Time for a Fully Integrated Nonclinical–Clinical Risk Assessment to Streamline QT Prolongation Liability Determinations: A Pharma Industry Perspective

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Defining an appropriate and efficient assessment of drug-induced corrected QT interval (QTc) prolongation (a surrogate marker of torsades de pointes arrhythmia) remains a concern of drug developers and regulators worldwide. In use for over 15 years, the nonclinical International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) S7B and clinical ICH E14 guidances describe three core assays (S7B: *in vitro* hERG current & *in vivo* QTc studies; E14: thorough QT study) that are used to assess the potential of drugs to cause delayed ventricular repolarization. Incorporating these assays during nonclinical or human testing of novel compounds has led to a low prevalence of QTc-prolonging drugs in clinical trials and no new drugs having been removed from the marketplace due to unexpected QTc prolongation. Despite this success, nonclinical evaluations of delayed repolarization still minimally influence ICH E14-based strategies for assessing clinical QTc prolongation and defining proarrhythmic risk. In particular, the value of ICH S7B-based "double-negative" nonclinical findings (low risk for hERG block and *in vivo* QTc prolongation at relevant clinical exposures) is underappreciated. These nonclinical data have additional value in assessing the risk of clinical QTc prolongation when clinical evaluations are limited by heart rate changes, low drug exposures, or high-dose safety considerations. The time has come to meaningfully merge nonclinical and clinical data to enable a more comprehensive, but flexible, clinical risk assessment strategy for QTc monitoring discussed in updated ICH E14 Questions and Answers. Implementing a fully integrated nonclinical/clinical risk assessment for compounds with double-negative nonclinical findings in the context of a low prevalence of clinical QTc prolongation would relieve the burden of unnecessary clinical QTc studies and streamline drug development.

Between 1988 and 2001, 10 diverse therapeutic drugs were withdrawn from the global marketplace due to sudden cardiac death and an unbalanced benefit to risk assessment for patients.[1] These sudden deaths were attributed to torsades de pointes (TdP), a ventricular tachyarrhythmia that is preceded by prolongation of the corrected QT (QTc) interval of the

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electrocardiogram (ECG) and may be self-limiting or degenerate into life-threatening ventricular fibrillation. The prevalence of drug-induced TdP is rare and seldom detected during drug development because it requires a coincidence of risk factors: sufficient drug exposure in cardiac tissue, hERG blockade, and a patient-specific susceptibility.[2] Subsequent preclinical safety pharmacological investigations determined that the withdrawn drugs had a common feature of inhibiting hERG channel function.[3] The hERG channel mediates the major outward potassium current known as I_{Kr}, a predominant repolarizing current driving ventricular repolarization. Drug-induced QTc prolongation *in vivo* is a consequence of hERG block *in vitro* that can be detected with high sensitivity in humans and nonrodent animal models with ECG monitoring.[4–6]

In response to the recognized link between drug treatment, delayed repolarization and TdP, two regulatory documents were implemented. Both were finalized to Step 4 in 2005: the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) S7B document described two principal nonclinical studies (*in vitro* hERG and *in vivo* QT assays) useful to assess the risk of QTc prolongation, and the ICH E14 document described protocols to assess clinical QTc prolongation (defining the "thorough QT" (TQT) study[7,8]). This regulatory response led to the eventual use of the *in vitro* hERG & *in vivo* QT assays for selecting and profiling emerging drug candidates, and clinical (TQT) studies to assess the risk of QTc prolongation (a surrogate marker of TdP risk) to guide further clinical evaluations and eventual product (drug) labeling.

Based on our collective experience in drug discovery and development, and cardiac safety consortium reports, the ICH S7B and E14 workflows have proven successful as evidenced by the fact that no new approved drugs have been associated with an unacceptable TdP risk, which was the intent.[9] However, any preclinical or clinical signal, i.e., hERG blockade or QTc prolongation may have had the unintended consequence of preventing the development of otherwise safe and efficacious drugs.[10] Furthermore, the paradigm does not directly assess the arrhythmogenic risk of a compound and instead relies on QTc prolongation, a sensitive end point for delayed ventricular repolarization and surrogate biomarker for TdP. In 2013, the Comprehensive *in vitro* Proarrhythmia Assay (CIPA)[11] was originally proposed to further evaluate TdP risk based on a mechanistic electrophysiological understanding of proarrhythmia with three primary nonclinical assays—multiple cardiac ion channel screening, *in silico* reconstruction of drug-induced repolarization abnormalities based on the ion channel profile, and proarrhythmic signals in human stem cell-derived cardiac myocytes.[9,12,13] Such an approach provided the additional advantage of guiding early selection of novel drug candidates and avoiding costly failures due to QTc prolongation detected much later in drug development. A complementary objective was subsequently added to CIPA aimed at understanding early first-in-human (FIH) QT studies and reducing the need for a mandatory TQT assessment. Two years after the initial CIPA proposal, a new revision to the ICH E14 Q&A (2015, E14 Q&As (R3))[14] document was published that enabled the use of concentration-QTc modeling as an alternate clinical approach to assess QTc prolongation without the need for a burdensome TQT study.[14–16]

