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Comprehensive In Vitro Proarrhythmia Assay (CiPA) Update from a Cardiac Safety Research Consortium / Health and Environmental Sciences Institute / FDA Meeting

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Abstract

A Cardiac Safety Research Consortium / Health and Environmental Sciences Institute / FDA-sponsored Think Tank Meeting was convened in Washington, DC, on May 21, 2018, to bring together scientists, clinicians, and regulators from multiple geographic regions to evaluate progress to date in the Comprehensive In Vitro Proarrhythmia Assay (CiPA) Initiative, a new paradigm to evaluate proarrhythmic risk. Study reports from the 4 different components of the CiPA paradigm (ionic current studies, in silico modeling to generate a Torsade Metric Score, human induced pluripotent stem cell–derived ventricular cardiomyocytes, and clinical ECG assessments including J-Tpeakc) were presented and discussed. This paper provides a high-level summary of the CiPA data presented at the meeting.

Keywords

balanced ion channel-blocking drugs, CiPA, human induced pluripotent stem cell-derived ventricular cardiomyocytes, J-Tpeakc, torsade de pointes, torsade metric score

Introduction

Early public scientific discussions of the Comprehensive In Vitro Proarrhythmia Assay (CiPA) Initiative were held at a Think Tank Meeting convened at the US Food and Drug Administration (FDA) headquarters on July 23, 2013, and sponsored by the FDA, the Health and Environmental Sciences Institute (HESI), and the Cardiac Safety Research Consortium (CSRC).[1] The goals of that Think Tank were to suggest components of CiPA, a new paradigm for assessing proarrhythmic risk, facilitate transparent stakeholder input and discussions, propose potential member organizations of a collaborative program to develop the specifics that would be needed, and consider first pragmatic steps. Since then, many international collaborators on the CiPA Initiative have continued to work on its individual components, and productive discourse has occurred at multiple meetings, including those cosponsored by FDA, CSRC, HESI, and the Safety Pharmacology Society (SPS),[2-4] dedicated sessions at the SPS Annual Meeting for the last 3 years, and a 2017 FDA Advisory Committee meeting.[5]

To bring together scientists, clinicians, and regulators from multiple geographic regions to evaluate progress to date, a CSRC/HESI/FDA-sponsored Think Tank Meeting was convened in Washington, DC, on May 21, 2018. This paper provides a high-level report of the presented results.

Background

While the International Council on Harmonisation (ICH) S7B/E14 regulatory landscape has successfully prevented new drugs with an unrecognized propensity to induce torsade de pointes (Torsade) arrhythmia from entering the market, important unanticipated limitations have become increasingly clear. The

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current landscape focuses largely on 2 surrogate measures that do not have high positive predictive value in identifying torsadogenic drugs—a single outward cardiac potassium repolarizing ionic current (I_{Kr}, flowing through potassium channels encoded by the human ether-à-go-go-related gene [hERG], and referred to as the hERG current throughout this paper) and a single associated electrocardiogram (ECG) characteristic, the QT/QTc interval—rather than on direct evaluation of proarrhythmic risk. This focus has influenced whether drug candidates progress into human testing, since up to 70% of such candidates can exert an influence on hERG[6,7] and are often terminated during nonclinical development programs, and whether clinical development proceeds past early-phase clinical trials if a human QTc effect is demonstrated. Additionally, delays in New Drug Application filing and/or approval of drugs with an otherwise favorable safety profile and a demonstrated therapeutic benefit may have occurred. In contrast, the CiPA approach, which is predicated on a deep mechanistic understanding of the factors that cause Torsade, represents a paradigm shift involving strategies that have the potential to improve specificity in the early detection of genuine torsadogenic proarrhythmic risks by focusing on a drug's actual propensity to cause Torsade.

