Which Protocol Should I Use: The Standard ICH E14 Thorough QT/QTc Study or Concentration-effect Modelling?

The article by Dr Robert Kleiman in the previous issue of this journal[1] described a method for evaluating repolarisation effects of new drugs that has recently been accepted[2], and to a considerable extent, advocated[3] by the US Food and Drug Administration (FDA). The concentration-effect modelling approach is appealing because it is intended to be performed at the very beginning of the clinical development phase, and to be a simple add-on to the usual first-in-human dose escalation pharmacokinetic study. This means that the ethical issue of exposing volunteers and patients through Phases I and II, before definitively determining if the drug is electrophysiologically safe, is solved, and the time, effort and cost of the drug's development that would have taken place through Phase II can be avoided for drugs with prohibitive ECG effects. In addition, moving the ECG assessment to the beginning of Phase I clinical development may make some sponsors more willing to bring drugs with a non-clinical ECG signal to the clinic, knowing that the ECG issue will be resolved much sooner than usual. This reduces concern that potentially safe and effective treatments are being discarded because of non-clinical observations that might not be real safety issues in clinical use.

The purpose of this article is to help pharmaceutical sponsors decide between the two accepted methods for assessing ECG liability of new drugs. First we consider those situations in which only one of the two options for thorough ECG screening is appropriate, and then we consider the host of factors that would favour one or the other approach when there is a choice. Finally, we provide some qualitative estimates of the risk of using one rather than the other method. The concentration-effect modelling approach will be referred to as CEM, and the standard ICH E14 approach described in the original Guidance[4] and its first two Q&As[2] will be referred to as TQTS.

No-choice Situations

Neither Method Appropriate

First, let's examine the situations for which neither method is appropriate or necessary. These are listed in Table 1 and are, for the most part, self-explanatory. Toxic drugs that cannot be administered without a potential benefit cannot be placebo controlled, except when tested as an add-on to standard treatment, but in the latter situation a rigorous TQTS or CEM design is usually not possible. Drugs that do not reach the systemic circulation or cannot access the intracellular compartment are not required to undergo QT testing, with rare exceptions. Finally, drugs known or intended to prolong QT are waived from the requirement. Note, however, the drugs waived because of placebo control and other protocol design limitations still require an alternative assessment of their QT effects.

CEM Method Not Appropriate, but TQTS Appropriate

Known pharmacokinetic – pharmacodynamic (PK-PD) hysteresis: If a drug's effect on the ECG is known to be delayed, with its peak effect occurring an hour or more after Cmax is achieved, the drug is a poor candidate for the CEM approach. While there are several options for dealing with hysteresis, none seem to be perfect solutions, especially in the presence of potential participant-related random effects.[5,6]

Very long half-life: Drugs that persist in the circulation for many days or weeks with little change in plasma concentration are not good candidates for CEM because the variability of ECG measurements over such a protracted period of sampling may obscure or simulate a drug effect. This problem may, in some cases, be manageable by collection of frequent samples while the drug is being administered, in the case of infusions, or immediately after oral administration, making it unnecessary to track the subsequent slow decline in plasma concentration.

Cytotoxic oncology drug
Other drugs that cannot be placebo-controlled
Drugs without systemic availability
Biologicals too large to access the cytosol
Drugs with already proven QT effects
Antiarrhythmic and other drugs that intentionally prolong QT

Table 1: Categories of drugs for which a thorough ECG assessment cannot or should not be done

Herbal and multiple-moiety drugs: When the active chemical entity is not known, or multiple parent entities are potentially active, the CEM method cannot be used because a clinically or regulatorily useful relationship between plasma concentration and ECG effect cannot be established. Dose-effect modelling might be an alternative in some of these cases, but a time-point-oriented E-14 approach is more appropriate.

Factor	Favoured Method	Weight of Factor
Price and time very critical to sponsor	CEM	H
Clinical dose cannot be reliably predicted	CEM	M
Tmax highly variable	CEM	M
Known PK-PD hysteresis	TQTS	H
Very long half-life	TQTS	H
Herbal, multiple moieties	TQTS	H
Multiple days of dosing required	TQTS	L
Only relatively low exposure achievable	TQTS	M
Crossover cannot be done	TQTS	L
H – high; M – medium; L – low weight		

Table 2: Factors Bearing on Choice of Method

TQTS Not Appropriate, but CEM Appropriate

There may be no real situations in which a standard TQTS approach could not be used, but a CEM approach could be used. A theoretical possibility would be a drug with unpredictable or random Tmax. In this situation, the time-point-oriented analysis might miss a substantial ECG effect because it would be diluted across time, whereas the CEM method would capture the relationship of drug concentration to effect.

