QT Evaluation in Early Clinical Development

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Vice President, Medical Affairs
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ACPU Annual Meeting Cincinnati
Background

- Global regulatory agencies remain concerned that some non-antiarrhythmic drugs may cause a delay in ventricular repolarization which may predispose a patient to serious, sometimes fatal ventricular arrhythmias, specifically torsades de pointes (TdP).

- Although less than ideal, electrocardiographic QT interval prolongation is correlated with increased duration of ventricular depolarization and repolarization.

Ref: Guidance for Industry E 14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs October 2005
Do all drugs require rigorous QT evaluation?

- New drugs with systemic bioavailability, other than antiarrhythmics which can prolong the QT/QTc interval as a part of their mechanism of clinical efficacy.

- Approved drugs when a new dose or route of administration is being developed that results in significantly higher exposure (Cmax or AUC) or a new indication or patient population.

- Drugs, when other members of its chemical or pharmacological class have been associated with QT/QTc interval prolongation, TdP, or sudden cardiac death during postmarketing surveillance.
Cardiac Conduction
Cardiac Conduction

- **P Wave**: Activation of the atria
- **QRS Complex**: Activation of the ventricles
- **T Wave**: Recovery wave
Cardiac Action Potential

**Figure 5.** Cardiac action potential. Phase 3 depolarization is mediated by $I_{Kr}$, the delayed rectifier potassium current. Almost all of the drugs that cause LQTS block this current.
Preclinical Evaluation

“A 30-fold margin between C max and hERG IC may suffice … but companies should consider increasing this margin, particularly for drugs aimed at non-debilitating diseases. However, interactions with multiple cardiac ion channels can either mitigate or exacerbate the prolongation of APD and QT that would ensue from block of I currents alone, and delay of repolarisation per se is not necessarily torsadogenic. Clearly, an integrated assessment of in vitro Kr and in vivo data is required in order to predict the torsadogenic risk of a new candidate drug in humans “.
“Most (9/10) drugs eliciting essentially no hERG block at maximal concentrations demonstrate no QTc prolongation…a hERG safety margin of 45 provided optimal overall performance linking safety margins to QTc prolongation…the overall limitations of hERG safety margins shown using these quantitative, evidence based approaches highlight the need for additional preclinical assays and adaptive strategies throughout drug discovery to reliably mitigate QTc prolongation risk”.
Preclinical Evaluation (con't)

![Bar graph showing count of QTc Prolongation compared to free hERG Safety Margin](chart.png)
Preclinical Evaluation (con't)

Figure 6.
TdP scores derived based on the criteria in Table 1 BCL = 2000 ms. The free TPC of the compounds was obtained from previously published studies.3,40–42 The symbols of * and ** indicate $p < 0.05$ and $p < 0.01$, respectively, when compared with the control value of the compound. $n = 4$ for each compound.

Liu, Kowey et al 2006

Arterially Perfused Rabbit Wedge
Electrocardiogram

- RR Interval
- QRS Complex
- T Wave
- ST Segment
- P Wave
- PR Interval
- QRS Interval
- QT Interval
- Voltage: 1 mV
- Time: 0.2 sec
- Voltage: 0.1 mV
- Time: 0.04 sec
Lead Placement

12 lead Holter or telemetry
12 lead ECG

V1  Fourth Intercostal space at the right sternal border
V2  Fourth Intercostal space at the left sternal border
V3  Midway between V2 and V4
V4  Fifth intercostal space at the left of the midclavicular line
V5  Anterior axillary line at same horizontal level as V4
V6  Mid-axillary line on same horizontal level as V4 and V5

Ref: Mortara user manual
QT Prolongation

Ayad et al 2010
Torsade de Pointes

Ayad et al 2010
Torsades de Pointes (con't)
Torsades de Pointes (con’t)
# Common Drugs that Cause QT Prolongation