As a result of these changes, drug makers now had multiple approaches to evaluate proarrhythmia risk and delayed repolarization using new nonclinical assays or clinical concentration-QTc methods (respectively) to potentially avoid an obligatory TQT study. While these changes were promising, the actual framework for their validation (i.e., CIPA), implementation, impact on regulatory decision making, global adoption, and integration with established S7B/E14 processes was unclear. A potential consequence of the clinical concentration-QTc response modeling in E14 is that it unintentionally diminished the regulatory impact and value of the ICH S7B core assays and mechanistic approaches inspired by the CIPA proposal. The lack of an explicit link between ICH S7B and E14 is a recognized example of a misaligned regulatory strategy with significant negative consequences:[1] (i) excessive and wasteful resource utilization to conduct obligatory TQT assessments, especially for low risk agents;[17] (ii) increased drug development costs, e.g., more than $1 billion spent on 450-plus TQT studies;[12] and (iii) little to no impact on approval and product labeling for drugs that demonstrate a positive TQT finding.[6] From the pharmaceutical company perspective, the lack of association of these seemingly independent but related guidances signaled a regulatory mindset that only clinical TQT data have importance, and that nonclinical hERG/QTc data have minimal influence or are dismissed completely in regulatory decisions in some regions. From our perspective, important questions remain regarding the nonclinical guidances some 15 years after their implementation: (i) How can drug sponsors improve and elevate the regulatory value of the nonclinical ICH S7B core assays, and (ii) How can sponsors leverage current and new nonclinical models to improve proarrhythmia assessment to minimize (or eliminate) the need for intensive and costly clinical QTc monitoring of promising drugs in development?

The views expressed in this manuscript reflect the collegial and consolidated experience of safety scientists from multiple pharmaceutical companies. Such discussions (originally prompted by the European Federation of Pharmaceutical Industries and Associations (EFPIA) and then endorsed by Pharmaceutical Research and Manufacturers of America (PhRMA) and Japan Pharmaceutical Manufacturers Association (JPMA), led to the formation of an international working group to discuss the opportunity presented by the ICH S7B-E14 Concept paper.[18] The members of the ICH S7B-E14 Industry Support Group (35 representatives) have a collective knowledge and practical wisdom based on 500-plus years of drug development experience. Furthermore, this group has also contributed to the progression of more than 1,800 drug candidates (e.g., small molecules, biologicals, and other modalities) into clinical development and successful registration of over 150 new drug products.

Our objective is to lay out the state of present and emerging science that advocate for the integration of the ICH S7B and E14 strategies and practice. Our recommendations offer opportunities to enhance drug development and assure safe selection and progression of novel pharmacologic therapies for unmet medical diseases.

ICH S7B-E14 CONCEPT PAPER AND IMPLEMENTATION WORKING GROUP

In 2018, an ICH S7B-E14 Q&A Concept Paper[18] was endorsed with the explicit objective to link these separate guidance documents for the first time, a process that will be overseen by the Implementation Working Group (IWG, membership published on the ICH website) through a Q&As process. As described in the Concept Paper, the primary aims of Stage 1 are to use more informative nonclinical evaluations to reduce the clinical burden of TQT assessment, while those of Stage 2 include the facilitation of proarrhythmia risk assessments to supplement QTc interval studies, especially for drugs associated with minimal QTc prolongation. For example, Stage 1 will primarily address the requirements to improve the data quality needs and robustness of the hERG/*in vivo* QT (ICH S7B) assays. There will be Q&As for an ICH S7B integrated risk assessment and on principles of proarrhythmia models in preparation for Stage 2. The step 2a/2b endorsement of the draft Stage 1 Q&As is due in the third quarter of 2020 and will be released for public consultation and public meetings immediately thereafter with public comment to be received from the different regions by year end.[19] In Stage 2, the IWG will address gaps, models, and data needs oriented towards interpretation of clinical QTc prolongation and associated proarrhythmia risk, as well as appropriate late-phase monitoring, risk mitigation, and drug labeling.

