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Early Investigation of QTc Liability
The Role of Multiple Ascending Dose (MAD) Study

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Abstract

The International Conference on Harmonization (ICH) guidance note E14 requires a thorough QT (TQT) study to characterize proactively the potential of a new drug to affect cardiac repolarization, as determined by prolongation of the corrected QT (QTc) interval. A typical TQT study is reviewed herein with a discussion on various practical issues concerning the use of a supratherapeutic dose, establishing assay sensitivity, the application of QT rate-correction methods, and restricting analyses of ECGs and plasma samples to key timepoints.

We then discuss, and provide examples of, how multiple ascending dose (MAD) study protocols can be modified to integrate robust ECG monitoring and analyses to gather key information provided by a TQT study. Among the main advantages of this approach are the ability to study the ECG effects of a wide range of doses to the maximum tolerated doses, eliminating routine analyses at unnecessary timepoints, making early go-no-go decisions, making phase II studies more efficient and, if necessary, being able to implement rigorous ECG monitoring in populations and pivotal studies of regulatory interest. If clear evidence for the presence or absence of QTc effect is found, the data from a modified MAD study may support a request for a waiver from the requirement to conduct a TQT study. In the event that a TQT study is considered unnecessary, there are obvious significant savings without compromising collection of vital safety data.

Drug-induced prolongation of the corrected QT (QTc) interval of the surface ECG has attracted considerable attention from clinicians, academics, regulators and the pharmaceutical industry since the early 1990s. A large number of drugs have been found to prolong this interval and induce a potentially fatal ventricular tachyarrhythmia, typically of the torsade de pointes type.[1] Not surprisingly, a number of otherwise beneficial drugs have been withdrawn from the market as a result of their QTc liability.[2]

In December 1997, the EU's scientific advisory body, the Committee on Proprietary Medicinal Products, adopted its ''Points to Consider'' document entitled ''*The Assessment of the Potential for QT Interval Prolongation by Non-Cardiovascular Medicinal Products*''.[3] Later, in May 2005, under the auspices of the International Conference on Harmonization (ICH), the regulatory authorities of the EU (European Medicines Agency), Japan (Pharmaceutical and Medical Devices Agency) and the US (FDA) adopted two internationally harmonized guidance notes, ICH S7B and ICH E14.[4,5] Whereas ICH S7B provides guidance on preclinical strategy, ICH E14 deals with the strategy for the clinical evaluation of the QTc liability of a drug.

Recognizing that the ICH E14 guidance may require revision with experience and advancing science, the ICH Steering Committee also established an Implementation Working Group which later issued a 'questions and answers' (Q&A) document in June 2008, providing clarity on aspects of the guideline that were ambiguous and responding to issues on which there were uncertainties.[6]

ICH E14 focuses on the need during drug development to conduct a 'thorough QT/QTc study', popularly referred to simply as a TQT study, which is typically conducted in healthy volunteers as the primary method for evaluating the potential effect of non-cardiac agents on cardiac repolarization.[5] The primary objective of ICH E14 is to determine whether a drug adversely affects cardiac repolarization sufficiently, as determined by prolongation of the QTc interval, to require intensive cardiac monitoring in later phase clinical trials or to evaluate the further development of the drug.

A centralized interdisciplinary review team (QT-IRT) was formed within the FDA Center for Drug Evaluation and Research to implement the ICH E14 guideline. The QT-IRT team includes clinical, pharmacology, statistical and clinical pharmacology reviewers who collaboratively provide expert advice to both the FDA's review divisions and to the sponsors on the design, analysis and interpretation of TQT studies. During 2006–11, the QT-IRT reviewed and provided advice on over 400 TQT study protocols, 250 reports and 400 other submission types (e.g. ECG monitoring proposals, TQT study waivers, meeting packages) [Garnett C, unpublished data]. Therefore, it is estimated that at present, the FDA reviews about 40–45 new TQT study reports per year. With the experience gained from these studies and advances in scientific knowledge, regulatory requirements and technical aspects of TQT studies have also evolved during this period.

1. A Typical Thorough QT (TQT) Study

Central to the conduct of an ICH E14-compliant TQT study are (i) the use of supratherapeutic doses to simulate in healthy volunteers the worst-case scenario in the patient population; and (ii) the use of a positive control with a QTc effect of 5–10 ms to establish assay sensitivity. Although ICH E14 does not specify the positive control to be used, a single oral dose of 400 mg of moxifloxacin is the most widely used agent for this purpose. The technical aspects of the design, analysis and interpretation of a TQT study have been reviewed previously by a number of authors.[7-12]

A typical TQT study is a parallel or crossover design study, depending on the pharmacokinetics of the new agent, usually employing four treatment arms (placebo, moxifloxacin, and the clinical and supratherapeutic doses of the investigational drug) administered in a randomized fashion to a study cohort, usually 50–60 subjects in a crossover, or 200–240 in a parallel-design study. Over the period, there has been an increasing shift towards crossover design studies. In a sample of 21 TQT studies reported in 2010, 8 (about 40%) had used parallel group design,[11] whereas in an unpublished analysis by one of the authors (RRS) of 75 TQT studies published as of June 2012, only 26 (approximately 35%) had used parallel group design. In a typical study, ECGs are recorded (using continuous digital 12-lead recorders) and corresponding plasma samples for measurement of parent drug and often metabolite concentrations are taken at pre-defined timepoints over a 24-hour period following a single dose or the first dose at steady state. A vast majority of TQT studies employ 10–12 such postdose timepoints, although a few have used fewer or greater than that number. The guidance recommends that a TQT study should characterize the effect of a drug on the QTc interval throughout the dosing interval and it emphasizes that care should be taken to perform ECG recordings at timepoints around the peak concentrations (C_{max}). It cautions, however, that time to reach C_{max} (t_{max}) does not always correspond to the time of peak effect on QTc interval. Although the primary focus is on QTc interval, all ECG intervals and wave form morphology should be analysed and reported.

ICH E14 recognizes the importance of correcting the measured QT interval for changes in heart rate (to derive rate-corrected QTc interval) and makes references to a number of approaches, including generic population-derived correction

formulae such as the Fridericia's correction (QTcF) and the Bazett's correction (QTcB), or correction formulae derived from the entire study population (QTcS) or calculated in each individual in the study (QTcI).

