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Estimation of the Power of the Food Effect on QTc to Show Assay Sensitivity

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Abstract

The most recent International Conference on Harmonisation E14 Q&A document states that a separate positive control would not be necessary provided sufficiently high exposures are achieved in the early-phase studies. Realistically, a phase 1 study is unlikely to include a pharmacological positive control, and in cases in which plasma levels of the drug exceeding therapeutic levels are not achieved, the lack of a positive control can constitute a limitation when excluding an effect of regulatory concern. It has been proposed to use the effect of a standardized meal on the estimate of the diurnal time course of QTc to show assay sensitivity. We conducted simulations by subsampling subjects from a 3 different studies and could show that the effect on food on QTc can be reliably prove assay sensitivity for sample sizes as low as 3 × 6 subjects with a power greater than 80%.

Keywords

assay sensitivity, food, QT, early phase, positive control

The use of concentration–response modeling of QTc data has gained regulatory acceptance and can be used as the primary analysis to characterize the potential for a drug to influence QTc. This type of analysis can be used in phase 1 studies as the definitive assessment of cardiac risk, and the possibility to do so is also explicitly mentioned in the recent update to the International Conference on Harmonisation (ICH) E14 regulation.[1] The original ICH E14 guidance states that "the confidence in the ability of the study to detect QT/QTc prolongation can be greatly enhanced by the use of a concurrent positive control group (pharmacological or non-pharmacological) to establish assay sensitivity." This need to confirm that a study is capable of detecting a small relevant difference in QTc remains unaltered.

When using concentration–response analysis, the upper bound of the 2-sided 90% confidence interval for the QTc effect of a drug treatment should be <10 milliseconds at the highest clinically relevant exposure to conclude that a drug does not have QT effects of clinical significance. For this end, a high span of supratherapeutic plasma concentrations must be achieved,[1] and in these cases a positive control may not be necessary.[1,2] Other methods of ensuring assay sensitivity as recommended by ICH E14 are therefore needed. Methods for bias evaluation were also considered to increase the confidence in the data collected from the IQ-CSRC study.[3] This published study demonstrated that significant bias has to be introduced to cause false-negative results.

For some studies high exposures cannot be achieved, and the level of confidence and the power of concentration–response analysis may raise concerns. In phase 1 studies in which subjects are often disturbed and mobilized for performance of various study assessments, the ECG measurement can be biased, and errors potentially leading to false-negative results cannot be reliably detected without a positive control.

Attempts to introduce moxifloxacin, the most commonly used positive control, have been made using a separate arm/period.[4,5] The inclusion of a pharmacological positive control entails significant changes in the study design of a typical phase 1 study to determine assay sensitivity resulting in increased study complexity.

A shortening of the QTcF after a standardized meal has been documented, and it has been suggested that this effect could be used to replace a positive control and show assay sensitivity to detect small changes in the QTc.[6] The effect of a standardized meal is reflected in the estimates of the "spontaneous" diurnal changes that need to be included in the concentration–response model if individual placebo-corrected changes from the baseline of QTcF values (ΔΔQTcF) are not available.[7]

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By construction, these estimates are independent of the concentration of the drug under investigation. If the change in these estimates of a time effect from before to 1–4 hours after a meal are significantly negative (on a 1-sided 95% level), this can be interpreted as evidence for assay sensitivity. Previous experience with the use of food to demonstrate assay sensitivity in this way has shown that the physiological effect of a meal on the QTc can be readily and reliably used as a positive control in a phase 1 environment as per ICH E14 guidelines.[6,8] As the required data are already available as a byproduct of the concentration–effect analysis, provided electrocardiogram (ECG) readings at appropriate times before and after standardized meals are available, the implementation of this approach eliminates the burden of increasing the sample size of an early clinical study.

Although the usefulness of this approach has been demonstrated based on a number of studies, no systematic investigations of its statistical power have been performed so far. Therefore, we used simulation techniques to determine the power of this approach to show assay sensitivity in studies with small cohorts. The approach used is similar to that previously reported.[9,10]

Methods

The simulation work was based on data from 3 clinical crossover studies, 2 thorough QT (TQT) studies and 1 single-escalating-dose phase 1 study in healthy volunteers.

