

Concordance between the exposure-QTc response relationship in the pooled Phase 1 data vs. thorough QTc study

T. J. Carrothers, Sc.D.

Pharsight Corporation

Mountain View, CA, USA



Acknowledgements

Several Pharsight colleagues contributed to the materials presented herein:

- Tatiana Khariton, Ph.D.
- Kevin Dykstra, Ph.D.
- Smita Kshirsagar, Ph.D.
- Helen Kastrissios, Ph.D.

Foreword

- Examples presented here are based on modeling and simulation work performed by Pharsight under contract with drug company clients.
- Drug names, doses, and data have been disguised to protect confidentiality without compromising the message.

Outline of Presentation

- **Introduction**
- **Example**
 - Pooled Concentration-Response Model
 - Thorough QT Study Results
- **Discussion**

Concentration-QTc Modeling

- Models concentration effect on QTc.
 - Establishes mean effect, quantifies how well it is known
 - Uses various model shapes (linear, saturable)
 - Studies variability (period, subject, measurement)
- Speaks from the full ECG dataset across all completed studies.
- Linked with population pharmacokinetic model
 - Better understanding of variability
 - Assessment of covariate effects on QTc
 - Ready for simulation of subpopulations
- Summary metric: Projected prolongation at mean peak steady-state exposure.

Outline of Presentation

- Introduction
- **Example**
 - Pooled Concentration-Response Model
 - Thorough QT Study Results
- Discussion

Drug X

- Anti-diabetic compound (end Phase 2)
- Modeling and simulation conducted throughout clinical development for
 - selecting doses and regimen
 - illuminating efficacy/safety tradeoffs
 - qualifying biomarkers
 - modeling disease progression
- QT was one of several PD endpoints

Outline of Presentation

- Introduction
- **Example**
 - Pooled Concentration-Response Model
 - Thorough QT Study Results
- Discussion

Pooled Phase I/II Conc-QTc Model

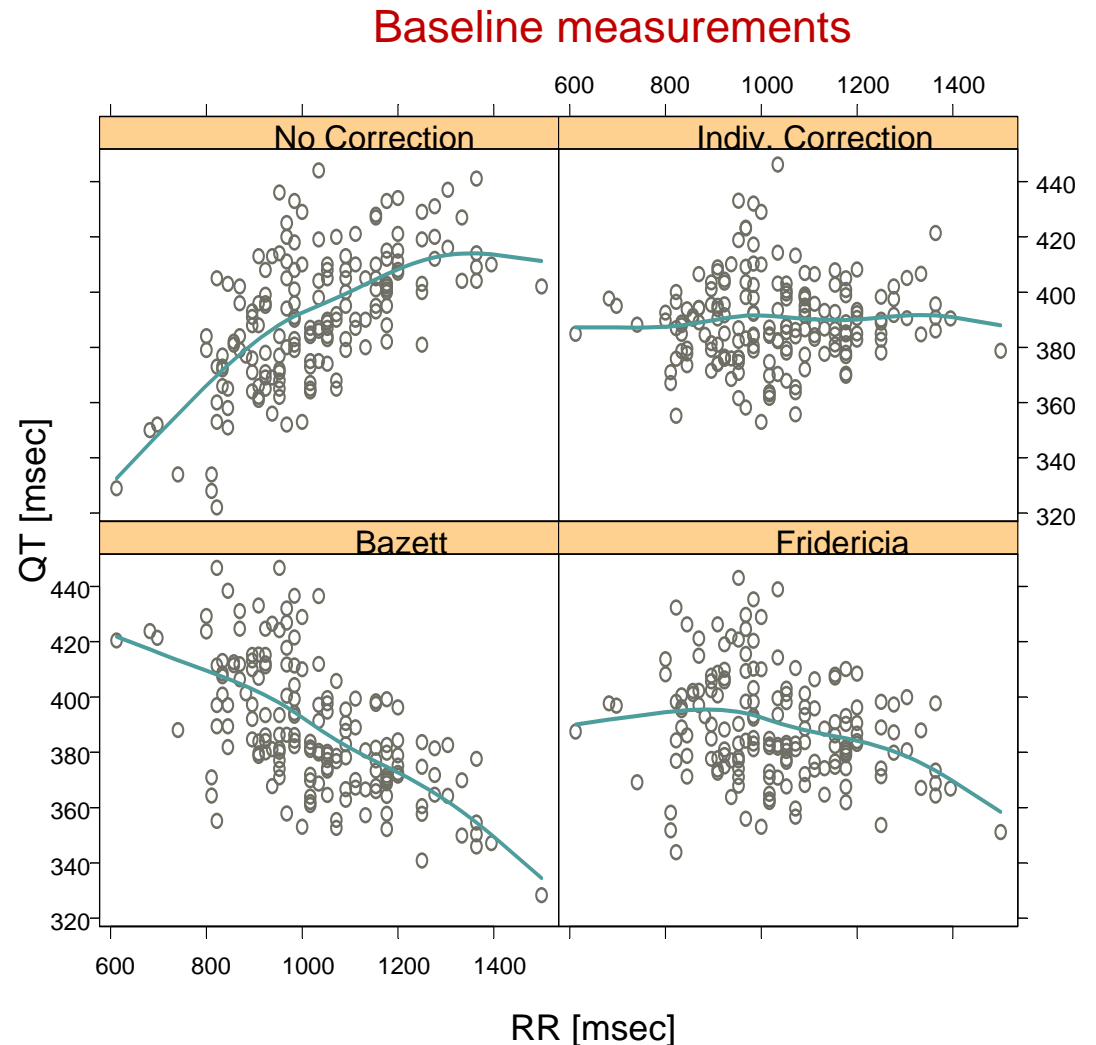
- Conducted before TQT
- Connected to pooled population PK/PD
 - Individual estimates of exposure, allowing direct accounting for exposure variability.
 - Several Phase I and two Phase II studies, including doses 2 to 4 times expected marketed dose.

