THOROUGH QT TRIALS: EXPLORING TRADITIONAL AND ALTERNATE ROUTES

INTRODUCTION
Before the Health Authorities give the green light to put a new drug on the market, they generally request a clinical study dedicated to the evaluation of the potency for this drug to induce or not a QT interval prolongation. To reach this objective, the ICH E14 guidelines have been developed to give the framework for conducting TQT studies and analyse the ECG data. However, depending on the drug characteristics and pharmaceutical laboratory clinical development strategy, the QT standard study design sometimes has to be adapted.

This paper aims at presenting the key points to conducting a TQT study, as well as several case studies recently conducted at SGS Clinical Pharmacology Units (CPU) that illustrate various traditional and alternate routes.

A CLOSER LOOK AT QT PROLONGATION
A prolonged QTc interval is, among other, a predictor of sudden cardiac death. Many cardiac and non-cardiac marketed drugs prolong ventricular repolarization and have the potential to induce life-threatening ventricular tachyarrhythmias. It is generally recognized that some individuals are more susceptible than others to the QT-prolonging effects of drugs even at standard dosage regimen (genetic factors, female gender), and that high blood concentrations (due to overdose or drug interactions) increase the risk of drug-induced arrhythmias. Drugs that can prolong the QT interval are first belonging to two subsets of the anti-arrhythmic drugs, i.e. the Class Ia (e.g. quinidine and procainamide) and the Class III (e.g. dofetilide, sotalol and amiodarone). Other drugs which can prolong QT interval can be found in many other non-cardiac drug categories, including anti-histamines, antibiotics, gastrointestinal prokinetics, antipsychotics.

Marked QT prolongation associated with torsades de pointes occurs in 1% to 10% of patients receiving QT-prolonging anti-arrhythmic drugs and much more rarely in patients receiving non-cardiovascular drugs with QT-prolonging potential\(^2\). Therefore, an early assessment of the potential for drug candidates to delay cardiac repolarization has become necessary before reaching later phase of drug development, e.g. confirmatory Phase 3 trials.

Preclinical and clinical programs have been developed to identify compounds that can potentially induce a QT prolongation in human. In 2005, a preclinical ICH Guideline has been released that support a multi-test preclinical in vitro and in vivo evaluation of the QT interval prolongation of drugs. Also, an ICH Guideline has been developed that “gives recommendations concerning the design, conduct, analysis, and interpretation of clinical studies to assess the potential of a drug to delay cardiac repolarization”, the so-called thorough QT trial (TQT)\(^2,3\). The fact that non-antiar-
E14 ICH GUIDELINE: TQT STUDY

Rhythmic drugs may delay cardiac repolarization and thus may induce life-threatening cardiac arrhythmias (e.g. torsade de pointe) represents an unacceptable risk for patients. This is the reason why the pre-marketing investigation of the safety of a new candidate drug must include a rigorous characterization of its effects on the QT/QTc interval in human.

A TQT study based on the recommendations of the harmonized tripartite guideline E14 is aimed at providing a quantitative response as to whether a candidate drug does not prolong the QT interval to a threshold of concern. TQT study applies to new drugs as well as to approved drugs when a new dose or route of administration has been developed that leads to an increased systemic exposure. This guideline does not apply to a) antiarrhythmic drugs that can prolong the QT/QTc interval as a part of their mechanism of action, b) topical drugs that are not absorbed and c) biological products, although obviously in these cases the safety pharmacology endpoints must be evaluated during toxicology and/or pharmacodynamic studies.

Overall, the TQT study is technically difficult, mainly because it is difficult to choose the data points to be used for the measurement of the QT interval, and because the raw data (actual QT interval) are corrected for heart rate. Also, additional difficulty arises when considering the great complex-to-complex variability of the QT interval (up to 25 ms), and the small changes in the mean QT interval values that must be determined between the active drug under evaluation and the placebo (between 5 and 10 ms).

The rational for choosing these threshold values was based on the observation that drugs which prolong the mean QT/QTc interval by around 5 ms or less do not appear to cause torsade de pointe. Subsequently, the E14 Guideline indicates that a negative TQT study is one in which the upper bound of the 95% one-sided confidence interval (CI) for the largest time-matched mean difference between drug and placebo (baseline adjusted) on the QTc interval excludes 10 ms. This definition is believed to provide reasonable assurance that the mean effect of the study drug on the QT/QTc interval is not greater than around 5 ms. When the largest time-matched difference exceeds 10 ms, the study is termed “positive”.

