Feasibility of Replacing the Thorough QT (TQT) Study with Intense ECG Data Collection in Early Clinical Studies

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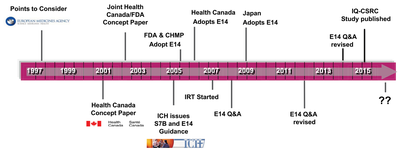
INTRODUCTION

The International Conference on Harmonization (ICH) E14 guidance document in 2005 mandated that virtually all new chemical entities (NCE) with systemic bioavailability undergo a rigorous clinical electrocardiographic (ECG) evaluation in a Thorough QT (TQT) study[1]. The objective of this study is to assess potential effects on ventricular repolarization and arrhythmia risk by detecting a small change in the corrected QT (QTc) interval. In the decade since finalization of this guidance, a tremendous amount of work has gone into evaluating how ECG and QTc data are collected, reviewed, and analyzed with over 3,000 articles published which include "QT interval" in the abstract or title. The goal of this transformative work has been to evaluate ways to reduce QTc data variability, improve measurement precision and/or reduce the resulting burden of this guidance on drug development while still appropriately characterizing arrhythmia risk of new compounds.

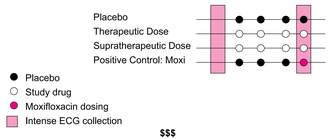
Figure 1: The Evolution of ICH E14



STUDY DESIGN

2005-2007

Figure 2. Traditional Parallel TQT Design



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Advantages: Standard design well accepted by regulatory authorities, dosing to steady state means QTc prolongation due to metabolites or accumulation can be characterized, may have shorter conduct timelines relative to crossover TQT design

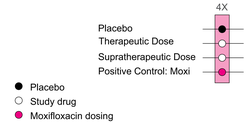
Disadvantages: Cost driven by large number of subjects (N=50-60 per treatment arm), greater variability relative to crossover design contributes to higher false positive rate

- The TQT study design is typically a parallel or 4-way crossover design with dosing out to steady state.
- Four treatment arms: placebo, positive control (moxifloxacin), therapeutic dose, supratherapeutic dose.
- Sample size 50-60 subjects per treatment arm.
- Baseline ECG evaluation typically consists of monitoring subjects for 24 hours prior to dosing with ECGs acquired at timepoints matching post-dose ECG timepoints.
- Cost $2-4 million with parallel studies typically higher relative to crossover studies.

The FDA Interdisciplinary Review Team (IRT) was established in 2007 to provide clarity and recommendations for applying E14. IRT reviews all TQT protocols and reports and has had a tremendous impact on improving consistency in feedback for study design and data analysis from the FDA.[2]

2008-Present

Figure 3: Single Dose Crossover TQT Design



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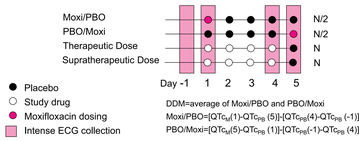
Advantages: Standard design well accepted by regulatory authorities, lower subject number needed relative to parallel design TQT, lower ddQTcF data variability potentially reducing risk of false positive

Disadvantages: Conduct timeline can be longer than parallel design TQT for a 4-way crossover depending on washout duration, pharmacokinetics of study drug may not permit a crossover design (i.e. long half-life)

Figure 4: Parallel with Nested Crossover TQT Design



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Advantages: Reduced cost relative to standard parallel study due to reduced number of subjects, dosing to steady state means QTc prolongation due to metabolites or accumulation can be characterized, shorter conduct timelines relative to crossover TQT design, reduced variability in Moxi/PBO crossover potentially reduces false positive rate

Disadvantages: Blinding moxifloxacin is required, complicated statistical analysis requires experienced statistician

- Parallel or crossover design is used, often with single doses that approximate steady state plasma levels. Crossover design is used if possible due to reduced costs and reduced data variability.
- If single dose is not feasible for a compound with a long half-life or one that requires titration, a nested crossover design may be used to lower costs.
- Three to four treatment arms: therapeutic dose treatment arm may be omitted if no prolongation is anticipated at supratherapeutic dose; combining placebo and moxifloxacin in the nested crossover design can also be used to reduce sample size by 25%.
- Sample size is 40-50 subjects per treatment arm.
- Baseline ECG evaluation typically consists of three triplicate ECG timepoints prior to dosing[3]. The exception is still parallel design studies.
- Cost is $1-3 million with an increasing cost gap between parallel and crossover studies.

DATA ANALYSIS

2005-2009

- ECG data are collected initially using standard ECG carts with a quick shift to collecting continuous 12-lead Holter data and extracting triplicate ECGs.
- Lead II predominantly is used for measuring the QT interval.
- Extraction and ECG interval measurements are performed manually with cardiologists performing all ECG interval measurements.
- Initially, QT was often corrected for heart rate based on individual correction factors (QTcI) or population-based (QTcP) correction factors due to known limitations for both Bazett's (QTcB) and Fridericia's (QTcF) methods. However, QTcB and QTcF were still to be submitted.

