Statistical evaluation of QT/QTc prolongation and proarrhythmic potential for non-antiarrhythmic drugs

Christos Stylianou

CLINBAY - 30 rue Bon Air; B-1470 Genappe Belgium - christos@clinbay.com - www.clinbay.com

Introduction
Delay in cardiac repolarization may trigger potentially life-threatening tordrse de pointes arrhythmias. The QT/QTc interval is used as indicator for the duration of cardiac repolarization. As a result thorough clinical QT/QTc evaluation is mandated by the ICH E14 guideline to support marketing authorization and labeling information for non-antiarrhythmic drugs.

Study design
Crossover design:
- Require smaller number of subjects than parallel
- Four period crossover design can be used to compare two dosing schemes (therapeutic and supra-therapeutic), positive control (assay sensitivity) and control (placebo).
- Williams design can be used (Figure 1)

Parallel design:
- Can be used for drugs with long elimination half-lives or other carryover effects
- Up-titration from therapeutic to supra-therapeutic doses is a possibility for the investigational product
- The below design can be used (Table 1)

Analysis of assay sensitivity
Hypothesis:

H0: \( \mu_{\text{Moxifloxacin}(t)} = \mu_{\text{Placebo}(t)} \)

H1: \( \mu_{\text{Moxifloxacin}(t)} \neq \mu_{\text{Placebo}(t)} \)

\( \mu_{\text{Moxifloxacin}(t)} \) and \( \mu_{\text{Placebo}(t)} \) are the mean change from baseline of QTcF respectively at timepoint t. If any of the p-values is less than 0.0125 (Bonferroni correction) then assay-sensitivity is claimed.

Assay Sensitivity in Crossover Studies
Statistical methods:
- Paired t-test on dQTc
- Mixed model on dQTc suitable for crossover design
- or one-sample t-test on dQTc

Crossover studies allow the calculation of dQTc which is the difference Treatment-placebo for change from baseline in QTc

Analysis of one historical study
- dQTc was analyzed using paired-test (Table 2)
- All the one-sided p-values were below the significance level of 0.0125

Sample size calculation
- Minimum effect size observed: \( d = 1.17 \)
- Figure 3 illustrates sample size for assay sensitivity in a cross-over

Conclusion
- Crossover is somewhat more efficient than parallel designs for assay
- The two-sided t-test on change from baseline in QTc
- All p-values were below the 0.0125

Sample size
- Minimum effect size for change from Time-matched baseline: \( d = 1.1 \)
- Minimum effect size for change from Mean baseline: \( d = 1.28 \)
- Figure 4 illustrates power needed for the two respective baselines

Analysis of Historical study
- Study was analyzed using paired-test (Table 3)
- All p-values where below the 0.0125

Conclusion – Assay sensitivity
- Crossover is somewhat more efficient than parallel designs for assay sensitivity
  - If crossover study design is chosen 25 subjects are needed to reach 90% power for Assay sensitivity.
  - If parallel is considered, a total of 30 subjects are required under Moxifloxacin + Placebo to reach a comparable power for assay sensitivity.
- For parallel studies:
  - Additional subjects are required for the study drug but an unbalanced randomization can be used.
  - From one historical trial, mean baseline appears to be more efficient than time-matched baseline, however ICH E14 recommends time-matched baseline to be used.

Useful graphical presentation
QTC analysis
All the two-sided 90% must not include values ±10ms. This procedure is conservative as the Type I error might be smaller than the intended 0.05 level (Zhang and Machtado, 2008)

PK/PD analysis
- Recommended by ICH E14 to assess relationship between change from baseline in QTcF and the investigated drug concentration in plasma.
- The two-sided 90% CI must be below 10ms

Other useful outputs
An outlier analysis is also recommended by the ICH E14

Table 4: Number and percentage of subjects meeting or exceeding clinical noteworthy QTcF interval changes (outlier analysis)

Reference list: