Comparing QT interval variability of semiautomated and high-precision ECG methodologies in seven thorough QT studies—implications for the power of studies intended for definitive evaluation of a drug's QT effect

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Background: In studies of drug effects on electrocardiographic parameters, the level of precision in measuring QTc interval changes will influence a study's ability to detect small effects.

Methods: Variability data from investigational, placebo and moxifloxacin treatments from seven thorough QT studies performed by the same sponsor were analyzed with the objective to compare the performance of two commonly used approaches for ECG interval measurements: semiautomated (SA) and the high-precision QT (HPQT) analysis. Five studies were crossover and two parallel. Harmonized procedures were implemented to ensure similar experimental conditions across studies. ECG replicates were extracted serially from continuous 12-lead recordings at predefined time points from subjects supinely resting. The variability estimates were based on the time-point analysis of change-from-baseline QTcF as the dependent variable for the standard primary analysis of previous thorough QT studies. The residual variances were extracted for each study and ECG technique.

Results: High-precision QT resulted in a substantial reduction in Δ QTc variability as compared to SA. A reduction in residual variability of approximately 50% was achieved in both crossover and parallel studies, both for the active comparison (drug vs. placebo) and for assay sensitivity (moxifloxacin vs. placebo) data.

Conclusions: High-precision QT technique significantly reduces QT interval variability and thereby the number of subjects needed to exclude small effects in QT studies. Based on this assessment, the sample size required to exclude a QTc effect >10 ms with 90% power is reduced from 35 with SA to 18 with HPQT, if a 3 ms underlying drug effect is assumed.

KEYWORDS

QTc interval, ICH E14, TQT studies, variability, sample size, healthy subjects

1 | INTRODUCTION

The International Conference of Harmonisation E14 clinical guidance document which was adopted in 2005 identifies the thorough QT (TQT) study as the designated way of demonstrating that a new

drug does not have a clinically relevant effect on the QT interval (ICH Harmonized Tripartite Guideline E14, 2005). The study is typically performed in healthy subjects and should be powered to allow exclusion of a treatment-related QT effect exceeding 10 ms. The TQT study includes placebo and a positive control, in most cases 400 mg

oral moxifloxacin, with the role to ensure that the study is sufficiently sensitive to detect a small QT effect. Moxifloxacin at this dose typically causes 10–14 ms QTc prolongation (Florian, Tornøe, Brundage, Parekh, & Garnett, 2011) and the study's "assay sensitivity" is demonstrated if the peak effect is statistically significantly above 5 ms, i.e., the lower bound of the two-sided 90% confidence interval (CI) of the placebo-corrected, change-from-baseline QTc ($\Delta\Delta\text{QTc}$) is above 5 ms (see Question 1 in [ICH E14 Questions & Answers (R3), 2015]). If assay sensitivity has been shown, a negative result for the drug is viewed as conclusive. With the approach initially described in ICH E14, the drug's QT effect is tested separately at each time point postdosing and multiplicity is adjusted, for example, by using the so-called Intersection Union Test (ICH Harmonized Tripartite Guideline E14, 2005; Hutmacher, Chapel, Agin, Fleishaker, & Lalonde, 2008; Zhang & Machado, 2008; Zhang, 2012, 2015). This necessitates a relatively large number of subjects to ensure the study has sufficient power: With this analysis, the number of postdosing time points considered for analysis has some impact on the power of the study (the more time points, the lower the power), whereas the magnitude of the effect of the drug and the variability in the QTc measurement are more critical (Zhang & Machado, 2008).

