TQT Studies: Their Impact on Drug Development and the Key Elements of a Successful TQT Study

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Introduction

The first governing body to issue guidance was the European Agency for the Evaluation of Medicinal Products, (EMEA) releasing a ‘Points to Consider’ document in 1997. The proposed experimental, non-clinical/clinical models for the consideration of assessing QT prolongation1.

Health Canada issued a guidance document in 2001 relating to the assessment of QT prolongation potential of non-antiarrhythmic compounds. It listed the non-clinical and clinical methodologies to be used in the development of NCEs2.

Definitive guidance was provided from an expert working group, (EWG), of the International Conference of Harmonization, (ICH) releasing the ICH Topic E14 guideline which was brought into operation and adopted by the European Union and The United States in 20053.

A Q&A document released by the FDA in 2008 provided further clarification on a number of emerging issues as studies were being reported and submitted4.

Regulatory Guidance

A positive signal in a TQT study does not mean that a NCE will cause Torsades de Pointes (TdP) with the associated risk of death but it has, however, a major impact on the development of a NCE.

The early conduct of a TQT study is desirable but the cost of designing and implementing a study to detect TQTQ prolongation can be greatly enhanced by the use of a consonant group control (i.e., non-cardiovascular medication or a placebo or a non-pharmacological) to establish assay sensitivity. The positive control should have an effect on the QT interval (i.e., an effect that is close to the QTcTQ prolongation that represents the threshold of regulatory concern5.

The extent of the prolongation caused by this positive control is then usually expressed by the point estimate at the time point of the greatest effect. It is usual in later publications that the 90% or 95% two-sided confidence interval would be given. The size of this confidence interval is a derivative of the variability of the data caused by either physiological variation on experimental size. In order to narrow the confidence interval the better the quality of the study results.

Table 1 shows design and key results from data published during the last five years. In this table the first publications using two-sided Confidence Interval (CI) of 90%. It is intrinsically narrower than the two-sided 95% CI which has been used in six publications shown at the bottom of the table. In three of the studies only the lower boundaries of the 95% CI have been reported; the upper boundary has been reconstructed for the above comparison.

The table clearly shows that studies using a cross-over design and multiple standard bed side 12-lead ECG appear to perform much better than those performed in parallel groups and or using holter when considering the width of the confidence interval. When comparing cross-over trials, then the sample size seems positively related to a narrow CI.

ECC Analysis

The size of the effect on QT of a 400 mg oral dose of moxifloxacin has now been investigated intensively and presumably is be demonstrated to be a potential marker of the impact on the safety of this medicine. A post hoc analysis5 of holter recordings taken during a study administering an intravenous 400 mg dose of moxifloxacin has further added to our understanding of its effect on QT. Considering only publications where the lower boundary of the 90/95% CI is greater than 5 ms, more than two-fold increase of QTcF has been detected (range 8-17.4) following a 400 mg dose of moxifloxacin, which is also not currently available.

The QTc prolongation has been reported to be 18 ms in lean healthy subjects following a 40 min iv infusion of 400mg moxifloxacin6.

Various methods of ECC analysis have been applied: different baseline corrections, manual, semi-automated and fully automated methods of QT interval measurement, different means of arriving at a numeric value for a given point time. This diversity of analysis methods may explain some of the observed differences. The width of the CI intervals range from 2 to 15ms, a 15ms CI may not be explained by sample size alone7 and as some studies used the same sample size to detect the anticipated effect.

In our view, automatic reading of digitally recorded 10 second 12-lead ECGs with subsequent cardiovascular over reading is the current gold standard. There are still differences in opinion how this is best done. Not only QT intervals but all ECC parameters (PR, QRS, T-wave morphology) need to be analysed and reported.

It is beneficial for a QTC study to be performed under one roof and its entire ECC data does not need to be transferred and it is easier to maintain consistent effective quality systems using multiple feedback loops.

References

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