

Evaluation of a Drug Induced-QT/QTc Prolongation in the Presence of the Drug Induced Changes in Heart Rate by Using Population PK/PD Modeling Approach: Sildenafil Experience.

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ABSTRACT

BACKGROUND: Traditional statistical analysis suggested that sildenafil prolongs QTc despite no support from its mechanism of action (β 2-adrenoceptor/dopamine D2-receptor agonist) and pre-clinical findings. This study compares the difference between the use of biostatistical and population PK/PD modeling approaches to evaluate if sildenafil induced QTc prolongation in addition to its impacts on heart rate.

METHODS: 32 subjects were enrolled into a placebo-controlled, randomized, single-blind, 4-way crossover study to investigate the effects of multiple dosing of 3 doses of sibenadet (250 μ g, 500 μ g, 750/1000 μ g) or placebo on ECG parameters. Data from 16 subjects completing day 1 of the multiple dosing study were used for the data analysis. Mean and 95% one-sided CI for baseline and placebo subtracted QTc were calculated by two different baseline (pre-treatment and pre-period baseline), and five heart rate correction methods (Bazett, Fridericia, study-specific correction using pre-treatment

baseline ECGs only, study-specific and subject-specific correction using pre-period baseline and placebo ECGs). Population PK/PD modeling was conducted by simultaneously analyzing QT, RR and sibenadet concentration with NONMEM software. Sibenadet dose was modeled as a covariate of the correction factor to evaluate corrector change among different doses.

RESULTS: The maximum upper bound of the 95 % one-sided CI across sampling times exceed 10 ms for all different baselines and different correction factors for all three sibenadet doses by biostatistical analysis. The population mean

correction factor estimated in 750/1000 μg dose group was 29% higher than the rest of dose groups and no significant slope for QTc and sibenadet concentration was identified by population PK/PD modeling approach.

CONCLUSION: The population PK/PD modeling approach demonstrated no QTc prolongation for sibenadet, consistent with the mechanism of its action and pre-clinical findings.

BACKGROUND

- **Sibenadet**

- a β_2 -adrenoceptor/dopamine D_2 -receptor agonist
- mechanistically increases heart rate but has no direct impact on cardiac repolarization
 - Confirmed by extensive *in vitro* and *in vivo* pre-clinical studies

➤ A clinical study to investigate the potential of QTc interval prolongation of sibenadet

- 4-way cross-over study in placebo, 250, 500, and 750/1000 ug dose
- ECG data every 20 minutes starting around 8:00 AM for 14.50 hours on day 0 of visit 3 at resting status
- Extensive ECG and PK data (>14 samples) on day 1 and day 4 at visit 3-6

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Study day			0, 1, 2, 3, 4	1, 2, 3, 4	1, 2, 3, 4	1
Screening		Exercise grading test	Placebo, 250, 500 or 1000 µg	Placebo, 250, 500 or 1000 µg	Placebo, 250, 500 or 750/1000 µg	Placebo, 250, 500 or 750 µg

➤ Correction factor changed between exercise and rest

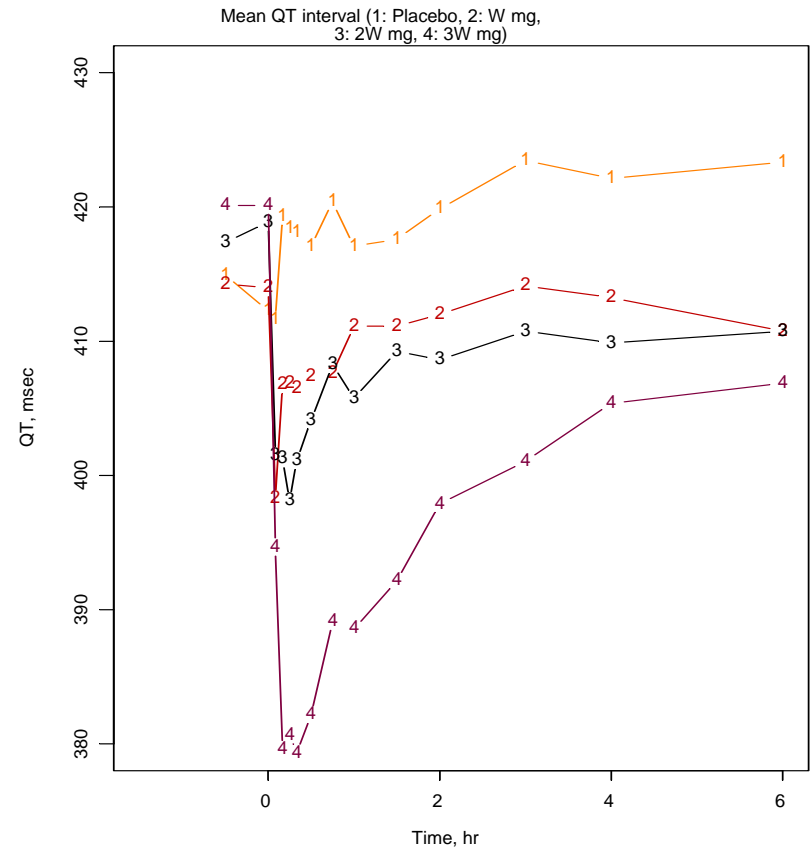
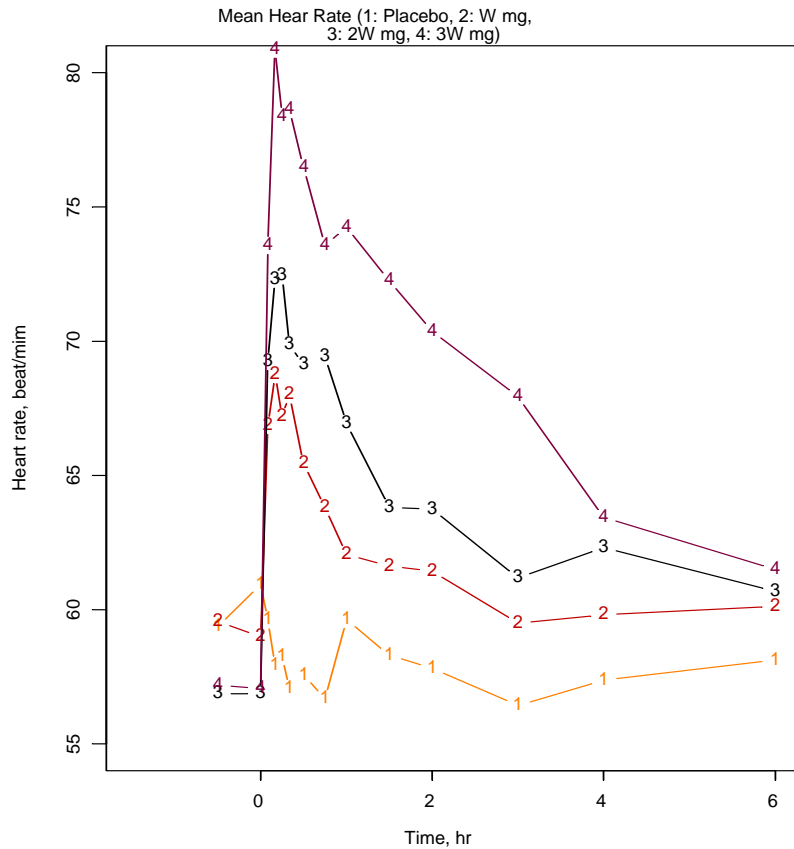
- **Newbold et al, Lack of correlation between exercise and sibenadet-induced changes in heart rate corrected rate corrected measurement of the QT interval, Br. J Clin Pharmacol, 63:3, 79/287, 2007**

Correction Factor	Heart Rate	Range	Mean	Median	Range of r^2	Mean r^2
QTcX	47-153	0.28–0.54	0.40	0.39	0.85–0.98	0.93
QTcR	40-89	0.12–0.51	0.27	0.26	0.10–0.93	0.52

QTcX = a subject-specific correction method from exercise alone

QTcR = a subject-specific correction factor from resting day only

➤ Significant increase in heart rate for the 3 sibenadet dose groups



➤ **Purpose of the study**

- Examine the difference in concluding the QTc prolongation between using ICH14 statistical method and PK/PD modeling approach**

METHOD

- **ICH14 Biostatistical method**

- **Two-stage method**

- The first-stage: Correct the heart rate effect on QT to obtain QTc

- **Bazett correction: $QTc = QT/RR^{0.5}$**

- **Fridericia correction: $QTc = QT/RR^{0.33}$**

- **Study-specific correction (QTcM)**

- **Subject (individual) -specific correction (QTcI)**

- **etc.**

– The second-stage: analyze the QTc data by $\Delta\Delta$ QTc method

$$\Delta QTc_d(t_i) = QTc_d(t_i) - QTc_{d_Baseline}(t_i)$$

$$\Delta QTc_p(t_i) = QTc_p(t_i) - QTc_{p_Baseline}(t_i)$$

d: drug

p: placebo

$$\Delta\Delta QTc(t_i) = \Delta QTc_d(t_i) - \Delta QTc_p(t_i)$$

– Assessment of QTc interval prolongation

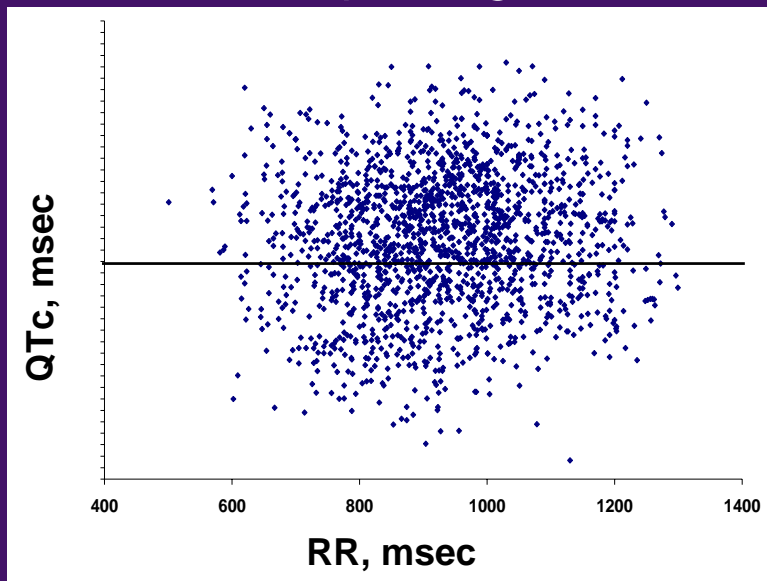
- Mean and 95% CI one-sided upper limit at each sampling point
- A positive QT study: the maximum 95% CI one-sided upper limit of $\Delta\Delta QTc(t_i) > 10$ msec

- **PK/PD modeling approach**

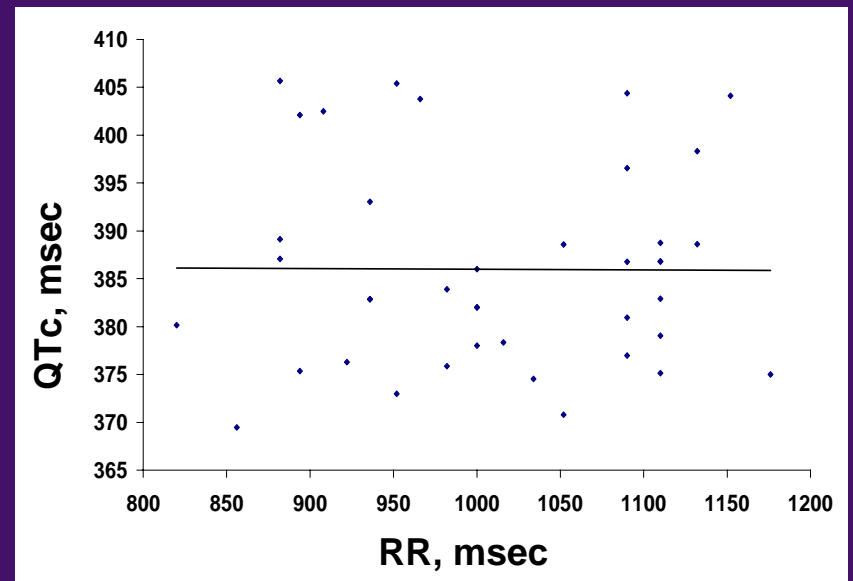
- **Based on a criterion of good correction factor**

