

# Phase I study with the novel *Pseudomonas aeruginosa* antibiotic POL7080 in healthy volunteers

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## Abstract

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

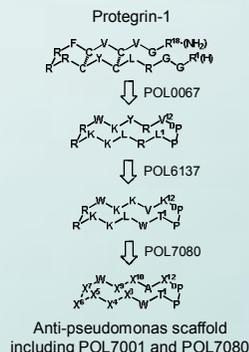
**Methods:** Forty-eight healthy male subjects, aged 18-40, were randomized and participated in a double blind, placebo-controlled study with single ascending doses. Each of the 8 dose groups consisted of 4 subjects randomized to receive POL7080 and 2 to receive placebo. All doses were given as three hour infusions. Plasma concentrations of the drug were determined by LC-MS/MS analysis and interim (using nominal time) PK parameters were calculated using WinNonlin®.

**Results:** POL7080 was detected in plasma of all dose groups with  $C_{max}$  at the end of infusion. PK was dose proportional and plasma exposure increased linearly with respect to  $AUC_{0-\infty}$  and  $C_{max}$ . Inter-subject variability was generally less than 20% for both parameters. Dose normalized  $AUC$  and  $C_{max}$  averaged for all groups were  $9.2 \pm 2.0 \mu\text{g} \cdot \text{h} \cdot \text{mL} / \text{mg}$  and  $1.9 \pm 0.4 \mu\text{g} \cdot \text{kg} / \text{mL} / \text{mg}$ , respectively. The mean half-life ( $t_{1/2}$ ) ranged from 2.6- 5.5 hours (study grand mean  $\pm$  SD =  $4.6 \pm 1.2$  h). No serious adverse events (SAEs) were reported for any dose group and all adverse events (AEs) were mild, transient 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 all dose groups.

**Conclusions:** Single doses of POL7080 were well tolerated at plasma concentrations expected to exceed efficacious levels and no serious adverse event was reported. A multiple ascending dose study has been initiated to assess safety and tolerability of repeated dosing over 5-7 days.

## Background

POL7080 is a representative of a new class of PEM antibiotic compounds with potent activity specifically against *Pseudomonas* spp. including multidrug-resistant (MDR) *P. aeruginosa* (PA). At right, the synthetic evolution of PEM antibiotics is shown. Analogues of protegrin-1 such as POL0067 retain broad antimicrobial activity, while POL6137, POL7001, and POL7080 are active only against *Pseudomonas* spp.



## Methods

**Clinical study design:** Single administration, dose escalation study using a randomized, double blind, placebo-controlled design in one center. Administrations were by three hour intravenous infusions. A total of 8 cohorts (0.05, 0.15, 0.5, 1, 1.5, 2.2, 2.8 and 3.5 mg/kg) with 6 subjects each (4 active + 2 placebo).

**Safety evaluation:** Safety was assessed via AEs, physical examination, clinical laboratory data, cardiac monitoring via Holter ECG, 12-lead ECG and vital signs. Local tolerance at the injection site was monitored and recorded.

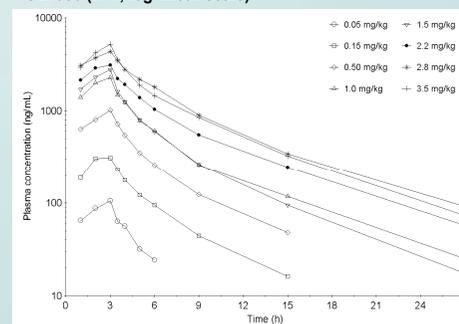
**PK evaluation:** Two 5-ml blood samples were taken at predose, then 1h, 2h, 3h, 3.5h, 4h, 5h, 6h, 9h, 15h, and 27h after the start of infusion. POL7080 in plasma was determined by validated LC-MS/MS methods. The lower limit of quantification (LOQ) in plasma was 10 ng/mL. Pharmacokinetic analysis was performed on blinded plasma concentration data and nominal sampling times using WinNonlin® Professional, version 5.2 standard non-compartmental analysis.

## Results

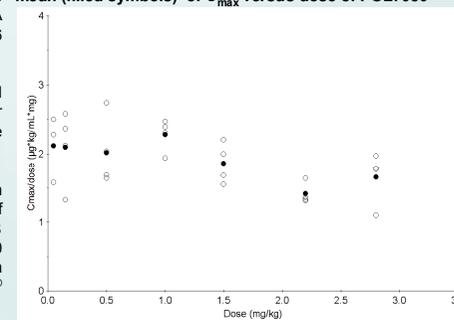
**Table 1: Summary of POL7080 plasma PK parameters (Mean and SD, n=4)**

