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Population pharmacokinetics modelling of murepavadin (POL7080) and simulation of target attainment in a population with ventilator associated pneumonia due to infection with Pseudomonas aeruginosa

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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. Earlier studies have shown that POL7080 exhibits a specific and potent antimicrobial activity against *P.aeruginosa* with a MIC_{90} at 0.12 mg/L. Plasma protein binding was similar across species with a free fraction of 22.4±6.4% (mean±SD). From a mouse infection model it was determined that an AUC_{24h} /MIC of 200 resulted in a 1-log drop in CFU. The objective was to determine the murepavidin dose required to achieve the PK/PD target of AUC_{24h} /MIC=200 in a VABP population.

Material/methods: A population PK model was built based on plasma concentrations and demographic data determined in 211 subjects from seven clinical studies using Monolix software following standard procedures. By means of the derived population model, Monte Carlo simulations (MCS) were performed with Simulx software for a VAP population to estimate the target attainment, which is the percentage of patients with an AUC_{24h}/MIC >200 for a MIC of 0.25 or 0.5 mg/L.

Results: From the population PK analysis it was found that POL7080 distributed into two compartments and was eliminated via linear clearance (CL) from the first compartment. Terminal $t_{1/2}$ in VAP patients was 8.4 h, the central compartment volume 13 L and the total V_D was 46 L. Creatinine clearance (CrCl) was found to be a significant covariate on murepavidin CL with a covariate exponent of 0.5. MCS were run for a VAP population to estimate the target attainment. In a sensitivity analysis, body weight and age were found to have no relevant impact on target attainment supporting the use of fixed- instead of body weight-adjusted dosing. CrCl was found to have a considerable impact on murepavidin PK and consequently also on target attainment. For individuals with a normal CrCl, a dose of 630 mg total daily dose was selected. For individuals with renal impairment and low CrCl, the dose was reduced to 420 mg total daily dose to compensate for the lower CL of murepavidin, and to ensure that in patients critical exposure limits will not be exceeded. Finally, for individuals with augmented clearance, a dose of 840 mg total daily dose was recommended. Regardless of the kidney function, a loading dose of 420 mg, given as a 4 hour infusion, was proposed

Conclusions: With the proposed dose the entire patient population was predicted to achieve the target attainment at a MIC of 0.25 mg/L. For a MIC of 0.5 mg/L, the target attainment was predicted to be approximately 90% for all dose groups. Applying our proposed dose of murepavidin could be a promising new antimicrobial to treat pseudomonal VABP.