Overview of Dataset

- QTc analysis from one Phase I study
 - Other studies only had ECG at pre-dose and study exit
 - Primary study had 24 subjects in a 3 period crossover {10, 20, 60 mg}.
 - Each period: Drug X QD for 4 days
 - Intensive PK sampling on each Day 1 (up to 24 h post dose) and Day 4 (up to 72 h post dose).
 - ECGs taken on each of the 4 dosing days at pre-dose, 2, and 4 hours post-dose.
 - Manually-read triplicate observations at each sample point.
 - Each observation was the average of 3 cardiac beats.

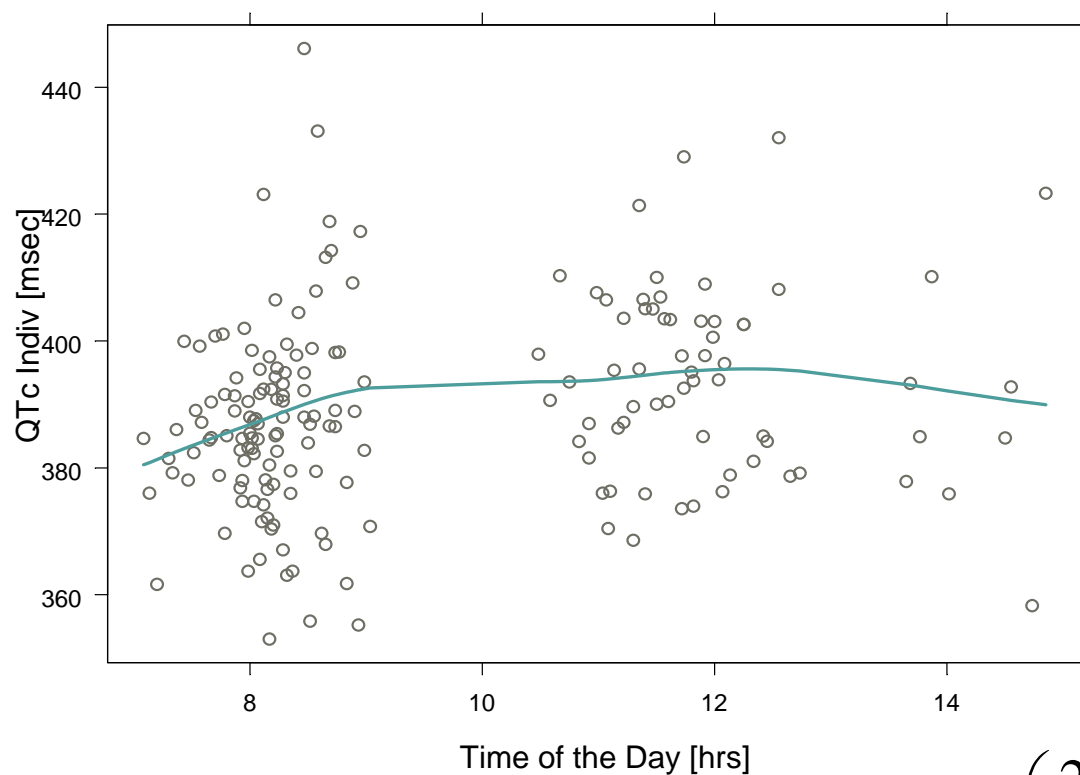
A Mixed-Effects Model for Individual Correction

