PEER-REVIEWED ARTICLE

Clinical ECG Assessment

The Early Precision QT methodology discussed in this article was originally developed by iCardiac Technologies, which was acquired by Clario in late 2017. This methodology now forms the basis of Clario's Expert Precision QT (EPQT) solution.

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CLARIO.

Clinical ECG Assessment

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Contents

Abstract

With the adoption of the ICH E14 guidance, the thorough QT/QTc (TQT) study has become the focus of clinical assessment of an NCE's effects on ECG parameters. The TQT study is used as a guide to the liability of a drug to

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cause proarrhythmias on the basis of delayed cardiac repolarization. Around 300 TQT studies have been performed since 2005 and through interactions between sponsors and regulators, especially FDA's Interdisciplinary Review Team (IRT) for QT studies. These studies can today be performed more effectively and with great confidence in the generated data. This chapter will discuss technical features and the design and analysis of TQT studies, how assay sensitivity is demonstrated, and examples from recently conducted studies. ECG assessment for drugs that cannot be safely given to healthy volunteers is also addressed, and examples from studies in cancer patients and in healthy volunteers with tyrosine kinase inhibitors are discussed. The TQT study is resource intensive and designed to solely evaluate whether an NCE prolongs the QTc interval. If data with similar confidence can be generated from other studies that are routinely performed as part of the clinical development, this would represent a more optimal use of human resources. Methods and approaches to increase the confidence in ECG data derived from "early QT assessment" in single-ascending/multiple-ascending dose studies are therefore discussed, and a path toward replacing the TQT study using these approaches will be outlined.

Keywords

Healthy subjects • Precision • Publications • QT method • QTc • Sample size • Thorough QT studies • Variability

Abbreviations

CI	Confidence interval
E14	ICH Harmonized Tripartite Guideline E14: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IRT	FDA's Internal Review Team for QT studies
ER	Exposure-response
LB	Lower bound
MAD	Multiple-ascending dose
MTD	Maximum tolerated dose
NCE	New chemical entity
PK	Pharmacokinetic
QTc	Heart rate-corrected QT interval
ΔQTc	Change-from-baseline QTc
ΔΔQTc	Placebo-corrected change-from-baseline QTc
QTcF	QT heart rate-corrected according to Fridericia

QTcI	QT subject-specific heart rate correction
SAD	Single ascending dose
SD	Standard deviation
TM	Time-matched
Tmax	Time of peak plasma level
TQT	Thorough QT/QTc study
UB	Upper bound

1 Introduction

As part of the development program of a new chemical entity (NCE), there is an expectation that the effect of the on ECG parameters should be well characterized. With the adoption of the International Conference on Harmonisation (ICH) E14 guidance in 2005, the center piece of this evaluation has become the thorough QT/QTc (TQT) study, typically performed in healthy volunteers (Darpo 2010; ICH Harmonized Tripartite Guideline E14 2005). Despite the referral to only one of several ECG parameters, the QTc interval, it has become increasingly apparent that this study also can and should assess the effect of the NCE's effect on heart rate and the PR and QRS intervals, since these variables may also be adversely affected. This chapter will discuss features of the TQT study and address definitive ECG assessment for drugs that cannot be safely administered to healthy volunteers, such as many oncology drugs. Lastly, methods and approaches to increase the confidence in ECG data derived from "early QT assessment" in single-ascending/multiple-ascending dose (SAD/MAD) studies will be described, and a path toward replacing the TQT study using these approaches will be outlined.

It should be borne in mind that the objective of ECG assessment in healthy volunteers is limited to the evaluation of the drug's effect on ECG parameters, such as the heart rate-corrected QT interval (QTc). In this context, drug-induced QT prolongation is regarded as a biomarker for proarrhythmic risk in susceptible patients, and testing in healthy volunteers has the purpose of detecting drugs that have a sufficiently large effect to warrant further characterization in the targeted patient population (ICH E14 Questions & Answers 2012). For drugs with a "positive TQT study," i.e., a study in which an effect on QTc exceeding 10 ms cannot be excluded, further ECG monitoring is required in late-stage development. Objectively verified proarrhythmias are however very rarely observed in development programs of normal size or even in programs up to 20,000 patients, with a few notable exceptions with more potent QT-prolonging drugs (Caprelsa US NDA 022405 2011; Darpo 2007). Even in the absence of demonstrated proarrhythmic events, drugs with a more pronounced QTc effect, i.e., above 20 ms, are generally regarded as proarrhythmic by regulators and come with warnings and precautions in the label (Park et al. 2013).

This chapter intends to discuss the assessment of changes of ECG parameters as part of the drug development, with focus on studies and approaches specifically designed to evaluate drug-induced changes. Recent approvals of drugs with a relatively potent QT-prolonging effect, e.g., vandetanib (Thornton et al. 2012) and, most recently bedaquiline, illustrate that QT prolongation and the proarrhythmic risk associated therewith are a part of the benefit/risk assessment that all drugs must undergo; an informed discussion on this topic requires an in-depth understanding of the targeted indication and of the drug's effectiveness and is therefore out of scope for this text.

2 The Thorough QT/QTc (TQT) Study

2.1 The TQT Study

The "International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use" issued the E14 clinical guidance in May 2005: "The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs" (ICH Harmonized Tripartite Guideline E14 2005). The guidance was implemented in Europe and in the United States during the same year, but only more recently in Japan (November 2010). The TQT study is a dedicated study with the primary objective to quantify the effect of the NCE on the QT interval. In 2007, the US FDA formed an Interdisciplinary Review Team for QT studies (IRT) with the responsibility to oversee the clinical assessment of QT prolongation for all drugs that the agency reviews. The IRT serves in an advisory function to the reviewing divisions, reviews all TQT study protocols, and advises sponsors on the design of the study and supports the reviewing division in the interpretation of data. Individual members of the IRT have shared their experience at various meetings (e.g., DIA meetings) and through publications (see, e.g., Florian et al. 2011; Garnett 2012; Garnett et al. 2008; Malik et al. 2010; Zhu et al. 2010); this level of transparency has been of great value for sponsors and most likely also for regulators in other regions. Based on these interactions and experience from a large number of completed TQT studies (more than 300, July 2013), a standard for TQT studies has evolved. In line with this accumulated experience, clarifications to the E14 guidance have been issued in June 2008 and April 2012 (ICH E14 Questions & Answers 2012). Even so, there is clearly more than one way of performing a TQT study that will be accepted, and there are also areas which remain debated at the present time, e.g., how to best correct the QT interval for heart rate changes (Garnett et al. 2012).

To serve as a basis for discussion on the design of recent TQT studies, a PubMed search was done (December 31) using the search terms "thorough QT study 2012" and "thorough QTc QT study 2012." Eighteen TQT studies published in 2012 were identified; the key features of these studies and the response to the positive control, in all cases moxifloxacin, are summarized in Table 1. The limitations of this approach should be acknowledged: The list is most likely not complete; only a

Table 1 Thorough QT studies published in 2012

	Drug	References	Indication	Population (*n*)	Design	Treatments	Main result	Peak moxi ΔΔQTc[a] ms	SD of ΔQTc # of ECG replicates/ timepoint
1	Betrixaban	Morganroth et al. (2013)	Antithrombotic	HV; M + F $n = 96$	4-way XO; SD	T, ST, M, P	Negative	11.5 ± 2.7	SD = 11.3 ms with $n = 96$ for M/P #ECG: 3
2	Vismodegib	Graham et al. (2013)	Basal cell carcinoma	HV; F $n = 60$ (20 in 3 groups)	Parallel; nested XO MD; 7 days	T, M, P	Negative (UB of CI 10.0 ms)	19.0 ± 3.9	SD = 10.5 ms with $n = 40$ for M/P #ECG: 3
3	Bitopertin	Hofmann et al. (2012)	Schizophrenia	HV; M $n = 169$ (56–57/3 groups)	Parallel; nested XO MD; 10 days	T, ST, M, P	Negative	10.6 ± 3.7	SD = 11.9 ms with $n = 57$ for M/P #ECG: 3
4	Inhaled dihydroergotamine	Kori et al. (2012)	Migraine	HV, M + F $n = 54$	3-way XO SD	ST, M, P	Negative	11.3 ± 2.35	SD = 7.4 ms with $n = 54$ for M/P #ECG: 3
5	Exenatide	Darpo et al. (2013)	Type 2 diabetes mellitus	HV; M + F $n = 74$	3-way XO MD; 3 days	T + ST, M, P	Negative	10.9 ± 2.2	SD = 8.1 ms with $n = 74$ for M/P #ECG: 4
6	Sugammadex	de Kam et al. (2012)	Reversal of neuromuscular blockade	HV, M + F $n = 58$	4-way XO SD	T, ST, M, P	Negative	18.6 ± 3.6[b] 400 mg IV	SD = 11.7 ms with $n = 58$ for M/P #ECG: 3
7	Semagacestat	Zhang et al. (2012a)	Alzheimer disease	HV; M + F $n = 54$	4-way XO SD	T, ST, M, P	Negative	12.9 ± 1.9	SD = 5.8 ms with $n = 52$ for M/P #ECG: 4

(continued)

Table 1 (continued)

