

A primer on ECG measurement precision and why it matters

Robert Kleiman

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Introduction

The analysis of the effects of a new drug on ECG measurements has become increasingly important during clinical trials. In particular, regulatory changes during the past few years have made ECG measurement precision increasingly important, as better ECG measurements allow for smaller, faster, less expensive trials. This paper describes the types of ECG measurements used in clinical trials, advances in the precision of these measurements and how this relates to recent changes in how the cardiac safety of new drugs is assessed.

A brief history of ECG measurements

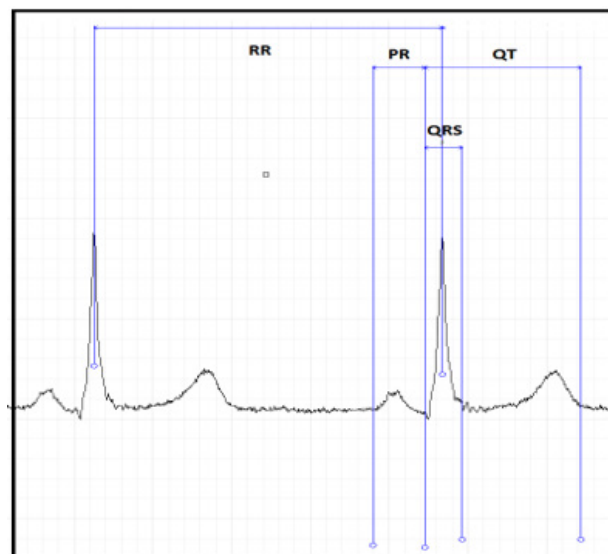
The first ECGs were recorded during the late 19 century, and Einthoven is credited with recognizing what we now think of as the components of the ECG. Einthoven described the pattern of waves that represent atrial and ventricular events and ultimately created the naming convention that is still used today.¹ A typical ECG complex, as shown in Figure 1, contains a P wave (representing electrical activation of the atria), a QRS complex (representing electrical activation of the ventricles), a T wave (electrical repolarization of the ventricles) and a small U wave (whose genesis remains a matter of debate).

Figure 1. Single ECG complex showing P, Q, R, S, T and U waves



Based on these features on the ECG, a series of measurements can be performed. First, the RR interval is the interval between successive QRS complexes and is inversely related to heart rate. For each ECG complex, we measure the PR interval (also known as the PQ interval), QRS duration and QT interval. Each of these interval duration measurements (IDMs) has a physiologic analog: the PR interval represents the time it takes for the initiation of atrial activation, conduction through the atria and conduction through the AV node and His-Purkinje system. The QRS complex begins with the initiation of depolarization of the ventricles, and the QRS duration is the total duration of electrical activation of all ventricular tissue. Finally, the QT interval (that also includes the QRS duration) is the total duration from the first electrical activation of the ventricles until the end of ventricular repolarization, which sets up the cardiac tissue for the next electrical cycle. These measurements are illustrated in Figure 2.

Figure 2. Standard ECG measurements



Since the QT interval varies inversely with heart rate (i.e., shortens at faster heart rates and prolongs at slower heart rates), we traditionally use the “corrected” QT interval, or QTc interval,

for analysis. There are a number of different methods for correcting the QT interval for heart rate; the most commonly used are the Bazett correction ($QTcB = QT / (RR)^{1/2}$) and the Fridericia correction ($QTcF = QT / (RR)^{1/3}$).

All the IDMs are important to consider during drug development. Drugs may increase or decrease the heart rate; depending on the magnitude and the particular patient population, this may have significant consequences. Drugs that lengthen the PR interval may produce heart block and symptomatic bradycardia or syncope. Drugs that prolong the QRS duration may predispose patients with structural heart disease to an increased risk of sudden cardiac death. The QTc interval, however, is by far the ECG measurement that generates the most interest during drug development. In fact, detection of drug-induced QT prolongation is probably the single most important aspect of cardiac safety during the drug development process.

Our interest in QTc dates back to the 1990s and early 2000s, when approximately a dozen drugs that had undergone the standard approval procedures of the time had to be withdrawn from development or from the market due to cases of drug-induced sudden cardiac death.² The mechanism by which these drugs produced sudden cardiac death was soon determined to be related to drug-induced block of the hERG-encoded ventricular IKr channel, which alters cardiac repolarization and sets up conditions that favor the development of a potentially lethal ventricular arrhythmia known as Torsades de Pointes (TdP). At the same time, reevaluation of the ECGs collected during the clinical trials of the drugs pulled from the market due to excess sudden cardiac death demonstrated that all of these agents produced prolongation of the QTc interval on the surface ECG, which could be detected with the ECG technologies of the time.

