A Comparison of Moxifloxacin-Induced QTcH Prolongation in the Telemetered Nanopig™ Versus the Telemetered Beagle Dog via the Evaluation of Minimum Detectable Difference

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Background

Model sensitivity and validity are both of the utmost importance when evaluating the safety and efficacy of novel therapeutics. The ability of a preclinical model to accurately determine a drug candidate's potential is critical with regards to its future success in clinical trials, as well as providing an assurance in the substantial resource investments involved in developing these compounds. Current preclinical guidelines (International Conference on Harmonization, ICH E14/S7B) indicate that, to avoid the potential for further clinical safety analysis, the effect of a novel therapeutic compound on the heart rate (HR)-corrected QT interval (QTcH, Holzgrefe et. al, 2007) must be interrogated via high fidelity nonclinical safety pharmacology studies.

Moxifloxacin is a fluoroquinolone antibiotic characterized by a reliable and dose-dependent induction of QT prolongation, a well-known risk factor of both life-threatening arrythmias and sudden cardiac arrest. Thus, the pharmaceutical industry, along with its associated regulatory agencies, have widely recognized moxifloxacin as an important positive control in the evaluation of model sensitivity within both clinical and preclinical cardiovascular drug development studies via QT prolongation assessments (Chen et. al., 2009).

The minimum detectable difference (MDD) is a quantitative measure of the variance that occurs between treatment groups as compared to a control to identify a statistically significant result. Here, in both a telemetered pig study and a telemetered dog study, MDD was evaluated via moxifloxacin-induced QTcH interval prolongation, to assess these model's sensitivity and reliability.

Objective

To use escalating doses of moxifloxacin to assess the effect on the QTcH interval in both telemetered Sinclair Nanopigs™ and telemetered beagle dogs, thus providing a model to examine the reproducibility and validity of our procedures.

Methods

Study Design for Telemetered Nanopigs™ and Dogs: Non-naïve female Nanopigs™ aged 9−10 months (n = 4; body weight range: 26.8−33.6 kg from Sinclair Bio Resources [Auxvasse, MO]) were group-housed and fed a 16% protein pig diet, while non-naïve male beagle dogs aged 15−16 months (n = 8; range: 9.2−12.7 kg from Marshall BioResources, Inc.; North Rose, NY) were single-housed and fed a 25% protein dog diet. Animals were kept in a room maintained at approximately 18–27°C, with humidity set at 30–70% and illuminated to simulate a 12-hour light, 12-hour dark cycle. Body weights were obtained immediately prior to dosing, and each animal was observed regularly for clinical signs. At least 2 weeks prior to study initiation, animals were implanted with a Data Sciences International (DSI; St. Paul, MN) telemetry device (model L11) for electrocardiographic (ECG) evaluation. Each animal was orally administered vehicle (0.5% methylcellulose [MC] in deionized water) and escalating doses of moxifloxacin (pig study: 30 mg/kg, 100 mg/kg and 300 mg/kg; dog study: 10 mg/kg, 30 mg/kg and 100 mg/kg) in a Latin square design. ECG (PR interval, QRS duration and QT interval) and heart rate (HR) data were continuously recorded for 24 hours after each dose.

Overall Data Analysis: Individual beta constants for the corrected QTcH calculations were made as 10-second data blocks. Both ECG parameters and HR were analyzed using 15-minute averages; these values were then averaged into 1-hour superintervals from predose to 24-hours post dose. Values from each individual animal were pooled to determine an average for each variable at individual doses. Percent change from time-matched vehicle (%TMV) comparisons were used as the primary analysis method for test compound data. The median standard error (STDERR) was calculated on the mean QTcH interval values as the difference in least square means between the control group and across all treatment groups.

MDD Calculations: MDD was calculated as: MDD = Min{[t(0.05, ddf) + t(0.80,ddf)] x STDERR}, where "ddf" is equal to the treatment denominator degrees of freedom. MDD was calculated using this formula both for all animals on the study combined as well as for each individual animal throughout each of its 24-hour dosing epochs. Using the individual MDD values, each animal was then ranked as the most and least sensitive on study (pigs: n = 3; dogs: n = 4 and n = 6), with shorter MDDs receiving a better ranking. Once ranked, these condensed groups were interrogated for their new MDD values. Additionally, individual QTcH:RR plots (a calculation that relates the corrected QT interval to the RR interval, which is the time between heartbeats) for each animal were subsequently created using 10-second data. Alternative rankings (more sensitive/less sensitive on study for both Nanopigs™ and dogs) using the QTcH:RR plots were then assigned to each animal by either the proximity of the data across treatment groups (density), the absolute values of the complete study slope, or the absolute values of the prestudy slope. New MDD values for these condensed groups were once again calculated for comparison.

