

## Commentary: On the Revised ICH E14 and S7B Q&As

The International Council on Harmonisation (ICH) released a new set of questions and answers (Q&As) for ECH E14 and ICH S7B in August 2020 (available at: <https://www.ich.org/news/ich-e14s7b-draft-qas-available-now-ich-website>). This represents Step 2 of the ICH process; these Q&A documents are now currently open for public review and comment. On October 15 and 16, FDA hosted a webinar on the Q&A document and we would like to share some thoughts and considerations in terms of what this may mean for drug developers.

Since the release of the S7B and E14 guidances in 2005, all new drugs with systemic exposure have been required to undergo assessment of their risk of producing Torsades de Pointes (TdP), a ventricular arrhythmia that is often lethal. Torsades is very rare, even for most of the drugs removed from the market due to an excess of deaths due to this arrhythmia. As a result, it is not feasible to directly detect an increased risk of TdP in the clinical trials performed during the drug development process. Instead, the E14 guidance described use of a surrogate endpoint, drug-induced QT prolongation, and for the most part, since 2005 all new drugs have undergone an assessment of the drug's effect on the QT interval as measured on the 12-lead ECGs that are collected during clinical trials. The assessment of risk for TdP has almost entirely been based on a review of the ECG data (and more recently on the relationship between drug exposure and QT prolongation), whereas the non-clinical assays described in the S7B guidance mostly have been used to ensure that a drug is safe to take into first-in-human (FIH) studies, and have played a minor role for the subsequent clinical development. However, since 2005, we have learned a great deal about how drugs affect the QT interval and how they may produce TdP, and our scientific understanding of the biological mechanisms responsible for drug-induced ventricular arrhythmias has grown tremendously.

The ICH E14 document has been clarified through several Q&A documents, which have been attached to the guidance, most recently in December 2015. The latest Q&A document (R3 from December 2015) allowed concentration-QTc (C-QTc) analysis to be applied to data from healthy subjects to definitively demonstrate that a drug did not cause clinically relevant QTc prolongation, defined as exclusion of an effect on the placebo-corrected, change-from-baseline QTc larger than 10 ms<sup>1</sup>. An important point was then that a separate positive control would not be necessary if the following condition is met: *There are data characterizing the response at a sufficiently high multiple of the clinically relevant exposure (see ICH E14 Section 2.2.2)*. This allows C-QTc analysis to be applied to serial ECG and PK data from first-in-human (FIH) studies and if sufficiently high concentrations are achieved, waive the request for a later, dedicated thorough QT (TQT) study, and thereby allowed a more efficient method for ECG evaluation of new drugs<sup>2,3</sup>. Current FDA practice, not necessarily followed by all other regulators, has been to request a TQT study with a positive control in cases where very high concentrations (supratherapeutic concentrations in the graph below) cannot be, or have not been, achieved in e.g., FIH study, as shown in Figure 1:

Term	Definition	Example for Drug X (assume no accumulation and linear pharmacokinetics)
Therapeutic dose	Dose evaluated in Phase 3 trial or recommended in product labeling	10 mg QD
Clinical exposure	Mean steady state maximum concentration ( $C_{max,ss}$ ) associated with the <b>maximum therapeutic dose</b>	$C_{max,ss} = 100$ ng/ml
High clinical exposure scenario	Increase in exposure ( $C_{max,ss}$ ) when the <b>maximum therapeutic dose</b> is given with intrinsic or extrinsic factors	3-fold $C_{max,ss}$ with DDI Target: 300 ng/ml
Supratherapeutic dose (TQT study)	Dose that provides exposures that cover high clinical exposure scenario	Dose gives $C_{max}$ of at least 300 ng/ml ≥30 mg
Dose/exposure needed to waive positive control in Q&A 5.1	≥2-fold the high clinical exposure	Dose gives $C_{max}$ of at least 600 ng/ml ≥60 mg

Source: Slide 4 in Dr. Gamett's presentation at the public webinar on S7B/E14 Q&A, October 15–16, 2020: Revised E14 Q&As and Presentation of Examples to Highlight the Impact of Nonclinical Data on Clinical Development and Interpretation.

