

**Final Concept Paper**  
**E14 Q&As (R3): Revision of ICH E14 Q&As (R2)**  
**dated 8 June 2015**  
**Endorsed by the ICH Steering Committee on 9 June 2015**

**Type of Harmonisation Action Proposed**

Category 3: Revision Procedure

**Statement of the Perceived Problem**

The current version of ICH E14 recommends a thorough QTc study (TQT) to assess the potential for QTc prolongation during drug development. *Concentration-response modelling* applied to early clinical QT data is mentioned in E14 and in a subsequent Q&A as a “promising” methodology with potential to detect QTc prolongation. However, there is no harmonised guidance on whether and how concentration-response QTc modelling from Phase I studies could be used to satisfy the regulatory requirements for evaluating the effect of a drug on QTc interval.

There is now consensus within the E14 Discussion Group that the accumulated experience with concentration-response modeling has matured sufficiently to warrant consideration of this approach as a reasonable (or in some situations a better) approach to the assessment of QT prolongation that could serve as an alternative to a TQT study and therefore satisfy the regulatory requirement for QT assessment. The Discussion Group recognises two approaches to incorporating *Concentration-response modelling* into the E14 Guidance (revise E14 vs. revise Q&A on concentration-response). Regardless of which approach is taken, all members of the Discussion Group agree that the highest priority is to generate guidance on *Concentration-response modelling* and the initial focus of the Working Group would be on generating language on how *Concentration-response modelling* could be used.

**Recommendation: An E14 Implementation Working Group should be formed to revise the Q&A on *Concentration-response modelling*** – The previously issued Q&A on *Concentration-response modelling* does not provide guidance on how these analyses could be used for regulatory decision making. The Working Group would focus on revising the Q&A to generate harmonised guidance on how *Concentration-response modelling* could be used for regulatory decision making. Once the Working Group has achieved consensus on a revised Q&A but prior to issuing the Q&A for approval, the Working Group should consider what would be required to incorporate the revised Q&A on *Concentration-response modelling* along with the previously published Q&A into a revised E14 document. If, at that time, it appeared that the revision of E14 would require a substantial amount of time, then the Working Group would advance the Q&A to *Step 4*. If however, the Working Group believed that revision of E14 into a single cohesive document could be accomplished in a short period of time, then the Working Group would return to the Steering Committee and request approval to form an Expert Working Group to revise E14 such that the new guidance on *Concentration-response modelling* and the prior Q&A could be incorporated into a single cohesive document.

## Issues to be Resolved

There are a number of issues that require resolution related to how concentration-response modeling should be integrated into E14 and how concentration-response modeling should be conducted and interpreted. Ultimately, E14 must specify the circumstances in which Phase I concentration-response modeling would obviate a TQT study.

The issues that require resolution fall into 3 major categories:

1. What features of the design of early Phase I studies (Single Ascending Dose [SAD], Multiple Ascending Dose or pooled data from multiple studies) are important with regard to how data should be optimally collected for the purpose of concentration-response modeling of the change in QTc.
2. What approaches to modeling concentration and QTc data are recommended and how should a model be evaluated as providing sufficient reassurance that a clinically significant signal has been excluded/included?
3. What thresholds should be used for defining relevant QTc prolongation based on the model?

## Background to the Proposal

E14 and S7B were signed off as *Step 4* documents in May 2005. In the original E14 document, Section 3.2.3 (page 12) “Analysis of Relationship Between Drug Exposure and QT/QTc Interval Changes” states: “Establishing the relationship of drug concentrations to changes in QT/QTc interval may provide additional information to assist the planning and interpretation of studies assessing cardiac repolarization. This area is under active investigation.”

Three sets of Q&As documents have been generated to further clarify issues based on the evolution of science and the accumulated experience with the clinical assessment of a drug’s effect on QTc. The first set of Q&As were released on 4 June 2008. Two additional sets of Q&A’s were issued on 5 April 2012 (E14 Q&A(R1)) and 21 March 2014 (E14 Q&A (R2)); all of the Q&A were subsequently integrated into a single document.

