Implementation of nonclinical C-QTc analysis: Demonstration of clinically relevant detection sensitivity with ICH E14/S7B Q&A

○Emi Matsumoto [1), 2)], Naoki Kitajou [2)], Mitsutoshi Kamada [1)], Ryouta Hayashi [1)], Yoshiyuki Furukawa [1)], Mayumi Sato [1)], Toshiyuki Hamashima [1)], Hiroyasu Miyazaki [1)]
1) Axcelead Drug Discovery Partners, Inc., 2) Axcelead Tokyo West Partners, Inc.

Introduction

In recent years, the sensitivity to detect QT prolongation of non-clinical in vivo QT study has been greatly improved through standardization of the Best Practice methods, etc. However, in Japan, there are few reports how much sensitivity the optimized in vivo QT study has concretely, because their analytical method had not been standardized. On the other hand, ICH E14/S7 Q&A (2022) requires that non-clinical in vivo QT study has the sufficient sensitivity to detect a small QT prolongation, comparable to clinical trials, in order to waive Thorough QT (TQT) study. Then, the sensitivity of the optimized in vivo QT study employed in our facility were verified.

Methods

Two cardiovascular (CV) telemetry studies in cynomolgus monkeys and beagle dogs were conducted using moxifloxacin by a Williams square design (N=4; 4 doses), with pharmacokinetic (PK) study after CV phase. RMSE (root mean square error) and Fisher's LSD (least significant difference) were calculated using 30-min average QTc values for each PK time point (T30) and super-intervals average QTc values (SI) by single-delta ANOVA. The concentrations producing a 10 msec ΔΔQTc prolongation (ng/mL) was calculated by concentration-QTc (C-QTc) analysis using linear regression model. RMSE/LSD and C-QTc were compared between conventional T30 and SI.

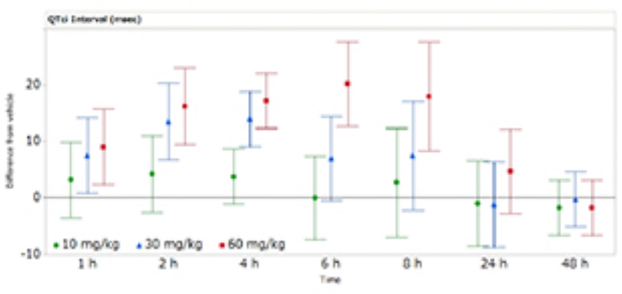
	Monkey	Dog
Test article	Moxifloxacin	
Dose	0, 10, 30, 60 mg/kg	0, 3, 10, 30 mg/kg
Individual QT correction	log (QTc) = log (QT) – β [(log (RR) – log (RR ref)]	
PK analysis point	1, 2, 4, 6, 8, 24 and 48 hours after dosing	
SI analysis point	0.5-4, 6-10, 10-16, 16-22, 22-25 and 46-48 hours after dosing	
LSD/RMSE	Single-delta ANOVA, $LSD=[t_{1-\alpha,\ 3(n-2)}]\sqrt{2/n}\cdot RMSE$	
C-QTc analysis	Linear regression model based on PK and QTc at PK or SI analysis point	

Vehicle: 0.5 w/v% methylcellulose solution
Statistical analysis was performed using JMP (ver. 18.2).