Figure 1

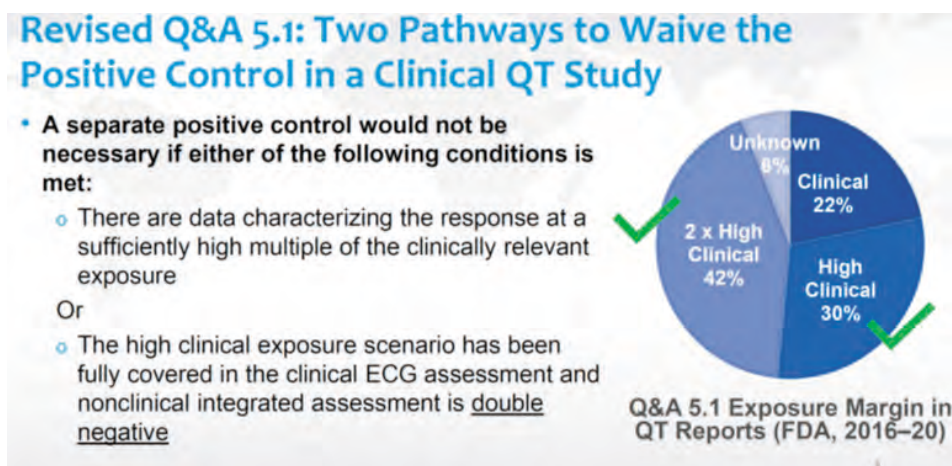
### Q&A 5.1

Q&A 5.1 has now been revised to also state: "If the maximum therapeutic exposure has been fully covered in the clinical ECG assessment (e.g., concentrations representative of the maximum recommended dose at steady-state in situations of intrinsic and/or extrinsic factors that increase bioavailability), but sufficiently high multiples **cannot be obtained** (e.g., for reasons of safety, tolerability, saturating absorption), then a nonclinical integrated risk assessment that includes the hERG assay, an *in vivo* QT assay, and any follow up studies can be used as supplementary evidence. See ICH S7B Q&A 1.1 for details; in summary, the nonclinical studies should include<sup>1</sup> a hERG safety margin higher than the safety margins computed under the same experimental protocol for a series of drugs known to cause torsade de pointes (TdP) and<sup>2</sup> no QTc prolongation in an *in vivo* assay of sufficient sensitivity conducted at exposures of parent compound and human-specific major metabolites that exceed clinical exposures."

The proposed change will therefore, to some extent, further decrease the number of TQT studies, and enable acceptance of robust high-quality ECG data, using C-QTc analysis, supplemented by non-clinical data, to demonstrate that the drug does not cause clinically relevant QT prolongation. It should then be emphasised that as the text is written, this applies only to drugs for which sufficiently high concentrations cannot be obtained (e.g., for reasons of safety, tolerability, saturating absorption). If the assumption that *'the maximum therapeutic exposure has been fully covered'* is shown to be correct, higher concentrations will not be seen in patients, including those with impaired clearance of the drug and those at risk for proarrhythmic events, and the revised text then gives a path forward without performing a stand-alone TQT study.

In this context, it is important to point out the role of high concentrations in terms of detecting the QT effect of a drug<sup>4</sup>. We know that high concentrations are key for the ability of C-QTc analysis to detect small QTc effects, and thereby to increase our confidence in the data. We have made this observation in several projects, including one recently published example, based on a multiple ascending dose (MAD) study<sup>5</sup>. It therefore seems prudent to restrict 5.1 to those cases where sufficiently high concentrations cannot be obtained, rather than broadly applying these criteria.