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiarrhythmics</strong></td>
<td></td>
</tr>
<tr>
<td>Amiodarone (Cordarone)</td>
<td>Procainamide (Pronestyl)</td>
</tr>
<tr>
<td>Disopyramide (Norpace)</td>
<td>Quinidine (Quinaglute)</td>
</tr>
<tr>
<td>Dofetilide (Tikosyn)</td>
<td>Sotalol (Betapace)</td>
</tr>
<tr>
<td>Ibutilide (Corvert)</td>
<td></td>
</tr>
<tr>
<td><strong>Antipsychotics</strong></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine (Thorazine)</td>
<td>Quetiapine (Seroquel)</td>
</tr>
<tr>
<td>Clozapine (Clozaril)</td>
<td>Risperidone (Risperdal)</td>
</tr>
<tr>
<td>Haloperidol (Haldol)</td>
<td>Thioridazine (Mellaril)</td>
</tr>
<tr>
<td><strong>Antibiotics</strong></td>
<td></td>
</tr>
<tr>
<td>Azithromycin (Zithromax)</td>
<td>Ketoconazole (Nizoral)</td>
</tr>
<tr>
<td>Ciprofloxacin (Cipro)</td>
<td>Levofloxacin (Levaquin)</td>
</tr>
<tr>
<td>Clarithromycin (Biaxin)</td>
<td>Moxifloxacin (Avelox)</td>
</tr>
<tr>
<td>Erythromycin (Erythrocin)</td>
<td>Ofloxacin (Floxin)</td>
</tr>
<tr>
<td>Fluconazole (Difucan)</td>
<td>Sparfloxacin (Zagam)</td>
</tr>
<tr>
<td>Gatifloxacin (Tequin)</td>
<td>Telithromycin (Ketek)</td>
</tr>
<tr>
<td>Itraconazole (Sporanox)</td>
<td>Trimethoprim-Sulfa (Bactrim)</td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline (Elavil)</td>
<td>Imipramine (Norfranil)</td>
</tr>
<tr>
<td>Citalopram (Celexa)</td>
<td>Nortriptyline (Pamelor)</td>
</tr>
<tr>
<td>Desipramine (Pertofrane)</td>
<td>Paroxetine (Paxil)</td>
</tr>
<tr>
<td>Doxepin (Sinequan)</td>
<td>Sertraline (Zoloft)</td>
</tr>
<tr>
<td>Fluoxetine (Prozac)</td>
<td>Venlafaxine (Effexor)</td>
</tr>
<tr>
<td><strong>Antiemetics</strong></td>
<td></td>
</tr>
<tr>
<td>Ondansetron (Zofran)</td>
<td>Prochlorperazine (Compazine)</td>
</tr>
</tbody>
</table>
# QT Related Drugs Withdrawn

## Table 1  Drugs withdrawn from the US market as a result of QT-associated proarrhythmia

<table>
<thead>
<tr>
<th>Compound</th>
<th>Class</th>
<th>Year withdrawn (reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astemizole</td>
<td>Antihistamine</td>
<td>1999 (1)</td>
</tr>
<tr>
<td>Cisapride</td>
<td>Prokinetic agent</td>
<td>2000 (2)</td>
</tr>
<tr>
<td>Grepafloxacin</td>
<td>Fluoroquinolone antibiotic</td>
<td>1999 (3)</td>
</tr>
<tr>
<td>Lidoflazine</td>
<td>Calcium channel blocker</td>
<td>Never approved in the United States</td>
</tr>
<tr>
<td>Sertindole</td>
<td>Antipsychotic agent</td>
<td>Rejected by the US Food and Drug Administration in 1996</td>
</tr>
<tr>
<td>Terfenadine</td>
<td>Antihistamine</td>
<td>1997 (4)</td>
</tr>
<tr>
<td>Terodiline</td>
<td>Antimuscarinic agent</td>
<td>1993 (5)</td>
</tr>
</tbody>
</table>

Whellan et al 2009
## Table 1 – Risk factors for ‘torsade de pointes’ in case of QTc prolongation

