celerion
Translating Science to Medicine

White Paper

Best Practices for Evaluating Clinical Proarrhythmia Risk in Early Drug Development

- **Sabina Paglialunga, PhD** Associate Director, Scientific Affairs
- **Julie Grenier, PhD** Associate Director, Clinical Pharmacology and Pharmacometrics
- **Bruce H Morimoto, PhD** Vice President, Scientific Affairs
- **Robert M Lester, MD FACC** Chief Cardiologist & Global Medical Director, Early Clinical Research

The Choice is Yours

Drug developers face many challenges bringing a new therapeutic product to market. Achieving a low/acceptable potential for proarrhythmic risk is one such hurdle. Since 2005, a dedicated Thorough QT (TQT) study was required for most investigational products to conform with the International Council for Harmonization of Technical Requirement for Pharmaceuticals for Human Use (ICH) E14 guidelines [1]. More recently, new guidance adopted by the FDA in 2017 gives drug developers the choice between a traditional TQT study or an exposure-response modeling approach regressing time-matched ECG data against pharmacokinetic measurements to examine proarrhythmia risk [2]. Clinical pharmacology is founded on understanding the relationship between dose, exposure, and response. The assessment of cardiac risk also follows this basic principle, and Phase I studies conducted in early clinical development present an opportunity to explore a variety of drug doses across a broad range of exposures which may never be subsequently tested. This broad spectrum of drug exposure is ideal to evaluate the potential for cardiac liability. To this end, the single-ascending dose (SAD) Phase I study which typically explores three or more escalating drug dose regimens provides an excellent opportunity to evaluate exposure-response (ER) relationships. The option to choose between clinical approaches for risk assessment can impact study design, timelines and development costs. This review will highlight the similarities, differences and best practices for proarrhythmia risk assessment for both approaches.

A Dedicated TQT Study

A typical TQT study design has four study arms; the investigational product is administered at both a therapeutic and supra-therapeutic dose, while the latter two arms comprise a placebo and positive control group. Moxifloxacin is a quinolone antibiotic used to treat bacterial infections, as it is a well-defined producer of QT lengthening and the most common positive control for TQT studies. As noted above, the therapeutic dose must be established prior to commencing a dedicated TQT, therefore this study is often performed later in drug development usually after Phase II trials. The supra-therapeutic dose or highest clinically relevant exposure refers to the 'worst case' scenario; and reflects the increased plasma drug concentrations that may be observed based upon intrinsic and extrinsic factors. These include food effects, drug-drug interactions or related to patients with renal insufficiency or hepatic impairment. If not dictated by earlier studies, this dose is recommended to be 3-5 times the clinically relevant exposure [3].

TQT studies are typically analyzed using a by time point analysis employing the Intersection Union Test (IUT). The threshold of regulatory concern in a TQT trial is a drug-induced effect on the heart rate corrected QT interval (QTc) beyond an upper bound limit of 10 msec while the one-sided upper 95% confidence interval (CI) for the mean difference in baseline corrected QTc of the drug and the baseline corrected time-matched placebo must be below this value for all time points for a negative finding. Values above 10 msec are deemed a positive test and indicate potential QT liability that may require further investigation like ECG monitoring in Phase III clinical studies.

Both parallel and crossover study designs are acceptable for a dedicated TQT study, and the choice of one approach over the other depends on drug half-life, the presence of metabolites, and the potential for carry-over effects and posology. Typically, sample sizes can range from 40-80 participants for a crossover design and up to four times as many individuals in a 4-way parallel group study design. While modified study designs may lower sample size [4], a designated TQT study remains a resource intensive, and costly undertaking [5].

Study design consideration:
Best practice suggests at least 3 time points around the maximum concentration (C_{max}) to ensure ample data collection.

