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A Bayesian Approach for Investigating the Risk of QT Prolongation

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Abstract

The standard approach to investigating a drug for its potential for QT prolongation is to construct a 90% two-sided (or a 95% one-sided) confidence interval (CI), for the difference in baseline corrected mean QTc (heart-rate corrected version of QT) between drug and placebo at each time-point, and to conclude non-inferiority if the upper limit for each CI is less than a pre-specified constant. An alternative approach is to base the non-inferiority inference on the largest difference in population mean QTc (baseline corrected) between drug and placebo. In this paper, we propose a Bayesian approach to resolving this problem using a Monte Carlo simulation method. We use simulated data to assess the performance of the proposed approach, discuss its advantages over the standard approach, and illustrate the method by applying it to a real data set obtained from a thorough QT study conducted at GlaxoSmithKline (GSK).

Keywords

Bayesian inference; ICH E14; Monte Carlo simulation; QT/QTc interval; thorough QT/QTc study

1 Introduction

An undesirable property associated with some non-antiarrhythmic drugs is their ability to delay cardiac repolarization, more generally known as QT prolongation. The QT interval is a segment of the surface electrocardiogram (ECG) and represents the duration of ventricular depolarization and subsequent repolarization, and is measured from the beginning of the QRS complex to the end of the T wave. QT values are correlated with heart rate and hence a corrected version (QTc) is used for data analysis (see International Conference of Harmonization (ICH) E14 guidelines, available at www.fda.gov/cder/guidance/). The ICH E14 guidelines recommend conducting a ‘thorough QT/QTc study’ to determine whether the drug has a threshold pharmacological effect on cardiac repolarization, as detected by QTc prolongation. The study is typically carried out in healthy volunteers (as opposed to individuals at increased risk of arrhythmias) and is used to determine whether or not the effect of a drug on the QTc interval in target patient populations should be studied intensively during later stages of drug development.

The standard approach to investigating a drug for its potential for QT prolongation is to construct a 90% two-sided (or a 95% one-sided) confidence interval (CI), for the difference in mean QTc between drug and placebo at each time-point, and to conclude non-inferiority if the upper limits for all these CIs are less than a pre-specified constant. Usually, a positive control that is known to have an increasing effect on the QTc interval is included to assess the sensitivity of the study in detecting the QT effects. If the positive control demonstrates an effect as compared to the placebo, then the assay is considered reasonably sensitive to detection of QTc prolongation. Under the standard normality assumptions, the standard approach corresponds to both intersection-union test and the likelihood ratio test but is conservative and biased (Patterson and Jones, 2005). However, this approach is conceptually simple to understand and easy to implement, and being conservative it goes well with the regulatory agencies. But, by the same virtue this approach is very stringent and may result into a high false positive rate. Hence, the industry needs a better approach and this drives the quest for new methodologies that check the false positive rates while safeguarding the interests of the consumers and regulatory agencies.

The ICH E14 guidelines defines a negative ‘thorough QT/QTc study’ as the 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. This definition is chosen to provide reasonable assurance that the mean effect of the study drug on the QTc interval is not greater than 5 ms. When the largest time-matched mean difference exceeds the threshold, the study is termed positive. Hence, an alternative approach is to base the non-inferiority inference on the largest difference in population mean QTc between drug and placebo. Constructing an interval estimate for the maximum difference however is a non-trivial task. Since the current FDA guidelines for QT studies were put in place in November 2005 there has not been much research done in this area until recently.

Recent attempts to address this area include articles by Eaton et al. (2006) and Boos et al. (2007). The method proposed by Eaton et al. (2006) involves constructing asymptotic confidence interval for the parameter of maximum difference by approximating it with a smooth function and then using the ‘delta method’ to obtain an approximate confidence interval. Boos et al. (2007) proposed new bounds for the maximum difference, which are based on analytical and bootstrap methods. The first upper bound that they propose can be obtained analytically and uses an expression for the approximate moments of the maximum of random variables. Their second upper bound is based on a parametric bootstrap, bias-corrected percentile method, whereas their third upper bound is based on a non-parametric bootstrap, bias-corrected percentile method. Their methods, however, rely heavily on the large sample theory and asymptotic approximations and hence may not be satisfactory when the sample sizes are small and/or when the number of time points at which QTc is measured is large.

A good approach to analyzing a thorough QT study would be one that protects the interests of both the industry and the consumers, and keeps in line with the ICH guidance. In this paper, we propose a Bayesian approach to obtaining an interval estimate for the maximum time-matched mean difference. We provide a thorough description of the Bayesian framework for analyzing QTc prolongation in Section 2. In Section 3, we use simulated data to assess the appropriateness of this approach as compared to the standard method. In Section 4, we apply the proposed method to a real data set on QTc obtained from a thorough QT study conducted at GlaxoSmithKline (GSK). We compare the results with those obtained from the standard method. We present a short conclusion in Section 5 and finally, in Section 6, we present some discussions of the future research in this area.

2 A Bayesian framework for parallel QTc study

Suppose, in a parallel QTc study, n_1 and n_2 denote the number of subjects receiving drug and control (placebo) respectively, with baseline corrected QTc measurements calculated at p time points. We denote the vector of p measurements taken on the subjects on drug by $\mathbf{x}_i$, $i = 1, \dots, n_1$, and those on control by $\mathbf{y}_j$, $j = 1, \dots, n_2$, respectively. The measurements are assumed to be distributed identically and independently (*iid*), arising from two independent p -variate normal distributions (denoted by $\mathcal{N}_p$), and can be represented as follows:

$$\begin{aligned} \mathbf{x}_i &\stackrel{iid}{\sim} \mathcal{N}_p(\boldsymbol{\mu}_1, \boldsymbol{\Sigma}), \quad i=1, \dots, n_1 \text{ and} \\ \mathbf{y}_j &\stackrel{iid}{\sim} \mathcal{N}_p(\boldsymbol{\mu}_2, \boldsymbol{\Sigma}), \quad j=1, \dots, n_2, \end{aligned} \quad (2.1)$$

where $\boldsymbol{\mu}_1$ and $\boldsymbol{\mu}_2$ are the population means for the drug and the control groups, respectively, and we make no assumptions about the structure of the unknown common covariance matrix $\boldsymbol{\Sigma}$. Let $\boldsymbol{\delta} = \boldsymbol{\mu}_1 - \boldsymbol{\mu}_2$ be the vector of differences in mean QTc between drug and control. Then the parameter of interest which is the maximum difference between the two groups is denoted by

$$\theta = \max_{1 \leq k \leq p} \delta_k \equiv \max_{1 \leq k \leq p} (\mu_{1k} - \mu_{2k}). \quad (2.2)$$

The goal of a QT study is to obtain an interval estimate of θ . Notice that θ is a non-differentiable function of $\boldsymbol{\mu}_1$ and $\boldsymbol{\mu}_2$ and hence we can not use the delta-method (Casella and Berger, 2002, p.245) based on the maximum likelihood estimate (MLE) $\hat{\boldsymbol{\mu}}_1 = \bar{\mathbf{x}}$ and $\hat{\boldsymbol{\mu}}_2 = \bar{\mathbf{y}}$, where $\bar{\mathbf{x}} = \sum_i \mathbf{x}_i / n_1$ and $\bar{\mathbf{y}} = \sum_j \mathbf{y}_j / n_2$ denote the sample means. It is well known that $\hat{\boldsymbol{\delta}} = \hat{\boldsymbol{\mu}}_1 - \hat{\boldsymbol{\mu}}_2$ is the MLE of $\boldsymbol{\delta}$ and $\mathbf{S} = (\sum_{i=1}^{n_1} (\mathbf{x}_i - \bar{\mathbf{x}})(\mathbf{x}_i - \bar{\mathbf{x}})^t + \sum_{j=1}^{n_2} (\mathbf{y}_j - \bar{\mathbf{y}})(\mathbf{y}_j - \bar{\mathbf{y}})^t) / (n_1 + n_2)$ is the MLE of $\boldsymbol{\Sigma}$.