- **Lack of correlation between QTc and RR**

Naïve pooling



Individual



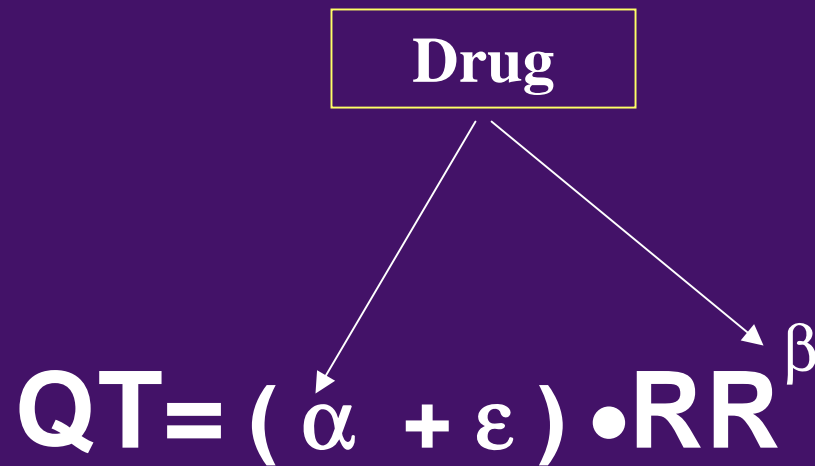
➤ Drug free

- $QT_c = QT / RR^\beta = \alpha + \varepsilon$ $\varepsilon \sim N(0, \sigma^2)$
 - $QT = (\alpha + \varepsilon) \cdot RR^\beta$
 - Equivalent to $QT = \alpha \cdot (RR)^\beta + \underline{\varepsilon \cdot (RR)^\beta}$
- * Not a typical residual error model

➤ On-treatment

- $QT_c = QT / RR^\beta = [\alpha + f(\text{drug})] + \varepsilon$ $\varepsilon \sim N(0, \sigma^2)$
- $QT = ([\alpha + f(\text{drug})] + \varepsilon) \cdot RR^\beta$ $\varepsilon \sim N(0, \sigma^2)$

