WHITE PAPER

The Early Precision QT approach

Driving earlier assessments of cardiac safety and supporting regulatory change

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January 2025

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Introduction

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 an 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 the QT interval and other ECG parameters in well-controlled clinical trials is a good mechanism to ensure cardiac safety. However, there are concerns that the historical method of studying a drug's effect on ECG parameters – thorough QT (TQT) studies – is negatively impacting drug pipelines. Delaying characterizing QT liability in humans (the current surrogate marker of proarrhythmia) at the end of Phase II or later adds substantial burden while increasing the risk of late-phase attrition.

Alternatively, studying safety in early-phase studies 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 are not 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 NCEs, regardless of whether they have any evident connection to cardiac side effects, is a common topic of 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 was typically conducted at the end of Phase II or in parallel with Phase III studies and included 40-60 healthy volunteers in crossover studies or up to 240 volunteers in parallel design studies. 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 delaying approval and potentially resulting in the termination of the development program.

A "positive finding" in a TQT study could delay approval and potentially result in the termination of a 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 participants, often up to the maximum tolerated dose. Plasma concentrations are often achieved that, thereafter, will not be exceeded in healthy participants or patients in later phases of development.

While some SAD or MAD studies include more rigorous assessments for changes from baseline in QT and other ECG intervals, the more common approach is a safety assessment based on the principal investigator's read of 12-lead ECG printouts. This approach cannot confidently detect changes in QT intervals 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*, now Clario, introduced a transformative cardiac safety testing method.[1] Early Precision QT (EPQT), previously referred to as Expert Precision QT and Early QT Assessment, 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.[2]

Early Precision QT (EPQT) improves the overall productivity of pharmaceutical development and has been tested successfully in a comprehensive clinical trial.[2]

This approach brought regulatory changes to cardiac safety testing. Supported by the FDA and industry consortia, these changes impact most pharmaceutical development programs.

Beyond TQT: the IQ-CSRC prospective clinical Phase I study

The Consortium for Innovation and Quality in Pharmaceutical Development (IQ) and the Cardiac Safety Research Consortium (CSRC) collaborated to design a clinical study with healthy participants 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, Clario 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.[3]

*iCardiac Technologies LLC was acquired by eResearchTechnology, Inc. in 2017, which then merged with BioClinica, Inc. to become Clario in 2021.

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 uses algorithms and digital data processing with the goal of doing more accurate QT assessments early in the drug development lifecycle. EPQT was used 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 in which TQT assessment was performed, five drugs demonstrated QT prolongation above the threshold of regulatory concern.[3] A randomized, placebo-controlled study involving 20 healthy participants was designed with similar power to exclude small QTc effects in an SAD study design. Two doses (low and high) of each drug were administered on separate, consecutive days to nine participants. Six participants 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 participants, lack of substantial heart rate effect and 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, which was expected to result in QTc prolongation of approximately 15-20 ms, was given on Day 2. The higher dose was chosen to mimic a typical SAD study that includes doses that target efficacious concentrations then adds higher doses to explore the maximum tolerated dose.

Data were analyzed using ER analysis. Criteria for QT-positive drugs were 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 the ER relationship. The criterion for a QT-negative drug was a 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 that 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 promise, 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 an NCE.[2]

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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 I study. The methodology leverages both concentration effect modeling and 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 I study.[4,5]

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 the:

- 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 concentration QTc (C-QTc) analysis and on the results from the IQ-CSRC study, the ICH E14 guidance 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.[6]

Core benefits underlying Early Precision QT

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

Allow earlier assessments of cardiac safety to better minimize risk and 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, potentially saving millions of dollars in study costs. Furthermore, the higher precision afforded by EPQT for measuring the QT-interval means a much smaller number of participants need to be enrolled in a TQT to rule out a >10 ms effect, when a TQT study has to be conducted. Most TQT studies now use C-QTc as the primary analysis, and with EPQT, this only requires 24 to 26 evaluable participants for sufficiently high power to rule out a >10-ms increase in the QTc interval. When this is compared with a traditional TQT study conducted without EPQT and using by time point as the primary analysis, anywhere from 60 participants or more may need to be enrolled to adequately power the study. Therefore, the benefits of using EPQT are still applicable even when a TQT study may still need to be conducted.

Apply Early Precision QT in early-phase studies

Results on the use of data from early-phase clinical QT assessments represent a tremendous opportunity for the pharmaceutical industry. Clario 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.

