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Concentration–Effect Modeling Based on Change From Baseline to Assess the Prolonging Effect of Drugs on QTc Together With an Estimate of the Circadian Time Course

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Abstract

As ICH E14 was adopted by the US FDA and the EU CPMC in 2005, thorough QT studies have routinely been analyzed by looking at the time-matched difference between (baseline corrected) QTcF or QTcI under the supra-therapeutic dose and placebo. A study is considered negative, if the two-sided 90% confidence interval for this difference is below 10 ms for all investigated time points. ICH E14 suggests including a positive control, such as moxifloxacin, for assay sensitivity. Concentration–response analysis has been considered a more powerful alternative, but its application to parallel group studies was hampered as a double difference of QTcF per subject cannot be calculated. Recently, a new model based on change from baseline with fixed time and concentration effects has been proposed. It allows for a placebo-corrected prediction of the drug effect with an unbiased standard error, and the estimate of a time effect can be used for assay sensitivity. We demonstrate this approach, utilizing 2 studies reported elsewhere with a crossover design. We compare the results from a conventional concentration–response analysis based on the difference to placebo with results from the novel analysis based on the change from average baseline that includes a fixed time effect.

Keywords

thorough QT study, QTc, concentration–response model, moxifloxacin, assay sensitivity

Since the E14 guideline of the International Conference on Harmonisation[1] was adopted by the EU and the US in 2005 and later by the Japanese health authorities, a thorough QT (TQT) study has become part of nearly every drug development program. Although the planning, conduct, and analysis of such a study have become routine, it still represents a burden not only with respect to costs, but also because it is usually performed in healthy volunteers who do not benefit from the treatment.

Therefore, it is not surprising that considerable resources have been invested in the search for alternatives to a TQT study.[2] In particular, it has been discussed whether ECG data obtained during Phase I could be used to replace a TQT study at least in some development programs. This research identified three points that need to be addressed: (1) it needs to be ascertained that the ECG data obtained in a Phase I setting are of the same quality as those collected in a dedicated TQT study. (2) The analysis method recommended as primary in ICH E14 needs to be replaced by one that is more suitable for the setting of a single or multiple ascending dose study and (3) a substitute for the positive control used in a TQT study to show assay sensitivity needs to be found.

It seems that an experienced Phase I unit is able to fulfill the first point. We will therefore spend some thoughts on the second and third one here. The paper is structured as follows: In Section 2 we elaborate on concentration–response analysis, while Section 3 deals with the role of the positive control. Sections 4 and 5 are devoted to two examples: in Section 4 we introduce an example of a QT prolonging drug, namely moxifloxacin, given in the fed and fasted state and Section 5 gives an example of the analysis of an analgesic substance that clearly has no prolonging effect on QTc. Section 6 provides a general discussion and conclusions are presented in Section 7.

Concentration–Effect Analysis as an Alternative for the Classical TQT Analysis

Depending on the number of time points investigated and on the anticipated prolongation seen under the drug of interest, a sample size of 40–60 subjects per arm is needed

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