TQT WAIVERS
Overcoming Design Challenges

ICH E14 Regulatory Guidance 2005 and 2015

In 2015 the International Conference on Harmonisation (ICH) updated its 2005 cardiac safety guidelines. The update allows for specific QT interval analysis based upon concentration effect modeling up to supratherapeutic during Phase I as a reasonable substitute for a Thorough-QT (TQT) dedicated trial. These Phase I data along with preclinical results are submitted to the FDA prior to Phase III as a waiver request from a separate TQT study. This is good news! A dedicated TQT study involving time-wise comparisons of baseline corrected data is an expensive and lengthy endeavor. It typically takes place after proof of concept but before Phase III. Collection of QT information during an existing Phase I study costs substantially less and can provide go/no-go decisions much earlier.

The purpose of gathering QT interval information has not changed. It is a regulatory requirement to evaluate the proarrhythmic potential of all small molecule noncardiac drugs that have systemic bioavailability. A prolonged QT is the accepted regulatory biomarker for drug-related torsades de pointes – a fatal ventricular arrhythmia. Currently, more than 90 drugs on the market are known to cause QT prolongation and have received appropriated labeling. Conversely, cardiotoxicity has been one of the main reasons for both non-approvals and market withdrawals in the last two decades.

Selecting Appropriate Drug Candidates

Many drugs will benefit from QT evaluation during Phase I. However, certain drugs may not be good candidates for a TQT waiver strategy. These include drugs that: 1) have a positive hERG in preclinical development, 2) increase heart rate or have other autonomic effects, 3) require lengthy up-titration to achieve therapeutic levels, 3) have a delayed effect, or 4) are an extended release formulation. Additionally, the Phase I ECG data that are collected and analyzed must be similar to that of a dedicated TQT with interval analysis that uses a proven methodology. The model must also be predefined and include adequate data collected over a wide range of plasma concentrations from subtherapeutic to at least three to five times higher than exposures required to achieve efficacy. If these criteria cannot be met, a standard TQT study might be necessary.
TQT Waiver Limitations

While clinical trials designed to support a TQT waiver have been conducted in oncology for several years, the ICH (2015) update was based on newer findings. Feasibility and design are key considerations, especially with smaller subject/patient cohorts. There are no published guidelines for determining exposure response-QT modeling. Current designs assume false negative and false positive rates will be minimal. Drugs that have a borderline effect may not be detected. As blinded ECG over-read is recommended for unbiased QT analysis, the blinding status of the ascending dose study needs to be taken into considerations. Food can also change the QT interval. Clinical evidence has found that a carbohydrate meal shortens the QT up to 27 milliseconds, which can lasts for up to 4 hours post-meal. Future guidance for QT waivers might offer insights into the food effect or specific patient, ethnic or gender differences. The best strategy is to plan Phase I QT design early and seek expert advice to overcome both clinical and regulatory challenges.

COMMON STRATEGY AND DESIGN QUESTIONS

► Does the preclinical data support following a TQT waiver approach?
► Will incorporating a QT waiver into our FIH study result in a major study design modifications?
► We do not know our asset's clinical PK data yet. How do we include Exposure Response Modeling to capture QT data?
► Is a QT Waiver the best strategy to mitigate regulatory risk?
► Does collection of QT data during Phase I ensure my asset will qualify for a Waiver?
► When is the best time to collect QT Waiver data and how many subjects are required?

REFERENCES


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