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O1063 WCK-771 (INN: levonadifloxacin): pharmacodynamic index (PDI) and PD target (PDT) determination studies involving methicillin /quinolone-resistant *Staphylococcus aureus* (MRSA/QRSA) employing neutropenic mouse lung infection model

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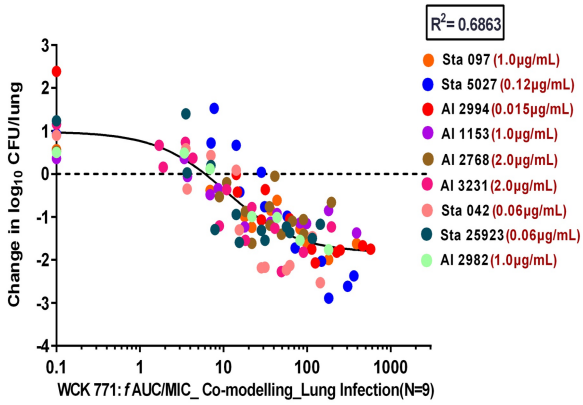
Background: WCK 771 is a broad spectrum, bactericidal antibiotic belonging to benzoquinolizine sub-class of quinolones. The absence of conventional amine at C-8 position and presence of tricyclic chiral benzoquinolizine core imparts WCK 771, a differentiated mechanism of action involving high-affinity targeting towards Staphylococcal DNA gyrase. Robust *in vivo* PDTs were determined employing multiple QRSA strains to support the clinical dose selection for WCK 771. WCK 771 and WCK 2349 (INN: alalevonadifloxacin, L-alanine ester oral prodrug of levonadifloxacin) have recently completed Phase 3 ABSSSI study in India.

Materials/methods: PDI & PDT identification studies were undertaken employing 24h dose fractionation studies in neutropenic mouse lung infection model. Post, two doses of cyclophosphamide, mice were infected with ≈10^7 CFU/lung. Subcutaneous treatment of WCK 771 was initiated 2h post infection. The lung viable counts were determined at 2h and 25h post-initiation of therapy. For PDI determination studies (one each MSSA and MRSA), a range of WCK 771 total doses were administered as fractionated regimens (q3h, q6h, q12h & q24h) to generate various exposure-response (E-R) scenarios. PDT determination was carried out by employing levonadifloxacin as q12h and q24h regimen, involving nine *S. aureus* strains (3 MSSA, 1 MRSA and 5 MRSA + QRSA; MICs: WCK 771-0.015-2 mg/L, Levofloxacin-0.25 -32 mg/L).E-R analyses were carried out by using non-linear sigmoidal dose-response model (GraphPad Prism Version 7).

Results: For SA, E-R analyses showed that best E-R correlation was obtained with *f*AUC/MIC, identifying it as PDI for WCK 771 (co-efficient of regression, R^2 for *f*AUC/MIC: 0.92-0.93, *f*Cmax/MIC: 0.80-0.88 & *f*T>MIC: 0.82-0.84). PDT studies employing nine *S. aureus* strains showed *f*AUC/MIC requirement in the range of 2.2 to 22.1 and 10.1 to 45.9 were associated with static and 1 $\log_{10}$ kill effects, respectively. Co-modelling based (Figure) *f*AUC/MIC requirement of 6.0 (static effect) and 25.4 (1 $\log_{10}$ kill) were identified as PDTs for undertaking probability of target attainment (PTA) analyses.

Conclusions: The *f*AUC/MIC is *in vivo* efficacy driver of WCK 771. The PDT determining studies that included 5 QRSA strains helped determine robust PDTs for WCK 771.

Figure: Co-modelling based PDT of WCK 771 against *S. aureus* (N=9)



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