Evaluation of QT Correction Methods and Gender Effect on QTc Intervals following Moxifloxacin Administration

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Abstract

ICH E14 requires a Thorough QT (TQT) study for most new compounds to assess for the potential to prolong QT/QTc intervals, which is associated with Torsade de Points (TdP). Females have longer QT intervals. TQT studies are conducted with two doses of the investigational drug, placebo and a positive control to assess assay sensitivity. Moxifloxacin 400 mg is the most commonly used positive control in TQT studies. Usually, several methods (Bazett, Friderica and study-specific) for correcting the QT intervals for heart rate (QTc) are used in the evaluation. In this work, we evaluate the relationship between QTc interval data (corrected for heart rate for different methods including Fridericia, Bazett and study specific) and RR using both pre dose and post dose data from placebo and moxifloxacin administration in several TQT studies conducted by Janssen R&D, to evaluate the selection of a primary correction method. We will also evaluate the gender effect on moxifloxacin response.

Key Words:

QT correction methods, QTc intervals, Gender effect, Moxifloxacin

1. Objective

i. To compare the selection of primary correction method using predose or postdose correlation between QTc and RR intervals.

ii. Evaluate the gender effect of moxifloxacin on QTc Intervals.

2. Datasets

Data sets from four thorough QT (TQT) trials were used for this analysis.

i. All studies were 4-way crossover with 4 periods and 4 treatments (Therapeutic dose, supra therapeutic dose, placebo and moxifloxacin 400 mg).
ii. The triplicate ECG data from 2 treatments moxifloxacin 400 mg and placebo were used for this analysis.
iii. Types of baseline measurements used for each study are given in Table 1.

Table 1: Baseline values

Study	Baseline
1	Time-matched: The values obtained at the corresponding time point on Day -1 of that period.
2	Time-matched: The values obtained at the corresponding time point on Day -1 of that period.
3	Predose: The average of the values obtained at 60 minutes, 30 minutes, and 10 minutes prior to dosing on Day 1 of the same period.
4	Predose: The average of the values obtained at 30, 20 and 10 minutes before dosing on Day 1 of each treatment period.

3. QTc correction methods

The 4 correction methods (Bazett, Fridericia, study-specific and individual) were evaluated for each study

For Study-specific and Individual correction;

I. Study 1 and 2 used linear regression fitted to data from predose and placebo days with QT and RR on original scale, because they were done prior to draft FDA guidance

II. Study 3 and 4 used mixed effects models of logQT vs. logRR. Only predose data from each period were used

3. Statistical methods

3.1 Selection of primary QTc correction

For the selection of primary correction method QTc vs. RR correlation was evaluated.

Does predose or postdose data make a difference?

I. Predose data: The final analysis of treatment comparison based on post dose data is not influenced by selection; any changes in RR due to drug have no influence.

II. Postdose data: Even if QT and RR uncorrelated at predose, the relationship may not be same at post dose and may want to select the method most suitable for postdose.

3.2 Gender effect

Gender effect was evaluated for Fridericia correction using Maximum and minimum difference in change from baseline ($\Delta\Delta$QTc) between moxifloxacin and placebo for female vs. male comparison from linear mixed effects models.

3. Results

3.1 Selection of primary QTc correction

Table 2: Correlation coefficient between QTc and RR intervals

Study	Correction method	Predose	Postdose
1	Fridericia	0.17	0.13
	Bazett	-0.30	-0.33
	Study-specific	0.09	0.06
	Individual	0.09	0.06
2	Fridericia	0.03	-0.09
	Bazett	-0.45	-0.50
	Study-specific	-0.09	-0.20
	Individual	-0.08	-0.19
3	Fridericia	0.06	0.05
	Bazett	-0.37	-0.40
	Study-specific	0.22	0.22
	Individual	0.21	0.22
4	Fridericia	0.06	0.15
	Bazett	-0.43	-0.31
	Study-specific	0.33	0.38
	Individual	0.35	0.41

