Statistical Power Analysis of Standard Cardiovascular Safety Pharmacology Studies in Telemetry Implanted Dogs and Nonhuman Primates

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Introduction

Cardiovascular safety assessment serves as a critical gatekeeper for novel therapeutics entering first-in-human (FIH) trials, with QT/QTc interval prolongation risk being paramount—drug-induced ventricular repolarization delay may trigger fatal arrhythmias. The recent ICH E14/S7B Q&As enable the incorporation of high-quality nonclinical QTc data into integrated risk assessments to support Thorough QT (TQT) study waivers, contingent upon meeting rigorous validation criteria. Robust understanding of statistical sensitivity underpins confidence in study results, yet systematic power analysis of standard CV studies remains limited.

To address this gap, we conducted a retrospective analysis of cardiovascular telemetry studies in standard cynomolgus monkeys (n=132) and beagle dog (n=140), separately, to determine the statistical power of these experimental models. Studies typically utilized a 4x4 (dog) or 4x4 (NHP) in Latin-Square manner paradigm. Data were collected for approximately 24 hours, and derived results from the predose and each 1 hour period for statistical analysis using a linear ANOVA model.

Results

The minimum detectable differences (MDD) with 80% statistical power were calculated for standard parameters (e.g. heart rate (HR), ECG intervals etc). MDDs for dogs, using a N=4 and 8 crossover design, were: QRS-interval (3.3 msec in males and 3.1 msec in females), PR-interval (7.6 msec in males and 7.7 msec in females) and QTc-interval (10.1 msec in males and 10.3 in females). MDDs for NHP, using a N=4 and 8 crossover design, were: QRS-interval (2.8 msec in males and 2.8 msec in females) , PR-interval (5.8 msec in males and 7.5 msec in females), and QTc-interval (10.5 msec in males and 9.7 in females). Additionally, we also report reference intervals of root mean square error (RMSE) and he 2.5th and 97.5th percentile of the RMSE as a measure of variability in the studies.

Conclusion

Overall, our results indicate that the nonrodent CV model is a sensitive tool to detect CV risk in early safety studies. Furthermore, the results also demonstrate assay sensitivity of functional endpoints, and support use of data in the contest of ICH E14/S7B Q&As.