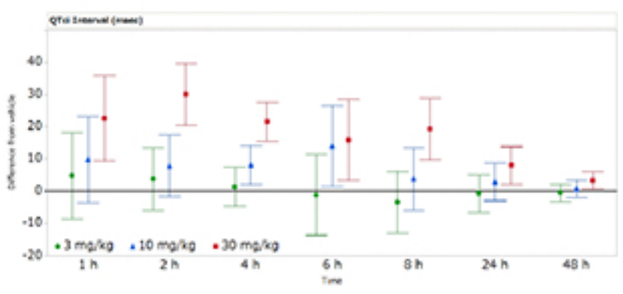
Result

LSD/RMSE

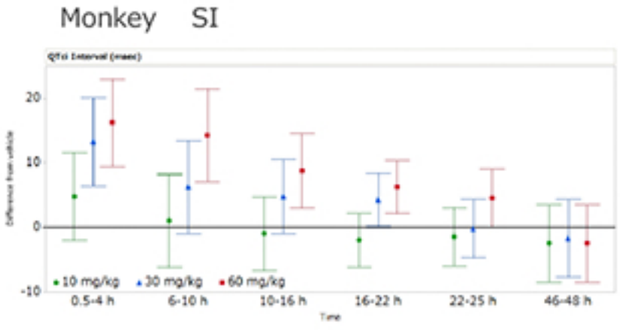
Monkey T30



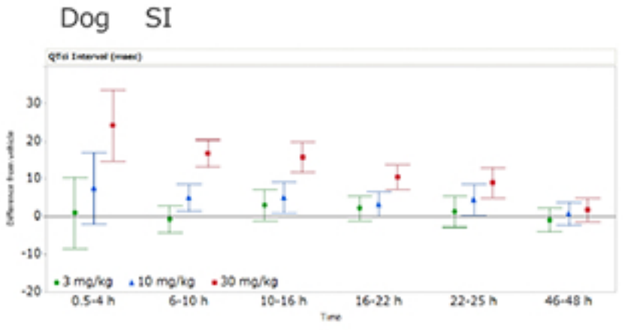
Dog T30



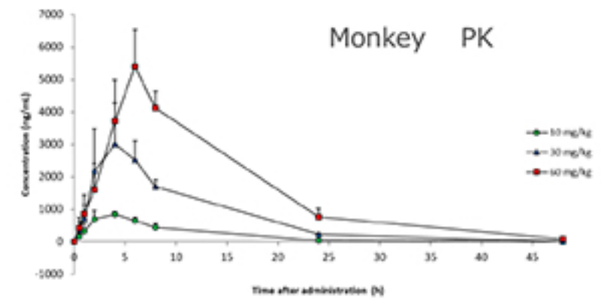
Monkey SI



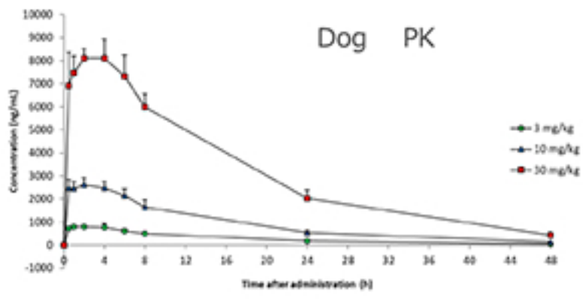
Dog SI



Monkey PK



Dog PK

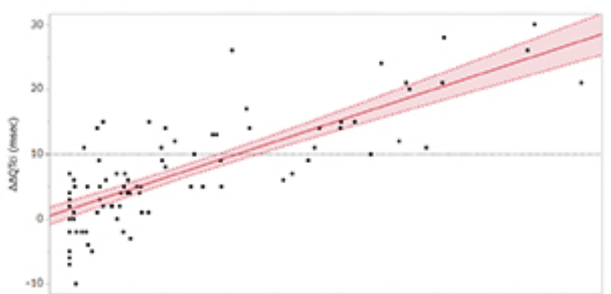


Both studies had sufficient sensitivity to detect a 10-msec prolongation of QTc (LSD<10 msec), and the analysis using SI showed higher sensitivity than that using T30.