2010-Present

- Continuous 12-lead Holter or telemetry data most commonly used with ECGs extracted at the end of the recording session.
- A global or representative beat is most frequently used for QT measurements, minimizing data variability particularly when lead II may be missing.
- Extraction and ECG interval measurements are often automated.
- E14 Q&A (2012) stated that QTcB is, "no longer warranted in all applications" and that QTcI is not likely to work well with sparse data or when baseline data does not cover the heart rate range observed on a study.

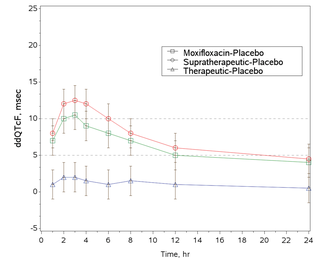
STATISTICAL ANALYSIS

Some aspects of the cardiodynamic analyses that have not changed over time are the need for a categorical summarization of QTc by treatment and time point based on actual values and change from baseline. Similarly, morphological changes need to be summarized.

2005-Present – The TQT Study

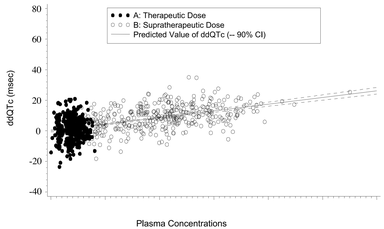
- The primary analysis in the TQT study is an analysis of variance (ANOVA) where change from baseline in QTc (dQTc) is the dependent variable and the factors in the model reflect the study design.
  - The upper confidence limits (UCL) of the 95% one-sided confidence interval (CI) for the difference (drug-placebo) in least-squares means (LSM), denoted ddQTc, is calculated for each time point.
  - If the UCL is less than 10 msec at all time-points, the study is negative for QT prolongation.
- An assay sensitivity analysis, testing the study's ability to detect a QTc prolongation of 5 msec, is performed by calculating the lower confidence limits (LCL) of the 95% one-sided CI for the difference (moxifloxacin-placebo) in LSM. Assay sensitivity, for moxifloxacin, is established if:[4]
  - The largest ddQTc is ~ 8-15 msec and occurs between 1 and 3 hours postdose.
  - The lower confidence limit (LCL) of the 95% one-sided CI of ddQTc (moxifloxacin-placebo) is greater than 5 msec for at least one relevant time point.
  - The ddQTc versus time-curve is typical of moxifloxacin.

Figure 5: Placebo-Corrected Change from Baseline in QTc (ddQTc) Versus Time – Results of the Primary and Assay Sensitivity Analyses in the TQT Study



- Exposure-response (ER) modeling is usually included in TQT studies as exploratory analysis.
  - Models can be as simple as regressing subjects' ddQTc on their time-matched plasma concentrations, allowing for the prediction of average ddQTc at C_{max} of the therapeutic and supratherapeutic doses using the estimated regression coefficients and C_{max}.

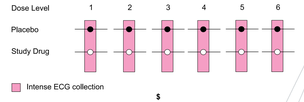
Figure 6: Placebo-Corrected Change from Baseline in QTc (ddQTc) Versus Time-Matched Plasma Concentrations



- ER modeling can also help clarify any ambiguous results.

2014-Present – Single Ascending Dose (SAD)/Multiple Ascending Dose (MAD) Study: Exposure-Response Modeling

Figure 7: SAD



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Advantages: Significant cost and time reduction compared to TQT study by combining objectives of TQT with objectives of SAD, additional data allows for earlier go/no-go decisions

Disadvantages: Pharmacokinetic information (i.e. T_{max}, metabolite profile, potential accumulation) unknown during SAD thus risk having to repeat change in QTcF analysis on later studies once more is known about the PK

- Features of SAD/MAD studies:
  - Small cohorts, parallel design – therefore not powered for by-time-point analysis.
  - No positive control.
  - Plasma concentrations for wide range of doses allows for ER modeling.
- ER modeling can be an important part of SAD/MAD studies for the following reasons:[5]
  - Informing dose selection for later studies.
  - Providing insight into regimens not studied directly.
  - Predicting the QTc effects of intrinsic and extrinsic factors that affect PK.
- A linear, mixed-effects model is used with subjects' dQTc as the dependent variable, their time-matched plasma concentration as a covariate, and time point as a fixed effect.
- The expected mean effect at C_{max} can be estimated for various dose levels.
- Bootstrapping methods are preferable for calculating CIs of the mean effects.
- Assumptions for the model (eg, absence of hysteresis [here defined as the maximum ddQTc being delayed compared to C_{max}] and linearity of the concentration-response relationship) may be investigated.

CONCLUSION

Since the advent of the ICH E14 guidance in 2005, the field of drug development has witnessed multiple advancements in TQT study design, technology for ECG data collection and analysis, and statistical analysis of TQT data. There is now another major transition underway, shifting intense ECG data collection from the dedicated TQT study to an add-on component of many early phase studies. This transition exemplifies how drug development can be streamlined through the collaboration of thought leaders from the industry, government, and academia.

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