


27th **ECCMID**

Vienna, Austria
22 – 25 April 2017

The congress of  ESCMID

Session: P063 Murepavadin

Category: 5c. New antibacterial agents: clinical trials

24 April 2017, 12:30 - 13:30
P1308

Pharmacokinetic and efficacy analysis of murepavadin (POL7080) co-administered with standard-of-care (SoC) in a phase II study in patients with ventilator-associated pneumonia (VAP) due to suspected or documented *Pseudomonas aeruginosa* infection

Apostolos Armaganidis¹, F Frantzeskaki¹, C Diakaki¹, Spyros Zakynthinos², E Ischaki², Konstantinos Mandragos³, C Katsenos³, M Paraschos³, E.J. Giamarellos-Bourboulis⁴, A Pistiki⁴, P Ramirez⁵, Maria Victoria De la Torre-Prados⁶, A Rodriguez⁷, Kay Sommerville⁸, Achim Wach⁹, Christian Zwingelstein¹⁰, Laura Beni¹⁰, Leon Hooftman¹⁰, Glenn Dale^{*11}, Antoni Torres¹²

¹*Athens University Medical School*

²*Evangelismos Hospital, Medical School of Athens*

³*Red Cross Hospital*

⁴*Univeristy General Hospital "Attikon"*

⁵*Hospital Universitario Politecnic la Fe*

⁶*Hospital Universitario Virgen de la Victoria*

⁷*Joan XXIII University*

⁸*Charles River Laboratories Edinburgh*

⁹*Polyphor Ltd.*

¹⁰*Polyphor AG*

¹¹*Polyphor Ltd.; Clinical Development*

¹²*Servei de Pneumologia, University of Barcelona, Idibaps, Ciberes, Hospital Clinic, Barcelona, Spain*

Background: 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*. Positive pressure ventilation causes complex changes in functioning of cardiovascular, pulmonary and renal systems, which in association with extensive fluid administration necessary to compensate the produced changes, could influence the distribution and elimination of water soluble drugs. This study investigated the plasma PK and efficacy of POL7080 (2.5 mg/kg, 2h IV-infusion; TID for 10-14 days) co-administered with SoC in VAP patients with suspected or confirmed *P. aeruginosa* infection.

Material/methods: This is an analysis of a phase II, open-label study conducted in subjects of either sex diagnosed with VAP due to suspected/confirmed *P. aeruginosa* infection for which treatment with SoC anti-pseudomonas antibiotics is necessary (n=25, PK population, defined as patients with at least one dose of POL7080). Blood samples were taken at doses 1 and 19 before the start of the infusion, during the infusion (+0.5h, +1.5h), and post-infusion (+5min, +30 min, 1h, 2h, 4 h). The primary efficacy variable was clinical cure at test-of-cure (TOC) at 7 ± 2 days after end-of-treatment (EOT) in the mITT population. Baseline *P. aeruginosa* isolates and isolates from daily endotracheal aspirate cultures (ETAs) were evaluated for *in vitro* susceptibility to POL7080 and selected anti-pseudomonas antibiotics.

Results: The plasma PK of POL7080 in patients under mechanical ventilation (n=25) reveals a mean exposure on Day-1 of $C_{max} = 6.2$ ng/mL and $AUC = 65.1$ h*ng/mL. The PK of POL7080 on Day-7 in patients (n=12) under ventilation reveals a mean exposure of $C_{max} = 8.3$ ng/mL and $AUC = 134.7$ h*ng/mL. Of the twelve patients in the microbiological intention to treat set the clinical cure rate at TOC was 91% and the day 28 all cause mortality was 9%. From the 12 patients with positive *P. aeruginosa* at baseline isolates were cultured from ETAs in 11 of 12 patients at $\geq 10^5$ CFUs/mL and 1 patient had a positive blood culture. Five patients had a MDR *P. aeruginosa* at baseline. There was no emergence of resistance related to POL7080 during this study.

Conclusions: Although a decrease in POL7080 exposure was expected due to the hemodynamic changes in ventilated ICU patients, the mean exposure at steady-state of POL7080 seems to be similar, if not marginally increased to that observed in healthy volunteers. The high rate of clinical cure and low rate of mortality at Day 28 in this severely ill patient population combined with the consistent improvement in the efficacy variables of the phase II study underscore the potential therapeutic value of POL7080 in the treatment of VAP patients with *P. aeruginosa* infection and warrant further clinical investigations.