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

RESULTS FROM A RESAMPLING SIMULATION STUDY

Georg Ferber, Jorg Taubel

Richmond Pharmacology Ltd., St George's University of London, Cranmer Terrace, London, United Kingdom

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 crossover TQT study, it will only be a fraction of them that is exposed to doses of the drug that are at or 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 a way out 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.

Here we present the results of resampling simulation study that used data of three Phase I studies for CE analysis to investigate its power for detecting clinically significant QTc prolongation.

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 where PK and ECG measurements were obtained, data for 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 values obtained in 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 dependent variable and concentration as a covariate. In order to correct for spontaneous circadian effects, a factor representing time was also added. The two models differ in the inclusion of an additional treatment effect. From each model we predicted the effect at the geometric mean C_{max} obtained from the subjects in the simulation and its two sided 90 % confidence interval. Note, that we did not take into account the random variability of this estimate in order to keep the computational burden within reasonable limits. 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, as per ICH E14 guideline.

1 **Concentration-effect models**
Time and treatment as factors.

Fixed effects

$$Model\ 1: \Delta QTcF \sim C + time + treatment$$

$$Model\ 2: \Delta QTcF \sim C + time$$

Random effects

$$intercept\ per\ subject$$

2 **Scenarios used to investigate the influence of selection of time points**

Designation	Maximum total Number	Number of time points in time window			
		$0 < t < 2h$	$2h \le t \le 4h$	$4h < t \le 8h$	$8h < t \le 24h$
All	All	all	all	all	all
Equi 8	8	≤ 2	≤ 2	≤ 2	≤ 2
Few T_{max}	7	≤ 2	≤ 1	≤ 2	≤ 2
Exclude T_{max}	6	≤ 2	0	≤ 2	≤ 2
Sparse	4	≤ 1	≤ 1	≤ 1	≤ 1

We simulated studies of various sample sizes. In addition, we also reduced the number of time points included in the models. Here we wanted to answer two questions: the influence of the number of time points in general, and the importance of sampling around C_{max}. We therefore subsampled time points according to the scenarios depicted in Figure 2.

DATA

Data used for this analysis come from moxifloxacin arms of three studies.

Study 1: This randomised, placebo-controlled, double blind crossover study consisted of 96 volunteers. Moxifloxacin was given in the fasted state on day 16 of moxifloxacin study period (placebo given on 15 preceding days). ECG data were collected on day 16 of moxifloxacin period at 12 time points: pre-dose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12 and 24h post-dose.

Study 2: This randomised, placebo-controlled, double blind crossover study consisted of 64 volunteers. Moxifloxacin was administered in the fasted state on day 2 of moxifloxacin study period (placebo given on a preceding day 1). ECG data were collected at 12 time points: pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 8, 12 and 24h post-dose.

Study 3: This randomised, placebo-controlled, double blind crossover study consisted of 49 volunteers. Moxifloxacin was given in the fasted state on day 1 of moxifloxacin study period, preceded by placebo on a baseline day. ECG data were collected at 14 time points: pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12 and 24h post-dose.

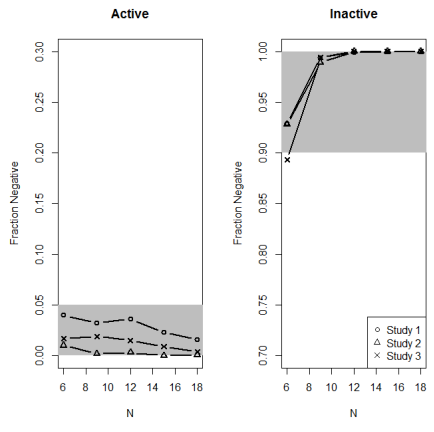
ECGs were recorded in triplicate with subsequent blinded manual adjudication of the automated interval measurements.

Results

For each study taken for CE analysis, we display the fraction of negative studies as function of the sample size (per treatment group) [Figure 3 and 4].