	Drug	References	Indication	Population (*n*)	Design	Treatments	Main result	Peak moxi $\Delta\Delta QTc^a$ ms	SD of ΔQTc # of ECG replicates/ timepoint
8	Bilastine	Tyl et al. (2012)	Allergic rhino-conjunctivitis	HV; M + F $n = 30$	5-way XO MD; 4 days	T, ST, T + keto, M, P	Negative	19.9 ± 2.9 MD 3 days	SD = 6.7 ms with $n = 30$ for M/P #ECG: 3
9	Lersivirine	Vourvahis et al. (2012)	HIV infection	HV; M $n = 48$	3-way XO SD	ST, M, P	Negative	15.3 ± 1.85	SD = 5.5 ms with $n = 48$ for M/P #ECG: 3
10	Gabapentin enacarbil	Chen et al. (2012)	Restless legs syndrome	HV; M + F $n = 50$	4-way XO SD	T, ST, M, P	Negative	7.5 ± 2.2	SD = 6.6 ms with $n = 50$ for M/P #ECG: 3
11	Midostaurin	del Corral et al. (2012)	TKI; acute myeloid leukemia	HV; M + F $n = 192$ 44, 68, 80/3 groups	Parallel MD; 3 days	T, M, P	Negative	10.7 ± 4.3	SD = 13.1 ms with $n = 43$/ 64 for M/P #ECG: 3
12	JNJ-Q2	Eichenbaum et al. (2012)	Antibiotic	HV; M + F $n = 58$	4-way XO MD; 4 days	T, ST, M, P	Positive	11.5 ms (CI not given)	NA
13	Dapagliflozin	Carlson et al. (2011)	Type 2 diabetes mellitus	HV, M $n = 50$	4-way XO SD	T, ST, M, P	Negative	11.5 ± 2.3	SD = 6.9 ms with $n = 50$ for M/P #ECG: ~10

14	Mirabegron	Malik et al. (2012)	Overactive bladder	HV, M + F $n = 352$ 88/4 groups	Parallel group with XO vs. placebo MD; 10 days	T, ST, M, P	Positive for females	Males, 9.14 ± 1.56 Females, 8.58 ± 2.21	SD = 5.0[c] ms with $n = 42$ for males and $n = 37$ for females for M/P XO #ECG: 5
15	Insulin; food methodology study	Taubel et al. (2013)	Diabetes mellitus	HV; M + F $n = 32$	2-way XO SD	Insulin, food, M, P	Negative	14.4 ± 2.5	SD = 6.0 ms with $n = 32$ for M/P #ECG: 3
16	Bupivacaine	Naseem et al. (2012)	Local anesthetic	HV, M + F $n = 49$	5-way XO SD	T, ST, M, P	Negative	11.3 ± 2.5	SD = 7.4 ms with $n = 48/49$ for M/P #ECG: 3
17	Saquinavir	Zhang et al. (2012b)	HIV infection	HV, M + F $n = 66$	4-way XO MD; 3 days	T, ST, M, P	Positive	12.2 ± 4.1	SD = 13.5 ms with $n = 60$ for M/P #ECG: 3
18	Prucalopride	Mendzelevski et al. (2012)	Chronic obstipation	HV, M + F $n = 120$ 60/ 2 groups	Parallel; nested XO MD 15 days	T, ST, M, P	Negative	13.38 ± 4.24[d]	SD = 14.0 ms with $n = 60$ for M/P #ECG: 3

The SD of ΔQTc was estimated based on the assumptions that the 90 % CI for peak moxifloxacin ΔΔQTc was calculated from a 2-sample *t*-test with equal variance for moxifloxacin and placebo data

HV, healthy volunteers; M, males; F, females; XO, crossover; SD, single dose; MD, multiple dose; T, therapeutic dose; ST, supratherapeutic dose; P, placebo; M, moxifloxacin, single oral dose of 400 mg; nested XO, nested crossover comparison for moxifloxacin/placebo within a parallel group study; T + keto, therapeutic dose concomitant with ketoconazole. TKI, tyrosine kinase inhibitor; CI, confidence interval; LB, lower bound. Negative: upper bound of CI < 10 ms for doses studied

[a]QTcI or QTcF; confidence interval (CI) calculated from given lower or upper bound

[b]Intravenous moxifloxacin 400 mg; CI not detailed; visually estimated from graph

[c]Average across male and female group

[d]Personal communication from the authors

small fraction of TQT studies are published and most likely subject to selection bias, and some studies may have been conducted several years ago. Despite this, the sample seems representative of the types of TQT studies that have been conducted during the last few years.

2.2 Timing of the TQT Study

There is no formal regulatory requirement on when the TQT study should be performed, but in most cases, the results are expected to be available before initiating late-stage, confirmatory efficacy trials; the consequence of not having these results available before starting phase III trials is that the level of ECG monitoring will be as intense as if the NCE were found to be positive in the TQT study. On the other hand, it is critical to have sufficient knowledge of the pharmacokinetic (PK) characteristics of the NCE in the targeted patient population, in particular data from patients with impaired clearance due to intrinsic or extrinsic factors, such as drug interactions. The timing of the TQT study will also be influenced by "QT signals" determined from safety pharmacology studies; for a drug with an unambiguous nonclinical QT signal, it may be important to determine the level of QTc effects in humans early in clinical development, as this will have a bearing on the benefit/risk assessment and thereby the potential viability of the project. For NCEs targeting more severe medical indications, e.g., oncology drugs, in particular when no other effective therapy exists, it may be preferable to conduct the TQT at a stage when some confidence in the clinical effectiveness has been gained. There have been advancements in the ability of chemists to design NCEs without hERG inhibition (Leeson and Springthorpe 2007), but even so, NCEs from certain pharmacological classes, e.g., fluoroquinolone antibiotics, often demonstrate QT liability. For such classes, it may also be advisable to perform the TQT relatively early in the program.

2.3 Design Considerations

When considering the clinical study trial design, it is critical to know the variability that exists between study types. The "within-subject" variability is lower than the "between-subject" variability, and a crossover-designed TQT study is therefore more efficient than a parallel-designed study and as such requires a slightly reduced sample size and, obviously, fewer subjects. This was pointed out in the E14 guidance and has been emphasized by the IRT on several occasions (Zhang 2012). When the NCE needs to be dosed for more than approximately a week to reach sufficiently high steady-state plasma levels due to accumulation, or needs to be titrated based on tolerability, a parallel-designed study is preferable. The study duration, i.e., from first-subject-in to last-subject-out, can also be shorter with a parallel-designed study, provided the clinical site can handle sufficiently large cohorts concurrently. A parallel-designed study can be made more effective as

compared to the standard design with four treatment groups (i.e., placebo, moxifloxacin, and a therapeutic and supratherapeutic dose of the NCE), by using a nested crossover comparison within a combined placebo/moxifloxacin group, as suggested by Dr. Joanne Zhang from the IRT (Zhang 2009). In this nested design, half of the subjects in the combined placebo/moxifloxacin group are dosed with the positive control on the first day of treatment, and in the other half of subjects, dosing occurs on the day after the last treatment day. At the time of data analysis, results from both halves are combined for the placebo-component of the ΔΔQTc effect of the NCE, which therefore is not impacted by this design (for details on the analysis, see Darpo 2010). The advantage of this design is that the number of subjects in the placebo and moxifloxacin groups is reduced by 50 %, even though the number of days on which ECGs are analyzed remains essentially the same. This design now seems to be generally accepted and was used in 3 of 5 parallel-designed TQT studies published in 2012 (Graham et al. 2013; Hofmann et al. 2012; Mendzelevski et al. 2012); the remaining 13 were crossover studies (Table 1).

Study Population The concept that underlies the TQT study is that if an NCE causes QT prolongation and proarrhythmias in patients, then the QT effect can be demonstrated in healthy volunteers, if sufficiently high doses (i.e., multiples above the therapeutic dose) of the NCE are given. The challenges associated with TQT studies performed in patients are numerous and are the result of many factors including the number of clinical trial sites, adequate training of investigators, and higher incidence of cardiovascular disease leading to larger variability of ECG interval measurements. Accordingly, the vast majority of TQT studies today are performed in healthy volunteers provided the NCE can be safely dosed to this population. There are however occasional examples of "TQT-like" studies conducted in a relatively limited patient population, such as Parkinson's disease, where group sizes are small ($n = 130$) with stringently controlled experimental conditions (Malik et al. 2008).

Initially, there were no requirements on gender or ethnicity considered in the conduct of the TQT study. Since the adoption of the E14 guidance, gender has been discussed twice in the Q&A documents released in June 2008 and April 2012 (ICH E14 Questions & Answers 2012). It is known that women have a somewhat longer QTc interval than men (Burke et al. 1997; Rautaharju and Zhang 2002; Sarapa et al. 2004), and it has been shown that the degree of drug-induced QTc prolongation may vary in different phases of the menstrual cycle (Rodriguez et al. 2001). It is also well documented that women are at higher risk for the development of proarrhythmias caused by drugs with an effect on cardiac repolarization, i.e., drugs that prolong the QTc interval (Bednar et al. 2002; Ebert et al. 2000; Makkar et al. 1993). It would therefore seem reasonable to assume that women also react with a larger degree of QTc prolongation than men at the same plasma exposure of a drug, and there are a few documented examples thereof (Rodriguez et al. 2001; Benton et al. 2000; Shin et al. 2007; Darpo et al. 2012). For drugs with only a mild effect on the QT interval, it has been difficult to demonstrate a gender difference in sensitivity for the drug-induced QTc prolongation. In a

pooled analysis of data from 2 studies in healthy Japanese and Caucasian volunteers who were dosed with levofloxacin, age and gender did not have an effect on the level of QT prolongation when analyzed with a linear exposure-response (ER) model (Sugiyama et al. 2012). Sex differences in QTc prolongation for moxifloxacin were investigated in a pooled analysis of 20 TQT studies that used moxifloxacin as a positive control (Florian et al. 2011). Women had approximately 40 % higher moxifloxacin peak plasma levels than men and a statistically significant larger peak QTcF effect with a placebo-corrected ΔQTcF of 12.4 ms (confidence interval (CI): 11.1–13.7 ms) compared to 9.1 ms (CI: 8.1–10.1 ms) in men. There was however no difference in the slope estimate for the exposure-response (ER) relationship, which means that the observed difference in QTcF prolongation can be explained by the differences in plasma levels. In line with these considerations, the latest version of the Q&A document states Question 8 in (ICH E14 Questions & Answers 2012):

The thorough QT study is primarily intended to act as a clinical pharmacology study in a healthy population using a conservative primary objective defining the drug's effect on QT. It is unlikely that any of a variety of baseline demographic parameters would introduce a large difference in QT response to a drug in subpopulations defined by factors such as age, co-morbidity, and gender that is not explained by exposure. It is encouraged, but not mandatory, to include both men and women in the thorough QT study. Analyses of concentration response relationship by sex can be helpful for studying the effect of the drug on QT/QTc interval in cases where there is evidence or mechanistic theory for a gender difference. However, the primary analysis of a thorough QT study should be powered and conducted on the pooled population. If the primary analysis is negative and if there is no other evidence suggesting gender differences, subgroup analysis by sex is not expected.

