Chapter 16
Visualization of QT Data for Thorough QT Study Analysis and Review

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Abstract The focus of this chapter is on visualization of QT data for thorough QT (TQT) study analysis and review. The use of graphics is particularly important for QT data due to the high variability and to explore the adequacy of heart rate QT correction, baseline adjustments, choice of positive control to establish assay sensitivity, and the relationship between exposure and QT prolongation. A QT knowledge management system implemented in the R package "QT" standardizes and automates the QT data analyses, graphical representation, and reporting. This allows for easier communication of the results because the analyses are consistent and enables pooled data analysis across TQT studies to address drug development related questions.

16.1 Introduction

The objective of a thorough QT (TQT) study is to determine whether a drug has a pharmacological effect on cardiac repolarization as detected by a QT prolongation on the surface electrocardiogram (ECG) as described in the guideline (ICH E14). Refer to Chap. 18 for more information about ECGs and the QT interval.

The ΔQTc (time-matched baseline adjusted QTc) and ΔΔQTc (time-matched change from placebo- and baseline-adjusted QTc) used for the central tendency and concentration–QTc analyses are calculated by

$$\Delta\mathrm{QTc}_{\mathrm{drug}}(t) = \mathrm{QTc}_{\mathrm{drug}}(t) - \mathrm{QTc}_{\mathrm{drug}}(\mathrm{baseline})$$

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A. Krause and M. O'Connell (eds.), *A Picture is Worth a Thousand Tables: Graphics in Life Sciences*, DOI 10.1007/978-1-4614-5329-1_16,

$$\Delta QTc_{placebo}(t) = QTc_{placebo}(t) - QTc_{placebo}(\text{baseline})$$

$$\Delta\Delta QTc(t) = \Delta QTc_{drug}(t) - \Delta QTc_{placebo}(t),$$

where the baseline QTc is calculated as the mean of the pre-dose ECG measurements for each treatment.

A key component for assessing the QT prolongation potential of a drug is to create informative graphs that are tailored to address the key questions to be answered. For that purpose, the R package "QT" (requires SAS™) was developed based on the accumulated review experience from the FDA's interdisciplinary review team for QT (IRT-QT) (Tornoe et al. 2011). The purpose was to develop standardized graphics to increase the productivity, consistency, and quality-thereby ensuring faster and easier communication between the team of inter-disciplinary scientists.

While other papers focus on issues related to TQT study design, conduct, and analysis methods, the objective of this chapter is the visualization of QT data for TQT study analysis and review to make informed decisions through the following 10 steps:

1. Data integrity
2. QT correction method
3. Adequacy of sampling times
4. Baseline corrections
5. Assay sensitivity
6. Measure of central tendency
7. Assessing delay between drug and QT effects
8. Relationship between drug exposure and QT prolongation
9. Prediction of QT prolongation at different exposure levels
10. Benefit-risk assessment

16.2 Developing Standardized Graphics for QT Data

The high variability and low signal-to-noise ratio (trying to exclude a 10 ms QT prolongation) in QT measurements makes it difficult to spot trends and relationships based on individual data points. For this purpose, tailored quantile plots were developed.

The quantile plot is generated by binning the independent variable (e.g., RR or concentrations) into quantiles (bins with equal numbers of observations) and plotting the local median or midpoint of the observations in each of the independent variable bins against the corresponding local mean dependent variable (e.g., QT or ΔΔQT and associated 90% confidence interval). This is the binning method implemented in the R package.

A potential issue arises when using the local means across the dependent variable quantiles. The different bins can potentially be imbalanced in the number of individuals. Taking the mean of all observations in each bin and calculating the standard deviation for that mean ignores that some of the observations are correlated since they arise from the same subject. This is most likely to be an issue when pooling data from different studies with different variability in PK. One way to account for this imbalance is to use precision weighted averages in each bin by

$$\mathrm{SD}^2 = \frac{1}{\sum_{i=1}^{N} \frac{1}{\sigma^2 / n_i}}$$

$$\bar{M} = \mathrm{SD}^2 \sum_{i=1}^{N} \frac{1}{\sigma^2 / n_i} \bar{M}_i,$$

where σ^2 is the variance of the measurements in the bin, N is the number of subjects in the bin, and n_i is the number of measurements for the ith subject in the bin. M_i is the mean of the ith subject's measurements that fall into the bin.

Another way to avoid the complex calculations of the mean of the dependent variable is to calculate it for each sampling time thereby ensuring that only one measurement per subject is present in each of the bins. The disadvantage, however, is that the bins are not distributed evenly over the range of measurements.

16.3 QT Knowledge Management System

The QT knowledge management system developed for automatic QT data analyses and reporting is implemented in the R package "QT" (http://www.cran.r-project.org) that performs the data manipulation and graphical presentation of results, executes the linear mixed-effects analyses in SAS, and generates an analysis report with key results and figures.

The data template for the R package is shown in Table 16.1.