The primary endpoint of interest in a TQT study, determined from mean values of the study population, is the maximum time-matched, placebo-corrected change in QTc interval (ΔΔQTc). The primary statistical method of analysis is a non-inferiority intersection-union test (IUT) versus placebo to exclude a clinically significant effect. The threshold level of regulatory concern is set at a mean ΔΔQTc effect of about 5 ms, as evidenced by a 10 ms upper bound of the 95% confidence interval (CI) around the mean. The nominal determination of a drug as a potential QT-prolonger from the results of a TQT study is independent of whether the above threshold is breached at the therapeutic or supratherapeutic dose or at one timepoint or more following its administration. A drug is deemed to be devoid of a QT liability if the upper limits of one-sided 95% CIs around the mean ΔΔQTc are below 10 ms at *all* the timepoints ('negative TQT study'). When a TQT study is not negative (that is, if at least one of these upper bounds breaches the 10 ms threshold), the study is declared as a 'positive TQT study'. However, when the study is nominally positive because the threshold is breached at just one single timepoint, a concentration-response or pharmacokinetic/pharmacodynamic (PK/PD) analysis can provide valuable information concerning the drug's potential to prolong QTc interval. When the study is deemed to be positive, an increased risk of drug-induced proarrhythmia due to the drug cannot be precluded and this results in either (i) the termination of the development of a new compound if, regardless of the relatively small effect size, the sponsor perceives a significant regulatory hurdle;[11] or (ii) significant labelling restrictions on its use if a marketing application is approved.[1,13]

From the public health perspective, a false positive TQT study could result in denying deserving patients access to a potentially beneficial drug, either through restrictive labelling (typically contraindications) or the drug being dropped from further development. A simulation study has highlighted significant problems following the application of IUT in TQT studies, resulting in high false positive rates, particularly for inadequately powered parallel study designs when variability is large.[14] It has therefore been suggested that alternative analytical approaches such as PK/PD modelling could provide additional power to interpret a drug signal and evaluate the risks and benefits of the drug.[14,15]

Indeed, ICH E14 also recommends that an adequate drug development programme should ensure that the dose-response and generally the PK/PD relationship for QTc prolongation have been characterized, including exploration of effect at concentrations that are higher than those achieved following the anticipated therapeutic doses. In our experience, most TQT studies completed to date have complied with the recommendation. Garnett et al.[15] have described their experience with reviewing TQT studies and concluded that understanding the relationship, if any, between individual drug concentration and change in QTc interval provides important additional information to support the regulatory decision-making process. The PK/PD relationship has been suggested to provide a credible argument for *no effect* on QTc interval when the TQT study might be nominally positive, as explained earlier. Therefore, regulatory review of a TQT study by the FDA routinely includes characterization and evaluation of the PK/PD relationship when feasible. This information has also been used to predict QTc risk in subpopulations of special interest, to make dose adjustments, to identify lower, potentially safer doses that may warrant investigation for their efficacy and to construct informative drug labels. For drugs that prolong the QTc interval, the approval and labelling decisions are based to a large extent on dose- and concentration-QT relationships.[15]

2. Practical Issues Concerning the Conduct of TQT Studies

We discuss in this section certain practical issues that frequently arise with regard to the conduct and analysis of TQT studies.

2.1 Timing of the TQT Study During Drug Development

One frequent issue is determining when to conduct a TQT study during new drug development. As recommended in ICH E14, a TQT study cannot be conducted before the pharmacokinetics of the drug are characterized in phase I studies and its therapeutic dose determined, usually by the end of phase II studies. In the event a TQT study is positive and phase III studies are justified, intensive ECG monitoring is then required in phase III studies. This scenario positions a TQT study before phase III trials are initiated. In these pivotal trials with a positive TQT study agent, ICH E14 recommends that intense analyses of the ECG and adverse event data from certain patient subgroups are of particular interest. These include patients with:

- electrolyte abnormalities (e.g. hypokalaemia);
- congestive heart failure;
- impaired drug metabolizing capacity or clearance (e.g. renal or hepatic impairment, drug interactions);
- certain demographic characteristics (sex and age).

Since many of the above populations have usually already been studied as part of early-phase human pharmacology studies or are frequently excluded from phase III studies, there is a strong case for undertaking an early evaluation of the new drug's potential to prolong the QTc interval, beginning with phase I. This can be achieved efficiently by integrating intense ECG monitoring in early-phase clinical pharmacology studies, also enabling the sponsor to explore the clinical relevance of any preclinical signals and to make an early go-no-go decision.

2.2 Determining a Supratherapeutic Dose

Understandably, there are also questions concerning the selection of the multiple of the therapeutic dose that constitutes a reasonable supratherapeutic dose for use in the TQT study. The exact supratherapeutic dose selected can simply be the maximum tolerated dose (MTD) of the drug as determined from early-phase clinical pharmacology studies assuming that the MTD is correctly determined. If an MTD is not established, the selection of the supratherapeutic dose must ideally cover the concentration of the new drug likely to be encountered clinically under the worst-case scenario in the target population; such as following metabolic inhibition, food effect, hepatic or renal impairment, etc. In our experience, we have found that the investigators often opt for an arbitrary 3–5 times the therapeutic dose as the supratherapeutic dose when an MTD is not known.

2.3 Heart-Rate Correction to Derive Rate-Corrected QT (QTc) Interval

It has been shown that although the QT/RR relationship shows marked inter-individual variability, it is highly stable intra-individually[16-18] and the use of an inappropriate formula can give false results in the presence of substantial drug-related changes in heart rate.[19] Therefore, sponsors often seek advice on which is the most appropriate but cost-effective correction to apply. In the unpublished analysis of 75 published TQT studies referred to earlier, 32 (42%) had used QTcF correction, 31 (41%) used QTcI correction and 12 (17%) employed QTcS correction as the primary endpoint. Twenty-three studies had used only one correction (19 QTcF and 4 QTcI). Of the 39 TQT studies that had used QTcI (n = 27) or QTcS (n = 12) correction as the primary endpoint but also other secondary corrections, all 39 also employed QTcF correction as a secondary endpoint. Of the 13 TQT studies that had used QTcF correction as the primary endpoint but also other secondary corrections, 10 also employed QTcI correction as a secondary endpoint. Except in two studies (one on a drug that increased the heart rate by a mean of 23 beats per minute [bpm] and the other on a drug that had a glucose-lowering effect), all the remaining studies that used more than one correction have consistently reported that the results from different corrections were comparable although the QTcI values tended to be slightly lower (in the order of 2–3 ms). Beasley et al.[20] have also reported that statistical results using QTcI correction were similar to results using other QT correction methods that included QTcF correction and a

non-linear population-based QTcP formula. More recently, using QTcF correction as the primary method, Vandemeulebroecke et al.[21] prospectively set out in their TQT study with their investigational drug (BX471) to compare it with QTcB, QTcS, QTcI and sex-specific QTcS corrections, and reported that the estimates of QTc prolongation tended to be slightly smaller with QTcI correction than for the population-based corrections, with the corrections per sex in between them. The corrections based on the logarithmic method tended to yield slightly larger point estimates than those based on the linear or exponential method. Generally, the differences were small.