It is our collegial opinion that if the emergent Q&As are to have a meaningful positive impact on drug development, some key points need to be addressed and considered by the IWG:

1. *A High Prevalence of Negative TQT Studies:* Multiple sponsors have determined the translation between nonclinical and clinical effects of compounds and have established internal quality standards for the execution of nonclinical assays such that most FIH-QTc and TQT evaluations for new chemical entities are negative; this has been confirmed by multiple analyses[6,20,21] (**Table 1**). In addition, the quality of QTc/ECG monitoring in repeat-dose toxicology studies has improved since the issuance of ICH S7B.[22–25] Integration of multiple data sets spanning acute (cardiovascular safety pharmacology) and chronic (toxicology) safety studies may now allow detection of delayed QTc effects due to drug accumulation, effects on hERG channel trafficking, or hERG-blocking metabolites. Based on this evidence, could these nonclinical data be utilized more effectively, confidently, and systematically by the regulatory community to inform and reduce the need for intensive clinical QTc assessment for low-risk compounds? There is substantial precedence for doing so: The probability of hERG inhibition and QTc prolongation of monoclonal antibodies (mAbs) and antibody–drug conjugates is scientifically understood and has been judged to be sufficiently low to allow them to be developed with only routine safety ECG assessment in clinical trials.[14,26,27] The cardiac QTc/TdP safety of mAbs has been substantiated by numerous reports[28,29] (**Table 1**). Building upon this knowledge, the same science-based rationale should be applied to small chemical molecules that demonstrate a low probability of prolonging ventricular repolarization, by having demonstrated minimal (or no) *in vitro* hERG/I_{Kr} block and minimal (or no) *in vivo* QTc prolongation at concentrations exceeding clinical exposures ("double-negative nonclinical findings"), in a robust, comprehensive and integrated ICH S7B data package (see section "Linking ICH S7B and ICH E14: Acknowledging the Predictive Value of the Core Assays").
2. *Conduct of the TQT Study Can be Confounded or Not Feasible*: There are instances when a TQT evaluation is not feasible, limited, unethical, impractical, or potentially equivocal, including in oncology settings. This can occur if the exposure tested in a concentration-QTc analysis is insufficient to offer reassurance with respect to sensitivity, when the drug causes large changes in heart rate that will confound QTc assessment,

Table 1 Summary of clinical TQT/QT outcomes for new drug candidates and biotechnology-derived therapeutics: high prevalence of negative studies

TQT/QT reports	Source (analysis years)	Drug type	Total drugs	Negative drugs	Positive drugs	Comment on positive effects
Wisniowska *et al.*, 2020[a]	Literature (2005–2019)	NCE	154	123	16	Effect size not reported
Park *et al.*, 2018	FDA database (2006–2012)	NCE	150	107	43	17: < 10 milliseconds 19: 10–20 milliseconds 7: > 20 milliseconds
Ewart *et al.*, 2014[b]	Proprietary database (2001–2012)	NCE	111	97	14	Effect size not reported; identified in FIH
Jackson *et al.*, 2015	EMA database & literature (1998–2015)	mAb	28	27	1	Effect size not reported; an indirect mechanism
Schrieber *et al.*, 2014	FDA database (not stated)	mAb & ADC	15	15	0	No need for TQT study

ADC, antibody–drug conjugate; EMA, European Medicines Agency; FDA, US Food and Drug Administration; FIH, first-in-human; mAb, monoclonal antibody; NCE, new chemical entity; TQT, thorough QT.

[a]15 drugs were reported to have inconclusive or unstated results in the original information source. [b]113 agents were included in the complete data set, but two caused QT shortening (FIH) and were excluded.

when the studies must be conducted in patients where there may be confounding cardiac effects, or when a placebo control or positive control arm is technically not possible. Rather than require more clinical assessment, carry forward the uncertainty into late-phase clinical testing, or potentially limit postmarket drug use with cautionary label language, can the nonclinical data supplement the available clinical data to reduce uncertainty and provide confidence in clinical cardiac safety? Relying on our experience-based opinion, the answer to this question is yes.