Results

Escalating Doses of Moxifloxacin in Female Nanopigs™ Resulted in Dose-Dependent QTcH Prolongation and Increases in HR, with No Notable Changes in PR Interval or QRS Duration

- Baseline values were within typical ranges for the female Nanopig™. No vehicle-related (0.5% methylcellulose in deionized water) changes were noted in ECG parameters or HR.
- As expected, orally administered moxifloxacin increased the QTcH interval in a dose-dependent manner, with the maximum effect ranging from +14% to +54% with increasing doses when assessed as %TMV values.
- The PR interval, QRS duration and HR values remained similar to the vehicle control throughout dosing, when assessed as %TMV values.

Table 1. Effects of Escalating Doses of Moxifloxacin Administered via Oral Gavage on ECG and HR Parameters in Telemetered Nanopigs™ (Min/Max Mean Range Over 24 Hours)

Parameter	Vehicle (n=4)	30 mg/kg Moxifloxacin (n=3-4)	100 mg/kg Moxifloxacin (n=3-4)	300 mg/kg Moxifloxacin (n=4)
QTcH (ms)	301-337	321-355	319-383	320-473
HR (bpm)	79-114	73-110	73-114	71-108
PR Interval (ms)	96-114	99-118	101-115	104-114
QRS Duration (ms)	46-53	46-54	48-55	46-53

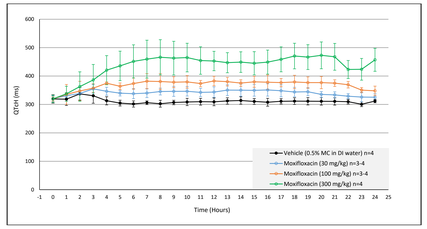
ECG, electrocardiographic; HR, heart rate; Min, minimum; Max, maximum.

Table 2. Effects of Escalating Doses of Moxifloxacin Administered via Oral Gavage on ECG and HR Parameters in Telemetered Nanopigs™ (Percent Change from Time-Matched Vehicle Data)

Parameter	30 mg/kg Moxifloxacin (n = 3–4)		100 mg/kg Moxifloxacin (n = 2–4)		300 mg/kg Moxifloxacin (n = 3–4)	
	Change (%)	Time Point of Maximum Change (hours post dose)	Change (%)	Time Point of Maximum Change (hours post dose)	Change (%)	Time Point of Maximum Change (hours post dose)
QTcH	0 to +14	8, 12, 16	0 to +26	8	0 to +54	8
HR	-16 to +16	2, 8, 22	-23 to +22	7	-22 to +9	13
PR Interval	-3 to +7	10	-5 to +4	23, 24	-4 to +14	4
QRS Duration	-13 to +9	9	-1 to +17	7	-4 to +8	7

ECG, electrocardiographic; HR, heart rate.

Figure 1. Effects of Escalating Doses of Moxifloxacin Administered via Oral Gavage on the QTcH Interval in Telemetered Nanopigs™



Evaluation of MDD via Moxifloxacin-Induced QTcH Prolongation in Both the Telemetered Nanopig™ Model and the Telemetered Beagle Dog Model Yielded Remarkable Sensitivity

The MDD of the overall study for moxifloxacin-induced QTcH interval prolongation was found to be notably sensitive in both the telemetered pig model (8.2 ms) and the telemetered beagle dog model (3.2 ms).

Ranking the Most Sensitive and Least Sensitive Animals Via Individual MDD Values, QTcH:RR Plot Density or QTcH:RR Plot Slope Yielded Similar Overall MDD Results

When both Nanopigs™ and dogs were ranked either via their individual MDD values, their QTcH:RR plot density across treatments, the absolute values of the complete study slope, or the absolute values of the prestudy slope, all ranking methods produced similar results in terms of overall MDD values. Ranking telemetered beagle dogs in this manner also produced similar results in terms of individual animal order.

This key links the color-coded results with each individual animal ranking method used in this presentation.

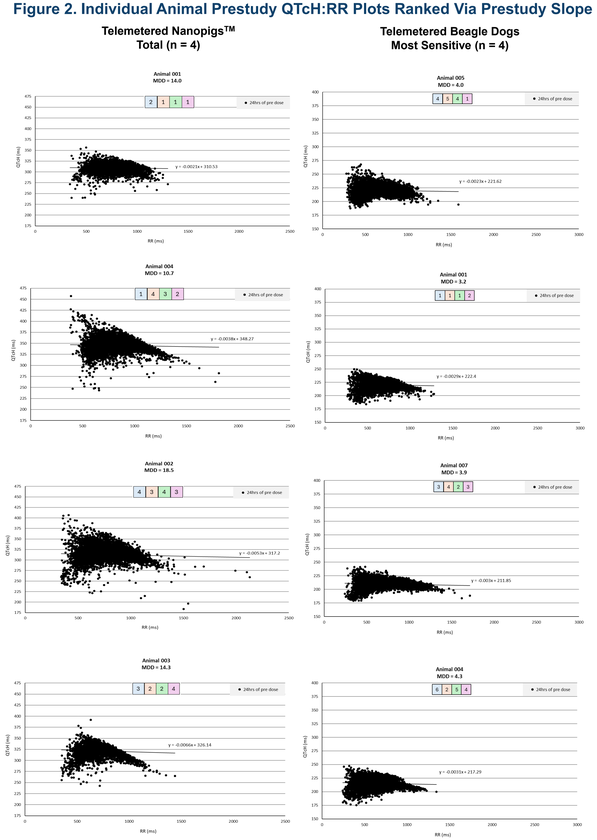
Individual Animal MDD Values	Complete Study Slope, Absolute Values
Complete Study QTcH:RR Plot Density	Prestudy Slope, Absolute Values