Applying QTc Exposure Response Modeling in a Phase I Study

Prior to gaining regulatory acceptance as an alternative method to the TQT, ER modeling of intensive ECG data collection studies were vigorously examined in a number of clinical trials to establish assay sensitivity, sample size, and false positive and false negative rates [6-8]. Through simulation and modeling of moxifloxacin data from a standard TQT study, several groups have concluded that 8-9 subjects is sufficient to detect a drug-induced QTc prolongation [7, 8]. This sample size is typical for a SAD study and pooling placebo controls across investigated doses to achieve a minimum of 6 subjects is sufficient for ER modeling of the data [7]. Moreover, subanalysis from five TQT studies with a sample size of 9 on active drug and 6 on placebo modeled false negative rate of 5% or lower from moxifloxacin exposure and other drugs with a large QTc effect [9]. Finally, results from a canonical prospective study from the Consortium for Innovation and Quality in Pharmaceutical

Development and the Cardiac Safety Research Consortium (CSRC) examined 5 known marketed drugs with documented QTc prolongation above the 10 msec threshold of regulatory concern (ondansetron, quinine, dolasetron, moxifloxacin, and dofetilide) and 1 drug which had no QT prolonging effects (levocerterizine). The protocol was a 2-dose, SAD-like study design employing ER analysis as the primary analysis tool. The results determined that intensive QT assessment in early phase clinical development is an appropriate alternative and could replace a dedicated TQT trial [6].

To achieve high-quality results from intensive ECG monitoring in Phase I studies, a number of parameters need to be strictly controlled, such as standardization of extraction time points, subject positioning, meals and physical activity. 12-lead continuous digital ECG recordings using a Holter device are preferred in lieu of discrete ECG collection by a bedside electrocardiograph as replicate ECGs can be readily extracted at pre-specified time points with optimal signal-to-noise ratio. For best practices, serial recordings should be obtained at baseline (pre-dose) and over 6-15 time points post-dose in order to capture the anticipated drug or metabolite C_{max}. Prior to a first in-human (FIH) study, the C_{max} and T_{max} can be estimated from preclinical results or physiologically-based pharmacokinetic (PBPK) modeling. In addition, time-matched ECG and plasma samples with low drug or metabolite concentration should also be captured, for most investigational products this is typically ~24 hours post dose.

Dose escalating ER modeling:
Having sufficient paired ECG-PK measurements is crucial for data modeling purposes. A higher rate of false negatives may be inferred when the time to maximum concentration (T_{max}) sample was missing from the model [7].

In a typical SAD study at least 3 or more dose levels are explored potentially up to the maximal tolerated dose (MTD), which generally represents the widest exposure range that will be studied during drug development. This permits a large range in drug concentrations for ER modeling. Although the threshold of regulatory concern is still considered to be 10 msec, the conclusions from an ER analysis are not as dichotomous as the results obtained from a TQT study (positive/negative) based on 2 dose levels. A negative QTc effect finding may be concluded when the upper bound of the two-sided 90% CI estimated by ER is less than 10 msec at the highest clinical relevant exposure [10]. In order to potentially obtain a TQT waiver, “multiples” of exposure must be assessed during the early phase study to fulfill assay sensitivity [1]. Most often, twice the highest clinically relevant exposure is sufficient to meet this criterion. In addition, more than one study result can be combined assuming homogeneous subject conduct for exposure response analysis if ample exposure is not achieved from the SAD alone. Alternatively, when exposures do not reach at least twice the “worst case scenario” the use of a positive control may be introduced into the study design. Finally, intensive ECG monitoring should be incorporated into a multiple ascending dose (MAD) study if the MTD is not achievable; or the investigational product or a metabolite accumulates; or displays non-linear or a time-dependent PK profile.

Statistical assessment of ER modeling:
Our recently published review article on QTc ER model types and analysis describes the clinical and statistical considerations for ECG data modeling. A link to the review can be found on our webpage: https://www.celerion.com/other-resources