<table>
<thead>
<tr>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
</tr>
<tr>
<td>Age ≥65 years</td>
</tr>
<tr>
<td>Bradycardia (especially recent heart-rate slowing)</td>
</tr>
<tr>
<td>Congestive heart failure or cardiac hypertrophy</td>
</tr>
<tr>
<td>Clinical or subclinical congenital LQTS</td>
</tr>
<tr>
<td>Ion-channel polymorphisms</td>
</tr>
<tr>
<td>Baseline ECG that shows prolonged QT or T-wave lability</td>
</tr>
<tr>
<td>Post-exposure ECG that shows: QT prolongation, pathological TU morphology and marked post-extrasystolic QTU</td>
</tr>
<tr>
<td>Mitral valve prolapse?</td>
</tr>
<tr>
<td>Diuretic use (independent of electrolyte serum concentrations)</td>
</tr>
<tr>
<td>Pro-arrhythmic drugs</td>
</tr>
<tr>
<td>Hypokalaemia, hypomagnesaemia</td>
</tr>
<tr>
<td>High drug concentrations</td>
</tr>
<tr>
<td>Anorexia nervosa, ‘liquid proteins diets, major gastrointestinal by-pass’</td>
</tr>
<tr>
<td>Nervous system injuries (subarachnoid haemorrhage, righ neck dissection, pheochromocytoma)</td>
</tr>
<tr>
<td>AIDS?</td>
</tr>
</tbody>
</table>

Torsade de Pointes and Gender

Drugs for men and women — How important is gender as a risk factor for TdP?

Susan J. Coker *

Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, 27 Taylor Street, Glasgow G4 0NR, United Kingdom

Abstract

The cardiac arrhythmia known as torsade de pointes (TdP), which is a very rare but potentially lethal side effect of a variety of drugs, occurs approximately twice as often in women as it does in men. Most drugs that have this adverse effect prolong the repolarization phase of the cardiac action potential which can be detected by a lengthening of the QT interval on the ECG. The gender difference in susceptibility to TdP only appears after puberty suggesting that sex hormones are contributory factors. Studies in patients indicate that testosterone-induced shortening of action potential duration may account for the shorter rate-corrected QT interval in men rather than any effect of estradiol in women, whereas drug-induced QT prolongation can be potentiated by estradiol. Experimental investigations suggest that sex hormones may alter either Ca\textsuperscript{2+} currents, K\textsuperscript{+} currents, or both and that actions on these ionic currents may account for the gender differences in cardiac repolarization. Although estradiol exacerbated drug-induced TdP in an in vivo model, no similar information is available for progesterone or testosterone. Further studies are required to clarify the influence of these sex hormones and to investigate the importance of the balance between sex hormones in both genders. Such information would assist in risk:benefit analysis and may allow the development of “drugs for men” and “drugs for women”.

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Torsade de Pointes and Gender (con’t)

Fig. 3. The percentage of TdP cases by gender in patients receiving antiarrhythmic drugs and in those receiving non-antiarrhythmic drugs. Adapted from Bednar et al., (2002).
### Table 2  Variation of average QTc with age and gender

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age, 20–29 years</th>
<th>Age, 70–79 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>387 ms (351–426)(^a)</td>
<td>401 ms (363–446)(^a)</td>
</tr>
<tr>
<td>Females</td>
<td>400 ms (362–440)(^a)</td>
<td>410 ms (369–459)(^a)</td>
</tr>
</tbody>
</table>

\(^a\)Averages are the means at 2% of the 98th percentile.
QTc Variability

Figure 2  Distribution of standard deviations of QTc values measured in baseline (day -1) recordings of individual study subjects. The standard deviations were calculated from all the measurements made on day -1, that is, both the measurements corresponding to the individual data points and the measurements used to derive the individual QT/RR relationship. (On average, 326 ± 6 QT measurements were used during day -1 in individual subjects.)

Mean SD value: 4.49 ± 1.03 msec
Figure 4. ΔQTc values (differences between postdose QTc values and time-matching QTc values at baseline) in 12 placebo subjects pooled from all 6 cohorts of the study. Double-sided 95% confidence intervals are shown.
Mean change is ~3.0 msec, and SD 3.9 msec. 90% of the mean changes from baseline lie between ~9.4 msec and 3.4 msec.

Figure 12  Sampling distribution of time-matched mean changes from baseline in QTcF.
Guidance for Industry

E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs

ICH Topic E 14
The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs

Step 5

NOTE FOR GUIDANCE ON THE CLINICAL EVALUATION OF QT/QTc INTERVAL PROLONGATION AND PROARRHYTHMIC POTENTIAL FOR NON-ANTIARRHYTHMIC DRUGS (CHMP/ICH 2/04)

<table>
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<th>Event</th>
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<td>TRANSMISSION TO CHMP</td>
<td>June 2004</td>
</tr>
<tr>
<td>TRANSMISSION TO INTERESTED PARTIES</td>
<td>June 2004</td>
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<tr>
<td>DEADLINE FOR COMMENTS</td>
<td>December 2004</td>
</tr>
<tr>
<td>FINAL APPROVAL BY CHMP</td>
<td>May 2005</td>
</tr>
<tr>
<td>DATE FOR COMING INTO OPERATION</td>
<td>November 2005</td>
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ICH Topic E 14
The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs

Step 5

QUESTIONS AND ANSWERS
(EMEA/CHMP/ICH/310133/2008)

<table>
<thead>
<tr>
<th>TRANSMISSION TO CHMP FOR INFORMATION</th>
<th>June 2008</th>
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</thead>
<tbody>
<tr>
<td>RELEASE FOR INFORMATION</td>
<td>June 2008</td>
</tr>
</tbody>
</table>
Approach to Evaluating Drug Effects on QT/QTc Interval

- Drugs are expected to receive a clinical electrocardiographic evaluation, beginning early in clinical development, typically including a single thorough QT (TQT) study at some point in the clinical program, generally prior to phase III.

- Factors that could reduce the need for such a study include the inability to conduct the study in healthy volunteers or patients, how the drug is studied and used (e.g., administered under continuous monitoring), as well as nonclinical data.
Approach to Evaluating Drug Effects on QT/QTc Interval (con’t)

Until the effects of the drug on the QT/QTc interval have been characterized, the following exclusion criteria are suggested:

- Marked baseline prolongation of QT/QTc interval (e.g., repeated demonstration of a QTc interval > 450 msec)
- History of additional risk factors for TdP (e.g., heart failure, hypokalemia, family history of Long QT Syndrome)
- Concomitant medications that prolong the QT/QTc interval

With QT/QTc interval data from early clinical studies, later clinical trials could expand the eligibility criteria to include a broader spectrum of patients who are likely to receive the drug once approved.
The FDA / ICH E14 Guidance for thorough QT (TQT) studies was last revised in 2005, but things have evolved somewhat since then. 12 lead ECG data collection via holter (or telemetry) has become the standard and the agency is almost always interested in the association of QT interval with drug concentration, the so called QT concentration relationship as part of the TQT review process.

- An “ECG warehouse” has been established for sponsors and core labs to upload digital ECG data for agency review.
- The FDA has set up an interdisciplinary review team (IRT) for sponsor consultation (indirect) and ECG data review.
- QT correction methods and modeling have developed over the last few years with a large body of statistical literature - it is no longer adequate to provide only QTcB and QTcF correction for a TQT review.
TQT Process (con’t)

- Usually conducted in healthy volunteers in a phase I unit with at least some overnight inpatient monitoring.
- The patient is instructed to remain supine and quiet for 10-15 minutes around the chosen ECG time points which can be 7-15 times in a day and repeated over multiple days depending on the pK of the drug and whether the study is a parallel design or crossover study.
- Multiple "safety" ECGs are done at the site and reviewed by the PI before starting and prior to continued dosing.
- Depending on pK and maximum tolerated dose (MTD), a therapeutic and a supratherapeutic (4-5x) dose of the active drug are evaluated.
- Placebo and a positive control (moxifloxacin) are also tested, the latter to assure the sensitivity of the process and study conditions in the unit to be able to detect a significant increase in QTc.
TQT Process (con’t)

- A 12 lead Holter monitor or 12 lead telemetry monitor, such as the Mortara Surveyor system like we at Medpace have in our CPU, are used to collect continuous ECG data. The data is reviewed by a trained ECG technician to select the best 3-5 replicates of ten second ECGs at or within a 2-5 minute window at each desired time point.

- ECGs must be taken and chosen with no noise and with a stable heart rhythm and rate, the latter to avoid a hysteresis effect which can cause significant errors in the calculation of QT correction for heart rate.

- The selected ECGs are then measured for the standard intervals and the raw QT interval. This measurement can be done manually with or without algorithm guided placement of the electronic calipers which will then be manually over read by a cardiologist.

- Semiautomatic methods can be used with the construction of a global median beat consisting of an overlay of all 12 leads of a given ECG with algorithm guided placement of electronic calipers and manual cardiology over read of the caliper placement on every ECG.
The data must be blinded completely (to the reader and also to the technician to varying extent) with respect to patient demographics, including gender, age, date, time and sequence collected and of course study medication. The ICH E14 guidance and subsequent Q&As (November 2008) requires that the same reader read all of the same patient’s ECGs and that the total number of readers be limited to a “few skilled readers”. There must be mechanisms in place to assure minimal inter and intra reader variability. In addition to training and testing of readers and technicians, a certain percentage of the TQT ECG database (~ 2%) must be re-read to assure minimal variability.
Global Superimposed Beat

Piccini et al 2009
TQT Process (con’t)

- QT correction for heart rate is performed utilizing standard correction factors, such as Bazett’s and Fridericia’s formulas. Additional correction based on linear and non-linear regression and individual subject data are utilized. Gender correction and study period correction (with multiple cohorts) of heart rate may also be utilized.
- The QTc intervals of the ECGs selected at each time point are averaged.
- The primary objective is to evaluate the central mean tendency of the QT interval, corrected for heart rate and with placebo and baseline subtraction. The data is often time matched depending on the study design. Categorical analyses for outliers are also evaluated as are T and U wave morphologies.
- Of note, a recent RFP required triplicate ECGs at 13 time points in a day repeated over several days. This totaled over 20,280 ECGs plus 3120 “safety” ECGs for a total of 23,400 ECGs. This may vary, but it is fairly typical. The subject number can be up to 260, depending on the study design, particularly cross over vs parallel, the latter requiring more patients than the former.
ECG Parameters

Absolute QTc interval prolongation (msec):
- QTc interval > 450
- QTc interval > 480
- QTc interval > 500

Change from baseline in QTc interval:
- QTc interval increases from baseline >30
- QTc interval increases from baseline >60

Morphological Analyses of ECG Waveforms
- T and U waves
QT Correction Methods

- Bazett's correction
  \[ QT_c = \frac{QT}{\sqrt{RR}} \]

- Fridericia's correction
  \[ QT_F = \frac{QT}{RR^{1/3}} \]

- Linear regression techniques

- Linear or nonlinear regression modeling based on pooled data from large databases

- Derived from within-subject data (QTci)
QT and QTc

(a) Uncorrected QT interval (ms) vs RR interval (ms)

(b) QTc interval (fridericia) vs RR interval (ms)

(c) QTc interval (bazelets) vs RR interval (ms)
QT Correction

Evaluation of Vardenafil and Sildenafil on Cardiac Repolarization

Joel Morganroth, MD, Bernard E. Ilson, MD, Bonnie C. Shaddinger, PharmD, Guissou A. Dabiri, PhD, Bela R. Patel, PhD, Duane A. Boyle, PharmD, Venkat S. Sethuraman, MS, and Timothy H. Montague, MS

Morganroth et al 2004
E14 Definition of a Negative Study

To assure that the mean effect on the QT interval is not greater than around 5 ms:

“…a negative thorough QT/QTc study is one in which the upper bound of the 95% one-sided confidence interval for the largest time-matched mean effect of the drug on the QTc interval excludes 10 ms”.

