

Applications of Modeling and Simulation (M&S) in Cardiac Safety Studies



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What is Modeling and Simulation?

- Modeling (creating a mathematical and physiological model that best explains what has been observed)



- Simulation (using the mathematical and physiological model to predict what will be observed)



Why is M&S important in QT studies?

- Is founded upon the pharmacology of drug-induced prolongation.
- Offers better dosage determination/adjustments for special populations.
- C-QT modeling has rescued several compounds that showed false positive results in the primary E14 analysis.

Applications of M&S

3 case studies that demonstrate the utility of M&S will be discussed. These examples will show how M&S was used in:

- Supra-therapeutic dose selection for a thorough QT (TQT) study.
- Interpreting the results of a TQT study.
- Predicting QTc effects at lower doses.

Application 1: Dose Selection

- Sponsor had limited phase I data and wanted to perform thorough QT study.
- Sponsor wanted to make a “Go-No Go” decision based on results of the TQT study.
- Proposed TD: 40 mg QD. Proposed SD: 160 mg QD.

TD: Therapeutic dose

SD: Supratherapeutic dose

“Are Selected Doses appropriate?”

Supra-therapeutic dose should delineate QTc effects at exposures that are representative of those obtained when therapeutic dose is administered :

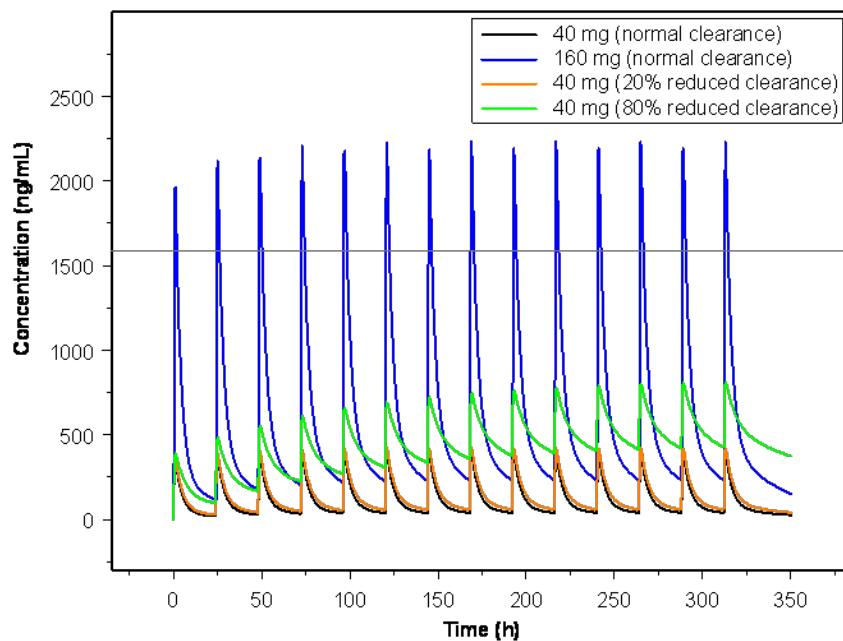
- (i). with an interacting drug, and/or
- (ii). to subjects showing compromised clearance.

Simulation of PK data

Based on an oral 2-compartment PK model, concentration-time profiles for QD dosing were simulated under the following clinical scenarios:

- 40 mg QD, normal clearance
- 160 mg QD, normal clearance
- 40 mg QD, (20% ↓CL) – mild impairment
- 40 mg QD, (80% ↓CL) – severe impairment

Simulated Exposure: Clinical scenarios



Peak exposures achieved with the SD will be greater than those achieved in subjects with impaired clearance dosed the TD.

Choice of 160 mg QD as SD is appropriate.

Application 2: Interpreting TQT Results

- A 4-treatment arm parallel TQT study : Low dose (40 mg), high dose (160 mg), placebo, and moxifloxacin 400 mg.
- Four days of dosing. Day -1: baseline day and Day 4: steady state day.
 - Triplicate ECGs and matching PK samples at several timepoints.
 - Change from baseline was calculated as the time-matched difference between Day 4 and Day -1.
 - Placebo-correction was made on the means .