Among the 18 TQT studies published in 2012, the majority ($n = 14$) were conducted in both male and female healthy volunteers, whereas three studies were conducted only in males (Carlson et al. 2011; Hofmann et al. 2012; Vourvahis et al. 2012) and only one in females (Graham et al. 2013).

Dose A high, supratherapeutic dose of the NCE, which results in plasma levels in excess of what would be observed in patients with impaired clearance of the drug, should be used in the TQT study. The E14 states: "If not precluded by considerations of safety or tolerability due to adverse effects, the drug should be tested at substantial multiples of the anticipated maximum therapeutic exposure." The overriding principle is that plasma levels achieved with the supratherapeutic dose should exceed the "worst-case scenario" in patients, taking into account both intrinsic (e.g., renal impairment) and extrinsic factors (e.g., drug interactions). As an example, for NCEs that are CYP 3A4 or 2D6 substrates, the achieved exposure must exceed that observed with concomitant administration with potent 3A4 inhibitors, and in 2D6 poor metabolizers (Abbas et al. 2012; Boyce et al. 2012; Chaikin et al. 2005; Dalen et al. 2010; Malhotra et al. 2007; Robert et al. 2007; Tyl et al. 2012; Zhu et al. 2010). For a renally cleared drug, plasma levels that are only

observed in patients with severe renal impairment (i.e., where the glomerular filtration below 30 mL/min) may not have to be covered in the TQT study if the drug is contraindicated in this population. The selection of the supratherapeutic dose is the most common reason for discussions between regulators and sponsors, and failure to study a sufficiently high dose has occasionally led to a requirement for a repeat TQT study; this is therefore an important part of the dialogue between sponsors and regulators before the TQT study is initiated. It should also be borne in mind that formulation changes that result in substantially higher plasma levels of a drug may require conduct of an additional TQT study. A recent example is exenatide, a GLP-1 agonist intended for the treatment of type 2 diabetes mellitus. Two separate TQT studies had to be conducted for two different exenatide formulations (Byetta® and Bydureon®), both of which were negative (Darpo et al. 2013; Linnebjerg et al. 2011). The first TQT study was conducted with the daily subcutaneous formulation (Byetta®) at the approved therapeutic dose (10 μg twice daily). On chronic administration with a therapeutic dose of the later developed once-weekly formulation (Bydureon®, 2 mg once weekly), exenatide plasma levels were at least twofold higher than those with the daily formulation and even higher in patients with impaired renal function. Accordingly, the FDA required to conduct a second TQT study, in which substantially higher plasma levels were achieved through an IV infusion of the drug (Darpo et al. 2013).

In most TQT studies to date, both a therapeutic and a supratherapeutic dose of the NCE have been studied. There are, however, a few studies in which only a supratherapeutic dose of the NCE was included (Iwamoto et al. 2008; Krishnaswami et al. 2011; Vourvahis et al. 2012; Zhang et al. 2007). This approach is obviously sufficient if results are clearly negative. Most sponsors tend however to also include the therapeutic dose, in case the high dose is "slightly positive." It can be argued that the effect of the therapeutic dose can be projected by ER analysis, and it would therefore be sufficient to include only a supratherapeutic dose, but this has so far not gained widespread acceptance. There is no requirement per se on dosing to steady state of the NCE, and single doses can be used in the TQT study, provided that a sufficiently high exposure of both parent and major metabolites can be achieved. If there are slowly appearing metabolites, which require many days of dosing to achieve sufficiently high exposure, multiple dosing is warranted.

2.4 Analysis of the TQT Study Results

The objective of the TQT study is to demonstrate that an NCE does not prolong the QTc interval by more than 5 ms, as evidenced by the upper bound (UB) of the 2-sided 90 % CI of the placebo-adjusted change-from-baseline QTc (ΔΔQTc) being below 10 ms.

In crossover-designed TQT studies, the baseline assessment can be made either through time-matched recordings on a full baseline day before each treatment period (time-matched baseline) or through a limited number of recordings (e.g.,

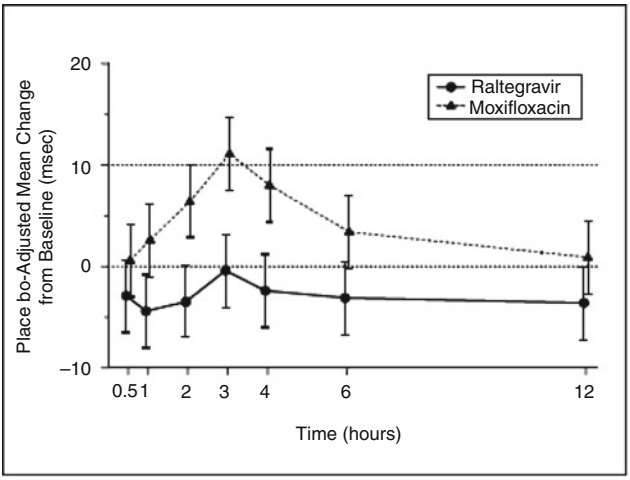
3 timepoints) before each treatment period (predose baseline). Based on the experience from several sponsors (Bloomfield et al. 2008), core ECG laboratories, and the IRT (Zhang and Machado 2008), it is fully sufficient to use a predose baseline since adjustments for subject- and study-specific diurnal variation are accounted for by the inclusion of a separate placebo treatment period (see question 6 in E14 Q&A document (ICH E14 Questions & Answers 2012). For parallel-designed TQT studies, a full baseline day is still the most widely used approach and change-from-baseline QTc (ΔQTc) is then calculated by comparing the QTc value for each timepoint at baseline and post-dosing ("time-matched"). There are some data suggesting that results would be the same and the variability lower if baseline was generated through averaging of all values from a full baseline day (Sun et al. 2012), then more research and analyses across TQT studies can be expected (Lu 2013).

The criterion for a negative TQT study specifically is that the UB of the 90 % CI of the ΔΔQTc estimate is below 10 ms, which applies to *all* post-dosing timepoints. Since the analysis uses a non-inferiority approach, there is no need for adjustment for multiplicity in this part of the analysis (Stockbridge et al. 2012; Tsong et al. 2008, 2010; Zhang and Machado 2008). Figure 1 shows two examples of clearly negative TQT studies (Tyl et al. 2012; Iwamoto et al. 2008).

The role of the positive control is to demonstrate the study's ability to detect a small effect on the QT interval, establishing assay sensitivity. In an overwhelming majority of TQT studies, moxifloxacin, a fluoroquinolone antibiotic with a mild QT-prolonging effect (Culley et al. 2001), has been used. In the studies published in 2012, all used moxifloxacin as the positive control; 16 of 18 studies used a single oral dose of 400 mg, 1 used multiple dosing for a 3-day duration (Tyl et al. 2012), and one used an IV infusion (de Kam et al. 2012). In most studies, moxifloxacin has caused a larger peak effect than 5 ms, more in the range of 8–15 ms (Garnett et al. 2008). The differences in peak response across studies is however quite striking and ranges between 7.5 ± 2.2 ms (Chen et al. 2012) and 19.0 ± 3.9 ms (Graham et al. 2013) in the studies published in 2012 that used a single oral dose of 400 mg moxifloxacin. The criteria for demonstrating assay sensitivity with moxifloxacin have been addressed in the first round of the E14 Q&A document [Question 1 in ICH E14 Questions & Answers (2012)] and subsequently clarified through interactions between IRT and sponsors. The criteria include:

(a) The lower bound (LB) of the 90 % CI of ΔΔQTc should be above 5 ms for at least one prespecified post-dose timepoint.
(b) The peak ΔΔQTc should be within the range of responses seen in similar studies, i.e., about 8–16 ms, even though the exact cutoff points are less clear.
(c) The mean peak ΔΔQTc should be observed between 1 and 4 h post-dose and thereafter declines. Note that lately, the IRT has also asked for a timepoint earlier than the peak effect.