The rise of QTc

The response to this “epidemic” of drug-induced sudden cardiac death included individual efforts by the national drug regulatory bodies and led to the international effort culminating in the release of the ICH E14 Guidance in 2005.³ This guidance described the recommended process for the clinical assessment of a new drug to assess the risk of sudden death and relied on the detection of drug-induced QTc prolongation. The guidance described the design, conduct and statistical endpoints for a dedicated ECG study (known as a Thorough QT/QTc trial or TQT) to precisely determine the extent to which a new drug prolongs QTc, if any. Drug-induced QTc prolongation thus became a surrogate marker for detection of drugs with an increased risk of producing TdP and sudden cardiac death. Assessment of a new drug’s effect on QTc (as well as other IDMs) became a critical component of the development of any new drug.

However, QTc is a difficult surrogate marker. QTc has a large daily variability and is affected by many different intrinsic and extrinsic factors (including gender, heart rate, meals, medications and electrolyte shifts). The QT interval is also sometimes difficult to measure precisely (particularly if an ECG has poor quality or if the T waves have complex shape or low amplitude). In a healthy individual with no cardiac disease and taking no medications, QTc varies by up to 75 ms over the course of a 24-hour period. Yet the ICH E14 guidance requires the detection of a mean drug-induced QTc increase of 5 ms (with the 90% upper confidence interval for QTc increase of <10 ms). In the face of wide variability over time, detecting these small drug-induced QTc changes requires precise QT measurements, a large number of participants and a very large number of ECGs. Furthermore, a TQT is required to have a positive pharmacologic control arm or sequence to demonstrate assay sensitivity.

In other words, to demonstrate that a trial had the statistical power to detect a QTc signal this small, a typical TQT would have required 40-50 participants (for a crossover design – a parallel arm study would be even larger) and might involve collection and analysis of 8,000-30,000 ECGs!

Statisticians have developed methods for estimating the sample size required for a TQT. The major determinants of the sample size are the true magnitude of the QTc effect of the drug (not much that one can do about this), the number of time points evaluated (one has some leeway here) and the precision of the ECG measurements.⁴ The precision of the QTc measurements is reflected by the within-subject variability – the mean of the standard deviations of the measurements for each participant. The better the precision of the QTc measurements (the lower the within-subject variability), the smaller the number of participants required to be able to demonstrate the lack of a QTc effect of the study drug as well as to demonstrate the expected QTc increase by the positive control (nearly always a single 400 mg dose of moxifloxacin).

At the time that the ICH E14 Working Group began working on the E14 guidance, ECGs were generally measured the same way that Einthoven measured them in the 19th century – by measuring the intervals on the printed ECG using a pair of calipers or a rate ruler. The precision of such measurements is relatively low. Given that the width of the ink line on a printed ECG is 5-10 ms and the tip of a pair of metal calipers is also about the equivalent of 10 ms, these measurements cannot be very accurate. A human electrocardiographer measuring an ECG by hand cannot measure more accurately than about 10-20 ms.

In the early 1990s, eResearch Technology (ERT – now Clario since 2021) developed a much higher resolution method for performing ECG measurements using a high magnification jeweler's loupe and a digitizing board. This allowed for much more precise ECG measurements; the within-subject variability using this method was on the order of 10-12 ms. This meant that, in the early 2000s, when the ICH E14 Working Group was developing the ICH E14 guidance, the highest precision QT measurements available had a precision of 10-12 ms. As a result, once the E14 guidance was released, the sample size required for a TQT with a crossover design was 60-80 participants.

At about the same time, the FDA began the "digital ECG initiative," urging the collection of digital ECGs during clinical trials. Modern ECG machines collect ECGs as digital recordings, which typically have sampling rates of 500-1000 Hz. With a sampling rate of 1000 Hz, each pixel is only 1 ms apart. If one displayed this ECG at a high enough magnification and had a sufficiently precise measuring instrument, one could reproducibly measure ECG intervals to millisecond resolution!