Therefore, TQT study should be carefully designed so that to favour homogeneity of the study subjects, the ease of the measurements, while the environmental conditions should avoid inconsistency within and between study subjects.

DESIGNING A TQT STUDY

Healthy subjects (females and males should be equally balanced) are generally enrolled in TQT studies in order to minimize the risk of arrhythmia. Subjects with a history of torsade de pointe in their family as well as subjects with hypokalemia should be excluded.

Treatments should include two dose level of the candidate drug (the therapeutic dose and a supra-therapeutic dose), one standard dose of a positive reference control (e.g. 400 mg moxifloxacin) and a placebo treatment. The positive reference control should prolong the mean QT interval by about 5 ms (this is an effect that is close to the QT prolonging effect that represents the threshold of regulatory concern). Eliciting this effect establishes the TQT study as enough sensitivity to detect a similar effect with the candidate drug. Depending on the pharmacokinetic and metabolic characteristics of the drug, as well as on the expected use in patients (e.g. drug used as a single dose or on a needed basis or long term administration) the TQT study should be performed with a single or a “steady-state” dosage regimen.

The TQT study is most generally conducted as a cross-over, which has more statistical power than the parallel groups. However, when the candidate drug has a long half-life, which would increase the wash-out period in a cross-over design to an unacceptable duration, then the parallel group design is preferred.

Sample size determination is one of the critical point to consider for a successful conduct of a TQT study. Generally, ECG data for the candidate drug are available before designing the TQT study (QT assessment during single and multiple dose Phase 1 studies). In these conditions, historical within subject standard deviation for QT change from baseline can be considered as true within subject standard deviation, which is then used to compute the power to detect an absolute mean difference in QT change of 5 ms or less for several sample size.

The choice of the baseline should aim at minimizing the standard deviation of the change from baseline. Considering that the prolongation of the QT interval is planned to be evaluated on the basis of the double difference (versus pre-dose and placebo), time matched baseline on study day -1 should be used in parallel group design (in this case, only time matched baseline eliminates the random circadian effect), while in a cross-over design (which eliminates circadian effect) the pre-dose baseline is generally used.

ECG Recording

ECG data should be recorded under strictly standardized conditions from 12 lead standard ECG (digital records) or from 12 lead Holter ECG devices. It is worthy to note that 100% automatic ECG evaluations are not accepted. Conversely, manual or semi-automated with manual ECG evaluation are accepted. Blinded ECG data (with regard to time, treatment and subject identification) are first managed by an ECG technician and then analyzed by a cardiologist. Importantly, the same cardiologist should analyze the whole data set of a given study subject. ECG data should be further validated by providing the intra and inter-reader variability (repeated analyses by the same reader or another reader in a blinded manner).
As the QT interval is influenced by the heart rate, it is not possible to compare QT interval values recorded at different heart rates. Therefore, heart rate correction is needed in the analysis of change in QT interval. Several heart rate correction formulae have been developed since the “historical” Bazett correction. Importantly, the E14 Guideline recommends by default the use of the Bazett correction and the Fredericia correction. However, in an ideal world, the individual correction would be the best. So generally, other corrections than Bazett and Fredericia are additionally used. Once the QT and QT-corrected (QTc) data are available, a two-step analysis is required. First, a statistical analysis on the double difference (versus pre-dose and placebo) is performed, and then a categorical analysis followed by a morphological analysis of the T-wave is done. The statistical analysis is done not only to provide data on the treatment difference (drug versus placebo) but also to confirm that the reference control induced QT prolongation is consistent with historical values thus confirming the study sensitivity. Overall, five TQT study outcomes can be obtained (Figure 1).

Although the cases 1-3 meets ICH-E14 criteria as “negative outcome” for a TQT study, the Case 3 outcome might result in adverse labeling for a drug intended for a wide chronic use in non-life threatening condition. Case 4 and 5 typically represent a positive outcome, i.e. the drug has elicited a QT prolonging effect (drugs inducing a QT prolongation of more than 20 ms are considered as pro-arrhythmic).

**Standard and atypical QT study designs – case studies**

The TQT study is technically difficult and complex. Additionally, the cardiac safety of candidate drugs is an active area of investigation where knowledge is rapidly evolving. In these conditions, it is not surprising that the corresponding study protocols done over a short period of time may vary a lot. The following case studies illustrate this situation as experienced at SGS CPUs.

**Standard cross-over study design**

This cross-over study design was developed to manage two ways of using the baseline (pre-dose and time matched). In this study, 30 young healthy subjects (male and female with at least 40% of each gender) were enrolled. The four-treatment periods consist of a) a single dose of placebo, b) 400 mg moxifloxacin, c) one therapeutic and d) one supra-therapeutic dose corresponding to maximum tolerated dose (MTD) reached during in a Phase 1 single ascending dose. Each treatment was administered as a single dose on day 1 of each period.