Panel A



Panel B

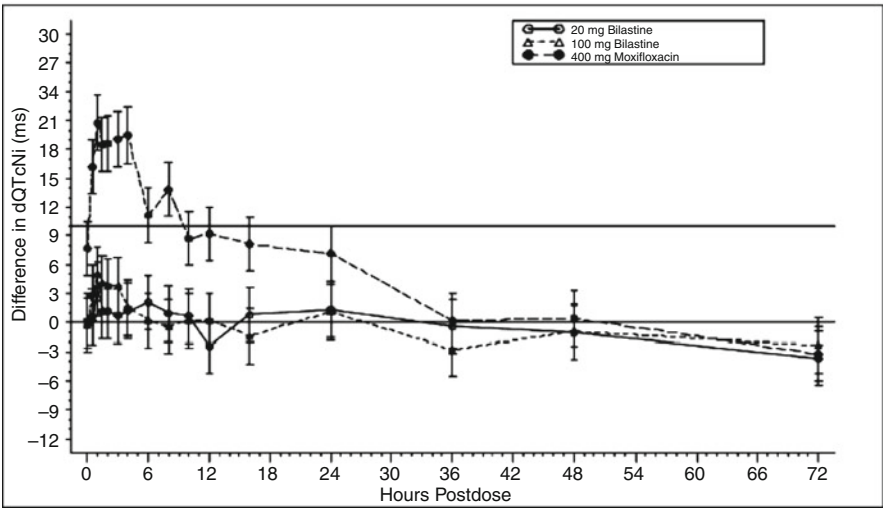


Fig. 1 Panel (**a**). An example of a negative TQT study where ΔΔQTcF (mean ± 90 % CI) is determined after dosing with a single-dose of 1,600 mg raltegravir (Isentress) and 400 mg moxifloxacin. For raltegravir, the UB of the CI is below 10 ms at all post-dosing timepoints, thus demonstrating a negative TQT study. After dosing with moxifloxacin, the LB of the CI is above 5 ms at the observed peak effect at 3 h, thereby demonstrating assay sensitivity for the study. *Reproduced from Iwamoto et al. (2008) with permission from J Clin Pharmacology, American College of Clinical Pharmacology and John Wiley & Sons, Inc.* Panel (**b**). An example of a negative TQT study where ΔΔQTcNi (individualized QTc; mean ± 90 % CI) is determined after 4 days of dosing with bilastine (Bilaxten) 100 mg and 200 mg once daily and 400 mg moxifloxacin for 3 days. Bilastine produces a clearly negative effect, whereas the moxifloxacin response is relatively high (19.9 ± 2.9 ms), and the LB of the CI is above 5 ms at multiple post-dosing timepoints. *Reproduced from Tyl et al. (2012) with permission from J Clin Pharmacology, American College of Clinical Pharmacology and John Wiley & Sons, Inc.*

Since this analysis is about detecting an effect, an adjustment for multiplicity has to be made, and it is therefore advisable to limit the number of timepoints to those around the peak plasma concentration (Tmax) of moxifloxacin, usually 1–3 h post-dose. A number of methods have been used for the multiplicity adjustment and accepted by the IRT, of which the Hochberg procedure seems to be the least conservative (Hochberg and Benjamini 1990). Even though the primary model-based analysis of ΔΔQTcF on moxifloxacin can be restricted to a few timepoints to avoid diluting the statistical power, there is an expectation that more timepoints are analyzed descriptively to ensure that the moxifloxacin response diminishes over time. The studies shown in Fig. 1 are good examples of studies in which the criteria for demonstration of assay sensitivity were clearly met. In Fig. 2, panels (a) and (b) describe two examples of relatively recently published studies in which the criteria for moxifloxacin assay sensitivity that were not met are shown (March and Cardi 2009; Morganroth et al. 2010). The peak effect of ΔΔQTc after moxifloxacin (a single oral dose of 400 mg) was comparable with other studies, but the precision of the ΔΔQTc estimate is poor, which resulted in very wide limits of the 90 % CI with the LB below 5 ms at all timepoints. Based on the IRT's experience, the assay sensitivity test with moxifloxacin has failed in about 5 % of cases (Garnett 2012), but for the majority of the studies, the confidence in the data is very high.

Initially, the IRT mandated blinding of the positive control, but this requirement was later dropped based on an internal IRT review of TQT studies presented in 2008 (Garnett et al. 2008) and subsequent discussions in the E14 Implementation Working group [Question 7 in ICH E14 Questions & Answers (2012)]. Exceptions exist: when the nested crossover moxifloxacin/placebo comparison is used in parallel-designed TQT studies, moxifloxacin has to be blinded to protect the blinding of placebo.

2.4.1 Sample Size

The difference in sample size is quite striking among studies published in 2012 (see details in Table 1), ranging from 60 (Graham et al. 2013)[1] to 352 subjects in parallel-designed studies (Malik et al. 2012) and from 32 subjects for 2 treatment periods [(Taubel et al. 2013); methodology study] to 96 subjects for 4 periods (Morganroth et al. 2013) for crossover studies.

When calculating the sample size for a TQT study, the power of the study to exclude a QTc effect above 10 ms, the underlying assumed effect of the NCE (often 3–5 ms), and the variability of QTc are important factors that need to be factored into the equation. Using the same assumptions (90 % power and 3 ms assumed effect), the required sample size varies from approximately 50 subjects with a SD of ΔQTc of 8 ms to around 100 subjects with a SD of 12 ms, which underlines the importance of tightly controlled experimental conditions and ECG methodologies (Darpo et al. 2011). The variability of the moxifloxacin peak ΔQTc can be estimated using the width of the 90 % CI, based on the assumptions that it was

[1] This study was powered to exclude a 20 ms QTc effect.

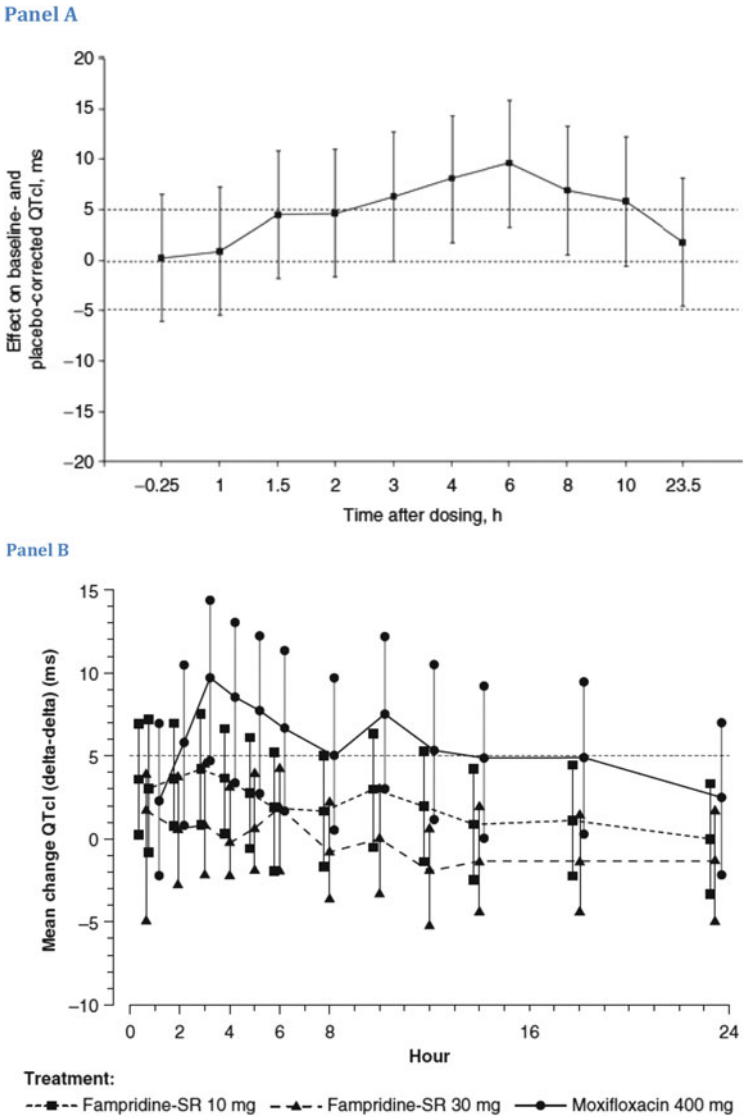


Fig. 2 Panel (**a**). The moxifloxacin response (single 400 mg oral dose, ΔΔQTcI; mean ± 90 % CI; $n = 47$) in a TQT study with an alfa-receptor blocker, silodosin (Rapaflo). The peak magnitude of the moxifloxacin response is similar as compared to other TQT studies, but the time-to-maximum ΔΔQTcI occurs somewhat later. Due to poor precision of the ΔΔQTc estimate with unusually wide CIs, none of the LB exceeds 5 ms. The assays sensitivity test, as defined by ICH E14, has thereby failed. *Reproduced from Morganroth et al. (2010) with permission from Clinical Pharm & Therapeutics, American Society for Clinical Pharmacology and Therapeutics and Nature Publishing Group*. Panel (**b**). The moxifloxacin response (single 400 mg oral dose ΔΔQTcI, mean ± 90 % CI; $n = 51$) in this example of a TQT study conducted for fampridine (Ampyra) peaks at 9.4 ms with very wide CIs, for which the LB does not exceed 5 ms at any timepoint

calculated from a 2-sample *t*-test with equal variance of the moxifloxacin and placebo data. These assumptions are not always entirely true, but the approach gives a fair estimate of the QTc variability using a consistent methodology across studies. Since the estimated variability is calculated from the moxifloxacin ΔΔQTc, it is independent of the NCE and can be used for comparisons between studies irrespective of the size. It should be emphasized that QTc variability results from many different factors. Some of the more important non-NCE-related factors include the experimental conditions at the clinical trial site, ECG recording/extraction methods, and ECG interval measurement techniques. The largely observed difference in QTc variability across the studies published in 2012 is surprising and cannot easily be attributed to one single factor: the standard deviation of ΔQTc ranged from 5.5 ms to 14.0 ms (Table 1). Expectedly, many of the studies with the lowest variability are single-dose crossover studies (7 of 8 with standard deviation below 8 ms), and the ones with the highest variability are all parallel group designed. With the exception of the TQT study with dapagliflozin, which utilized a technique proprietary to the sponsor, most studies used manual or semiautomated measurement techniques. Given the differences in variability with similar ECG methodologies, these data also suggest an important role for the clinical conduct and the level of experimental control at the clinical trial site, in addition to the study design (crossover or parallel).