In December 2015, the ICH E14 Q&A document was revised and now allows exposure response (ER) analysis to confidently exclude that a drug causes clinically relevant QT prolongation (ICH E14 Questions & Answers (R3), 2015). With this analysis, ECG and drug concentration data from all time points and doses are used in the same model to conclude that the predicted QT effect is below 10 ms and the precision around the estimated effect is therefore substantially better, which enables the technique to be applied also to relatively small-sized, standard clinical pharmacology studies (Darpo et al., 2014; Ferber, Zhou, & Darpo, 2014). In a setting with reduced sample size like first in human studies, tight control of experimental conditions at the conducting clinical site and the method by which the QT interval is measured continuous to be fundamentally important. We have strived to reduce the variability in ECG parameters by harmonizing the conduct of these studies at clinical sites by implementing rigorous standards for handling of subjects and experimental conditions. These harmonized procedures have been in place since 2012 and have resulted in a relatively consistent variability in the postdose raw QT data. To investigate whether further efficiencies can be provided for these studies, we studied the impact of the QT interval measurement techniques *per se* on variability. Most central ECG laboratories extract serial ECGs from continuous 12-lead Holter recordings, and the clear majority of laboratories use a so-called semiautomated (SA) ECG interval measurement techniques (see Question 4 in ICH E14 Questions & Answers, 2014 and, e.g., Tyl, Kabbaj, Fassi, De, & Wheeler 2009). This technique is widely used and has been accepted for over well 20 years of clinical studies and in numerous TQT studies (Morganroth, Dimarco, Anzueto, Niederman, & Choudhri, 2005; Morganroth, 2007; Morganroth, Lepor, Hill, Volinn, & Hoel, 2010; Morganroth, Gretler, Hollenbach, Lambing, & Sinha, 2013).

More recently, so-called "high precision" QT techniques have been developed internally by one sponsor (Dota, Skallefjell, Edvardsson, & Fager, 2002; Dota et al., 2003) and by one central ECG laboratory,

iCardiac Technologies (Darpo et al., 2011, 2014, 2015; Darpo, Ferber, Zhou, Sumeray, & Sager, 2013), with the objective to further reduce the variability in the QT interval measurement. This latter technique was recently applied to some of our TQT studies, and the objective of this study was therefore to evaluate the impact of the High-Precision QT (HPQT) technique on QT interval variability and the potential implication for the statistical power of TQT studies in comparison to the semiautomated manual-adjudicated ECG method.

2 | METHODS

Data from seven TQT studies in healthy subjects were used. The studies were performed consecutively over 3 years by one sponsor (Novartis Pharma AG) using harmonized procedures for study conduct and analyses of data. Key characteristics of the studies are shown in Table 1. In all studies, ECG data were acquired using continuous 12-lead digital ECG recordings (Holters) for the time period encompassing the predose and postdose PK/PD time points specified in each study protocol. Studies 1, 3, 4, and 7 were performed using a SA ECG measurement method; Studies 2, 5, and 6 utilized the HPQT measurement method. Both methods are described below.

In all studies, subjects were silently resting in the supine position in an undisturbed environment for at least 15 min prior to each protocol-specified time point. Replicate 12-lead ECGs were extracted from the last 5 min within this time window provided that the heart rate had been stable for the preceding 2 min. Vital signs and blood sampling were performed after the ECG extraction.

All ECGs were extracted and measured by a central ECG laboratory. The central ECG readers were blinded to study treatment or ECG sequence. All ECGs from a subject were read by the same reader, and all QT measurements were performed on a single predetermined lead (typically Lead II). Measured ECG parameters included uncorrected QT, heart rate, RR, PR, QRS intervals, and qualitative assessment of T-wave morphology.

2.1 | Semiautomated ECG measurement

Ten-second 12-lead ECG tracings were extracted by the core laboratory in triplicates from continuous 12-lead recordings at the protocol-specified time points. The triplicates were separated by approximately 2 min. The calipers for interval measurements were preplaced by a computer algorithm, and the measurements were thereafter manually adjusted by the operator, if deemed necessary. The intervals from three consecutive interpretable beats in each of the three ECG replicates at each protocol time point were measured. The process results in a combination of QT interval measurements derived by the computer algorithm, and some measurements having been adjusted by the reader. For each beat, the QT interval was heart rate corrected using the preceding RR interval, and the mean QTc value across the nine beats (three ECG replicates $\times$ three measured beats) was used as the reported value for the subject at this time point. The final assessment is reviewed by a cardiologist before being released.

TABLE 1 Studies

Study	ECG method	Study design	Subjects <i>n</i> ^a	Females <i>n</i> (%)	Age years mean (SD)	BMI kg/m ² mean (SD)	Peak moxifloxacin effect, ms mean (90% CI)
1	SA	Parallel 3 groups	281	32 (10.5)	35 (7.6)	26.1 (2.6)	12.6 (10.21–15.03)
2	HPQT	Parallel 3 groups	229	All male	31.7 (7.8)	24.9 (2.3)	10.0 (8.28; 11.64)
3	SA	XO	73	38 (52%)	28 (6.8)	26.2 (3.36)	10.9 (8.88; 13.03)
4	SA	XO	82	30 (36%)	32.4 (7.96)	26.2	11.7 (10.01; 13.46)
5	HPQT	XO	84	36 (43%)	32.7 (7.5)	24.8 (2.3)	13.6 (12.27; 14.85)
6	HPQT	XO	84	All male	32.8 (7.4)	24.5 (2.27)	11.9 (10.91; 12.90)
7	SA	XO	89	11 (12%)	32.3 (8.6)	26.8 (3.5)	12.5 (11.18; 13.87)

^aNumber of subjects in the ECG analysis; XO: crossover; peak moxifloxacin effect, the largest effect on placebo-corrected change-from-baseline QTc after dosing with 400 mg moxifloxacin.

SA, semiautomated; HPQT, high-precision QT technique.

2.2 | High-precision ECG measurement

During the protocol-specified ECG extraction time windows, ten 10-s digital 12-lead ECG tracings are extracted from the Holter recording and analyzed using the TQT Plus algorithm and high-precision QT (HPQT) technique, as previously described (Darpo et al., 2011). As HR stability is a critical driver of QT variability, TQT Plus integrates analysis algorithms with a statistical quality control oversight that identifies a selection of ECG recordings within the 5-min extraction window with the minimum heart rate variability and noise and classifies them as high and low confidence beats without manual interaction. TQT Plus defines a “stable” heart rate range suitable for extraction as <10% variation in beat-to-beat RR. HPQT analysis was performed by default on all analyzable normal beats in the 10 ECG replicates. Low confidence beats are reviewed manually by the core laboratory reader and adjudicated (accepted for analysis or rejected) with no operator adjustment or remeasurement.

Measurements of the QT and RR intervals were performed using COMPAS software (Couderc et al., 2011). For each 10-s ECG tracing (replicate), the median QT and RR value from all accepted beats is calculated, and the mean value of all replicates’ medians is reported for that time point. This method encompasses QTc interval measurements from approximately 80 to 100 beats for each time point (10 ECG replicates × 8–12 beats per 10-s replicate). The procedure and final assessment is overseen and reviewed by a cardiologist.

2.3 | Statistical analysis

2.3.1 | Calculation of residual variance

In all studies the primary endpoint was the change from baseline in QTcF (Δ QTcF). The treatment difference in active compound versus placebo (Δ Δ QTcF) was estimated for each time point together with the corresponding two-sided 90% CI according to the respective primary model prespecified in each study. The same analysis was

repeated for the analysis of moxifloxacin versus placebo. The residual variances estimated by these analyses form the basis for the post hoc analyses. The residual variances are presented for all studies and time points by ECG measurement method (SA or HPQT) and type of study design (parallel or crossover), together with the respective mean of the maximum variance observed across all time points per ECG measurement method.

2.3.2 | Sample size and power calculation

The residual variances were used to calculate the sample size for a fictitious new TQT study to illustrate the effect of the different variances observed on the sample size and power.

Sample size calculations were performed with the objective to demonstrate a negative TQT following the ICH guideline (ICH Harmonized Tripartite Guideline E14, 2005, 2014), i.e., to demonstrate that the upper two-sided 90% confidence bound for the largest mean difference between the test drug and placebo was below 10 ms at all postdosing time points, using the Intersection Union test (Zhang, 2008; Zhang & Machado, 2008). The endpoint was the change-from-baseline QTcF (Δ QTcF) and the null hypothesis was to be rejected if the upper two-sided 90% confidence bounds for tests at all time points were <10 ms. Using this analysis approach, no adjustment is needed to maintain the overall α -level. However, in sample size calculations, the need for simultaneous rejection requires β (type II error) and thus the power should be adjusted using the Bonferroni multiplicity adjustment strategy, to ensure sufficient power levels are maintained.

For the sample size calculations, maximum expected treatment differences between 0 and 5 ms in Δ QTcF were assumed to be attained in three of the investigated time points.