The "QT" R package consists of 5 main functions (the R and SAS code can be found at http://qttool.googlecode.com):

- QTcorrections: This function performs the QT-RR analysis on off-drug treatment data and evaluates the ability of the different QT corrections to remove the heart rate effect on on-drug treatment data using PROC MIXED in SAS
- DataCheck: The DataCheck function visualizes key data to check the integrity of the analysis dataset
- MeanData: The MeanData function calculates and plots the mean profiles, and creates the dataset for the QTc-time and concentration–QTc analyses

Table 16.1 Data template for QT package

Column identifier	Description	Units	Type
subjid	Subject identifier		Character
treat	Treatment group		Character
period	Period		Numeric
day	Day relative to first dose of period	Days	Integer
time	Time relative to dose	h	Numeric
rr	RR interval	ms	Numeric
hr	Heart rate	bpm	Numeric
qt/qtc	QT/QTc interval	ms	Numeric
qt.bs/qtc.bs	QT/QTc baseline	ms	Numeric
qt.cfb/qtc.cfb	QTc/QTc change from baseline	ms	Numeric
conc	Parent drug concentration		Numeric
meta	Metabolite concentration		Numeric
moxi	Moxifloxacin concentration		Numeric
wt	Body weight	kg	Numeric
age	Age	years	Numeric
sex	Gender	M = male, F = female	Controlled term

- QTtime: The central tendency analysis of QTc versus time is performed in SAS using PROC MIXED
- QTconc: The concentration–QTc analysis is performed in SAS using PROC MIXED. Three models are estimated, i.e., (1) "with intercept," (2) "no intercept," and (3) "intercept fixed to zero with variability." The results are summarized in tables and graphs

16.4 Visualization of QT Data in Ten Steps for TQT Study Analysis and Review

In the following, the 10 visual steps for TQT study analysis and review are illustrated using simulated data included in the R package "QT." The simulated TQT study is a 4-way crossover design with placebo, moxifloxacin (active control), and therapeutic and supra-therapeutic doses of the drug candidate. The colors used for the different treatment arms are consistent in the following figures with black, orange, blue, and red representing placebo, moxifloxacin, therapeutic dose, and supra-therapeutic dose, respectively. Mean and 90% confidence interval are used throughout.

16.4.1 Data Integrity

Initially, the derived dataset containing QT-, RR-, and concentration–time profiles are inspected by visualizing the data to ensure the merging of data is performed correctly. In Fig. 16.1, the QT, RR, moxifloxacin, and drug X concentrations are plotted for the 4 treatments to assess whether there are outliers, unrealistic values, or unit differences in the measurements.

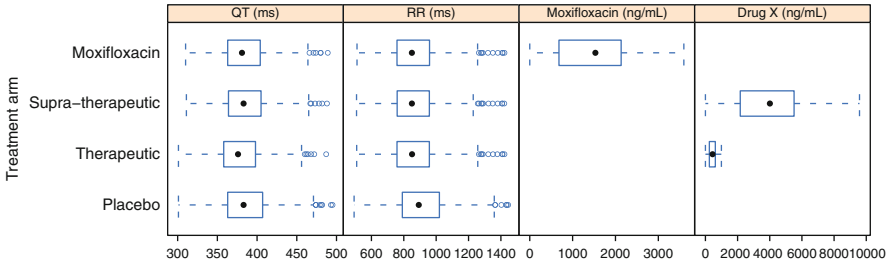

Fig. 16.1 Box plot of QT, RR, moxifloxacin, and drug X for each treatment

16.4.2 QT Correction Method

Before assessing the QT prolongation potential of a drug, the heart rate effect should be removed first since it is known to affect the QT interval. The relationship between QT interval length and heart rate (using the RR interval) is investigated using the available off-drug data only (Fig. 16.2 top). Given the high variability in QT measurements, it is difficult to assess the adequacy of the QT correction method when visualizing the individual data points and comparing it to the estimated regression line (Fig. 16.2 top). However, by using the previously described quantile plot a different intercept (at RR = 1,000 ms) and slope between males and females are clearly seen in Fig. 16.2 (bottom).

In Fig. 16.3, the individual relationship between QT, QTcB (Bazzett's), QTcF (Fridericia), and QTcI (Individual correction) and RR indicates that QTcB overcorrects for heart rate whereas QTcF and QTcI both seem to be appropriate correction methods.

The choice of the heart rate correction method to use for further analyses is further investigated by estimating a linear model using on-drug data to see whether the slope is significantly different from zero indicating whether there still is a relationship between QT and heart rate. The quantile plots in Fig. 16.4 show that the slopes for QTcF and QTcI are both significantly different from zero on a 0.05 α-level but QTcI appears to be the most appropriate QT correction methods.

Furthermore, to ensure that it is not only a global trend shown between the different QT correction methods (QTc) and RR, the average sum of squared individual slopes are calculated and compared to the QTcI having the lowest average (see Table 16.2).

