

Integrated Cardiac Safety Programs

Assessing Cardiac Safety throughout Clinical Development

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Introduction

Regulatory requirements for assessing the proarrhythmic liability of investigational noncardiac drugs are now widely acknowledged. One clinical trial of particular note is the ICH E14 Thorough QT/QTc (TQT) study.¹⁻⁴ This is dedicated to the meticulous evaluation of a drug's liability to delay myocardial repolarization and hence prolong the QT interval as seen on the surface electrocardiogram (ECG). However, the TQT study is best conceptualized as one component of an integrated cardiac safety program that incorporates nonclinical investigation and several additional clinical assessment strategies. This article focuses on the latter.

The TQT Study: A Very Brief Overview

To put subsequent discussions in context, the TQT study is reviewed very briefly here. The "traditional" study design employs four treatment arms:

- A positive control that is known to increase the QT/QTc interval (typically moxifloxacin) to establish assay sensitivity;
- A placebo control, against which the following two drug doses are compared;

- The proposed therapeutic dose of the drug;
- A suprathreshold dose that is several multiples of the proposed therapeutic dose, intended to mimic what may happen should the drug be approved and prescribed for patients who have compromised metabolism or excretion and/or are taking other medications, each of which may lead to greater -than- intended concentrations of the drug in the body.

Results from the TQT study determine the extent to which ECG monitoring should take place in therapeutic confirmatory studies.

Complementary Assessment Strategies

Three important considerations in an integrated cardiac safety program are:

- At what point should the TQT study be conducted?
- How should the suprathreshold dose be chosen?
- How best to collect and analyze subsequent ECG?

These are addressed in turn.

Maximizing Information from Early-phase Studies

The most appropriate point to conduct the TQT study is arguably as early as it can be meaningfully conducted. Fundamental knowledge of the drug's clinical pharmacokinetics (T_{max} and half-life) is necessary to design the study appropriately, but beneficial preliminary information concerning QT/QTc prolongation liability can also be gleaned from early-phase studies. Certainly, there are challenges in conducting formal, ICH E14-type analyses based on a single early-phase study with a (very) low sample size. Singlet ECGs typically used here (rather than triplet ECGs extracted during the TQT studies) combined with a low number of subjects will almost certainly yield a high one-sided 95% CI upper bound. However, judicious use and combination of data from single and multiple ascending dose studies, along with those from the maximum tolerated dose (MTD) study, can be informative. Data from the MTD

study, along with information from modeling and simulation (discussed in the preceding article) can be of great assistance in choosing the suprathreshold dose.

ECG Monitoring in Later Studies

The results of the TQT are not to empower a regulatory “approve the drug if all else is OK/fail to approve the drug no matter what” decision. Rather, the true intent, as noted earlier, is to determine the degree of ECG assessment that should be done in later studies to more accurately evaluate the drug’s proarrhythmic liability: The greater the degree of regulatory concern generated by the TQT study’s results, the more extensive the required monitoring.

In cases where more extensive assessment is conducted, a centralized ECG analysis approach similar to that employed for TQT studies is recommended.⁵ While the benefits of centralization have been widely embraced for TQT studies for some time, adoption of this practice for therapeutic confirmatory trials has been less swift. However, awareness is growing that ECG analysis at hundreds of sites by hundreds of individual physicians can be highly problematic. A paradigm shift is occurring in which sponsors are beginning to realize the scientific and clinical (and indeed cost) advantages of ECG centralization in such circumstances, thereby facilitating more accurate and efficient assessment of an investigational drug’s cardiac safety.

Development of New Antidiabetic Drugs

New guidances from the FDA⁶ and the European Medicines Agency⁷ detail additional cardiovascular safety assessments now required during the development of new antidiabetic drugs. Cardiovascular clinical endpoints are to be compared between the investigational drug and control drugs

in a meta-analysis incorporating data from the majority of therapeutic exploratory and confirmatory trials conducted throughout the clinical development program. The major adverse cardiovascular events (MACE) composite index, comprising myocardial infarction, stroke, and cardiovascular death, is likely the primary endpoint of choice. Point estimates of relative risk and estimates of their precision (confidence intervals placed around the point estimates) are to be presented to regulators, with the goal of prospectively excluding unacceptable cardiovascular risk. These regulatory guidances have recently been reviewed, and similarities and differences discussed.^{8,9}

Concluding Comment

This paper has illustrated how an integrated cardiac safety program that builds cumulatively during a clinical development program facilitates the accurate and efficient creation an investigational drug’s cardiac safety profile, enabling sponsors to present solid data to regulators when requesting marketing approval.

References

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