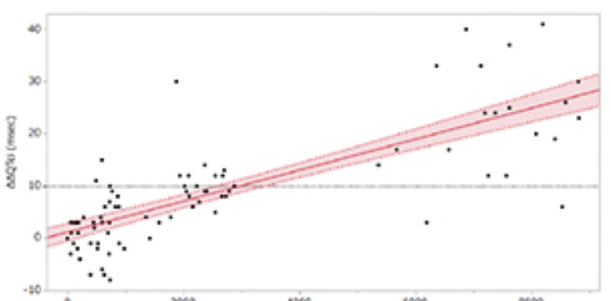
LSD /RMSE (msec)	Monkey		Dog	
	T30	SI	T30	SI
Study LSD [Median]	6.8	5.9	9.6	3.8
LSD (Min – Max)	(4.9 - 9.6)	(4.1 - 7.2)	(2.7 – 13.2)	(3.1 – 9.5)
Study RMSE [Median]	3.9	3.4	5.5	2.2
RMSE (Min – Max)	(2.8 - 5.6)	(2.4 - 4.2)	(1.6 – 7.7)	(1.8 – 5.5)

C-QTc analysis

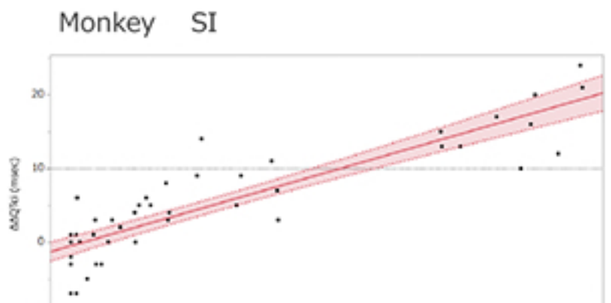
Monkey T30



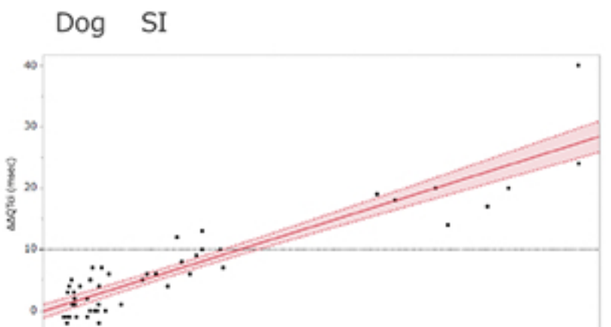
Dog T30



Monkey SI



Dog SI



The linear regression model-predicted concentrations producing a 10-msec ΔΔQTc prolongation in both studies were generally within a 2-fold of the clinical concentration.

E-R Analysis	Monkey		Dog	
	T30	SI	T30	SI
Slope (msec per ng/mL)	0.00407 [p<0.001]	0.00428 [p<0.001]	0.00297 [p<0.001]	0.00299 [p<0.001]
Intercept (msec)	1.50	-0.53	1.15	0.96
ΔΔQTc +10 msec conc, total (ng/mL) Mean (90%CI LB, UB)	2087 (1849, 2352)	2461 (2198, 2775)	2979 (2561, 3412)	3021 (2730, 3339)
ΔΔQTc +10 msec conc, free (ng/mL) Mean (90%CI LB, UB)	1717 (1522, 1936)	2025 (1809, 2284)	2115 (1818, 2422)	2145 (1938, 2371)
in vivo/human* ratio Mean/90%CI LB	1.5/1.6	1.8/1.9	1.9/1.9	1.9/2.0

UB: Upper bound, LB: Lower bound,
* Critical concentration (ng/mL) that gives a 10-msec increase in humans
Mean (90%CI LB, UB) total: 1866 (1591, 2188) free: 1120 (955, 1313)

Conclusion

Both the in vivo QT studies in monkeys and dogs were optimized and demonstrated sufficient sensitivity to detect QTc prolongations. This supports an integrated risk assessment for a TQT waiver with LSDs of less than 10 msec and in vivo/clinical concentration ratios within two-fold.

Reference

- *Eric I. Rossman, et al*. J Pharmacol Toxicol Methods 123 (2023) 107270
- *Li, D*., and *Nichols, J*., Statistical Best Practices to Support the New ICH S7B Q&A, Safety Pharmacology Society Webinar, 2022.
- ICH E14/S7B Q&As Training Materials, 2022

Conflicts of interest (COI): None

Axcelead Drug Discovery Partners, Inc.
https:// www.axcelead.com

WEB YouTube