0})$$

- ΔQTcF: change from baseline QTcF interval
- θ_0: intercept; θ_1: treatment-specific intercept
- θ_2: slope
- θ_3: placebo time course
- θ_4: effect of baseline QTcF

- RMarkdown file (report.Rmd) contains code which generates all graphics, summaries, model fits, and predictions

References

- IQ-CSRC Study Design: https://www.ncbi.nlm.nih.gov/pubmed/24372708
- IQ-CSRC Study Results: https://www.ncbi.nlm.nih.gov/pubmed/25670536
- ICH E14 Q&A (R3): https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E14/E14_Q_As_R3__Step4.pdf
- Scientific White Paper on Concentration-QTc Modeling: https://www.ncbi.nlm.nih.gov/pubmed/29209907
  - White Paper Erratum: https://pubmed.ncbi.nlm.nih.gov/29330761/