([http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E14/E14\\_Q\\_As\\_R2\\_Step4.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E14/E14_Q_As_R2_Step4.pdf)).

In the integrated document, Q&A 5.1 entitled “Use of CRRs of Early Phase studies to enhance evaluation of QT prolongation” was issued to address the following question: “The ICH E14 Guideline states (in Section 3, page 12) that analysis of the relationship between drug concentration and QT/QTc interval changes is under active investigation. Has this investigation yielded a reasonable approach to concentration-response modeling during drug development? How can assessment of the CRR guide the interpretation of QTc data?” The final section of this Q&A concludes that *Concentration-response modelling* “applied on early clinical QT data from healthy volunteers seems promising in terms of enhancing our confidence to characterise QTc prolongation.”

During the discussions of this Q&A, members of the ICH E14 IWG suggested that prospective data would be helpful in generating confidence that a Phase I concentration-response analysis could provide sufficient information on the effect of a drug on QTc such that a separate study with a positive control would not be necessary. Following those discussions, sponsors and representatives

of regulatory agencies met outside of the ICH process (including a Cardiac Safety Research Consortium Think Tank in 2012) and designed a study to address these issues. The IQ-CSRC study was designed to prospectively evaluate the veracity of using a concentration-response relationship to assess the potential for QTc prolongation in a Phase I like setting. The study was designed as a 3-period, third-party blinded, randomised, placebo-controlled study in 20 healthy volunteers conducted in a design similar to a SAD Phase I study with the primary objective to estimate the effect of change-from-baseline QTc ( $\Delta$ QTcF) of 9–12 ms. The design and results of this study were recently published<sup>i-ii</sup>.

In the study, the primary analysis was based on an Exposure–Response (ER) analysis of the relationship between drug plasma concentrations and QTc. The primary variable was change-from-baseline QTcFridericia ( $\Delta$ QTcF), and adjustment for placebo and circadian variability was performed within the ER model. Data from nine subjects receiving each drug was analysed separately and data from the six subjects receiving placebo included in each analysis (i.e., nine subjects on drug vs six on placebo for each treatment). The analysis was based on a linear mixed-effects model with  $\Delta$ QTcF as the dependent variable, drug plasma concentration as a continuous covariate and nominal time post–first dose as a factor. Tests were formulated based on 2-sided 90% CI and the confidence intervals for slopes were derived directly from the model.

The IQ-CSRC study prespecified criteria for a positive QT assessment and a negative QT assessment. A “QT-negative” drug was defined as having an upper bound (UB) of the 2-sided 90% confidence interval of the predicted placebo-corrected  $\Delta$ QTcF below 10 ms at the observed geometric mean Cmax level of the suprathreshold dose. All 5 drugs known to prolong QT met all the criteria for a positive QT assessment and the one drug known not to prolong QT met the criteria for a negative QT assessment. The data from this study were initially presented to the ICH E14 Discussion Group at the 16 September 2014 teleconference. The study demonstrated that QT assessment using exposure–response analysis of data from a small study in healthy volunteers was able to detect mild QT prolongation at the level of regulatory concern and that a QT effect above 10 ms could be excluded for a drug with no underlying effect. The study thereby provides validation of the concept of definitive ECG assessment in early-phase clinical studies.