Drug-induced ventricular repolarization and risk of Torsade are not due solely to hERG block. Rather, they are dependent on a "balance" of multiple inward and outward ionic currents active during the ventricular action potential that together define ventricular repolarization.[4] With regard to drug-induced Torsade, the most important currents in addition to hERG are 2 inward depolarizing currents, the late component of the sodium current (flowing through channels encoded by the Nav1.5 sodium channel gene, and referred to as late sodium current throughout this paper) and the L-type calcium current (flowing through channels encoded by the Cav1.2 calcium channel gene, and referred to as calcium current throughout this paper). Drugs that also reduce late sodium and/or calcium currents at approximately equipotent concentrations to hERG are said to have balanced effects, resulting in a low risk of Torsade. Such drugs are referred to as balanced ion channel–blocking drugs.[8]

Collectively, the 4 components of CiPA seek to characterize more clearly the torsadogenic risk of drugs by providing a more comprehensive assessment of a drug's effect on multiple cardiac ionic currents using human-derived models. The first component is the in vitro assessment of drug-induced effects on multiple ionic currents, focusing on 3 dominant plateau currents, namely hERG, late sodium, and calcium currents. The second is in silico computer modeling, in which individual ion channel data are integrated together in a model of the human ventricular myocyte with the goal of predicting clinical risk of Torsade. This modeling yields a Torsade Metric Score, termed qNET. When calibrated with clinically used drugs categorized into high, intermediate, and low Torsade risk categories, qNET provides a reliable measure of proarrhythmic risk. A third component, in vitro drug effects on human induced pluripotent stem cell–derived ventricular cardiomyocytes (hiPSC-CMs), can also be optionally employed to check for unanticipated effects compared with nonclinical ion channel data and in silico modeling predictions. The fourth component, assessments made during phase 1 clinical trials, plays an important role in determining if there are unexpected ion channel effects manifesting on the human surface ECG compared with nonclinical ion channel data, perhaps because of a human-specific metabolite or differences in predicted protein binding or tissue concentration (eg, leading to unexpected QTc prolongation).

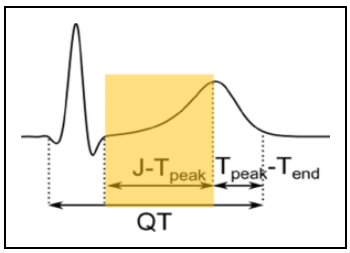

Figure 1. Stylistic representation of QT, J-Tpeak, and Tpeak-Tend. (J-Tpeakc, heart rate–corrected J-Tpeak interval; Tpeak-Tend, the time between the peak of the T-wave and the end of the T-wave.)

In this paradigm, therefore, risk of Torsade will be predicted via in silico modeling of ion channel data, and an ECG biomarker(s) will be used to determine whether there are unexpected ion channel effects in humans. This requires an ECG biomarker that is capable of discriminating between multichannel block with predominant hERG block and balanced ion channel block. The heart rate–corrected J-Tpeak interval (J-Tpeakc), the time between the end of the QRS interval and the peak of the T-wave, has been proposed as such a biomarker. Figure 1 presents a stylistic representation of QT, J-Tpeak, and Tpeak-Tend. Drugs that predominantly block hERG prolong QTc by prolonging both J-Tpeakc (early repolarization) and Tpeak-Tend (the time between the peak of the T-wave and the end of the T-wave, which represents late repolarization). In contrast, balanced ion channel–blocking drugs involving hERG along with late sodium and/or calcium prolong QTc by prolonging Tpeak-Tend without prolonging J-Tpeakc. The absence of significant J-Tpeakc prolongation in the presence of QTc prolongation is therefore thought to be an "ECG signature" of a balanced ion channel–blocking drug.[4]

It is important to note that the ECG assessment is not being performed in isolation, but rather as a part of an integrated risk assessment with the nonclinical data. The assessment of proarrhythmic risk comes from the in silico Torsade Metric Score qNET. As proposed at the meeting, in the presence of a modest QTc prolonging drug (eg, 10- to 20-millisecond [ms] prolongation at highest therapeutic concentrations), a Torsade Metric Score consistent with low proarrhythmic risk and an absence of meaningful J-Tpeakc prolongation suggests a reduced need for ECG monitoring in phase 3 clinical trials, and can also inform labeling. For example, in the future a drug label might state that while a drug prolongs QTc by 15 ms, its integrated risk assessment suggests it is not associated with Torsade.

