Phase I (multiple ascending dose) study with the novel *Pseudomonas aeruginosa* antibiotic POL7080 in healthy volunteers □P 1421

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Abstract

Objectives: POL7080 is a novel PEM (Protein Epitope Mimetics) antibiotic selectively targeting Pseudomonas species with demonstrated potent *in vitro* activity and *in vivo* efficacy in murine infection models. A multiple ascending dose (MAD) study was conducted to evaluate safety, tolerability, plasma pharmacokinetics (PK) and urinary excretion.

Methods: Twelve healthy male subjects, aged 18-40, were randomised and participated in a double blind, placebo-controlled study with multiple ascending doses. Each of the 2 dose groups consisted of 6 subjects which were randomised, 4 to receive POL7080 and 2 to receive placebo. POL7080 was administered as multiple 3 h infusions of 1 mg/kg twice daily (bid) 12 h apart (cohort 1) or as multiple 3 h infusions of 2 mg/kg three times a day (tid) 8 h apart (cohort 2). Plasma concentrations of the drug were determined by LC-MS/MS analysis and interim (using nominal time) PK parameters were calculated using WinNonlin®.

Results: The mean plasma concentration-time profiles of POL7080 both following multiple dose administrations were characterized by an increase during the 3 hour infusion period followed by a multi-phasic decline. By visual inspection of trough (pre-dose) values following multiple bid or tid administration of POL7080, steady-state was considered to have been reached on Day 2. The mean accumulation ratio based on Cmax (Rac,C_{max}) or AUC_{tau} (Rac,AUC_{tau}) was 1.0 or 1.1 following 1.0 mg/kg bid administration and 1.2 or 1.5 following 2.0 mg/kg tid administration. Following multiple dose administration for 6 days (at steady-state), POL7080 was excreted in urine with a mean concentration of 7.57 μg/mL and a mean CLR of 79.3 mL/h. No serious adverse events (SAEs) were reported for either dose group and all AEs were mild and not prohibitive to dose increases. Blood chemistry and clinical laboratory results were normal during dosing and at follow up, indicating that POL7080 was well tolerated in both dose groups.

Conclusions Multiple doses of POL7080 were well tolerated at plasma concentrations expected to meet or exceed efficacious levels and no serious adverse event was reported. The PK of POL7080 showed no accumulation following 6 days twice-daily or three times a day dose administration by intravenous infusion.

Introduction and purpose

Health-care-associated infections are a significant cause of morbidity and mortality and represent a major challenge to patient safety. The management of bacterial infections is becoming increasingly difficult due mainly to the increased prevalence of multi-drug resistant (MDR) pathogens. Mid to long-term strategies to prevent antimicrobial resistance in the intensive care unit include shorter courses of appropriate antibiotic treatment and narrowing of antimicrobial spectrum based on culture results.

Antimicrobial peptides such as protegrin-I show a great potential largely due to their activity against MDR Gram-negative bacteria and low incidences of bacterial resistance formation (1). However, their clinical development as systemic drugs has so far been hampered by some unfavourable ADMET properties.

POL7080 from Polyphor, which was derived from protegrin-I applying the Protein Epitope Mimetic (PEM) technology, has been shown to have potent and specific antimicrobial activity against *Pseudomonas aeruginosa* by targeting the ß-barrel protein LptD (Imp/OstA), which functions in the outer-membrane biogenesis (2). Here we report the results from the multiple ascending dose (MAD) study that was conducted to evaluate safety, tolerability, plasma pharmacokinetics (PK) and urinary excretion

Methods

Clinical study design: Multiple ascending dose (MAD) using a randomized, double blind, placebo-controlled design in one center. POL7080 was administered as multiple 3 h infusions of 1 mg/kg twice daily (bid) 12 h apart (cohort 1) or as multiple 3 h infusions of 2 mg/kg three times a day /tid) 8 h apart (cohort 2). The last dose administered in the MAD was the Day 6 morning dose.

Safety evaluation: Safety was assesed via AEs, physical examination, clinical laboratory data, continuous cardiac monitoring via Holter ECG and blood pressure. Local tolerance and injection site was monitored and recorded.

PK evaluation: Two 5-ml blood samples were taken at predose, then 1h, 2h, 3h, 3.5h, 4h, 5h, 6h, 9h and/or before the administration of each dose after the start of infusion. Urine fractions were collected predose, then at [0-6h], [6-12h], [12-18h] and [18-24h] post dosing. POL7080 in plasma and urine was determined by validated LC-MS/MS methods. The lower limit of quantification (LOQ) in plasma was 10 ng/ml. Pharmacokinetic analysis was performed on blinded plasma concentration data and nominal sampling times using WinNonlin® Professional®, version 5.2 standard noncompartmental analysis.

