Pharmacokinetics of POL7080 co-administered with standard of care in patients with ventilator-associated pneumonia due to suspected or documented *Pseudomonas aeruginosa* infection

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Introduction and Purpose

POL7080 is a novel cyclopeptide being developed by Polyphor for the treatment of serious infections by Pseudomonas *aeruginosa*, one of the most frequent nosocomial organisms to cause ventilator-associated pneumonia (VAP). POL7080 utilizes a novel mode of action that disrupts bacterial processes necessary for outer membrane lipopolysaccharide biogenesis (Srinivas N, *et al*, 2010).

Positive pressure ventilation (PPV) causes complex changes in the functioning of cardiovascular, pulmonary and renal systems. These changes, and the extensive fluid administration necessary to compensate for the produced changes, could influence the distribution and elimination of water soluble drugs.

It has been observed for gentamicin that PPV altered the pharmacokinetic (PK) disposition of the drug resulting in a increase (40%) in apparent volume of distribution (Vz) which resulted in lower than desired peak plasma concentrations (Triginer *et al*, 1991). Similarly, PPV was shown to have an influence on the PK of ceftazidime where the Vz was increased 2.5 fold (Conil *et al*, 2007). For both, gentamicin and ceftazidime the PK is defined by high renal excretion and a Vz similar to that of the extracellular space.

Similar to gentamicin and ceftazidime, the PK data of POL7080 suggest that it is distributed in extracellular space and is renally cleared followed by tubular re-absorption.

This study investigated the PK of POL7080 (2.5 mg/kg, 2h intravenous infusion; *t.i.d* for 10 to 14 days) co-administered with standard of care (SoC) in VAP patients with suspected or confirmed *P. aeruginosa* infection.

Methods

This was an interim analysis of a Phase II, open-label study conducted in subjects of either sex diagnosed with VAP due to suspected or confirmed *P. aeruginosa* infection for which treatment with SoC anti-pseudomonas antibiotics is necessary (n=19 PK population, defined as patients with at least one dose of POL7080).

Blood samples were taken at various time points on Day 1 (prior to infusion, during infusion, and post-infusion), Day 7 (during and post-infusion), and daily prior to the first dose to allow for a complete PK profile over the treatment period.

POL7080 plasma concentrations were analysed with validated methods and PK data were interpreted using non-compartmental procedures to allow for a complete PK profile over the treatment period.

Results

- The PK of POL7080 in patients under ventilation has a mean C_{max} and AUC_{tau} of 5.49 ± 1.78 mg/L, and 21.55 ± 6.03 h*mg/L, respectively, and a mean Vz of 0.56 ± 0.14 L/kg.
- The PK of POL7080 on Day 7 in patients under ventilation shows a mean C_{max} and AUC_{tau} of 7.97 ± 1.85 mg/L and 41.96 ± 15.49 h*mg/L, respectively, and Vss of 0.35 ± 0.07 L/kg

Figure 1: Plasma concentration–time profiles for all subjects on Day 1

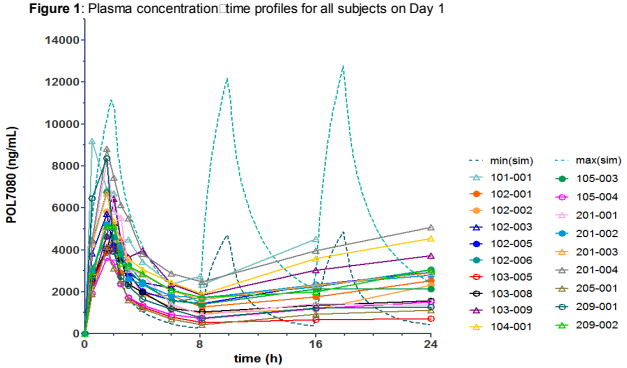
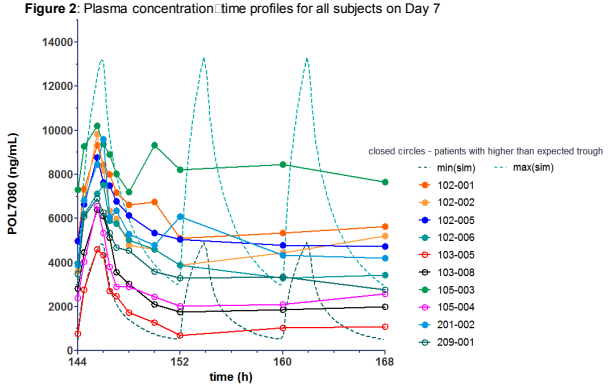


Figure 2: Plasma concentration–time profiles for all subjects on Day 7



- The mean total CL (128.7 ± 60.9 mL/min) on Day 1 is similar to the Cr_{CL} (121.8 ± 48.7 mL/min) calculated at screening using the Cockcroft-Gault equation.
- The mean total CL (94.4 ± 52.8 mL/min) on Day 7 is similar to the Cr_{CL} (118.8 ± 49.8 mL/min) calculated using the Cockcroft-Gault equation.
- By visual inspection Steady-State seemed to be reached on Day 3 and there is little or no accumulation.
- The steady state exposure of POL7080 dosed at 2.5 mg/kg tid in critically ill patients under positive pressure ventilation are similar to that observed in healthy volunteers with the mean C_{max} = 7.36 ± 0.96 mg/L and AUC_{tau} = 26.26 ± 4.44 h*mg/L)