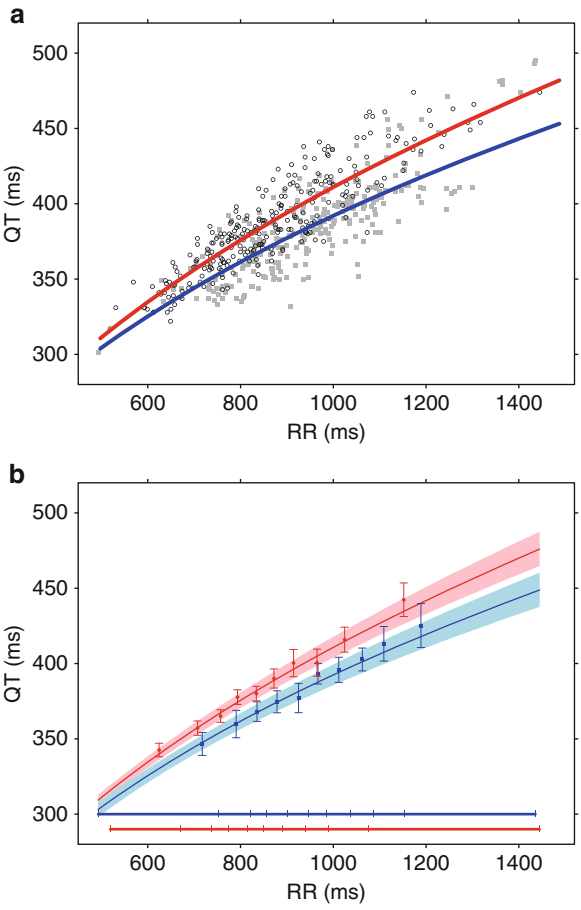

Fig. 16.2 Placebo QT vs. RR relationship. (*Top*) Observed placebo QT-RR for males (*gray squares*) and females (*black circles*) together with the mean predictions (males = *blue*, females = *red*). (*Bottom*) Mean (90% confidence interval) predicted QT-RR curves. The *dots* represent the observed median RR quantiles and associated mean (90% confidence interval) QT. RR quantile ranges for males (*blue*) and females (*red*) are shown along the *x*-axis

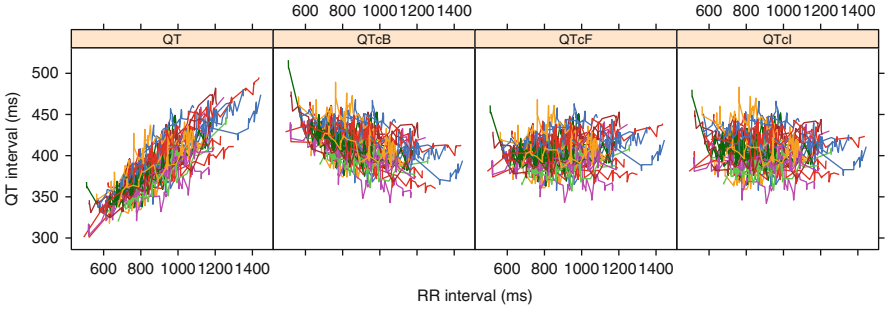

Fig. 16.3 Individual QT, QTcB, QTcF, and QTcI versus RR interval

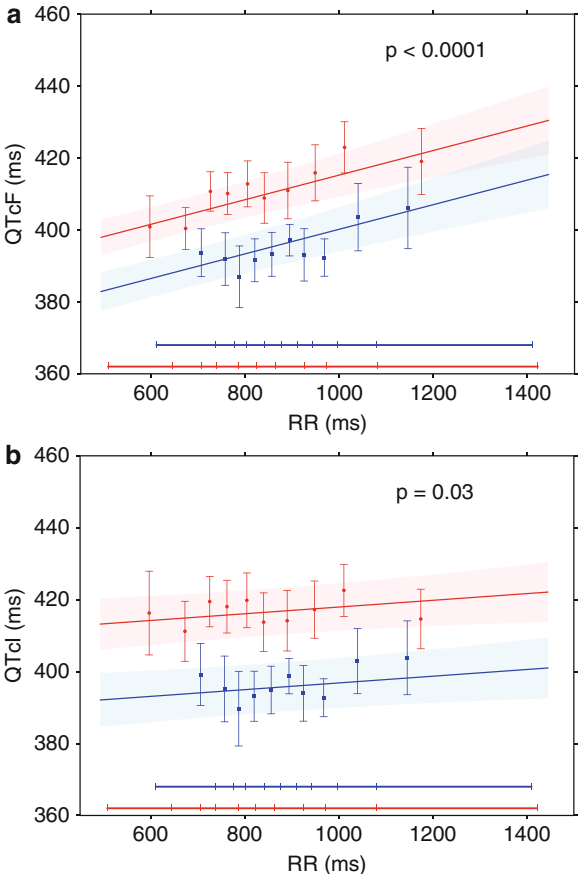

Fig. 16.4 Mean (90% confidence interval) predicted QTcF and QTcI versus RR relationship (*solid line* and *shaded area*) for male (*blue*) and female (*red*). The *dots* represent the observed median RR quantiles and associated mean (90% confidence interval) QT. RR quantile ranges for males (*blue*) and females (*red*) are shown along the *x*-axis

