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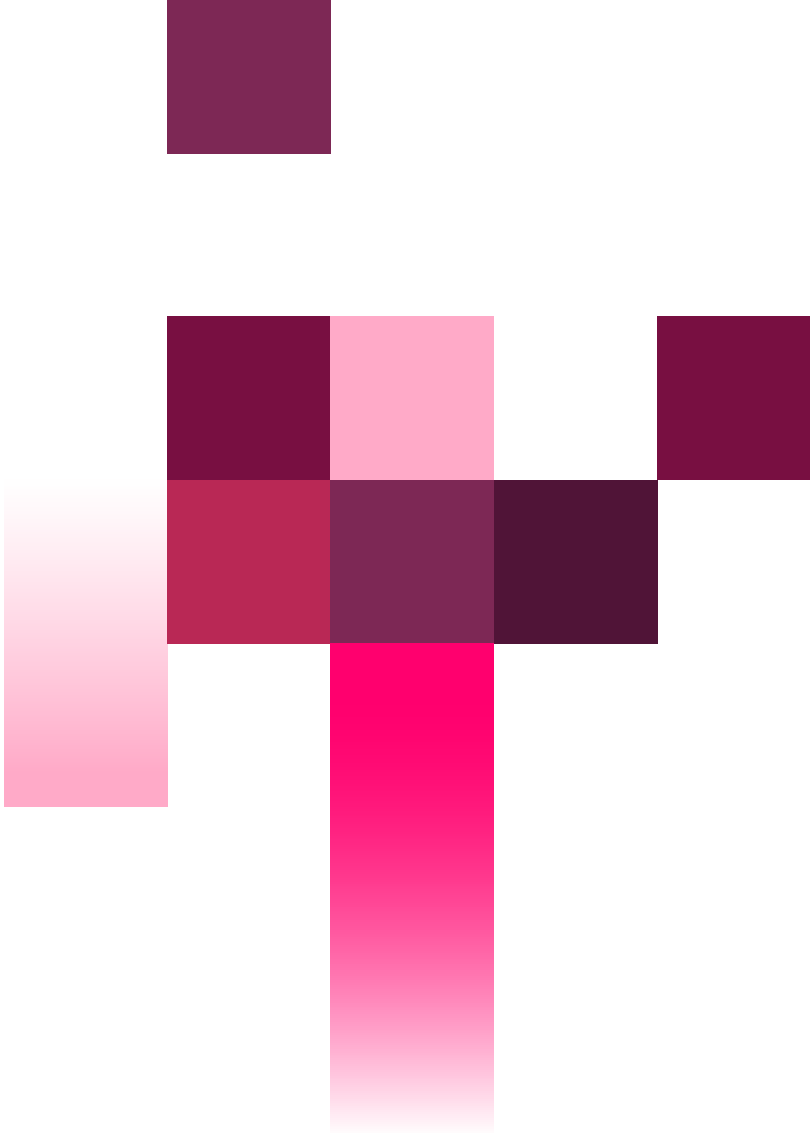

The Early Precision QT Approach

Driving earlier assessments of cardiac safety and supporting regulatory change

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CLARIO.

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The FDA directive for every new chemical entity (NCE) to undergo intensive cardiac safety assessment in clinical development is being reviewed. Since 2005, all compounds in development must undergo rigorous testing for its potential to prolong the QT interval on electrocardiogram (ECG), as defined in the ICH E14 Guidance. Implementation of this directive has virtually eliminated post-market withdrawals due to arrhythmia and sudden cardiac death, and has proven that careful assessment of QT and other ECG parameters in well-controlled clinical trials is a good mechanism of ensuring cardiac safety. However, there are concerns that the historical way of studying a drug's effect on ECG parameters — Thorough QT (TQT) studies — is negatively impacting drug pipelines. In delaying characterizing QT liability in humans (the current surrogate marker of proarrhythmia) at the end of Phase 2 or later, adds substantial burden while increasing the risk of late-phase attrition.

