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WCK 4873 (Nafithromycin): PK/PD analysis for H. influenzae (HI) through murine lung infection model

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Background: WCK 4873 is a novel lactone ketolide with potent activity against respiratory tract pathogens including HI strains. Recent global surveillance studies have demonstrated that WCK 4873 MIC_{90} for HI (n=1002), was 4 µg/mL. Phase 1 studies including pulmonary PK studies with WCK 4873 have been completed recently. PK/PD analyses aimed at identifying the efficacy driving PK/PD index and its magnitude employing mouse serum and ELF PK to support PK/PD breakpoint for HI infections.

Material/methods: WCK 4873 dose fractionation studies were performed against 3 HI (one reference ATCC strain and one each- β-lactamase expressing and Fluoroquinolone-resistant) strains in neutropenic (cyclophosphamide - 150 and 100 mg/kg, IP at -4 and -1 days) mice lung eradication model. Lung infection was initiated by intranasal instillation of 10^7-10^8 CFU/mL. The three strains were selected based on their good lung colonization ability as evidenced by 27h stable lung infection. Oral treatment was initiated 2h post-infection (2h count: 6.87-7.29 $\log_{10}$ CFU/lung) administered over 24h. For all HI, WCK 4873 doses (2.5 to 300 mg/kg) were fractionated as q6h, q12h and q24h to assess the impact of dose fractionation. Bacterial enumeration in lungs was undertaken 27h post-infection for all groups.

PK data was obtained for single oral doses (2.5 - 300 mg/kg) of WCK 4873 in fed Swiss mice. Blood and ELF samples were collected at various time points up to 24h. WCK 4873 concentrations in serum and ELF were estimated by validated LC-MS/MS method. Urea measurement (colorimetric assay) in serum and BAL fluid were used to determine WCK 4873 concentrations in ELF. Serum and ELF pharmacokinetic parameters were estimated by non-compartmental analysis using Phoenix Win

NonLin 6.2. Exposure-response analysis to arrive at PK/PD index and its magnitude was undertaken using Graph Pad prism software.

Results: WCK 4873 (PO dose range: 2.5 to 300 mg/kg) demonstrated 1 and 1.7 log kill at 150 and 300 mg/kg, respectively against HI ATCC 9006. For this strain (WCK 4873 MIC: 4 µg/mL) PK/PD analysis showed that 24h *f*AUC/MIC and *f*C_{max}/MIC indices best correlated with R^2=0.939 and R^2=0.935, respectively. For HI 151 and 42 (WCK 4873 MIC: 8 µg/mL), WCK 4873 exhibited ~1 to 1.5 log kill at dose of 100-300 mg/kg, respectively. For HI 9006, 151 and 42, serum *f*AUC_{0-24}: MIC of 0.85, 0.20 and 0.37 respectively was associated with 1 log CFU reduction from the baseline. Coefficient correlation for unbound serum AUC/MIC and ELF AUC/MIC on basis of co-modelling of three HI resulted into PK/PD target of unbound serum AUC_{0-24}: MIC of 0.45 and ELF AUC_{0-24}: MIC of 16.19 associated with 1-log kill.

Conclusions: WCK 4873 PK/PD studies provided targets which would be utilized to arrive at the PK/PD breakpoint for *H. influenzae*.