TQT Study Results

Maximum $\Delta\Delta$ QTcl and Confidence Intervals for 40 mg and 160 mg

Treatment	Time of Max. Mean $\Delta\Delta$ QTcl (h)	Max Mean $\Delta\Delta$ QTcl (ms)	Upper 2-sided 90% CI (ms)
40 mg	3 h	3.9	7.6
160 mg	1.5 h	9.3	13.1

“Negative” TQT outcome for low dose.

“Positive” TQT outcome for high dose.

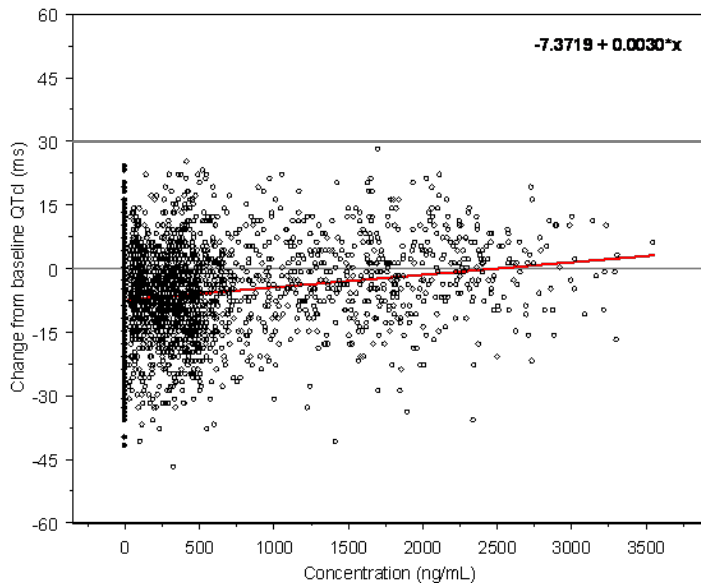
C-QT Modeling

A C-QT Model was developed for this study.

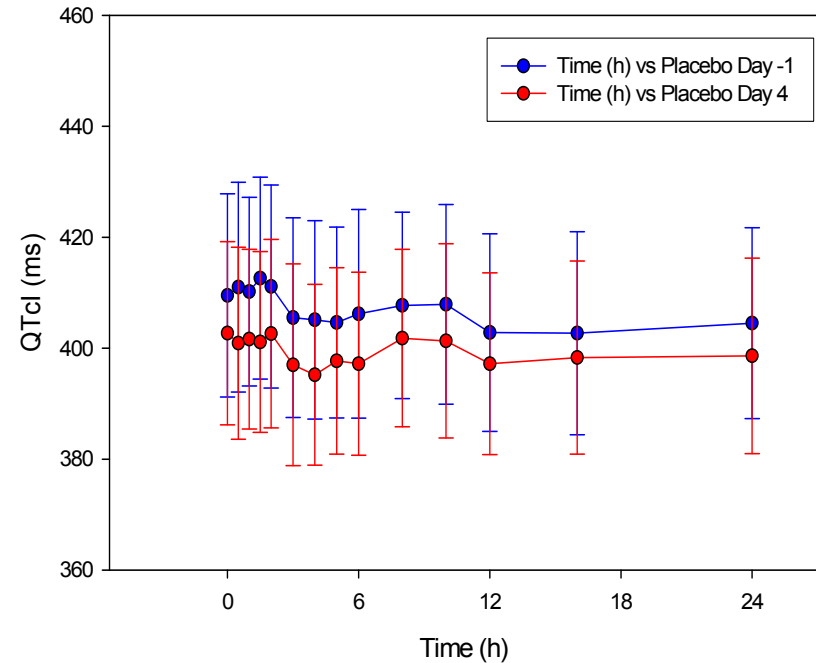
- *“Regulatory review of QT study is not complete without an assessment of concentration-QTc relationship” – (Federal register, Notice. Fed Regist. 2005; 70:61134-61145).*
- *“Exposure-response information is at the heart of any determination of the safety and effectiveness of drugs” – (Exposure-Response Relationships – Guidance for Industry.2003)*

Exploratory Analysis

Concentration vs CFB



Placebo: Day -1 versus Day 4



A significant placebo effect was observed.