At the webinar, Dr Garnett from FDA showed the following graph (Figure 2):



Source: Slide 9 in Dr. Garnett's presentation at the public webinar on S7B/E14 Q&A, October 15–16, 2020: Revised E14 Q&As and Presentation of Examples to Highlight the Impact of Nonclinical Data on Clinical Development and Interpretation.

Figure 2

The key point, which is not acknowledged in this slide, is that 5.1 applies to drugs for which suprathreshold concentrations cannot be obtained. Furthermore, the chart does not provide insight as to why 'suprathreshold concentrations' were not obtained, which in some cases is simply because doses in FIH studies were not being pushed high enough, and not necessarily due to reasons of safety, tolerability, or saturated absorption. It is therefore not clear to what extent the proposed 5.1 pathway will further reduce the proportion of TQT studies, but we can certainly expect a continued debate between sponsors and regulators on this point.

It may be appropriate and clarifying to specifically point this out in the text by, e.g., adding a statement along the following lines: If sufficiently high multiples of maximum therapeutic exposure were not obtained in the clinical ECG assessment, it should be clarified why sufficiently high exposures cannot be achieved.

### Q&A 6.1

In the answer to Q&A 6.1 in the proposed E14 Q&A revision, it is stated that: *In situations where it is not possible to evaluate the QT/QTc effects at higher exposures than are anticipated with the recommended therapeutic dose, it is particularly important that the nonclinical in vivo studies are conducted at exposures exceeding the clinical therapeutic exposures.*

Under Decision-Making, point 2., the following is said (our bolded text): *A totality of evidence argument based on the results of an integrated nonclinical and clinical QT/QTc assessment could be made at the time of marketing application. To support a drug as having low likelihood of proarrhythmic effects due to delayed repolarization, the assessment should demonstrate the following:*

Further down, under 2):

2. *The high-quality ECG data (see ICH E14 and E14 Q&A 1) collected in the alternative QT clinical assessment do not suggest QT prolongation, generally defined as  $\Delta QTc$  greater than 10 ms, as computed by the concentration-response analysis (see E14 Q&A 5.1 for details) or the intersection-union test. The strength of the clinical ECG data depends on the upper bound of the two-sided 90% confidence interval around the mean  $\Delta QTc$  estimate...*

### 'Low Likelihood of Proarrhythmic Effects':

Since this refers to a claim that a sponsor can make at the time of marketing application, it should be noted that the risk/benefit assessment and labelling are performed separately by

each regulatory authority (see E14 5.2), and may therefore vary across regions, especially when an effect on  $\Delta QTc > 10$  ms cannot be excluded. It may well be that regulators will see this in a similar way for a drug with a small effect, e.g., 4 ms with an upper bound (UB) of the 90% CI of 12 ms, as in the example shared by Dr. Garnett at the webinar (slide 18 and 19; available at: <https://www.fda.gov/drugs/news-events-human-drugs/new-approaches-integrated-nonclinical-clinical-qtproarrhythmic-risk-assessment-10152020-10162020>). It is, however, not evident, in our view, that the same is true for a drug with a larger effect, still within the 6.1 definition, e.g., mean  $\Delta QTc$  of 9 ms, UB of the 90% CI 17 ms. If a harmonised regulatory approach is desired, it seems better to retain the threshold that most parties can agree on, i.e., exclusion of a 10 ms effect (UB of the 90% CI less than 10 ms).

