Introduction

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

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.

Results

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

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 level α=0.05
- upper equivalence limit S=110ms
- "true" difference Δ=20ms
- (accounts for the bias due to the selection of the largest confidence limit)

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.

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).

References