This document presents a strategic approach that allows drug companies to gain early and detailed insight into the cardiac safety profile of a compound to better position, prioritize and resource drug development programs. This approach allows companies to better manage pipelines by introducing new drugs earlier to the marketplace and ensuring that promising drugs aren’t inappropriately eliminated because of inaccurate cardiac safety data.

THE CARDIAC SAFETY TESTING LANDSCAPE

Cardiac safety assessment and the practice of conducting TQT testing on all new chemical entities (NCEs), regardless of whether they have any evident connection to cardiac side effects, is a common topic for debate in the industry. Many question whether this resource-intensive approach truly confers best practice in today's drug development programs. The directive, described by the ICH E14 Guidance, has been in place since 2005 when it was introduced in response to concerns regarding the public health implications of drugs being approved that could cause the potentially lethal ventricular arrhythmia torsade de pointes (TdP).

All NCEs with systemic exposure routinely undergo a dedicated TQT study to evaluate the effect of the drug on ECG parameters and determine the potential of the compound to prolong the QTc interval. This trial is typically conducted at the end of Phase 2 or in parallel with Phase 3 studies and includes 40-60 healthy volunteers in crossover or up to 240 in parallel design. A "positive finding" using this strategy can have a major, and often negative, impact on the remainder of a drug's development, warranting extensive ECG assessments, likely approval delays and potentially resulting in the termination of the development program.

Increased efficiency could be realized if cardiac safety data were generated from studies performed as part of the clinical development program. In single ascending dose (SAD) or multiple ascending dose (MAD) first-in-human (FIH) studies, escalating doses of the NCE are given to small cohorts of subjects, often up to the maximum tolerated dose. Plasma concentrations are often achieved which, thereafter, will not be exceeded in healthy subjects or patients.

While some SAD or MAD studies include more rigorous assessments for changes from baseline in QT and other ECG intervals, more common is a safety assessment based on the principal investigator’s read of 12-lead ECG printouts. This approach cannot confidently detect changes in QT interval at the precision level of a TQT trial, as only gross abnormalities can be detected based on visual assessment or manual measurement. Spurious ECG effects from 12-lead ECG printouts can be difficult to interpret and are of little value in the decision-making process.

In response, iCardiac Technologies, acquired by ERT in late 2017, introduced a transformative cardiac safety testing method. Expert Precision QT (EPQT), originally named Early Precision

QT under the iCardiac brand, was developed to improve the overall productivity of pharmaceutical development and, in collaboration with the FDA, has been tested successfully in a comprehensive clinical trial.

The approach brings regulatory changes to cardiac safety testing. Supported by the FDA and industry consortia, these changes impact the majority of pharmaceutical development programs.

BEYOND TQT: THE IQ-CSRC PROSPECTIVE CLINICAL PHASE 1 STUDY

The Consortium for Innovation and Quality in Pharmaceutical Development (IQ) and the Cardiac Safety Research Consortium (CSRC) collaborated to design a clinical study in healthy subjects demonstrating that the desired objectives of a successful TQT study can be achieved through robust ECG monitoring and exposure-response (ER) analysis of data generated from SAD or MAD studies. As an expert at conducting such studies, iCardiac was the sole ECG core laboratory involved in the comprehensive validation of this new type of study for definitive QT assessment using its high precision analysis approach[1].

PROVING THE POTENTIAL OF EARLY PRECISION QT ASSESSMENT

The IQ-CSRC group, in collaboration with the FDA, designed a multi-drug comparison study to investigate the claims of a higher accuracy QT assessment process. This study utilizes algorithms and digital data processing with the goal of doing more accurate QT assessments early in the drug development lifecycle. EPQT was utilized in the study. The high precision algorithms and processes draw upon 30 years of expertise and ECG data collected from research conducted at the University of Rochester Medical Center.

