InTRoDuCTIon

Figure 1: The Evolution of ICH E14

The objective of this study is to assess potential bioavailability undergo a rigorous clinical electrocardiographic (ECG) evaluation to improve measurement precision and/or reduce the resulting burden of this transformative work has been to evaluate ways to reduce QTc data variability, this guidance, a tremendous amount of work has gone into evaluating how ECG effects on ventricular repolarization and arrhythmia risk by detecting a small

Figure 2. Traditional Parallel TQT Design

Cost driven by large number of subjects (N=50-60 per treatment arm), greater variability relative to parallel design TQT, lower ddQTcF data variability potentially reducing risk of false positive

Figure 3: Single Dose Crossover TQT Design

If single dose is not feasible for a compound with a long half-life or one that accumulation can be characterized, shorter conduct timelines relative to crossover TQT

Figure 4: Parallel with Nested Crossover TQT Design

Advantages: Reduced cost relative to standard parallel study due to reduced number of

Figure 5: Pharmacologically-Corrected Change from Baseline in QT (ms) Versus Time - Results of the Primary and Assay Sensitivity Analyses in the TQT Study

Exposure-response (ER) modeling can be an important part of SAD/MAD studies for the following reasons:

The International Conference on Harmonisation (ICH) E14 guidance document in 2005 mandated that virtually all new chemical entities (NCEs) with systemic effects in a Thorough QT (TQT) study. The objective of this study is to assess potential bioavailability undergo a rigorous clinical electrocardiographic (ECG) evaluation to improve measurement precision and/or reduce the resulting burden of this transformative work has been to evaluate ways to reduce QTc data variability, this guidance, a tremendous amount of work has gone into evaluating how ECG effects on ventricular repolarization and arrhythmia risk by detecting a small

STAtIStIcAl ANALYsIs

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

ConCluSIon

Since the advent of the ICH E14 guidance in 2005, the field of drug development has witnessed significant advancements in TQT study design, methodology for ECG data collection and analysis, and statistical analysis methods to assess the QTc effects of intrinsic and extrinsic factors that affect PK.

REFERENCES


2. Extracted clinical evidence from acrilomide, diltiazem hydrochloride, digoxin, disopyramide, etamivan, and verapamil that a positive peak QTc response is associated with a positive peak cardiac safety of the drug. The FDA Interdisciplinary Review Team (IRT) was established in 2007 to provide clinical and statistical support for the review of QTc data in new drug applications. The IRT is a multidisciplinary team that includes experts from the Division of Cardiovascular and Renal Drugs, Division of Critical Path Innovation, Division of Metabolism and Endocrinology Drugs, Office of PK/Pharmacodynamic Modeling and Simulation, and Office of Clinical Pharmacology and Pharmacometrics.

3. The TQT study design is typically a parallel or 4-way crossover design with dosing to steady state.

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