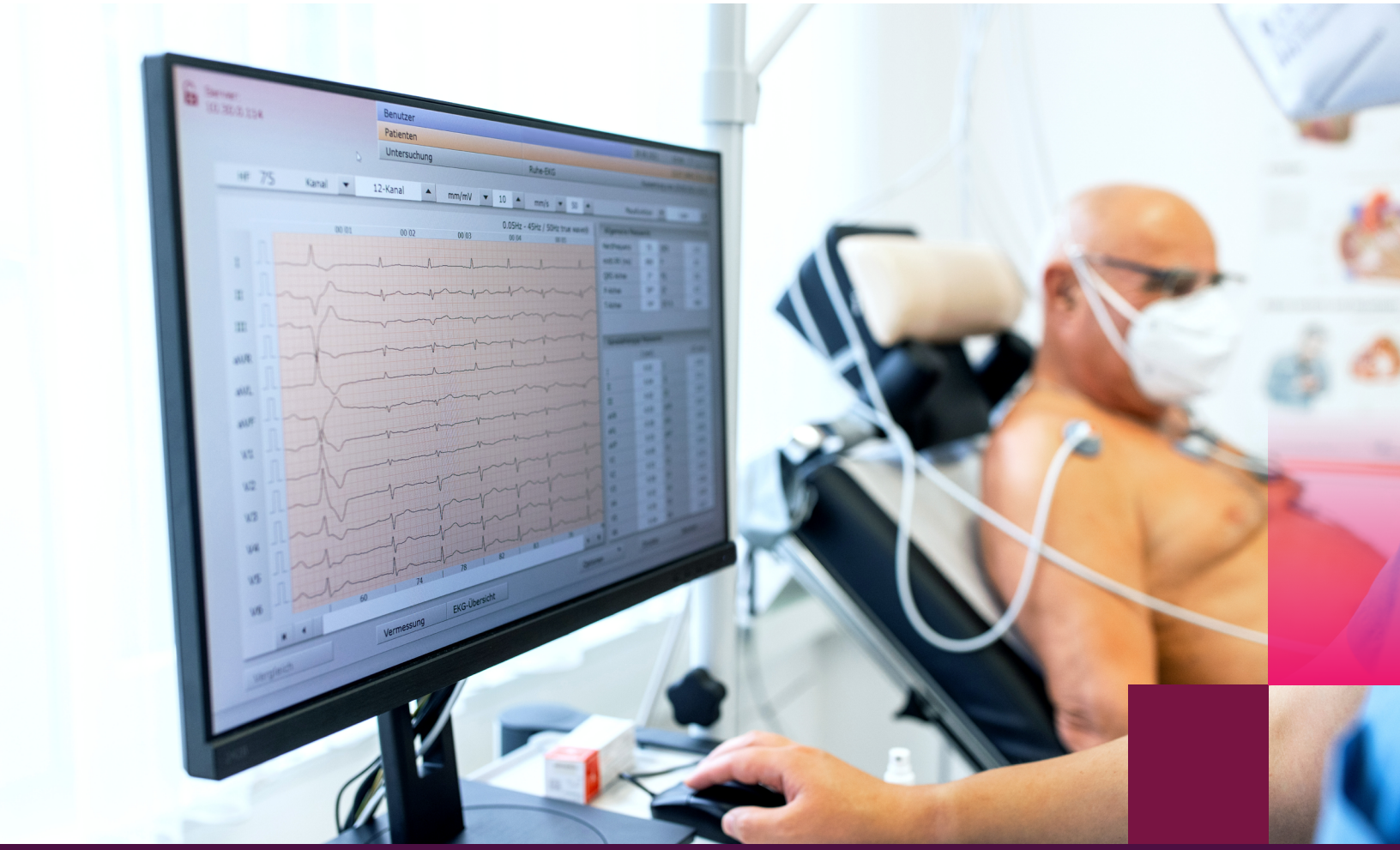
Benefits of implementing EPQT

More data and greater precision	Clario developed and pioneered the EPQT method, which analyzes 10x more data than traditional semi-automated analysis methods and offers precision unmatched by other ECG core laboratories (data available upon request).
Validated methodology	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.
Deep expertise	With more than 1,000 Phase I cardiac safety studies, Clario has deep expertise in the utilization of concentration-effect modeling in conjunction with large-volume, high-precision ECG data analysis.[7] Clario has some of the industry's most experienced medical and scientific experts to help develop and refine study protocols to leverage EPQT in SAD and 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 assessment of its potential benefits. Innovations in monitoring 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.

With more than 1,000 Phase I cardiac safety studies, Clario is uniquely positioned to build confidence in this approach in a way that reduces potential risk for sponsors, empowering them to implement this methodology and drive more accurate QT assessments early in a drug trial's timeline.[2,7] 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.



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Appendix A: Early Precision QT FAQ

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

Yes. ER 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 than in 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 that 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 Clario, and by the FDA independently,[4] demonstrated that the risk of false negatives with a drug with a QT effect similar to moxifloxacin is less than 1% with nine participants on the active drug (at the targeted or higher dose) and six participants 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.[4]

3. Is QT assessment in Phase I reliable?

Method bias sensitivity (MBS), an advanced quality metric, provides a measure of reliability in an EPQT study.[8] 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 I 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. Clario 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 studies where QT is being measured to characterize QT effect or seek a waiver of a TQT study.[8]

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

It will work no better or worse than in TQT studies.[9] If a substantial heart rate 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 participants and/or dose groups that I need in my FIH study to apply this technique?

The IQ-CSRC study, supported by simulations,[5] indicates six to nine participants on a sufficiently high dose (plasma level) as the minimum number of participants. Adding participants 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 participants on placebo, typically pooled from several dose groups. A minimum number of eight participants on placebo is ideal. In summary, it seems prudent to use at least four dose groups with six/two on active/placebo and with two of the doses higher than what is believed to be the therapeutic dose.[4]

Appendix B: Value proposition proof points

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

Obtaining 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 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 II or beginning of Phase III, 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 cardiotoxic). 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 a 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.[5]

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.

Proof point: Planning and conducting a TQT study typically takes at least one year. By using EPQT, the cardiac safety assessment can be completed in parallel with an 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.

Use the ECG methodology selected by the IQ-CSRC.

Clario developed and routinely deployed the same high-precision method of EPQT used in the validation study conducted by the IQ consortium and CSRC.

Proof point: Together with regulators, sponsors and cardiac safety experts, Clario designed and conducted the study. Clario analyzed ECG using the EPQT method, and the results were reviewed by the FDA. At the December 12 ICH E14 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 illustrate 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.

References

1. "FDA: Study Demonstrates Potential for Faster Drug Development." PR Newswire. Available at: https://www.prnewswire.com/news-releases/fda-study-demonstrates-potential-for-faster-drug-development-285822741.html (accessed on January 3, 2025).
2. Darpo, Borje et al. "Results From the IQ-CSRC Prospective Study Support Replacement of the Thorough QT Study by QT Assessment in the Early Clinical Phase." Clinical pharmacology and therapeutics vol. 97,4 (2015): 326-35. doi:10.1002/cpt.60
3. Darpo, Borje et al. "Cardiac Safety Research Consortium: can the thorough QT/QTc study be replaced by early QT assessment in routine clinical pharmacology studies? Scientific update and a research proposal for a path forward." American heart journal vol. 168,3 (2014): 262-72. doi:10.1016/j.ahj.2014.06.003
4. Ferber, Georg et al. "Detection of QTc Effects in Small Studies--Implications for Replacing the Thorough QT Study." Annals of noninvasive electrocardiology : the official journal of the International Society for Holter and Noninvasive Electrocardiology, Inc vol. 20,4 (2015): 368-77. doi:10.1111/anec.12227
5. Ferber, Georg et al. "Study Design Parameters Affecting Exposure Response Analysis of QT Data: Results From Simulation Studies." Journal of clinical pharmacology vol. 58,5 (2018): 674-685. doi:10.1002/jcph.1065
6. "E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs Questions and Answers (R3) Guidance for Industry." U.S. Food & Drug Administration. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e14-clinical-evaluation-qtqtc-interval-prolongation-and-proarrhythmic-potential-non-antiarrhythmic-1 (accessed on January 3, 2025)
7. Clario internal, proprietary data
8. Ferber, Georg et al. "Can Bias Evaluation Provide Protection Against False-Negative Results in QT Studies Without a Positive Control Using Exposure-Response Analysis?." Journal of clinical pharmacology vol. 57,1 (2017): 85-95. doi:10.1002/jcph.779
9. Malik, Marek et al. "Implications of Individual QT/RR Profiles-Part 1: Inaccuracies and Problems of Population-Specific QT/Heart Rate Corrections." Drug safety vol. 42,3 (2019): 401-414. doi:10.1007/s40264-018-0736-1

About Clario

Clario is a leading healthcare research and technology company that generates high quality clinical evidence for our pharmaceutical, biotech, and medical device partners. We offer comprehensive evidence generation solutions that combine eCOA, cardiac solutions, medical imaging, precision motion, and respiratory endpoints.

Since our founding more than 50 years ago, Clario has delivered deep scientific expertise and broad endpoint technologies to help transform lives around the world. Our endpoint data solutions have supported clinical trials over 26,000 times in more than 100 countries. Our global team of science, technology, and operational experts have supported over 60% of all FDA drug approvals since 2019.