QTcI does provide more accurate information when there are large changes in heart rate; however, this is only true if QTcI is computed using drug-free data obtained over a wide range of heart rates. If it is computed based on the narrow range of resting heart rates, then QTcI will perform worse than population-based methods. It has also been claimed that the individual QT/RR relationship shows a residual variability, in part related to long-term autonomic changes, and that the QT/RR relationship might be modulated by the drug tested and, therefore, the QT/RR relationship obtained during the drug-free period in a given patient cannot necessarily be used as a fingerprint throughout a drug trial.[22]

2.4 Establishing Assay Sensitivity

The criteria for establishing assay sensitivity were clarified through the ICH E14 Q&A document referred to earlier.[6] Accordingly, the positive control must cause a significant effect on the QTc interval (defined as: the lower bound of the one-sided 95% CI of the placebo-corrected QTcF must be above 0 ms) and, furthermore, the study should be able to detect an effect of about 5 ms. Therefore, the most common statistical criteria used lately has been to use a positive control such as moxifloxacin with an effect size greater than 5 ms, and an effect significantly greater than 5 ms must be demonstrated. This is taken to mean that at least at one timepoint the lower bound of one-sided 95% CI of the mean moxifloxacin effect on ΔΔQTc should be above 5 ms. The Q&A document also points out that the effect of the positive control (magnitude of peak and time course) should be reasonably similar to its usual effect. After reviewing 20 TQT studies, Yan et al.[23] reported that the maximum moxifloxacin effect occurs in the time window between 1 and 4 hours postdose, and that the largest ΔΔQTcF occurs at 3 hours postdose in the crossover studies and at 4 hours in the parallel-design studies. These findings are consistent with an earlier proposal by Zhang[24] that the moxifloxacin-induced QTc effect can be evaluated between 1 and 4 hours after administration of a single 400 mg oral dose, that is, near the time of its peak plasma concentration (t_{max}) instead of all the 9–12 timepoints at which its QT effects are usually measured in a TQT study. Given the close relationship between plasma concentration and QTc effect of a drug,[25-28] this suggests that if the concentration and QTc effect of moxifloxacin during the 1–4 hours window are both of the expected magnitudes, it would be safe to assume that moxifloxacin concentrations versus time and QTc-effect versus time profiles are also reasonably similar to its usual profiles, whereby the increase in QTc interval peaks between 1 and 4 hours and dissipates after 8 hours.

2.5 QTc Data on Investigational Drug

There seems to be much redundancy in the amount of data collected over the 10–12 timepoints in a formal TQT study as conducted and analysed at present when investigating drugs with standard pharmacokinetics such as a t_{max} consistently within a few hours of dosing and lack of any electrophysiologically active metabolites. The use of 10–12 timepoints has been justified based on the need to (i) establish the 24-hour profile of the positive control used for assay sensitivity; (ii) provide enough timepoints to obtain a sufficient number of ECGs over a wide range of heart rates to adequately calculate the QTcI; and (iii) assess fully the exposures to the parent drug and its late-appearing metabolite(s), and capture any potentially delayed effects.[29,30] An unpublished analysis of a random sample of 30 published TQT studies by one of the present authors (RRS) indicates that for all the drugs concerned, the study

outcome, as determined by the largest ΔΔQTc (90% CI), was evident during the period of population-based t_{max} and three additional timepoints thereafter. This is not altogether too surprising since the effect of a drug on QTc interval most frequently is closely related to its concentration[25-28] and a lot of orally administered drugs have a t_{max} between 1 and 4 hours.[30] Neither are the authors aware of any regulatory or clinical use being made of the data collected outside this window, although the FDA has announced its interest in obtaining all of the continuous ECG data (not just around the nominal timepoints) to explore changes in ECG intervals and morphology between the preselected intervals. Zhang and Stockbridge[30] have commented in detail on the selection of timepoints for a TQT study. Since the determination of a TQT as a positive or negative study is based frequently on the result of a single timepoint, questions arise regarding the need to collect data at all the 10–12 timepoints over the 24-hour period. Furthermore, the risk of a false positive signal is also greater when evaluation of the effect involves a large number of timepoints, and it has been suggested previously that it might be sufficient to use substantially less than the numerous timepoints typically used in a TQT study,[31] especially if the above justifications for 10–12 timepoints do not apply to a particular study.

2.6 Cost of a TQT Study

One major concern, especially for small to medium sized pharmaceutical companies who are also at the forefront of developing novel medicines, is the cost of a TQT study. This of course varies with the study design, sample size, the number of ECGs collected and plasma concentrations measured. With the current designs, ECG datasets range in size from 2425 to 14 128 digitized ECGs per study, in populations that range in size from 31 to 181 subjects.[32] The main reason for the high costs associated with TQT studies is the highly technical methods applied to the analysis of a large number of ECG recordings. Although the cost of TQT studies is not generally discussed or its figure published, estimates vary, with one reliable source placing it at just over $US1 million.[33] Based on our experience, a realistic estimate for the current cost of a typical TQT study is likely between $US1 and 3 million, depending on the complexity of the study. While it is difficult to put a monetary value on important safety information, it is worth considering whether there are alternative approaches to gathering, at an earlier stage, the key information that a TQT study provides, which may then obviate the need for a TQT study (particularly if clear evidence for the presence or absence of QTc effect is found). As the rising costs threaten to make the development of new drugs increasingly unaffordable, Rawlins[34] has called for efforts to address this problem, recommending that all aspects of the drug discovery and development process be examined for potential cost savings. In one recent cost-effectiveness study, a TQT study has been reported to be highly cost ineffective in terms of clinical outcomes, given the less than satisfactory correlation between QT interval duration and QT-related proarrhythmias and their rarity.[35] Therefore, these cost concerns, especially those arising from analysis of ECGs and redundancy of much of the data gathered in a TQT study, provide an incentive to explore alternatives to gathering the same key information as provided by a formal TQT study but with a substantial reduction in costs.