The issue we see with Q&A 6.1 is that the consequences for patient studies of 'low likelihood of proarrhythmic effects' are not described. The stated purpose of the ICH E14 guidance is to inform the level of ECG monitoring that will be required for Phase III studies, even though the data from a TQT will also be used in an integrated non-clinical and clinical assessment of proarrhythmia risk. Even though it is clearly stated that the claim about 'low proarrhythmic effect' can be made at the time of marketing application, the clinical QT evaluation will in many cases be performed before pivotal studies are initiated, e.g., by applying C-QTc analysis on data from the FIH study in cancer patients. It can then be argued that a drug that can be categorised as having low likelihood of proarrhythmic effects based on 6.1 criteria, can be given safely to patients in Phase III trials, without exclusion criteria or cautionary statements in regard to concomitant medications with drugs that are known to cause QT prolongation, or to patients at risk based on, e.g., family history of LQTS, cardiovascular disease or hypokalemia. As defined under 6.1, a drug that causes a mean  $\Delta QTc$  of 9 ms with a UB of 17 ms could be regarded as 'safe' from this perspective. We disagree that such a drug can be taken into large patient trials without specified exclusion criteria and precautions and without ECG monitoring, but much more importantly – there is consensus across regulators on this point. This conflict between the proposed 6.1 pathway and the current regulatory consensus means that sponsors will not know what to expect and that the desired harmonisation across regulators will not be achieved.

It is important to describe the consequences for subsequent patient studies by referring to the E14 section 2.3 if a new term is introduced into the guidance. We suggest that it would be better

to keep the threshold on which there is consensus (exclusion of a 10 ms effect, as defined above) and then allow regulators to make case-by-case decisions, depending on the severity of the indication and the unmet medical need. Alternatively, the text under 2) in Q&A 6.1 can be revised along the following lines (added text in bold): ...generally defined as  $\Delta QTc$  greater than 10 ms, as computed by the concentration-response analysis (see E14 Q&A 5.1 for details) or the intersection-union test. The strength of the clinical ECG data depends on the upper bound of the two-sided 90% confidence interval around the mean  $\Delta QTc$  estimate. *In case QT evaluation as described here is completed before patient studies are initiated, the level of the mean QTc effect and the 90% confidence interval will be used to determine the need for precautions, exclusion criteria and the level of ECG monitoring in subsequent patient trials (see E14 2.3).*

### Drugs with a Pronounced Heart Rate (HR) Effect

In Q&A 6.1, it is also stated that: An integrated QT/QTc risk assessment can also be particularly valuable for drugs with confounding heart rate effects (i.e., >20 bpm) that could impact accurate determination of the QTc. Advanced methodologies for controlling or correcting for heart rate changes in the nonclinical *in vivo* studies and/or conducting QTc assessments in patients with the disease might be informative in this situation. If tolerance to the chronotropic effect develops with repeat dosing, upward titration regimens can sometimes be employed to avoid or minimize the confounding effects of drug-induced heart rate changes on the QTc assessment.

We agree on the point that QT evaluation conducted in patients may be informative in case the drug has a pronounced HR effect and that dose titration can be useful, but it also seems important to emphasise that in most cases there will be a need for ECG monitoring in Phase III trials based on this level of HR effect. As pointed out by the E14/S7B IWG group on several occasions, the role of the QT assessment in healthy subjects is to define which drugs would need ECG monitoring in patients, with the objective to further characterise this effect in the targeted patient population. An HR effect of this magnitude will in most cases be detected during Phase I studies, which further underscores the need of defining the consequences it has for subsequent patient studies. Under Decision-Making, it is stated that a drug with this level of HR effect can be categorized as having 'low likelihood of proarrhythmic effects due to delayed repolarization', if 6.1 requirements #1 and #3 are also met. This seems correct if the drug causes a HR increase of this magnitude, since TdP is closely associated with bradycardia. Such drug may however trigger coronary ischemia or worsen congestive heart failure, and thereby cause life-threatening arrhythmias on this basis. A drug that causes a reduction of HR of this size, i.e., is having a strong negative chronotropic effect, is likely to cause clinically significant bradycardia and may trigger sinus pauses and AV blocks. Moreover, if the mean effect on  $\Delta QTc$  is only somewhat below 10 ms, as an example, 9 ms with an upper bound of the 90% CI of 17 ms, it is probably incorrect, or at least not convincingly shown, that the drug can be categorised as having a 'low likelihood of proarrhythmic effects due to delayed repolarization'. An important question is then whether data have been shared within the IWG to support this latter point?