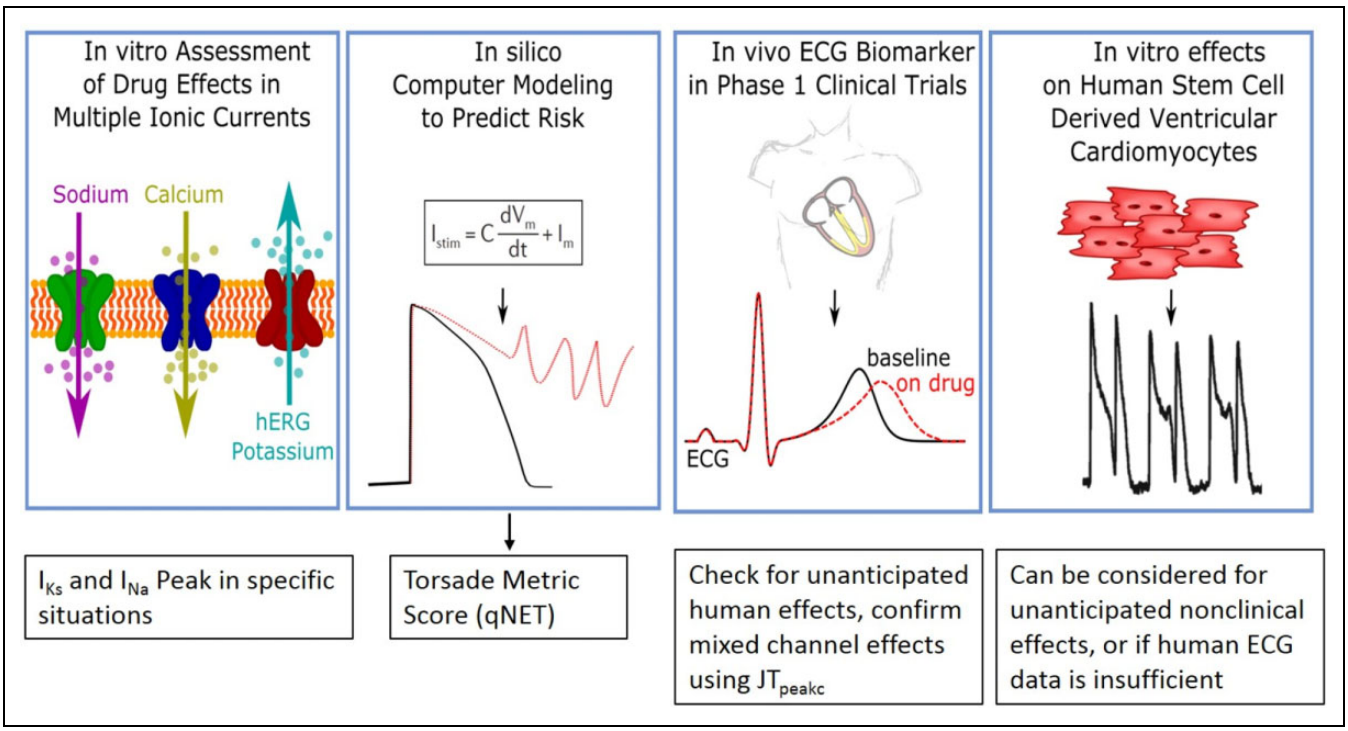

Figure 2. Stylistic representation of CiPA components and early-phase ECG assessment. (CiPA, Comprehensive In Vitro Proarrhythmia Assay; ECG, electrocardiogram.) Adapted from Figure 3, Vicente and colleagues.[8]

It should also be emphasized that the CiPA paradigm allows sponsors the flexibility to employ individual components of the CiPA component core set however they wish, incorporating information obtained into the compound's overall integrated cardiac safety risk assessment. This flexibility includes the freedom to choose to employ none of the components, although this choice would hamper the ability to define proarrhythmic risk and lead to a reliance on prior regulatory pathways. To use CiPA for regulatory decision making, certain aspects will be required. This notion of flexibility is itself an important new development discussed at the Think Tank Meeting, independent of results presented for each of the CiPA components.

The multiple components of the CiPA paradigm are represented in Figure 2.