3. *Multiple Ion Channel Blockade:* There is increased awareness that other cardiac currents can mitigate or modulate the effects of hERG current block on repolarization and proarrhythmia, e.g., I_{Na} (late sodium) and I_{Ca} (calcium) currents. While not new, the concept of multichannel block has emerged to explain the lack of concordance between potency of hERG current block and delayed repolarization observed preclinically or clinically[30]. As proposed through CIPA, nonclinical assessments of multichannel effects can be pursued by two approaches: (i) *in silico* reconstruction of human ventricular repolarization utilizing *in vitro* data (inhibitory potency of a given drug for the potentially relevant cardiac ion channels) to classify the risk of TdP based on changes in net repolarizing current;[31,32] or (ii) drug-induced changes in ventricular repolarization are assessed using extracellular field potential recordings (or transmembrane potential recordings) using native human primary cardiomyocytes or human induced pluripotent stem cell derived cardiomyocytes to assess changes in repolarization.[33] Both approaches provide a more comprehensive integrated assessment of the potential of a drug to affect myocyte repolarization mechanistically (*in silico*) or phenotypically (human induced pluripotent stem cell derived cardiomyocyte). Progress has been gradual with these models, and best-practice approaches are presently being described and defined,[34,35] so the Q&A process will need to define principles for validating these new assays such that all stakeholders have confidence in the quality and robustness of the models. Similarly, there may be a need to reevaluate other *in vitro* and *in vivo* proarrhythmia models, e.g., ventricular wedge, atrioventricular blockade in nonrodents, methoxamine-induced TdP in rabbits, and electromechanical window, given their proposed predictive safety value and use by some pharmaceutical companies.[36–40] Consistent methodologies will need to be uniformly adopted to assure that these new tools add value to regulatory decisions.[41] As a result, these approaches to assessing the potential proarrhythmia effects have been relegated to Stage 2.
4. *Direct vs. Indirect Effects on QTc Prolongation:* There are various indirect factors that may affect drug-induced QTc prolongation, including hemodynamics, heart rate, glycemic state, and body temperature. Other conditions that may affect the sensitivity of the myocyte to hERG block include intracellular pH changes, hyperkalemia or hypokalemia, and alterations in sympathetic/parasympathetic tone. Do these carry the same risk for TdP as direct cardiac effects of hERG inhibition or block of other cardiac ion channels? The answers to these questions will require additional time for investigation.

LINKING ICH S7B AND ICH E14: ACKNOWLEDGING THE PREDICTIVE VALUE OF THE CORE ASSAYS

Although the ICH S7B and ICH E14 guidance documents were never linked in a regulatory context, our companies have practically integrated combined nonclinical hERG/QTc findings together with phase I (FIH) QTc evaluations to support internal decision making over many years. The combination of assays and their performance from the earliest stages of discovery through early clinical testing has minimized unexpected results in TQT study outcomes, which has then led to a drastic reduction of TdP incidence in the clinic. Thus, the time has come to introduce and incorporate a fully integrated proarrhythmia risk assessment based on both nonclinical ICH S7B findings and early clinical QTc experience to (i) better understand the torsadogenic risks of minimal QTc prolongation, (ii) rationalize the need for clinical tests required on a case-by-case basis, (iii) improve product safety and labeling, and (iv) guide future studies to understand the mechanisms and liabilities of minimal QTc prolongation (**Figure 1**).

During drug development, safety-related decision making relies on an integrated weight of evidence approach. Since there are few simple predictive tests for drug responses, the weight of evidence is built upon multiple assessments. ICH E14 relies on a single assessment, albeit built on a comprehensive understanding of drug exposure and a rigorous standardized practice for QT interval analysis. The performance of the TQT study as a predictor of TdP liability was never evaluated formally; the assay is generally considered to be sensitive but to lack specificity[9] (see **Supplementary Material**). This specificity deficiency introduces bias, thus the discriminatory power is asymmetric and favors a negative result. That is, a negative TQT outcome is far more likely to be a true negative and not a false negative (**Figure 2**). On the other hand, when the TQT finding is positive, it is possible that the signal might be a false positive, i.e., the drug may not be truly associated with an increased TdP risk (**Figure 2**). This latter instance can have negative unintended consequences, including the worst-case scenario: the unnecessary termination of an innovative new drug.[6,12,17]

In contrast to ICH E14-based studies, the positive and negative discriminatory power of the hERG and *in vivo* QT assays in relation to clinical outcomes, i.e., TQT and TdP, have been assessed over many years, and consistent observations have been described regarding their prognostic utility. For example, independent analyses have characterized the ability of these assays to detect compounds likely to be TQT positive[5,6,42,43] or have enhanced TdP risk.[44–49] The translation of QTc interval prolongation specifically from large animals to the clinic has also been extensively evaluated (dog,[20,50,51] nonhuman primate,[46,52] and multiple species[53]) and their predictive value demonstrated, which was unknown 15 years ago when ICH S7B was introduced. Within our companies, these core assays, in concert with early-stage or exploratory screening assays[54] (**Figure 1**) have directly driven the design and selection of molecules with low hERG potency and reduced the clinical likelihood of QTc prolongation and TdP risk. An example of such a process and its impact has been described by Price *et al.*[55] and Hasselgren *et al.*[56] and typifies our large pharmaceutical company experiences.

