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Pharmacokinetic-pharmacodynamic (PK-PD) target attainment analyses to support WCK-771 (INN: levonadifloxacin) clinical dose selection

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Background: Levonadifloxacin is a broad spectrum, bactericidal antibacterial agent belonging to benzoquinolizine sub-class of quinolones. PK/PD TA analyses were performed to provide levonadifloxacin dose selection to support Phase 3 ABSSSI clinical trial. WCK 771 and WCK 2349 (INN: Alalevonadifloxacin) have recently completed Phase 3 ABSSSI study in India.

Materials/methods: Analyses utilized Phase 1 and Phase 2 population PK (PoP PK) model, non-clinical PK/PD targets from a neutropenic murine-lung infection model, and levonadifloxacin MIC data for *S. aureus (*SA). The final model represented a 2-compartment model with first-order elimination where all the clearance and volume parameters were allometrically scaled to a mean body weight of 70 kg and an exponent of 0.75 and 1 respectively. Using PK parameter estimates, free-drug plasma (*f*) concentration-time profiles were simulated for 2000 patients administered 800 mg BID. A separate PTA analyses for WCK 2349 was not required as 1000 mg BID WCK 2349 provides C_{max} and AUC comparable to WCK 771 800 mg BID. Average AUC_{0-24} over Days 1 and Day 5 was calculated. The mean *f*AUC/MIC ratio (8.4 and 25.8, respectively) targets associated with static and 1-$\log_{10}$ CFU reduction from baseline for *S. aureus* (MSSA, MRSA/QRSA) were evaluated. Percent probabilities of PK/PD TA (% PTA) by MIC and SA MIC distributions were determined.

Results: Using more conservative mean *f*AUC/MIC target of 8.4, %PTA for WCK 771 800 mg BID dosing regimen was >95% at MIC of 4 mg/L for SA isolates (see Figure). Using mean *f*AUC/MIC target of 25.8 , %PTA was >95.0% for MIC of 1 mg/L. Based on large-scale MICs, *S. aureus* MIC_{90} of LND is 0.5-1 mg/L.

Conclusions: The PTA analyses showed that WCK 771 800 mg BID dose would provide therapeutic efficacy for MRSA/QRSA strains up to the MIC of 4 mg/L.

Figure 1: Levonadifloxacin 800 mg BID: Probability of Target Attainment Analyses