Study 1

Study 1 was a double-blind, randomized, placebo-controlled, single-dose, 4-period crossover study in 56 healthy subjects.[11] Each period consisted of a baseline ECG day (day -1) and a treatment day (day 1). The ECG and samples for plasma PK analysis on the treatment day were taken at the corresponding clock times as on the baseline day. A 10-day washout interval between study drug administrations (day 1) separated the study periods. ECGs were taken predose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 12, and 24 hours postdose. On days -1 and 1, meals were served as follows: breakfast, 30 minutes prior to study drug administration, consumed up to 10 minutes before dosing; lunch, 7 hours postdose; dinner, 11 hours postdose; and snack, 13.5 hours postdose. Breakfast, which is the reference meal in this study, contained 515.7 kcal with an approximated ratio of 23% carbohydrate to 58% fat to 19% protein.

Study 2

Study 2 was a randomized, double-blind, placebo- and positive-controlled, 4-way crossover TQT study with 40 subjects.[12] Each period consisted of a placebo baseline ECG day (day -1) preceding the respective treatment days. ECG recordings were made at the following times: predose and 2, 8, and 30 minutes and 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours postdose.

Subjects participating in this study were served breakfast (reference meal) 1 hour before dosing and completed 30 minutes prior to the dosing time and lunch and dinner approximately 6 and 12 hours postdose, respectively. On baseline and treatment days, breakfasts were identical across all periods, delivering 652.8 kcal with an approximated ratio of 73% carbohydrate to 16% fat to 11% protein.

Study 3

Study 3 was a double-blind, randomized, placebo-controlled, 4-way, crossover phase 1 study in 32 healthy subjects.[8] Each period consisted of a placebo baseline ECG day (day -1) preceding the respective treatment days, and ECGs were taken predose and 15, 30, and 45 minutes and 1, 1.25, 1.5, 1.75, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, and 96 hours postdose of each period.

Standardized meals identical in all 4 periods with similar nutritional value were served as follows: lunch, dinner, and an evening snack 5, 9, and 13 hours postdose, respectively. The reference meal for this study was lunch, which was required to be completed within 20 minutes. Lunch contained 575 kcal and had an approximated ratio of 58% carbohydrate to 22% fat to 23% protein.

ECG Assessment

For all studies, 12-lead ECGs were recorded and stored electronically on the MUSE CV information system (GE Healthcare). Before any ECG recording, the subjects maintained an undisturbed supine resting position for at least 10 minutes and avoided postural changes during the ECG recordings. At each point, the ECGs were recorded in triplicate at 1-minute intervals during 3 minutes. Each ECG lasted 10 seconds.

Automatic ECG analysis was performed by the Marquette 12SL ECG Analysis Program. All ECGs and their associated automated interval measurements were subsequently reviewed by qualified cardiologists. If manual adjustments of the automated measurement became necessary, a second cardiologist confirmed the assessment. Any disagreement between first and second reader was adjudicated by a third and most senior cardiologist. Details of this process have been described elsewhere.[13] For further analysis, the mean across the triplicates was used.

In our simulation studies we used QT corrected according to Fridericia (QTcF).[14] Taubel et al (2012) have shown that compared with other correction formulas, with this correction, an immediate onset of the QTc shortening and a maximum size effect can be obtained.[6]

Data Analysis

Simulations were performed separately for each study using 3 dose groups: therapeutic, supratherapeutic, and placebo. For the simulations, subjects were randomly selected with replacement and assigned to the 3 dose groups as necessary. Study simulations were conducted with equal numbers of subjects in each dose group. For each scenario 1000 studies were simulated with i = 3, 4, 6, and 8 subjects in each dose group.

ΔQTcF (change from predose baseline) and concentration data from the respective treatment arm for each subject were selected, and a concentration–effect model was fitted to these studies. This model used concentration and the centered baseline value as fixed covariates, treatment (active or placebo) and time as discrete fixed factors, and intercept and concentration (slope) as random effects per subject.