Table 16.2 Average sum of individual squared slopes for different QT-RR correction methods

α-QTcF (where QTcF is subset to α)	0.001816
α-QTcI (where QTcI is subset to α)	0.000448

$\alpha_x = 1{,}000/n\sum b_x(i)^2$, where $b_x(i)$ is the estimated slope for correction x

16.4.3 Adequacy of Sampling Times

The timing of ECG samples should be guided by the available information about the PK properties of the drug candidate and the QT effect should be characterized throughout the anticipated dosing interval (FDA 2005).

ECG and PK should be sampled frequently enough to ensure the peak drug concentration is captured and ECG recordings at time points around the maximum concentration time, t_{max} in case the peak effect on QT does not correspond to peak concentration. The sampling should be for at least 24 h post dose in case the cardiac

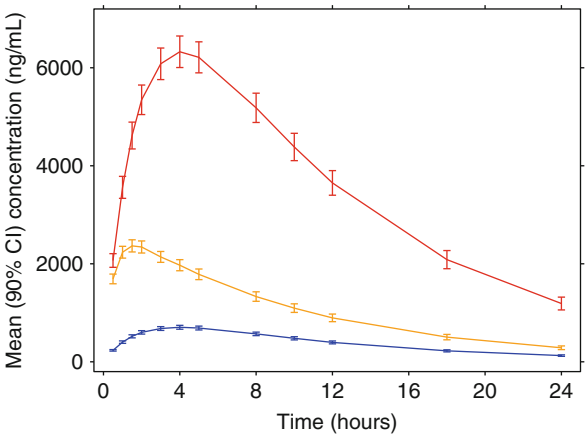

Fig. 16.5 Mean (90% confidence interval) concentration–time profiles following a therapeutic dose (*blue line*), supra-therapeutic dose (*red line*), and 400 mg moxifloxacin (*orange line*)

repolarisation effect is delayed. The PK concentration–time profiles for therapeutic, supra-therapeutic doses and the positive control moxifloxacin are shown in Fig. 16.5 with a t_{max} around 4 h for the test drug and around 2 h for moxifloxacin. The sampling is more frequent up until 5 h post dose to ensure the individual C_{max} (maximum concentration) is captured. The time-matched ECGs are sampled just prior to the PK sample to ensure that the venipuncture does not affect the ECG sample.

16.4.4 Baseline Correction

Baseline corrections are necessary in TQT studies due to the large inter-individual variability. For a crossover study design, baseline measurements before each period are used with the diurnal variability in QTc accounted for by each subject receiving all 4 treatments at exactly the same time points. In Fig. 16.6, the mean QTcI and ΔQTcI (change from baseline) are illustrated showing a clear separation of moxifloxacin and supra-therapeutic dose from placebo and the therapeutic dose. The diurnal variation in all treatment arms is clearly visible with peaks around 4 and 18 h post dose and nadirs around 12 and 24 h post dose. This variability can be a result of many factors including activity level, postural changes, circadian patterns, and food intake. Finally, it is noticed that all treatment arms return to baseline 24 h post dosing where the exposure of the drug is negligible (see Fig. 16.6).

16.4.5 Assay Sensitivity

The purpose of including a positive control is to ensure confidence in the ability of the TQT study to detect changes in the mean QT prolongation of around 5 ms