In order to obtain the posterior distribution of θ we first derive a class of conjugate priors for $\boldsymbol{\mu}_1, \boldsymbol{\mu}_2$ and $\boldsymbol{\Sigma}$, and then derive the posterior distribution of θ from the closed form posterior distribution of $\boldsymbol{\mu}_1, \boldsymbol{\mu}_2$ and $\boldsymbol{\Sigma}$. It is easy to verify that the following class of prior distributions is conjugate for the two-sample problem (Box and Tiao, 1973, chap.8),

$$\begin{aligned} \mu_1 | \boldsymbol{\Sigma} &\sim \mathcal{N}_p(\boldsymbol{\mu}_{10}, \frac{1}{n_{10}} \boldsymbol{\Sigma}), \\ \mu_2 | \boldsymbol{\Sigma} &\sim \mathcal{N}_p(\boldsymbol{\mu}_{20}, \frac{1}{n_{20}} \boldsymbol{\Sigma}) \quad \text{and} \\ \boldsymbol{\Sigma}^{-1} &\sim \mathcal{W}_p(a_0, \mathbf{B}_0), \end{aligned} \quad (2.3)$$

where $\mathcal{W}_p$ denotes a p -dimensional Wishart distribution with degrees of freedom a_0 and scale matrix $\mathbf{B}_0$ (Anderson, 1984, p.245). The tuning parameters n_{10} and n_{20} can be thought of as strength of belief in the prior means $\boldsymbol{\mu}_{10}$ and $\boldsymbol{\mu}_{20}$ in the sense that one's belief is essentially "equivalent" to having observed n_{10} observations $\mathbf{X}_i$ and n_{20} observations $\mathbf{Y}_j$. In the absence of prior information we can use the reference prior (Bernardo, 1979) which turns out to be the Jeffreys prior given by

$$\pi(\boldsymbol{\mu}_1, \boldsymbol{\mu}_2, \boldsymbol{\Sigma}) \propto |\boldsymbol{\Sigma}|^{-(p+1)/2}. \quad (2.4)$$

Notice that the Jeffreys prior (2.4) can be obtained as a limiting case of the conjugate prior (Geisser and Cornfield, 1963) described in (2.3) by setting $\boldsymbol{\mu}_{k0} = 0$ and letting $a_0 \rightarrow 0$ and $n_{k0} \rightarrow 0$ for $k = 1, 2$.

Thus, it is enough to obtain the posterior density of θ under the conjugate prior (2.3) and then take suitable limits to obtain the posterior distribution under the Jeffreys prior (2.4). By conjugacy it follows that the joint posterior distribution of μ_1, μ_2 and Σ is given by

$$\begin{aligned} \mu_1 | \Sigma, X, Y &\sim \mathcal{N}_p\left(\frac{n_{10}\mu_{10}+n_1\bar{x}}{n_{10}+n_1}, \frac{1}{n_{10}+n_1}\Sigma\right), \\ \mu_2 | \Sigma, X, Y &\sim \mathcal{N}_p\left(\frac{n_{20}\mu_{20}+n_2\bar{y}}{n_{20}+n_2}, \frac{1}{n_{20}+n_2}\Sigma\right) \text{ and} \\ \Sigma^{-1} | X, Y &\sim \mathcal{W}_p(a_0+n_1+n_2, B), \end{aligned} \quad (2.5)$$

where $B^{-1} = B_0^{-1} + (n_1+n_2)S + \frac{n_{10}n_1}{n_{10}+n_1}(\bar{x}-\mu_{10})(\bar{x}-\mu_{10})^t + \frac{n_{20}n_2}{n_{20}+n_2}(\bar{y}-\mu_{20})(\bar{y}-\mu_{20})^t$ and X and Y denote the list of observed x_i 's and y_j 's, respectively. Although (2.5) provides a closed form posterior distribution of (μ_1, μ_2, Σ) , and hence a multivariate t-type distribution for δ , it is almost impossible to obtain the posterior distribution of θ analytically. So, we develop a simple Monte Carlo sampling scheme to obtain iid samples from the (marginal) posterior distribution of θ given X and Y as follows.

MC algorithm to obtain iid samples from $\theta|X, Y$

For $l = 1, 2, \dots$ generate

step 1: $A^{(l)} | X, Y \sim \mathcal{W}_p(a_0+n_1+n_2, B)$, and set $\Sigma^{(l)} = A^{-1(l)}$,

step 2: $\mu_1^{(l)} \sim \mathcal{N}_p\left(\frac{n_{10}\mu_{10}+n_1\bar{x}}{n_{10}+n_1}, \frac{1}{n_{10}+n_1}\Sigma^{(l)}\right)$,

step 3: $\mu_2^{(l)} \sim \mathcal{N}_p\left(\frac{n_{20}\mu_{20}+n_2\bar{y}}{n_{20}+n_2}, \frac{1}{n_{20}+n_2}\Sigma^{(l)}\right)$, and

step 4: compute $\theta^{(l)} = \max_{1 \leq k \leq p} (\mu_1^{(l)} - \mu_2^{(l)})$.