Based on the IQ-CSRC study results and the extensive experience with ER analysis for evaluation of QT effects over the last 10 years, QT assessment in early-phase clinical studies can be proposed as an alternative to the TQT study. The following criterion could then be used as a basis for a request for a TQT waiver: the upper bound of the two-sided 90% confidence interval of the predicted placebo adjusted  $\Delta$ QTc should be below 10 ms at the highest clinically relevant plasma concentrations of the drug. These and other data related to the use of concentration-response modeling were extensively discussed within the E14 Discussion Group at subsequent meetings including 8 teleconferences (14 October 2014, 17 November 2014, 16 December 2014, 13 January 2015, 24 February 2015, 24 March 2015, 21 April 2015 and 12 May 2015). In addition, the second day of a 2-day public meeting (12 December 2014), held at the FDA headquarters in Silver Spring, MD, (sponsored by the Cardiac Safety Research Consortium and the International Consortium for Innovation & Quality in Pharmaceutical Development) was devoted to discussing the use of concentration-response modeling from Phase I data to assess the potential for QTc prolongation including a presentation of the results of the IQ-CSRC Study. Following this meeting, members of the ICH E14 Discussion Group met face-to-face and discussed these data and their potential impact on ICH E14. At this meeting, representatives from PhRMA, FDA, EMA, EFPIA, JPMA, and

PMDA were together in Maryland, and the representative from Health Canada participated by phone (the member representing Swissmedic was not available).

At the E14 Discussion Group teleconferences additional data were presented by scientists from Pfizer and from Novartis based on their experience using concentration-response modeling from Phase I studies as well as data from thorough QT studies from the same compounds. In addition, a cardiologist consultant, Borje Darpo, presented a preliminary perspective on relevant quality metrics that could be used in the absence of a positive control. An example of utility of this approach in the regulatory context is provided as an attachment<sup>iii</sup>.

The use of concentration-response modeling of QTc data overcomes a number of limitations of the TQT study and has a number of distinct advantages:

1. First, it is consistent with the way in which concentration-response modeling is used in other aspects of drug development (e.g., modeling the impact of drug-drug interactions, intrinsic and extrinsic factors that can impact exposure, evaluating new formulations).
2. Second, this approach would begin to build a concentration-response model in early Phase I studies when the highest exposures of a drug are typically achieved and would enable the identification of a potentially meaningful QT effect, or its absence, earlier in a drug's development. While this approach would require collecting high quality ECGs alongside pharmacokinetic sampling in one or more Phase I studies, the ability to extract ECGs from digital 24-hour ECG recordings makes this feasible in most Phase I studies. Concentration-response modeling provides a methodology that allows data to be analysed across multiple cohorts (and potentially multiple studies) in a single model. This is important given that most Phase I studies utilise small cohorts for a given dose level and pool placebo data across cohorts. This approach would estimate the relationship between the exposure of a drug and its effect on QTc over a wide range of concentrations and takes advantage of all of the data collected rather than restricting the evaluation to a specific time point at a specific dose.

In order for concentration-response modeling to become an accepted alternative method to satisfy the regulatory requirement for evaluating a drug's effect on QTc, a number of issues require further clarification:

1. Concentration-response models are often created post hoc. Ideally, criteria for model selection and the threshold for classifying results as positive or negative based on the model should be pre-specified.
2. Since positive controls (e.g., moxifloxacin) are not used in Phase I studies, methods for assessing the robustness of the QT/ECG measurements and the concentration-response model from Phase I data without a positive control must be stipulated.
3. Biases that may be associated with concentration-response modeling must be identified and the implication of these biases explored.

The use of concentration-response modeling of Phase I data to evaluate the effect of a drug on QTc has important implications if it has the potential to provide drug developers with a pathway for assessing drug-induced QT prolongation without a TQT study. The use of concentration-response modeling in Phase I would enable characterisation of a drug's QT effects earlier in a drug's development. Ultimately, this approach is likely to provide a more efficient (and probably more effective) assessment of a drug's potential to cause QTc prolongation if it becomes widely accepted as an alternative to a TQT study.

### **Type of Implementation Working Group (IWG) and Resources**

The IWG will be comprised of two members nominated by EU, EFPIA, FDA, PhRMA, MHLW, JPMA, Health Canada, and Swissmedic. One member can also be nominated by WHO Observer, each Interested Party as well as RHIs, DRAs/DoH (if requested). The IWG should include representatives with an expertise in clinical development. Expertise in modelling and simulation as well as biostatistics will be important to the IWG in these deliberations. However, expertise in these areas is welcomed but need not be represented in each ICH party. The IWG will engage with experts in these areas as needed on an *ad hoc* basis.