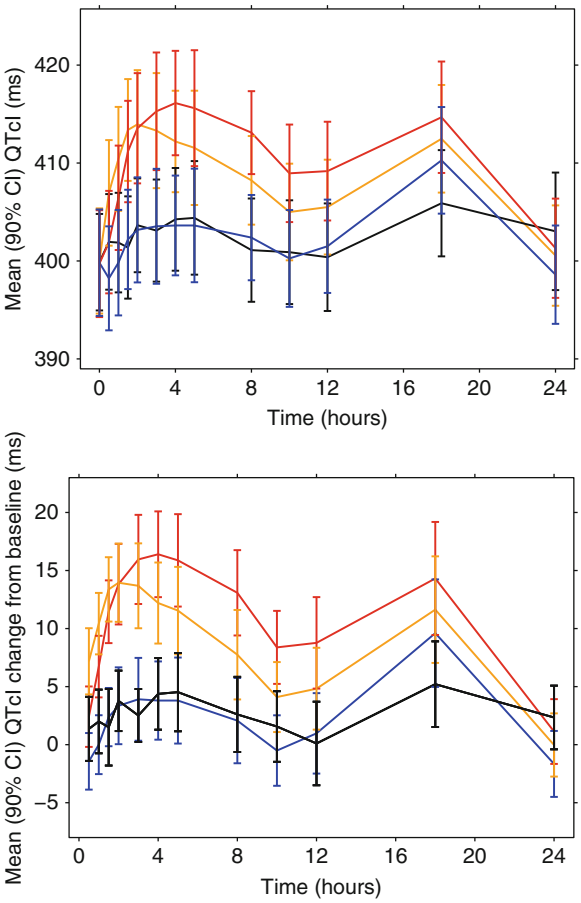

Fig. 16.6 Mean (90% confidence interval) (*top*) QTcI and (*bottom*) ΔQTcI (change from baseline) following placebo (*black line*), 400 mg moxifloxacin (*orange line*), therapeutic dose (*blue line*), and supra-therapeutic dose (*red line*)

(FDA 2005). Moxifloxacin (a fluoroquinolone used for respiratory infections) is the most commonly used positive control in TQT studies because it reliably prolongs the QT interval with no significant effect on heart rate and is considered relatively benign.

Assay sensitivity is established if at least one time point excludes a 5 ms difference in the mean ΔΔQTc (baseline and placebo adjusted) with a one-sided 95% confidence interval thereby preserving at least 50% of the previously reported ΔΔQTc effect of 10–14 ms following 400 mg moxifloxacin (Bloomfield et al. 2008). The shape of the ΔΔQTcI-time profile is shown in Fig. 16.7 with peak effect excluding 5 ms around 2–4 h post dose and return to baseline at 24 h post dose as expected (Florian et al. 2011). Similarly, the slope of the moxifloxacin concentration–QTc relationship shown in Fig. 16.7 can be used to confirm assay sensitivity in cases with reduced moxifloxacin exposure, e.g., due to over-encapsulation (Florian et al. 2011).

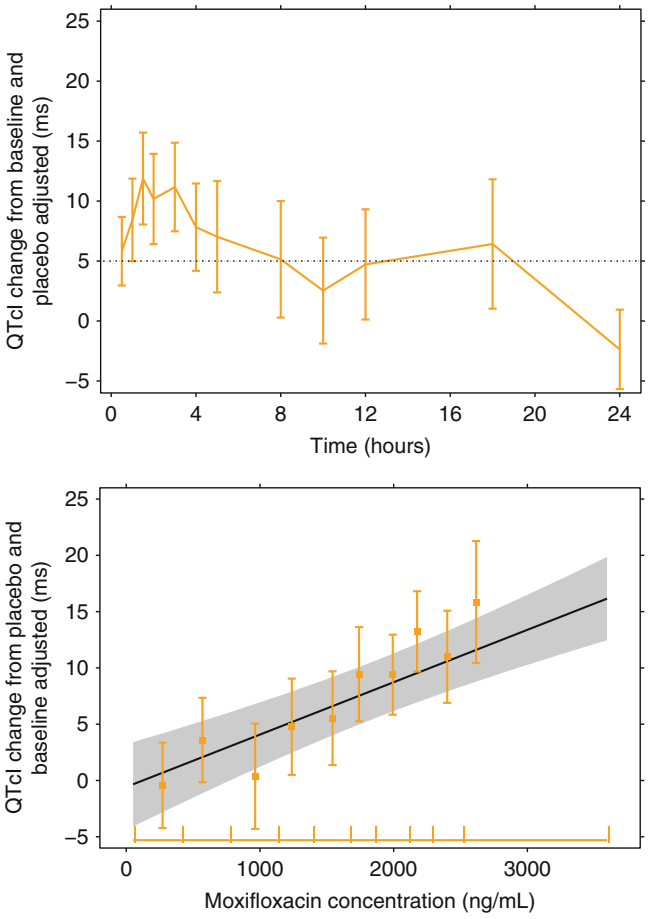

Fig. 16.7 (*Top*) Mean (90% confidence interval) ΔΔQTcI–time profile and (*bottom*) mean (90% confidence interval) moxifloxacin concentration–ΔΔQTcI observations (*dots*), and the estimated relationship (*solid black line* and *shaded gray area*) following 400 mg moxifloxacin with the moxifloxacin concentration quantile range is shown along the *x*-axis

16.4.6 Measure of Central Tendency

The FDA E14 guidance (FDA 2005) sets the threshold of regulatory concern for the drug candidate around 5 ms evidenced by an upper bound of the one-sided 95% confidence interval around the mean ΔΔQTc (time-matched difference in baseline and placebo adjusted QTc) excluding 10 ms. The TQT study is considered to be negative if the mean excludes 10 ms at all time points. In Fig. 16.8, the therapeutic treatment arm clearly excludes 10 ms at all time points whereas the upper 95% confidence interval includes 10 ms between 1.5 and 18 h post dose for the supra-therapeutic treatment arm.