Results Presented at the Think Tank

The nonclinical data presented at the Think Tank involved studying a set of 28 "CiPA Drugs." These 28 gold standard compounds were chosen to represent a varied spectrum of multiple electrophysiological mechanisms, including multichannel blocking drugs. Each drug was ranked on clinically demonstrated risk of Torsade—high, intermediate, or low—based on published reports, FDA's Adverse Events Reporting System database, other published data sources, and the opinion of expert clinical electrophysiologists and safety specialists. Two subsets were then created: 12 training drugs (4 high Torsade risk, 4 intermediate risk, and 4 low risk) to be used in in silico model development and optimization and 16 validation drugs (4 high Torsade risk, 7 intermediate risk, and 5 low risk) to be used in model validation (see Table 1).

Table 1. CiPA Model Training and Validation Drugs.

Risk Level for Torsade	Model Training	Model Validation
High	Bepridil	Azimilide
	Dofetilide	Ibutilide
	Quinidine	Vandetanib
	Sotalol	Disopyramide
Intermediate	Chlorpromazine	Astemizole
	Cisapride	Clarithromycin
	Terfenadine	Clozapine
	Ondansetron	Domperidone
		Droperidol
		Pimozide
		Risperidone
Low	Diltiazem	Loratadine
	Mexiletine	Metoprolol
	Ranolazine	Nifedipine
	Verapamil	Nitrendipine
		Tamoxifen

Abbreviation: CiPA, Comprehensive In Vitro Proarrhythmia Assay.

In silico Modeling Approach and Validation Results

The patch clamp data that are obtained on human cardiac ion channels are used as inputs for an in silico model of the human ventricular myocyte. Simulations are run, and a metric that classifies a drug's level of risk for Torsade is calculated.

Biophysical electrophysiology models were initially applied to cardiac cells approximately 60 years ago, when Denis Noble applied the Hodgkin & Huxley model to cardiac cells. This represented the first quantitative in silico reconstruction of cardiomyocyte excitability. These models described the dependence of currents on membrane voltage and on time, and how cardiac electrical activity emerged from the interaction of multiple currents. For the purposes of CiPA, an open-source, electrophysiological model based on recordings of human ventricular tissue and cell data[9] was enhanced and validated for proarrhythmic risk prediction as follows:

- Employ ionic current study results from a subset of 12 CiPA drugs (representing high, intermediate, and low Torsade risk) for model training, optimization, and metric development.[10-12]
- Freeze the optimized model, CiPAORdv1.0 (including risk classification thresholds), for subsequent validation.
- Predict the proarrhythmic risk of the remaining 16 CiPA drugs based on qNET scores, and assess the ability to correctly categorize the drugs into high, intermediate, and low Torsade risk categories using predefined performance measures.

The validation process was performed for 2 different ionic current data sets, each including dynamic kinetic data for drug block of hERG current as well as simpler estimates of block potency for calcium and late sodium currents. The first data set contained manual patch clamp data for all 3 currents (obtained at 37°C), while the second "hybrid" data set consisted of manual hERG current data along with automated patch clamp measurement of calcium and late sodium currents (the latter 2 obtained at room temperature).

Torsade Metric Score performance was evaluated in 4 different ways, with the first 2 measuring the performance of ranking validation drugs according to Torsade risk levels and the last 2 evaluating the performance of classifying validation drugs using predefined classification thresholds. The first evaluation employed receiver operating characteristic (ROC) curves, that is, curves of sensitivity plotted against [1 – specificity]. In the present context, the area under the curve (AUC) of an ROC curve is the probability of correctly ranking a higher-risk drug above a lower-risk drug. Two analyses were conducted: one for low-risk versus high-or-intermediate risk drugs and one for low-or-intermediate versus high-risk drugs. Results generally fell in a range with AUC $\geq$0.9 for both the manual patch clamp and hybrid data sets, which was in the predetermined Excellent range.

The second performance evaluation utilized rank performance using pairwise comparisons. The model is used to predict pairwise ranking for each drug pair included, comparing the results to known ranking of risk of Torsade. "Correct prediction fraction" across the 211 pairs indicates ranking performance across all 3 categories. This is then repeated 10,000 times through random sampling, thereby estimating the confidence interval of the correct prediction fraction. Results again fell in the Excellent range.

