P1269

Electrocardiographic Effects of WCK 2349

Jay W. Mason[1], R. Chugh[2], F. Lakdavala[2], A. Bhatia[2]

[1]University of Utah, Salt Lake City Utah, USA and Spaulding Clinical Research, West Bend WI, USA; [2]Wockhardt Ltd., Mumbai, India

INTRODUCTION AND PURPOSE

WCK 2349 is a novel L-alanine ester prodrug of levonadifloxacin being developed as an oral fluoroquinolone antibacterial agent that displays excellent coverage for methicillin-resistant *Staphylococcus aureus* (MRSA). This agent is being developed for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and hospital-acquired bacterial pneumonia (HABP) caused by MRSA.

The primary objective of the study was to determine the effect of a supratherapeutic dose of WCK 2349 on the heart-rate-corrected QT interval (QTc) in healthy adult male and female subjects, in accordance with the ICH E-14 Guidance on The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.

METHODS

- This was a randomized, double-dummy, placebo and positive-controlled, 3-way crossover study, 48 subjects were randomized in a crossover design to receive orally 2600 mg (supratherapeutic dose) of WCK 2349, 400 mg of moxifloxacin or placebo.
- Moxifloxacin was included as an active control to demonstrate the capability of the study design to detect small changes in QTc.
- Three 10-scond, 12-lead electrocardiograms (ECGs) spaced on minute apart were collected immediately before dosing and at hours 0.5, 1, 1.5, 3, 4, 6, 8, 10, 16, 24 and 36 after dosing.
- Plasma samples for pharmacokinetic analysis were obtained at each time point.
- The primary analysis was a mixed effects model of change over baseline of QTcF in the WCK 2349 compared to the placebo arm, the difference between WCK 2349 termed ddQTcF. Subject was included as a random effect and treatment, hour, treatment*hour, and treatment sequence were included as fixed effects.
- Secondary analysis included ddHR (heart rate), ddPR (PR interval) and ddQRS (QRS interval), concentration-effect modelling of ddQTcF versus plasma concentration, and assessment of assay sensitivity based on the moxifloxacin response. 2 hour time-point was only for PK.

RESULTS

- **Exposure:** A mean C_{max} of levonadifloxacin of 40.6 µg/ml was achieved at 3 hours (T_{max}), and the mean plasma AUC_{0-t} was 412.29 h·mg/mL following administration of 2600 mg of WCK 2349. These values exceed the usual C_{max} and AUC during clinical treatment by approximately 2-fold.
- **QTcF: Figure 1** shows the unadjusted change in ddQTcF in the WCK 2349 and moxifloxacin arms and **Table 1** shows the hourly group mean ddQTcF and its 90% 2-sided confidence band from the mixed effects model.

Figure 1. Unadjusted ddQTcF and 90% CI, msec

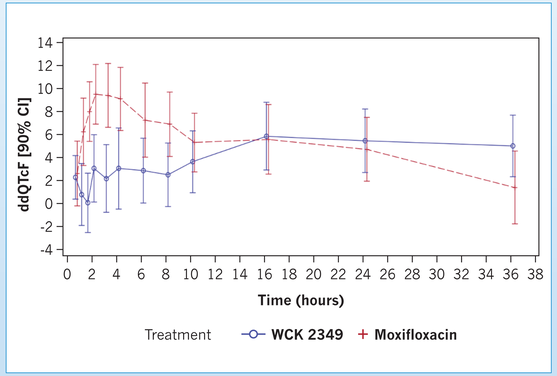


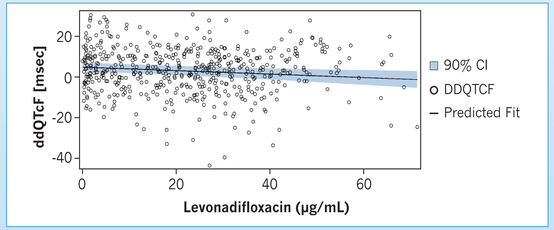
Table 1. ddQTcF and 90% CI, msec, from mixed model

Time point (hour)	WCK 2349		Moxifloxacin	
	Mean	90% CI	Mean	90% CI
0.5	2.7	0.2, 5.2	2.7	0.2, 5.3
1	1.2	-1.3, 3.7	6.3	3.8, 8.9
1.5	0.4	-2.2, 2.9	8.1	5.6, 10.6
2	3.4	0.8, 5.9	9.6	7.1, 12.1
3	2.3	-0.2, 4.8	9.5	7.0, 12.0
4	3.2	0.7, 5.7	9.2	6.7, 11.7
6	3.2	0.7, 5.8	7.4	4.8, 9.9
8	2.8	0.3, 5.3	7.0	4.5, 9.5
10	3.6	1.1, 6.1	5.4	2.9, 8.0
16	6.0	3.5, 8.5	5.7	3.1, 8.2
24	5.8	3.3, 8.3	4.8	2.3, 7.4
36	5.2	2.7, 7.8	1.5	-1.0, 4.1

CI = confidence interval; * = CI excludes zero

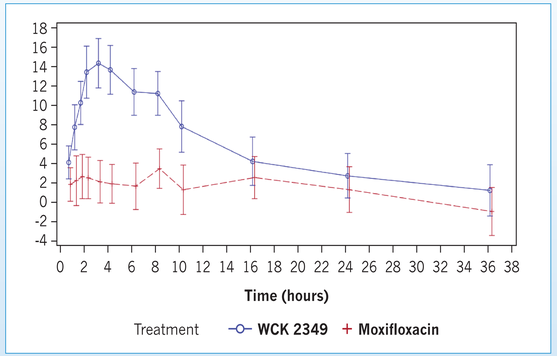
- **Figure 2** shows a linear concentration-effect model for QTcF. The slope is modestly negative and the upper bound of the 90% CI (blue) is well below 10 msec.
- These observations confirm assay sensitivity (moxifloxacin's lower 90% CI exceeded 5 msec at multiple time points) and indicate that at supratherapeutic exposure, WCK 2349 has no clinically or statistically significant effect on QTc (its upper 90% CI was below 10 msec at all time points).

Figure 2: ddQTcF (msec) versus Concentration of Levonadifloxacin



- **HR, PR, QRS:** The PR the QRS intervals were unaffected by any of the treatments. However, HR (ddHR) increased substantially in response to WCK 2349 (**Figure 3**), and there was a small increase in HR in the moxifloxacin arm.

Figure 3. Change in Heart Rate (ddHR, bpm)



- The increase in HR was transient and not associated with any clinical signs and symptoms. An increase in HR above 20 beats/min was associated with high plasma C_{max} (range - 40-70 µg/mL) of levonadifloxacin at 2600 mg supratherapeutic dose. Therapeutic dose C_{max} is 20-25 µg/mL at 1000 mg, b.i.d.
- Single doses of 1000 or 1500 mg of levofloxacin have also been reported to cause significant increase in HR.[1]

CONCLUSIONS

- **The thorough QT study of WCK 2349 was successful.**
- **WCK 2349 was shown to have no clinically or statistically significant effect on QTc, PR or QRS.**
- **WCK caused a transient increase in HR. HR increase associated with antibiotics of several classes is well known, but usually obscured in clinical practice due to treatment-related defervescence.**

REFERENCES

1. J Clin Pharmacol 2004;44:464-473

DISCLOSURES

This study was sponsored by Wockhardt Bio AG, Switzerland.
www.wockhardt.com

Jay W. Mason, MD
Professor of Medicine
University of Utah
Email: jmason12@charter.net

This material is copyrighted to Wockhardt.

Poster presented at the 26th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), 9th –12th April, 2016, Amsterdam.