THE POWER OF PHASE I STUDIES TO DETECT CLINICALLY RELEVANT QTc PROLONGATION

RESULTS FROM A RESAMPLING SIMULATION STUDY

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Introduction

Recently, the use of QTc data obtained in phase I studies has been extensively discussed [1]. One question that needs to be answered is whether analyses based on data obtained from these studies will have a sufficient power to reliably show QTc prolongation and, what is even more important, to reliably predict the absence of such an effect.

There are substantial differences between a TQT study and a SAD or MAD study. Although the total number of subjects involved in a SAD study may not be much less than in a cross-over TQT study, it will only be a fraction of them that are exposed to doses of the drug that are 3× and above the level that will be used in future therapies. Moreover, while in a TQT study, at most two doses of the test drug are used, in a SAD or MAD study, we have many doses and only a few subjects are given each of the doses. Concentration-effect modelling has been suggested as one way of this dilemma. This technique is well established as a secondary analysis in TQT studies. One of the key points to address is the power of such an analysis in a situation like a Phase I study. Simulations based on data from TQT studies can help answer this question.

The simulations presented in what follows allow for the evaluation of the power of analyses based on data obtained from phase I studies, which is a very important aspect if QTc prolongation is a concern. In such studies, the power of an analysis is crucial, and is mainly determined by the number of subjects, the number of dose points, and the range of concentrations. Such data is readily available in Phase I studies, and analyses of this type can be performed even if the number of subjects involved is relatively small. The simulations presented in what follows can thus be used to calculate the power of analyses based on data obtained from such studies.

Methods

The simulation work is based on moxifloxacin and placebo data of crossover TQT studies. By taking a subsample of subjects and, optionally – of the time points when PK and ECG measurements were obtained, data from subjects under placebo and under active drug can be obtained. To simulate a drug that does not prolong QTc, we combined the PK data obtained under moxifloxacin with the time matched QTcF data obtained on the same subject under placebo.

For each simulated study, two concentration-effect models were fitted [Figure 1]. The models use the change from baseline of QTcF as the dependent variable and concentration as a covariate. In order to correct for spontaneous circadian effects, a factor representing time was included into the model.

For each simulated study, two concentration-effect models were fitted [Figure 1]. The models use the change from baseline of QTcF as the dependent variable and concentration as a covariate. In order to correct for spontaneous circadian effects, a factor representing time was included into the model. The upper bound of the confidence interval was compared to a number of thresholds and a study was declared negative if this bound was below the threshold of 10 ms, per ICH (Q1B). The models were fitted using a stepwise procedure based on statistical criteria only.

Concentration-effect models

Time and treatment as factors

Model 1: ΔQTcF = c × time × treatment

<table>
<thead>
<tr>
<th>Model 1</th>
<th>Model 2</th>
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<tbody>
<tr>
<td>ΔQTcF</td>
<td>ΔQTcF</td>
</tr>
<tr>
<td>c × time</td>
<td>c × time</td>
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<tr>
<td>treatment</td>
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Scenarios used to investigate the influence of selection of time points

<table>
<thead>
<tr>
<th>Scenario</th>
<th>6 time points</th>
<th>12 time points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 12, 24h post-dose</td>
<td>pre-dose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 10, 12, 24h post-dose</td>
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<tr>
<td>2.</td>
<td>pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 12, 24h post-dose</td>
<td>pre-dose, 0.5, 1, 1.5, 2.5, 3.5, 4, 6, 12, 24h post-dose</td>
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<tr>
<td>3.</td>
<td>pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 12, 24h post-dose</td>
<td>pre-dose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 24h post-dose</td>
</tr>
</tbody>
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Random effects

Intercept per subject

<table>
<thead>
<tr>
<th>Random effects</th>
<th>Intercept per subject</th>
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</thead>
<tbody>
<tr>
<td>te</td>
<td>t = 0, t = 1, t = 2, t = 4, t = 6</td>
</tr>
</tbody>
</table>

Conclusions

1. Concentration-effect analysis may be confidently used to demonstrate the QTc changes of approximately 10 ms in early Phase Studies where 9 subjects are planned per treatment group.
2. With a power of 90%, it is also able to confirm lack of effect on QTc.
3. Where a positive control is detected in the ECG assay to confirm sensitivity, the effect of food is the method of choice. As the effect will be anywhere present at some point after dose as long as volunteers will have to be fed.

Abbreviation List

- CE: Concentration-effect
- CSRC: the Cardio Safety Research Consortium
- ICH: International Conference on Harmonisation
- MAD: Multiple Ascending Dose
- PK: Pharmacokinetics
- PKT: Pharmacology
- QT: QT interval
- QTc: QT interval corrected with heart rate
- SAD: Single Ascending Dose
- STD: Standard
- TQT: Thorough QT
- TDI: Time Delay of Intervals

References