The third and fourth performance measures evaluated classification accuracy. The third measure employed likelihood ratios (LRs), with LR positive (sensitivity/[1 – specificity]) indicating how much more likely a higher-risk drug will be classified into the higher risk category than a lower-risk drug, while inverse of LR negative (specificity/[1 – sensitivity]) indicated how much less likely a high-risk drug will be classified into the lower risk category than a lower-risk drug. Here, the sensitivity and specificity were calculated based on specific classification thresholds predetermined by the training data, and the performance on 2 thresholds were evaluated separately: one separating low-risk from high- or intermediate-risk drugs and one separating high- from low- or intermediate-risk drugs. The fourth performance measure calculates mean classification error for all validation drugs across 3 risk categories using both classification thresholds, thus giving an assessment of the overall classification performance. Over the 2 data sets and the 2 classification performance measures, the results were all above the predefined acceptable level, with 80% falling in the excellent or good range (5/10 times excellent and 3/10 times good).

Ion Channel Assays and Data

The flexibility of the in silico model and Torsade Metric Score was demonstrated based on training and validating the model with 2 patch clamp data sets for the 12 training and 16 validation CiPA drugs. The model achieved high performance across both data sets, demonstrating flexibility and robustness. However, there were notable differences in IC50 values between the 2 data sets for the late sodium and calcium currents. To minimize the need for every lab to run the full set of CiPA training drugs in the future to calibrate the model, the following topics and recommendations for ion channel experiments under CiPA were presented:

1. how the data with hERG, calcium, and late sodium currents were generated and used to train and validate the model;
2. how differences in experimental procedures for calcium and late sodium lead to data variability; and
3. how ion channel pharmacology can be standardized under CiPA.

For hERG, the importance of using a long (10-second) depolarizing pulse to 0 mV to define kinetics of hERG block at physiologic temperatures (37°C) was emphasized as necessary to differentiate drugs into high, intermediate, and low proarrhythmic risk in subsequent in silico evaluations/reconstructions. Attention to hERG stability, background/leak current, and general recording quality was emphasized to ensure high-quality recordings. For calcium studies, standardization of charge carrier used (Ca^{2+} vs Ba^{2+}), region of analysis, temperature, and current stability prior to drug application were

shown to affect IC50 values. For late sodium studies, choice of agonist to induce late sodium current (ATX-II vs veratridine), time required to achieve stable current recordings ("run-up" of current as agonists' effects are activity-dependent), and region of analysis for drug effect on late sodium current were shown to affect the potency of drug block.

With standardized quality criteria, sponsors would be able to demonstrate data quality by submitting digital ion channel testing waveform data to regulatory agencies (as done with the ECG Warehouse for clinical QT studies) and perform a limited number of positive controls to demonstrate that results are not different from data used to train the model.

Human Induced Pluripotent Stem Cell–Derived Ventricular Cardiomyocytes

The role of hiPSC-CMs under CiPA is to provide an option to check for missed or unanticipated effects, although they may play additional roles early in drug development. In drug discovery or early development, hiPSC-CMs can be used in the early assessment of electrophysiological drug effects over a wide range of exposures. Later in development, hiPSC-CMs may be used for follow-up studies, including instances where there is discordance between ion channel/in silico and clinical ECG findings, or when high clinical exposures are not possible in human ECG studies.

Prior studies[13-15] were reviewed and results from the CiPA Myocyte Validation Study[8] were presented. The study design is summarized as follows:

- 10 sites;
- 5 electrophysiological devices: 4 microelectrode array (MEA) devices and 1 voltage-sensitive dye (VSD) device;
- 2 hiPSC-CM lines: iCell^2 (10 data sets), and Cor.4U (5 data sets);
- 28 blinded drugs, 4 concentrations, 5-6 replicate wells at each concentration, acute effects (30-minute drug exposure); and
- standard proprietary media throughout: serum containing (MEA sites), serum-free (VSD site).