C-QT Modeling Approach

Raw QTcl data on Day -1 (baseline), and Day 4 (active and placebo) were modeled together.

$$\text{QTcl} = \beta_0 + f(t) + \varepsilon \quad (\text{Day -1})$$

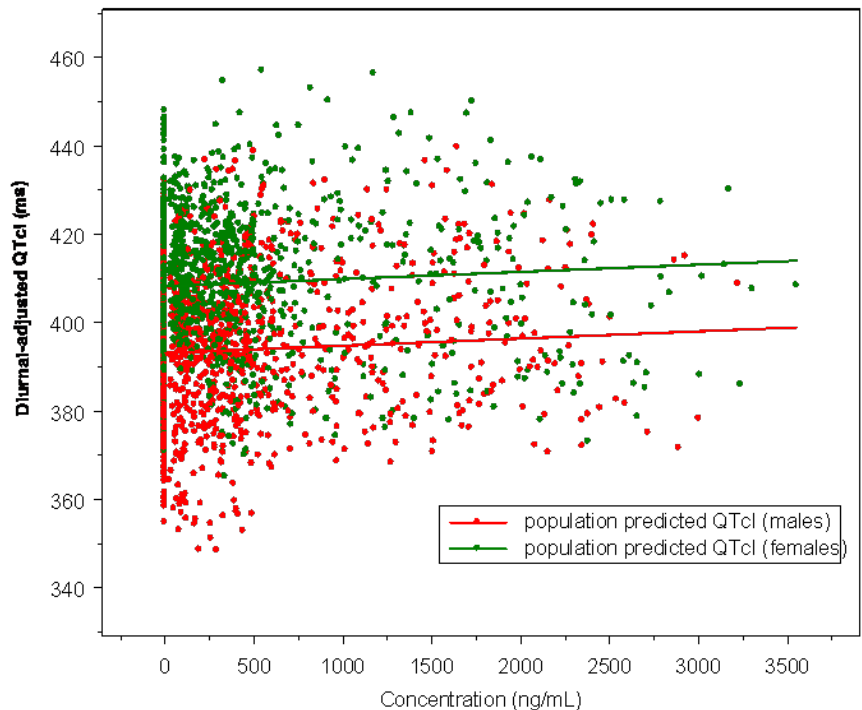
$$\text{QTcl} = \beta_0 + \text{PE} + f(t) + \varepsilon \quad (\text{Day 4, Placebo})$$

$$\text{QTcl} = \beta_0 + \text{PE} + f(t) + f(\text{Cp}) + \varepsilon \quad (\text{Day 4, Active})$$

β_0 is the mesor baseline parameter (separate for males and females), $f(t)$ is the diurnal variation in QTcl, PE is the placebo effect.

C-QT Model Information

- Diurnal effects were modeled using a cosinor model with 3 periodicities (24h, 8h, and 4h).
- A simple linear model was adequate for the drug-effect model.



Estimates of QT prolongation

Treatment	Maximum Mean effect (upper 95% CI) [ms]	Maximum Mean effect (upper 95% CI) [ms]
	E14 Analysis	C-QT Analysis
40 mg	3.9 (7.6)	0.8 (1.2)
160 mg	9.3 (13.1)	3.6 (5.2)

C-QT model showed lower estimates of prolongation that were under the regulatory specified threshold of concern.