In the E14 Q&A(R2) it is stated that concentration response modeling ‘can be an important component of a totality of evidence assessment of the risk of QT prolongation.’ We believe that non-clinical data represent an extremely significant constituent of the totality of evidence approach to understanding the influence of a potential drug on the risk of arrhythmia. However, at the present time, the focus of the Implementation Working Group will be on the revision of E14 and not on S7B. With this in mind, the primary representatives from each ICH Party should have expertise in clinical development. It is important to note that the E14/S7B Discussion Group plans to continue its discussion of another area of emerging science related to the use of a Comprehensive *in vitro* Proarrhythmia Assessment (CIPA). The CIPA initiative, seeks to enhance the specificity and efficiency of the current cardiovascular safety testing standard for potential proarrhythmic effects of new drugs (S7A & B and E14).

The proposed CIPA paradigm incorporates an *in vitro* ion channel assessment of drug effects coupled to *in silico* reconstructions of the cardiac action potential to generate a scaled prediction of human clinical proarrhythmic potential. Verification of the predicted effect will be evaluated with human stem cell-derived cardiac myocytes. It is not anticipated that CIPA would replace preclinical ECG evaluation or the need for careful clinical assessment of electrophysiologic effects in at least one Phase I clinical ECG safety study. However, it is possible that successful implementation of the CIPA paradigm would substantially augment our understanding of the potential proarrhythmic effects, which when combined with Phase I QT concentration-response QTc data would eliminate the need for a thorough QT study for compounds entering clinical development. The framework for the development and validation of the CIPA approach was initiated in 2013. An international, multi-disciplinary, and multi-sector team of experts has been convened by the Health and Environmental Sciences Institute (HESI) and the Cardiac Safety Research Consortium to design and execute the program collaboratively. Members of the CIPA project Steering Committee Team members contacted the E14/S7B Discussion Group when the project was initiated.

While this initiative has the potential to be transformative in the evaluation of the potential for drugs to be pro-arrhythmic, it is anticipated that this work will not be completed in the short term. The E14/S7B Discussion group acknowledged the importance of this work and plans to be updated on its progress on a regular basis.

With this in mind, the E14/S7B Discussion Group recommends that the preclinical (S7B) experts continue to participate in the discussions of the E14 IWG on an agenda driven basis related to when updates of the CIPA initiative will be provided.

### Timing

If approved, the E14 IWG would begin revising the concentration-response Q&A during our discussion at Fukuoka. Given the previous work on *Concentration-response modelling* and the meetings the group has had over the past 6-month, the E14 Implementation Working Group will likely be able to develop a draft document while in Fukuoka. Issues that require further discussion would be identified. The IWG would meet by teleconference monthly and it is possible that the Q&A could be completed at the next face-to-face meeting in the fall 2015.

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<sup>i</sup> Darpo B1, Sarapa N, Garnett C, Benson C, Dota C, Ferber G, et al. The IQ CSRC prospective clinical Phase I study: Can early QT assessment using exposure response analysis replace the thorough QT study? *Ann Noninvasive Electrocardiol* 2014 Jan. 19(1):70-81.

<sup>ii</sup> Darpo B, Benson C, Dota C, Ferber G, Garnett C, Green CL, et al. Results From the IQ-CSRC Prospective Study Support Replacement of the Thorough QT Study by QT Assessment in the Early Clinical Phase. *Clin Pharmacol Ther* 2015 97:326-35.

<sup>iii</sup> Nelson CH, Fang L, Cheng F, Wang L, Hepner M, Lin J, et al. Concentration-QTc Modeling in First-in-Human Study to Assess the Effect of the Investigational Drug GS-4997 on Cardiac Repolarization. Poster presented at the annual meeting of Am Soc of Clin Pharm and Therapeutics March 2015.