Seven hiPSC-CM predictors were evaluated in Torsade risk categorization models. The 3 that proved to be most useful for drug categorization were the following:

- the presence of drug-induced cellular arrhythmias (repolarization abnormalities) at any concentration;
- maximum drug-induced repolarization change (ms) observed at any concentration; and
- drug-induced repolarization change (ms) at Cmax.

Regarding the first of these useful predictors, most low-risk drugs did not induce any cellular arrhythmias. A few sites showed arrhythmias for ranolazine, metoprolol, and mexiletine. Few arrhythmias were reported for intermediate-risk drugs risperidone, terfenadine, clozapine, and chlorpromazine, but most of the data sets showed arrhythmias induced by domperidone, ondansetron, droperidol, pimozide, clarithromycin, astemizole and cisapride. Most high-risk drugs induced arrhythmia-like events, with bepridil being an exception.

Regarding the second predictor, all high-risk drugs induced repolarization prolongation. Drug-induced change in repolarization for intermediate-risk drugs was less than for high-risk drugs. Five of 9 low-risk drugs induced repolarization duration shortening, and while the other 4 prolonged repolarization, the average across all 9 drugs was a shortening. Regarding the third predictor, estimated drug-induced repolarization prolongation at Cmax was highest for ibutilide, dofetilide, quinidine, and vandetanib in the high-risk category; the category average reflected substantial prolongation. Intermediate-risk drugs induced moderate repolarization prolongation at Cmax. Five of 9 drugs in the low-risk category shortened repolarization duration at Cmax, while drug-induced prolongation was observed for the other 4. The average change in repolarization duration in this category reflected a small shortening.

Two models of Torsade risk prediction were employed. Model 1 compared the probability of predicting high- plus intermediate-risk drugs versus low-risk drugs. The associated ROC-AUC value for all 28 drugs was 0.87 (Good rating). Model 2 compared high- versus low-risk drugs, as well as intermediate- versus low-risk drugs. The associated ROC-AUC for high- versus low-risk (0.92) fell in the Excellent rating range, and the ROC-AUC for intermediate- versus low-risk (0.81) fell in the Good rating range. Variability by site was lower than that introduced by cell type, and both were lower than the contribution provided by drug concentration (all assessed as fixed effects). Site-induced variability was lower than all other sources of random variability, demonstrating the ability of hiPSC-CMs to reproducibly detect concentration-dependent effects of single and multiple ion channel–blocking activity.

Phase 1 ECG Biomarker(s) Under CiPA

The role of phase 1 ECG data under CiPA is to determine if there are unexpected human in vivo ion channel effects compared with nonclinical ion channel data. Identification and validation of ECG signatures that facilitate such determination are therefore important considerations. As noted previously, J-Tpeakc represents early repolarization and is of particular interest in the present context.

Three previous investigations set the scene for the work reported in this domain. In an initial analysis of 34 drug safety clinical studies,[16] J-Tpeakc was identified as an ECG biomarker that could differentiate drugs with predominant hERG block from those associated with hERG block combined with calcium and/or late sodium block (ie, balanced ion channel blockers). Predominant hERG blockers prolonged J-Tpeakc, while balanced ion channel blockers had no effect or a shortening effect on J-Tpeakc. A prospective clinical trial involving

dofetilide, quinidine, ranolazine, and verapamil confirmed this finding. Dofetilide and quinidine, which are predominantly hERG channel blockers and high Torsade risk drugs, prolonged J-Tpeakc; in contrast, ranolazine and verapamil, which are balanced ion channel blockers with hERG + late sodium block and hERG + calcium block, respectively, did not prolong J-Tpeakc.[17]

A second prospective clinical study addressed whether it was possible to re-create the ECG signature of ranolazine by combining a predominant hERG blocker, dofetilide, with a late sodium blocker, mexiletine or lidocaine.[18] The combination of a hERG blocker with a late sodium blocker was able to re-create the ECG signature of ranolazine, a low-risk drug that blocks both of these ion channels at clinically relevant exposures. In a separate arm of this study, diltiazem (calcium block) did not shorten QTc prolongation by moxifloxacin (predominant hERG block), a result which may have been confounded by study design.