FDA ICH E14 Guidance 2005
TQT Positive Control

- Moxifloxacin 400 mg
- Time Points: 1.0hr, 2.0hr, 3.5hr
- 5 msec
TQT Negative Study

Study Drug
Study Drug vs Positive Control

Figure 1. Mean (90% confidence interval) QTcf change from baseline differences (active-placebo) following single oral doses of 100- and 800-mg sitagliptin and moxifloxacin in healthy male and female subjects.
Automatic Extraction of ECG Strips from Continuous 12-lead Holter Recordings for QT Analysis at Prescheduled versus Optimized Time Points

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From the *AMPS-LLC, New York, New York; and †CPCS Pharma Consulting LLC, Morristown, New Jersey

**Background:** Continuous 12-lead ECG monitoring (Holter) in early-phase pharmaceutical studies is today widely used as an ideal platform to extract discrete ECGs for analysis. The extraction process is typically performed manually by trained readers using commercial Holter processing systems.

**Methods:** Antares, a novel method for automatic 12-lead extraction from continuous Holter recordings applying minimal noise criteria and heart-rate stability conditions is presented. A set of 12-lead Holter recordings from healthy subjects administered with sotalol is used to compare ECG extractions at fixed time points with ECG extractions generated by Antares optimizing noise and heart rate inside 5 minute windows centered around each expected time point of interest.

**Results:** Global, low- and high-frequency noise content of extracted ECGs was significantly reduced via optimized approach by Antares. Heart rate was also slightly reduced (from 69 ± 13 to 64 ± 13 bpm, P < 0.05). Similarly, the corrected QT interval from optimized extractions was significantly reduced (QTCB from 414 ± 32 to 402 ± 30 ms, P < 0.05). Using only baseline data, and after adjusting for intersubject variability, the standard deviation (SD) of QT intervals was highly reduced with optimized extraction (SD of QTCF from 11 ± 8 to 7 ± 2 ms, P < 0.05).

**Conclusions:** Extraction of discrete 12-lead ECG strips from continuous Holter generates less noisy and more stable ECGs leading to more robust QTc data, thereby potentially facilitating the assessment of ECG effects on clinical trials.

Optimizing ECG Extraction

Among the stable strips, select the one with minimal noise!!
Figure 2. Trend display of RRs and RRo intervals within the optimum window from a representative example (see text for more description of RRs and RRo intervals).
Figure 5. Example of ECGs extraction using a fixed time point (left-hand side) and using Antares (right-hand side) in a representative example with the presence of heart-rate fluctuations. The superimposed (butterfly) display of the median beats is also displayed and the QT/RR parameters computed by CalECG are shown.
# Optimal ECG Selection

## Table 1. Comparison of Select Quantitative and Qualitative ECG Parameters between Optimized and Fixed-Time Point Extractions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fixed</th>
<th>Optimized</th>
<th>Δ (F – O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global noise (µV)</td>
<td>76 ± 75</td>
<td>52 ± 38</td>
<td>24 ± 77*</td>
</tr>
<tr>
<td>HF noise (µV)</td>
<td>0.86 ± 0.31</td>
<td>0.82 ± 0.22</td>
<td>0.03 ± 0.32*</td>
</tr>
<tr>
<td>LF noise (µV)</td>
<td>93 ± 77</td>
<td>67 ± 41</td>
<td>26 ± 80*</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>69 ± 13</td>
<td>64 ± 11</td>
<td>5.1 ± 8.8*</td>
</tr>
<tr>
<td>QT (ms)</td>
<td>392 ± 39</td>
<td>394 ± 39</td>
<td>−2 ± 10*</td>
</tr>
<tr>
<td>QTcB (ms)</td>
<td>414 ± 32</td>
<td>402 ± 30</td>
<td>12 ± 17*</td>
</tr>
<tr>
<td>QTcF (ms)</td>
<td>407 ± 28</td>
<td>399 ± 26</td>
<td>8 ± 13*</td>
</tr>
</tbody>
</table>