3. Early-Phase Clinical Pharmacology Studies

According to ICH E14, alternatives to the use of the TQT study could include evaluation of the relationship between concentration and QT effect (PK/PD), or more intensive evaluation of ECGs during early-phase clinical studies. This provision affords a valuable opportunity of examining the potential for integrating the essential elements of a TQT study into early-phase clinical pharmacology studies where measurement of plasma concentrations of the drug are routine and the range of doses explored is much wider than those that can be explored in a formal TQT study. When adequately conducted, data from modified early clinical pharmacology studies may provide sufficient information to support a well reasoned request

Table I. Types of early-phase clinical pharmacology studies

Single ascending dose studies to determine pharmacokinetics and tolerance
Multiple ascending dose studies to steady-state to further characterize the pharmacokinetics and accumulation potential of the drug and determine the maximum tolerated dose
Drug-drug interaction studies
Food interaction studies
Special population studies (investigating the influence of race, age, sex and co-morbidities such as renal or hepatic dysfunction)
Enantiomer studies
Pharmacogenetic studies (focusing on polymorphic drug metabolizing enzymes)
Studies investigating inter-ethnic differences in pharmacology

for a waiver from the need to conduct a formal TQT study.

Table I shows the usual set of studies that constitute a typical clinical pharmacology programme during drug development. The sponsors of new drugs can maximize the efficiency of some of these studies, and potentially eliminate the need for a TQT study. The protocol of a clinical pharmacology study can be so modified as to enable collection of robust ECG and pharmacokinetic data to meet many of the objectives of a TQT study. In the opinion of the present authors, the study that lends itself ideally to this purpose is the multiple ascending dose (MAD) study conducted to steady state following administration of multiple doses to characterize further the pharmacokinetics of the drug. MAD studies invariably follow single ascending dose (SAD) tolerance studies in which the initial pharmacokinetic parameters (especially the t_{max} and half-life of the parent drug and its major metabolites at various single doses) would have already been characterized.

MAD studies are intended not only to characterize further the pharmacokinetics of the investigational drug and often its metabolites at several doses at steady state, accumulation potential and dose-concentration linearity or non-linearity but also to determine the MTD. A review of the protocols of 20 MAD studies on the clinical trials registry[36] by one of the authors (RRS) revealed these studies to be placebo-controlled but otherwise very heterogeneous in their designs. The number of doses used in these studies, typically from three to six doses, range from very low (potentially subtherapeutic) doses to the MTD. These studies may have complex designs but each subject, or a cohort of subjects, receives multiple doses of each dose to steady state during the study period. On average, these studies enrolled a total of 40 (range 25–72) subjects per study using several doses. By comparison, the number of subjects in a random sample of 24 published TQT studies of crossover design averaged 56 (range 31–117) subjects per study, a figure that compares well with an average sample size of 55 (range 19–124) reported by Yan et al.[23] in a review of moxifloxacin data from 14 crossover TQT studies usually using two doses of the investigational agent.

The two key features of MAD studies, namely use of more than one dose and plasma sampling for measuring concentration of the investigational drug and usually also its metabolites, are also two of the key elements of a TQT study. This similarity enables the design of the MAD study to be modified to include the recording of continuous 12-lead digital ECGs as is currently the practice in a TQT study. However, if it is intended to collect the required high-quality ECG data from a MAD study, it is critical that the sample size of the study is also adequate for the purpose. We discuss below how the efficiency of a typical MAD study could be maximized to characterize the QT liability of a new drug without compromising the pharmacokinetic objectives of the study but gathering the key safety information provided by a TQT study.

4. Using Robust ECG Monitoring in the Multiple Ascending Dose (MAD) Study

The ability of early-phase clinical pharmacology studies to characterize the QT liability of a drug has been demonstrated frequently and this approach is generally the one advocated for oncology drugs.

An early example of phase I studies, aimed at characterizing the QT liability of a non-oncology drug, included a double-blind, randomized, placebo-controlled, four-period, crossover study of sparfloxacin in 23 healthy volunteers.[37] This

single ascending dose study investigated the QT liability of sparfloxacin, administered in doses of 400, 800, 1200 and 1600 mg. Each period was separated by a 14-day washout period. Six volunteers received placebo during each period. 12-lead ECG, together with plasma samples for drug concentrations, were gathered predose and at 10 timepoints to 48 hours postdose. Primary endpoint was a change in QTcB interval. For each dose, increases in QTcB were apparent at 1.5 hours postdose. Both mean and the mean maximum changes in QTcB interval from baseline, corrected for placebo changes, increased in a dose-dependent manner and correlated with C_{max} (but not the overall exposure to the drug as defined by area under concentration-time curve). The QT liability of sparfloxacin, as determined from this single ascending dose study, was later confirmed in a loading dose/daily multiple dose steady-state study.[38] The results of both these studies are shown in table II. The ECG findings on cardiac repolarization were deemed sufficient to waive further detailed characterization of the QT interval effects of this agent before approval. The drug was subsequently withdrawn from most major markets of the world because of its phototoxicity as well as its cardiac QT liability.

The recently completed TQT study on citalopram using a titration schedule to test multiple doses within the same arm also illustrates the close similarities between a TQT study and a modified MAD study.[39] This study, the results of which led to a regulatory restriction in the maximum daily dose of citalopram to 40 mg, included a cohort of 119 subjects, of whom 93 completed the study. In a crossover design study, this cohort received moxifloxacin as well as placebo in addition to receiving gradually ascending doses of citalopram, beginning with daily doses of 20 mg for 9 days, 40 mg for 4 days and 60 mg for a further 9 days. Although the study employed 12 postdose timepoints at baseline, ECGs for determining treatment effects were monitored at only seven postdose timepoints over 24 hours on days 9 and 22.

We describe in the rest of this section how a modified MAD protocol may provide high-quality QTc data that may meet the key objectives of a TQT study, but earlier in the drug development process and with a reduced cost.