Subject Characteristics

An early phase SAD or MAD study will typically enroll healthy participants and exclude participants with marked baseline QT/QTc prolongation, a history of cardiovascular disease, or the use of concomitant medication that prolongs the QT/QTc interval. These criteria are similar to the guidelines outlined by the ICH E14 for subject enrollment in a TQT study [1]. Comprehensive participant cardiovascular work up is recommended prior to enrollment in an SAD/MAD protocol with careful review of any history, exam or ECG findings that would disqualify a participant from enrollment. Twelve- to 24-hour baseline telemetry may also be employed to exclude participants with underlying arrhythmias. A TQT study and intensive ECG data collection can be performed in both genders, since it is unlikely that baseline demographic parameters would introduce large differences in QT drug response. Vicente et al. recently examined the role of gender in QTc prolongation in a double-blind, 5-way crossover study with 11 male and 11 female subjects. Drug-induced QTc elongation was observed with dofetilide, quinidine and ranolozine yet no sex difference was reported after adjusting for differences in exposure [11]. Kannannkeril et al. also observed no sex effect in a large study of 253 participants (153 were women) examining QTc prolongation upon intravenous ibutilide administration [12], a drug known to prolong QTc [13]. Interestingly, the authors did report that the magnitude of change in ibutilide-induced QTc prolongation was greater in obese and overweight participants than underweight or normal groups. Although, the influence of body mass index (BMI) on increasing the QTc interval has been reported in a number of previous studies [14-16], it is thought that drug-induced QTc prolongation may be related to the absolute dose given when based on body weight, autonomic tone, or sympathetic drive associated with elevated free-fatty acids in this population [12]. Therefore, adhering to weight and BMI exclusion criteria is an important aspect to mitigate against a false positive ECG signal.

QTc ER Modeling and Disease States

It is widely recognized that therapies for oncology have benefited the most from the ER modeling approach. As a standard TQT study requires the administration of doses covering for both therapeutic

and supra-therapeutic exposures, it is rare if not impossible or unethical to reach this level of exposure of oncology drugs in healthy participants. Therefore, time-matched PK samples with triplicate ECGs acquired during Phase II and III studies of patients, coupled with ER modeling is the most optimal approach to evaluate a compound's cardiac liability.

Another area of interest involves studies with diabetes patients. Cardiovascular disease is the leading cause of death for patients with type 2 diabetes mellitus; a chronic metabolic disorder associated with impaired glucose handling and insulin resistance. Hypoglycemia, an adverse event caused by some glucose-lowering drugs, may lead to QT/QTc prolongation and is a risk factor for potentially fatal ventricular arrhythmias. Moreover, diabetes patients tend to display prolonged QT/QTc compared to healthy participants and therefore may be at greater risk of proarrhythmia when exposed to a QT-prolonging drug (reviewed in [17]). Therefore, glucose-lowering agents should undergo rigorous cardiodynamic and cardiovascular safety monitoring throughout all phases of drug development. A summary of TQT studies of antidiabetic drugs reviewed by the FDA's QT-IRT (2006-2013) prior to the ICH E14 revisions in 2015, revealed good concordance between the standard TQT analysis and ER relationship [17]. Nonetheless, due to the stringent cardiodynamic assessments required for antidiabetic medication, nearly all drug developers, despite the updated ICH E14 guidance still elect to conduct a designated TQT study. There are exceptions, however; recently some antidiabetic drug development programs include ER modeling in early clinical phase protocols. In a SAD and MAD healthy participant study, intensive ECG collection matched with PK analysis was examined to evaluate the proarrhythmia risk of omarigliptin, a once-weekly DPP-4 inhibitor [18]. Based on ER modeling, a 2.8 msec QTc prolongation was predicted for plasma (C_{max}) of 10 µM, a QTc value below the threshold of concern. These initial results were confirmed by a TQT study conducted later in development [19].

TQT vs Exposure Response Modeling – How Do They Stack Up

One of the key elements when running a TQT study is selection of the therapeutic and supra-therapeutic dose. Sufficient clinically relevant information including PK, safety and efficacy is needed to determine these doses. The timing of when to conduct the TQT study is important to gain insight into the compound's cardiac liability prior to committing additional resources in later stage clinical studies. However, if insight about QT risk can be gained in Phase I, go/no-go decisions or at least the integrated risk assessment can be made early in the drug development process.

