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 torsade 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)

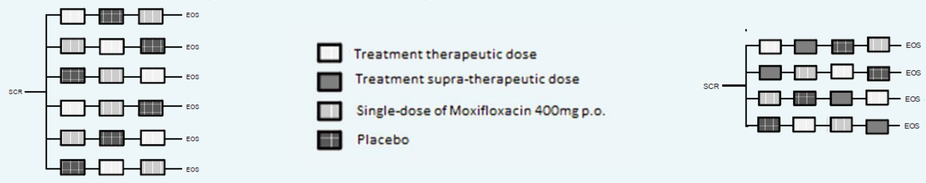

Figure 1: Williams design for 3 way (left) and 4 way (right) crossover studies.

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)

	Screening	Baseline	Part 1	Part (Optional)
Arm A	No drug	Placebo	Treatment therapeutic dose	Treatment Supra-therapeutic dose
Arm B	No drug	Placebo	Placebo	Placebo
Arm C	No drug	Placebo	Active control	Active control

Table 1: Design for parallel design study.

Assay sensitivity

- Assay sensitivity is suggested by ICH E14 to validate the study
- Positive control should have an effect on the mean QTc interval of about 5ms
- Positive control is Moxifloxacin.
- QTc assessments at 1, 2, 3 and 4h after a single 400mg dose.

Moxifloxacin

- Moxifloxacin is a commonly used positive control
- Figure 2 illustrates Pooled analysis of moxifloxacin-induced QTc effect
- Confidence interval at 1, 2, 3 and 4h is above 5ms

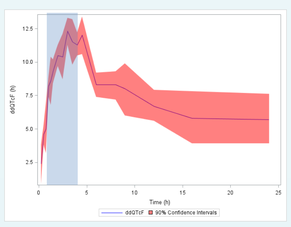

Figure 2: Pooled analysis of moxifloxacin-induced QTc effect by time. Data taken from Yan et al (2010)

Analysis of assay sensitivity

Hypothesis:

$$H_0^P : \cap\{(\mu^P_{Moxifloxacin(t_i)} - \mu_{placebo(t_i)}) \le 0\},\ i = 1,2,3,4 \text{ , versus}$$

$$H_1^P : \cup\{(\mu^P_{Moxifloxacin(t_i)} - \mu_{placebo(t_i)}) > 0\},\ i = 1,2,3,4$$

$\mu^P{}_{\text{Moxifloxacin}(t_i)}$ and $\mu_{\text{Placebo}(t_i)}$ are the mean change from baseline of QTcF respectively at timepoint t_i. 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 ddQTc

Crossover studies allow the calculation of ddQTc 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

Times	Mean ddQTc (sd)	P-value
1h	11.59 (9.84)	<0.001
2h	9.54 (7.34)	<0.001
3h	12.64 (7.37)	<0.001
4h	11.45 (7.45)	<0.001

Table 2: Analysis of a study using paired-test

Sample size calculation

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

Reference list:

-ICH E14 (2005) Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs; October.

-Yan LK, Zhang J, Ng MJ, et al, (2010) Statistical characteristics of moxifloxacin-induced QTc effect. J Biopharm Stat. May; 20(3):497-507.

-Zhang J, Machado S (2008). Statistical issues including design and sample size calculation in thorough QT/QTc studies. Journal of Biopharmaceutical Statistics; 18:451-467.

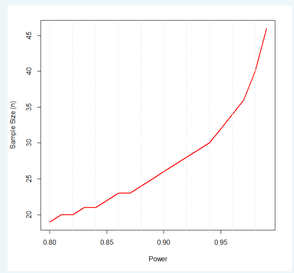

Figure 3: Power and sample size calculation for the minimum effect size observed in our study

Parallel design:

- One-sided two-sample t-test on change from baseline in QTc.
- Time-matched baseline (preferred) or mean baseline can be used.

Analysis of Historical study

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

Times	Mean difference (sd)	P-value
1h	11.77 (10.70)	<0.001
2h	11.49 (9.31)	<0.001
3h	12.62(9.81)	<0.001
4h	11.78(9.86)	<0.001

Table 2: Analysis of study using two sample t-test

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

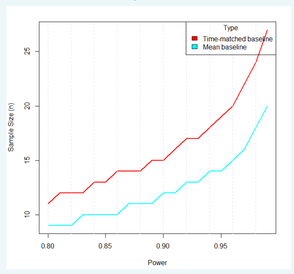

Figure 4: Power and per group sample size relationship for the Time-matched and mean baselines observed in our study

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.

Study drug

- Endpoint is change from baseline in QTc.
- Compared vs placebo using one-sided t-tests at the level of α=0.05.
- Upper bound of two-sided 90% CI must be lower than 10ms for all points
- Number of points varies between 7-10

Useful graphical presentation

QTc analysis

All the two-sided 90% must not include values ≥10ms. This procedure is conservative as the Type 1 error might be smaller than the intended 0.05 level (Zhang and Machado, 2008)

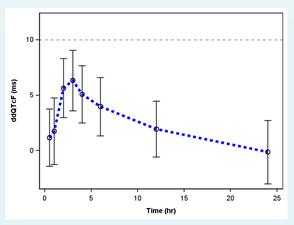

Figure 5: Estimated mean difference to Placebo and 90% CI for change from baseline in QTcF by time-point

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

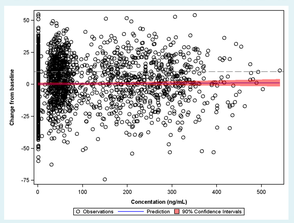

Figure 6: Concentration Response for change from time-matched baseline in QTcF (the predictions and their CI are pointwise not continues).

Other useful outputs

An outlier analysis is also recommended by the ICH E14

Variable		Moxifloxacin (N=92) n/m (%)	Placebo (N=92) n/m (%)	Investigated drug (N=92) n/m (%)	Total (N=276) n/m (%)
QTcF (ms)	Increase >30ms	**3 / 92 (5%)**	**1 / 92 (1%)**	0 / 92 (0%)	**2 / 276 (2%)**
	Increase >60ms	0 / 92 (0%)	0 / 92 (0%)	0 / 92 (0%)	0 / 276 (0%)
	New >450ms	**1 / 92 (2%)**	0 / 92 (0%)	0 / 92 (0%)	**1 / 276 (1%)**
	New >480ms	0 / 92 (0%)	0 / 92 (0%)	0 / 92 (0%)	0 / 276 (0%)
	New >500ms	0 / 92 (0%)	0 / 92 (0%)	0 / 92 (0%)	0 / 276 (0%)

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

Conclusion

- We recently analyzed several parallel and cross-over thorough QT trials.
- We have shared some insights on the statistical inference, PK/PD methods and presentation of key results.
- This experience will be useful to better design and power future thorough QT studies for our pharmaceutical partners.