It follows easily that $\theta^{(l)}$'s are iid samples from the posterior distribution of θ given X and Y . Thus, we can compute any desired posterior summary as an estimate of θ using the set of Monte Carlo (MC) samples $\theta^{(l)} : l = 1, 2, \dots$. In particular, we compute the upper 95th percentile for the posterior density of θ as a 95% one-sided upper interval estimate for θ for our QT data. We compute it based on the MC samples $\{\theta^{(l)} : l = 1, \dots, N\}$, where the MC sample size N is chosen so that the overall MC error is less than some pre-assigned value $\epsilon > 0$. In particular, a choice of $N > 4V(\hat{\theta})/\epsilon^2$, where $V(\hat{\theta})$ is an estimate of the variance of $\hat{\theta}$, ensures that the estimated mean of θ is within $\pm\epsilon$ of θ with 95% probability. The main advantage of an MC sampling over the widely used Monte Carlo Markov Chain (MCMC) sampling is that one does not have worry about running a chain long enough to ensure convergence of, say, a Gibbs sampler. Moreover, the MC standard error (MCSE) can be obtained in a straightforward manner by computing the standard error of the MC samples $\{\theta^{(l)} : l = 1, \dots, N\}$.

3 Simulation studies

We conducted a Monte Carlo simulation study to assess the coverage properties of our proposed approach for different combinations of the operating characteristics drivers, namely, n_1, n_2, σ , and ρ , where we assume that the true $\Sigma = \sigma^2[\rho I + (1-\rho)\mathbf{1}\mathbf{1}^t]$ for our illustration. Notice that our proposed method does not require Σ to have a specific correlation structure. For the purpose of simulations, we used a parallel study setup with $p = 6$, and true values of $\mu_1 = (400, 400, 400, 400, 400, 400)$ and $\delta = (1, 3, 5, 5, 3, 1)$. We vary $n = n_1 + n_2 \in \{60, 90, 120\}$, $n_1 = n_2 = n/2$, $\rho \in \{0.5, 0.9\}$ and $\sigma \in \{10, 12\}$. These operating

characteristics provide a $3 \times 2 \times 2$ experimental design and we compute the posterior upper 95% quantile for θ for all possible 12 combinations of the operating characteristics.

We used a class of normal conjugate priors for μ_1, μ_2 with the hyperparameters $\mu_{k0} = 0$, and tuning parameters $n_{k0} = 0.001$ for $k = 1, 2$, and a Wishart prior for Σ with the hyperparameters $a_0 = p+2$ and $B_0 = I$ to obtain the corresponding closed form posterior distribution and then derived the posterior distribution of θ using an MC algorithm. We used the algorithm outlined at the end of Section 2 to obtain *iid* samples from the posterior distribution of θ . To calculate posterior interval estimate, we generated $N = 5000$ samples from the posterior distribution using the algorithm described in the previous section, and computed the posterior upper 95th percentile for θ for the given combination of the operating characteristic parameters. We repeated this procedure 500 times to obtain an estimate of the coverage probability as the proportion of times the true value of the parameter $\theta (= 5)$ was included in the posterior upper 95% one-sided interval.

Table 1 summarizes the results of this simulation study. The results based on simulations indicate that the coverage of the posterior upper 95th percentile for θ for all the settings is over the desired 95%. The results appear slightly conservative although the observed patterns suggest that coverage approaches the nominal value with an increasing ρ and this remains largely unchanged for moderate fluctuations in n and σ .

We find that our approach performs quite well given the fact that we have not used a specified structure of the common covariance matrix Σ . If we use the true structure of the Σ , the coverage will get even closer to the nominal value (not reported here). However, in practice a specific parametric structure of the covariance may not be available and any such parametric assumption may increase the bias of the interval estimator of θ .

The coverage of the posterior upper 95th percentile is higher than desired for small values of ρ making it slightly conservative, but it is close to the desired value of 0.95 for reasonably large values of ρ . Since the p observations are taken on the same individual they are expected to have a moderate to high correlation depending on the length of the time intervals between the observations. Overall, we find that our Bayesian method seems to be working well for the most plausible range for the values of ρ that is expected to be between 0.5 to 0.9 (personal communication with a GSK scientist) among the time-points. A GSK conducted thorough QT study had the value of ρ over 0.8.