ERT (Clario) introduced its first fully digital ECG management system, EXPERT®, in late 2002. This system allowed the onscreen measurement of digital ECG files at very high magnifications, significantly improving the precision compared with the older measurement methods using measurements performed on paper ECG tracings using metal calipers or digitizing boards. The first version of the EXPERT system allowed a reduction in the QTc measurement precision to 8-9 ms, enabling a reduction in the sample size required in a TQT with crossover design to 40-50 participants.

Current QTc measurement precision

In the 12 years since the ICH E14 guidance was released, we have seen further improvements in the precision of QTc measurements. In 2013, the FDA asked ERT (Clario) to perform a study designed to investigate the effects of ethnicity on the QT effect of drugs.⁵ ERT (Clario) designed a trial that was much like a TQT but involving only the placebo and moxifloxacin treatment sequences. This was conducted with two groups of participants – healthy ethnic Japanese individuals at a site in Japan and healthy Caucasian individuals at a site in the United States. The intention was to see if the QTc response to moxifloxacin was equivalent for the two ethnic groups (It was).

As part of this trial, ERT (Clario) also evaluated the effect of the number of ECG replicates collected per ECG time point on the precision of the trial.⁶ Most ECG core labs generally collect three ECGs around each time point during a QT study.

The analysis of the effect of the number of ECGs on the precision of the QTc measurements revealed the following: as expected, the more ECGs analyzed at a time point, the better the precision and the lower the within-subject variability. Of note, however, the data showed that using the standard three ECGs per time point and a standard “semi-automated” manual adjudication measurement methodology, the within-subject variability for QTcF was <6 ms (Table 1). Increasing the number of ECGs analyzed at each time point did further reduce the variability but at increased cost. The “sweet spot” for maximizing precision in a dedicated TQT study without unreasonable expense appears to be collection of 3–4 ECGs per time point.

Table 1. QTc precision by number of ECGs per time point during an FDA ethnicity trial

ECGs per time point	QTcF within-subject variability SD (ms)
1	7.3
2	6.4
3	6.0
4	5.6
5	5.4
6	5.2
7	5.1
8	5.1
9	5.0
10	4.9

More recently, we evaluated our precision in recent TQTs. For crossover TQTs, the within-subject variability is between 5 ms and 6 ms, while for parallel design TQTs, the within-subject variability is between 6 ms and 7 ms (Table 2). These results are identical to those reported

as “best in practice” for a highly automated, “high-precision QT” analysis method, although this method relies on the use of 10 ECGs per time point rather than the standard three ECGs per time point (“triplicate ECGs”) used until approximately 2018.⁷

Table 2. Precision of recent TQTs conducted by Clario using triplicate ECGs

Study	QT correction method	Design	Arms	N	Placebo residual variability	Placebo within-subject variability	Moxifloxacin residual variability	Moxifloxacin within-subject variability
1	QTcI	Crossover	4	54	28.8	5.4	38.7	6.2
2	QTcI	Parallel	3	180	46.5	6.8	52.5	7.2
3	QTcF	Crossover	4	50	26.4	5.1	39.7	6.3
4	QTcF	Crossover	3	48	29.3	5.4	31.6	5.6
5	QTcF	Parallel	4	240	33.7	5.8	42.9	6.5
6	QTcF	Crossover	4	52	27.8	5.3	35.6	6.0
7	QTcI	Crossover	4	44	30.2	5.5	36.7	6.1
8	QTcF	Crossover	6	57	30.2	5.5	42.1	6.5
9	QTcF	Crossover	4	54	30.4	5.5	35.5	6.0

Early precision QT analysis

As observed in the analysis of the relationship between the number of ECG replicates per time point and the measurement precision, the precision improves by approximately 1 ms as the number of replicates increases from three to 10. Furthermore, precision is further increased if the number of complexes measured per ECG replicate is increased while focusing on “high-quality” beats and thereby avoiding adjustment of IDMs. This was the impetus for the development of Early Precision QT Analysis (EPQT), formerly known as High Precision QT analysis. In this methodology, up to 10 replicates, each 14 seconds in duration, are extracted from a continuous 12-lead recording at each nominal time point. The RR interval and QT interval of all high-quality beats on the 14 second strip are measured, resulting in upwards of 100 RR/QT pairs per time point compared with the total of 9 RR/QT pairs using the standard method of measuring three complexes on triplicate ECGs. As shown in Table 3, using EPQT, the mean SD of $\Delta QTcF$ in 39 crossover TQTs measured using EPQT was 6.3 ms.

