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Pharmacokinetics and pharmacodynamics of murepavadin (POL7080) in neutropenic lung infection models

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Background: Murepavadin (POL7080) represents the first member of a novel class of outer membrane protein targeting antibiotics. It specifically interacts with LptD and inhibits LPS transport. Murepavadin is being developed by Polyphor for the treatment of serious infections by *Pseudomonas aeruginosa* (PA). POL7080 displays potent antimicrobial activity against *P. aeruginosa* with an MIC_{90} at 0.12 mg/L. This study aimed to determine the pharmacokinetics of POL7080 in plasma and ELF (pulmonary) in infected animals as well as determining the exposure response relationship. The goal was to determine the most important PK/PD index that correlates with efficacy and the PI estimates for the static, one and two log kills.

Material/methods: The pharmacodynamics of POL7080 were explored in neutropenic mouse lung and thigh models. POL7080 MICs of *Pseudomonas* strains ranged from 0.125-0.5 mg/L. Pharmacokinetic profiles were determined in infected animals for 8 different dose levels after a single dose s.c., 0.125 – 16 mg/kg in plasma and ELF. In the pharmacodynamic studies, mice were inoculated in the lung and treatment commenced 2 hours (t=0h) after infection and lasted for 24 hours (t=24h). Full dose fractionation studies were performed for 2 *P. aeruginosa* strains. A dose rage of 0.25-32 mg/kg was used divided into1, 2, 4 or 8 fractions over 24h. CFU counts were obtained by homogenization of tissue and compared to t=0. Exposure-response was modelled using the E_{max} model with variable slope. Validation experiments were performed for 13 additional strains at 3 facilities. The pharmacodynamic target was estimated using 14 different strains (9 MDR) in the neutropenic lung infection model and plasma protein binding that was similar across species with a free fraction of 22.4±6.4% (mean±SD).

Results: POL7080 showed linear pharmacokinetics in plasma for total drug and was dose proportional and had a good penetration in ELF with a mean penetration (AUC) ratio of 25.6% for total drug and 114.5% for free drug. The dose fractionation study, POL7080 given every 3h, 6h, 12h or 24h, indicated that the total daily dose and fAUC were the main determinants for efficacy in both the lung and the thigh model. In the validation study, one strain did not respond to therapy. The mean fAUC for a static effect of the 14 strains evaluated was 6.46 mg.h/L, and the mean fAUC/MIC 29.8. For a 1 log-drop reduction these values were 9.79 mg.h/L and 44.98 respectively. A 2-log reduction was observed for only 7 strains and fAUC/MIC calculated to be 45.27

Conclusions: POL7080 showed linear pharmacokinetics and was dose proportional. The compound has good penetration into the ELF. The efficacy of POL7080 was primarily dependent on AUC. The mean *f*AUC/MIC ratios for a static and 1-log drop were 29.9 and 45.0, respectively for the 14 *P. aeruginosa* isolates analysed.