Results of a new prospective clinical trial were presented at the Think Tank. The primary objective of Part 1 was to confirm that concentration-response analysis of the electrocardiographic QTc and J-Tpeakc intervals in phase 1 clinical pharmacology studies can be used to confirm that balanced ion channel–blocking drugs (ranolazine, verapamil, and lopinavir/ritonavir) do not cause J-Tpeakc prolongation, while a predominantly hERG-blocking drug (chloroquine) does cause J-Tpeakc prolongation.[8] As expected, the balanced ion channel blockers (ranolazine, verapamil, and lopinavir/ritonavir) prolonged QTc and had flat or negative J-Tpeakc slopes. For verapamil and lopinavir/ritonavir, the upper bounds of the respective 90% confidence intervals for J-Tpeakc fell below the prespecified threshold of 10 ms, but ranolazine's upper bound was 2 ms above this threshold. The predominant hERG blocker (chloroquine) had an upper bound above 10 ms for both QTc and J-Tpeakc as expected, although J-Tpeakc prolongation with chloroquine was not concentration-dependent.

Part 2 of the study investigated whether diltiazem (calcium block) reduces the QTc prolongation by dofetilide (predominantly hERG block) by shortening J-Tpeakc. In combination with dofetilide, diltiazem did not shorten QTc, but shortened J-Tpeakc. While this ECG signature of diltiazem + dofetilide differed from what was observed in the prior study for late sodium current block (mexiletine or lidocaine) when combined with hERG potassium channel block (dofetilide), verapamil and lopinavir/ritonavir (which have hERG and calcium block) prolonged QTc without prolonging J-Tpeakc in Part 1 of the study.

Summary

CiPA has multiple goals and potential areas to impact drug discovery and development. These include (1) aiding candidate selection early in drug discovery; (2) enabling mechanistic studies so promising new drugs that have a false positive signal of potential risk (eg, hERG block or modest QTc prolongation) are not prematurely discontinued; (3) enabling a pathway for de-risking of drugs with demonstrated hERG block and/or QTc prolongation (in nonclinical or clinical studies) and, when appropriate, not requiring intensive ECG monitoring in phase 3 trials; and (4) providing more informative drug labels for new drugs and currently marketed drugs. Points 3 and 4 were also discussed at an FDA Advisory Committee in 2017,[5] where the committee voted 11 to 2 in favor of CiPA being fit-for-purpose for determining whether ECGs need to be collected in phase 3 trials and informing proarrhythmic risk language in drug labeling, assuming the validation studies were positive, as they are.

The Think Tank had multiple presentations of study results, and also intensive discussion around these topics, with different viewpoints expressed during main sessions on day 1 (May 21) and subsequent break-out sessions, each focusing on one of the CiPA components, on day 2 (May 22). The purpose of this paper is not to capture the discussions, but rather to focus on summarizing the core CiPA studies that were presented at the meeting. Additional details will need to be resolved, such as how to handle potential interactions among multiple QTc-prolonging drugs, including in labeling.

Additional presentations commented on how CiPA is already being implemented in a regulatory setting to permit an alternative risk assessment for drugs with significant heart rate increases or other factors that confound QTc assessment; FDA has already recommended this approach to multiple sponsors with drugs in development. In addition, standardized nonclinical assays may be able to reduce the exposure margins in phase 1 QTc assessments and permit an earlier assessment of proarrhythmic risk for phase 1 oncology drugs, for which current studies are only able to rule out a 20-ms QTc effect.

As a final summary note, results from validation endeavors for each of the CiPA components were presented, thus setting the stage for further discussion with the ICH S7B/E14 Discussion Group.

Author Note

This article reflects the views of the authors and should not be construed to represent FDA's views or policies.

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Declaration of Conflicting Interests

Dr Strauss reports no relevant disclosures. Dr Gintant is an employee of AbbVie, a pharmaceutical company involved in new drug development. Dr Li reports no relevant disclosures. Dr Wu reports no relevant disclosures. Dr Blinova reports no relevant disclosures. Dr Vicente reports no relevant disclosures. Dr Turner is an employee of DRT Strategies, Inc. Dr Sager has disclosed consulting relationships with ERT, BioTelemetry Research, ICardiac, Charles River, and AnaBios.

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