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Population pharmacokinetics of Murepavadin (POL7080) and Monte Carlo simulations to develop clinical dosing regimens, including the renally impaired

Brenda De Winter[1], Anouk Muller*[2], Glenn Dale[3], Achim Wach[4], Johan Mouton[5]

[1]*Erasmus University Medical Center; Clinical Pharmacy*

[2]*Medical Centre Haaglanden; Department of Medical Microbiology*

[3]*Polyphor Ltd.; Clinical Development*

[4]*Polyphor Ltd.*

[5]*Erasmus University Medical Center; Department of Medical Microbiology and Infectious Diseases*

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). In this study a combined population pharmacokinetic analysis is performed to determine if the pharmacodynamic targets as derived from preclinical studies could be reached (AUC/MIC of 208), including studies in patients with Ventilator Associated Pneumonia (VAP) and renal impairment.

Material/methods: A population pharmacokinetic model was built based on concentrations determined in 211 subjects included in seven preclinical trials (including single and multiple dose ascending, renal impairment, VAP and COPD) using nonlinear mixed effects modeling (NONMEM, FOCE+I) with logarithmically transformed data. Doses ranged from 0.05 mg/kg up to 10 mg/kg iv. The final structural model and the covariate model were validated using bootstrap and NPDE. The validated final model was used to evaluate the influence of covariates on the exposure to Murepavadin. Monte Carlo simulations using the structural model without covariates were used to calculate the target attainment using a target AUC/MIC of 208 and MICs of 0.125, 0.25 and 0.5 mg/L.

Results: Data were best described using a two-compartment model with interpatient variability (IPV) on clearance, central volume of distribution, intercompartmental clearance and peripheral volume of distribution (see table). In the final covariate model we found four significant covariates: creatinine clearance, age, height and VAP. Only changes in creatinine clearance resulted in significant changes in AUCs. In patients treated with 600mg total daily dose (tdd) target attainment for MIC of 0.25 mg/L was reached in almost 95% of the subjects. Treatment with 750mg tdd resulted in almost 99% target attainment. For MIC of 0.5 mg/L higher daily doses than 750mg tdd were needed to reach > 90% target attainment. The simulations suggest that doses should be adjusted for renal function: creatinine clearance of 70-120 mL/min to 600mg tdd, creatinine clearance of 30-70 mL/min to 450mg tdd and creatinine clearance of <30 mL/min to 300mg tdd.

Conclusions: A two-compartment model best describe the pharmacokinetics of Murepavadin, in which impaired renal function caused a clinical relevant decrease of drug clearance. To reach 95% target attainment for an MIC of 0.25 mg/L a 600mg tdd is required. The dose should be decreased in patient with impaired renal function. These data provide a robust basis for dosing strategies in clinical studies.

Parameter	**Estimation (RSE)**	**Shrinkage (%)**
Clearance (L/h)		
TVCL (L/h)	7.03 (2%)	
A (influence of CRCL)	0.714 (5%)	
B (influence of height)	1.71 (17%)	
IPV (%)	21.4 (7%)	4.0
Central volume of distribution (L)	13.6 (2%)	
IPV (%)	21.5 (14%)	15.2
Intercompartmental clearance (L/h)		
TVQ	4.66 (3%)	
C (influence of VAP)	2.64 (12%)	
IPV (%)	27.1 (14%)	19.4
Peripheral volume of distribution (L)		
TVVp	24 (3%)	
D (influence of age)	0.663 (11%)	
IPV (%)	26.8 (9%)	17.0
Residual error	0.182 (6%)	9.7

Table I: final parameter estimates Estimations are presented as value (RSE). CL=TVCL(CRCL/120)^{A}*(height/173)^{B} (CRCL=creatinine clearance estimated using Cockroft-Gould with a maximum value of 120 mL/min, height=height in cm), Q=TVQ*(C)^{VAP} (VAP=1 for VAP patients and VAP=0 for all other subjects), Vp=TVVp*(age/44)^{D} (age=age in years)*