The overall predictive value and discriminatory power of the hERG and *in vivo* QT assays based on a collection of

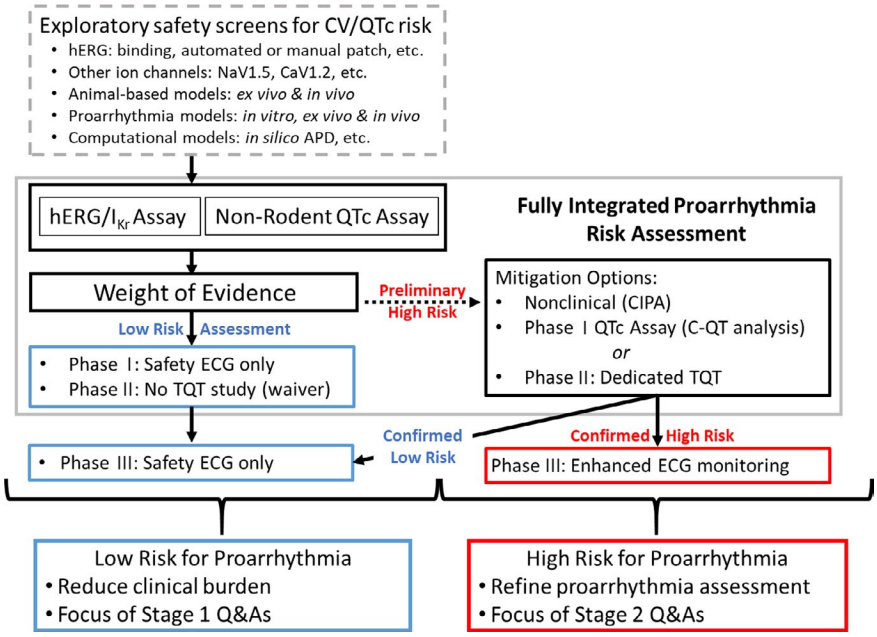

Figure 1 Fully integrated proarrhythmia risk assessment: leveraging exploratory safety data, ICH S7B core and phase I QT assays for a new and balanced approach. The schematic outlines the overall process and data streams that can be used to integrate the ICH S7B & E14 documents. The nonclinical core assays (hERG/*in vivo* QT; black box) and early-stage screening assays (gray dash box) are primary inputs for a WoE-based proarrhythmia risk assessment (see section "Linking ICH S7B and ICH E14: Acknowledging the Predictive Value of the Core Assays"). New drug candidates identified as low risk ("double-negative") based on nonclinical WoE (blue boxes) would bypass a TQT study and benefit from basic safety ECG monitoring during clinical development. Examples of low-risk drugs include mAbs and small molecules with large hERG and *in vivo* QTc margins. Some promising new drug candidates may have proarrhythmic signals ("Preliminary High Risk") that require more nonclinical and/or clinical assessment ("Mitigation Options"). This additional safety data would augment the WoE and confirm agents as having either low or high proarrhythmia risk, i.e., inform the degree of phase III ECG collection. The ICH S7B-E14 Stage 1 and 2 Q&As process will address key nonclinical and clinical assay elements to improve current practices, and enable this new approach to develop a fully integrated proarrhythmia risk assessment for future drug candidates. APD, action potential duration; C-QT, concentration-QT modelling; CaV1.2, cardiac calcium channel; CIPA, Comprehensive *in vitro* Proarrhythmia Assay; CV, cardiovascular; ECG, electrocardiogram; hERG, human Ether-à-go-go-Related Gene; ICH, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use; IKr, rapid component of the delayed rectifier potassium current; mAbs, monoclonal antibodies; NaV1.5, cardiac sodium channel; QTc, corrected QT interval; TQT, thorough QT; WoE, weight of evidence.

nonclinical–clinical data sets (N ≈ 200) was determined, and the details of the quantitative analysis are striking (**Figure 2; Table 2**; **Supplementary Material**). This analysis indicates conclusively that an agent that is considered negative in both ICH S7B nonclinical tests has a very low probability of QTc prolongation (3.8%) and TdP risk (< 0.1%) regardless of the outcome of the clinical testing. The results (**Supplementary Material**) also demonstrate that the *in vivo* QT assay is the stronger predictor of a TdP liability compared with the *in vitro* hERG assay. Based on this high predictive value, there are several scenarios where a robust ICH S7B data package provides a solid foundation for a fully integrated proarrhythmia risk assessment that obviates the need for enhanced QTc assessment in the clinic (**Table 2**):