Study Methodology

Six marketed drugs with well-characterized QTc effects were identified in discussions with the FDA. In late-phase studies where TQT assessment was performed, five drugs demonstrated QT prolongation above the threshold of regulatory concern[1]. A randomized, placebo-controlled study involving 20 healthy subjects was designed with similar power to exclude small QTc effects in a SAD study design. Two doses (low and high) of each drug were given on separate,

consecutive days to nine subjects. Six subjects received placebo. The study was conducted by one of the world's largest clinical research organizations (CROs) using a clinical pharmacology unit with extensive experience managing QT measurement centric studies.

The selection criteria for the five drugs included the requirement for a toxicity profile that would allow administration to healthy subjects, lack of substantial heart rate effect as well as a known degree of QTc prolongation. The FDA recommended that a lower dose be given on Day 1 to achieve a mean placebo-corrected, change-from-baseline QTc of 9-12 ms. A higher dose, that was expected to result in QTc of approximately 15-20 ms, was given on Day 2. The higher dose was chosen to mimic a typical SAD study which includes doses that target efficacious concentrations and then adds higher doses to explore maximum tolerated dose.

Data were analyzed using ER analysis. Criteria for QT-positive drugs was the demonstration of an upper bound (UB) of the two-sided 90% confidence interval (CI) of the projected QTc effect at the peak plasma level of the lower dose above the threshold of regulatory concern (currently 10 ms) and a positive slope of ER relationship. The criterion for a QT-negative drug was an UB of the CI of the projected QTc effect of the higher dose <10 ms.

Study Results

The results of the study, verified by the FDA and other study partners, indicate pre-determined endpoints were met and that data can be achieved with the same high level of confidence as for a substantially larger traditional TQT study. High data accuracy and precision promises, in many cases, to eliminate the need for TQT studies in later stages of clinical development. The successful outcome in this study has provided clear evidence supporting the replacement of the TQT study with ECG assessments in standard early clinical development studies for a NCE[1].

A CLOSE LOOK AT WHAT THE STUDY FINDINGS MEAN FOR THE INDUSTRY

New Proven Methodology: Early Precision QT

Instead of having to conduct a separate dedicated cardiac safety study, this methodology allows definitive testing to be embedded into an existing Phase 1 study. The methodology leverages

both concentration effect modelling, as well as high precision analysis of 10x more data than conventional measurement methods. This provides an alternative path to cardiac safety testing by leveraging large amounts of precisely analyzed ECG data from a standard Phase 1 study[2,3].

Regulatory Changes

The new methodology is changing the regulatory landscape in cardiac safety assessment to reflect these scientific and technological breakthroughs. The objective of these changes is to improve the productivity of pharmaceutical research and development.

Method Reviewed by the FDA and Consortia from Industry and Cardiac Safety Experts

This regulatory change is supported by the FDA and other governing standards groups, including:

- Cardiac Safety Research Consortium (CSRC)
- International Consortium for Innovation and Quality in Pharmaceutical Development (IQ)
- QTc Working Group

Based on increasing experience and confidence among regulators and industry with C-QTc analysis and on the results from the IQ-CSRC study, the ICH E14 was revised in December 2015. The guidance now allows the use of ECG data from early clinical studies, such as FIH studies, analyzed with C-QTc to replace the TQT study[4].

CORE BENEFITS UNDERLYING EARLY PRECISION QT

Adopting an EPQT methodology offers multiple benefits to research sponsors. The approach can:

Make earlier assessments of cardiac safety to better minimize risk, position, prioritize, and resource programs. Better cardiac safety information earlier allows companies to prioritize clinical programs with strong safety profiles and appropriately resource or re-focus programs exhibiting potential downstream cardiac safety issues.

Ensure that promising drugs are not inappropriately eliminated because of inaccurate cardiac safety data. Traditional approaches to cardiac safety have a high incidence of inconclusive, positive and false positive results (i.e., safe drugs being labeled as QT-prolonging). More accurate early QT studies can eliminate these issues and, as a result, allow pharmaceutical companies greater confidence in their development programs.

Introduce new drugs to the marketplace earlier. The ability to avoid complex and time-consuming cardiac safety studies offers the potential of bringing new drugs to market on an expedited basis.

Eliminate unnecessary late stage TQT studies. More accurate early QT studies may eliminate the need for later stage TQT studies, saving millions of dollars in study costs.