Figure 3 shows that the CE method reliably detects an effect, such as moxifloxacin, and can exclude such an effect for an inactive drug. Based on this figure, we can conclude that 9 subjects provide a sufficient power to detect or exclude a "moxi-like" effect.

3 Fraction of negative studies by number of subjects per treatment arm. Model with treatment effect, all time points used. Shaded range is considered acceptable region.



4 Fraction of negative studies by number of subjects comparing two models of CE analysis: a model with treatment effect (above) and without a treatment effect (below).

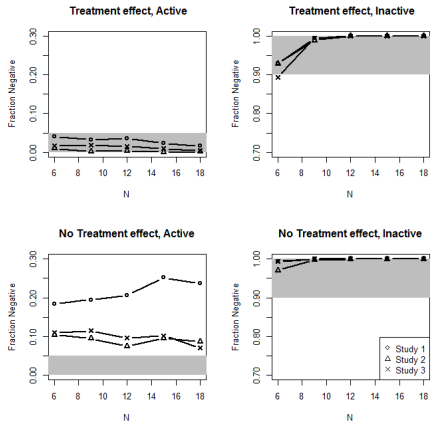
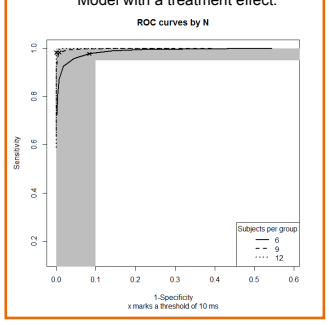


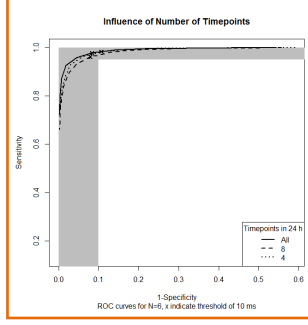
Figure 4 demonstrates the comparison between two proposed models [Figure 1]. As shown on bottom left graph, omitting a treatment effect increases the number of false negatives.

In order to look into more detail, receiver-operating characteristics have been used, which were plotted for the average fraction negatives across the three studies. We have produced plots showing the fraction of correctly positive studies (moxifloxacin) on the y axis plotted against the fraction of false positive studies (simulated inactive drug) on the x axis for varying thresholds. The values for a the standard threshold of 10 ms are marked with an x [Figure 5, 6 and 7].

5 Discrimination power as a function of the threshold. Display is based on the averages across all three studies. All time points were used. Model with a treatment effect.



6 ROC curves based on studies with 6 subjects per treatment group. Model with treatment effect.



7 ROC curves based on studies with 6 subjects per treatment group. Model with treatment effect.

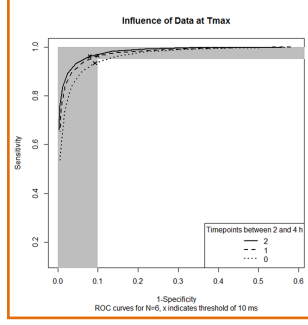


Figure 5 demonstrates that the threshold of 10 ms constitutes a good compromise between false negatives and false positives for studies where sample size is down to 6 subjects per group.

To investigate the influence of the selection of time points, ROC curves based on studies with only 6 subjects per treatment were used (worst case scenario) [Figure 6 and 7].

The analysis presented in figure 6 is based on studies, where the number of time points was reduced uniformly across the range of 24 h. This seems to have little influence on the rate of false negatives or false positives.

Figure 7 presents the analysis, where the number of time points during the interval of highest concentration was reduced. As a consequence of lack of measurements around T_{max}, the sensitivity of the method is decreased, i.e. the number of false negatives increases.