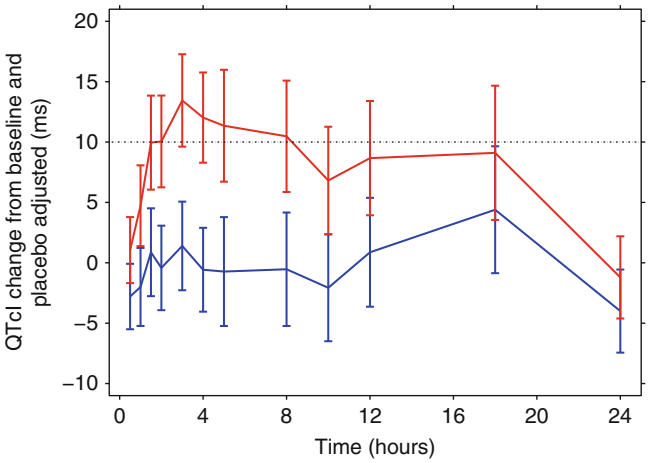

Fig. 16.8 Mean (90% confidence interval) ΔΔQTcI (baseline and placebo adjusted) following a therapeutic (*blue line*) and supra-therapeutic (*red line*) dose

16.4.7 Assessing Delay Between Drug and QT Effects

Before investigating the potential relationship between drug exposure and QT effect, it is important to assess whether there is a temporal delay between drug concentrations and ΔΔQTc. This could potentially indicate that an active metabolite is causing the QT prolongation, and it often requires more advanced modeling to account for the delay if the metabolite is not measured directly. Due to the inter-individual variability in PK and QT, the individual QTc versus drug concentration is expected to show very different slopes (positive and negative) and potentially also hysteresis (the effect on QT lags the change in concentration). Instead, the mean concentrations at each sampling time are plotted against the corresponding mean (90% confidence interval) ΔΔQTcI and connected in chronological order in Fig. 16.9. The slope for the therapeutic and supra-therapeutic treatment arms appear similar and there does not appear to be any clear sign of hysteresis except for the last 2 sampling times at 18 and 24 h post dose. A linear exposure-response model therefore seems adequate to assess the relationship between drug concentration and ΔΔQTcI.

16.4.8 Relationship Between Drug Exposure and QT Prolongation

An adequate TQT study should ensure that the dose- and exposure-response relationship for QT prolongation has been characterized at concentrations covering the worst case clinical exposure scenario in order to support regulatory review (Garnett et al. 2008).

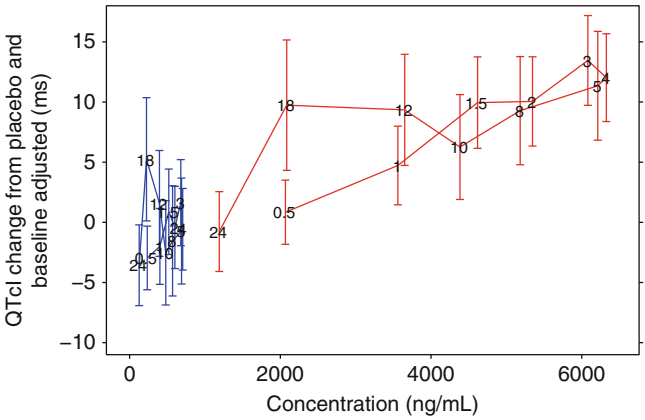

Fig. 16.9 Mean (90% confidence interval) ΔΔQTcI following a therapeutic (*blue line*) and supra-therapeutic dose (*red line*) connected in chronological order with the numbers representing the sampling time

It is important to understand the relationship between drug exposure and QT prolongation when (1) the primary E14 analysis is positive, (2) it is not possible to test doses high enough to cover the worst case clinical exposure scenario, or (3) when the TQT study is positive based on the E14 analysis but there is lack of dose- and exposure-response (Garnett et al. 2008, 2011).

The relationship between drug concentration and ΔΔQTcI is shown in Fig. 16.10 with a clear linear dependency, and the relationship appears similar for therapeutic and supra-therapeutic exposures.

The individually estimated linear mixed-effects regression lines are furthermore shown in Fig. 16.11 (top) to assess whether the relationship between concentration and ΔΔQTcI is more or less pronounced compared to the population mean predictions. All subjects have a positive slope very similar to the estimated population slope while there is some variability in the intercept. The residuals are shown in Fig. 16.11 (bottom) to see whether there are outliers or subjects that are poorly fitted by the linear mixed-effects model.