The estimated time effect 3 and 4 hours after the start of the meal was used to show assay sensitivity for studies 1 and 2 and that 1 and 3 hours after the start of the meal for study 3. Although for studies 1 and 2, the change from the baseline value obtained before the start of the meal was the only candidate end point, the situation in study 3 allowed for several ways to calculate the reference for the change. The options included the selection of the last point before the meal or the use of the average of the 2 times preceding the meal. The latter choice is expected to give a more stable estimate. Both reference values were used here, but with an emphasis on the average of the 3- and 4-hour values, that is, the last 2 times before the start of lunch. In addition, the results based on the change from time 0, that is, the predose point, are also presented.

The original data set for studies 1 and 2 showed mean QTcF reductions of −5.2 milliseconds (90%CI, −7.5 to −3.8 milliseconds) and −6.8 milliseconds (90%CI, −9.2 to −4.4 milliseconds), respectively, 3 hours after mealtimes and 4 hours after the reference meal, a reduction of −6.7 milliseconds (90%CI, −8.6 to −3.0 milliseconds) and −6.8 milliseconds (90%CI, −8.6 to −5.0 milliseconds). For study 3 a shortening of the QTcF with respect to the average of the last 2 preprandial times of −4.3 milliseconds (90%CI, −6.5 to −2.2 milliseconds) 1 hour after the start of the meal and −3.4 milliseconds (90%CI, −5.8 to −0.9 milliseconds) 3 hours after the start of the meal were observed.

Because 2 postprandial times are considered, multiplicity needs to be addressed. Three ways to do this were considered: in the first strategy ("both"), the 2-sided 90% confidence interval had to be below 0 for both times; in the second strategy a Bonferroni correction was applied, that is, the 2-sided 95% confidence interval had to be below 0 for at least 1 time; whereas in the third strategy, a Hochberg method was used, which means that at least 1 of the 2 conditions above was to be fulfilled. Not unexpectedly, the Hochberg method provided slightly more powerful results. Because a positive correlation between the effects at adjacent times can be assumed, the necessary conditions for the Hochberg method to be applicable were considered fulfilled, and only results using this method are reported.

These investigations can be performed based on all 3 studies. The features of studies 1 and 3 allowed additional investigations. More specifically, the design of study 3 also allowed an estimate on the false-positive rate of the method, that is, its specificity. This was achieved by comparing the change from predose baseline to the 3 and 4 hours' times, that is, points at which the ECG was measured under fasted conditions before the reference meal was given. Again, a Hochberg procedure was used to correct for multiplicity.

In study 1, the drug under investigation did not show any QTc-prolonging effect. To investigate if the determination of assay sensitivity depends on the presence of a drug effect, a QTc prolongation proportional to the concentration of the drug was added, and the simulations above were repeated. More specifically, the simulated drug effect was created to result in a QTc prolongation of 0, 0.75, 1.25, 2.5, 3, 5, 6.6, and 10 milliseconds at the geometric mean C_{max} of the therapeutic dose. From this, a mean slope was calculated. A subject-specific random modification of this slope was achieved by adding a normally distributed, subject-specific variability of 65% of this slope to the common value. The power to show assay sensitivity was calculated as above. Because the Hochberg procedure performed best, only results based on this procedure are shown.

If moxifloxacin is used as a positive control in a TQT study, the formal test that the prolongation exceeds 5 milliseconds is supplemented by a critical appraisal of the time course of the effect. Likewise, the time course and size of the shortening seen after food would be part of an assessment of assay sensitivity based on this effect. However, in the present simulation study, we did not formalize this aspect.

All computations were performed using R version 2.13[15] and in particular the package lme4.[16]

Results

For the 3 studies, assay sensitivity was confirmed as described above. The fraction of studies in which assay sensitivity could be shown as a function of the sample size is displayed in Figure 1. Although for studies 1 and 2, the change from the baseline value at time 0 was used, the change from the average of the 3 and 4 hours' times is presented as baseline for study 3.

