

USE OF BASELINE ECGs IN THE EVALUATION OF THOROUGH-QT STUDIES WITH CROSSOVER DESIGN

Patricia Glomb, Dr. Arne Ring, Boehringer Ingelheim Pharma GmbH & Co. KG, Germany



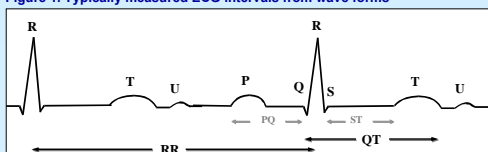
Introduction

In clinical development thorough QT/QTc (TQT) studies are performed to show that new investigational drugs do not change the cardiac repolarisation.

According to ICH E14, it shall be shown that the "largest time-matched mean difference between drug and placebo (baseline adjusted)" over the collection period does not exceed the limit of 10 ms.

Using the data of 3 crossover studies, we have investigated the statistical efficiency and cost effectiveness of 4 typical baseline designs based on the **standard error** of the QTc endpoints.

Figure 1. Typically measured ECG intervals from wave forms



Study Designs

Performance of Baseline Measurements

Many crossover TQT studies with 4 periods (active control, placebo and two doses of test drug) follow one of the following designs:

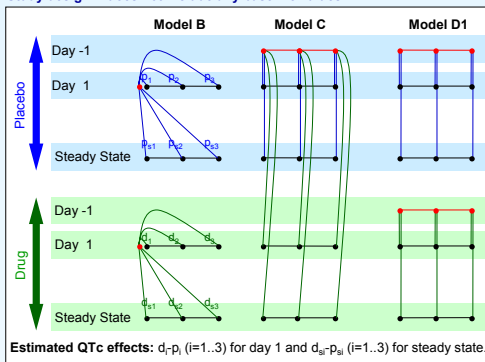
- A **No baseline values**, only the absolute difference between placebo and drug is evaluated;
- B One **pre-dose** value before the first dosing of each period;
- C One **separate** baseline profile before the begin of study;
- D One baseline profile before **each** crossover period.

Analysis of Baseline Measurements

For each of these 4 designs, the QTc effect was analysed using repeated measurements models. The schemes of these analyses are shown in Figure 2.

- A Absolute QTc interval;
- B Change from pre-dose baseline;
- C Time-matched change from separate baseline profile;
- D Change from period specific baseline
 1. time-matched baseline
 2. mean of baseline.

Figure 2. Estimation of QTc effect for the baseline designs B, C, and D. Scenarios are schematically shown for a cross-over-study with 2 periods and 3 time-points. The lines represent the relationship between time-point(s) at baseline (•) and time-points on day 1 / day of steady state (•). Design D.2 corresponds to Model B with • as mean of baseline day -1. Study design A does not include any baseline values.

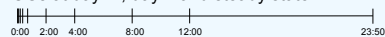


Data

Data from 3 TQT studies with design D were used to simulate designs A-C. For the evaluation, data of the positive control were removed and population or individual heart rate corrections were used for QTc.

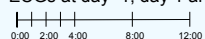
Multiple dose study for 12 days (n=53, inhaled drug q.d.)

➤ ECGs at day -1, day 1 and steady state



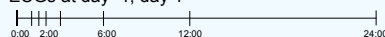
Multiple dose study for 3 days (n=79, oral drug b.i.d.)

➤ ECGs at day -1, day 1 and steady state



Single dose study (n=40, oral drug q.d.)

➤ ECGs at day -1, day 1



References

[1] Heilmann G. *The Statistical Analysis of Thorough QTc Studies*, Heidelberg, GMDS Workshop 2005

[2] Rieck M. *Baseline Adjustment in Central Tendency Analyses of QTc: Inefficient for Cross-over Designs?* Washington, DIA Cardiac Safety Conference 2007

Statistical Model

A statistical model for **repeated measurements analyses** of QTc intervals is given by (similar to [3, 4]):

$$y_{ijklm} = \mu + B_{ijk} + S_l + P_j + T_k + D_m + TD_{km} + TP_{jk} + \eta_l(S_l) + \varepsilon_{ijklm}$$

where for subject i , period j , time k and sequence l and dose m

y QTc measurements	S sequence effect	TD time-by-drug-interaction
μ grand mean	P period effect	TP time-by-period-interaction
ε residual variability	T time effect	$\eta(S)$ random subject-nested-in-sequence effect
B baseline effect	D drug effect	

The above equation models **baseline design D1** (one baseline profile before each period). For **baseline designs D2 and B** (one baseline value in each period) $B_{ijk}=B_{ij}$, while for **design C** (one separate baseline profile), $B_{ijk}=B_{ik}$. In **design A** (no baseline values), B_{ijk} is removed from the model.

Results

As the circadian rhythm changes slowly over time, how useful is a full baseline profile?

- Due to the changing circadian rhythm, some **auto-correlation of QTc parameters** over time can be found, which decreases with increasing time between baseline and on-treatment values.
- In consequence, the **variability of QTc endpoints increases up to 45% at steady state compared to day 1 (Figure 4)**.
- For different baseline designs the change of SE, compared to the SE resulting in design D1, of the Pbo-corrected QTc effects was calculated (Figure 5).