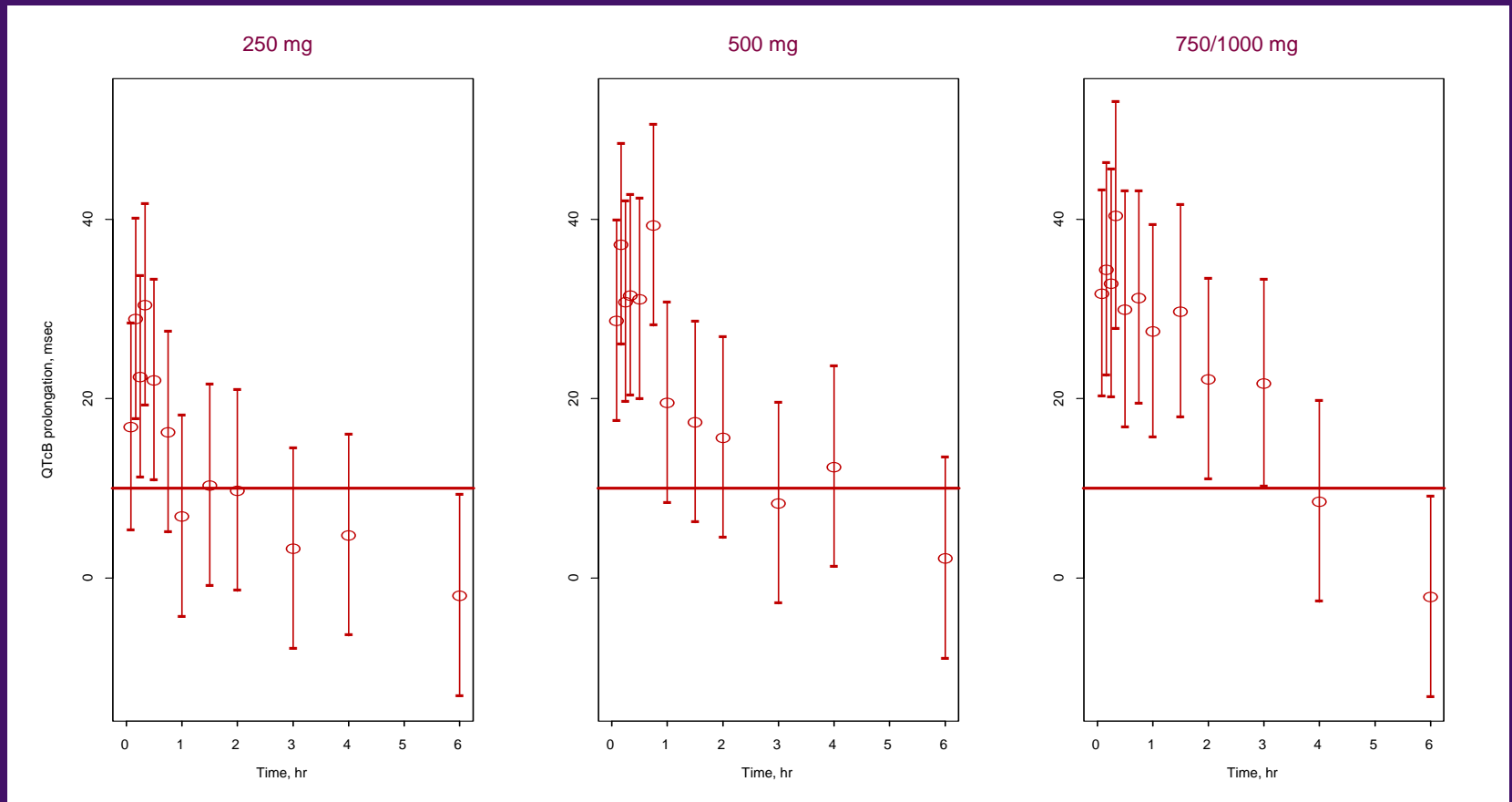
- Offer an approach to handle situations where the drug changes either the correction factor, QT or both of them