Discussion

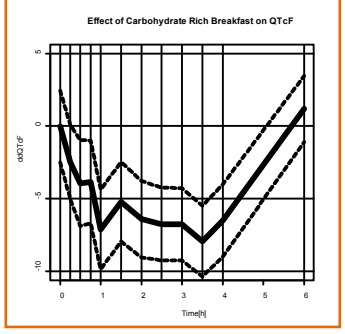
The simulations show that 9 subjects per treatment arm are sufficient to reliably demonstrate the QTc prolongation caused by 400 mg moxifloxacin, i.e. an effect slightly greater than 10 ms. They also show that a drug not causing any QTc prolongation can be identified with a power of greater than 90%.

The source of the data investigated here differs from data obtained in a SAD or a MAD study; the number of subjects in one cohort may be only 4-6 on active treatment. One major limitation of generalising our results to standard First Time In Human (FTIH) studies or Single Ascending Dose (SAD) studies is that these studies are busy with other assessments and that often there is uncontrollable bias from autonomic effects which will affect the ECG values obtained. The ECG may be accurate and appropriately measured, yet autonomic effects may have masked or exaggerated an effect at that time point and it will be difficult or impossible for an assessor of the data to determine whether or not that was the case.

On the other hand, in early phase studies (FTIH/SAD), the doses investigated may be higher than the doses tested in later phases of drug development and more than one cohort will contribute to the analysis. Because data is obtained from a wider concentration range, it can be assumed that the power obtained when using data from a FTIH/SAD study will be even higher than what can be seen here.

A limitation of the investigation presented here is that all simulations are based on moxifloxacin; drugs with other kinetics or with a more complex PK/PD relationship may give different results.

8 Time course analysis of food effect on placebo-controlled QTcF change from baseline



FTIH/SAD studies do not include a pharmacological control to confirm ECG assay sensitivity. This is a major limitation when using their data too exclude an effect as systematic errors may have occurred limiting the sensitivity of a study. Unlike random error, which will lead to very wide confidence intervals thereby not allowing to exclude a 10ms change in QTc, systematic errors cannot reliably detected other than by including a positive control, which is a generally well accepted principle in biologic research.

We have previously demonstrated [3] that the analysis of ECG obtained two to four hours after the intake of a meal offers the opportunity to use the QTc-shortening effect of c-peptide as means of confirming ECG assay sensitivity.

Since this effect is not related to the kinetics of the drug under investigation, it will show up in the estimates of the time effect. Figure 8 represents the QTcF shortening effect appearing 2-4h after the meal. In this example the analysis was performed on 32 subjects comparing breakfast effects to pre-dose fasting results [3]. It should be noted that the per time point analysis as suggested in ICH E14 tacitly assumes that the time course of QT prolongation is uniform across subjects. This is more likely in a physiological response compared to pharmacological one where a drug may be differently metabolised in a significant proportion of the study population.

The method is well publicised, highly reproducible and robust even in small populations and has been consistent across our published work [3-5]. The main factors that allow the analysis of food effects on QTc are as follows:

(1) we recommend that a minimum of three ECG samples are taken during 1.5-4 hours following a meal; (2) a carbohydrate-rich meal is to be given in order to provoke c-peptide release; (3) the research participants should not be c-peptide deficient, i.e. type 1 diabetic; and (4) in cases where more than one meal is given, subjects should be fasting for at least 4 hours before the meal used for analysis; this is in order to avoid collecting a false negative (still shortened after a previous meal) QTc baseline [4, 6].

Conclusions

1. Concentration-effect analysis may be confidently used to demonstrate the QTc change 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 desired in the ECG assay to confirm sensitivity the effect of food is the method of choice. As the effect will be anyway present at some point after dose as volunteer will have to be fed.

Abbreviation List

CE	Concentration-effect
CSRC	the Cardiac Safety Research Consortium
IQ	Leadership Group of the Consortium for Innovation and Quality in Pharmaceutical Development
MAD	Multiple Ascending Dose
PK	Pharmacokinetic(s)
QT	QT interval
QTc	QT interval corrected with heart rate
SAD	Single Ascending Dose
TQT	Thorough QT

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