Under the conditions tested, assay sensitivity can be detected with a power above 80% with only 6

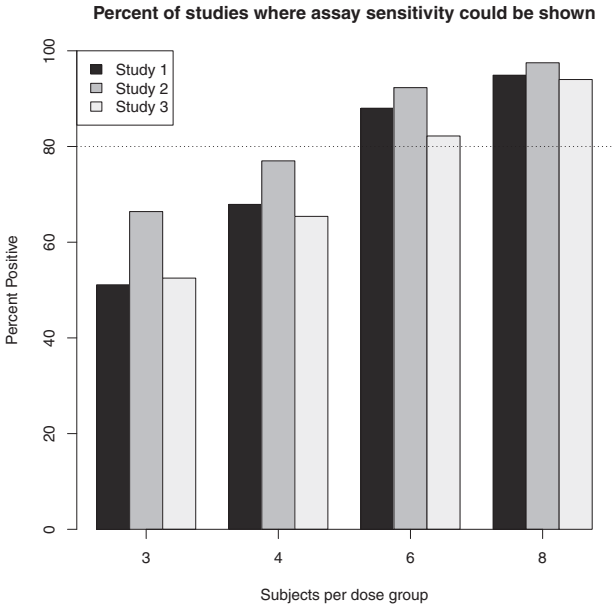

Figure 1. Performance of assay sensitivity as a function of the number of subjects included.

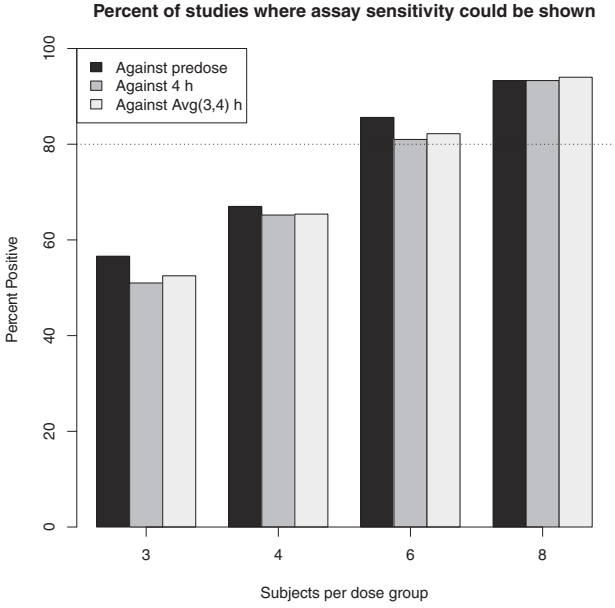

Figure 2. Influence of the choice of reference for the power to show assay sensitivity. Data from study 3 only.

subjects per treatment group when using the Hochberg approach. With 8 subjects in all treatment groups, a power greater than 90% is achieved, whereas there is insufficient power to reliably show assay sensitivity with 3 or 4 subjects in each dose group.

Because the design of study 3 allowed for several options, the performance of these is shown in Figure 2. The differences between the use of the preferred option, that is, the average of the 3 and 4 hours' times and the 4-hour time only are very small, whereas the comparison with the predose baseline yields a slightly higher proportion of positive findings.

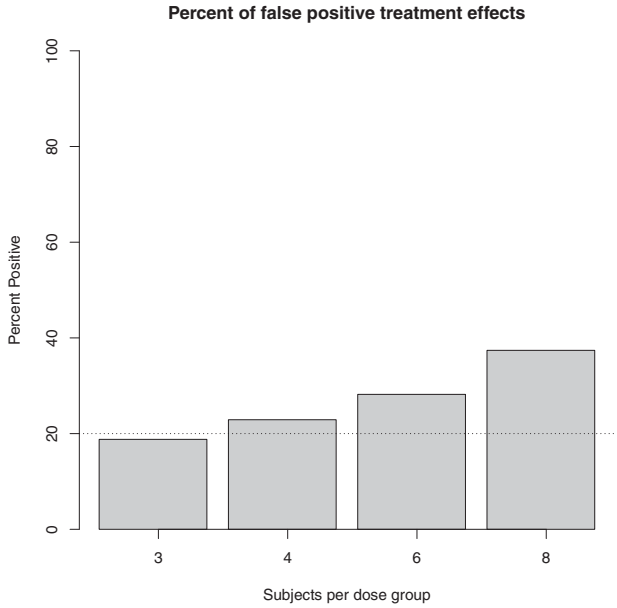

Figure 3. Percent of simulated studies based on study 3, in which a significant decrease was detected 3 or 4 hours after drug administration, that is, in a fasted state, compared with predose.

To understand the specificity of the proposed method, the change from predose to the last 2 points before the meal, that is, 3 and 4 hours after dosing, was also examined based on data from study 3. As can be seen in Figure 3, a proportion increasing with sample size of the simulations also showed a very small but significant shortening at these premeal times. In statistical terms this result by itself would suggest the method lacks specificity.

