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Pharmacokinetic of murepavadin (POL7080) and amikacin in a drug-drug interaction phase 1 study in healthy subjects

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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. Murepavidin is being developed by Polyphor for the treatment of serious infections by *Pseudomonas aeruginosa* (PA). Amikacin (as sulfate) is a semi-synthetic, broad spectrum antibiotic. This study investigated the potential PK drug-drug interaction between POL7080 and amikacin through membrane receptors. If approved to treat severe infections, POL7080 may be co-administered with other agents against PA such as amikacin. Understanding the extent of potential interactions is of critical relevance for the development of POL7080.

Material/methods: This was a single-center, open-label, 2-sequence, 3-period crossover drug-drug interaction study in adult male and female healthy subjects. Subjects were assigned to 1 of 2 treatment sequences and received repeated doses of POL7080 (2.5 mg/kg q8h, 7 doses as a 2-hr infusion) and amikacin (15 mg/kg q24h, 3 doses over 30 minutes) alone followed by combined treatment.
The study consisted of an screening period (within 4 weeks), up to 3 treatments periods with hospitalization from Day -1 to Day 4, a washout of at least 12 days between Periods, and a follow-up visit (14 ± 2 days after last dosing in Period 3).
Plasma and urine samples were collected after the last dose and measured by specific, and validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods. Lower limits of

quantifications in plasma were 10 ng/mL and 0.5 µg/mL for POL7080 and amikacin, respectively. PK data were analyzed using non-compartmental methods.

Results: In total, 9 of the 14 randomized subjects were included in the PK analysis population (i.e., subjects with non-missing primary PK parameters for POL7080 and amikacin in at least 2 periods). One subject had a PK blood sample taken from the infusion arm during POL7080 infusion. Results of the PK analysis indicated a 1.1-fold (90% CI: 1.04-1.26) higher plasma C_{max} and 1.1-fold (90% CI: 0.97-1.13) higher AUC_{tau} of POL7080 combined with amikacin when compared to administration of POL7080 alone.
C_{max} of amikacin combined with POL7080 increased by 1.0-fold (90% CI: 0.97-1.13) and AUC_{tau} by 1.1-fold (90% CI: 1.05-1.16) when compared to administration of amikacin alone.
The mean cumulative amount of unchanged POL7080 and amikacin excreted into urine within 24-h ($Ae_{(0-24)}$) and the mean fraction (f_e) of dose excreted unchanged into urine were similar after administration of POL7080 (12.6% vs 13.1%) or amikacin (92.3% vs 90.2%) alone and after combined administration.

Conclusions: The results of this drug-drug interaction study indicated no relevant increase in POL7080 and amikacin C_{max} and AUC_{tau} when administered concomitantly. Co-administration of POL7080 and amikacin did not influence renal excretion of both drugs. Multiple doses of POL7080 and amikacin were considered to be safe and with acceptable tolerability.