Table 3. Precision of recent crossover TQTs conducted by Clario using EPQT

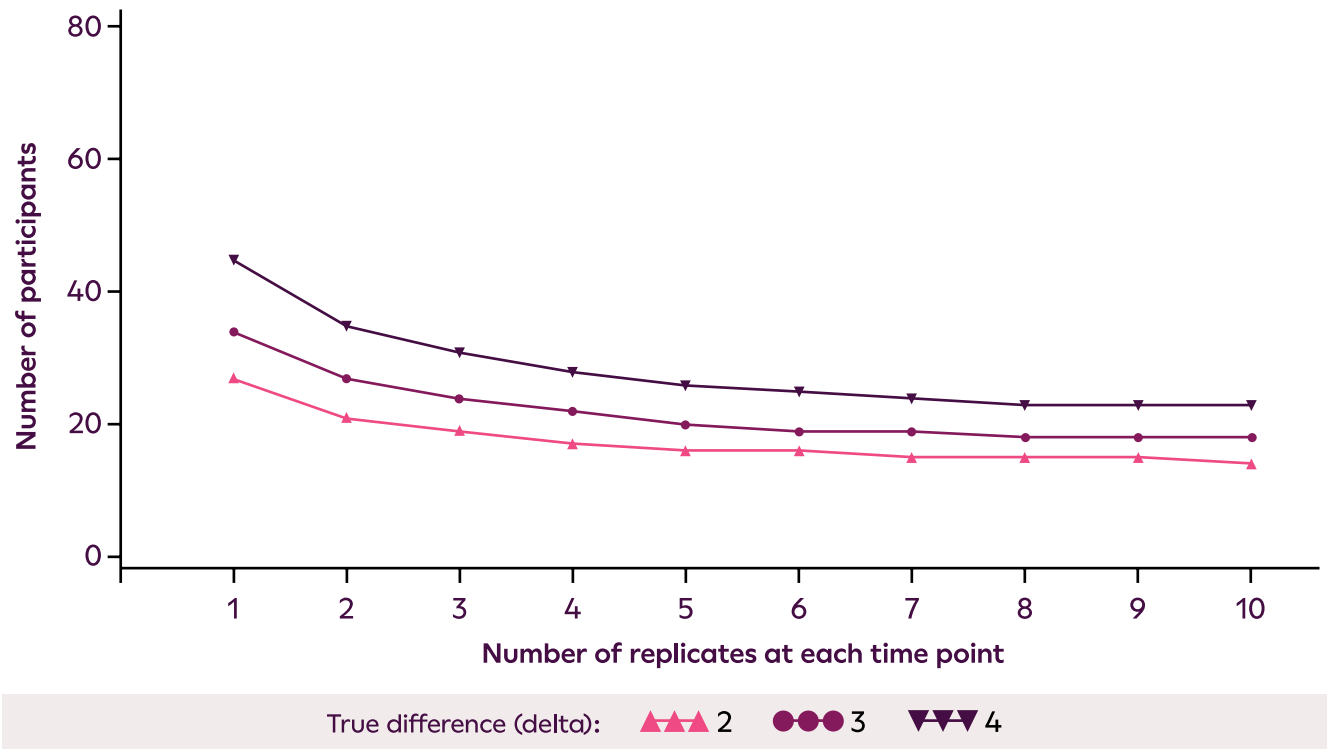
Study	Sample size	SD of $\Delta QTcF$ (msec)
1	52	5.8
2	24	5.4
3	48	5.1
4	49	5.6
5	59	6.2
6	58	6.9
7	30	6.8
8	42	7.3
9	15	7.7
10	49	6.5
11	36	6.2
12	27	6
13	63	6.5
14	48	7.3
15	30	5.3
16	34	7.3
17	59	3.6
18	63	8.1
19	31	6.7
20	38	6
21	32	9.1
22	31	5.8
23	32	7.1
24	36	7.4
25	33	7.3
26	32	6.3
27	48	4.9
28	58	6
29	30	6.4
30	27	6.6
31	31	5.8
32	30	5.2
33	35	5.7
34	36	5.6
35	36	6.6
36	36	5.6
37	32	5.6
38	65	5.6
39	35	7.5

Why does QTc measurement precision matter?