The HR example is too TdP-centric, and ignores other potential cardiac adverse effects due to large HR effects that clearly would warrant ECG monitoring in patients. As we see it, the example therefore leads in the wrong direction, and should be dropped from the document.

### Q&As for ICH S7B

This is the first set of Q&As for the S7B guidance, "The Non-Clinical Evaluation Of The Potential For Delayed Ventricular Repolarization (QT Interval Prolongation) By Human Pharmaceuticals" since its release in 2005<sup>6</sup>. The Q&As address the current 'best practices' for the design and conduct of non-clinical cardiac safety studies and discuss the role of non-clinical cardiac safety data in an integrated risk assessment of the risk of TdP by a new drug.

There has been renewed interest in using non-clinical tests to replace, or at least to supplement, clinical ECG data during the drug development process. The current Q&A documents are intended to address this issue, and provide recommendations about when and how a drug development programme might use the non-clinical cardiac safety data as part of an integrated risk assessment, particularly when the clinical ECG data collected in healthy volunteer trials cannot be tested at adequately high exposures, or when data on a drug's QT effects must be collected in patient trials with larger variability and lower precision.

The new S7B Q&A document consists of four sets of questions and answers related to four high-level topics (Table 1) and begins with a discussion about the general principles behind use of non-clinical data as part of an integrated assessment of the risk of drug-induced TdP.

Question 1: Integrated Risk Assessment
Question 2: Best Practice Considerations for <i>In Vitro</i> Studies
Question 3: Best Practice Considerations for <i>In Vivo</i> QT Studies
Question 4: Principles of Proarrhythmia Models

Table 1: Four Topics Discussed in ICH S7B Draft Document

The Q&A discusses, at a high level, the drug exposures that should be evaluated in non-clinical tests (generally at least as high as the expected high clinical exposure, if not a multiple of this), and the use of safety margins to evaluate patch clamp data about drug-induced block of the hERG encoded IKr cardiac channel ('hERG safety margin'). The Q&A describes some of the criteria for a "double negative" non-clinical assessment:

1. Ion channel studies that demonstrate that the hERG "safety margin" for the new drug and metabolites is higher than the safety margins for a series of drugs known to cause Torsades de Pointes.
2. An *in vivo* QT study that shows no evidence of drug induced QT prolongation at adequately high exposures of the new drug and its metabolites.

The answers to the first question also mention other factors, such as block of other ion channel, effects on ion channel trafficking, and non-ion channel mediated effects that may also prolong QT.

The second question in the S7B Q&A addresses, at a high level, the 'best practices' for *in vitro* cardiac ion channel studies and *in vivo* cardiomyocytes studies, including discussions of proper study design and conduct, study conditions and verification of the drug concentration used, verification of the quality of the collected data, and the integrity of the test systems. The Q&A specifically comments that the 'best practices' discussed are only intended to apply to sponsors who wish to use the non-clinical data for an integrated risk assessment, complementing the clinical ECG data. In contrast, sponsors intending to use the non-clinical cardiac data for routine screening activities or to inform the design of FIH clinical trials are not required to follow these 'best practices'. The first part of this



section discusses 'best practices' for ion channel studies, including the topics described in Table 2. The second portion discusses 'best practices' for cardiomyocytes studies, including discussion of the topics listed in Table 3.

Primary endpoints for patch clamp studies (IC50 and Hill Coefficient values)
Testing at physiologic temperatures
Monitoring of seal resistance, cell health, recording quality
Assessment of ion channel recording quality
Concentration verification
Use of positive and negative controls

Table 2: Best Practices for Ion Channel Studies Discussed in Question 2

Methods (MAP recordings, contractile activity, EADs)
Requirements for description of biological preparations (source of cells, maturity, viability)
Details of technology platform (transmembrane potential recordings, field potentials, contraction monitoring, calcium sensing dyes)
Description of analysis package used
Description of plates or chambers used and test conditions
Monitoring of cell contractions
Monitoring of drug concentration in test chambers
Defining sensitivity of cardiomyocyte assays – positive and negative controls for hERG
Assessment of inward currents; positive and negative controls
Presentation of representative recordings

Table 3: Best Practices for Cardiomyocyte Studies Discussed in Question 2

The third question in the Q&A discusses 'best practice' considerations for *in vivo* QT studies, including discussion of appropriate drug exposures to test heart rate, correct methods for use in animal ECG studies, assessment of assay sensitivity and the precision of the measurements, and the presentation of the data in reports (Table 4). Finally, the fourth question discusses principles of proarrhythmia models, and how proarrhythmia risk assessment models might be used in the context of an integrated assessment of proarrhythmia risk.

Appropriate species
Telemetered animals, anesthetized animals, pacing
Required drug and metabolite exposures
Methods to correct QT for heart rate
Establishment of assay sensitivity
Standards for presenting data

Table 4: Best Practices for *in vivo* QT Studies discussed in Question 3

## Discussion

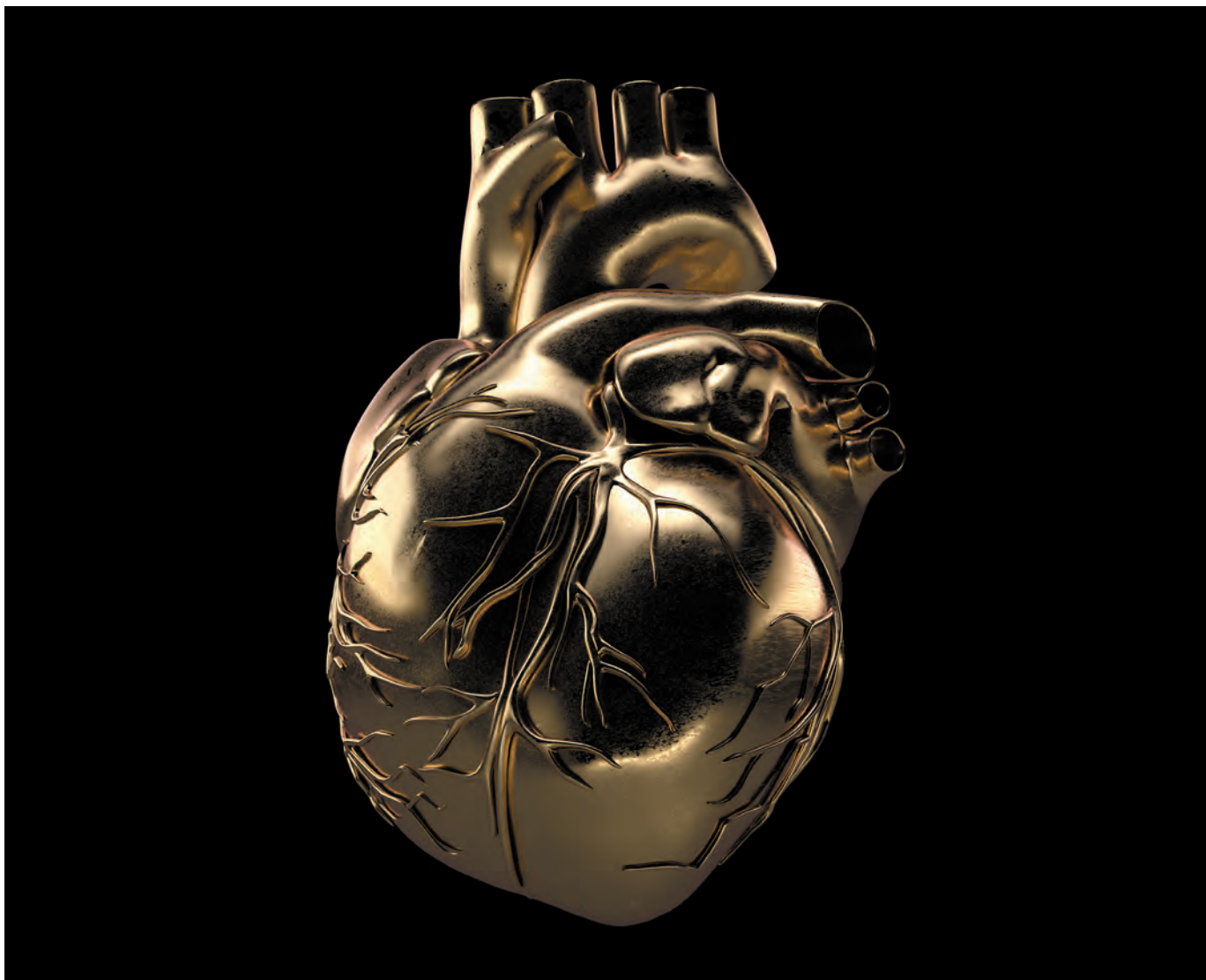
Current FDA practice has been to request a TQT study with a positive control in cases where very high concentrations cannot be, or have not been, achieved in e.g., the FIH study. The proposed change in Q&A 5.1 will therefore, to some extent, lower this requirement, i.e., decrease the number of TQT studies, and enable acceptance of robust high-quality ECG data, using C-QTc analysis, supplemented by non-clinical data, to demonstrate that the drug does not cause clinically relevant QT prolongation. As the text is written, this applies only to drugs for which sufficiently high concentrations cannot be obtained and the revised text then gives a path forward without performing a stand-alone TQT study. In this context, it should be emphasised that when C-QTc analysis is applied to data, high concentrations are key for the ability of C-QTc analysis to detect small QTc effects, and thereby increase confidence in the data. It therefore seems important to restrict 5.1 to those cases where sufficiently high concentrations cannot be obtained, rather than broadly applying these criteria.