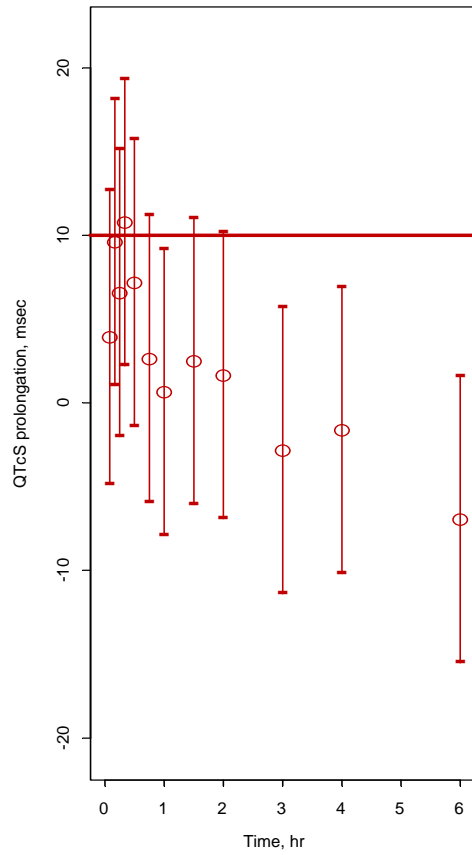
RESULTS

- ICH14 Biostatistical analysis using pre-study-period baseline

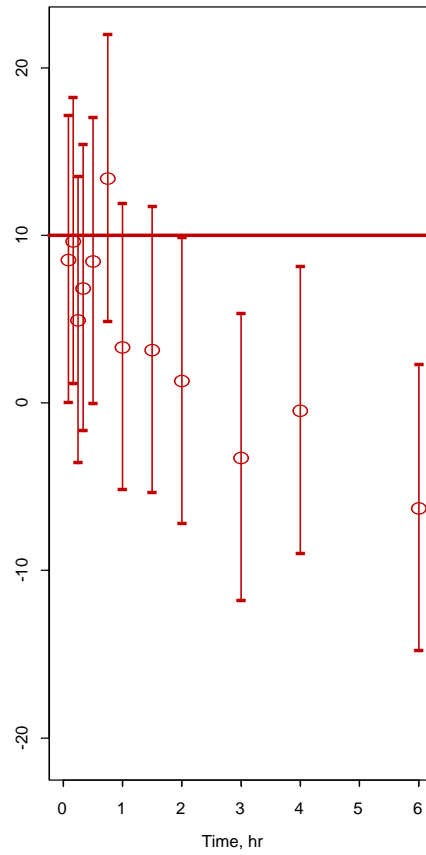
➤ QTcB



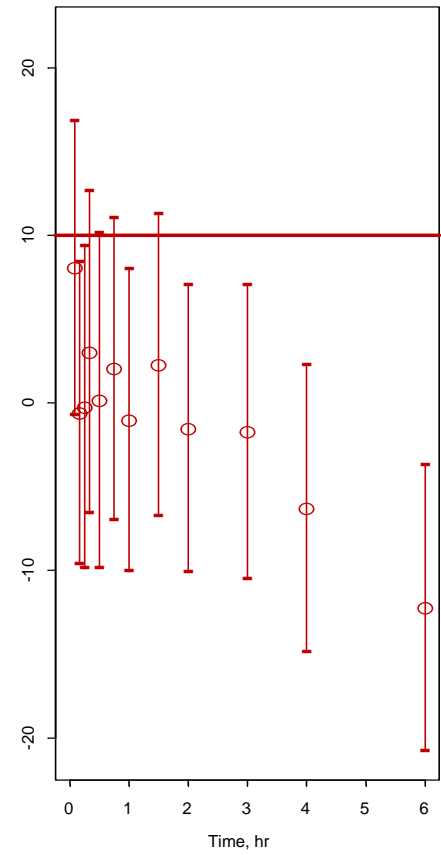
250 mg



500 mg

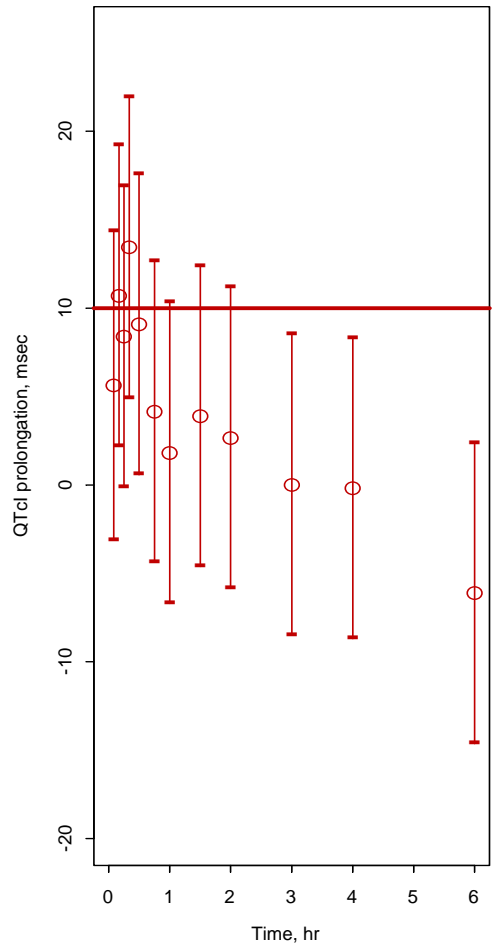


750/1000 mg

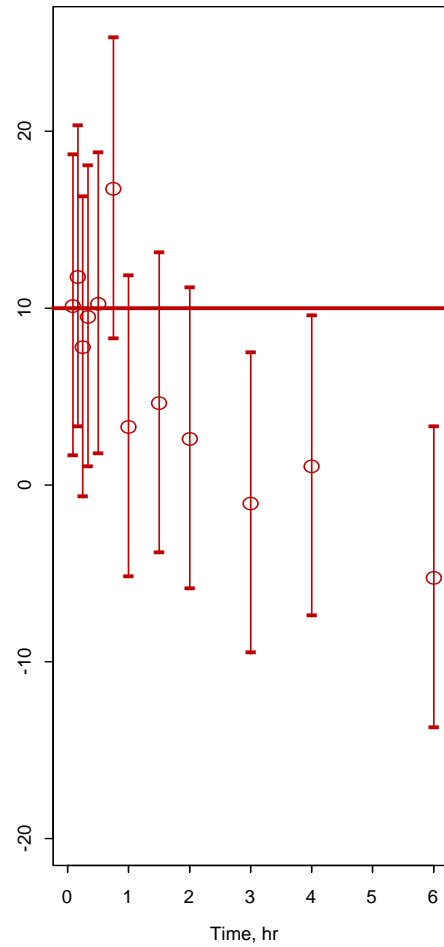


➤ QTcI