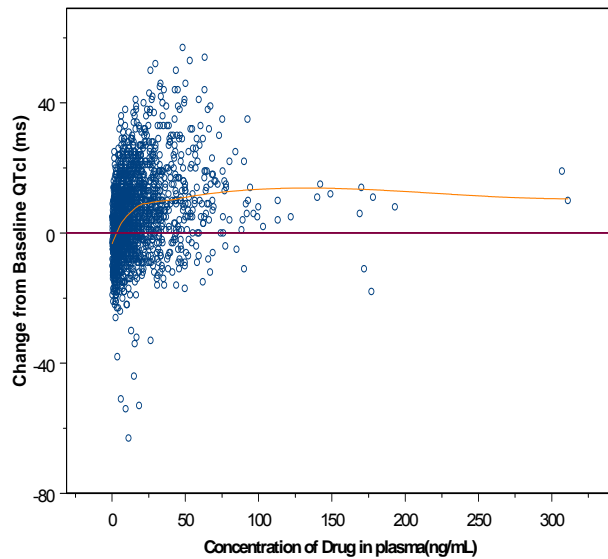
Application 3: Predicting effects at lower doses

Study details:

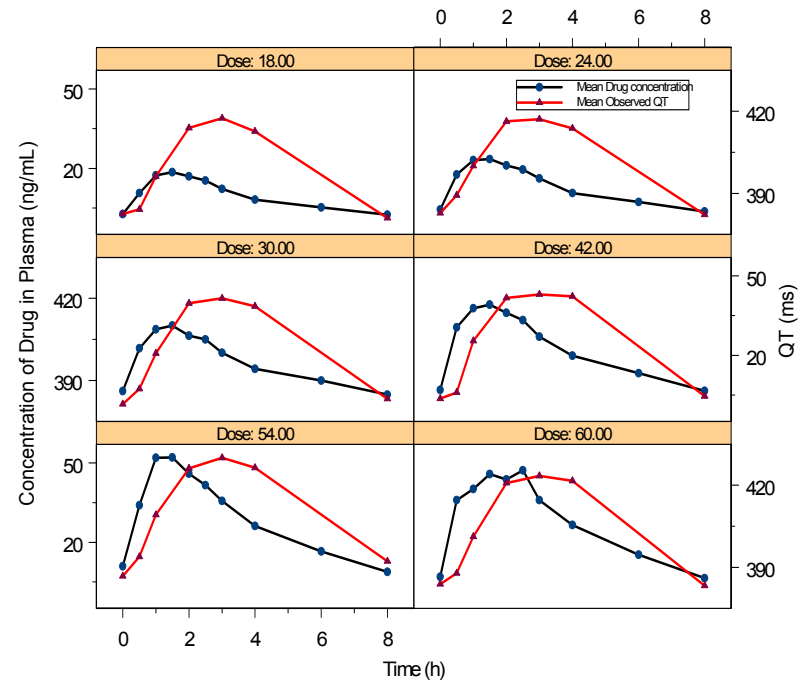
- TQT study in a patient population for a CNS drug.
- Double-blind, placebo and moxifloxacin controlled.
- Active and placebo doses were up-titrated from 2 mg/day to 60 mg/day.
- PK and ECG assessments were performed at 6 dose levels between 18 and 60 mg/day