Circadian Rhythm of QTc Intervals

Individual rhythms of QTc measurements can be observed. These are somewhat stable, but change slowly over time.

Figure 3. Circadian change of a subject in study 3 (In this study no QTc effect was shown).

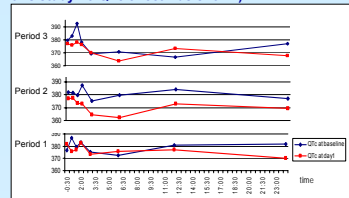


Figure 4. Increase in variability of QTc endpoint in design D1 at steady state relative to day 1.

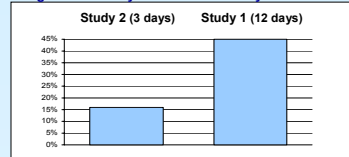
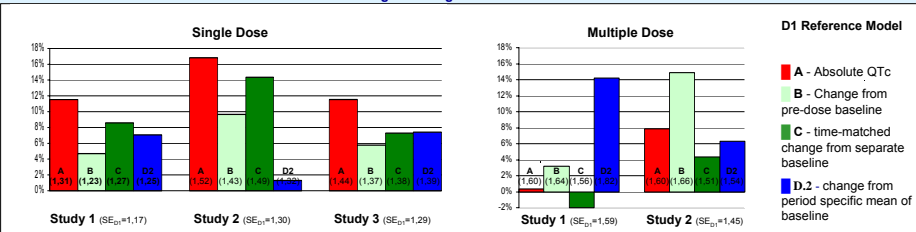


Figure 5. Increase in standard error of placebo corrected QTc effect estimations when using the baseline designs A, B, C, or D2, respectively, instead of D1. For each design the average standard errors, proportional to the average standard error resulting in design D1, are shown. The absolute standard errors and the reference values from design D1 are given in brackets.



Discussion

- In the recent past the use of baselines has been controversially discussed [1, 2]. Whereas the **rather large variability** of QTc endpoints was taken into consideration, the **circadian rhythm** of the endpoints and their potential correlation between subsequent days have often been neglected.
- As the circadian rhythm is slowly changing over time, **baseline profiles provide additional, but limited information**.
- Based on the estimated standard errors in the 3 studies, the **sample size** for achieving a power of 90% of concluding non-inferiority was calculated for each baseline strategy (Figure 6a); using the underlying assumptions (ICH E14):
 - one-sided test significance limit $\alpha=0.05$
 - upper equivalence limit $\delta=+10ms$
 - "true" difference $\Delta=+2ms$
 - (accounts for the "bias" due to the selection of the largest confidence limit)

Figure 6a. Sample sizes required for different baseline designs (cf. main text for assumptions).

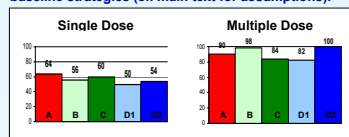
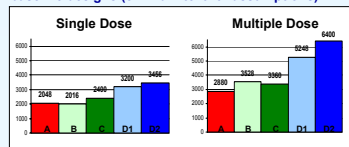


Figure 6b. Number of ECGs resulting for different baseline designs (cf. main text for assumptions).



- In **single dose studies**, the sample sizes are lowest for design D1 – hence the statistically most efficient design of a TQT study contains a full baseline day in each period. Thus, this design is recommended if the number of subjects is critical.
- Using the estimated sample sizes, the overall **number of ECGs** in a new TQT trial were determined as a measure of **costs** (Figure 6b), assuming an ECG profile with 8 on-treatment recordings.
- For **single dose studies**, the number of ECGs to be recorded is lowest in design B – hence the **most cost effective** TQTs design contains **one pre-dose baseline value in each period**.
- For **multiple dose studies**, the designs A-C require a similar number of ECGs, while design D cannot be recommended.

Conclusion

Based on the data of 3 clinical studies the following recommendations can be made:

- If feasible, **single dose studies provide more efficiency** in performance than studies which need to reach PK steady state.
- For single dose studies, the design D1 (full baseline day) was statistically most efficient and leads to the smallest sample size. However, designs A-C are more cost efficient for both single dose and multiple dose trials.
- For a final decision on the choice of baseline design, the variability of the endpoint is the most important, but not the only issue for consideration (e.g. change of heart rate by trial drug, PK-QTc evaluation [5]).

[3] Huttmacher MM, Chapel SC, Agin AA, Fleishaker JC, Lalonde RL: *Performance Characteristics for Some Typical QT Study Designs Under the ICH E14 Guidance*. Journal of Clinical Pharmacology 2008;48:215-224

[4] Patterson SD, Jones B, Zariffa, N. *Modeling and Interpreting QTc Prolongation in Pharmacology Studies*. Drug Information Journal 2005;39:437-445

[5] Li JJ, Birmingham BK, Sager P, Mosqueda-Garcia R. *Time-matched baseline versus pre-dose baseline for modeling ΔQTc-DCR*. White paper, <http://informa-ls.com/igt>.