In addition, the power was derived for the corresponding analysis of moxifloxacin to placebo. Again the residual variances of the different ECG measurement methods and study designs were used. The power to exclude a difference between the moxifloxacin and placebo groups of 5 ms from the lower two-sided 90% CI for at least one of the three

prespecified time points (e.g., 2, 3, and 4 hr postdose) was derived. The expected treatment effect of moxifloxacin over placebo was assumed to be 10 ms in at least one of the three time points. Adjustment for multiplicity was applied by using the Bonferroni approach maintaining an overall type I error of 5% (one sided).

3 | RESULTS

In all studies, assay sensitivity was demonstrated by the QT effect of moxifloxacin. The peak effect varied between 10.0 ms and 13.6 ms after dosing of 400 mg oral moxifloxacin (Table 1). In all studies, the lower bound of the 90% CI of $\Delta\Delta\text{QTc}$ exceeded 5 ms, thereby demonstrating assay sensitivity as defined by the ICH E14 clinical guidance (ICH E14 Questions & Answers (R3), 2015).

3.1 | Reduction in variability

The use of HPQT measurement technique resulted in a substantial reduction in variability in QT measurements as compared to the SA method. The reduction in residual variance was approximately 50% in both crossover and parallel designed studies (Figures 1,2). The reduction in the residual variance was in the same order of magnitude for the analysis of the drug effect (left panels in Figures 1,2) and the effect of the positive control, moxifloxacin (right panels).

3.2 | Impact on power and sample size of TQT studies

The ability to reduce variability has implications for the power of a TQT study and therefore on the sample size required to exclude a

FIGURE 1 Residual variance across time points for crossover TQT studies using SA ($n = 3$) and HPQT ($n = 2$) QT measurement techniques. The use of HPQT reduced the residual variance by approximately 50%, both for the analysis of the drug effect (left panel) and for the effect of moxifloxacin (right panel). Solid lines show variance across time points for each study with colors indicating the QT measurement method and dotted lines the mean maximum variance over all time points across ECG method

FIGURE 2 Residual variance across time points for parallel designed TQT studies using SA ($n = 1$) or HPQT ($n = 1$) QT measurement techniques. The variability is expectedly larger for parallel as compared to crossover designed trials, but the reduction seen with HPQT as compared to the SA QT measurement technique was comparable, around 50%. (Left panel) Comparison of drug versus placebo; (right panel) Comparison of moxifloxacin versus placebo. Solid lines show variance across time points for each study with colors indicating the QT measurement method and dotted lines the mean maximum variance over all time points across ECG method

small QT effect by the test drug. In Figure 3A sample sizes of crossover studies that would provide 80% power to exclude a QTc effect exceeding 10 ms (i.e., the upper bound of the 90% CI of $\Delta\Delta\text{QTc}$ falls below 10 ms) are shown across the assumed underlying 'true' QTc effect of the test drug ranging from 0 ms to 5 ms. For example, in a crossover study using the standard assumption of 3 ms underlying effect and the mean maximum residual variance observed in our studies, approximately 50% fewer subjects are needed to provide 90% power to exclude a QT effect exceeding 10 ms if HPQT is used, as compared to using a SA method; 18 versus 35 subjects (~49%). Similarly for parallel designed studies, with the same assumptions, approximately 50% reduction in the number of subjects needed is

TABLE 2 Sample size required to demonstrate absence of QT effect of test drug versus placebo

ECG Method	Design	Power	SD of ΔQTc^a (ms)	Required sample size ^b
HPQT	XO	0.8	5.2	15
SA	XO	0.8	7.3	29
HPQT	XO	0.9	5.2	18
SA	XO	0.9	7.3	35
HPQT	Parallel	0.8	6.8	38
SA	Parallel	0.8	10.3	76
HPQT	Parallel	0.9	6.8	48
SA	Parallel	0.9	10.3	92

^aBased on the largest observed residual variance (mean maximum) for each method and study design.

^bFor XO trials total sample size required; for parallel trials total sample size required for two treatment groups.

XO, crossover; SA, semiautomated; HPQT, high-precision QT technique.

