

How Modeling and Simulation Can Help in Obtaining More Information from a QT/QTc Study

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Introduction

Over the past years, cardiac safety of non cardiovascular drugs has become a major concern in drug development. As a result, there has been an increased demand for more thorough investigations on this critical safety aspect earlier in the clinical development of a drug. This may start as early as single- and multiple-ascending-dose (SAD/MAD) studies with rigorous electrocardiogram (ECG) collection during which the highest exposures with a compound are seen. A rigorous ECG collection at this stage can provide important information about the potential of a drug to induce QT prolongation. Based on these results, a decision can be made either not to go further with the development or if there is no significant effect, provide reassurance that the thorough QT/QTc (TQT) study can be done later in drug development.

The new Celerion Hybrid Phase I/ ECG Core lab facilitates the conduct of TQT studies. However, what about the analysis of the data? The QT interval on the surface ECG is presently used as a marker for assessing the risk of Torsades de Pointes, a rare but potentially fatal type of ventricular tachycardia with a characteristic twist of the QRS complex on the ECG. Guidelines and recommendations on the conduct of QT studies have been published.¹ However, methods for analysis of the data are an area still open for discussion. The most common type of statistical analysis, referred to as the E14 analysis (from the corresponding ICH document), does not answer all questions and sponsors may be confronted with “borderline” results from which no clear conclusion can be made. However, population pharmacokinetic-pharmacodynamic (PK/PD) modeling is a key tool which may improve the understanding through evaluation of a concentration-response relationship.²

What are the data obtained from a thorough QT/QTc study?

Very briefly, a classical TQT study contains 4 treatments: placebo, positive control, therapeutic dose of the drug and a suprathreshold dose of the drug. ECGs are obtained on a time-matched basis in each period and

blood samples are taken, on a time-matched basis, for pharmacokinetic (PK) assessment. In addition, baseline ECGs are obtained prior to each treatment as average pre-dose measurements for crossover studies (currently the FDA’s preferred design) or as time-matched for parallel studies. Each QT interval is then corrected for the heart rate (QTc), either on an individual basis (QTcI) or the Fridericia correction (QTcF), the latter being as good as QTcI but more convenient and less expensive as it requires fewer baseline ECG assessments. For the central tendency analysis, the baseline is then subtracted from each post-dose QTc value resulting in a Δ QTc for each treatment/period of the study. The principle endpoint for these studies is then the difference in Δ QTc between treatment and placebo or the $\Delta\Delta$ QTc (often called the double delta QTc). Categorical analyses are also performed on QTc values and change from baseline in QTc interval, however there is no consensus with respect to an acceptable upper limit value with this type of analysis.¹

What is obtained from the standard statistical analysis performed for QT studies?

Genetics, food intake, circadian rhythm, sex, obesity, age and blood pressure are just a few of the factors known to affect QT intervals. All these factors are part of the overall variability observed in QT/QTc measurements. The correction for heart rate is an attempt to account for some of this variability but a number of other factors are left unaccounted for. One method utilized by Celerion to analyze QT/QTc intervals is the analysis of central tendency which examines the time-matched $\Delta\Delta$ QTc over the assessment interval. The standard threshold for the maximum observed $\Delta\Delta$ QTc values is 5 ms with the upper-bound of the 95% confidence interval around the mean effect on QT/QTc being 10 ms. When the largest time-matched $\Delta\Delta$ QTc exceeds that threshold, the study is said to be positive and otherwise is said to be negative. The central tendency analysis has the advantage of being relatively simple and it is appropriate for assessing

the relationship with drug exposure, when there are sufficient measurements around the time of the maximum plasma concentration as in TQT studies. For non-anti-arrhythmic drugs, a mean maximum prolongation of more than 5 ms but less than 20 ms may be considered inconclusive from both clinical¹ and statistical perspectives^{3,4}, and may call for further ECG measurements during drug development. Considering the inherent variability of QT/QTc values and the fact that the central tendency accounts for very few of the sources of variability, there are some limitations associated to this type of analysis. The traditional central tendency statistical evaluation of QT/QTc studies may not provide sufficient information from a development perspective with regards to the activity and potency of a drug. When results are inconclusive, it may be beneficial to further investigate the potential relationship between the drug exposure and the QT/QTc prolongation prior to making a development decision, such as a go/no-go decision. The ultimate goal of analyzing these data is to assess what can be attributed to variability and what can be attributed to a real drug effect on QT/QTc prolongation. Therefore, controlling and identifying the sources of variability is of crucial importance. In that sense, population PK/PD modeling is an important tool to better understand the concentration-response relationship.

What is the additional value of Population PK/PD Modeling?

As mentioned above, a variety of sources of variability need to be taken into account in order to distinguish between baseline and measurement noise and a true drug effect on QT/QTc prolongation. Sources of variability may include things such as stimulation related heart rate changes, timing of meals etc., and variability inherent in the measurement of the QT interval. The method used in our Hybrid Phase I/ ECG Core lab minimizes the variability directly associated to QT measurements and the controlled environment allows for reproducible conditions across study arms. Population PK/PD modeling is by definition very well suited for handling different sources of variability. As

an example, the circadian variations in QT intervals can be well characterized by PK/PD modeling, therefore avoiding direct baseline subtraction. In addition, studies with different designs can be pooled, giving a broader picture of the concentration-response relationship.⁵ Assessment of the maximum QT/QTc prolongation, which is less limited by the sampling schedule of the study with population PK/PD modeling, accounts for the variability in time to peak plasma concentration between individuals. If the variability is well characterized, it is then easier to assess the effect of other factors, such as for example, gender and age. Finally, in the case of a positive study, once the population model is established for the PK of the drug and its relationship to QT/QTc prolongation, simulations can be performed. It is then possible to explore the outcome of different dosing regimens that could be used throughout the clinical phases of the drug's development. Therefore, the study design of planned studies can be optimized, not only for PK sampling schedule but also for the temporal placement of the ECG measurements/assessment.⁶

Conclusion

Central tendency statistical analysis provides useful information about the potential of a drug to prolong the QT interval in certain circumstances. However, modeling and simulation can potentially provide additional information which can support development decision making and interpretation of the QT-prolongation potential of a drug. In the spirit of the Critical Path Initiative⁷, population PK/PD modeling is a key tool to a more efficient drug development strategy. Its use for TQT studies is a great example⁸ but its application is much broader. Modeling and simulation allows for the integration of the knowledge gained from preclinical studies on an ongoing basis throughout the clinical phases. Once a model is established with all key elements, predictions can be made on a case by case basis which allows for selection of future dosing regimens and optimal sampling strategies. As a result, development programs and decisions can become more scientifically driven, more efficient and cost-effective.

References

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