Pharmacokinetics of Levonadifloxacin Administered as Intravenous WCK 771 and Oral WCK 2349 in Healthy Indian Male Adults

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Background: Levonadifloxacin, a novel broad spectrum, anti-methicillin resistant Staphylococcus aureus (MRSA) agent belonging to the fluoroquinolone class, is the active component of WCK 771 and WCK2349. The L-arginine salt of levonadifloxacin was evaluated as a parenteral formulation (WCK 771) and the L-alanine ester prodrug is being developed as an oral formulation (WCK 2349). Both WCK 771 and WCK 2349 are being developed for the treatment of patients with hospital acquired bacterial pneumonia (HABP) and acute bacterial skin and skin structure infections (ABSSSI). The primary objectives of this analysis were to characterize the pharmacokinetics (PK) of intravenous (IV) WCK 771 and oral WCK 2349 in healthy adult Indian male volunteers.

Methods: Intensive venous blood samples were collected per protocol, and levonadifloxacin plasma concentrations were measured with either HPLC or LC-MS/MS. For 771, data from escalating single doses (50 mg, 100 mg, 200 mg, 300 mg, 400 mg, 600 mg, 800 mg, 1000 mg and 1200 mg) and multiple doses (500 mg and 600 mg twice daily (BID) for 1 day; 600 mg, 800 mg, 1000 mg and 1200 mg for 5 days) was analyzed using a non-compartmental approach with Pheonix WinNonlin, whereas WCK 2349 observations from one single dose study (200 mg, 400 mg, 600 mg, 800 mg, 1000 mg, 1200 mg and 1500 mg) and one multiple dose study (600 mg, 800 mg, 1000 mg and 1200 mg twice daily for five days) in healthy volunteers under fasting conditions was used as well.

Results: A linear increase in $C_{\text{max}}$ and $AUC_{(0-\infty)}$ was observed for WCK 771 (50-1200 mg) and WCK 2349 (200-1500 mg) single doses. For BID for 5 days, the $AUC_{(\text{tau})}$ at steady state was not significantly different to the $AUC_{(0-\infty)}$ after respective single doses at all dose levels tested for WCK 771 and WCK 2349. Accumulation was negligible such that the accumulation index was 1.1-1.2 after BID doses. Terminal elimination half-life ($t_{1/2}$) remained constant at around 6 - 8 hrs throughout single and multiple doses for both formulations. Both WCK 771 and WCK 2349 were tolerated well at all doses.

Conclusions: Single and multiple dose PK studies for WCK 771 and WCK 2349 show that both formulations are well tolerated and the PK are linear across all dose levels.

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