FIGURE 3 Calculated sample size to provide 80% power to exclude a QTc effect exceeding 10 ms as a function of assumed underlying QTc effect at three time points, comparing SA and HPQT QT measurement techniques. Reduced variability in the QT interval measurements with HPQT results in a substantial reduction in the required sample size with identical assumptions. For parallel designed studies, the sample size for two treatment groups is given. The bands show the range of sample sizes between the minimum and the maximum residual variance observed for each method and the dotted line the sample size using the mean maximum variance. (A) Crossover designed studies. (B) Parallel designed studies

achieved with HPQT as compared to SA; 48 versus 92 subjects for a study with two treatment groups (Figure 3B with 80% power). Table 2 gives the required sample size for studies of crossover or parallel design to exclude a 10 ms QT effect with 80% (0.8) and 90% (0.9) power. In all scenarios, the sample size reduction around 50% with HPQT as compared to SA. Two treatment groups in a parallel designed TQT study is only possible if the doses of the NCE are combined into one group and placebo and moxifloxacin combined into one, with a nested crossover approach (see, e.g., Darpo et al., 2014; Hoch et al., 2015).

The reduction in variability also impacts the power to detect the effect of the positive control. In Figure 4, the power to demonstrate that moxifloxacin causes a QT effect exceeding 5 ms (i.e., the lower bound of the 90% CI of the $\Delta\Delta\text{QTc}$ falls above 5 ms) is shown as a function of the sample size for both methods. For both crossover and parallel designed studies, lower variability with HPQT measurement technique results in a substantial reduction in the required sample size to demonstrate assay sensitivity. To achieve 90% power in a crossover design and considering the maximum residual variance observed in the historical studies, 28 subjects would be needed with HPQT, as compared to 52 subjects with the SA method; corresponding numbers for parallel designed studies are 92 versus 202 subjects with two treatment groups, corresponding to approximately 45% and approximately 55% reduction in the required sample size to detect a 5 ms QT effect of moxifloxacin, respectively (Table 3). In Table 3, the required sample size for demonstration of assay sensitivity is shown for studies with crossover or parallel designed with 80% (0.8) and 90% (0.9) power. The calculations are based on the observed mean maximum observed residual variance per study design and ECG method and are based on the assumption of 10 ms ΔQTc effect after administration of 400 mg moxifloxacin in at least one of three time points. The sample size is reduced by 45% to 55% across the different scenarios.

FIGURE 4 Power to demonstrate assay sensitivity with 400 mg moxifloxacin in a TQT study as a function of sample size, comparing SA and HPQT QT measurement techniques; the dotted horizontal line depicts 80% power. In crossover studies (A), 45% less subjects (22 vs. 40) would be needed to demonstrate assay sensitivity (the lower bound of the 90% CI of $\Delta\Delta\text{QTc}$ falls above 5 ms (ICH E14 Questions & Answers, 2014) with HPQT as compared to SA QT measurement techniques. For parallel designed studies, approximately 55% fewer subjects (70 vs. 154) would be needed to ensure 80% power to demonstrate assay sensitivity with oral moxifloxacin (B). The bands show the power range between the minimum and the maximum variance for each method and the dotted line the power when using the mean maximum variance

4 | DISCUSSION

With substantial experience accumulated by industry and regulators since the E14 Guidance was introduced in 2005, it has become apparent that the 'by timepoint analysis' using the Intersection Union Test used in these studies (Zhang & Machado, 2008) is conservative and resource intense in terms of the study's power to exclude small QT effects (Hutmacher et al., 2008). Consequently, many TQT studies are performed with sample sizes ranging between 40 and 80 subjects in a crossover design or the same number per treatment group in parallel designed studies, i.e., a total sample size of 120–200 subjects, or more (e.g., see (Darpo & Clinical, 2015)). In recent years, a growing

TABLE 3 Sample size required to demonstrate assay sensitivity for the comparison of moxifloxacin versus placebo

ECG Method	Design	Power	SD of ΔQTc^a (ms)	Required sample size ^b
HPQT	XO	0.8	5.2	22
SA	XO	0.8	7.3	40
HPQT	XO	0.9	5.2	28
SA	XO	0.9	7.3	52
HPQT	Parallel	0.8	6.8	70
SA	Parallel	0.8	10.3	154
HPQT	Parallel	0.9	6.8	92
SA	Parallel	0.9	10.3	202

^aBased on the largest observed residual variance (mean maximum) for each method and study design.