Table 3. Individual Animal MDD Values

Species	Sensitivity Ranking	Animal No.	MDD (ms)
Nanopig™	All (n = 4)	001	14.0
		002	18.5
		003	14.3
		004	10.7
Beagle Dog	Most Sensitive (n = 2)	001	3.2
		003	3.6
	Least Sensitive (n = 2)	006	6.0
		008	7.9

MDD, minimum detectable difference; No., number.

Figure 2. Individual Animal Prestudy QTcH:RR Plots Ranked Via Prestudy Slope



Evaluation of Both Individual Animal MDD Values and Prestudy Slope Absolute Values from QTcH:RR Plots Exhibited Greater Sensitivity and Less Variability in Telemetered Beagle Dogs than in Telemetered Nanopigs™

Each animal was assessed for their individual animal MDD value. While still within reasonable ranges, the individual MDD values for telemetered Nanopigs™ were less sensitive than the individual MDD values for telemetered beagle dogs.

When individual animals were ranked by the absolute values of their QTcH:RR plot prestudy slopes, values from the telemetered Nanopigs™ (0.0021-0.0066) exhibited greater variability than values from the telemetered beagle dogs (most sensitive 4: 0.0023−0.0031).

Figure 3. Individual Animal Complete Study QTcH:RR Plots Ranked Via Plot Density

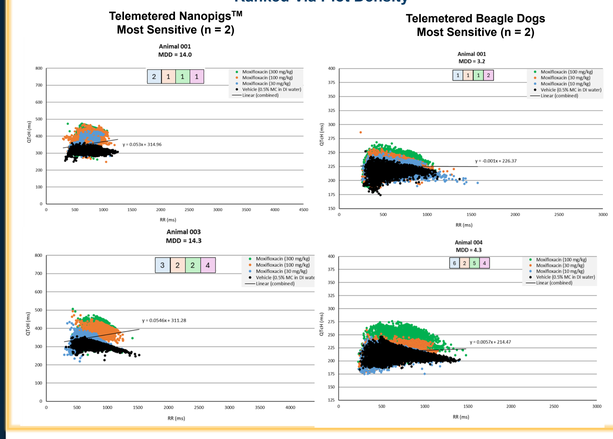


Table 4. Summary of Individual Animal Rankings Via Alternative Methods
Overall Nanopig™ Study MDD = 8.2 ms
Overall Beagle Study MDD = 3.2 ms

Ranking Method	Nanopig™		Beagle Dog	
	Most Sensitive Animals	Least Sensitive Animals	Most Sensitive Animals	Least Sensitive Animals
	n = 3	n = 3	n = 4	n = 4
Individual Animal MDD Values	8.3	10.1	2.4	5.3
Complete Study QTcH:RR Plot Density	10.1	9.4	2.5	4.6
Complete Study Slope, Absolute Values	8.3	9.4	3.8	5.7
Prestudy Slope, Absolute Values	9.7	9.4	2.7	5.0

MDD, minimum detectable difference.

Conclusion

Following evaluation via MDD, both the telemetered Nanopig™ model and the telemetered beagle dog model were found to be remarkably sensitive to the detection of statistically significant changes in the QTcH interval, a vital component of novel compound development. When this group of animals was ranked either by their individual MDD values, their QTcH:RR plot density across treatments, the absolute values of the complete study slope, or the absolute values of the prestudy slope, all ranking methods produced similar results in terms of overall MDD values, adding support to the utilization of any of these methods.

When comparing the individual MDD values across both telemetry models, the individual MDD values in the Nanopig model were less sensitive than the individual MDD values in the beagle dog model, though both remained within acceptable ranges.

When individual animals were ranked by the absolute values of their QTcH:RR plot prestudy slopes, values from the telemetered Nanopigs™ exhibited greater variability than values from the most-sensitive 4 telemetered beagle dogs.

Finally, when both the telemetered Nanopigs™ and the telemetered beagle dogs on study were ranked by the absolute values of their prestudy slopes across treatments, correlations were noted between the prestudy slope rankings and individual animal MDDs following dosing. This lends support to the prospect of researchers utilizing this method pre-study for optimal animal selection.

References

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COI Statement

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