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POL7001 is highly efficacious in the murine neutropenic lung infection model

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Background: POL7001 represents a member of a novel class of outer membrane protein targeting antibiotics. It specifically interacts with LptD and inhibits LPS transport. The MIC of POL7001 towards the infecting organisms covered a range from 0.063 mg/L to 0.25 mg/L which covers the MIC₉₀ range of POL7001 against this organism. In these studies the efficacy of POL7001 was assessed in neutropenic murine models of pneumonia due to sensitive and MDR *Pseudomonas aeruginosa* clinical isolates.

Material/methods: CD-1 mice were infected intranasally with a pipette with bacteria suspension containing approximately 10⁶ CFU. The mice were treated subcutaneously in the neck region with a single dose at 2 hour post infection or with b.i.d dosing at 2 and 14 hours post infection. The total daily dose ranged from 1.88 mg/kg given as a single dose to 60 mg/kg given b.i.d. The mice were then euthanized; the lungs were collected for determining the CFU counts. The lung bacterial burden was determined at 2 and 26 hrs post inoculation.

Results: Nine *P. aeruginosa* isolates were evaluated in the pneumonia model and compared to the control antibiotics (Polymyxin B, levofloxacin, ciprofloxacin or gentamicin) depending on the strains

susceptibility. All strains were susceptible to POL7001 and 5/9 was MDR to known anti-pseudomonal antibiotics. Generally, a greater than 3 log₁₀ increase in tissue burden at study termination compared to pre-treatment levels was observed in the in the vehicle group suggesting a robust infection. POL7001 showed a dose dependent reduction in CFUs in all strains tested. A significant reduction ($p < 0.05$) of bacterial loads of all strains in the lungs was observed after treatment with POL7001 compared to vehicle treatment. In all models, POL7001 induced a 1-log reduction in CFUs compared to pre- treatment indicating a bactericidal effect. The total daily dose of POL7001 required to reach a 1-log reduction compared to pre-treatment levels was generally less than 15 mg/kg and in many cases doses of ≤ 15 mg/kg reduced burdens to below the limit of detection.

Conclusions: POL7001 is highly efficacious in the neutropenic murine pneumonia model against both non-MDR and MDR *P. aeruginosa*.