ECG data were collected by using a continuous 12 lead 1000Hz Holter from at least one hour before dosing on the morning of day 1 to morning of Day 2. Pre-dose ECG recordings consist of three triplicates each being separated by 15 minutes.

**Standard parallel group design**

This parallel group design study included 128 young healthy male and female volunteers with at least 40% of each gender. The drug was given on a repeated basis until reaching the steady-state for drug and identified metabolites. The study treatments were a) placebo, b) placebo and 400 mg moxifloxacin on the last day, c) the therapeutic dose, and d) a supra-therapeutic dose (as mentioned in the cross-over design. The study also included a run-in placebo period on Day -1.

ECG were recorded by using a continuous 12 lead 1000Hz Holter from morning of
Day -1 to morning of Day 1 and then on the last administration day from 1 hour pre-dose to 24 hour post-dose.

Alternate study design: specific drug metabolic properties

This TQT study was requested by the Health Authorities because the drug, although marketed since more than 20 years, belong to a therapeutic class that raised cardiac safety concerns. A specific study design was developed because a long terminal half-life was characterized for one metabolite, with around 10-times increase of exposure in CYP 2D6 poor metabolizers. As recruitment of poor metabolizers was deemed to be very difficult, extensive metabolizers were enrolled alternatively and administered concomitantly with a CYP 2D6 inhibitor (paroxetine) so that the exposure matched that of the poor metabolizers. Overall, the study was designed as a single dose cross-over to assess the effect of the reference control moxifloxacin, followed by a randomization of the study subjects in two parallel groups, e.g. placebo combined with paroxetine (negative control), and the study drug combined with the paroxetine. Additionally, in order to assess the optimal duration of the paroxetine treatment, the study was split into a pilot step followed by the main study.

In the pilot part, 16 out of 128 subjects were included where the maximum CYP 2D6 inhibition was evaluated. Then, the main study part was performed for the remaining study subjects with duration of paroxetine treatment as determined in the pilot part.

Alternate study design: new indication

As part of the development of a new indication for a drug marketed for many years, patient studies were needed at high dose, while the MTD in healthy subjects was not available. Therefore, the study was divided in two parts, the first consisting of a single multiple ascending dose up to the MTD, and the second being designed as a standard TQT parallel group where the supratherapeutic dose was the MTD as defined in the first study part.

DISCUSSION AND CONCLUSIONS

Cardiovascular safety concerns may arise from preclinical data, experimental in vitro and in vivo studies, clinical trials, and pharmacovigilance and literature reports. Among these cardiac safety programs TQT studies in human should be viewed as ultimate step before administering a candidate drug to large patient population. The development of TQT study protocol is complex and needs the combination of strong statistical expertise, validated ECG data collection/management and analysis as well as an optimal clinical organization to appropriately handle the safety of the study subjects and the standardization of the ECG data collection.

The TQT study is part of the global cardiac safety evaluation during the drug development, which includes the assessment of the impact of the drug on the blood pressure, the heart rate, ECG parameters, in vitro and in vivo methods for evaluation of repolarization and conductance abnormalities.

The timing for conducting a TQT study is highly dependent on the information obtained during the preclinical and early Phase 1 clinical development of the drug. If there is evidence from these data that the drug does not prolong the QT/QTc interval, then the conduct of the TQT study can wait until late Phase 2 clinical trials. Conversely, if the preclinical and early Phase 1 human data cannot rule out a QT/QTc prolongation, then it is wise to conduct the TQT study earlier, e.g. in late Phase 1. Last, if there is evidence for a QT/QTc prolongation, then either the drug development is stopped and there is no need to run a TQT study, either the drug development is still maintained and therefore the TQT study is needed in order to design which extensive ECG investigation should be planned for late Phase 2 trials.

Collecting ECG during the early Phase I clinical trials efficiently complement the preclinical data as it can identify trends for the prolongation of the QT/QTc interval and thus help defining when the TQT study should be done. By doing so, it is also important to recognize the need for exploring large ranges of dose in these first-in-human studies including the MTD, which not only help defining the supratherapeutic dose for the TQT study, but also allow the complete evaluation of concentration/QT prolonging effect relationship, which will further support the design of the TQT study.

With innovative study designs, optimal facilities and strong regulatory intelligence, SGS can favorably impact client’s drug development timelines and decision-making process.
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