When There is a Choice

In this section we explore the relative importance of multiple features of the two methods, as well as potential features of the study drugs in choice of the method to be used. Most of these factors are summarised in Table 2.

Price

The standard TQTS approach costs more than the CEM approach in most cases. For the "pure" case of a single dose experiment with relatively few (i.e., four) dose levels, the CEM methods cost about half as much as the standard TQT study. The lower cost is related primarily to the smaller number of participants and lack of need for the confinement during washout that is associated with the typical crossover TQTS.

There is a very interesting sidebar to the price consideration. While the sponsor may save money by doing a CEM study instead of a TQTS, using the CEM strategy for all of the sponsor's drugs that reach clinical development may, in the long run, cost more. While virtually all drugs that graduate to clinical assessment undergo a first-in-human PK study (where the CEM ECG assessment would be grafted on), many drugs fail to reach the end of Phase II, at which point the standard TQTS has usually been done. If the average cost of the latter is double, but fewer than half of the drugs that enter Phase I are successful enough to undergo a TQTS preceding Phase III, the sponsor would spend less using the standard method at the end of Phase II.

Speed

In general, using the CEM approach is much faster, because the PK and the ECG objectives are achieved in a single study, eliminating the time required to perform the standard TQT study at the end of Phase II. In addition, in most situations the CEM study can be completed more quickly than the standard TQTS. This is primarily due to the fact that most standard TQT studies have a crossover design, requiring a washout period between arms, and virtually all treatment arms in the standard TQTS are completed using two or more cohorts. In the CEM approach, assuming that a parallel design is used, each arm is completed without the need for an inter-arm washout, and each arm is completed with a single cohort. Exceptions to this time difference would include PK studies with a large number of tested doses and those in which it is necessary to await PK results before proceeding to the next escalation.

SAD/MAD Studies Already Done

In this early period of availability of the CEM method for QT assessment, many sponsors have already completed their SAD/MAD experiments. Naturally, they are reluctant to consider repeating the PK studies (modified to include thorough ECG assessment), because it seems redundant and wasteful. But, in fact, it is not fiscally wasteful, in most instances, and the previous completion of PK studies provides an additional advantage. As pointed out above, the CEM study costs less and can be completed more rapidly than the standard TQTS. Thus, there is no waste in repeating a PK-style protocol, but rather a saving in both money and time. And, with the safety and tolerance information derived from the original PK study, the CEM study can use a non-serial, parallel design with multiple dose cohorts run simultaneously without the need to determine safety and tolerance between cohorts. If higher doses need to be explored, only those doses would need to follow the usual serial assessment. Thus, if PK studies were already done, the CEM study can be done very quickly and efficiently.

Single vs Multiple Dose

If multiple doses of the test drug over multiple days are required to achieve the necessary supratherapeutic exposure, depending on the details, this situation might favour the standard TQTS protocol. In the latter, multiple days of dosing would only be required for the supratherapeutic dose of the test drug and the placebo arms, while the remaining moxifloxacin treatment could be achieved with a single dose. But, in a CEM study, a

lengthy dosing period would be required for all arms. If many dose levels were required, the duration of the CEM approach would exceed that of the TQTS, despite its washout confinement, and the cost of housing the volunteers might raise the cost of the CEM beyond that of the standard TQTS.

Achievability of the Exposure Requirement

This may be the deciding factor in many instances. FDA has repeatedly made it clear that the maximum exposure achieved in the CEM approach must exceed that of the standard TQT method. Exactly what multiple of the usual clinical exposure is required for either study method, however, is not specified in the ICH E14 Guidance or its subsequent Q&As. The original ICH E14 document refers to "substantial multiples" (Section 2.2.2[4]). In practice, a three-fold exposure has commonly been achieved in TQT studies and this has been considered sufficient during the review process. Of course, there are surely exceptions to this rough guideline – both higher and lower multiples being appropriate for specific drugs. Thus, in the typical CEM protocol, it would seem necessary to achieve at least four-fold exposure in a substantial number of subjects, and I have recently been recommending five-fold as the minimal target. For many new drugs, a five-fold exposure cannot be achieved. In these cases, the standard TQTS approach is more likely to satisfy regulators. The recent Q&A, ICH E14 Q&A (R3)[2], and public statements by FDA officials, indicate that the positive control of the standard TQTS provides the needed reassurance when only three-fold or even lower supratherapeutic exposures can be achieved.

