

Deciding Factors

Early Phase Precision Drives Faster Go/No-Go Plans

Challenge

An unfavorable FDA review of a proposed cardiac safety early phase testing protocol for a compound left a customer's plan to get comprehensive clinical data for a go/no-go decision uncertain.

Solution

PK-PD Modeling and Simulation scientists from Quintiles rescued the sponsor's TQT protocol by determining key inputs needed to satisfy FDA guidelines.

Results

Our customer was able to confidently proceed with development at an early stage without further clinical tests.

Quintiles' expertise in Phase I/IIa biomarkers and specialist techniques such as Modeling and Simulation provide the critical data needed to make go/no-go decisions in Early Phase drug development.

Critical Insights, Early

With increasing R&D costs and declining success in getting your product to market, you need to maximize the amount of critical data you can glean early in a Phase I/IIa study to make quicker go/no-go decisions. Incorporating biomarkers and specialist techniques in early phase drug development can help make the entire process more efficient and cost-effective, while increasing safety. With your company's future resting on effective clinical research, the importance of determining the most strategic Phase I/IIa study shouldn't be understated.

Getting the Complete Picture

A customer turned to Quintiles to conduct a cardiac safety Thorough QT (TQT) study to FDA guidelines using the sponsor's existing protocol for a compound where preclinical work showed no evidence of QT interval prolongation.

The objective of the sponsor's study was clear, i.e., to produce comprehensive clinical data to enable a go/no-go decision. The sponsor sought the assistance of our pharmacokinetic-pharmacodynamic (PK-PD) Modeling and Simulation scientists after an unfavorable review of the proposed protocol at the FDA.

Precision Rescue

We rescued the sponsor's TQT protocol by determining key inputs needed for their TQT study and provided a written justification for the new design, including dosage (therapeutic and supratherapeutic) and dosing regimen selection.

In addition, the sponsor's new protocol was supplemented with a tailored population PK-PD analysis plan to allow a comprehensive evaluation of the results from the TQT study. The revised protocol and the selected dose and dosage regimen were agreeable to the FDA's interdisciplinary review team (IRT).

Quintiles has more than 25 years of experience in the design and conduct of complex studies, and over 1,000 first-in-human clinical trials already conducted in the last seven years.

With moxifloxacin as an active control, and placebo as the reference, both therapeutic and suprathapeutic doses were administered over 4 days to 240 volunteers following a baseline QT day. Using the standard biostatistical analysis (E14), we found the therapeutic dosage to be within the 10ms 95% one-sided upper interval limit for QT prolongation, but determined that the suprathapeutic dose showed an increase in QTc over the regulatory-specified limit.

Innovative Approach, Rigorous Standards

Approximately 24,000 ECGs from a total of 240 subjects were analyzed in a blinded fashion by trained cardiologists from the Quintiles' central ECG laboratory, using rigorous quality control procedures. Detailed Holter monitor analyses to detect potential arrhythmic events were also performed by the core ECG lab.

Our state-of-the-art ECG capture and analysis techniques, and breadth of expertise made it possible to review the large number of ECGs in a short timeframe at a reasonable cost. Our PK-PD scientists supported the TQT study by bringing our vast PK-PD Modeling and Simulation expertise to bear in the re-design of the original protocol for the customer and to perform key supportive PK-PD analyses; namely, the concentration-QT (C-QT) method of modeling.

Quality Data for Lasting Difference

Although the E14 biostatistical analysis showed a positive TQT result for the suprathapeutic dose, using PK-PD Modeling (C-QT), we presented critical information on the Concentration QT relationship which indicated a non-positive study at the suprathapeutic dose. The C-QT analysis has its foundation in the pharmacology of drug-induced prolongation, and the results from these analyses have been considered favorably by the FDA in several TQT submissions.

Thanks to the experience of our strong PK-PD team, the data arising from PK-PD analysis confirmed the drug's QTc results to be within the regulatory-specified threshold of non-concern for both doses. Our customer was able to reach an early, confident go development decision without further clinical tests.

Quintiles' expertise in Phase I/IIa biomarkers and specialist techniques such as Modeling and Simulation give you the critical data you need to make go/no-go decisions in Early Phase drug development.

We've done it for many. We can do it for you. Contact Quintiles to find out how.

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