Q&A 6.1 allows sponsors to argue at the time of marketing application that a drug 'has low likelihood of proarrhythmic effect', if requirements under 6.1 are met. It should then be noted that the risk/benefit assessment and labelling are performed separately by each regulatory authority (see E14 5.2), and may therefore vary across regions, especially when an effect on  $\Delta QTc > 10$  ms cannot be excluded.

In our view, the main issue in Q&A 6.1 is, however, that the consequences for patient studies of 'low likelihood of proarrhythmic effects' are not described. Many times, the clinical ECG assessment is performed before Phase III studies. It can then be argued that in case 6.1 requirements are met, the drug can be safely given in subsequent patient studies with medications known to prolong the QTc interval and to patients at risk for proarrhythmias and with limited ECG monitoring (see E14 2.3). Within the 6.1 definitions, a drug that causes a mean  $\Delta QTcF$  of 9 ms with an upper bound of the confidence interval of 17 ms, will then be regarded as 'safe' from this perspective. As we see it, it seems important to describe the consequences in terms of exclusion criteria and level of ECG monitoring in subsequent patient trials, in case 6.1 requirements are met before pivotal trials are performed.

This first set of Q&As for the S7B guidance is a welcome first step in increasing the use of non-clinical cardiac safety data to complement clinical ECG data for an integrated assessment of the proarrhythmia risk of a new drug. Many of the answers in the draft document, however, contain discussions at a high level only, with a minimum of prescriptive detail. Additional details about the 'best practices' for ion channel studies (such as what constitutes an adequate hERG safety margin, or the stimulation protocols that are required) would be very instrumental towards standardising the design and conduct of ion channel studies across sponsors and commercial laboratories. Additional details about *in vivo* QT studies, including specifics about sample size, drug exposure requirements, ECG collection and measurement methods, requirements for demonstration of assay sensitivity, and guidelines as to what constitutes a 'negative' *in vivo* QT study, would also be welcome. Specific details would help standardise the design and performance of such trials and would be extremely helpful for sponsors who wish to understand if the non-clinical data that they have collected are of adequate standard to be used to support an integrated assessment of proarrhythmia risk. In its current state, the S7B Q&A contains enough specific details to allow sponsors to identify some of their non-clinical cardiac data as inadequate to support an integrated assessment of proarrhythmia risk. However, it does not contain the level of detail that is required for a sponsor to be confident that their non-clinical cardiac safety data are adequate.