2.5 Correction of the QT Interval for Heart Rate Changes

There are numerous ways of correcting changes in the heart rate to obtain the corrected QT interval (QTc), and there is no clear consensus on the preferred algorithm (Malik 2001). The limitations of Bazett's QT correction (QTcB) are widely acknowledged, since this algorithm overcorrects the QT interval with increasing heart rate, thereby producing a false-positive QTc prolongation. Consequently, it is no longer a requirement to report this interval for TQT studies [Question 11 in ICH E14 Questions & Answers (2012)]. For drugs without clear effect on the heart rate, it has been the experience of the IRT, and of many sponsors, that QTcF works well (Zhang 2012). For these drugs, there does not seem to be much of an advantage to use a subject-specific QTcI derived from supinely resting drug-free data only, which is the standard way of generating QTcI and often results in a correction factor near 0.33 (i.e., very similar to Fridericia, QTcF). Furthermore, the derivation of QTcI is sometimes used to justify an additional full baseline day in crossover-designed studies, which is difficult to defend when there is no added

Fig. 2 (continued) post-dose. Therefore, this study does not establish assay sensitivity. *Reproduced from March and Cardi, Assessment of the cardiac safety of fampridine-SR sustained-release tablets in a thorough QT/QTc evaluation at therapeutic and supratherapeutic doses in healthy individuals. Expert Opin Investig Drugs 18: 1807–1815, copyright 2009, Informa Healthcare. Reproduced with permission from Informa Healthcare*

value of using this correction method. Drugs with an inherent, substantial (e.g., more than 8 bpm peak effect) heart rate effect pose much more of a challenge, and there is no firm guidance. The Cardiac Safety Research Consortium (http://www.cardiac-safety.org/) recently issued a white paper on this topic, which discussed five alternative ways for QT assessment of drugs with a heart rate effect. Methods include "Holter-bin" (Badilini and Maison-Blanche 2005; Malik 2005; Extramiana et al. 2005), QTcI derived from a broad range of QT/RR pairs through continuous Holter recordings at baseline, beat-to-beat analysis (Fossa et al. 2007, 2011), PK/PD modeling with heart rate as a covariate (Li 2008), and assessment of the QT interval at a fixed heart rate through, e.g., submaximal exercise (Demolis et al. 1996, 2000, 2003). The advantages and disadvantages of the methods are discussed, but there is a lack of comparative data across methods. A shared feature of all methods is that baseline QT/RR pairs must be collected from a sufficiently broad range of heart rates, which covers the ranges seen post-dosing with the NCE [see also Question 11 in ICH E14 Questions & Answers (2012)]. When more than one method for heart rate correction is used, it is also advisable to prospectively define the methodology by which the primary endpoint will be chosen.

It was recently suggested by Dr. Joanne Zhang, lead statistician on the IRT, that the variability around the correction factor for the slope estimate should also be taken into account when analyzing ΔΔQTc (Zhang 2012). Obviously, there would be a penalty in terms of wider CIs if the slope is derived from a limited data set according to standard practice and no penalty at all if the choice was to use QTcF, which uses a fixed correction factor of 0.33 ($QTc = QT * RR^{-0.33}$). Since QTcF is regarded as not fully reliable for drugs with a heart rate effect (Garnett et al. 2012), the bottom line is however to use much richer data sets with a broad range of heart rates for the calculation of an "optimized" QTcI.

2.6 ECG Recordings and QT Interval Measurements

The experimental conditions of the TQT study must be stringently controlled and study procedures identical between treatment arms and groups. Several components of the study conduct, which are routinely implemented in TQT studies, have an impact on the variability of the data (Darpo 2010), in addition to the variability of the interval measurements as such (Darpo et al. 2011). Experimental conditions must be strictly standardized with regard to meal intake and composition and physical activity. To minimize heart rate fluctuations, subjects should be supinely resting for at least 10 min in an undisturbed environment at the prespecified timepoints for ECG recordings. The use of continuous 12-lead ECG recordings (Holter's) is preferred as it allows extraction of replicate ECGs around prespecified timepoints with optimal signal-to-noise ratio. Blood draws should always be done immediately after the ECG recording to avoid confounding stress and should be performed in all treatment periods, even though the samples from the placebo and positive control may not be analyzed. A rationale for storing samples from the positive control arm can be that ER analysis sometimes can help explain ambiguous

results. For example, there have been cases with lower-than-expected moxifloxacin QTc effects due to low plasma levels when encapsulation has been used for blinding. Awareness of treatment may introduce a confounding effect on the QT interval, and double-blind administration of placebo/NCE is therefore an absolute requirement that remains in effect. The pharmacokinetic properties of the NCE must be well characterized before the TQT study is initiated (or alternatively, doses up to maximum tolerated (MTD) can be used), and ECG acquisition and blood samples should encompass the anticipated Tmax of the drug and major metabolites (and of moxifloxacin) and at least one timepoint before and several timepoints after Tmax. Often, this can be achieved with 6 to 8 timepoints, and the balance between the number of timepoints and the likelihood of false-positive results needs to be taken into account; this likelihood increases with the number of timepoints. Even so, it is important to also include some late timepoints, e.g., 24 h after dosing, to capture delayed effects including hERG trafficking (Dennis et al. 2012; Ficker et al. 2004; Kuryshev et al. 2005; Ponte et al. 2010). To avoid alterations of autonomic tone, which also has an impact the QTc interval, it is important to avoid timepoints at which subjects may be sleeping, i.e., nighttime.

Averaging replicates of ECG recordings from each timepoint is now standard as it reduces the variability of the QT measurement and therefore increases the power to exclude small QTc effects. With semiautomated methods of ECG measurement, where the computer-based measurements are "overread," i.e., adjusted manually, there are several data sets that demonstrate that the reduction of variability is pronounced when averaging up to triplicates and then levels off [an example is given in Patterson et al. (2005)], and most ECG laboratories today use triplicate ECG recordings at each timepoint (14 studies in Table 1 used 3 replicates (triplicates), 2 studies used 4 replicates, 1 used 5 replicates, and 1 used 10 replicates, respectively). Even though there appears to be a limitation to the extent that variability can be reduced with replicates of intervals measured with a semiautomated technique, this does not seem to hold true for other techniques, which do not blend computer-based and manually performed interval measurements. The utility of fully or partially automated measurement techniques has been compared with manual techniques in a number of studies, and these techniques have been shown to produce similar results when tested on drugs with a QT-prolonging effect (Azie et al. 2004; Darpo et al. 2006; Sarapa et al. 2004, 2009; Fosser et al. 2009). It has also been shown that different techniques generate different absolute QT intervals (Kligfield et al. 2006, 2007) and that some automated techniques consistently demonstrate the same QTc effect measured as change from baseline as manual techniques. The absolute QT interval is of interest in clinical assessment of, e.g., QT prolongation but less important when change from one timepoint to another is the main objective, as in TQT studies.

The variability of the QT measurement (SD of ΔQTc) can be reduced to around 5–6 ms by the use of more computer-intensive techniques with optimization of the ECG extraction and measurement of substantially more beats per timepoint (Dalen et al. 2010; Darpo et al. 2011); see Fig. 3 for an example. There may be concerns regarding the ability of fully automated methods to identify individual patients with

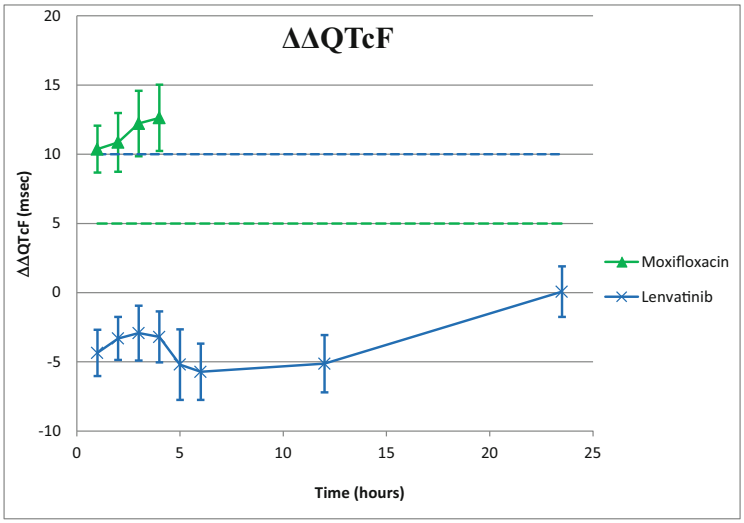


Fig. 3 Placebo-corrected, change-from-baseline QTcF (ΔΔQTcF, mean ± 90 % CI; $n = 52$) after a single 32 mg oral dose of the tyrosine kinase inhibitor, lenvatinib, currently in development for the treatment of various types of cancer and 400 mg moxifloxacin. The drug is clearly negative. ECG intervals were measured with a high-precision QT (HPQT) technique, and the resulting CIs are very tight. The LB of the CI for the moxifloxacin response is above 5 ms at all 4 analyzed timepoints. *Source: Shumaker et al. Poster presented at the AARC-NCI-EORTC 2011, San Francisco, November, 2011*

drug-induced changes in T-wave morphology, and the E14 Q&A document (Question 4B) therefore recommends some degree of manual oversight in terms of assessment of T-wave morphology. This is also advisable for overall signal and measurement quality control as fully automated analysis may not be completely reliable and therefore lead to higher variability of the data (Tyl et al. 2009). In this context, it is however interesting to note that automated algorithms in fact are able to *improve* the detection of subtle T-wave changes, induced by, e.g., moxifloxacin (Couderc et al. 2008).