4.1 Heart-Rate Correction for the QT Interval to Derive QTc Interval

Although the use of QTcI does provide more accurate information when there are large changes in heart rate, it may be adequate for the purpose of a modified MAD study to apply only the Fridericia correction. A vast majority of the drugs do not affect the heart rate substantially and what constitutes a large increase in heart rate to preclude the use of QTcF correction is a matter of debate. However, in our experience, which is similar to that of others,[40] mean increases in heart rate of less than 6 bpm were associated with similar results following QTcF, QTcI and QTcS corrections. As discussed above in section 2.3, it is very uncommon for the use of QTcI instead of QTcF to make a significant difference to the

Table II. Clinical pharmacology studies and the effect of sparfloxacin on Bazett's corrected QT interval

Study design and results	400 mg	800 mg	1200 mg	1600 mg
Single ascending dose study[37]				
Baseline QTcB (ms)	398	398	398	397
Placebo-adjusted mean increase from baseline [ms (SE)]	16 (7)	33 (9)	49 (11)	55 (11)
Placebo-adjusted mean maximum increase from baseline [ms (SE)]	16 (8)	29 (11)	51 (12)	60 (12)
Multiple-dose study[38]	**Study day**	**200/100 mg**	**400/200 mg**	**800/400 mg**
Placebo-adjusted mean increase from baseline [ms (SE)]	Day 1	9 (5)	16 (5)	28 (5)
	Day 4	7 (6)	12 (6)	26 (6)
Placebo-adjusted mean maximum increase from baseline [ms (SE)]	Day 1	10 (5)	19 (5)	31 (5)
	Day 4	7 (6)	13 (6)	21 (6)

QTcB = Bazett's corrected QT interval; **SE** = standard error.

study being determined as positive instead of negative or vice versa. In the interest of practicality and cost effectiveness, we suggest therefore that the default correction method should be QTcF correction if there is sufficient preceding evidence of a lack of large drug-induced changes in heart rate. If a TQT study becomes necessary, it may be prudent to consider whether the use of QTcI correction is more appropriate.

4.2 Assay Sensitivity

Florian et al.[41] have also recently reported on the concentration-QT response of moxifloxacin on the QTcF interval from across 20 TQT studies submitted to the FDA. This analysis, using ΔΔQTcF, revealed an estimated mean slope of 0.0031 ms/ng/mL with a wide range from 0.0016 to 0.0048 ms/ng/mL. At present, therefore, we do not believe that the slope of the moxifloxacin concentration-QT response can be used on its own for establishing assay sensitivity, and cannot see an alternative to the traditional ICH E14 approach of using IUT. Given the current high standards of study designs and the technical advances, we do not believe there is any need for assay sensitivity. Following an analysis of 250 TQT studies, Zhang[42] reported that only 30 (12%) were inconclusive and, of these, less than half concerned the moxifloxacin time profile or magnitude of its effect. If assay sensitivity is judged to be necessary to establish the validity of the study conduct, then a single 400 mg oral dose of moxifloxacin and placebo can be administered to all subjects in a randomized, double-blind manner during days 1–3 of a 1-week run-in period in a random cohort in the MAD trial. Establishing assay sensitivity may be particularly important if a 'negative' MAD study is used to claim a waiver from the requirement to conduct a TQT study. Concerns regarding the power of the modified MAD study to establish assay sensitivity can be alleviated by enrolling 35–50 subjects during this run-in period of the study. During this period of moxifloxacin and placebo dosing, plasma samples, together with ECG data, can be collected as usual at all 10–12 timepoints following their administration. However, to establish assay sensitivity, analyses of plasma samples and ECGs could be restricted to the timepoints between 1 and 8 hours postdose so the statistical definition can be applied and the profile of the effect of moxifloxacin on QT interval for at least 8 hours is confirmed.

4.3 QTc Data on Investigational Drug

During the active treatment period, plasma samples, together with corresponding robust ECG data, can be collected in the cohort receiving the placebo and the active drug in a randomized, double-blind manner as usual at all 10–12 timepoints during the postdosing period on each ascending dose at steady state. Since the MAD study is intended to characterize the pharmacokinetics of the investigational drug, plasma samples would be analysed for the concentrations of the drug and its metabolite at all timepoints, as is customary in these studies, providing information on steady-state C_{max} and t_{max} at each dose. However, analysis of the ECGs may be restricted to t_{max} and three to four additional timepoints thereafter. Further analysis of ECGs at additional timepoints may be carried out only if warranted by preclinical data and the human pharmacokinetic data from the SAD and MAD studies.

4.4 Concentration-QT Response (Pharmacokinetic/Pharmacodynamic) Analysis

Experience with analysis of a large number of TQT studies has shown that analysis of concentration-QT response relationship is a more accurate and reliable approach to determining the QT liability of a drug at a whole range of clinical concentrations. In contrast, analysis of a TQT study by application of IUT suffers from failure to take concentration into account. Because the active treatment in the MAD study is administered across a whole range of doses from (possibly very) subtherapeutic to the MTD, this new approach of analysing the plasma samples and corresponding ECGs at only t_{max} and three to four additional timepoints thereafter should still provide a sufficiently large dataset for determination of a reliable PK/PD relationship of the

investigational drug across a very wide range of concentrations. If not, continuous ECG recording can be analysed for additional ECG data to enrich the PK/PD modelling.

4.5 Outlier Analysis

Although outlier analysis adds little to the conclusions drawn from drug effect on ΔΔQTc and PK/PD analysis as noted above, outlier analysis should also be restricted to those with new on-treatment QTc intervals >500 ms or those who develop an increase of >60 ms in QTc interval from baseline. There seems to be no value in analysing data by various categorical responses of no clinical relevance; specifically, the subjects developing on-therapy absolute QTc interval >450 ms or an increase of 30–60 ms from baseline. These responses are non-specific and very often seen on placebo. Since the effect of the drug on repolarization dissipates with decreasing plasma concentrations, the above recommended outlier analysis may also be restricted to the t_{max} and additional three to four timepoints thereafter. Outlier analysis restricted to a narrow time window of peak effects may be more sensitive than the current approach of analysis across the whole postdose period for a whole range of categorical responses.

A vast majority of the TQT studies concern orally administered products to which the above modifications can be applied without much effort. For products to be administered by other routes, the design of the MAD study can be modified to suit individual products on a case-by-case basis. ICH E14 encourages the investigational approach used for a particular drug to be individualized, depending on the pharmacodynamic, pharmacokinetic and safety characteristics of the drug, as well as its proposed clinical use.