Hopefully, this first Q&A for ICH S7B will lead to further detailed recommendations about 'best practices', similar to the example of the ICH E14 2015 Q&A document. This Q&A was released in December 2015 and contained a high-level discussion of how concentration response modelling of QTc data might be used as an alternative to the standard by timepoint analysis utilising the Intersection Union Test as a primary endpoint for a QT study. While this was enthusiastically received, the level of detail was not sufficient to completely inform the design and analysis of QT studies. In 2017, members of the FDA and industry published a 'Scientific white paper on concentration-QTc modeling' that described many of the elements required for a successful early-phase QT study<sup>7</sup>. Hopefully, more details about the new ICH revisions will follow quickly, enabling drug developers to take advantage of the new pathways described by the E14 5.1 and 6.1



pathways. A step towards this will be the planned training material on the S7B Q&As, which the ICH Implementation Working group will release over the next year.

## REFERENCES

1. ICH E14 Questions & Answers (R3) December 10, 2015.
2. Darpo B, and Garnett C. Early QT assessment--how can our confidence in the data be improved? *Br J Clin Pharmacol.* 2013;76(5):642-8.
3. Darpo B, Garnett C, Keirns J, and Stockbridge N. Implications of the IQ-CSRC Prospective Study: Time to Revise ICH E14. *Drug Saf.* 2015;38(9):773-80.
4. Darpo B, Sarapa N, Garnett C, Benson C, Dota C, Ferber G, Jarugula V, Johannesen L, Keirns J, Krudys K, et al. The IQ-CSRC prospective clinical Phase 1 study: "Can early QT assessment using exposure response analysis replace the thorough QT study?". *Ann Noninvasive Electrocardiol.* 2014;19(1):70-81.
5. Timmers M, Sinha V, Darpo B, Smith B, Brown R, Xue H, Ferber G, Streffer J, Russu A, Tritsmans L, et al. Evaluating Potential QT Effects of JNJ-54861911, a BACE Inhibitor in Single- and Multiple-Ascending Dose Studies, and a Thorough QT Trial With Additional Retrospective Confirmation, Using Concentration-QTc Analysis. *J Clin Pharmacol.* 2018;58(7):952-64.
6. S7B IHTG. 2005.
7. Garnett C, Bonate PL, Dang Q, Ferber G, Huang D, Liu J, Mehrotra D, Riley S, Sager P, Tornoe C, et al. Scientific white paper on concentration-QTc modeling. *Journal of pharmacokinetics and pharmacodynamics.* 2018;45(3):383-97.

## Dr. Robert Kleiman

Dr. Robert Kleiman is a board-certified cardiologist and cardiac electrophysiologist who has performed research in both basic cellular electrophysiology as well as clinical electrophysiology. Dr. Kleiman completed his training at the University of Pennsylvania and was a member of a cardiology practice for 12 years before joining ERT in 2003. Dr. Kleiman is currently ERT's Chief Medical Officer and Vice President, Global Cardiology. His responsibilities include oversight of ERT's cardiology services, consulting with external clients and managing overall satisfaction of ERT's global customers, including all aspects of ERT's solutions.



## Borje Darpo

As ERT's Chief Scientific Officer, Borje Darpo, MD, PhD oversees ERT's cardiology services and consults with external customers to ensure the cardiac safety of their compounds in development. He is board-certified in cardiology and internal medicine and has 20 years of experience overseeing projects across all phases of clinical development.

