

Complex Concentration-QT Analysis



A Concentration-QT (C-QT) Analysis is a modeling and simulation technique used to help establish the risk of prolonging the QT interval. C-QT analysis can sometimes eliminate the need for a TQT study, which is more expensive and time-consuming. In a C-QT analysis, pharmacokinetic data (concentration of a drug over time) is time matched with EKG data to create a measure of exposure and response. A C-QT analysis is a low-cost and efficient service compared to running a TQT study.

The Problem

A QT evaluation was needed for a development program, but the drug was not amenable to a traditional thorough QT study because healthy volunteers cannot take clinically relevant or supratherapeutic doses of the drug. Evaluation of the drug's effect on the QT was further complicated by the use of many concomitant medications known to affect heart rate or QT interval in the patient population, as well as a disease with symptoms potentially affecting heart rate. Finally, some of the clinical studies in patients included run-in doses of the drug which, when combined with the concomitant medications, made it difficult to establish baseline QT intervals in many patients.

Our Solution

To leverage the extensive, high quality EKG and PK data from multiple clinical studies in patients, a concentration-QT analysis on the pooled data was used to assess the effect of the drug on the QT interval. The first step in the model building process was to account for the effect of concomitant medications and symptoms on the heart rate and QT interval in the absence of the drug. After accounting for these other factors, the effect of the drug and its metabolite on the QT interval were added to the model. This final model was used to predict the change in QT and 90% confidence intervals at therapeutic and supratherapeutic concentrations of the drug, which ruled out an effect of the drug or metabolite on the QT interval.

Outcome

This was a unique, robust concentration-QT analysis using data from several clinical studies in patients where an effect of a drug concentration on the QT was ruled out, after correcting for the effects of concomitant medications and disease symptoms on heart rate and QT interval.