We also conducted a simulation study to compare our Bayesian method to the standard method for a few of the operating characteristics settings. To compare the two methods we looked at the errors rates for the two intervals, i.e., confidence level and accuracy, as described in Lehmann and Romano (2005, p.72). More specifically, if we denote by u_1 and u_2 the upper 95% interval estimates for θ using Bayesian and the standard methods respectively, then to compare accuracy, we empirically estimate $P[u_j \geq \theta^*]$, for $\theta^* > \theta = 5$ and $j = 1, 2$. A better interval is one that minimizes this probability. The reason is that in addition to having good coverage probability or confidence level, a good set estimator should overestimate the parameter by as little as possible. We compared the accuracy for $\theta^* = 8, 10, 12$. We calculated the nominal confidence levels for both the intervals by estimating $P[u_j > \theta = 5]$ for $j = 1, 2$. We performed the calculations for the configuration $n = 90$, $\sigma = 10$, $\rho = 0, 0.5, 0.9$.

Table 2 summarizes the results for these comparisons. It can be seen that both the intervals have nominal confidence levels greater than the desired 0.95, with the Bayesian interval slightly closer to 0.95 than the standard one for high correlations. Comparing the intervals for accuracy, we see that for all the three values of θ^* the Bayesian interval is superior to the standard one. Even in the case of independence when $\rho = 0$ the Bayesian intervals were

marginally more accurate than the standard ones. The comparison results were similar for other configurations of the operating characteristics. Thus, it is easy to see that for all the settings of the operating characteristic parameters the Bayesian method consistently outperforms the standard method.

4 Application to a thorough QT study

The primary end-point of interest in a QT study is usually the change from baseline in QTc values, where baseline is defined according to the study design, the dosing pattern and other study specific considerations.

In Table 3, we present the data schematics of a typical QT study. Multiple (usually triplicate) measurements are taken at baseline to provide a mean baseline measurement by averaging across the replicates. Usually, a positive control that is known to have an increasing effect on the QTc interval is also included to assess the sensitivity of the study in detecting the QT effects. If the positive control demonstrates an effect as compared to placebo, then the assay is considered reasonably sensitive to detection of QTc prolongation.

The data used in this paper were obtained from a GSK conducted thorough QT study with placebo, a positive control (Moxifloxacin), and multiple drug concentration arms for the study drug, with QTc (Bazett) measurements taken at baseline (mean of triplicates) and multiple time-points ($p = 10$). Although the actual study design was crossover, only data from a single period of the entire dataset were used and only data on placebo and the positive control arm (called drug henceforth) were included to mimic a parallel study design, with 36 subjects in each arm, for the purpose of illustration. The end-point of interest was change from baseline QTc values and the parameter of interest was maximum time-matched mean difference between drug and placebo for baseline corrected QTc.

The primary aim of this research was to obtain an interval estimate of θ using a Bayesian approach. We used a class of normal conjugate priors for μ_1, μ_2 , with the hyperparameters $\mu_{k0} = 0$, and tuning coefficients $n_{k0} = 0.001$ for $k = 1, 2$, and a wishart prior for Σ^{-1} , with the hyperparameters $a_0 = p+2$ and $B_0 = I$, to obtain the corresponding closed form posterior distribution and then derived the posterior distribution of θ based on it. To obtain an interval estimate for θ , we generated $N = 10000$ samples from the posterior distribution of θ and calculated the upper 95th percentile that came out to be 22.37. Figure 1 presents a plot for the histogram of MC samples and posterior density of θ using a kernel density estimate based on $N = 10000$ MC samples and a bandwidth of 0.3482.

We compared our results to those obtained by using the standard method. The standard method based on a mixed effect model with drug, time-point and drug by time-point interaction as fixed effects, and subject nested in drug as a random effect (confidence intervals calculated at each time-point), yielded the largest 90% two-sided upper confidence limit to be 22.98. It should be noted that a 90% two-sided upper confidence interval is equivalent to a 95% one-sided upper confidence interval under the standard normality assumptions. A comparatively simpler model with drug as the only factor with the confidence intervals calculated at each time-point, yielded the largest 90% two-sided upper confidence limit to be 22.36.