4.6 Adequacy of Data from a Modified MAD Study

As stated above, there may be concerns that restricting the analysis of the effect of a drug to t_{max} and additional three to four timepoints thereafter may not provide adequate information concerning the exposure to metabolite-mediated effects on QT interval. As a general principle, drugs that lend themselves to such concerns have certain pharmacological features, usually identified well before the MAD study. These are: (i) preclinical studies may have signalled the potential of the metabolite to have an effect on cardiac repolarization; (ii) the metabolite is predominantly, if not exclusively, responsible for the QT effect of the drug; (iii) the metabolite circulates in sufficient concentration to exert the effect; and (iv) the t_{max} of the culprit metabolite consistently and significantly lags behind that of the parent drug (which must, of necessity, have a shorter half-life). If any of these features are identified, the window of ECG analysis can be appropriately extended in the modified MAD study. However, such compounds are very uncommon. Most drugs with a QT-prolonging metabolite are also the drugs that are by themselves QT-prolongers (e.g. astemizole, sertindole, halofantrine, citalopram) and the metabolite is either generally less potent than the parent drug[43] or is circulating at a concentration well below that required to exert an effect. Propoxyphene is a rare exception where the metabolite, norpropoxyphene, is as potent as the parent drug in inhibiting the human Ether-à-go-go Related Gene (hERG) channel.[44]

5. Example of a MAD Study Successfully Averting a TQT Study

Although the possibility of exploring the QT liability of a new drug during early-phase clinical pharmacology, and possibly replacing TQT studies with these data, has been discussed previously,[45] the present authors have been able to identify only one publication that systematically addressed this possibility by providing data.

Rohatagi et al.[46] pooled data from available SAD and MAD studies to construct population PK/PD response models, with *post hoc* predictions of concentration from a pharmacokinetic model. These studies had employed a customized robust QTc assessment with time-matched triplicate ECGs and centralized manual QTc reading. The results of population prediction of QTc prolongation were compared with available TQT study results, and the PK/PD response model was evaluated to determine whether it could establish

the QTc prolongation relationship without the TQT study results. Negative TQT study results confirmed negative simulation results from phase I/II PK/PD response models. Simulations were undertaken to characterize the ability of pooled PK/PD response modelling to obviate the need for a TQT study. These investigators concluded that PK/PD response modelling should be implemented as a standard part of modelling and simulation at different phases of drug development and used in conjunction with other data that influence the need and/or timing of a TQT study.

Clinically, a MAD study has been used successfully to characterize the QT liability of the opioid analgesic, propoxyphene,[47] and the need for a TQT study was averted on the basis of conclusive data from the MAD study. This MAD study, designed as a prelude to a proposed TQT study in order to identify an appropriate dose for use in that study, was a randomized, double-blind, placebo-controlled, sequential MAD study of propoxyphene for 11 days. The lowest proposed dose level of 600 mg/daily corresponded to the maximum clinically recommended dose. Other dose levels designated for administration in this MAD study were 900, 1200, 1500, 1800 and 2100 mg, with 2400 mg/day as the highest dose level. There was no positive control. There were six subjects in each treatment group.

The first two cohorts of volunteers completed dosing with 600 mg and 900 mg total daily doses, with subjects receiving one-third of the dose on day 1, half the dose on day 2 and the full dose on day 3 through day 11. This dose schedule was sufficient to attain steady-state exposures to propoxyphene on day 11 of the study. Subjects were monitored with telemetry (12-lead Holters) and intermittent ECG recordings, comparable to the monitoring that would take place during a TQT study. Pharmacokinetic sampling and ECG recording were made at 0 hours and at 10 timepoints during 12 hours postdose on days −1, 1, 4 and 11. Cohort 1 (600 mg dose) had to be repeated because of a dosing error. The results of these first two dosing cohorts indicated significant QTc interval prolongations with the 600 mg and 900 mg dose levels, as shown in table III. The planned testing of higher doses was discontinued as a result and it was determined that the proposed TQT study was not necessary. An exposure-response analysis demonstrated a significant linear relationship between norpropoxyphene concentration and ΔΔQTcF. The mean ΔΔQTcF for 600 mg was 16.8 ms with an upper 90% CI of 21.8 ms (values lower than those determined from the IUT-based analysis). The results of this MAD study, together with safety concerns related to propoxyphene overdoses, led to the withdrawal of this drug from the market.

Table III. Results from multiple ascending dose (MAD) study with propoxyphene

Treatment	Time (h)	ΔΔQTcF Mean effect [ms (90% CI)]
600 mg	7	29.8 (11.7, 47.9)
600 mg repeat	2	18.8 (–0.2, 37.9)
900 mg	2	38.2 (19.0, 57.4)

ΔΔQTcF = placebo-corrected change in Fridericia-corrected QTc interval.

6. Advantages of Robust ECG Monitoring in a MAD Study

In terms of efficiency in drug development, resource commitment and gathering the data required by ICH E14, robust ECG monitoring in a MAD study has many advantages if the sole objective of a TQT study is to identify those drugs that have a QTc-prolonging liability that breaches the threshold level of regulatory concern.

6.1 Efficient Drug Development

If the MAD study protocol is adequately modified and the sample size is sufficient, the sponsor may be relieved of having to recruit cohorts for two different studies; effectively combining key elements of two studies in one novel study. The data gathered may permit the sponsor to make 'go-no-go' decisions much earlier in the clinical development of the drug. If the drug is deemed to have a QTc liability and its development continued, the sponsor can implement effective ECG monitoring in other studies, including clinical

pharmacology studies, and usually would not be expected to require conducting a TQT study. More importantly, the investigational drug can be studied at doses across a wide range, including not only the MTD but also the lower than normal therapeutic doses, which may be more appropriate in special populations. Since the investigational drug is studied at a variety of doses, restricting ECG analyses to fewer critical timepoints is unlikely to compromise gathering PK/PD data across a wide range of concentrations. Furthermore, PK/PD relationships can be assessed not only for the parent drug but also for metabolites since metabolites are routinely measured in MAD studies (as with norpropoxyphene in the MAD study referred to in section 5). The use of continuous ECG recording is the key to being able to sample and add additional ECG data to cover new findings such as the PK of metabolites from multiple dosing.

Since phase II dose-response or therapeutic exploratory studies involve a relatively larger number of patients and a range of doses, at least one of these studies could also include intensive ECG monitoring, in addition to the routine pharmacokinetic blood sampling. This enables the QTc effect to be assessed concurrently in the same study as some key efficacy parameters to better delineate the benefit-risk of the drug and to confirm the QTc safety of the dose to be investigated in phase III studies. Thus, robust ECG monitoring in a MAD study also improves the efficiency of the entire drug development programme, including the dose-ranging studies.

6.2 Reduction in Costs

In the event that a TQT study is considered unnecessary because the data from the MAD study are robust enough, there are obvious significant savings without compromising collection of vital safety data by modifying a MAD study to include highly focused ECG monitoring. This approach also identifies the highest dose that is devoid of any significant QTc prolongation. Therefore, unless justified by the benefit-risk assessment of the drug concerned, doses higher than the lowest dose that prolongs QTc interval in this modified MAD study might not require investigation in phase II dose-ranging studies.

When the costs of separately conducting a MAD study and a TQT study are considered, and assuming that a TQT study is avoided, the modified MAD study results in overall reduction in costs. There are obvious savings in terms of (i) not having to collect plasma samples required in a TQT study, whereas this is the norm in a MAD study; and (ii) the proposed reduction in ECG analysis and moxifloxacin sampling at fewer timepoints in the MAD study. Moxifloxacin use in a MAD study does not impose any more costs since it would have had to be done if a TQT study was conducted. While a TQT study has been shown to be cost ineffective,[35] we cannot be certain that a modified MAD study is cost effective. The discussion on the cost effectiveness of a modified MAD study is beyond the scope of this paper and would require a formal study but we can be certain that it is less cost ineffective than a TQT study.

7. Conclusions

If robust continuous ECG monitoring is included in a MAD study, its design begins to approximate that of an ICH E14-compliant TQT study. MAD studies offer advantages of studying the effects of multiple administrations of a variety of doses up to MTDs and permit making crucial decisions early in the drug development.

The MAD study with adequate sample size per cohort trying to reach the MTD should have intense ECG and pharmacokinetic sampling (with use of moxifloxacin in one cohort if study conduct and/or ECG handling needs validation) to determine if there is any evidence of drug-related effect on QTc interval. The design should include pre-dose measurements followed by 10–12 timepoints, with analysis restricted to t_{max} and perhaps three to four additional timepoints thereafter depending on the pharmacology of the drug using continuous recorded digital ECGs and simultaneous plasma sample measurements.

If clear evidence for an effect on QTc effect is found, the sponsor should consider the benefit-risk

of the drug, taking into account the effect size, all available chemical, preclinical and clinical evidence, and make an early go-no-go decision. If the development of drugs with a positive effect on QTc interval in MAD studies is to be continued, PK/PD data from a MAD study enables a suitable therapeutic dose devoid of a significant QTc effect to be identified for phase II dose-response studies, and intense cardiac safety monitoring in all future trials should be instituted without the need for a TQT study.

We estimate that the sensitivity/specificity of a negative intense MAD study will at best be 80–85% given the power we propose (increase sample sizes but not enough to drive costs substantially or to mimic a TQT study). Therefore, a negative MAD study will not automatically qualify for a waiver from a TQT study. The concentration-QT response relationship obtained from a modified MAD study (flat slope) would be a fairly powerful argument against having to conduct a TQT study, especially if this analysis excludes a 10 ms effect at high exposures. For the regulators to feel confident in granting a TQT study waiver on the basis of a negative MAD study, they are likely to require data correlating the results of a negative MAD study with a subsequent TQT study on a few drugs. Clear evidence for lack of an effect on QTc effect, even at the MTD with adequate sample size and with the design as suggested, may support a request for a waiver from the requirement to conduct a TQT study, depending on the robustness of the design and taking into account the effect size, available preclinical data and additional clinical evidence such as regular monitoring of routine ECGs in a phase II study.

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References

1. Shah RR. The significance of QT interval in drug development. Br J Clin Pharmacol 2002; 54: 188-202
2. Shah RR. If a drug deemed 'safe' in nonclinical tests subsequently prolongs QT in phase 1 studies, how can its sponsor convince regulators to allow development to proceed? Pharmacol Ther 2008; 119: 215-21
3. Committee for Proprietary Medicinal Products. Points to consider: the assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products (CPMP/986/96). London: EMEA, 1997 Dec 17 [online]. Available from URL: http://www.fda.gov/ohrms/dockets/ac/03/briefing/pubs/cpmp.pdf [Accessed 2012 Jan 26]
4. Committee for Medicinal Products for Human Use. ICH note for guidance on the nonclinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals (ICH S7B) [CHMP/ICH/423/02]. London: EMEA, 2005 Nov [online]. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002841.pdf [Accessed 2012 Jan 26]
5. Committee for Medicinal Products for Human Use. ICH note for guidance on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs (ICH E14) [CHMP/ICH/2/04]. London: EMEA, 2005 Nov [online]. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002879.pdf [Accessed 2012 Jan 26]
6. Committee for Medicinal Products for Human Use. ICH Topic E14: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs Questions and Answers (EMEA/CHMP/ICH/310133/2008). EMEA, London, June 2008 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002878.pdf [Accessed on 2012 Jan 26]
7. Shah RR. Drugs, QT interval prolongation and ICH E14: the need to get it right. Drug Saf 2005; 28: 115-25
8. Beasley Jr CM, Dmitrienko A, Mitchell MI. Design and analysis considerations for thorough QT studies employing conventional (10 s, 12-lead) ECG recordings. Expert Rev Clin Pharmacol 2008; 1: 815-39
9. Darpo B. The thorough QT/QTc study 4 years after the implementation of the ICH E14 guidance. Br J Pharmacol 2010; 159: 49-57
10. Malik M, Garnett CE, Zhang J. Thorough QT Studies: questions and quandaries. Drug Saf 2010; 33: 1-14
11. Salvi V, Karnad DR, Panicker GK, et al. Update on the evaluation of a new drug for effects on cardiac repolarization in humans: issues in early drug development. Br J Pharmacol 2010; 159: 34-48