3 Drug-Induced Effects on Other ECG Parameters

The TQT study is formally powered to exclude a small (around 5 ms) QTc prolongation. The variability of other ECG parameters (such as the PR and QRS intervals) are in fact lower than for the QTc interval, and it has become increasingly apparent that these studies also can and should be used for assessment of other ECG effects. These data, unfortunately, are not always given in publications on TQT studies, which makes it difficult to independently evaluate the QTc effect, or lack thereof. As an example, there is no mention of effects on heart rate, PR, or QRS interval in the publication on the TQT study with liraglutide (Chatterjee et al. 2009),

and no such effects are mentioned in the US prescribing information. In contrast, in the Health Canada Summary Basis of Decision, it is described that liraglutide at therapeutic doses causes a sustained increase in heart rate and prolongation of the PR interval. The incidence of subjects with heart rate values greater than 90 bpm was 20 % for 1.2 mg and 24 % for 1.8 mg liraglutide, as compared to 8 % and 4 % on the respective day for placebo. A peak placebo- and baseline-adjusted PR prolongation of 9–10 ms was seen. A PR prolongation of 7 % ms (maximum increase) was also observed in the TQT with the subcutaneous (SC) formulation of exenatide (Linnebjerg et al. 2011). The clinical relevance of these small increases in the PR interval can be debated but warrants further evaluation in terms of the incidence of high-degree AV block in late phase studies in the targeted patient population.

It seems prudent to analyze all ECG parameters in TQT studies using the same approach as for QTc, i.e., the placebo-corrected, change-from-baseline across timepoints after dosing, which also recently have been highlighted by IRT in comments on TQT study protocols.

4 ECG Assessment with Oncology Drugs

Based upon the likelihood for genotoxicity and poor tolerability, clinical ECG assessment with oncology drugs is often performed in cancer patients rather than in healthy volunteers. In this often immune-compromised and severely ill patient population, it is difficult to justify the use of placebo and an antibiotic (the positive control, moxifloxacin), and many ECG studies with oncology agents in cancer patients are therefore uncontrolled (Lesimple et al. 2013) and frequently powered to exclude a somewhat larger effect (around 20 ms) than TQT studies in healthy subjects (Bello et al. 2007; Graham et al. 2013; Rock et al. 2009; Sarapa and Britto 2008). Apart from these limitations, other elements from the TQT study design, such as strictly controlled experimental conditions, serial ECGs at baseline, and post-dosing, are implemented to the extent feasible into ECG studies in oncology patients (Rock et al. 2009).

A large number of tyrosine kinase inhibitors with indications in oncology have recently been approved or are in clinical development, and this class of drugs can illustrate the different approaches taken in terms of definitive ECG assessment (Shah et al. 2013). QT studies with these agents have been performed both in cancer patients and in healthy volunteers. Tasocitinib, a JAK 3 inhibitor in development as an oral treatment for rheumatoid arthritis (RA) and psoriasis, was evaluated in a TQT study in 60 healthy volunteers with a single supratherapeutic dose of 100 mg, placebo, and moxifloxacin. The 100 mg dose, which was estimated to generate 3.5-fold higher plasma levels than in patients on a therapeutic dose, was clearly negative, and a QTcF effect above 10 ms could be excluded at all post-dosing timepoints; the slope of the exposure-response relation was essentially flat, and the effect at the observed peak plasma level could be projected to around 0 ms (CI: −1.2 to 0.9) (Krishnaswami et al. 2011). Bosutinib, a dual Src/Abl kinase inhibitor

that targets the tyrosine kinase brc-abl, the key enzyme in the development of chronic myeloid leukemia (CML), was also tested in 60 healthy volunteers in a 2-part, single-dose, crossover, placebo-, and moxifloxacin-controlled study evaluating therapeutic and supratherapeutic exposures of the drug (Abbas et al. 2012). In a separate part of the study, supratherapeutic bosutinib plasma levels were obtained with concomitant dosing of 500 mg bosutinib (the therapeutic dose) and a strong CYP 3A4 inhibitor, ketoconazole. Since ketoconazole has a QTc effect in itself (Chaikin et al. 2005; Darpo et al. 2006; Tyl et al. 2012), the QTc effect of bosutinib in this part of the study was adjusted for ketoconazole. The UB of the 90 % CI were below 10 ms at all timepoints post-dosing for both therapeutic and supratherapeutic bosutinib plasma levels with the largest observed effect on ΔΔQTc of 4.5 ms (UB of 90 % CI: 6.8 ms) at 8 h post-dose. Lenvatinib, an orally administered tyrosine kinase inhibitor targeting VEGFR1–3, FGFR1–4, PDGFRβ, RET, and KIT, which is currently being studied in patients with solid tumors, has also been tested in healthy volunteers in a placebo-controlled study with moxifloxacin as positive control and a therapeutic dose with a negative result (Shumaker et al. 2011). Other tyrosine kinase inhibitors have only been tested in cancer patients. Sunitinib (Sutent), an oral, small-molecule, multi-targeted receptor tyrosine kinase (RTK) inhibitor approved for the treatment of renal cell carcinoma (RCC) and imatinib-resistant gastrointestinal stromal tumor (GIST), was evaluated in 24 patients with solid tumors (Bello et al. 2007), in whom QTc prolongation was demonstrated at supratherapeutic plasma levels. The largest mean ΔQTcF was 5.6 ms (UB of 90 % CI: 9.3 ms) at steady-state/therapeutic plasma levels and 15.4 ms (UB of 90 % CI: 22.4 ms) at supratherapeutic concentrations after dosing during 9 days and the ΔQTcF effect correlated with sunitinib exposure. Sorafenib (Nexavar), a bi-aryl urea inhibitor of several tyrosine protein kinases (i.e., VEGFR and PDGFR) and the C-Raf kinase approved for the treatment of advanced renal and hepatocellular carcinoma, was tested in 31 patients with advanced cancer in an uncontrolled, open-label study with a therapeutic dose of 400 mg BID (Tolcher et al. 2011). The primary endpoint in this trial was the QTc effect at each subject's Tmax at steady state (Day 1 of Cycle 2), and a mean QTc effect of 9.0 ms (SD 18 ms) was observed using this approach, whereas the time-matched effect ranged between 4.2 and 5.8 ms. Vandetanib (Caprelsa), a kinase 594 AU4 inhibitor with activity against vascular endothelial growth factor receptor 595 (VEGFR), epidermal growth factor receptor (EGFR), and the RET-tyrosine kinase, is approved for use in (metastatic) medullary thyroid cancers. The drug seems to be the most potent QT-prolonging drug among the tyrosine kinase inhibitors and was assessed in 231 patients with medullary thyroid cancer who received vandetanib 300 mg once daily in the phase 3 clinical trial (Caprelsa US NDA 022405 2011). Vandetanib was associated with a plasma concentration-dependent QTc prolongation, and based on exposure-response analysis, the mean ΔQTcF was projected to 35 ms (UB of 90 % CI: 36 ms) for the 300 mg dose (Fig. 4). Thirty-six percent of patients experienced greater than 60 ms increase in ΔQTcF, and 4.3 % of patients had QTcF greater than 500 ms, and cases of torsades de pointes and sudden death have been reported. As a result of these findings, this drug carries a black box

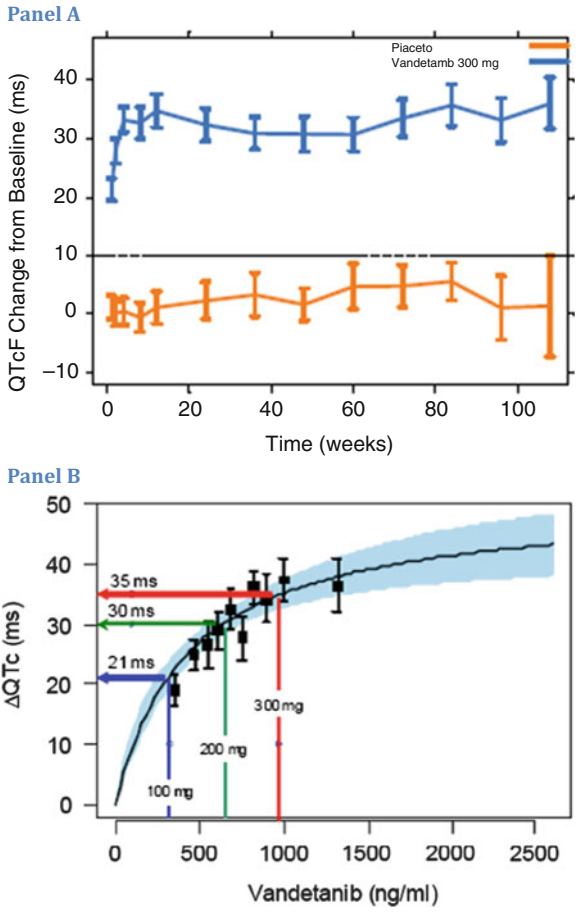


Fig. 4 QTcF prolongation in patients with medullary thyroid cancer dosed with vandetanib (Caprelsa) 300 mg daily or placebo ($n = 231$) in the pivotal trial. Panel (**a**) ΔQTcF in patients on placebo (*yellow*) and on vandetanib (*blue*). Panel (**b**) Exposure-response analysis using a mechanistic Emax model from the same patients described in Panel (**a**). The model-based estimates (*black line*) and 2-sided 90 % CI (*blue shaded area*) of ΔQTcF are shown and predicted ΔQTcF to 35 ms after daily dosing with 300 mg vandetanib and to 30 ms and 21 ms with dosing with 200 and 100 mg daily. *Source: Caprelsa US NDA 022405: Figures 3 and 4 in Clinical Pharmacology Biopharmaceutics Review, May 2011. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022405Orig1s000TOC.cfm*

warning for QTc prolongation, torsades de pointes, and sudden death and should not be administered with other drugs that can prolong the QTc interval.

