Some properties of different analyses in "Thorough QT studies", compared using a QT study of Tiotropium

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Introduction

According to the ICH E14 guideline [1], so called Thorough QT studies are to be performed to show that new investigational drugs do not change the cardiac repolarisation. The QT interval is the key parameter to assess the risk of such changes, and the heart rate corrected QTc interval is the basis for a primary endpoint in such a study. We have investigated several analyses to assess the QTc, based on different models for the data structure in a recently performed QT study with Tiotropium.

Background of the example drug

Tiotropium (Spiriva®) is a long-acting inhaled anticholinergic for the maintenance treatment of COPD.

Data and Methods

Fifty-six healthy male and female subjects received a single oral dose of 400 mg moxifloxacin as a positive control known to induce a moderate increase of the QT interval, followed by a randomized and blinded three-way cross-over (twelve days in each period) of once daily inhalation of 18 µg tiotropium (therapeutic dose), 54 µg tiotropium (threefold therapeutic dose), and placebo, with washout-periods of at least three weeks. All subjects underwent extended ECG recording on the days preceding each treatment (days -1), and on the first and last day of each treatment period (days 1 and 12). 12-Lead ECG recordings were performed in triplicates before dosing and at 5, 10, 20 and 40 minutes as well as 1, 2, 3, 4, 8, 12 and 24 hours after dosing, and 4 wave forms have been measured from each ECG. The total number of ECGs in this trial was almost 19,000. The sample size in this trial was based on a power consideration of 90% for the primary analysis. The pre-specified primary endpoint was the change from baseline at day 12 from 5 minutes to 2 hours (the time of maximum systemic exposure), of QTcN, which is the QT interval length corrected for heart rate with using the baseline data of all four periods. The primary analysis was an ANCOVA of the primary endpoint with covariate baseline, fixed factors treatment, period and sequence and random factor subject. In addition, the time-matched change from baseline has been analysed, using

a) the ANCOVA for each time point separately and

b) a repeated measurements analysis as proposed by Patterson et al.[2], using different structures of the covariance matrix.

For both analyses, the maximum change from baseline at all time points is determined. Alternative endpoints (e.g. change from mean baseline or absolute QTcN intervals) have been investigated as well.

Results

The results of the primary analysis (change from baseline) are presented in Table 1. The highest upper bound of the 95% one sided confidence intervals of the placebo-adjusted difference from baseline were +4.9 ms for 18 µg tiotropium and +2.2 ms for 54 µg tiotropium and thus well below the predefined non-inferiority margin of 10 ms.

	Adjusted Mean				**Comparison to Placebo**			
Treatment	Mean [ms]	SE [ms]	90% LCL [ms]	90% UCL [ms]	Difference [ms]	SE [ms]	90% LCL [ms]	90% UCL [ms]
Placebo	-1.37	1.27	-3.47	0.73	-	-	-	-
Tiotropium 18 µg	0.55	1.31	-1.62	2.72	1.92	1.82	-1.08	4.93
Tiotropium 54 µg	-2.13	1.30	-4.28	0.01	-0.77	1.81	-3.76	2.23

Table 1 Adjusted means and confidence intervals for the mean QTcN change from baseline at day 12 between 5 minutes and 2 hours post drug administration.

At day 1, the results were similar. However, the standard error of the adjusted mean at day 1 was only about 0.8 ms. For Moxifloxacin the respective effect on day 1 was 8.4 ms, which is in the range expected for this compound and demonstrates the ability of the study to detect changes in the QT interval length, if present. The results of the additional analyses of the time-matched change from baseline are presented in Table 2, using the placebo adjusted comparison which led to the largest difference (Tiotropium 18 µg at day 12). The largest time matched change from baseline was in all analyses observed at the same time point.

Analysis type	Covariance structure	Number of covariance parameter	Calculation time	AIC	Difference [ms]	SE [ms]	90% UCL [ms]
BY	-	-	< 1 min	-	3.33	2.13	6.85
REPEATED	Compound symmetry	2	< 1 min	11865	2.39	1.72	5.23
REPEATED	Autoregressive	2	< 1 min	11870	2.20	1.60	4.83
REPEATED	Toeplitz	11	6 min	11730	2.33	1.71	5.15
REPEATED	Unstructured	65	4:15 h	11584	1.97	2.14	5.54

Table 2 Difference, standard error and upper limit of the 90%-confidence interval for the largest time-matched QTcN change from baseline at day 12 for the comparison of Tiotropium 18 µg to placebo.

Discussion

The primary endpoint – mean of QTcN within a time frame with systemic exposure of the investigational drug – was chosen based on the pharmacokinetic profile of this inhaled drug formulation. Its standard error in the primary analysis was considerably reduced compared to all analysis which compared the time-matched changes from baseline (Table 1). The fact that the standard error of the primary endpoint at day 12 was about 50% higher than at day 1 could be explained by the longer distance to the baseline day, so that the correlation has decreased over time. The time-matched analysis of the QTcN change from baseline at each time point does not use further assumptions but leads to a biased estimation of the effect size and to a larger standard error. The repeated measurements analyses reduce both the bias and the standard error. However, the structure of the covariance matrix may be of debate, and the results differ by up to 0.7 ms. Using the AIC as model selection criterion, the unstructured model was to be selected in this trial, maybe also due to the fact that the ECG recording schema had no equidistant time schedule. However, the program running time using this covariance structure was quite large (Table 2). A sensitivity analysis showed that the impact of the QT correction formulas on the analyses was low because there was no relevant change of the heart rates during the course of the trial.

Conclusions

Based on several statistical analyses in this Thorough QT study, therapeutic and threefold supratherapeutic doses of Tiotropium do not prolong the QT intervals. We propose an analysis strategy based on a primary endpoint as a pre-specified "mean within a time frame with systemic exposure" – in conjunction with a validation of the underlying assumptions within the study. In addition, a supportive secondary analysis using time-matched changes from baseline as proposed by the ICH E14 [1] should be provided. Such an analysis strategy supports a "big picture" view on the potential of the drug to prolong the QT interval.

References

[1] ICH Harmonized Tripartite Guideline. The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrythmic Potential for Non-Antiarrythmic Drugs E14, 12 May 2005.

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