The significance of the steady improvements in the precision of QTc measurements relates back to the earlier discussion about the sample sizes required for a TQT. Since the number of participants required for a successful TQT is related to the precision of the QTc measurements, the better the precision, the lower the number of participants needed and the lower the overall cost of the study. Furthermore, improved precision results in narrower confidence bounds around the point estimate of QTc effect – thus increasing the ability to exclude a small QTc increase as described in the +ICH E14 guidance. With the precision of the early 2000s, we needed 60-80 participants to adequately power a TQT study. With the improvement in the precision of QTc measurements in the next few years thereafter, the size of TQT trials was reduced to 40-50 participants.

What about the latest improvements in QTc measurement precision to 5-6 ms? Does this further reduce the number of participants required for a standard TQT trial? The answer is that, unfortunately, further improvements in precision do not really lead to much further reduction in the size and cost of a TQT study. As shown in Figure 3, increasing the number of ECGs per time point beyond triplicate ECGs has little effect on the required sample size while increasing the cost of the trial. For purposes of calculating the sample size for a TQT, one normally assumes a true difference in QTc change between the study drug and placebo of 3-4 ms. With current QTc measurement precision, increasing the number of ECGs at each time point does not significantly reduce the sample size needed for a TQT study while dramatically increasing the cost.

Figure 3. Effect of the number of ECGs on sample size for a TQT trial



The December 2015 ICH E14 R3 Q&A revision and why QTc precision is important again

In late 2015, the ICH E14 guidance underwent a substantial revision. Based on accumulated evidence as well as a prospective trial, the ICH E14 guidance was revised to allow the use of either the standard by-time-point analysis or concentration effect modeling (CEM) endpoints for a QTc study.⁸ The significance of this change in the endpoints for a QT trial mean are quite significant. The use of CEM endpoints allows the use of studies with much smaller sample sizes to potentially evaluate the QTc effect of a compound and even allows for the use of Phase I single-ascending dose (SAD) and multiple-ascending dose (MAD) trials to provide enough data to completely assess the ECG effects of a new drug (“potentially” is the key word; in practice, this is not quite as simple as it sounds). The reason that this regulatory revision is significant is simple. When one uses a by-time-point analysis as the primary endpoint, each time point is analyzed in isolation. This requires a large sample size. In contrast, CEM uses all the time point data for all the participants in each analysis, which means that far fewer participants are needed. Instead of requiring a separate ECG trial with 40-50 participants, it may be possible to collect the same information during existing Phase I studies, which typically include 8-12 participants per cohort. Even more significant is that one may be able to collect all the data for a full analysis of the ECG effects of a new compound without

requiring a separate, dedicated ECG trial. When QTc assessments (as well as assessments of other ECG effects) can be performed during standard Phase I ascending dose studies, one may be able to avoid performing a dedicated QTc study, such as a TQT trial, potentially killing two cats with one stone and reducing program expenses by several million dollars. This is feasible if the doses reached in these early-phase healthy volunteer trials cover exposures of at least twice that would be needed in defining the supratherapeutic dose in a TQT.

Critical to being able to use Phase I ascending dose study data to replace a TQT trial is ensuring that the data are equivalent. To avoid the requirement for a TQT trial, one must collect data that is in every way equal – meaning that the trial design, trial conduct, ECG analysis and statistical methods must be equal to those used in a dedicated TQT study. The more precise the QTc measurements, the higher the likelihood that a small, standard design Phase I trial will collect adequate data to match the data from a dedicated TQT trial. The endpoints for a QTc trial are based not on the mean estimate of QTc effect but on the upper confidence limits. The higher the precision of the measurements, the lower the upper confidence bounds around the point estimate of the mean effect will be. Thus, the improvements in the precision of QTc measurements are critical to being able to potentially replace dedicated TQT trials with CEM assessments performed during standard Phase I ascending dose trials.