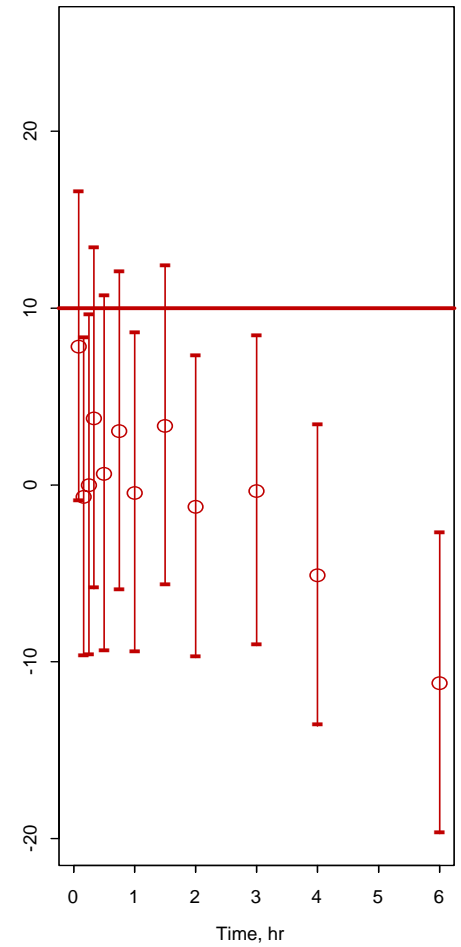
250 mg



500 mg



750/1000 mg



- **ICH14 Biostatistical analysis using pre-treatment baseline**

- **Similar results to pre-study-period baseline were obtained for QTcB, QTcF, QTcS and QTcI**
- **Positive QTc prolongation for different baseline and different correction strategy**