- Typical exponent was 0.24
- Analysis was carried to completion for both Fridericia and Individual correction datasets



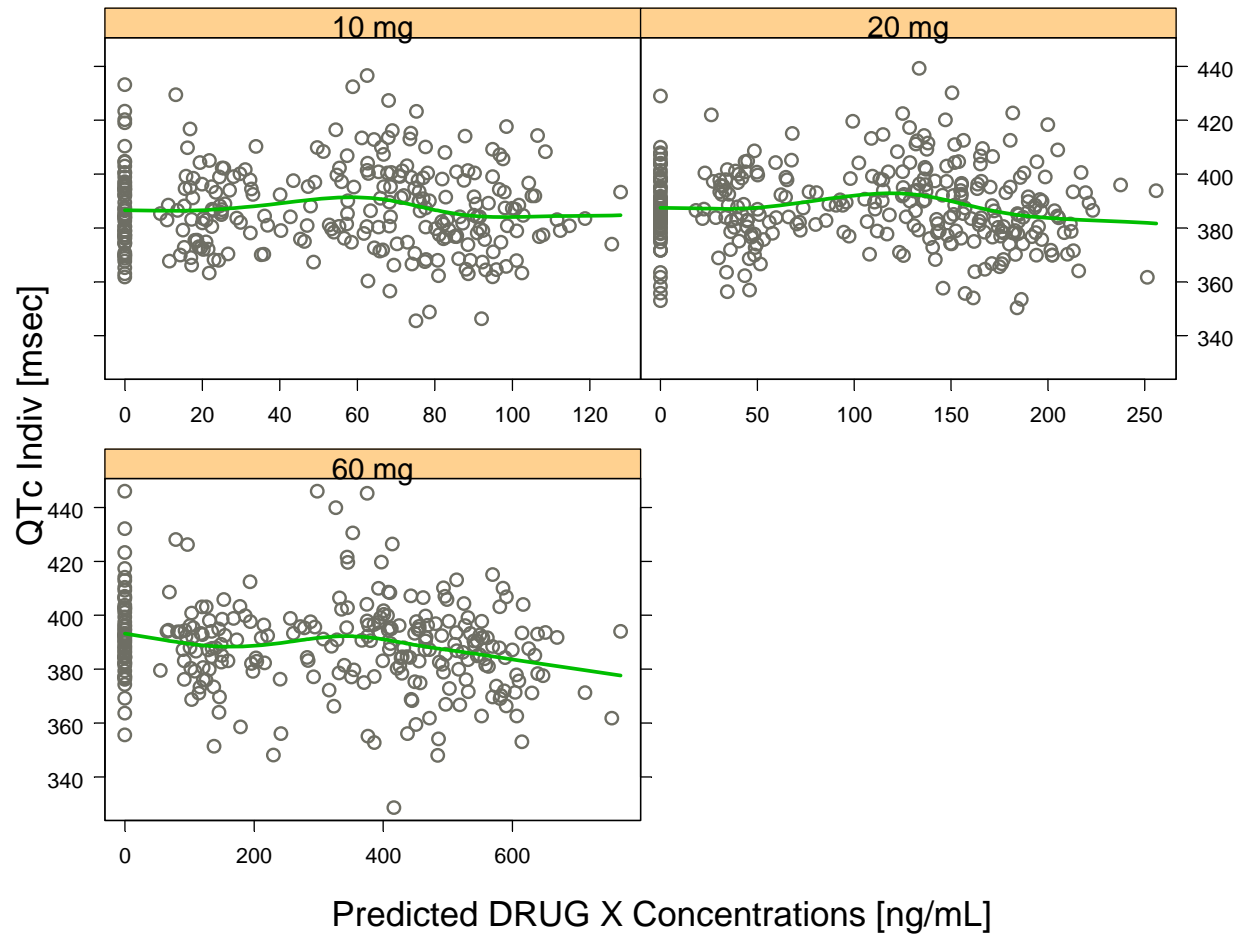
Time-of-day was explicitly modeled

