Safety and Pharmacokinetics of Multiple Ascending Doses of WCK 771 and WCK 2349

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ABSTRACT

Background: WCK 771 (IV) and WCK 2349 (PO) are L-arginine salt and L-alanine ester prodrug, respectively, of levonadifloxacin (active moiety), a benzoquinolizine quinolone. These agents are being developed for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and hospital-acquired bacterial pneumonia (HABP) caused by methicillin-resistant *Staphylococcus aureus* (MRSA). These studies were conducted to evaluate the tolerability and pharmacokinetics of multiple ascending doses of WCK 2349 and WCK 771 in healthy volunteers in US.

Material/methods: These were two separate trials wherein sequential cohorts (n=10 active, 2 placebo) received multiple twice daily doses (5 days) of WCK 771 (600, 800, or 1000 mg) or placebo and WCK 2349 (800, 1000, or 1200 mg) or placebo. Blood and urine sampling was done to assess levonadifloxacin pharmacokinetics. Safety and tolerability assessments were performed throughout dosing and during follow-up visit.

Results: The mean AUC_{0-12}, AUC_{0-24}, and C_{max} on Day 1 were 72.70 h•µg/mL, 157.43 h•µg/mL and 15.49 µg/mL respectively for 600 mg; 81.77 h•µg/mL, 178.54 h•µg/mL and 17.26 µg/mL respectively for 800 mg; and 111.49 h•µg/mL, 235.37 h•µg/mL and 21.98 µg/mL respectively for 1000 mg. The mean AUC_{0-24}, AUC_{0-t} and C_{max} on Day 5 were 183.68 h•µg/mL, 219.61 h•µg/mL and 15.84 µg/mL respectively for 600 mg; 208.97 h•µg/mL, 244.30 h•µg/mL and 18.00 µg/mL respectively for 800 mg; and 254.22 h•µg/mL, 295.97 h•µg/mL and 21.61 µg/mL respectively for 1000 mg.

The mean AUC_{0-12}, AUC_{0-24}, and C_{max} on Day 1 were 88.52 h•µg/mL, 186.53 h•µg/mL and 17.20 µg/mL respectively for 800 mg; 121.68 h•µg/mL, 264.00 h•µg/mL and 24.30 µg/mL respectively for 1000 mg; and 118.60 h•µg/mL, 247.60 h•µg/mL and 22.25 µg/mL respectively for 1200 mg. The mean AUC_{0-24}, AUC_{0-t} and C_{max} on Day 5 were 211.45 h•µg/mL, 252.42 h•µg/mL and 18.34 µg/mL respectively for 800 mg; 284.68 h•µg/mL, 329.75 h•µg/mL and 24.42 µg/mL respectively for 1000 mg; and 287.90 h•µg/mL, 338.94 h•µg/mL and 23.36 µg/mL respectively for 1200 mg.

There were no deaths or Serious Adverse Events (SAEs) during the studies. Adverse events (AEs) were generally mild or moderate in severity. No clinically significant abnormalities were observed in vital sign measurements, 12-lead ECG results, or phototoxicity assessments.

Conclusions: WCK 771 and WCK 2349 administered in multiple escalating doses were well tolerated by the healthy subjects in US. Mean total and peak exposures of levonadifloxacin increased from 800 to 1000 mg after WCK 2349 but the values remained relatively unchanged from 1000 to 1200 mg. Mean total and peak exposures of levonadifloxacin increased with an increase in dose from 600 to 1000 mg after WCK 771 was administered.

INTRODUCTION AND PURPOSE

- WCK 771 (IV) and WCK 2349 (PO) are L-arginine salt and L-alanine ester prodrug, respectively, of levonadifloxacin (active moiety), a benzoquinolizine quinolone. These agents are being developed for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and hospital-acquired bacterial pneumonia (HABP) caused by gram-positive bacteria, including MRSA.
- Multiple Ascending Dose (MAD) studies were conducted to evaluate the safety, tolerability and pharmacokinetics of WCK 2349 and WCK 771 in healthy adult volunteers in US.

METHODS

- Two separate randomized, double-blind, clinical trials were conducted wherein sequential cohorts (n=10 active, 2 placebo) received multiple twice daily doses (5 days) of WCK 771 (600, 800, or 1000 mg) or placebo and WCK 2349 (800, 1000, or 1200 mg) or placebo. In both the studies the study drug was administered twice daily at 12-hour intervals.
- Blood and urine samples to assess levonadifloxacin pharmacokinetics were collected at various time points on Days 1, 2, 3, 4, and 5 (blood) and Days 1 and 5 (urine). Safety and tolerability assessments were performed throughout dosing and during follow-up visit.

RESULTS

- Equal number of male and female subjects enrolled in both studies. Subject demographics summarized in **Table 1**.

Table 1. Summary of subject demographics

Study Drug	WCK 771 n = 36	WCK 2349 n =36
	Mean *(SD)*	Mean *(SD)*
Age (years)	27.2 (5.39)	32.7 (8.48)
Weight (kg)	77.03 (14.323)	75.79 (15.784)
Body mass index (kg/m2)	26.71 (3.677)	26.32 (3.847)

- After administration of WCK 771 and WCK 2349 twice daily on Day 1 and Day 5, mean AUC and C_{max} of levonadifloxacin increased as the dose increased. Mean $T_{1/2}$ of levonadifloxacin was similar between the doses and ranged from 9.7 to 10.4 hours and 8.28 to 9.62 hours for WCK 771 and WCK 2349 respectively.
- Plasma concentrations of levonadifloxacin versus time by treatment on Day 5 for WCK 771 and WCK 2349 is presented in figure 1 and 2 respectively.