It is important to understand that QT risk assessment needs to be evaluated in the context of accumulating clinical data. Pitolisant, a novel H3-receptor antagonist/inverse agonist was investigated for the use in narcolepsy and potentially in epilepsy, excessive diurnal somnolence, attention deficit hyperactivity disorder, dementias, and schizophrenia. PK and clinical data had raised the question whether the worst-case scenario would cover the 120 mg supra-therapeutic dose that was used in the TQT study. A SAD study covering 3 supra-therapeutic dose levels and a moxifloxacin arm was conducted and ER analysis performed in order to supplement the results from the TQT study [20]. The analytical application of IUT made the comparison between the results of the 2 studies rather difficult as 1) a SAD type study was not powered for such a statistical analysis, and 2) the dose levels were different. However, the ER analysis was performed post-hoc on the TQT study data thereby allowing for direct comparison. The authors concluded that the need for a TQT study could have been obviated by the SAD study, adding to the growing body of evidence that intensive ECG monitoring early in drug development may enable waiving the need for a full TQT study.

In addition, under certain situations, a TQT study design is not appropriate and modeling is the only option for QT exposure analysis. These special cases include safety or tolerability concerns, or practical issues that preclude examination in healthy participants. One caveat to the early phase exposure-response paradigm is that the clinically relevant dose may not be known in the FIH study, and metabolites may not be well characterized at that time, which may require future SAD/MAD studies or a dedicated TQT to establish cardiac safety. Nonetheless, there are now two study paradigm options to evaluate a drug's potential for proarrhythmic potential and cardiac liability; a dedicated TQT or early phase ER modeling, giving drug developers a choice on how to best proceed with their program.

Conclusion

Pharmaceutical and regulatory stakeholders have historically acknowledged that the dedicated TQT study, conducted late in drug development, is costly and resource intensive. Preclinical initiatives such as the Comprehensive in vitro Proarrhythmic Assessment (CiPA) [21-23], a mechanistic approach to proarrhythymic risk, involves multiple ion channel assessment, in silico computer modeling, and testing the drug's effect on induced pleuripotent stem cell cardiac myocytes. The profile of a drug's cardiac liability can be assessed by combining the knowledge gained from this more comprehensive preclinical testing strategy with the knowledge gained from exposure-response analysis in FIH studies. While concentration-effect modeling in FIH trials is still regarded as an "alternative" or "option" to a traditional TQT study, it has the advantage of significantly reducing cost and timelines during drug development thereby facilitating earlier go/no-go decisions, and may even obviate the need to perform a traditional TQT trial. Importantly, understanding cardiac risk of a new chemical entity early in drug development has advantages in being able to evaluate risk-benefit during the continuum of drug testing. This new paradigm is rapidly becoming a routine part of the conversation with pharmaceutical companies as they plan their early drug development program