However, the change from predose to premeal is negligible in the placebo group of this study (0.4- and 0.5-millisecond increase) and at most 3 milliseconds in the model-based time estimates, whereas the meal effect is −6 to −10 milliseconds.

Figure 4 shows the distribution of the observed effect of the meal at the times considered across the simulated studies. As a reference, the corresponding estimate based on all data of the respective study is given on the right vertical border of each panel. Not unexpectedly, the estimates become more stable with an increasing number of subjects. The median estimate is consistently at about 6 milliseconds for study 1, 6–7 milliseconds for study 2, and 5-millisecond (1-hour) and 3-millisecond (3-hour) shortening for study 3. In other words, there is no indication for bias depending on the sample size. With the exception of the 1-hour point for study 3, there is also reasonable agreement between the median of the results based on the simulated studies and the value obtained from all data. As was to be

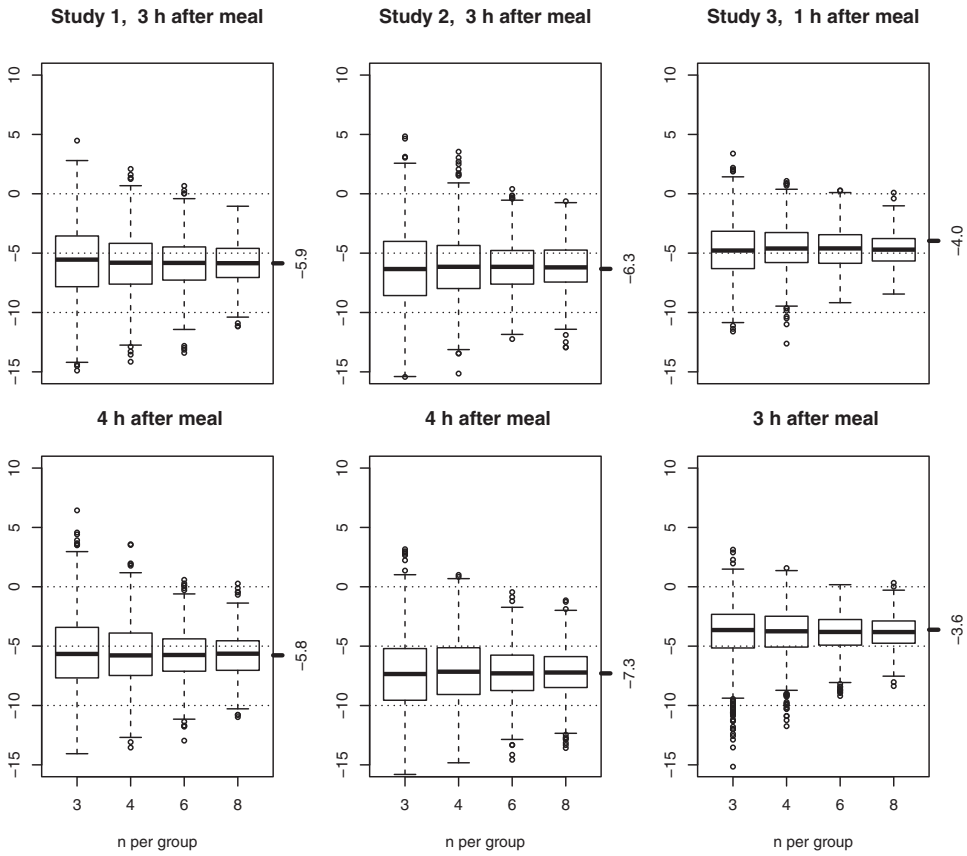

Figure 4. Distribution of the estimated change from preprandial baseline for the simulations based on the 3 studies. Each column presents 1 study, the panels giving the 2 postprandial times considered. Each box-and-whiskers element gives the distribution of the change of QTcF from the preprandial reference across the simulated studies with the respective sample size per group. The *y* axis gives predicted ΔQTcF of food effect in milliseconds. The tick on the right *y* axis represents the model-based effect.

expected, the standard error of the estimates decreased with increasing sample size (Supporting Information Figure S1).

The absence of an effect of the investigational drug on the QTc in study 1 gives the opportunity to investigate any potential bias because of a drug effect by simulating a drug effect of various sizes. As shown in Figure 5, there is no indication that the power to detect the effect of the meal is influenced by the size of the drug effect.

Discussion

The need to show assay sensitivity is currently a major challenge if a phase 1 study is to be used to exclude a clinically relevant effect of an IMP on the QT interval, and substantial multiples of the highest clinically relevant dose cannot be achieved in the study. As there is agreement that the introduction of a pharmacological positive control may be difficult in these studies, alternative methodologies are under investigation. One group of approaches attempts to make a positive control obsolete by investigating the

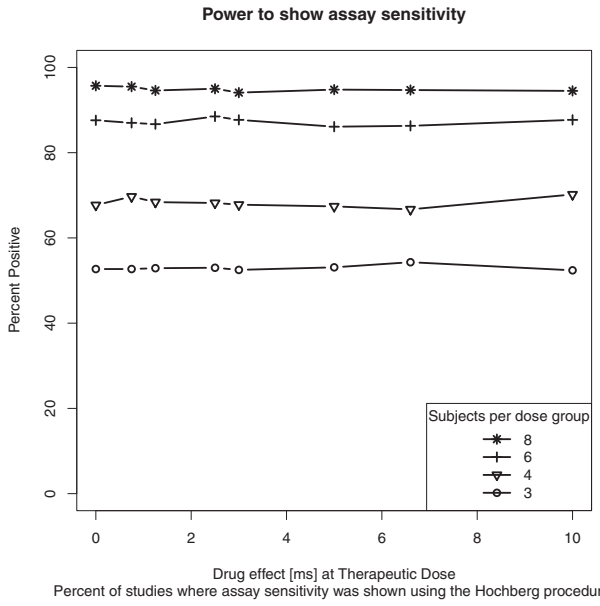

Figure 5. Power to detect assay sensitivity by size of simulated drug effect for various sample sizes. Each line gives the power, that is, the percentage of studies in which assay sensitivity could be shown for a different sample size over a range of simulated drug effects.

quality and reproducibility of QTc measurements. Malik et al[17] proposed measures to evaluate the quality of ECG data of TQT crossover studies, which, however, are challenging to apply in a phase 1 setting. Moreover, the proposed quality metric does not specifically address those types of error that could cause false-negative results, that is, a negative bias for long QT intervals and a positive one for short QT intervals. More recently, Ferber et al (2017) investigated a measure constructed to specifically identify bias that could lead to false-negative results by comparing the reported QTc values with those obtained by standard algorithms on continuous Holter recordings without any human intervention.[3] This method, although promising, needs further validation before it can be applied widely.

The method investigated in this publication follows a different approach in that it replaces a pharmacological positive control by the well-known and established effect of a meal on the QTcF, an effect that has been demonstrated to be a promising candidate.[6,8,18] Other groups have established that control of glucose levels is essential for studies investigating the QT effects of medicines altering glucose homeostasis.[19,20] QTc shortening after a meal may introduce bias, and it is therefore best practice to control meals and to conduct a formal investigation into the effects of the meals as part of every statistical analysis of thorough QTc studies. Application of concentration–response modeling to real clinical data in which the underlying PK/ECG relationship is not known would benefit from the incorporation of a positive control when multiples of the highest clinically relevant plasma levels cannot be achieved and in any event would provide a means of enhancing confidence in the ability of a study to detect a small change in the QTc. Phase 1 studies would thus benefit from this efficient approach for assay sensitivity evaluation, which is simple to implement, avoids unnecessary drug exposure and potential side effects, and does not require a separate arm/period. A further advantage is that this analysis can be performed for every individual study day if multiple ECG assessment days are included in a multiple-dose trial.