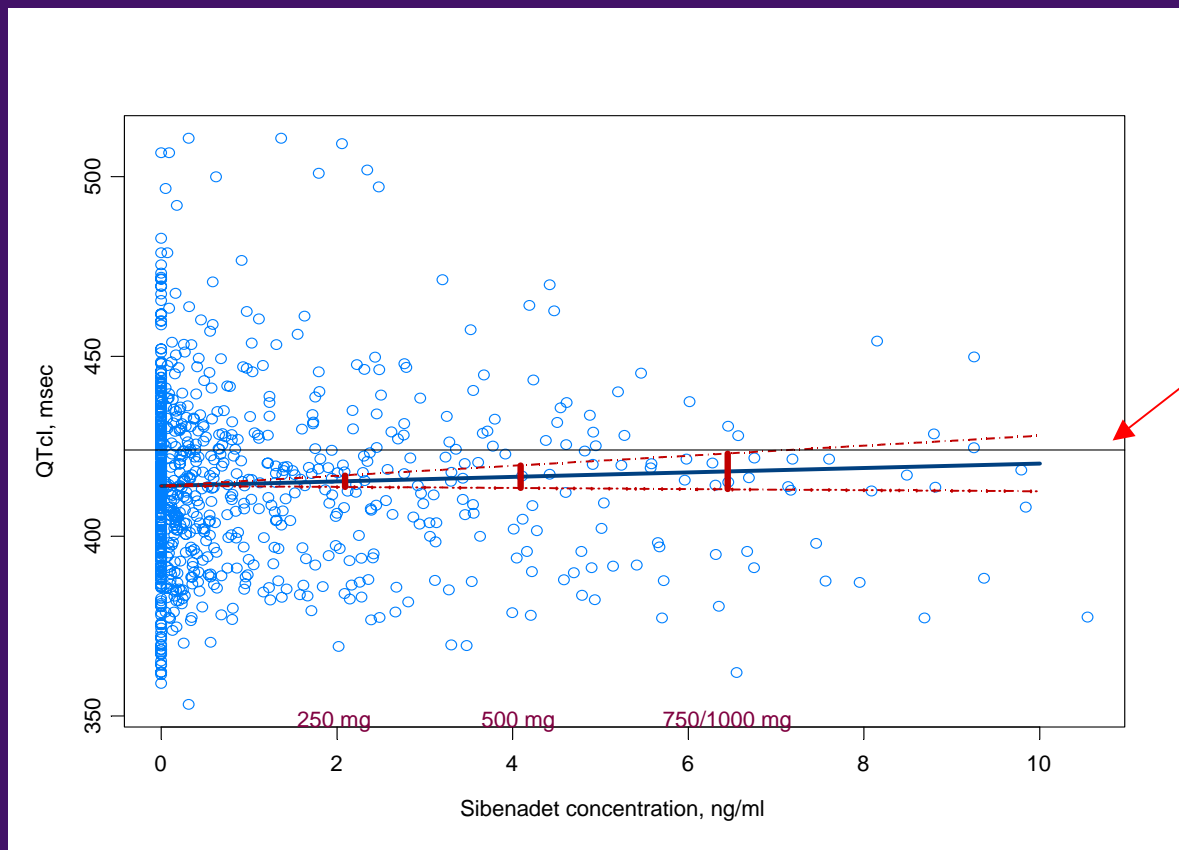
• PK/PD modeling: simultaneous analysis of QT, RR and sibenadet concentrations

$$\triangleright QT = (QTc_0 + Slope * Conc + \varepsilon) \cdot RR^\beta$$

Parameter Estimates of the Final Model			
Parameters (Units)	Description	Estimate ^a	% Relative Standard Error,
Fixed Effect			
θ1: TQTC0 (msec)	Population mean baseline QTc	414	2
θ2: TBETA	Population mean correction factor	0.193	19
θ3: TBETA_TRT4	Percent increase in population mean correction factor for 750/1000 mg dose	29%	15
θ4: TSLOPE (msec/(ng/ml))	Population mean slope of drug effect	0.622	76
Random Effects: Between subject variability (BSV)			
ω _{1,1} : BTQTC	Variance of BSV in baseline QTc	511 (22.6)	61
ω _{2,2} : BBETA	Variance of BSV in correction factor	0.0073 (0.085)	58
ω _{3,3} : BSLOPE	Variance of BSV in slope of the drug effect	3.85 (1.96)	89
Random Effects: Residual Error			
σ ₁₁ :	Additive residual error	136 (11.7)	4

- PK/PD model predicted 90% CI of QTcI interval prolongation

- less than 10 msec increase in the 95% one-sided upper CI relative to the intercept



Intercept+10

SUMMARY

- **ICH14 statistical method showed a positive QTc prolongation regardless the baseline QTc and correction method selected in the analysis**
- **Population PK/PD modeling approach allowing the correction factor to change between placebo and active treatments demonstrated no QTc prolongation for sildenafil, consistent with the mechanism of its action and the findings from extensive pre-clinical studies**

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 - Barbara Ewing, PhD

REFERENCE

- **Guidance for Industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and proarrhythmia Potential for Non-Antiarrhythmic Drugs**
- **Newbold et al, Lack of correlation between exercise and sibenadet-induced changes in heart rate corrected rate corrected measurement of the QT interval, *Br. J Clin Pharmacol*, 63:3, 79/287, 2007**
- **Garnett et al, Concentration-QT Relationships Play a Key Role in the Evaluation of Proarrhythmic Risk During Regulatory Review, *J. Clin. Pharmacol.* 2008; 48; 13**