Predictive Performance of Early Phase 1 Studies in Assessing Thorough QT Outcome Across 12 Compounds - Application of a Novel Analysis Method

Puneet Gaitonde1, Yeamin Huh1,2, Guenter Heimann3, Jianguo Li4, Kaifeng Lu5, Charles Benson6, Borje Darpo7, Georg Ferber8, Jim Keirns9, Bernard Sebastien10, Kuenhi Tsai11, Yaning Wang12, Meijian Zhou7, Steve Riley1


Background: Cardiac safety assessment is a key regulatory requirement for almost all new drugs. Thorough QT (TQT) studies are expensive and resource intensive. Efficiencies can be appreciated through use of Phase 1 single ascending dose (SAD) and multiple ascending dose (MAD) data to evaluate QT liability. Application of a standardized exposure-response methodology to quantify QT effects based on early clinical studies is demonstrated.

Methods: Twelve compounds with SAD/MAD and TQT data having time-matched drug concentrations and ECG measurements were selected. The change from baseline Fridericia-corrected QT interval (ΔQTcF) vs. drug concentration relationship was evaluated using linear mixed-effects (LME) model with known covariance structure based on the number of baseline time points. Drug concentrations and nominal time post first dose were modeled as fixed effects and subject as random effect. Heteroscedasticity was allowed across studies. Estimated slope and CIs were used to determine placebo-adjusted ΔQTcF (ΔΔQTcF) at the TQT supratherapeutic Cmax. Predicted ΔΔQTcF was compared with TQT study results. Analyses were performed in R and SAS.

Results: A LME model appropriately described the SAD/MAD data. QTc effects < 10 msec were detected for 9 compounds and > 10 msec for 1 compound. Results were discordant for 2 compounds. Predictions for 10 of 12 compounds were consistent with TQT study outcomes. R and SAS provided similar results.

Conclusion: Application of a standardized methodology to quantify QT effects was implemented in two widely used statistical softwares. Results from exposure-response analyses of early clinical data and TQT data were generally in agreement, and consistent with and supportive of conclusions from previous prospective analyses.

References:
1. Darpo B. et al., CPT 97 (4); 326-335; 2015