Baseline Visits

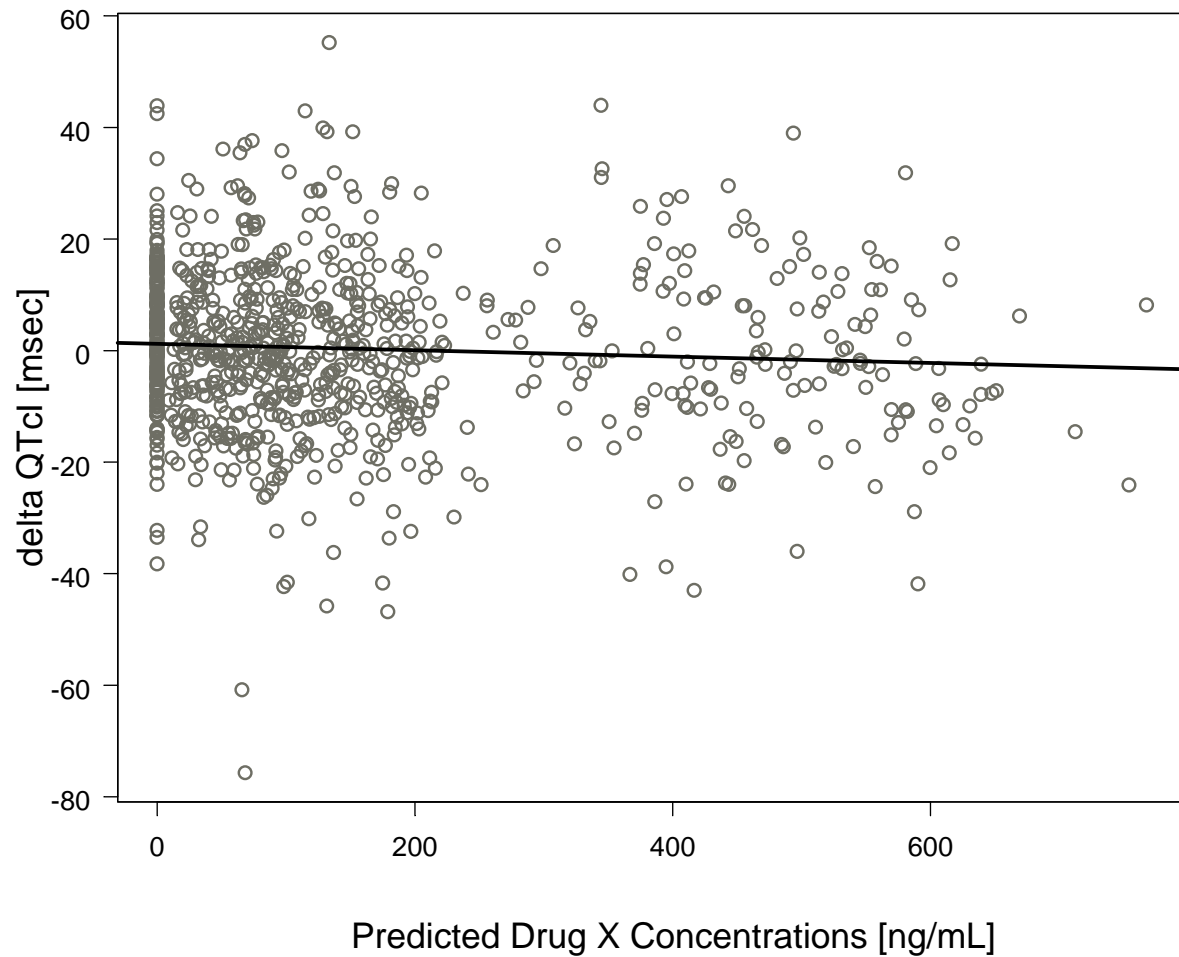


$$f(t) = A_1 \cos\left(\frac{2\pi(t - \phi_1)}{24}\right) + A_2 \cos\left(\frac{2\pi(t - \phi_2)}{12}\right)$$