Results

Table 1: Summary of POL7080 plasma PK parameters (Mean and SD, n=4)

Dose	Day	C_{max}	AUC_{tau}	CL	V_{ss}	V_z	$t_{1/2}$	MRT	fe	LI
[mg/kg]		[mg/mL]	[h*mg/mL]	[L/(h*kg)]	[L/kg]	[L/kg]	[h]	[h]	% of dose	
1 bid	Day 1	2300 (340)	11300 (1030)	0.079 (0.007)	0.334 (0.072)	0.449 (0.085)	3.95 (0.71)	4.24 (0.889)	N/D	
1 bid	Day 6	2390 (686)	11600 (2750)	0.09 (0.025)	0.422 (0.130)	0.607 (0.223)	6.21 (0.435)	4.66 (0.205)	N/D	0.934 (0.258)
2 tid	Day 1	5440 (1060)	18600 (3160)	N/D	N/D	N/D	N/D	N/D	N/D	
2 tid	Day 6	6720 (1090)	28700 (5250)	0.071 (0.012)	0.289 (0.069)	0.750 (0.214)	7.20 (1.03)	4.03 (0.525)	1.38 (0.225)	1.26 (0.043)

Figure 1: Mean plasma concentration-time profiles of POL7080 (n=4, linear scale)

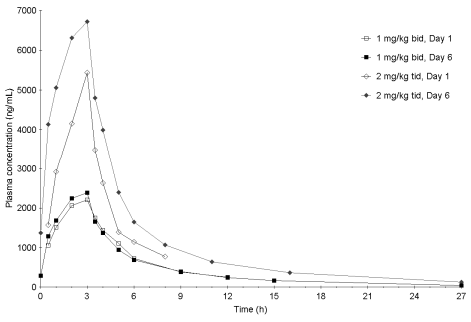

Figure 2: Mean plasma concentration-time profiles of POL7080 (n=4, log-linear scale)

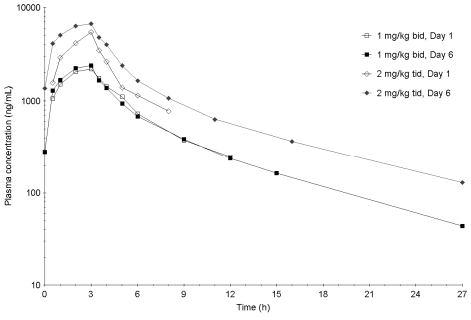

Figure 3: Pre-dose (trough) plasma concentrations versus time following 2 mg/kg tid POL7080 multiple intravenous 3 hour infusions (linear scale; Mean and SD, n=4)

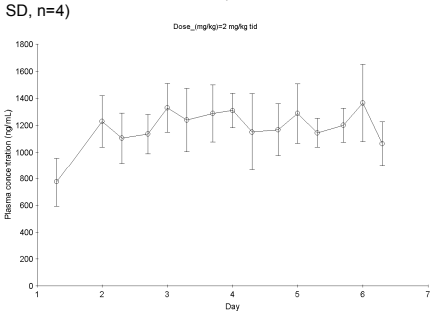

Table 2: Number of subjects reporting treatment emergent adverse events

Adverse event	1 mg/kg bid	2 mg/kg tid	Severity	Outcome
Infusion site reaction	2 (1a, 1c)		Moderate/Severe	resolved
Catheter site related reaction	2 (1b, 1c)	2 (1a, 1c)	Mild	resolved
Catheter site pain		1 (1c)	Moderate	resolved
Phlebitis	1 (1b)		Mild	resolved
Paraesthesia (local)	1 (1b)		Mild	resolved
Paraesthesia (oral)	1 (1a)		Mild	resolved

a,b,c refer to volunteers from each cohort

Conclusions

Six subjects were given POL7080 or placebo as a single 3 hour infusion at each dosing cohort and only subjects on active treatment were included in the analysis.

The inter-subject variability (CV%) in exposeure parameters was generally low, ranging between 9 and 26% for the $AUC_{0\text{-}inf}$, 14 and 30% for the C_{max} and 7 and18% for the $t_{1/2}$.

By visual inspection of trough (pre-dose) values following multiple bid or tid administration of POL7080, steady-state was considered to have been reached Day 2 (Figure 3). The mean accumulation ratio based on C_{max} (Rac,C_{max}) or AUC_{tau} (Rac,AUC_{tau}) was 1.0 or 1.1 following 1.0 mg/kg bid administration and 1.2 or 1.5 following 2.0 mg/kg tid administration. The ratio of AUC_{tau} Day 6/$AUC_{0\text{-}inf}$ Day 1 (Linearity Index, LI) was close to unity for both dose groups (Table 1).

The PK of POL7080 was time-independent following 6 days twice-daily or three times a day dose administration by intravenous infusion

Following multiple dose administration for 6 days POL7080 was excreted in urine with a mean amount excreted of 1.38% of dose and a mean CL_R of 79.3 mL/h. The CL_R was thus lower than the predicted filtration CL_R of 4600 mL/h, as estimated from glomerular filtration rate (GFR; 7500 mL/h)*fraction unbound POL7080 in plasma (0.61), indicating net tubular re-absorption of POL7080. The tendency for CL_R to increase with increased dose suggests that re-absorption occurs via saturable active transport.

No SAEs were reported for either dose group and all AEs were mild, transient and not prohibitive of dose increases. The AEs were local and generally infusion site related.

References

[1] Steinberg, D. A. *et al.* Protegrin-1: a broad-spectrum, rapidly microbicidal peptide with in vivo activity. *Antimicrob. Agents Chemother.* , 1997, **41:** 1738-1742)

[2] Srinivas N, *et al* Peptidomimetic antibiotics target outer membrane biogenesis in Pseudomonas aeruginosa□Science, 2010, 327: 1010-1013.