Summary: Why ECG precision matters

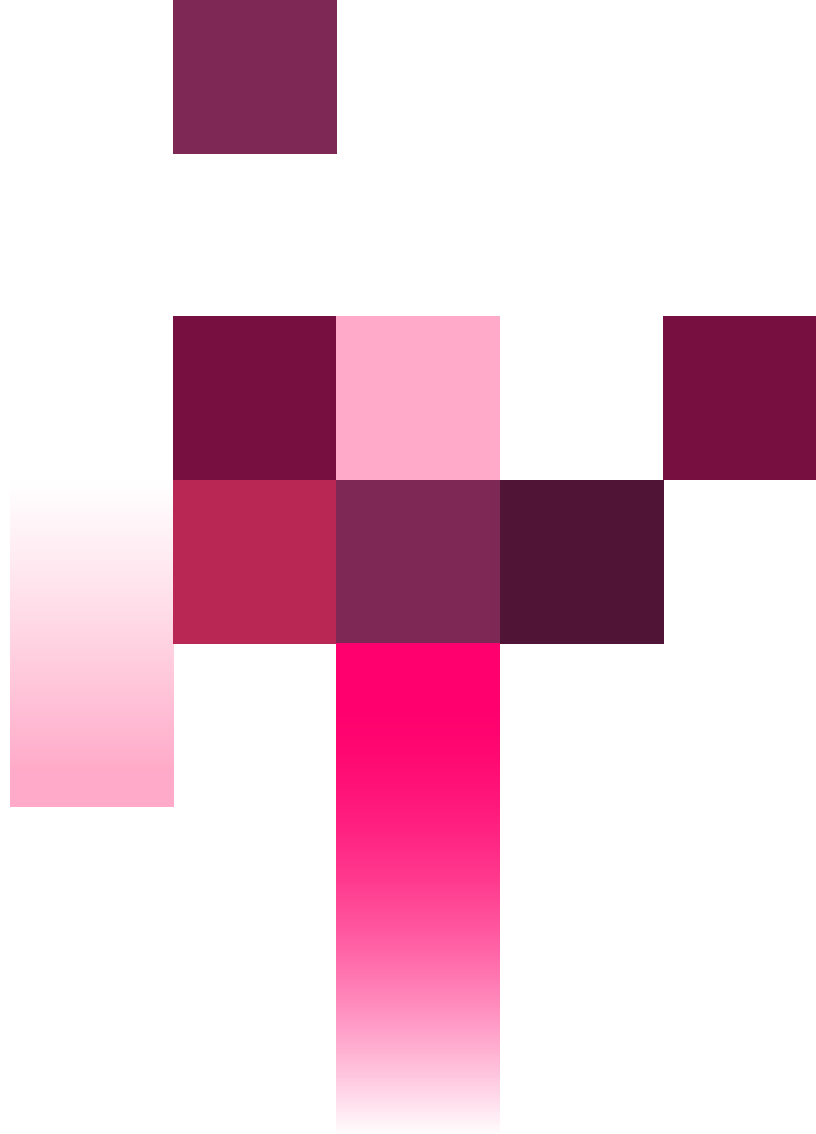
Since the early 2000s, when the ICH E14 guidance was being drafted, the best-in-class QT measurements had a precision of, at best, 10–12 ms, requiring large sample sizes for QT studies to be able to have adequate power to demonstrate a negative QT effect for a new compound. Improvements in measurement technology as well as better ECG collection methods have led to significant improvements in QT measurement precision; ERT (Clario) now routinely finds QTc within-subject variabilities in the range of 5 ms to 6 ms.

These improvements in ECG measurement precision have had modest effects on the size of standard TQT trials, as the use of by-time-point endpoints requires a large sample size, even with very precise QT measurements. We have seen the size of a standard crossover design TQT drop from 60–80 participants at the time of the ICH E14 ratification in 2005 to about 28–30 participants during the past few years, which is an improvement, but a modest one. A standard TQT remains a large and expensive project.

The real value of the improvement in ECG measurement precision is really not seen for standard TQT trials. Instead, the real value is observed when one uses Phase I QT data to replace the dedicated TQT study, as made possible by the December 2015 revision to ICH E14. Phase I ascending dose studies include small cohort sizes; in this setting, precise QT measurements are absolutely essential. With the QTc precision that is currently achieved with a combination of automation plus intense human involvement (semi-automatic method), a QTc precision of 5–6 ms has become the standard for QT studies and allows drug developers to retain their traditional SAD and MAD study designs while collecting accurate QTc data that may potentially avoid the need for a dedicated QT study. This truly represents a significant advance in the drug development process. It has been reported that, during the past few years, at least one-third of new drugs that would previously have required a dedicated TQT study were able to use first in human SAD/MAD data to replace a TQT trial.^{9,10}

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