PHARMACOKINETICS OF MUREPAVADIN (POL7080) AND AMIKACIN IN A DRUG-DRUG INTERACTION STUDY IN HEALTHY SUBJECTS

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Introduction and Purpose

Murepavadin (POL7080) represents the first member of a novel class of outer membrane protein targeting antibiotics, being developed by Polyphor for the treatment of serious infections by *Pseudomonas aeruginosa*. Murepavidin is a pathogen-specific antibiotic with a potent and specfic antibacterial activity both *in vitro* and *in vivo*.
This study investigated the potential PK drug-drug interaction between murepavadin and amikacin through membrane receptors such as megalin.

Methods

- A single-center, open-label, 2-sequence, 3-period crossover drug-drug interaction study in adult male and female healthy subjects. Treatment sequence was allocated at random (Table 1).

Table 1: Study Design

	Period 1	Period 2	Period 3
Sequence 1 (PAC)	POL7080	Amikacin	POL7080 + amikacin
Sequence 2 (APC)	Amikacin	POL7080	POL7080 + amikacin
P: POL7080 (murepavadin); A: amikacin; C: combination of POL7080 +amikacin			

- Subjects received repeated doses of murepavadin (2.5 mg/kg q8h, 7 doses as a 2-hour infusion) or amikacin (15 mg/kg q24h, 3 doses over 30 minutes) alone followed by combined treatment.
- The study consisted of an screening period, 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).
- Blood and urine samplings were performed after the last dose on each Period.
- PK parameters (C_{max}, AUC_{tau}) were estimated using standard non-compartmental methods.
- Two-sided 90% confidence intervals for the ratios (murepavadin + amikacin vs murepavadin alone, and murepavadin + amikacin vs amikacin alone) of the geometric means were derived.
- Plasma and urine samples were analyzed using validated LC-MS/MS methods. Lower limits of quantifications in plasma were 10 ng/mL and 0.5 µg/mL for murepavadin and amikacin, respectively.

Results

- In total, 14 White male and female subjects of non-childbearing potential participated in the treatment phase of this study (Table 2).
- Five subjects discontinued prematurely the study: 3 for amikacin-related AEs, 1 for a positive cotinine test, and 1 for an abnormal vestibular function test.

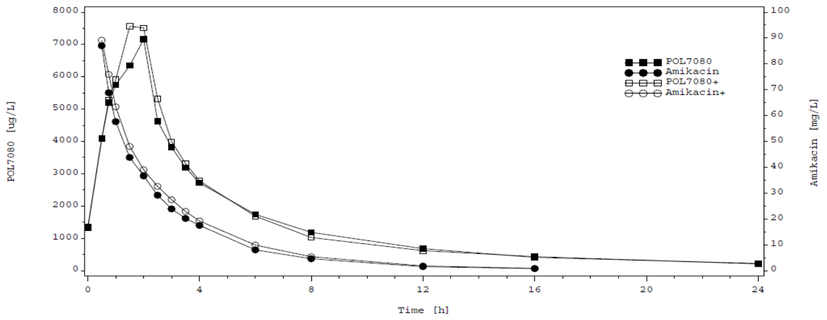
Table 2: Demographics

Parameter	Statistic	Safety set N=14	PK set N=9
Gender	n(%) male n(%) female	12 (87.5%) 2 (14.3%)	8 (88.9%) 1 (11.1%)
Age [years]	Mean (SD) Min-Max	35.57 (9.874) 20.0-50.0	36.22 (8.743) 38.0-50.0
Body weight [kg]	Mean (SD) Min-Max	79.39 (9.158) 66.6-94.6	79.33 (7.889) 69.2-90.4
Creatinine clearance [mL/min]	Mean (SD) Min-Max	119.36 (19.910) 97.0-153.0	118.22 (22.523) 97.0-153.0

Plasma Pharmacokinetics

- 9 of 14 subjects were included in the PK analysis set.
- One subject had a PK blood sample (1 hour into infusion) taken from the infusion arm during murepavdin infusion on Day 3 of the Period 3. PK results were calculated in a sensitivity analysis without this concentration value to investigate the impact on the PK results (Figure 1).

Figure 1: Geometric mean plasma concentrations of murepavadin and amikacin versus time



Statistical analysis of plasma PK parameters

- Murepavadin: for AUC_{tau}, the 90% confidence intervals were completely contained within the bioequivalence acceptance range of 80.00% to 125.00% (Table 3). The point estimates indicated an about 1.1-fold higher C_{max} (90% confidence interval [CI]: 103.56%-126.48%).
- Amikacin: overall exposure to amikacin in plasma was slightly increased after administration of the combination compared to amikacin alone but 90% CIs of AUC_{tau} and C_{max} were within the bioequivalence acceptance range.

Table 3: Point estimate and 90% confidence interval for primary plasma PK parameters of murepavadin and amikacin.

Analyte	Ratio	Parameter	PE [%]	90% CI	
				Lower limit	Upper limit
Murepavadin	C/M	C_{max}	114.45	103.56	126.48
		AUC_{tau}	104.99	97.38	113.21
Amikacin	C/A	C_{max}	104.66	96.94	113.00
		AUC_{tau}	110.74	105.31	116.45

A=amikacin; M=murepavadin; C=combination murepavadin+amikacin; PE=point estimate; CI=confidence interval

Urine

- The mean cumulative amount of unchanged murepavadin and amikacin excreted into urine within 24 hours ($Ae_{(0-24)}$) and the mean fraction (f_e) of dose excreted unchanged into urine were similar after administration of murepavadin (12.6% vs 13.1%) or amikacin (92.3% vs 90.2%) alone and after combined administration.

Conclusion

- The results of this drug-drug interaction study indicated no relevant increase in murepavadin and amikacin exposures when administered concomitantly.
- Co-administration of murepavadin and amikacin did not influence renal excretion of both drugs.
- Multiple doses of murepavadin and amikacin were considered to be safe and with acceptable tolerability.

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