*P < 0.05 with Student’s paired t-test.
Concentration-QTc

Concentration-QT Relationships Play a Key Role in the Evaluation of Proarrhythmic Risk During Regulatory Review

Christine E. Garnett, PharmD, Nhi Beasley, PharmD,
V. Atul Bhattaram, PhD, Pravin R. Jadhav, PhD,
Rajanikanth Madabushi, PhD, Norman Stockbridge, MD, PhD,
Christoffer W. Tornoe, PhD, Yaning Wang, PhD, Hao Zhu, PhD,
and Jogarao V. Gobburu, PhD

The criterion for assessing whether a drug prolongs QT as described in the International Conference on Harmonization topic E14 guideline does not explicitly account for individual drug concentrations. The authors’ experience with reviewing QT studies indicates that understanding the relationship, if any, between individual drug concentration and QT change provides important additional information to support regulatory decision making. Therefore, regulatory reviews of “thorough QT” studies routinely include a characterization of the concentration-QT relationship. The authors provide examples to illustrate how the concentration-QT relationship has been used to plan and interpret the thorough QT study, to evaluate QT risk for drugs that have no thorough QT studies, to assess QT risk in subpopulations, to make dose adjustments, and to write informative drug labels.

Keywords: Pharmacokinetics, pharmacodynamics, modeling, QT interval; ICH E14

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### Table I  Roles of Concentration-QT Assessment in Drug Development

<table>
<thead>
<tr>
<th>Planning of a thorough QT (TQT) study</th>
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<tbody>
<tr>
<td>Waive a TQT study for drugs found to have significant concentration-QT relationship</td>
</tr>
<tr>
<td>Interpretation of the TQT study</td>
</tr>
<tr>
<td>Routinely support assessment of whether a drug prolongs QT</td>
</tr>
<tr>
<td>Predict QTc at lower doses not included in the TQT study</td>
</tr>
<tr>
<td>Evaluate assay sensitivity of positive control</td>
</tr>
<tr>
<td>Quantify the drug’s benefit and risk</td>
</tr>
<tr>
<td>Assess need for dose adjustments in special populations</td>
</tr>
<tr>
<td>Effectively communicate risk</td>
</tr>
<tr>
<td>Determine QTc prolongation for drugs when a TQT study cannot be conducted</td>
</tr>
</tbody>
</table>
Figure 5  Predicted placebo-corrected QTc CFB mean values and upper 95% pointwise confidence limits by plasma concentration. Two observations with moxifloxacin concentrations < 1,000 were excluded. The confidence interval is not adjusted for multiplicity. CFB, change from baseline.
Concentration QTc

Figure 7. Relationship between drug plasma levels and ΔQTc values measured on placebo (pooled from all 6 cohorts) and on individual active drug doses. The dashed line shows a linear regression model between the plasma levels and ΔQTc values.
Fig. 3  Plot of individual $\Delta QT_{cSS}$ change from baseline versus plasma concentrations at corresponding time-points for 5 mg (○) and 30 mg levocetirizine (□) (a) and for moxifloxacin (b).
Concentration QT Modeling

Figure 2. QTcF interval change from baseline versus plasma concentration following single and multiple oral doses. Arrows indicate the mean peak plasma concentration ($C_{\text{max}}$) after the single dose (SD) and at steady state after 7 days (SS). Closed circles and vertical lines are the model-predicted mean and 90% confidence interval QTcF.
Concentration QTc