APPLY EARLY PRECISION QT IN EARLY- PHASE STUDIES

Results on the use of early-phase clinical QT assessment data represent a tremendous opportunity for the pharmaceutical industry. ERT is eager to share this knowledge so that clinical trial sponsors and CROs can quickly begin to experience the significant regulatory and internal benefits of implementing EPQT in their development efforts.

- iCardiac, acquired by ERT in late 2017, developed and pioneered the EPQT method, which analyses 10x more data than traditional semi-automated analysis methods and offers precision unmatched by other ECG core laboratories. (Data available upon request.)
- The EPQT method was used by the consortium as the ECG analysis method in the definitive, FDA-supported validation study, providing you confidence that you're leveraging the same standard of excellence.
- ERT has deep expertise in the utilization of concentration-effect modelling in conjunction with large volume, high-precision ECG data analysis. ERT can provide the industry's most experienced staff of medical and scientific experts to help develop and refine study protocols for leveraging EPQT in SAD/MAD studies.

SUMMARY

Clinical trials are becoming increasingly complex and it is imperative that study methodologies evaluate a novel drug in a way that provides the most reliable evaluation of its potential benefit to human health as possible. Innovations in assessing cardiac safety through EPQT potentially allow for much earlier assessment of QT prolongation and proarrhythmia risk, providing research sponsors with more detailed insight that potentially could save millions of dollars and shorten time to market for drugs in human trials.

ERT is uniquely positioned to build confidence in this approach in a way that eliminates any potential risk for sponsors, empowering them to implement this methodology and drive more accurate QT assessments early in a drug trial's timeline. Earlier assessment potentially eliminates the need for TQT studies in later stages of human trials while preserving drug development pipelines. This approach, developed in conjunction with the IQ and CSRC, and reviewed by the FDA, offers a strategic and highly pragmatic alternative to traditional cardiac safety assessments.

APPENDIX A: EARLY PRECISION QT FAQ

1. **Will this technique work in patient population studies in addition to working in healthy normal studies?**

   Yes. Exposure response analysis on ECG data (QT data) from patients is a useful tool to predict QT effects in other patient populations. The variability of the ECG interval measurements in patients will, however, in most cases be larger, and more patients are therefore needed as compared to healthy volunteer studies.

2. **How will not having a positive control (like moxifloxacin) affect our ability to rely on the study results?**

   The reason there is a positive control in TQT studies is to ensure that a negative result with a new drug is truly negative and not only based on poor study conduct. Therefore, if moxifloxacin causes an effect and the new drug does not, this provides assurance. Stated differently, this provides protection against 'false negatives' (i.e., the study concludes that there is no effect, even though the drug is a QT prolonger).

   With C-QTc analysis, the risk of a false negative result is very low, provided sufficiently high plasma levels of the drug have been achieved. Research using simulation of a large number of small studies on data from TQT studies, performed by iCardiac, acquired by ERT in late 2017, and by the FDA independently[2], demonstrates that the risk of false negatives with a drug with a QT effect similar to moxifloxacin is less than 1% with nine subjects on active (at the targeted or higher dose) and six on placebo.

   A simple way of explaining why the risk of a false negative result is so low, is to say that truly QT prolonging drugs in most cases cause this effect as a function of increasing plasma level. If the plasma levels are pushed high enough and the result is none the less negative, it is very likely that the drug is lacking a meaningful effect on the QT interval[2].

3. **Is QT assessment in Phase 1 reliable?**

   Method Bias Sensitivity (MBS), an advanced quality metric, provides a measure of reliability in an EPQT study. It offers insight into whether the ECG core lab's

methodology for measuring QT intervals introduces relevant bias into the results. MBS serves a similar function in Phase 1 QT studies as the positive control arm in TQT studies, in that they each help to minimize the possibility of a false negative result.

MBS also offers information confirming the accuracy and consistency of a core lab's ECG measurement method. It does this by comparing the QT measurements derived by the lab method to the automated measurements from each time point in the study.

MBS is especially helpful in assessing studies where sufficiently high multiples of the clinically relevant plasma concentration are not reached, which often cannot be determined until later in the development program. iCardiac helped develop and test the new metric in collaboration with several regulatory and industry experts, including the FDA. The analysis is especially useful in all new Phase 1 where QT is being measured to characterize QT effect or seek a waiver of a TQT study[6].

4. **Will the EPQT technique work with drugs that affect heart rate?**

   It will work no better or worse than in TQT studies. If a substantial HR effect has been observed in animal studies for example, it is prudent to collect a full baseline day in the early phase QT assessment study to enable an appropriate heart rate correction method for QTc.

5. **What is the minimum number of subjects and/or dose groups that I need in my FIH study to apply this technique?**

   The IQ-CSRC study, supported by simulations[3], indicates six to nine subjects on a sufficiently high dose (plasma level) as the minimum number of subjects. Adding subjects at lower doses helps only to some extent. Adding doses to achieve plasma concentrations above targeted therapeutic levels clearly helps.

   Another important consideration is the number of subjects on placebo, typically pooled from several dose groups. A minimum number of 8 subjects on placebo is ideal. In summary, it seems prudent to use at least 4 dose groups with 6/2 on active/placebo and with two of the doses higher than what is believed to be the therapeutic dose[2].

APPENDIX B: VALUE PROPOSITION PROOF POINTS

Make earlier cardiac safety assessments to better position, prioritize and resource programs.

Better cardiac safety information earlier allows companies to prioritize and package clinical programs with strong safety profiles and appropriately resource or re-focus programs exhibiting potential downstream cardiac safety issues.

> ***Proof Point 1:*** Small biotech companies generally seek to partner their compounds for development. By characterizing the cardiac safety of the compound earlier (using EPQT), the likelihood of partnering, and doing so at better economic terms, is increased.
>
> ***Proof Point 2:*** Larger pharmaceutical companies are often developing a particular therapeutic for multiple indications. By using EPQT, pharmaceutical companies can determine the expected risk/benefit ratio much earlier in development to appropriately prioritize development decisions.
>
> ***Proof Point 3:*** Approximately 20% of traditional TQT studies determine the drug to be potentially arrhythmia-inducing, which may lead to either a termination of the development program or a black box warning, which generally dramatically limits commercial potential. As a result of this information often becoming known towards the end of Phase 2 or around the time of Phase 3, the development efforts and massive investment leading up to this point may be wasted. EPQT allows pharmaceutical companies to avoid wasting resources on drugs that would later fail TQT studies.

Ensure that promising drugs are not inappropriately eliminated because of inaccurate cardiac safety data.

Traditional approaches to cardiac safety have a higher incidence of inconclusive, or false-positive results (i.e., safe drugs being labeled cardio toxic). More accurate and precise early QT studies can eliminate these issues and allow pharmaceutical companies greater confidence in their development programs.

> ***Proof Point:*** About 12% of traditional TQT studies are deemed to be inconclusive due to lack of assay sensitivity. As a result, the study may need to be repeated at a cost of

millions of dollars, with a delay in market launch also potentially costing hundreds of millions or the drug may be labeled with a warning that significantly decreases the economic returns on that drug. EPQT has been designed to minimize the risk of inconclusive cardiac safety studies as well as their negative impact.

Earlier introduction of new drugs to the marketplace.

The ability to avoid complex and time consuming cardiac safety studies offers the potential of bringing new drugs to market on an expedited basis.

> ***Proof Point:*** Planning and conducting a TQT study typically takes one year or more. By using EPQT, the cardiac safety assessment can be completed in parallel with a FIH study leading to earlier product introduction.

Eliminate unnecessary late stage TQT studies.

More accurate QT studies earlier in the development process may eliminate the need for later-stage TQT studies, saving millions of dollars in study costs.

> ***Proof Point:*** The total incremental clinical and analysis costs for a TQT study range from two million to five million dollars. The total incremental costs of an EPQT study are a small fraction of the cost of a TQT study.

