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P1667 Investigation of the in vitro time-kill kinetics and the rate of resistance development by spontaneous mutations and serial passage of murepavadin and standard-of-care antibiotics towards P. aeruginosa

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Background: Murepavadin (POL7080) represents the first member of a novel class of outer membrane protein targeting antibiotics (OMPTA), being developed by Polyphor for the treatment of serious infections by *Pseudomonas aeruginosa*. The objective of the current study was to evaluate the bactericidal activity and propensity to develop resistance of murepavadin and comparator antibiotics to a panel of eleven *P. aeruginosa* clinical isolates. The *in vitro* time-kill kinetics, resistance development by serial passage and the spontaneous mutation resistance rates were determined

Materials/methods: The spontaneous mutation frequency of murepavadin and comparators (meropenem, ciprofloxacin, amikacin, ceftazidime or colistin) for 11 different *P. aeruginosa* isolates was determined by inoculating agar containing the compounds at four and eight times the MIC. Resistance development during serial exposure was assessed using a broth 2-folddilution method used in tubes, by transferring cells from tubes showing growth to fresh media containing the antibiotics for up to 21 serial passages or the MIC breakpoint was reached for 3 consecutive passages. Time-kill assays were determined at multiples of the MIC (0.25 to 8 times MIC) at various time points (0, 2, 4, 8, 24 hours). The concentration and time to reach a 3 $\log_{10}$ reduction with no significant re-growth at 24 hours was recorded.

Results: The MIC of murepavadin towards the eleven isolates ranged from 0.06 to 0.25 mg/L. Seven of the 11 isolates were considered MDR. Murepavadin exhibited a rapid and irreversible 3-log reduction of bacterial counts at 2 times the MIC, within 2-8 hours. When assessed at 24 hours and 4x and 8x the MIC, spontaneous resistance developed for murepavadin at a median rate of 1.42E-09 (range 1.4E-07-4.0E-10) and 4.3E-09 (range 1.1E-09-<7.0E-10). This rate was generally better than the comparators with ceftazidime being the most prone to spontaneous resistance development. In serial passage experiments murepavadin demonstrated a lower propensity to develop resistance compared to standard of care whereas ciprofloxacin was the most prone to resistance development.

Conclusions: Murepavadin displays a potent *in vitro* bactericidal activity against *P. aeruginosa* and generally demonstrates a lower rate of resistance development than the standard of care antibiotics