Exploratory Analyses

- Non-linear increase in QTcI

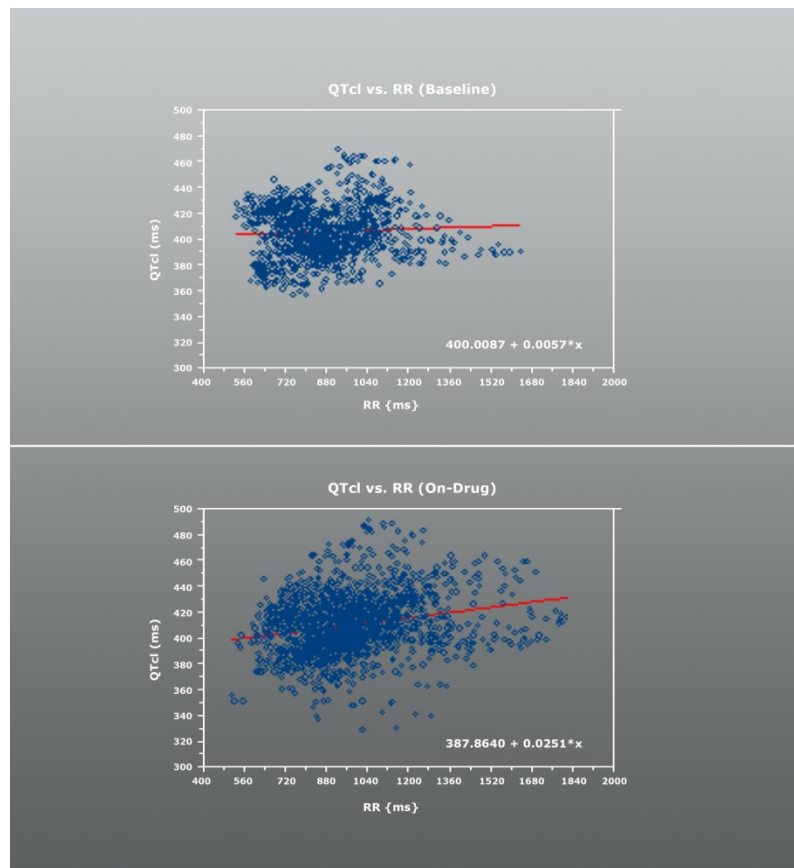
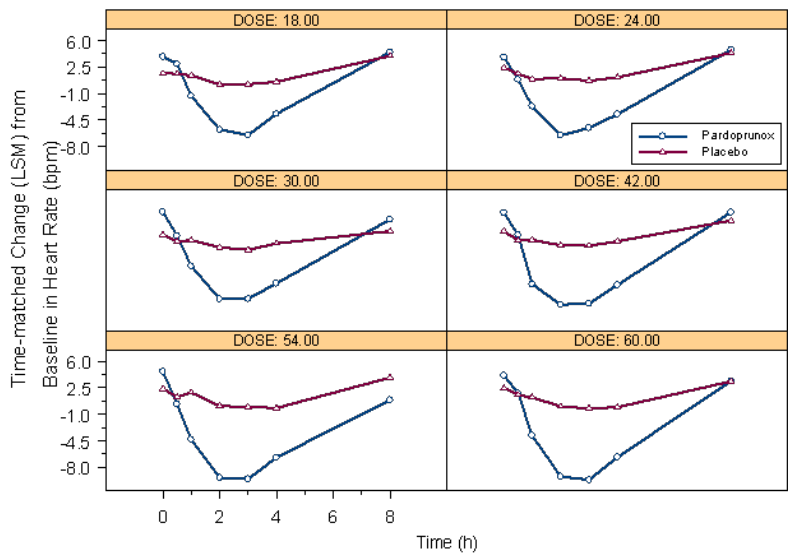


- Delayed effect



Exploratory Analyses

Drug effect on heart rate



C-QT Model Information

- Raw QT interval on baseline, placebo and active data were modeled together
- Separate individual correction factors were estimated for on-drug and drug-free data.
- Diurnal effects were modeled using 6-hour periodicity.
- A delayed effect sigmoid-Emax model was the drug effect model.

Estimates of QT Prolongation

Dose (mg)	E14 Analysis Mean (upper 95% CI)	C-QT Analysis Mean (upper 95% CI)
18	9.5 (12.8)	6.7 (8.7)
24	10.4 (14.0)	7.5 (9.5)
30	10.8 (14.8)	8.9 (11.2)
42	11.8 (16.2)	9.5 (12.7)
54	9.8 (17.2)	10.1 (14.3)
60	11.2 (16.9)	11.9 (15.2)

Prediction of QT liability at Lower Doses

Using the C-QT model, the extent of QT prolongation was estimated at lower doses that were not evaluated in the TQT study.

Dose (mg)	Mean (upper 95% CI) [ms]
3	0.7 (1.0)
6	2.0 (2.9)
12	4.9 (7.2)
15	6.2 (9.1)

Several of the therapeutic doses not evaluated were associated with insignificant QTc effects.

Conclusions

- M&S plays a key role in design and interpretation of cardiac safety studies.
- M&S can be used in Early Development to leverage data from early clinical studies to design optimal TQT studies.
- M&S allows a broader and more comprehensive assessment of a drug's pro-arrhythmic potential.