No relationship was seen with concentration



Best fit of model confirmed this



Final Model

$$QTc_{ij} = BLN_{ij} + TRT_{ij} + \varepsilon_{ij} \quad i = 1, \dots, N \quad j = 1, \dots, M_i$$

where BLN and TRT are baseline and active treatment effects respectively,

N is the number of individuals in the trial,

M_i are the number of measurements i -th individual has

$$BLN_{ij} = \beta_0 + f_{ij}(TimeOfDay) \text{ and } TRT_{ij} = \beta_1 * CONC_{ij}$$

$$\text{where } f_{ij}(TimeOfDay) = A_1 \cos\left(\frac{2\pi(t_{ij} - \phi_1)}{12}\right) + A_2 \cos\left(\frac{2\pi(t_{ij} - \phi_2)}{6}\right),$$

$$\beta_0 = \theta_0 + \eta_0 \text{ and } \beta_1 = \theta_1 + \eta_1$$

$$\varepsilon_{ij} \sim N(0, \sigma^2) \text{ and } \begin{pmatrix} \eta_0 \\ \eta_1 \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \varpi_0 & \varpi_{01} \\ \varpi_{01} & \varpi_1 \end{pmatrix}\right), \text{ where } \varpi_{01} = Corr(\eta_0, \eta_1)$$

Model Parameters

<i>Parameter</i>	<i>Population Mean</i>		<i>Intersubject variability</i>	
	<i>Estimate</i>	<i>SE^a</i> (% CV)	<i>Estimate^b</i> (%CV)	<i>SE^c</i> (%)
θ_0 [msec]	383.13	0.8	2.56	39.2
ϕ_1 [h]	12.85	1.7		
A_1 [msec]	10.27	33.1		
ϕ_2 [h]	1.42	14.2		
A_2 [msec]	-4.93	32.8		
θ_1 [msec/(ng/mL)]	-0.02	37.1	70.3	48.2
σ^d [msec]	11.98	2.1		

a Coefficient of variation of the estimates (100*SEestimate/estimate).

b Estimates of variability expressed as approximate percent coefficient of variation (%CV) $100 \sqrt{\Omega}$

c Percent square root of the relative standard error of the coefficient of variation.

d Residual intrasubject variability, expressed as standard deviation. $100 \sqrt{\frac{SE_{ETAestimate}}{ETAestimate}}$

Outline of Presentation

- Introduction
- **Example**
 - Pooled Concentration-Response Model
 - **Thorough QT Study Results**
- Discussion

Result of Later TQT: Negative

- “...Drug X non-inferior to placebo based on the largest LSM for placebo-corrected time-matched delta QTcF at any time point post-dose...”
- 60 and 200 mg QD 7 days
- Active control (Moxifloxacin): 14 msec at largest time point (3 h), placebo-corrected and time-matched.
- Flat relationship with concentration – no increase from baseline

Outline of Presentation

- Introduction
- Example
 - Pooled Concentration-Response Model
 - Thorough QT Study
- **Discussion**

How to define “concordance”?

1. Base it on the E14 positive-negative criterion.
 - The concentration-response model can be used to simulate the TQT study design
 - What is the likelihood of a positive TQT?
- Concerns
 - A “bright-line” approach is misleading
 - As much about study design as knowledge

How to define “concordance”?

2. Focus on the expected effect

- How does the mean C-R estimate (i.e., slope) compare to pooled analysis without TQT data?
- A TQT trial is just one of many trials in the dataset (but certainly an important one)
- Without the misleading false sense of importance of a bright-line “yes-no” judgment, the fuller decision-context can be emphasized.
 - Which treatment path has the best balance of risk and benefit for this patient?

A Potential Future?

- Rigorous, pooled concentration-response modeling of potential for QTc prolongation is undertaken before TQT.
- Design of TQT is influenced by modeling results.
 - TQT not required when modeling indicates *de minimis* risk.
 - More efficient and informative TQT when modeling indicates otherwise.
 - Learn and confirm.
- Focus is put on understanding central tendency and spread of a compound's QTc prolongation potential, using the entire set of available knowledge.
- QTc is seen as “one piece of the puzzle” for quantifying risk of TdP and overall cardiac risk.

Thank You