5 Can "Early QT Assessment" Replace the TQT Study?

Exposure-response (ER) analysis has become an important tool to interpret QT data from TQT studies and has been used to predict QT effects in patients for the targeted indication, including patients with impaired clearance of the drug (Garnett et al. 2008; Piotrovsky 2005). ER analysis has also been applied to QT data derived from early SAD/MAD studies. Since the doses in SAD studies are often escalated to MTD, high plasma levels often are obtained, which allows for the evaluation of potential ECG effects over a wide range of plasma concentrations. With increasing confidence in data derived from these types of studies, the relevant question as to whether "early QT assessment" can replace the TQT study has been raised (Darpo

and Garnett 2012; Rohatagi et al. 2009; Shah and Morganroth 2012). The thorough QT (TQT) study was initially perceived as a challenge for industry (Shah 2005), but with increasing experience and refined methodologies, studies in healthy volunteers can today be conducted more effectively and with high confidence in the generated data. The TQT study is entirely designated to evaluate the ECG effects of an NCE, and the resource efficiency of this approach can be debated (Bouvy et al. 2012). A more efficient approach could therefore be to collect the same ECG data in studies that are standard components of the clinical development program, provided the same level of confidence in the generated data can be achieved. SAD/MAD studies have as their main objectives tolerability/safety and pharmacokinetics of the NCE, and when doses are pushed up to MTD levels, plasma levels above those seen during later stages of development are often reached.

5.1 The Role of Exposure-Response Relationship

Modeling of the exposure-response (ER) relationship is certainly not a new tool and has been applied to QT data before the implementation of the TQT study, especially for antiarrhythmic drugs (Allen et al. 2000; Holford et al. 1981; Phillips et al. 2001; Piergies et al. 1987; Shi et al. 2001; Whiting et al. 1980). With the application of ER to data derived from TQT studies, the role of the methodology for non-antiarrhythmic drugs has expanded to include projection of QTc prolongation with doses and formulations not directly evaluated in the TQT study and projections of QTc prolongation in specific patient populations with increased exposure to a drug and, occasionally, to help to understand ambiguous results. In the TQT study, ER analysis is performed by applying a mixed-effect model that describes the relationship of data pooled across individuals in the placebo and active groups. To account for diurnal variation, baseline-corrected QTc or placebo- and baseline-corrected QTc data are used (Florian et al. 2011; Garnett et al. 2008). For most noncardiac drugs, the relationship can be described by linear models using either observed concentrations or logarithmic-transformed concentrations. The same ER models can be applied to data obtained from SAD/MAD studies, from which the time-matched concentration and baseline-corrected QTc data can be pooled across placebo and active cohorts. Figures 5 and 6 show two examples, one negative and one positive, from ER analysis applied to data derived from SAD/MAD studies. The first example illustrates that ER modeling applied to data derived from a typical SAD study with a carefully designed ECG schedule can, despite the small sample size in each dose group, achieve sufficient power to exclude a QTc effect exceeding the regulatory concern, i.e., 10 ms. The second example derives from a MAD study, which clearly demonstrated a QT-prolonging effect of the NCE; for every 100 ng/mL increase in plasma concentration, the QTc interval can be projected to increase by 1.9 (90 % CI: $\pm$ 0.45) ms and the UB of the CI clearly exceeded the 10 ms threshold. In the latter example, given the precision of the predicted QTc effect with a statistically positive slope, it seems highly likely that a subsequent TQT study would derive the same conclusion and the study can therefore be avoided, since the

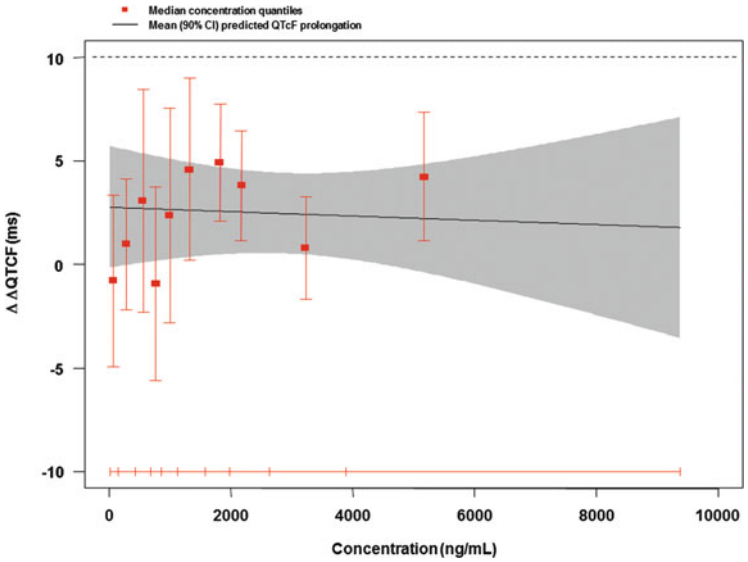


Fig. 5 Data from a standard design single-ascending dose (SAD) clinical study with 6 subjects on active treatment and two subjects on placebo in each dosing group. A total of 7 doses were studied with a 120-fold range between the lowest and the highest tested dose, resulting in 42 subjects on active treatment and 14 on placebo. Continuous 12-lead ECGs were recorded; ECGs were extracted and PK samples collected at prespecified timepoints at baseline and post-dosing. QT intervals were measured using a high-precision QT measurement (HPQT) technique on all beats from 10 replicates at each timepoint (Darpo et al. 2011). The figure shows the prediction of ΔΔQTcF across the plasma concentration range observed in the study with model-based estimates (*black line*) and 2-sided 90 % confidence interval (CI; *gray-shaded area*) of the QTc effect. The slope of the ER relationship was slightly negative and not statistically significant (−0.00026 ms per ng/mL; 90 % CI: −0.00063 to 0.00010). The upper bound of the CI was clearly below 10 ms at all concentrations observed in the study, meaning that the drug did not cause QT prolongation exceeding the threshold of concern. The average variability of the QTc estimate over all timepoints, measured as the between-subject SD of ΔQTcF, was very low, 6 ms. *Reproduced from Darpo and Garnett (2012) with permission from Br J Clin Pharmacology, The British Pharmacological Society and Blackwell Publishing*

consequence for further development of the compound would be the same if the benefit/risk assessment remained favorable: the QTc effect must be further characterized in the targeted patient population. This example therefore illustrates how a QTc effect can be detected using ER modeling of data derived from a MAD study and thereby potentially waive the need for a TQT study (Stockbridge et al. 2012). It should be acknowledged that the QTc effect in the example was large and detection or exclusion of smaller effect levels will pose more of a challenge and will require high standards for the clinical conduct and QT interval measurements.

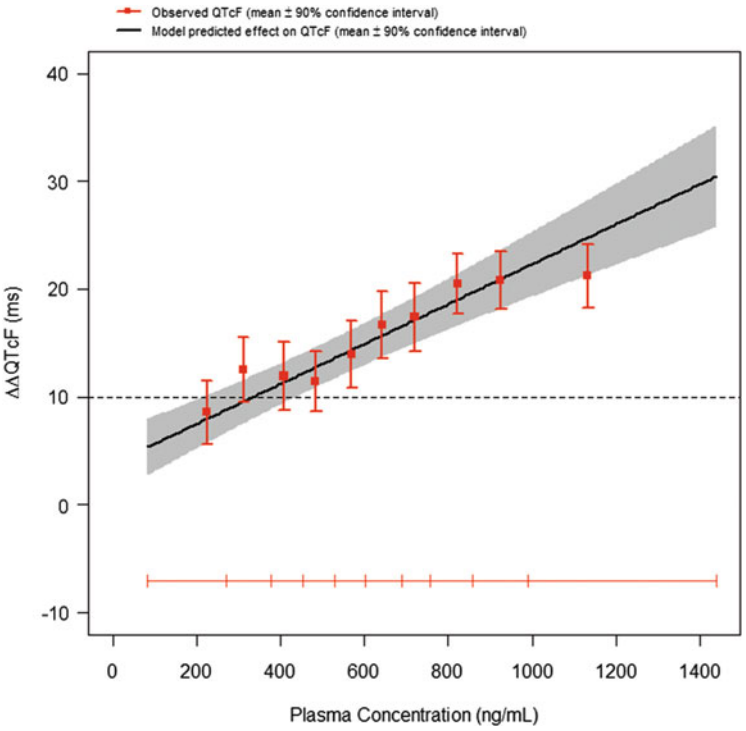


Fig. 6 Data from a MAD study in which subjects received either placebo or 2 dose levels of the NCE in a fixed sequence, resulting in 8 subjects on the lowest dose and 16 subjects on the 2 higher doses and on placebo. ECGs were extracted in 10 replicates from continuous 12-lead recordings at baseline (predose) on Day 1 and at 7 timepoints on Day 7, paired with PK samples. ECG intervals were measured using the same high-precision QT measurement (HPQT) methodology as in this figure, and observed between-subject standard deviation of ΔQTcF was 7 ms on active and 8 ms on placebo. A concentration-dependent effect of the drug on ΔΔQTcF was demonstrated with a statistically significant slope of 0.0185 ms per ng/mL (CI: 0.014 to 0.023, $p < 0.0001$). *Reproduced from Darpo and Garnett (2012) with permission from Br J Clin Pharmacology, The British Pharmacological Society and Blackwell Publishing*

