An Evaluation of Detection Sensitivity and Pharmacokinetic Profile for Conscious Telemetered Cynomolgus Monkeys

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Poster #: 022
Category: Animal Cardiovascular Telemetry, Q&A E14/S7B

Background

E14/S7B Q&As guideline outlined the best practice considerations for non-clinical in vivo QT studies. Assay sensitivity of relevant functional endpoints, the analysis of QTc interval together with adequate pharmacokinetic sampling, and the independence of QTc to RR intervals through QTc versus RR plots were encouraged. These provide high-quality preclinical data for an integrated nonclinical and clinical risk assessment, and support a possible waiver for a TQT study[1-3].

Objectives

Average sensitivities for the Latin-square design (4 × 4) with telemetered cynomolgus monkeys were calculated for ECG (QT, QTcI, PR, and QRS intervals) parameters. The effects of Moxifloxacin were studied in monkeys. Pharmacokinetic data were generated together with the monitoring of cardiovascular changes in order to compare effects relative to human exposure.

Methods

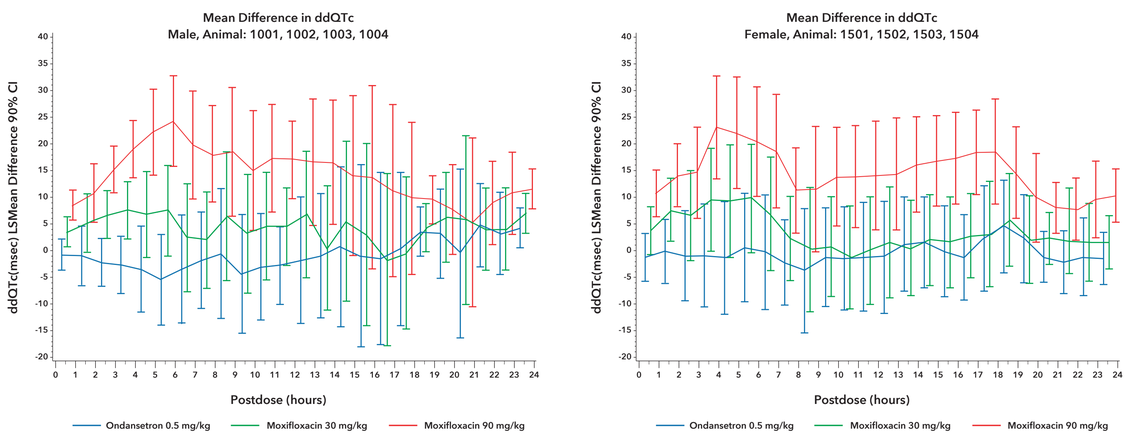
In the validated study, eight conscious telemetered monkeys received with controls, Ondansetron (0.5 mg/kg/dose), Moxifloxacin (30 mg/kg/dose) and Moxifloxacin (90 mg/kg/dose) by oral gavage in a 4 × 4 Latin-Square manner with a 5-days washout period from dose 1 to dose 4. Blood samples were collected from the monkeys at 90 mg/kg/dose at approximately 0, 0.5, 1, 2, 4, 6 and 8, 24 h post-dose in dose 5 after the completion of dose 4 for determination of Moxifloxacin plasma concentrations. ECG data were collected for at least 60 min prior to dosing (predose baseline) and continuously for at least 24 h post-dose. Reported timepoints were the average of 1-hour collections. The QTc (QTc = QT – β × (RR-500) was calculated for each 1 minute mean with individual QT correction based on QT-RR relationship on each dosing days. Based on the values change from predose, the output of the Waller-Duncan K-ratio t Test is the minimum significant difference (MSD)[4] at 80% power with SAS 9.4 software. To verify the effectiveness of correction, predose (the average over 2 hours) and postdose (the average over 1 hour) of the data will be used to generate scatter plots of QT vs RR and QTc vs RR for all animals at all dose levels. These plots will include a calculation of the 95% confidence intervals and slopes for the control data[5]. The statistical analysis of least-squares mean changes in the QTcI from baseline for each treatment. For each treatment versus control were conducted using the two-sided 90% confidence interval for the estimated ddQTc at each postdose time point and a 10 msec bound[6].

Results

Table 1 Average Study Sensitivities (MSD based on 80% power) for Male and Female Monkeys

	Male		Female	
Parameter	MSD mean(min-max)	95%CI	MSD mean(min-max)	95%CI
QT(msec)	11.7(3.8-22.7)	9.8-13.7	21.7(6.7-39.6)	17.5-25.8
QTcI(msec)	6.2(1.8-11.7)	5.0-7.5	5.4(2.8-7.7)	4.9-6.0
PR(msec)	4.3(1.9-9.5)	3.6-5.0	6.5(2.9-11.4)	5.5-7.5
QRS(msec)	2.2(0.9-4.1)	1.9-2.6	1.4(0.3-2.8)	1.2-1.7
HR(msec)	13.2(9.1-22.6)	11.6-14.7	21.3(6.7-34.6)	18.3-24.4

Figure 3 ΔΔQTc (LSMean±90 % CI) is determined after dosing with a single-dose of Ondansetron 0.5 mg/kg, Moxifloxacin 30 mg/kg and 90 mg/kg for male and female Monkeys



The peak ΔΔQTc were within the range of 23 ms to 24 ms. The mean peak ΔΔQTc were observed between 4 and 6 h post-dose and thereafter declined.

The study provided an average sensitivity to detect a 6.2 msec and 5.4 msec QTc change in male and female monkeys, respectively. This indicated that a less than 10 msec sensitivity was achieved in the 4X4 Latin square cardiovascular study design.