The same sources have indicated that inclusion of a positive control in a CEM protocol could reduce the need for a very high supratherapeutic dose. While this is an appealing strategy, I have seen results from a few studies recently in which the positive control arm failed to meet standard ICH E14 assay sensitivity criteria (the expected pattern of response over time, and a lower bound of the two-sided 90% confidence interval above 5 msec) – almost surely the result of the active control cohort containing the same small number of subjects enrolled in the other cohorts. Proving assay sensitivity in the CEM approach will probably require enrolling large active control cohorts, similar to or approaching the usual cohort size in the standard TQTS. This might tip the balance in favour of doing a standard TQTS rather than inserting a small active control cohort into the CEM approach.

Crossover Not Possible

When a crossover design cannot be used in a standard TQTS, should this influence the choice of study method? Perhaps. Typically, a sponsor would not select the parallel design for a standard TQTS if an efficient crossover is feasible, due to the extra cost of participant recruitment, the larger number of participants needed in each treatment arm, and the loss of power that might not be fully compensated for by the larger enrolment. But, for some drugs (especially those with long half-lives), the parallel design might be forced on the sponsor. In these instances, the speed advantage enjoyed by the CEM approach might be lost, as a parallel designed QT study can be executed faster than a crossover design in Phase I units large enough to accommodate large cohorts.

Relative Risk of the Two Approaches

Each of the two methods has a risk of failure. The relative risks should be considered in making a final choice.

Dose limitation: In the first-in-human setting, the sponsor only has an educated guess as to what maximum dose and exposure can be achieved in humans, and a less well-educated notion of how that relates to the usual clinical exposure. If, for example, only two or three doses can be tested due to intolerance, the experiment might not provide sufficient PK-PD sample pairs covering a sufficiently wide range of plasma concentrations. This would result in a failed CEM study. This risk could be averted by delaying the thorough ECG assessment to the end of Phase II. As a result, the maximum achieved exposure in the first-in-human experiments might, when more clinical experience has been collected, turn out to be insufficiently greater than the usual clinical exposure. In these cases, a standard TQTS might be the only way to resolve the issue, subjecting the sponsor to the loss of time and expense of doing both studies. This situation can be obviated by defaulting to the standard TQTS approach at the end of Phase II.

Unexpectedly high clinical exposure required for efficacy: This problem is related to the one above. The maximum achieved exposure in the first-in-human experiments might, when more clinical experience has been collected, turn out to be insufficiently greater than the usual clinical exposure. This would most commonly occur when the sponsor limited the SAD/MAD dosing levels on the basis of the expected clinical dose, rather than pushing the SAD/MAD doses to intolerance. In these cases, a standard TQTS might be required to resolve the issue, subjecting the sponsor to the lost time and expense of doing both studies.

However, this very same problem may affect a standard TQTS done at the end of Phase II, because, in general, it is only in Phase III that the final clinical dose is determined. Standard TQT studies have had to be repeated because of the Phase III finding that efficacy requires a large dose.[7,8]

Interestingly, the CEM approach is probably the best way to protect against this unwanted outcome. That is because ICH E14 Q&A (R3) specifically allows for meta-analysis of PK-PD data collected in multiple independent protocols. Thus, the sponsor could simply perform a limited CEM study covering the higher exposure levels, add the new data to the previous CEM data and produce a satisfactory analysis. This would be much easier, faster and less expensive than repeating an entire TQTS.

Failure to prove assay sensitivity: This is a risk only in the standard TQTS approach (assuming no active control is incorporated in the CEM study). If it occurs, the TQTS might have to be repeated. The risk can only be avoided by choosing the CEM approach. However, in cases in which assay sensitivity criteria are not met, there is often an explanation or mitigating circumstance, with the result that the TQTS findings are accepted and a repeat study is not required.

Summary

We now have two methods to fulfill the regulatory requirement to thoroughly evaluate ECG effects of new drugs. Superficially, the CEM approach may seem preferable because it gives early answers at a lower cost and with considerable time savings. But, there are many factors that must be considered in making the choice between the CEM and the standard TQTS approach. The standard approach will be found to be a better strategy in many circumstances, despite the attractiveness of the CEM method. A decision list like the one shown in Table 2 could be used to help direct the decision process.

References

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