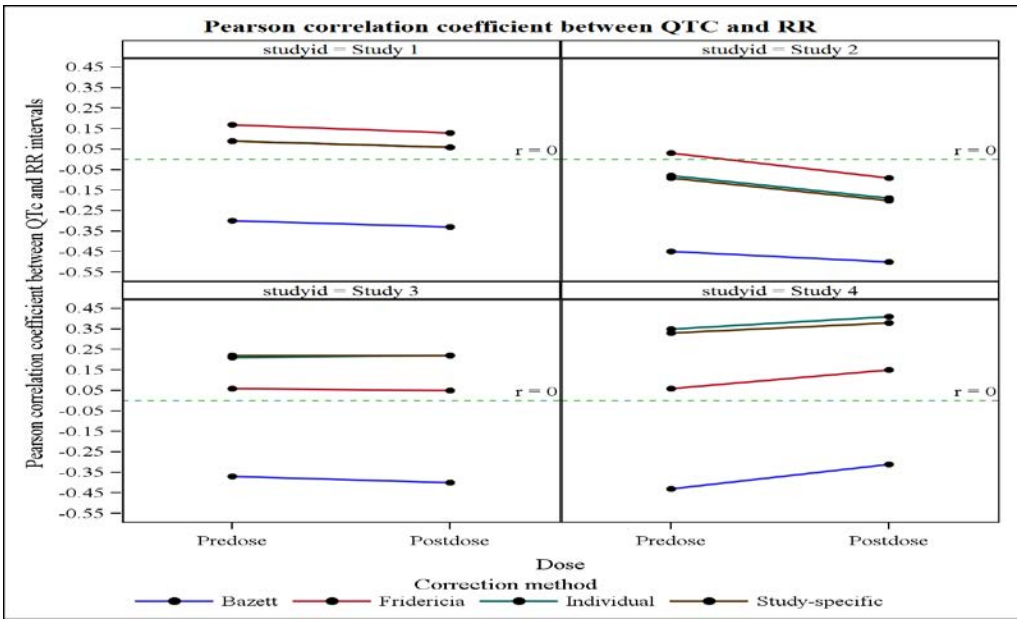

Figure 1: Correlation coefficient between QTC and RR

3.2 Gender effect

Table 2: Maximum LS mean ΔΔQTCF (90% CI) between moxifloxacin and placebo for females vs. male comparison

Study	Time point	p-value	Max diff (90%CI)
1	1h30min	0.014*	14.45 (4.74, 24.15)
2	4h	<0.0001*	17.94 (13.80, 22.08)
3	3h	<0.0001*	16.55 (13.48, 19.63)
4	3h	<0.0001*	16.40 (13.11, 19.69)

* Denotes significant at alpha = 0.05 level of significance.

Table 3: Minimum LS mean ΔΔQTCF (90% CI) between moxifloxacin and placebo for females vs. male comparison

Study	Time point	p-value	Min diff (90%CI)
1	1h	0.260	6.64 (-3.07, 16.35)
2	30min	0.167	3.47 (-0.67, 7.62)
3	30min	0.244	2.18 (-0.90, 5.25)
4	30min	0.003*	6.00 (2.71, 9.29)

* Denotes significant at alpha = 0.05 level of significance.

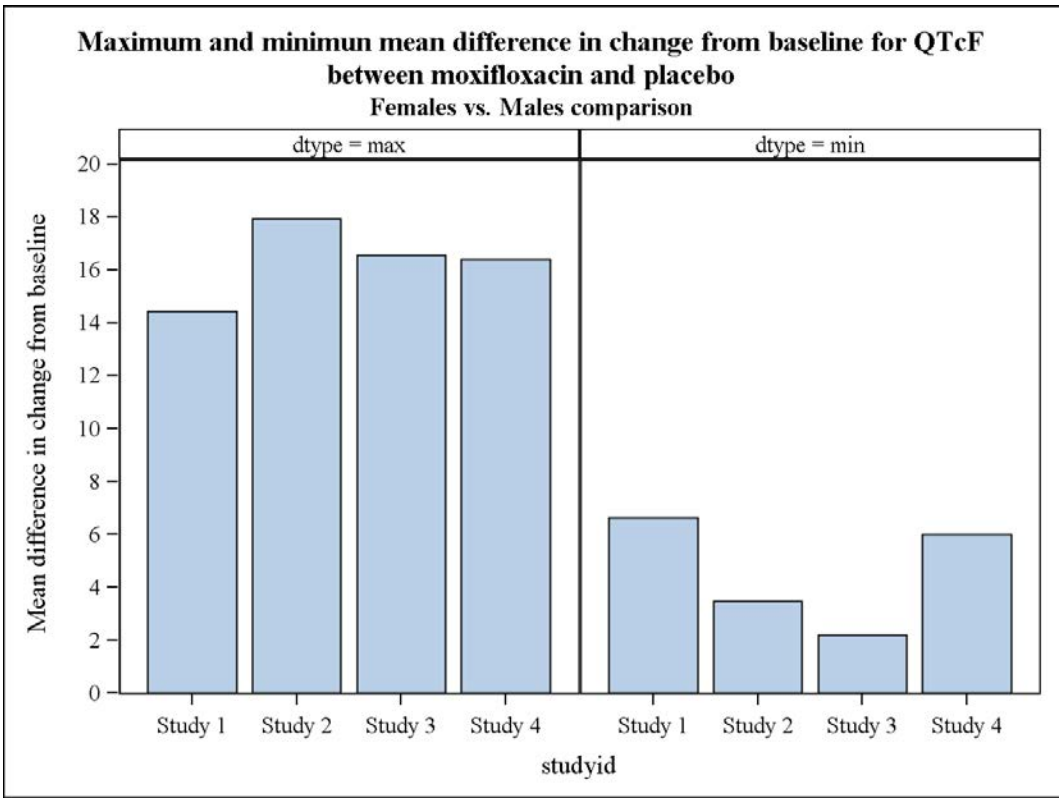

Figure 2: Maximum and minimum mean ΔΔQTCF for females vs. male comparison

4. Summary of results

4.1 Selection of primary QTc correction

i. It is not easy to distinguish whether predose or postdose data should be used for selection of primary correction, since both of them are similar for each study.

ii. Note that none of the studies mentioned here had a significant effect on RR.

4.2 Gender effect

i. The maximum mean difference for females vs. males comparison was significant for each study and ranged from 14.45 to 17.94 msec.

ii. The minimum mean difference for females vs. males comparison was significant only for study 4 and ranged from 2.18 to 6.64 msec.

iii. None of the studies mentioned here were designed or powered to test gender effect.

References

ICH E14 Guideline: The clinical evaluation of QT/QTc interval prolongation and proarrythmic potential for non-antiarrhythmic drugs.