References

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs E14. 2005. https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E14/E14_Guideline.pdf.
2. Food and Drug Administration. FDA Guidance for Industry E14 (2017) Clinical Evaluation of QT/QTc Interval Prolongation for Non-Antiarrhythmic Drugs – Questions and Answers (R3). 2017. https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm073161.pdf.
3. Lester RM, Olbertz J. Early drug development: assessment of proarrhythmic risk and cardiovascular safety. Expert Rev Clin Pharmacol. 2016;9(12):1611-8.
4. Ring A, Brand T, Macha S, Breithaupt-Groegler K, Simons G, Walter B et al. The sodium glucose cotransporter 2 inhibitor empagliflozin does not prolong QT interval in a thorough QT (TQT) study. Cardiovasc Diabetol. 2013;12:70.
5. Bouvy JC, Koopmanschap MA, Shah RR, Schellekens H. The cost-effectiveness of drug regulation: the example of thorough QT/QTc studies. Clin Pharmacol Ther. 2012;91(2):281-8.
6. Darpo B, Garnett C, Keirns J, Stockbridge N. Implications of the IQ-CSRC Prospective Study: Time to Revise ICH E14. Drug Saf. 2015;38(9):773-80.
7. Ferber G, Lorch U, Taubel J. The Power of Phase I Studies to Detect Clinical Relevant QTc Prolongation: A Resampling Simulation Study. Biomed Res Int. 2015;2015:293564.
8. Panicker GK, Karnad DR, Kadam P, Badilini F, Damle A, Kothari S. Detecting moxifloxacin-induced QTc prolongation in thorough QT and early clinical phase studies using a highly automated ECG analysis approach. Br J Pharmacol. 2016;173(8):1373-80.
9. Ferber G, Zhou M, Darpo B. Detection of QTc effects in small studies--implications for replacing the thorough QT study. Ann Noninvasive Electrocardiol. 2015;20(4):368-77.
10. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Implementation Working Group ICH E14 Guideline. The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. Q&A R3 2015. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E14/E14_Q_As_R3__Step4.pdf.
11. Vicente J, Johannesen L, Mason JW, Pueyo E, Stockbridge N, Strauss DG. Sex differences in drug-induced changes in ventricular repolarization. J Electrocardiol. 2015;48(6):1081-7.
12. Kannankeril PJ, Norris KJ, Carter S, Roden DM. Factors affecting the degree of QT prolongation with drug challenge in a large cohort of normal volunteers. Heart Rhythm. 2011;8(10):1530-4.
13. Murray KT. Ibutilide. Circulation. 1998;97(5):493-7.
14. Arslan E, Yiginer O, Yavasoglu I, Ozcelik F, Kardesoglu E, Nalbant S. Effect of uncomplicated obesity on QT interval in young men. Pol Arch Med Wewn. 2010;120(6):209-13.
15. Li W, Bai Y, Sun K, Xue H, Wang Y, Song X et al. Patients with metabolic syndrome have prolonged corrected QT interval (QTc). Clin Cardiol. 2009;32(12):E93-9.
16. Vardar SA, Ozturk L, Altun A, Turan N. Ventricular repolarization in overweight and normal weight healthy young men. Anadolu Kardiyol Derg. 2008;8(1):27-31.
17. Heller S, Darpo B, Mitchell MI, Linnebjerg H, Leishman DJ, Mehrotra N et al. Considerations for assessing the potential effects of antidiabetes drugs on cardiac ventricular repolarization: A report from the Cardiac Safety Research Consortium. Am Heart J. 2015;170(1):23-35.
18. Krishna R, Addy C, Tatosian D, Glasgow XS, Gendrano Iii IN, Robberechts M et al. Pharmacokinetics and Pharmacodynamics of Omarigliptin, a Once-Weekly Dipeptidyl Peptidase-4 (DPP-4) Inhibitor, After Single and Multiple Doses in Healthy Subjects. J Clin Pharmacol. 2016;56(12):1528-37.
19. Tatosian DA, Cardillo Marricco N, Glasgow XS, DeGroot B, Dunnington K, George L et al. A Thorough QTc Study Confirms Early Pharmacokinetics/QTc Modeling: A Supratherapeutic Dose of Omarigliptin, a Once-Weekly DPP-4 Inhibitor, Does Not Prolong the QTc Interval. Clin Pharmacol Drug Dev. 2016;5(5):383-92.
20. Shah RR, Maison-Blanche P, Robert P, Denis E, Duvauchelle T. Can an early phase clinical pharmacology study replace a thorough QT study? Experience with a novel H3-receptor antagonist/inverse agonist. Eur J Clin Pharmacol. 2016;72(5):533-43.
21. Cardiac Safety Research Consortium. Critical Discussion-Future of the Assessment of Drug-Induced Arrhythmias and the Comprehensive in Vitro Proarrhythmia Assay (CiPA). 2016. http://cardiac-safety.org/2016/12/critical-discussion-future-of-the-assessment-of-drug-induced-arrhythmias-and-the-comprehensive-in-vitro-proarrhythmia-assay-cipa/.
22. Fermini B, Hancox JC, Abi-Gerges N, Bridgland-Taylor M, Chaudhary KW, Colatsky T et al. A New Perspective in the Field of Cardiac Safety Testing through the Comprehensive In Vitro Proarrhythmia Assay Paradigm. J Biomol Screen. 2016;21(1):1-11.
23. An Update on CiPA Activities from an FDA Perspective 2017. http://cipaproject.org/wp-content/uploads/sites/24/2017/06/SPS2017Webinar_CiPA.pdf.