

Title: Role of Modeling and Simulation in Evaluating the QTc Prolongation Potential of Drugs

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Objectives:

- Characterize the relationship between drug exposure and potential for prolongation of the QTc interval.
- Quantitatively characterize the sources of variability in the QTc interval, including subject demographics, twenty-four hour time-of-day, study, occasion, individual, and measurement.
- Compare the conclusions from a compound's exposure-response model for QTc to conclusions from a completed thorough-QTc study.
- Determine the potential impact of using different methods to correct QT interval for differences in heart rate.
- Analyze the adequacy of first-in-man QTc predictions made based on allometric and cross-compound scaling methods using nonclinical *in vitro/in vivo* exposure and *in vivo* QTc data.

Methods: Concentration/Exposure-response (E-R) modeling of QTc prolongation has been conducted for multiple compounds currently in clinical development in different therapeutic areas. Data from available single and multiple ascending dose (SAD/MAD) studies were pooled to construct a population E-R model, with post-hoc predictions of concentration provided by a pharmacokinetic model. All SAD and MAD studies employed a customized robust QTc assessment with time-matched triplicate ECGs and centralized manual QTc reading. Sources of variability were characterized, and the relationship between covariates and model parameters was explored, with a particular emphasis on correcting QT interval for heart rate and modeling the diurnal variation using a truncated Fourier series. Where applicable, all detectable metabolites of the administered compound were examined for a potential relationship with QTc interval. The results of population prediction of QTc prolongation were compared to available thorough QTc (TQT) study results, and the E-R model was evaluated to determine whether it could establish the QTc prolongation relationship without the TQT results.

Results: Several benefits of the modeling approach were found. (1) Extrapolation of pre-clinical models in cynomolgus monkeys to humans using allometric scaling and potency scaling between two novel fluoroquinolones provided predictions for the QTc results of the first-in-human SAD study which compared well with the later observations. (2) Negative TQT study results confirmed the negative simulation results from a Phase 1/2 E-R model. (3) The superiority of individual correction of QT for heart rate was shown where typical population correction methods would have substantially overstated the E-R relationship and could have led to unnecessary restrictions on dose selection.

Conclusions: Exposure-QTc modeling should be implemented as a standard part of modeling and simulation across different phases of drug development and used in conjunction with other data that influence the need and/or the timing of a TQT study.