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Paper Poster Session
Levonadifloxacin

Safety and pharmacokinetics of multiple ascending doses of WCK 771 and WCK 2349

Rakesh Chugh*[1], Faranza Lackdavala[2], Ashima Bhatia[2]

[1]*Wockhardt, Global Clinical Development, Mumbai, India*

[2]*Wockhardt, Mumbai, India*

Background: WCK 771 (I V) and WCK 2349 (P O) 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 $AUC_{0\text{-}24}$ and C_{max} of levonadifloxacin after administration of WCK 771 on Day 1 were 157.43 h•µg/mL and15.49 µg/mL respectively for 600 mg; 178.54 h•µg/mL and 17.26 µg/mL respectively for 800 mg; and 235.37 h•µg/mL and 21.98 µg/mL respectively for 1000 mg. The mean $AUC_{0\text{-}24}$ and C_{max} on Day 5 were 183.68 h•µg/mL and 15.84 µg/mL respectively for 600 mg; 208.97 h•µg/mL and 18.00 µg/mL respectively for 800 mg; and 254.22 h•µg/mL and 21.61 µg/mL respectively for 1000 mg.

The mean $AUC_{0\text{-}24}$ and C_{max} of levonadifloxacin after administration of WCK 2349 on Day 1 were 186.53 h•µg/mL and 17.20 µg/mL respectively for 800 mg; 264.00 h•µg/mL and 24.30 µg/mL respectively for 1000 mg; and 247.60 h•µg/mL and 22.25 µg/mL respectively for 1200 mg. The mean $AUC_{0\text{-}24}$ and C_{max} on Day 5 were 211.45 h•µg/mL and 18.34 µg/mL respectively for 800 mg; 284.68 h•µg/mL and 24.42 µg/mL respectively for 1000 mg; and 287.90 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 ascending 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.