16.4.9 Prediction of QT Prolongation at Different Exposure Levels

The ΔΔQTc predictions at the geometric mean peak concentration following therapeutic and supra-therapeutic doses are assessed and compared to the primary E14 analysis. Figure 16.11 (top) shows the mean (90% confidence interval) ΔΔQTcI of 0.00 (−2.50; 2.51) and 12.5 (9.49; 15.5) ms at geometric mean peak concentrations of 691 and 6,230 ng/mL, respectively. These predictions based on the concentration–ΔΔQTcI relationship are consistent with the primary E14 analysis mean

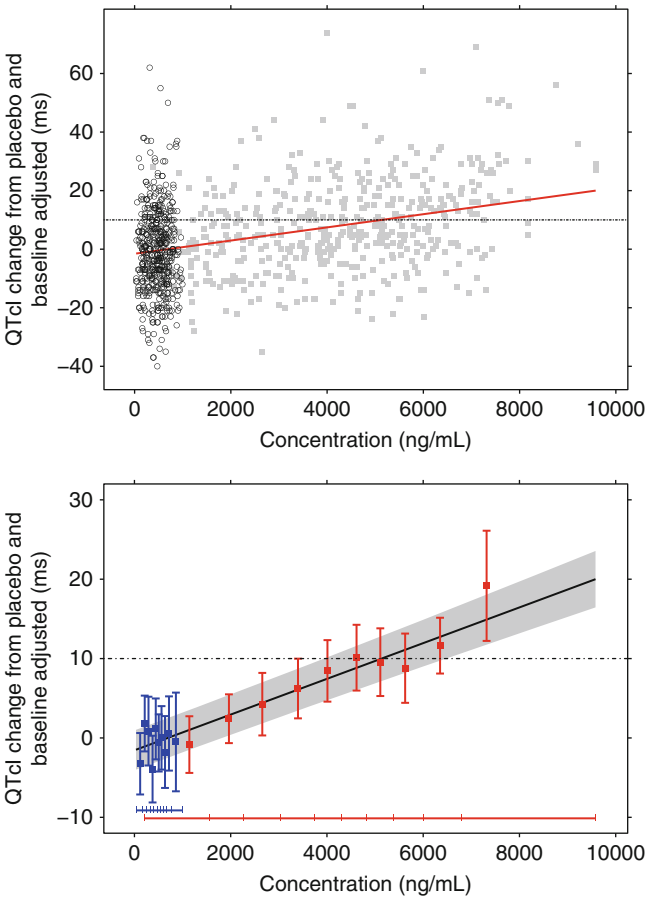

Fig. 16.10 ΔΔQTcI versus drug concentration. (*Top*) Observed data with population mean predictions (*solid red line*) and (*bottom*) observed concentration quantile–ΔΔQTcI plot with population mean and 90% confidence interval (*solid black line* with *shaded gray area*). The drug concentration quantiles following therapeutic (*circles*) and supra-therapeutic (*squares*) doses are shown as *horizontal bars* along the *x*-axis and the 10 ms threshold is shown as a *dotted line*

(90% confidence interval) estimates of 4.39 (−0.86; 9.65) and 13.4 (9.62; 17.3) ms at 18 h and 3 h post therapeutic and supra-therapeutic doses, respectively.

16.4.10 Benefit-Risk Assessment

The concentration–QTc relationship is used to perform the benefit-risk assessment for drugs that prolong the QT interval. The first question to ask is whether the supra-therapeutic dose covers the highest expected clinical exposure scenario. This is done by adding the fold-change in C_{max} and AUC for identified intrinsic and extrinsic