^bFor XO trials total sample size required; for parallel trials total sample size required for each treatment groups.

XO, crossover; SA, semiautomated; HPQT: high-precision QT technique.

interest in making the TQT study more efficient and reliable has resulted in the development of alternative ECG methods, often based on more data and measurements with computerized algorithms, and this has led to substantially reduced variability in QTc changes (Dalen, Vik, Alverlind, Jostell, & Hardemark, 2010; Darpo et al., 2011, 2013; Hoch et al., 2015). The recently revised ICH E14 (, 2015) places an equal weight on a negative QT assessment, i.e., a clinically concerning QTc effect is ruled out, regardless of whether it is based on the predicted QT effect using exposure response analysis applied to data from early-stage studies or on the observed 'by timepoint' effect using IUT in a TQT study (Darpo, Garnett, Keirns, & Stockbridge, 2015). It can therefore be expected that the number of dedicated TQT studies as defined in the original guidance will decrease as a consequence of an increasing number of early-stage clinical studies with intense ECG evaluation (Darpo & Garnett, 2013; Darpo et al., 2014; Nelson et al., 2015). The TQT study will, however, remain an option in select cases based on strategic or competitive considerations, a sponsor's decision to perform definitive QT testing only on compounds surviving into the late-phase development or to confirm or refute a QT signal observed in early-stage clinical studies. The TQT study will also be required when a sufficiently large margin (threefold) above clinically relevant plasma concentration levels could not be achieved in early-stage clinical studies, or when the QT assessment using ER analysis was inconclusive (the upper bound of the 90% confidence interval of the predicted effect exceeds 10 ms due to high variability (ICH E14 Questions & Answers, 2015)). Whatever the reason for performing a TQT trial, these studies can and should be made more effective and resource efficient by utilizing standardized procedures, experienced and qualified sites, and by using an ECG analysis methodology with low variability.

This post hoc analysis of seven TQT studies conducted under standardized procedures at the site level demonstrates that the chosen ECG analysis technique plays a crucial role in terms of further reducing the observed variability. With the use of the HPQT technique, the residual variance of the model for the primary analysis was reduced

approximately 50% as compared to the SA technique, which substantially increases the power of the TQT study. This reduction in variance and increased power can be leveraged to significantly reduce the number of subjects included in a study, or to increase the confidence in study results in the presence of a potential concern over a small underlying QT effect of the drug.

Based on the ICH E14 revision, an increasing number of studies will implement ER analysis of ECG data generated from first-in-human (FIH) studies to definitively exclude a QT effect at clinically relevant plasma concentrations, and thereby obviate the TQT study. As for TQT studies low variability in the QT interval measurement is key in these studies to ensure sufficient precision to achieve conclusive results. Standard FIH studies typically include several small dose cohorts, and often only include 2–3 cohorts at high doses. In preparation for the so-called IQ-CSRC study, pharmacometricians demonstrated that the power of these ER studies is largely driven by the number of subjects exposed to high concentrations of the drug, rather than the total number of subjects (Darpo et al., 2014). The impact of QT measurement variability has been further evaluated and was found to clearly have an effect on the power also in these studies using ER analysis. Simulations of a large number of small studies with an assumption of 3 ms underlying drug effect indicate that a study with nine subjects on a sufficiently high dose of the drug and six on placebo is able to exclude a QT effect >10 ms with 90% power in the presence of Δ QT variability of 6 ms, which is achievable with HPQT. With the larger variability seen with the SA technique (approximately 10 ms), the corresponding number of subjects required would be 21 subjects, approximately twice as many (Ferber, Lorch, & Taubel 2015). The same applies to TQT studies, which can be conducted with around 20 subjects in a three-way crossover design when using ER as the primary analysis (Liu, 2016).

Based on these observations, we conclude that the use of HPQT technique for QT interval measurement enables more efficient QT assessment studies and could enhance the confidence in the ECG outcomes of small early-stage clinical studies.

CONFLICT OF INTEREST

BD and SL own shares in iCardiac Technologies. BD is eligible for stock options in iCardiac Technologies.

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