The aim of this simulation study was to broaden the understanding of the power of the food effect to show assay sensitivity and to show whether a positive control such as the effect of food on the QTc interval can be integrated effectively in early-phase clinical trials with small sample sizes. Resampling data from 2 TQT studies and a phase 1 study that included placebo and therapeutic and supratherapeutic dose data, we performed a concentration-QTc analysis and looked at the fraction of studies in which the estimated time effect showed a significant shortening 1–4 hours after the end of a meal as a function of the number of subjects included in the study. For each individual study, the distribution of the estimate of the effect seen after the reference meal was evaluated. In all cases subsequent meals were served more than 4 hours after the reference meal and therefore did not affect the window of food effect assessment. However, because of the study-specific times and the lack of awareness of the decrease in QTc induced by a meal at the time study 3 was conducted, the time effect was evaluated 3 and 4 hours after the start of breakfast for studies 1 and 2 and 1 and 3 hours after the start of lunch for study 3. Nevertheless, the food effect seems to be independent of the timing of the meal.[21]

This simulation indicated that with 18 subjects, assay sensitivity can be shown reliably if the Hochberg procedure is used. This power seems similar for all 3 studies. The power was not affected by the size of the drug effect, as could be shown for study 1.

As no breakfast was given in study 3, the reference meal was lunch, which was consumed 5 hours postdose. Unlike studies 1 and 2, in which breakfast was given before administration of the study drug and only the change from predose baseline was possible, study 3 allowed us to investigate the selection of the appropriate contrast. Two options have been considered: difference to the last point before the meal and difference to the mean of the last 2 times before the meal. In addition, the change from the predose baseline has also been investigated. The results presented suggest that the change from predose is larger than that from the immediate preprandial times (see also Figure 5 in Täubel et al, 2015[8]).

Study 3 also allowed some investigation into the specificity of the method by looking at the change from predose baseline to preprandial points. The last 2 preprandial points were selected, 3 and 4 hours after dosing. In this study, the change from predose baseline to these points was statistically significantly negative in at least 1 of the times in about 20% of the studies simulated — depending on the sample size used. Apparently, there is a shortening of the QTcF of up to 3 milliseconds 3–4 hours after the start of the study, if we follow the time effect estimates of the model, which, however, is not seen in the placebo group. With increasing sample size, the fraction of studies in which this effect becomes statistically significant increases. This suggests that a more refined rule to declare assay sensitivity may be called for, that is, one that allows the distinction of a meal effect from other effects.

Indeed, as the power to detect the effect of a meal becomes >80%, with increasing sample sizes, there is room for a more refined rule. When assay sensitivity is assessed based on moxifloxacin effects, it is not only the test of the effect against the threshold of 5 milliseconds, but, in addition, the time course of this effect is considered.[22] In a similar way, the size

and time course of the effect seen after a meal could be considered to improve the specificity of the test, in particular, for larger sample sizes. It must remain unclear if this is a study-specific finding because we have only fasted data from 1 study.

Our investigations have a number of limitations. The simulations presented here are based on 3 crossover studies with placebo, 2 doses in studies 1 and 2 and 3 doses in study 3 of an investigational drug. Therefore, the studies simulated do not fully correspond to a typical first-in-human study, in which more cohorts with a wider range of doses — 5 and often more — would be used. One could therefore expect that our simulation results are conservative with respect to power. In addition, the studies used were conducted without the intention to use the effect of food for the establishment of assay sensitivity. Finally, although the studies cover settings that are important for assessing the power of the method, there is, for example, no replication for the setting in which lunch is the first meal. The only study data available at the time of conducting this analysis was from a study designed and conducted several months before the full effects of a meal on the QTc interval were known. Further work to elucidate this question in the setting of first-in-human studies is ongoing, as investigational medicinal products are given in a fasting condition in most early-phase studies. In all those trials a careful choice of the "premeal" baseline must be made.

To conclude, if a clinical study design includes rigorously standardized, and correctly timed meals in addition to sampling of PK and ECG data at appropriate points, assay sensitivity can be reliably demonstrated using the food effect on QTc with a power greater than 80%. For sample sizes beyond 18–24 subjects, a more refined rule may be developed to increase the specificity of the method proposed. The test for assay sensitivity is based on the same data as the investigation of the drug effect on QTcF. This is not only an economic advantage, but it also reduces the likelihood of a systematic error occurring only on drug effect, but not on food.

Declaration of Conflicting Interests

Jörg Täubel and Sara Fernandes are employees of Richmond Pharmacology Ltd. Georg Ferber is an employee of Statistik Georg Ferber GmbH who has received honoraria for consulting from Richmond Pharmacology.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.