Figure 2 presents the 90% two-sided CIs at each time-point for the baseline corrected difference between drug and placebo as contrasted with an upper bound for θ using the Bayesian method. It is easy to see that for the given data, the standard method appears to be slightly more conservative as compared to the Bayesian method.

5 Conclusions

The Bayesian methodology that we have proposed in this paper is a novel approach, aimed at resolving the important problem arising in the assessment of the risk of QT prolongation in thorough QT studies. The standard method to address this problem has been criticized for being overly conservative and the Bayesian method appears to be more accurate for plausible values of correlations between timepoints, thereby decreasing the sponsor's risk of failing the 'thorough QT/QTc study' while adequately controlling for the chances of a false favorable result. It is free from rather restrictive large sample assumptions, easy to implement and can be used efficiently to make inferences about a thorough QT study. Finally, the entire posterior density of θ (see Figure 1) can be well approximated to any desired level of accuracy instead of a point estimate and the standard error of the estimate.

6 Discussion and future research

A Bayesian approach appears to be a promising alternative to the standard approach for analyzing a 'thorough QT/QTc Study.' It goes with the spirit of the ICH guidelines that advocate making inferences based on an interval estimate of θ , and is free of the use of results from the large sample theory. A natural extension to this work will be to assess the feasibility of a Bayesian approach and its implementation for crossover designs or a more general regression model with more study specific factors.

A cautious reader may question our selection of priors for this approach. We selected conjugate priors for simplicity, with extremely small values of n_{10} and n_{20} so as to draw very little information from the priors. We did not find the posterior intervals to be sensitive to slight modifications of the priors in our simulation studies. Though we did not explore it in this research, it would be interesting to study extensively how the posterior density of θ changes with changes to the prior parameters elicited from historical data. It would also be of interest to study in greater details how our Bayesian method compares with other recently proposed methods based on a direct interval estimation of θ that claim to be superior to the standard method.

Finally, the model in (2.1) assumes a common Σ for both arms (i.e., for both drug and placebo groups). Within our Bayesian framework, we can relax this assumption and allow different Σ_1 and Σ_2 for drug and placebo groups, respectively. The inference will proceed

with the priors, $\Sigma_1^{-1}, \Sigma_2^{-1} \stackrel{iid}{\sim} \mathcal{W}_p(a_0, B_0)$. The three-step MC sampling algorithm described in Section 2 can be extended to obtain MC samples from the posterior distribution of θ . Although we have not explored such possibilities, the extensions appear to be quite straightforward.

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Figure 1.
Histogram and kernel density estimate obtained from 10000 MC samples from the posterior density of θ based on the GSK data.

Figure 2. 90% two-sided CIs at each time-point for the baseline corrected difference between drug and placebo as contrasted with an upper bound for θ using the Bayesian method for the GSK data.

Table 1Coverage of the Bayesian upper 95% interval for θ

n	σ	$\rho = 0.5$	$\rho = 0.9$
60	10	1.00	0.98
	12	1.00	0.97
90	10	1.00	0.97
	12	0.99	0.97
120	10	0.99	0.97
	12	1.00	0.97

Table 2

Comparison of Bayesian and standard intervals for $n = 90$, $\sigma = 10$

Confidence Level		Accuracy ⁺			
ρ	Bayes	Std	θ^*	Bayes	Std
0	1.00	1.00	8	0.96	0.97
			10	0.54	0.64
			12	0.09	0.18
0.5	1.00	1.00	8	0.83	0.87
			10	0.39	0.49
			12	0.06	0.11
0.9	0.97	0.98	8	0.67	0.76
			10	0.31	0.38
			12	0.04	0.09

⁺ A smaller value indicates higher accuracy

Table 3

Data schematics of a typical QT study.

Subject	Time (Hrs)	1	2	3		24
1	Baseline QTc	X1	X2	X3		X24
1	Post-Dose (Drug)	Y1	Y2	Y3		Y24
1	Change from baseline (Drug)	Y1-X1	Y2-X2	Y3-X3		Y24-X24
2	Baseline QTc	X1	X2	X3		X24
2	Post-Dose (Placebo)	Y1	Y2	Y3		Y24
2	Change from baseline (Placebo)	Y1-X1	Y2-X2	Y3-X3		Y24-X24