

TITLE: 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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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 sildenafil (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 sildenafil concentration with NONMEM software. Sildenafil 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 sildenafil doses by biostatistical analysis. The population mean correction factor estimated in 750/1000 μ g dose group was 29% higher than the rest of dose groups and no significant slope for QTc and sildenafil concentration was identified by population PK/PD modeling approach.

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