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

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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 POL7080 and 2 to 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). The last dose administered in the MAD was the Day 6 morning dose.

PK study: Two 5-ml blood samples were taken at predose, then 1h, 2h, 3h, 3.5h, 4h, 5h, 6h and 7h and before the administration of each dose after the start of infusion. Urine fractions were collected predose, then at [4h-6h], [6h-12h], [12h-18h] and [18h-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®. Version 5.2 standard noncompartmental analysis.

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,Cmax) or AUCmax (Rac,AUCmax) 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/L 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.

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

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. Mild 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. However, their clinical development as systemic drugs has so far been hampered by some unfavourable ADMET properties.

POL7080 from Polygyhr, which was derived from protegrin-I applying the Protein Epitope Mimetics (PEM) technology, has been shown to have potent and specific antimicrobial activity against Pseudomonas aeruginosa by targeting the β-barrel protein LptD (ImprintTM) and functions in the outer-membrane biogenesis (2). Here we report the results from the multiple ascending dose (MAD) study to assess safety, tolerability, plasma pharmacokinetics (PK) and urinary excretion.