Moxifloxacin induced a dose dependent increase in QTc interval. A maximum increase of 24 ms was observed following administration of 90 mg/kg Moxifloxacin. Interrogation of the PK–QTc relationship indicated a direct relationship between the systemic exposure of Moxifloxacin and increased QTc.

Figure 2 QTc versus RR plots and QT versus RR plots for male and female monkeys

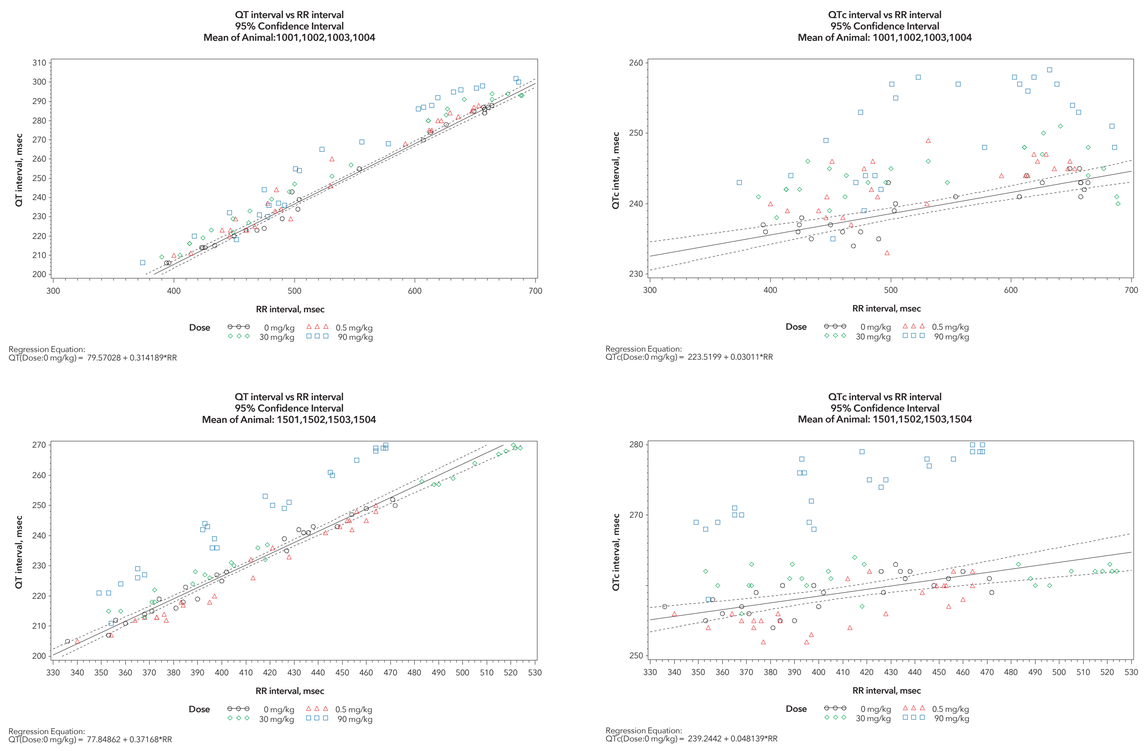
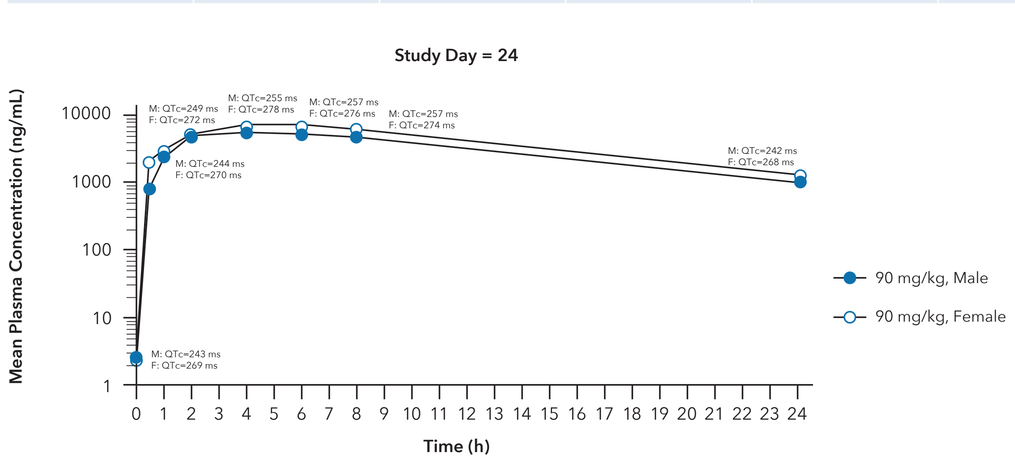


Figure 4 Moxifloxacin concentrations (ng/mL) with QTc interval prolongation during the cardiovascular phase of the investigation in monkey at 90 mg/kg



Dose (mg/kg)	Sex	C_{max} (ng/mL)	T_{max} (h)	$AUC_{0\text{-}24h}$ (h*ng/mL)	Max. QTc Prolongation (ms)
90	Male	6120 ± 1240	5.0 (2.0 - 8.0)	73000 ± 16100	24 ms
	Female	7670 ± 1200	5.0 (4.0 - 6.0)	96200 ± 6100	23 ms

Conclusions

The inclusion of power analysis (i.e., QTc sensitivity and QTc versus RR plots) data in a regulatory submission provides key information about the quality of the in vivo QTc assessment.

The exposure dependent increases in QTc observed following oral administration of Moxifloxacin to the cynomolgus monkey are in close agreement with those previously reported in human subjects.

Acknowledgements

We gratefully acknowledge with thanks the contributions to this poster by the safety pharmacology group at WuXi AppTec.

References

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