1. Since the prior probability of a new chemical entity exhibiting QTc prolongation (or being torsadogenic) is low, the nonclinical assessment may offer sufficient negative discriminatory power to negate the need for a quantitative clinical QTc assessment. This "low prior probability" scenario is already effectively acknowledged in existing ICH E14 clinical Q&As since mAbs do not require TQT assessment. Compounds from other classes, e.g., small molecules, that demonstrate low risk in the hERG assay (provisionally defined as > 30-fold ratio between the hERG-IC_{50} (concentration of drug producing 50% inhibition) value and the clinical free therapeutic drug level) and are negative in the nonclinical QTc evaluation (provisionally defined as > 10-fold ratio between the highest free plasma drug level with no QTc effect and the relevant clinical free therapeutic drug level) would benefit similarly, i.e., "double-negative nonclinical finding" outcome. Based on our collective experience, nonrodent QTc telemetry studies have the sensitivity to detect a wide range of QTc interval changes (e.g., 10 to 60 milliseconds) and are valuable for estimating safe human exposure margins.[20,42,53,57] The margin values for the hERG and *in vivo* QTc assessment have two components, a threshold change (% inhibition or degree of interval change) and a concentration multiple (based upon clinical supratherapeutic exposures). The margins described here are generally consistent with numerous published studies[5,6,21,43–46,48–50,58] (see **Supplementary Material**), although there were subtle differences in the threshold value and concentration multiple used in each publication. A more consistent agreement should be reached

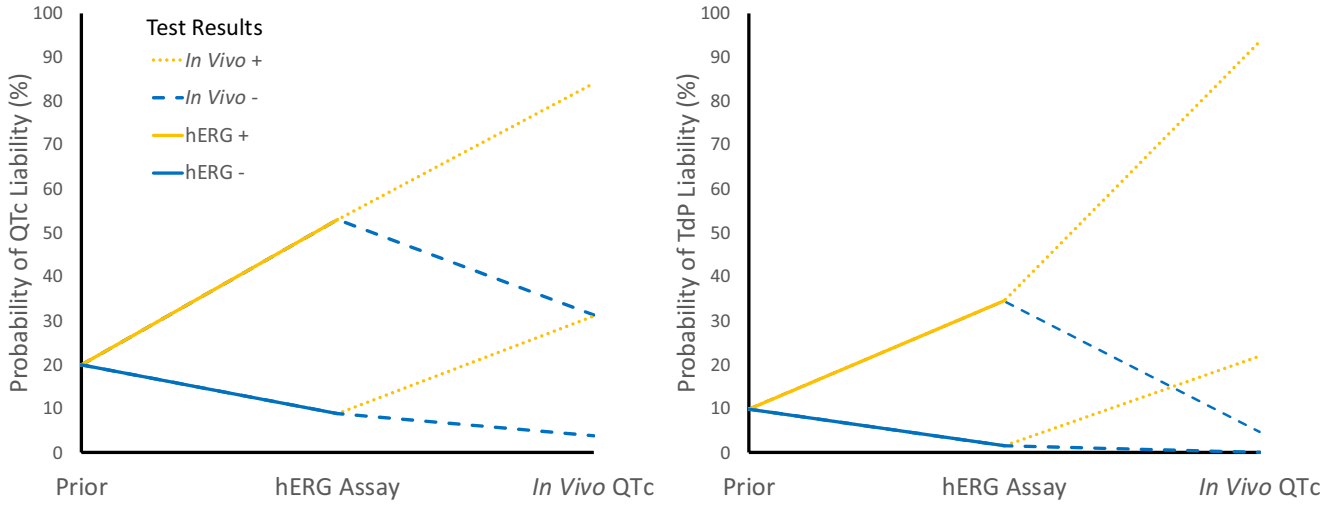

Figure 2 ICH S7B core assay outcomes and the probability of clinical proarrhythmia risk. The figure shows the posttest probability of a QT prolongation liability (left) or TdP liability (right) after the ICH S7B core assays (x-axis) have been conducted. After the hERG test there are two possible outcomes, and following the *in vivo* QT evaluation there are four possible outcomes. The prior probabilities (20% for QTc and 10% for TdP) are described in the Supplementary Material (**Supplement S1**). A higher prior probability for QTc is expected given that not all QTc-prolonging drugs are associated with TdP. The probability of QT prolongation in man following a nonclinical double-negative is 3.8% (solid + dash green lines). The probability of a TdP liability following a nonclinical double-negative is 0.1% (solid + dash green lines). It is anticipated that improvements in nonclinical study conduct or quality will reduce the probability even further (for the double negative cases). hERG, human Ether-à-go-go-Related Gene; ICH, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use; QTc, corrected QT interval; TdP, torsades de pointes.

on the threshold and concentration multiples and whether the prediction is based on clinical QTc prolongation.