ECG Methodology selected by the IQ-CSRC.

iCardiac, acquired by ERT in late 2017, developed and routinely deployed the same high precision method of EPQT used in the validation study conducted by the CSRC.

> ***Proof Point:*** Together with regulators, sponsors and cardiac safety experts, iCardiac, acquired by ERT in late 2017, designed and conducted the study. iCardiac analyzed ECG using the EPQT method and results were reviewed by the FDA. At the December 12th CSRC meeting, FDA representatives encouraged this approach in FIH studies. The EPQT methodology requires analysis be completed with extreme precision, which was optimized through 30 years of research. Recent comparison data illustrates this level of precision cannot be consistently matched by traditional ECG core laboratory analysis processes.

EPQT is currently the only high precision ECG analysis method reviewed and accepted for cardiac safety assessment in FIH studies. The IQ-CSRC study led to the revision of the ICH E14 guidance, further demonstrating that EPQT is currently the only high-precision ECG analysis method reviewed and accepted for cardiac safety assessment in FIH studies.

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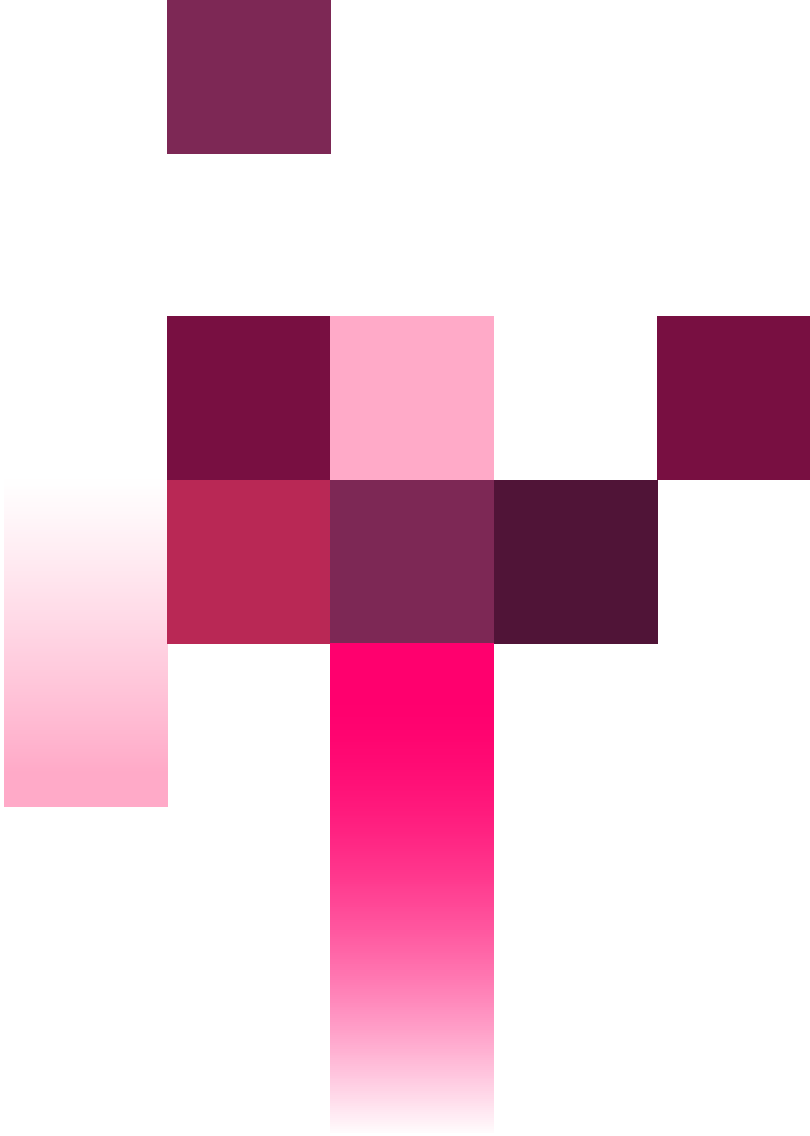

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