12. Morganroth J. Cardiac repolarization and the safety of new drugs defined by electrocardiography. Clin Pharmacol Ther 2007; 81: 108-13
13. Shah RR. Drug-induced prolongation of the QT interval: regulatory dilemmas and implications for approval and labelling of a new chemical entity. Fundam Clin Pharmacol 2002; 16: 147-56
14. Hutmacher MM, Chapel S, Agin MA, et al. Performance characteristics for some typical QT study designs under the ICH E14 guidance. J Clin Pharmacol 2008; 48: 215-24
15. Garnett CE, Beasley N, Bhattaram VA, et al. Concentration-QT relationships play a key role in the evaluation of proarrhythmic risk during regulatory review. J Clin Pharmacol 2008; 48: 13-8
16. Malik M, Färbom P, Batchvarov V, et al. Relation between QT and RR intervals is highly individual among healthy subjects: implications for heart rate correction of the QT interval. Heart 2002; 87: 220-8
17. Batchvarov VN, Ghuran A, Smetana P, et al. QT-RR relationship in healthy subjects exhibits substantial intersubject variability and high intrasubject stability. Am J Physiol Heart Circ Physiol 2002; 282: H2356-63
18. Malik M, Hnatkova K, Batchvarov V. Differences between study-specific and subject-specific heart rate corrections of the QT interval in investigations of drug induced QTc prolongation. Pacing Clin Electrophysiol 2004; 27: 791-800
19. Malik M. The imprecision in heart rate correction may lead to artificial observations of drug induced QT interval changes. Pacing Clin Electrophysiol 2002; 25: 209-16
20. Beasley Jr CM, Mitchell MI, Dmitrienko AA, et al. The combined use of ibutilide as an active control with intensive electrocardiographic sampling and signal averaging as a sensitive method to assess the effects of tadalafil on the human QT interval. J Am Coll Cardiol 2005; 46: 678-87
21. Vandemeulebroecke M, Lembcke J, Wiesinger H, et al. Assessment of QTc-prolonging potential of BX471 in healthy volunteers: a 'thorough QTc study' following ICH E14 using various QT correction methods. Br J Clin Pharmacol 2009; 68: 435-46
22. Extramiana F, Maison-Blanche P, Badilini F, et al. Individual QT-R-R relationship: average stability over time does not rule out an individual residual variability: implication for the assessment of drug effect on the QT interval. Ann Noninvasive Electrocardiol 2005; 10: 169-78
23. Yan LK, Zhang J, Ng MJ, et al. Statistical characteristics of moxifloxacin-induced QTc effect. J Biopharm Stat 2010; 20: 497-507
24. Zhang J. Testing for positive control activity in a thorough QTc study. J Biopharm Stat 2008; 18: 517-28
25. Kimura M, Umemura K, Ikeda Y, et al. Pharmacokinetics and pharmacodynamics of (+/−)-sotalol in healthy male volunteers. Br J Clin Pharmacol 1996; 42: 583-8
26. van Haarst AD, van 't Klooster GA, van Gerven JM, et al. The influence of cisapride and clarithromycin on QT intervals in healthy volunteers. Clin Pharmacol Ther 1998; 64: 542-6
27. Abernethy DR, Wesche DL, Barbey JT, et al. Stereoselective halofantrine disposition and effect: concentration-related QTc prolongation. Br J Clin Pharmacol 2001; 51: 231-7
28. Somberg JC, Preston RA, Ranade V, et al. QT prolongation and serum sotalol concentration are highly correlated following intravenous and oral sotalol. Cardiology 2010; 116: 219-25
29. Morganroth J. Response to "Design of the 'thorough QT study'". Clin Pharmacol Ther 2008; 83: 529-30
30. Zhang J, Stockbridge N. Selection of the time points for a thorough QTc study. Drug Inform J 2011; 45: 713-5
31. Darpo B, Sager P. Design of the "thorough QT study". Clin Pharmacol Ther 2008; 83: 528-9
32. Kligfield P, Green CL, Mortara J, et al. The Cardiac Safety Research Consortium electrocardiogram warehouse: thorough QT database specifications and principles of use for algorithm development and testing. Am Heart J 2010; 160: 1023-8
33. Tyl B, Kabbaj M, Fassi B, et al. Comparison of semi-automated and fully automated methods for QT measurement during a thorough QT/QTc study: variability and sample size considerations. J Clin Pharmacol 2009; 49: 905-15
34. Rawlins MD. Cutting the cost of drug development? Nat Rev Drug Discov 2004; 3: 360-4
35. Bouvy JC, Koopmanschap MA, Shah RR, et al. The cost-effectiveness of drug regulation: the example of thorough QT/QTc studies. Clin Pharmacol Ther 2012; 91: 281-8
36. ClinicalTrials.gov, a service of the US National Institutes of Health [online]. Available from URL: http://clinialtrials.gov [Accessed 2012 Mar 10]
37. Morganroth J, Talbot GH, Dorr MB, et al. Effect of single ascending, supratherapeutic doses of sparfloxacin on cardiac repolarization (QTc interval). Clin Ther 1999; 21: 818-28
38. Morganroth J, Hunt T, Dorr MB, et al. The cardiac pharmacodynamics of therapeutic doses of sparfloxacin. Clin Ther 1999; 21: 1171-81
39. Food and Drug Administration, Center for Drug Evaluation and Research. Celexa (citalopram hydrobromide): review of applications no: 020822Orig1s038, s040 and 021046Orig1s016, s017. Silver Spring (MD): FDA, 2011 Aug 12 [online]. Available from URL: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/020822Orig1s038s040_021046Orig1s016s017Rev.pdf [Accessed 2012 Jan 26]
40. Garnett CE, Zhu H, Malik M, et al. Methodologies to characterize the QT/corrected QT interval in the presence of drug-induced heart rate changes or other autonomic effects. Am Heart J 2012; 163: 912-30
41. Florian JA, Tornøe CW, Brundage R, et al. Population pharmacokinetic and concentration-QTc models for moxifloxacin: pooled analysis of 20 thorough QT studies. J Clin Pharmacol 2011; 51: 1152-62
42. Zhang J. Novel approaches to TQT study design and analysis. A presentation at the 3rd DIA Cardiac Safety Workshop; 2012 May 28-29; Tokyo
43. Shah RR. Drug-induced QT interval prolongation regulatory guidance and perspectives on hERG channel studies. In: Chadwick J, Goode J, editors. The hERG potassium channel: structure, function and long QT syndrome. (Novartis Foundation Symposium No. 266.) Chichester: Wiley Publications, 2005: 251-85

44. Ulens C, Daenens P, Tytgat J. Norpropoxyphene-induced cardiotoxicity is associated with changes in ion-selectivity and gating of HERG currents. Cardiovasc Res 1999; 44: 568-78

45. Shah RR, Morganroth J. Evaluating the QT-liability of a drug during its development. Pharm Med 2008; 22: 151-64

46. Rohatagi S, Carrothers TJ, Kuwabara-Waqq J, et al. Is a thorough QTc study necessary? The role of modeling and simulation in evaluating the QTc prolongation potential of drugs. J Clin Pharmacol 2009; 49: 1284-96

47. Food and Drug Administration. Darvon (propoxyphene): Multiple Ascending Dose (MAD) study review submission number: SDN 039/040, 3 September 2010. Silver Spring (MD): FDA, 2011 Aug 12 [online]. Available from URL: http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM234330.pdf [Accessed 2012 Mar 4]

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