5.2 The Power of Exposure-Response Analysis Compared to the E14 Time-Matched Analyses

The ICH E14 guidance requests that data are analyzed "by timepoint," which means that a QTc effect (measured as the placebo-adjusted change-from-baseline; ΔΔQTc) exceeding 10 ms must be excluded at each post-dosing timepoint irrespective of the observed plasma levels of the drug. Formal power calculation using an assumption of SD of ΔQTc of 10–12 ms, which is the QTc variability typically observed with a semiautomated QT measurement techniques (see Table 1), shows that 60–90 subjects are required to achieve acceptable power (90 %) to exclude a 10 ms effect (Tsong et al. 2010). For standard SAD/MAD studies with

sample sizes of around 6–8 subjects per dose group, the power of a time-matched analysis is therefore insufficient. In contrast, when using ER analysis, all observed QTc intervals at given plasma levels of the drug are analyzed in one model, and this approach therefore provides a higher power to detect or exclude a QTc effect. In a simulation study based on moxifloxacin and placebo data from 5 crossover-designed TQT studies, different underlying QTc effect levels (no effect, 3 ms, and 5 ms) were simulated, and the power to exclude a QTc effect was compared between the E14 time-matched (TM) analysis and ER-response analysis using 1,000 and 3,000 resamples of the data (Ferber 2012). When a small underlying effect of 3 ms was simulated, ER provided 76–99 % power to exclude a 10 ms effect with 9 subjects, whereas the power of the TM approach was too low (26–67 %). Likewise, if no underlying effect was simulated, the power of ER to exclude an effect above 10 ms was 92–100 % with 9 subjects and that of TM was 43–87 %. Even though these numbers should be confirmed using additional data sets and statistical approaches, the simulation exercise clearly confirms that ER analysis provides much higher power than the E14 time-matched approach and can therefore more effectively be used in SAD/MAD studies of typical size.

5.3 How Can Assay Sensitivity Be Demonstrated Without Using a Pharmacological Positive Control?

It seems unjustified and undesirable to use moxifloxacin or any other pharmacological positive control in SAD/MAD studies, and alternative methods must therefore be sought to confirm that the study is sufficiently sensitive to detect or exclude a small QT effect, i.e., to demonstrate assay sensitivity. The inclusion of moxifloxacin as a positive control in TQT studies has been a key factor for achieving a high confidence in the study's ability to demonstrate the absence of a drug effect, and it can be assumed that some method to demonstrate assay sensitivity will be needed if SAD/MAD studies are to replace the TQT study. It also may seem unlikely that a concept with "accredited" clinical study centers and central ECG laboratories will be implemented since this will not provide assurance that studies conducted some time apart will all have the same ability to exclude small QT effects based on various factors, such as staff turnover, differences across study populations, or just inherent variability of the data. A more realistic approach is to use data derived in each study to confirm that the study held sufficient quality to detect a small drug effect, even though there was none with the studied NCE. Recently published research supports this approach and suggests that study-specific quality criteria may replace the positive control (Malik et al. 2011). The within- and between-subject variability across several, complete baseline days from several TQT studies was evaluated, and proposed statistical analyses seem to differentiate between studies of high and poor quality. Small changes related to diurnal variability are certainly not the same as small drug-induced changes, but it seems appropriate that tests of "change" irrespective of the underlying mechanisms can provide the necessary assurance of assay sensitivity.

Given the small sample size of a typical SAD study, the risk of a false-negative result (the study fails to demonstrate a QT effect when there is one) is substantially larger than the risk of a false-positive one (inability to exclude a small QT effect when there is none). Given this imbalance, it may be that the requirement for demonstrating "assay sensitivity" eventually becomes less prescriptive as experience with "early QT assessment" accumulates.

6 The Path Forward Toward Replacing the TQT Study

Almost 8 years have now elapsed since the implementation of the ICH E14 guidance in May 2005, and several hundreds of TQT studies that basically follow the E14 guidance have been performed and submitted to regulatory authorities. As of October 2012, the FDA's IRT had evaluated 288 TQT studies. Based on the high confidence in data derived from the TQT study, it will be challenging to replace it with "early QT assessment," and the process, if successful, will likely include several steps. Generation of more prospective data to demonstrate that "early QT assessment" can provide results concordant to the results of TQT studies will be required, and alternative methods for demonstrating assay sensitivity will have to be successfully tested. It is the E14 "threshold of concern" ($<$10 ms) on which the confidence that a drug with a negative TQT study is truly devoid of proarrhythmic liability in patients is based. However difficult to prove, it is generally accepted that the TQT study has been very effective in terms of protecting patients by identifying "QT liability" for new drugs (Stockbridge et al. 2012), with consequent regulatory actions (precautionary statements, black box warnings, restricted access and withdrawals). It seems highly unlikely that a different threshold will be widely accepted across regions without substantial further advancement of our knowledge of the relationship between mild QT prolongation and its consequences in large populations. The same threshold should therefore be used for "early QT assessment" based on ER analysis, i.e., the upper bound of the 2-sided 90 % CI of the QTc estimate should be lower than 10 ms at concentrations that are relevantly high for the targeted patient population. The TQT study will not be replaced with "early QT assessment" overnight, and it seems unlikely that ICH E14 will be revised until a sufficient amount of data have convinced all participating parties that alternative approaches can provide data at the same level of confidence as the TQT study. Replacing the TQT study will therefore probably be a stepwise, staggered approach, in which the request for a TQT study may be waived for some compounds with certain characteristics, while others will have to undergo a TQT study. Examples of the former may include compounds from a pharmacological class known to have no members with QT liability, a clean nonclinical safety pharmacology package, and robustly negative ER analysis of SAD/MAD data with the upper bound of the 2-sided 90 % CI of the projected QTc effect below 10 ms at concentrations that are relevant for the targeted patient population. Other drugs, such as those with a small underlying effect or where "early QT assessment"

has not provided a sufficiently precise estimate of the QT effect, would still require an E14-compliant TQT study.

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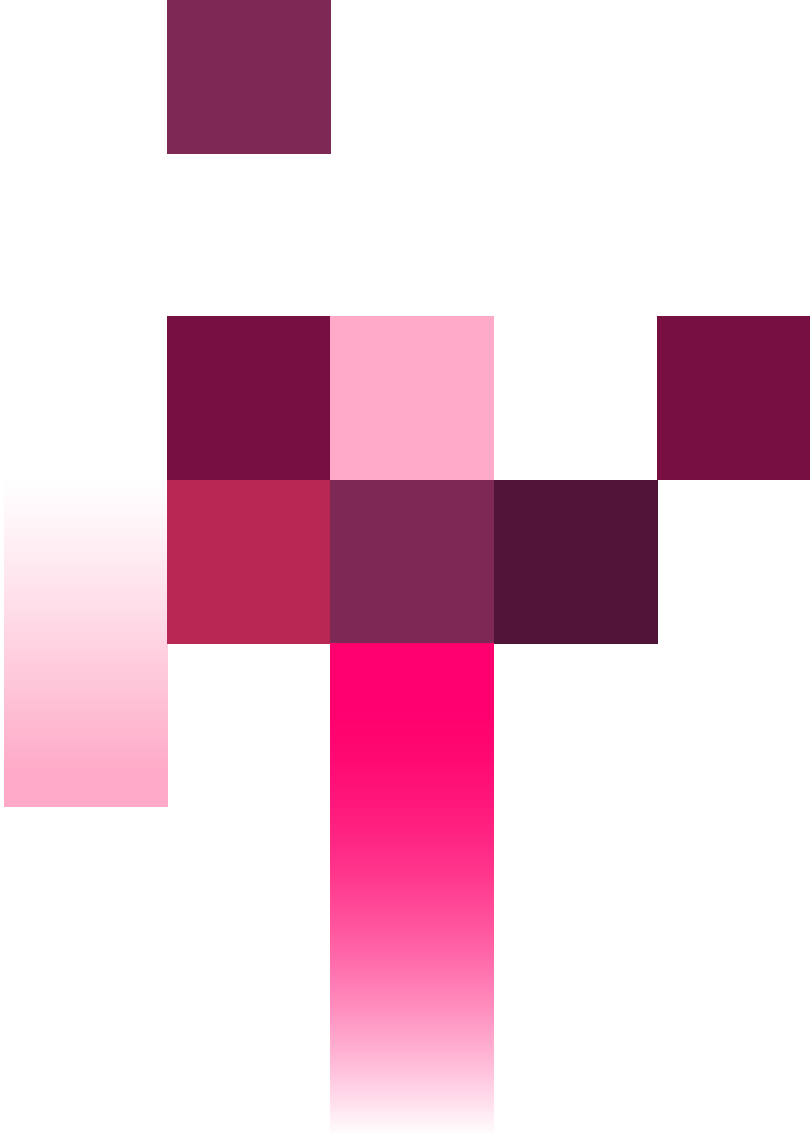

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