Dose (mg/kg)	$C_{max}$ (µg/mL)	$AUC_{0-\infty}$ (h·µg/mL)	CL (L/h/kg)	$V_{ss}$ (L/kg)	$V_z$ (L/kg)	$t_{1/2}$ (h)	MRT (h)
0.05	0.106 (0.020)	0.439 (0.076)	0.117 (0.021)	0.336 (0.110)	0.433 (0.166)	2.60 (0.97)	2.89 (0.75)
0.15	0.315 (0.082)	1.59 (0.40)	0.100 (0.029)	0.389 (0.153)	0.525 (0.193)	3.60 (0.30)	3.83 (0.42)
0.50	1.01 (0.25)	4.80 (1.22)	0.109 (0.026)	0.430 (0.051)	0.690 (0.078)	4.55 (1.02)	4.03 (0.53)
1.0	2.28 (0.23)	11.0 (0.5)	0.091 (0.004)	0.400 (0.052)	0.703 (0.082)	5.35 (0.45)	4.39 (0.41)
1.5	2.79 (0.45)	11.8 (1.9)	0.130 (0.021)	0.456 (0.052)	0.857 (0.169)	4.58 (0.56)	3.55 (0.39)
2.2	3.11 (0.34)	18.3 (1.9)	0.121 (0.013)	0.627 (0.053)	0.946 (0.044)	5.48 (0.74)	5.24 (0.79)
2.8	4.64 (1.07)	27.2 (6.5)	0.111 (0.036)	0.553 (0.121)	0.829 (0.216)	5.31 (0.84)	5.23 (1.49)
3.5	5.21 (0.34)	26.7 (3.1)	0.132 (0.014)	0.650 (0.057)	0.976 (0.112)	5.13 (0.53)	4.94 (0.50)

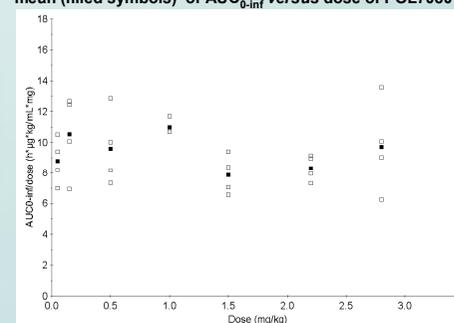
**Figure 1: Mean plasma concentration-time profiles of POL7080 (n=4, log-linear scale)**



**Figure 2: Dose-normalized individual (open symbols) and mean (filled symbols) of  $C_{max}$  versus dose of POL7080**



**Figure 3: Dose-normalized individual (open symbols) and mean (filled symbols) of  $AUC_{0-\infty}$  versus dose of POL7080**



**Table 2: Number of subjects reporting treatment emergent adverse events (from blinded data)**

Adverse event	0.05 mg/kg	0.15 mg/kg	0.5 mg/kg	1 mg/kg	Total
Headache					0
Lightheadedness					0
Decreased sensation in infusion arm					0
Heavy feeling in infusion arm					0
Pain in infusion arm					0
Parasthesia					0
Throat numbness					0
Infusion site erythema					0
Adverse event	1.5 mg/kg	2.2 mg/kg	2.8 mg/kg	3.5 mg/kg	Total
Headache			2 (1a)	2 (1b)	4
Lightheadedness				1b	1
Decreased sensation in infusion arm		1			1
Heavy feeling in infusion arm				1b	1
Pain in infusion arm		1			1
Parasthesia			2 (1a)	3 (1b)	5
Throat numbness				1b	1
Infusion site erythema				1	1

1a and 1b refer to the same subjects with multiple AEs

## Discussion

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 PK analysis.

Detectable plasma concentrations were observed for up to 9 hours after the start of infusion (six hours post dose) for the lowest dose (0.05 mg/kg), up to 15 hours after start of infusion for the 0.15 mg/kg dose group and then up to 27 hours after start of infusion for all other doses.

The maximum plasma concentration was recorded 3 to 3.5 hours after start of infusion for all dose groups and the mean  $C_{max}$  was 1.01 µg/mL for the lowest dose and 5.21 µg/mL for the highest dose group.

The inter-subject variability (CV%) in exposure parameters were generally low, ranging between 5 and 28% for the  $AUC_{0-\infty}$ , 10 and 30% for the  $C_{max}$  and 10 and 22% for the  $t_{1/2}$ .

When dose normalized there was a linear relationship between dose and  $AUC_{0-\infty}$ . There appears to be a tendency for a less than proportional increase in  $C_{max}$  in the dose range from 1.0 to 3.5 mg/kg. However, the deviation was small, only based on visual inspection of the data and not observed for  $AUC_{0-\infty}$ , thus when interpreting all data over the whole dose range, approximate dose proportionality is indicated.

No SAEs were reported for any dose group and all AEs were mild, transient and not prohibitive of dose increases. Since the data are not yet unblinded, the numbers refer to subjects both on placebo and active drug. The AEs were all local and generally infusion site related. The most common AE was parasthesia and was found in 3 subjects at the highest dose. Parasthesia is quite commonly seen during infusion of other antibiotics as well.

## Conclusions

Mean plasma concentration-time profiles of POL7080 showed a multi-phasic decline, in parallel between doses.

The PK of POL7080 was characterized by a volume of distribution of  $0.4 \square 1$  L/kg and a systemic clearance of  $0.09 \square 0.1$  L/h/kg suggesting that the compound is distributed in total body water. The resulting terminal half-life was  $4 \square 5$  h.

Approximate dose-proportionality in the i.v. kinetics of POL7080 was indicated for  $C_{max}$  and  $AUC_{0-\infty}$  in the dose range 0.05 to 3.5 mg/kg.

The inter-subject variability was generally low.

POL7080 was safe and well tolerated at all doses investigated.

## References

Srinivas *et al.* (2010). Peptidomimetic antibiotics target outer-membrane biogenesis in *Pseudomonas aeruginosa*. *Science*. **327**:1010-1013