2. Oncology therapeutics, including small molecules, are typically evaluated in patients during FIH trials, which makes it difficult to conduct early QTc evaluations. For these products, the nonclinical hERG and QTc assays could be leveraged primarily to determine the proarrhythmia risk assessment. This scenario deserves consideration, but also further regulatory discussion, given that ICH S9 guidance indicates that stand-alone cardiovascular safety pharmacology studies are not required for anticancer drugs to be first tested in oncology patients.
3. Compounds with low systemic exposure (e.g., topical agents or with low oral bioavailability) may not require -QT or TQT assessment if nonclinical data demonstrate low risk.
4. At a minimum, a "double-negative" ICH S7B evaluation could be leveraged when interpretation of clinical QTc studies is confounded or compromised by limited exposure range, prominent heart rate effects, lack of a placebo group, inability to safely dose subjects, or lack of a positive control. As regulatory confidence in the nonclinical models grows, there are a number of scenarios where the nonclinical data would reduce the clinical QTc evaluation burden. New therapeutic modalities like oligonucleotides and small interference RNA, which have intracellular targets and complex pharmacokinetic/pharmacodynamic relationships, are examples to consider using this integrated strategy.

Scenarios where nonclinical evaluation could be utilized to support a proarrhythmia assessment when the clinical QTc assessment is positive, which will be addressed in Stage 2, are also outlined (**Table 2**; **Supplementary Material**). These represent cases where a new clinical candidate demonstrates a positive signal ("hit") in one ("single positive") or both ("double positive") of the ICH S7B assays. In these scenarios, additional mechanistic evaluations, including approaches such as those described in the CIPA proposal, could clarify the proarrhythmia risk and provide a path forward for further development of that compound. The strategy and tactical aspects of applying the CIPA principles will be incorporated into Stage 2.

LIMITATIONS OF S7B CORE ASSAYS: NEED FOR BEST PRACTICES

While our drug development knowledge and practical experience with the S7B assays shape our views on their value for proarrhythmia risk assessment, our opinions are equally tempered by our understanding of the need for industry-wide best practices for the hERG and *in vivo* QTc assays. In contrast with the standardized execution and expectations for the TQT study, there are no standard protocols, experimental conditions, or regulatory expectations to guide the execution of the nonclinical core assays.[12,13,57] This could contribute to inconsistency in study execution or the interpretation of findings, important issues that emerging drug sponsors (e.g., new or small companies) may encounter without having significant experience using S7B assays. The lack of consensus in hERG assay conduct is likely the primary reason for variance in potency estimates, i.e., IC_{50},[12,35,45,59,60] which confounds the robustness of hERG-based safety margin calculations. Similarly, the absence of a standard in methodologies and protocols for *in vivo* QTc assays, lack of validation information, QTc sensitivity estimates, etc., make it difficult to assess the overall "quality" of the study data and may reduce the value of *in vivo* QTc data for human safety assessment.[57] Based on our current synopsis (this paper), the

Table 2 Implementing the fully integrated proarrhythmia risk assessment for low, intermediate, and high-risk scenarios: leveraging the predictive value of ICH S7B core assays

QT prolongation risk category	hERG assay[a]	*In vivo* QT Assay[b]	Probability of clinical QTc prolongation (%)[c]	Probability of TdP liability (%)[c]	ICH S7B follow-up studies for consideration	Potential early clinical QTc testing
Low	Negative	Negative	3.8	0.1	None	Collect safety ECGs.[d]
High	Positive	Positive	84.1	93.5	Potential use of proarrhythmia model, e.g., CIPA paradigm.	Quantitative assessment of QT and other intervals.
Intermediate	Negative	Positive	31.1	22.0	Consider (i) characterizing potential for hERG-blocking metabolite, (ii) other evidence of indirect QT effects e.g., temperature or hypokalemia, (iii) use of proarrhythmia model (e.g., CIPA paradigm).	Rigorous Quantitative assessment of QT and other intervals as indicated by follow-up studies.
	Positive	Negative	31.4	4.7	Consider heart rate effects. Consider additional ion channels or kinetics of hERG block. Consider use of proarrhythmia model (e.g., CIPA paradigm).	Rigorous quantitative assessment of QT and other intervals as indicated by follow-up studies.

CIPA, Comprehensive *in vitro* Proarrhythmia Assay; hERG, human Ether-à-go-go-Related Gene; ICH, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use; TdP, torsades de pointes.