Table 1: Individual Pharmacokinetic parameters Day 1 (infusion-1)

Patient ID	C_{max}	AUC_{tau}	Vz	CL	CrCL (screen)	$t_{1/2}$
	mg/L	h*mg/L	L/kg	(mL/min)	(mL/min)	h
101-001	9.19	33.4	0.41	59	70	6.8
102-001	4.59	18.3	0.65	113	106	5.0
102-002	5.83	19.0	0.51	133	127	3.3
102-003	5.71	19.1	0.64	88	142	7.6
102-005	4.21	18.7	0.65	98	70	5.4
102-006	4.62	21.0	0.56	97	56	5.3
103-005	4.05	13.3	0.70	242	183	3.0
103-008	5.14	17.5	0.62	141	143	4.1
103-009	6.43	25.8	0.43	123	186	4.4
104-001	5.37	24.7	0.51	114	149	5.6
105-003	6.75	23.0	0.52	103	200	4.6
105-004	3.62	12.9	0.87	191	175	4.2
201-001	8.17	25.1	0.34	153	126	2.7
201-002	5.22	21.5	0.69	76	99	7.8
201-003	6.70	25.3	0.49	101	66	5.0
201-004	8.83	34.7	0.33	57	68	4.6
205-001	4.15	12.0	0.69	301	171	2.6
209-001	8.36	21.4	0.47	152	127	3.2
209-002	5.09	22.7	0.54	103	50	5.5

Table 2: Individual Pharmacokinetic parameters Day 7 (infusion-19)

Patient ID	C_{max}	AUC_{tau}	Vss	CL	CrCL (Day 4)
	mg/L	h*mg/L	L/kg	(mL/min)	(mL/min)
102-001	9.33	55.8	0.26	56	106
102-002	9.84	45.3	0.29	69	91
102-005	8.77	50.3	0.28	58	58
102-006	7.53	42.5	0.33	78.4	75
103-005	4.61	16.8	0.43	223.2	205
103-008	6.39	27.6	0.36	120.8	160
105-003	10.20	69.2	0.29	48.2	100
105-004	6.55	26.5	0.48	125.8	175
201-002	9.58	48.5	0.37	63.6	71
209-001	6.90	37.1	0.37	101.1	148

Table 3: Summary of Pharmacokinetics

		C_{max} mg/L	AUC_{tau} h*mg/L	Vz or Vss L/kg	CL (mL/min)	CrCL (mL/min)
Day-1 (ITT)	mean	5.49	21.55	0.56	128.7	121.8
	SD	1.78	6.03	0.14	68.9	48.7
Day-1 (mITT)	mean	5.24	18.66	0.62	134.6	128.6
	SD	1.42	3.39	0.12	50.23	47.83
Day-7 (mITT)	mean	7.97	41.96	0.37	94.4	118.8
	SD	1.84	15.49	0.07	52.8	49.8

Figure 3: Correlation of AUC_{tau} at Steady-State with creatinine clearance

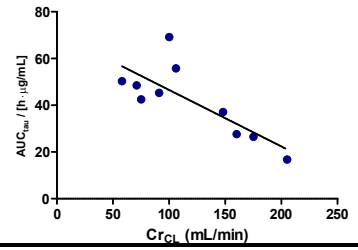
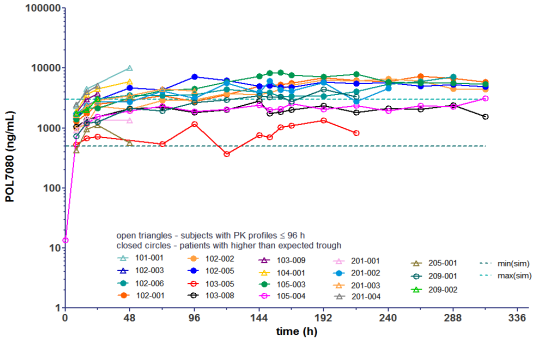


Figure 4: POL7080 trough plasma concentration-time profiles for all subjects



Conclusions

- Although a decrease in POL7080 exposure was expected due to the haemodynamic changes as a result of mechanical ventilation, the steady-state exposure of POL7080 seems to be increased as observed in healthy volunteers.

  Cmax : 7.97 ± 1.84 vs 7.36 ± 0.96 mg/L

  AUC_{tau}: 41.96 ± 15.49 vs 26.26 ± 4.44 h*mg/L

  CL: 118.8 ± 49.8 vs 120.16 ± 18.7 mL/min
- The total clearance of POL7080 is similar in VAP patients compared to healthy volunteers at steady-state thus the increase in exposure is likely due to a decrease in volume of distribution.
- The PK seems to be dominated by the Glomerular filtration rate in these patients.
- A dose adjustment may be necessary for patients with augmented creatinine clearance

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ECCMID, Amsterdam, 9 – 12 April, 2016; **Poster 3786**