Figure 1. Plasma concentration-time profiles by dose levels of WCK 771

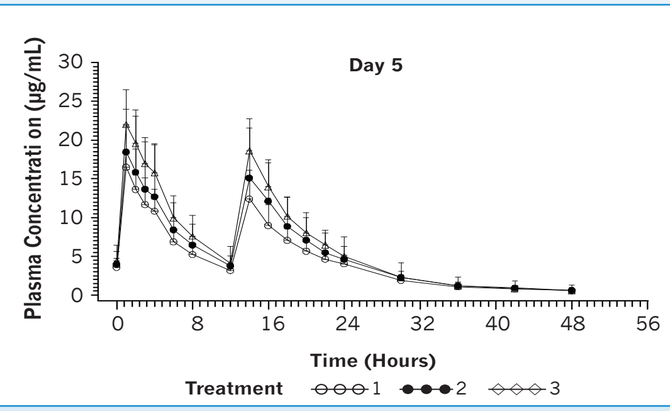
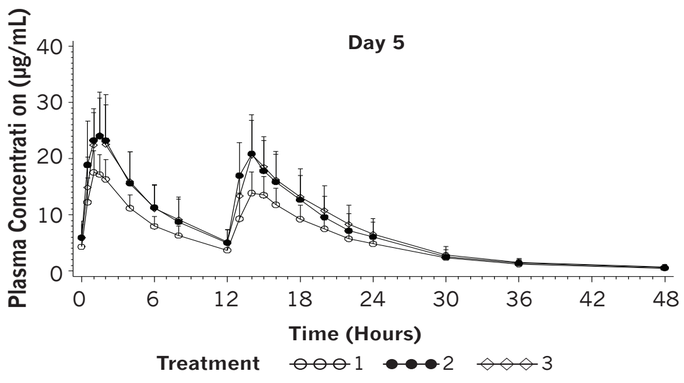


Figure 2. Plasma concentration-time profiles by dose levels of WCK 2349



- The mean AUC_{0-24} and C_{max} of WCK 771 and WCK 2349 is presented in figure 3 and 4 respectively.

Figure 3. Mean AUC_{0-24} (h•µg/mL) of WCK 771 and WCK 2349 on Day 5

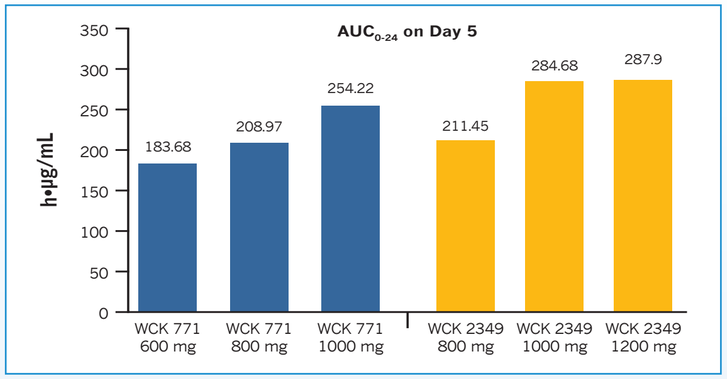
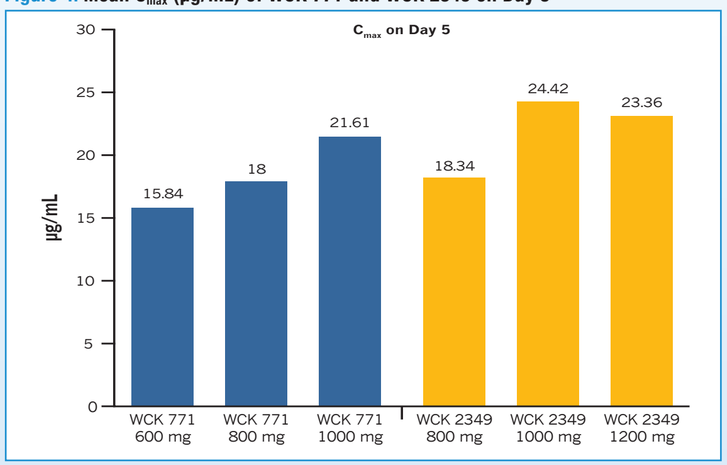


Figure 4. Mean C_{max} (µg/mL) of WCK 771 and WCK 2349 on Day 5



- There were no deaths or SAEs in both studies. One subject (WCK 771, 800 mg) discontinued from the study due to a moderate AE of hypersensitivity. The AE resolved by the end of the study.

CONCLUSIONS

- **WCK 771 and WCK 2349 administered in multiple escalating doses were well tolerated by the healthy subjects in US.**
- **Mean total and peak exposures of levonadifloxacin increased from 800 to 1000 mg after WCK 2349 but the values remained relatively unchanged from 1000 to 1200 mg.**
- **Mean total and peak exposures of levonadifloxacin increased with an increase in dose from 600 to 1000 mg after WCK 771 was administered.**

DISCLOSURES

This study was sponsored by Wockhard Ltd, Mumbai, India.
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Poster presented at the 26th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), 9th–12th April, 2016, Amsterdam.