[a]Negative or positive hERG outcome is defined by high (≥ 30-fold) or low (< 30-fold) margin, respectively. The hERG margin is based on ratio of hERG-IC_{50} (concentration of drug producing 50% inhibition) value relative to estimated clinical free therapeutic plasma concentration. [b]The *in vivo* QTc assay is considered negative when the ratio between the highest free plasma concentration without effect (e.g., < 10 milliseconds prolongation of QTc) and the estimated clinical free therapeutic exposure is ≥ 10-fold. If this ratio is < 10, the outcome is positive. [c]The determination of probability values is described in the supplement; the values are also depicted in **Figure 2**. [d]For low-risk agents, the emergence of QTc interval prolongation could be related to human-specific metabolites or confounding physiological effects like reduced body temperature or autonomic effects. Human metabolite assessment occurs routinely in early clinical development, thus relevant metabolites could be profiled in the S7B assays to expand the integrated risk assessment.

S7B core assays have value despite these shortcomings, and we acknowledge that their value can be enhanced further through the development and consistent implementation of best practices. The need for reproducible and consistent cardiovascular safety testing is recognized by the pharmaceutical industry, contract research organizations (that typically execute S7B core assays), and the regulatory community to improve overall confidence in the use of S7B core assays for risk assessment. The identification and implementation of best practices is necessary to continually improve the performance of S7B core assays, which is a key step in the development of consensus safety margin recommendations.

We also acknowledge that our opinions on the value of the S7B assays expressed in this paper are based largely on our professional experiences, as well as the available scientific literature, which is likely influenced by publication bias. Publication bias is a known factor given that "the majority of safety pharmacology cardiovascular assessments (of priority drugs) are not published in the scientific literature, although some reports become available when a new medicine is approved."[57] For our analysis on the predictive value of the S7B core assays (see section "Linking ICH S7B and ICH E14: Acknowledging the Predictive Value of the Core Assays" and **Supplementary Material**), we systematically reviewed and included all publicly available evaluations where multiple compounds defined as positive or negative relative to QTc prolongation or TdP liability were examined and where the data were in a form where sensitivity and specificity could be determined. These publications included those where reference agents and standard methods were used,[47,48,58] were performed or sponsored by established pharmaceutical companies with large data sets collected over many years,[5,20,42] and studies submitted across the pharmaceutical industry or published experience were examined.[6,43–45]

FULLY INTEGRATED PROARRHYTHMIA RISK ASSESSMENT: THE FUTURE

The ability to bring new medicines to patients requires innovation in all phases of drug discovery and development, including the pragmatic, effective, and efficient use of nonclinical and clinical resources. In clinical QTc evaluations, the initial obligatory use of TQT studies was challenged on various levels,[15,17,61] leading to strategies incorporating exposure response modeling from phase I studies as an alternative to the conduct of dedicated TQT studies.[16] In nonclinical evaluations, ICH S7B-based approaches (most importantly incorporating best practices consistently across the industry) as well as follow-up studies have matured and are established and widely adopted in earlier drug discovery efforts. These have significantly reduced the prevalence of clinical candidates eliciting clinical QTc prolongation.[5,6,20,21,42] The continuing improvement in nonclinical strategies provides the opportunity to "rethink" QTc risk assessment by meaningfully considering both nonclinical and clinical findings *in combination* to influence subsequent clinical evaluations, regulatory considerations, and product labeling. The continued prominence of clinical QTc interval evidence as the primary basis for safety decision making, in the face of changing prior probabilities for QTc prolongation (that have evolved with the continued use of nonclinical ICH S7B-based assays) can lead to poor decisions and increased

development costs.[61] The modest positive discriminatory power of a TQT study for TdP liability and the diminishing prior probability of clinical QTc prolongation leads to a low positive predictive value of a TQT study, much lower now than ever before, and places future NCEs at greater risk of inappropriate categorization and labeling. Uncertainty remains in the definition of the necessary exposure threshold and safety margin, with the potential for different interpretations globally; these questions should be systematically addressed, ideally in Stage 2 of the S7B/E14 Q&A process.

The improved evaluation of drugs demonstrating "double-negative nonclinical findings" (no hERG/IKr or *in vivo* QTc prolongation findings at appropriate exposure margins) provides an opportunity to implement a more fully integrated risk strategy in which nonclinical findings meaningfully influence clinical development. Future translational experience with drugs having more complex nonclinical (e.g., no hERG/I_{Kr} findings but minimal *in vivo* QTc prolongation) and clinical findings (e.g., QTc interval prolongation related to the formation of human-specific drug metabolites) will guide the implementation of a fully integrated nonclinical/clinical risk assessment for a wider range of NCEs (**Table 2**). These efforts may include additional nonclinical assays such as those advanced by CIPA, when appropriate. The need remains for harmonizing regulatory decision making worldwide incorporating both nonclinical (ICH S7B-based) and clinical (E-14 based) guidelines to enable the cost-effective use of resources to speed development of safe drug candidates devoid of TdP risk liabilities.

SUPPORTING INFORMATION

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