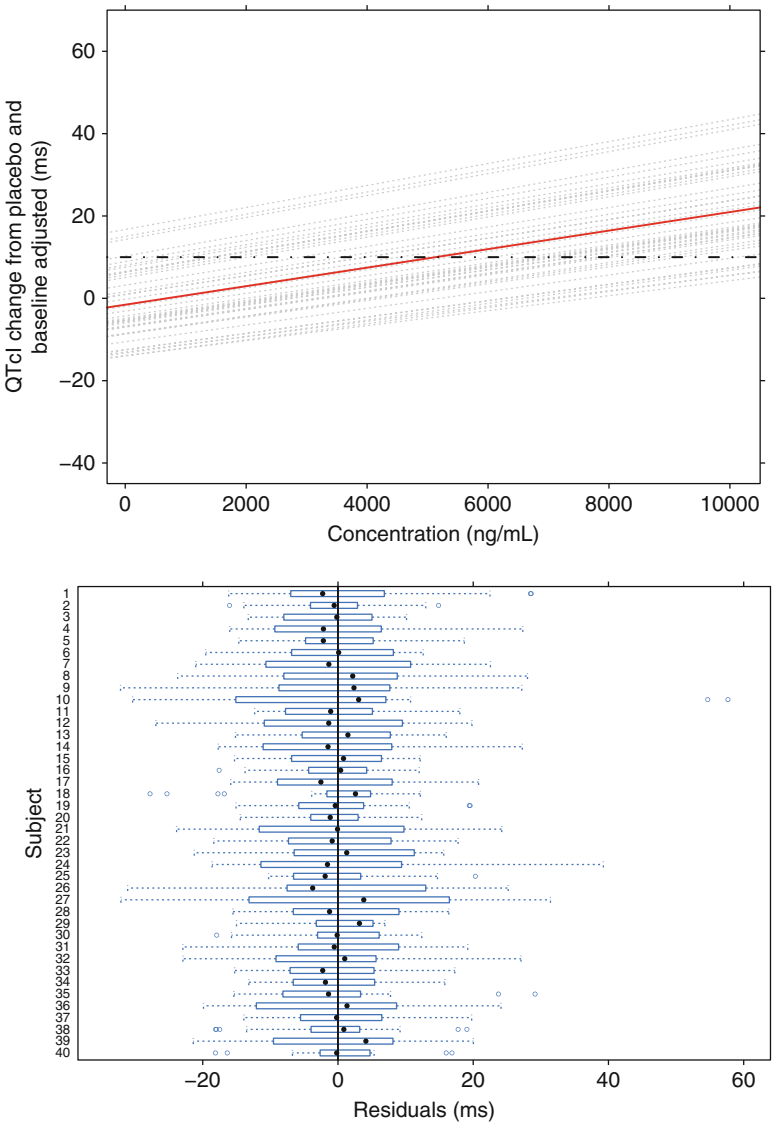

Fig. 16.11 Comparison of individual and population prediction linear mixed-effects regression lines (*top*). Box-plots of residuals for each subject (*bottom*)

factors (e.g., gender, race, organ impairment, drug–drug interactions, or food effects). This way the QT risk in subpopulations can be assessed and appropriate dose adjustments and ECG monitoring can be derived in order to write informative drug labels.

For the example shown in Fig. 16.12 (bottom), the geometric mean peak supra-therapeutic exposure shown in red is 9-fold higher than the therapeutic exposure

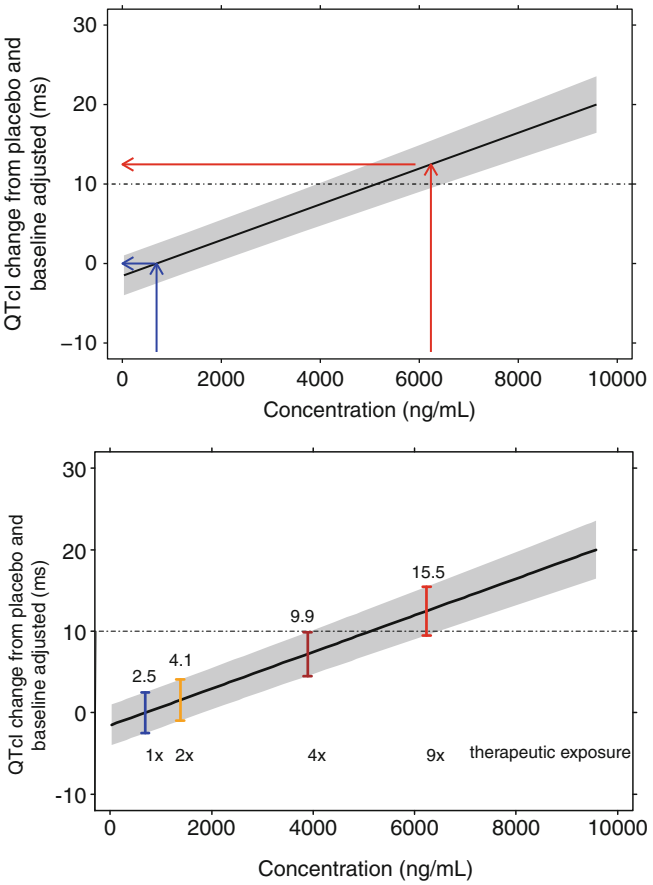

Fig. 16.12 (*Top*) Predicted ΔΔQTcI at the geometric mean peak drug concentrations following therapeutic (*blue*) and supra-therapeutic (*red*) doses. (*Bottom*) Predicted ΔΔQTcI at different multiples of therapeutic exposures

shown in blue and clearly prolongs the mean QT interval by more than 10 ms. However, if the worst case clinical exposure scenario is between 2- and 4-fold, there does not appear a high risk of QT prolongation.

16.5 Concluding Remarks

The purpose of creating a QT knowledge management system was to automate QT data analyses and reporting for consistent and timely review of TQT studies. Furthermore, the developed graphics and reporting standards allow for easier communication (internally and externally) of results.

An important aspect of QT data analyses is to explore the adequacy of the model assumptions (e.g., heart rate QT correction, baseline adjustments, choice of positive control to establish assay sensitivity, linear or nonlinear concentration–QTc relationship, and direct or delayed effects) through model diagnostics and graphical analyses.

The system furthermore enables leveraging prior information to answer drug development related questions through pooled data analysis since the data and results are in a consistent format that easily can be combined. Contributions to improve the science include (1) the use of concentration–QT modeling for regulatory review of new drugs (Garnett et al. 2008) and (2) evaluating TQT study design features on moxifloxacin response (Florian et al. 2011).

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