Figure 1. Predicted 90% confidence interval (shaded area) for mean QTcF change from baseline based on the concentration-QT model and the estimated concentration-time profiles at 20 mg and 50 mg once daily.
Concentration QTc Modeling (con’t)

Figure 3. Individual QTcf change from baseline (placebo-corrected) related with plasma sitagliptin concentration and the fitted linear PK/QTc model in healthy male and female subjects.
Concentration QTc (con’t)

Figure 5. Mean QTcf change from baseline differences/model estimates and upper confidence limit as a function of sitagliptin plasma concentrations following single oral doses of sitagliptin in healthy male and female subjects.
The QT arena continues to evolve, but essentially most non antiarrhythmic NCEs will have to go through the “TQT” process at least for the near future. Recently, there has been some discussion of even earlier phase I studies, the so called “near thorough QT study”, perhaps even as part of first in man studies to weed out drugs earlier or provide additional rigorous data in the drug development process on a time line prior to the TQT study.

In special situations, patients with the disease of interest are the study subjects such as in an oncology drug trial with rigorous ECG assessment and with considerable modification of TQT procedures and usually not in a Phase I unit.

The Cardiac Safety Research Consortium (CSRC) was founded 4 years ago as part of the Critical path Initiative of the FDA partnering with the Duke Clinical Research Institute, other academia and industry. The main focus has been on QT issues but also includes most areas of cardiac safety involving premarketing and post marketing of cardiac and non cardiac drugs and cardiac devices.
"When comparing the time-dependent effect of the drug on the QTc interval the automatic technique produced results similar to the measurements reported by contract research organizations to the Agency (FDA)."

Handzel et al 2008
Near-Thorough QT Study as Part of a First-In-Man Study

Marek Malik, PhD, MD, Katerina Hnatkova, PhD, John Ford, PhD, and David Madge, PhD

Detailed electrocardiographic (ECG) support was provided to a first-in-man, single-ascending-dose study that included 6 cohorts of 8 male volunteers each. In each cohort, 6 and 2 subjects received active compound and placebo, respectively. Long-term 12-lead ECGs were obtained on baseline day -1, dosing day 1, and day 2. Automatic QT-interval measurements were made at 63 time points (28 at baseline and 35 on treatment). Based on QT/RR distribution, 20% of measurements were visually verified. Baseline-corrected time-matched 

\[ \Delta QTc \]

values were obtained at 35 postdose time points. Placebo subjects of all cohorts were pooled. When 2 cohorts of the lowest, middle, and highest doses were pooled (12 subjects per active treatment group), the spreads of placebo-corrected 

\[ \Delta QTc \]

values were within the regulatory requirements (single-sided 95% confidence interval \(<10\) milliseconds) at all time points. Thus, this ECG support of the first-in-man study provided data of regulatory acceptable accuracy at a small fraction of the cost of a full thorough QT study.

Keywords: Electrocardiography; QT interval; first-in-man study

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Assessing proarrhythmic potential of drugs when optimal studies are infeasible

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Assessing the potential for a new drug to cause life-threatening arrhythmias is now an integral component of premarketing safety assessment. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use guideline (ICH) E14 recommends the “Thorough QT Study” (TQT) to assess clinical QT risk. Such a study calls for careful evaluation of drug effects on the electrocardiographic QT interval at multiples of therapeutic exposure and with a positive control to confirm assay sensitivity. Yet for some drugs and diseases, elements of the TQT Study may be impractical or unethical. In these instances, alternative approaches to QT risk assessment must be considered. This article presents points to consider for evaluation of QT risk when alternative approaches are needed. (Am Heart J 2009;157:827-836.e1.)
QT/QTc Shortening

Original article

Drug induced shortening of the QT/QTc interval: An emerging safety issue warranting further modelling and evaluation in drug research and development?

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PURPOSE

- This MAPP establishes an interdisciplinary review team (IRT) for the review of Thorough QT (TQT) protocols and studies within the Center for Drug Evaluation and Research (CDER).
Ask for Help Early