NKTR-061 (Inhaled Amikacin) BID Achieves High Epithelial Lining Fluid Concentrations in Pneumonic Portions of Lung

C.-E. Luyt, MD; M. Clavel, MD; K. Guntupalli, MD; J. Johannigman, MD; J. Kennedy, MD; M. Wood, PharmD; K. Corkery, BS; D. Gribben, BS; J. Chastre, MD

Hôpital Pitié-Salpêtrière, Critical Care, Paris, France, †Centre Hospitalier Universitaire Dupuytren, Critical Care, Limoges, France, ¶Baylor College of Medicine, Critical Care, Houston, Texas, United States, ‡University of Cincinnati, Cincinnati, Ohio, USA, #University of Alabama, Birmingham, Alabama, United States, ! Tennessee Health Science Center, Memphis, Tennessee, United States, ‡Nektar Therapeutics, Clinical Research, San Carlos, California, United States

Introduction
The incidence of nosocomial pneumonia ranges from 5 to 10 cases per 1000 hospital admissions in patients without major risk factors, but increases 6- to 20-fold in intensive care unit (ICU) patients who are receiving broad-spectrum antibiotic therapy.3

Clinical Pharmacology
Inhalation therapy is well established as a means of delivering antibiotics directly to the site of infection and to the most protected areas of the lung, including the deep lung infections has been hampered by the low efficiency of pulmonary drug delivery when using conventional nebulizers connected to ventilator circuits.5

Key Objectives
To determine the pharmacokinetic profile of aerosolized amikacin administered via the PDDS Clinical, as shown in Figure 1, in patients with nosocomial pneumonia caused by Gram-negative organisms.

Study Design
Partial-sequence, random-start, three-period crossover study. Participants were eligible if they were intubated and mechanically ventilated patients with severe ventilator-associated pneumonia (VAP). The study had two phases: dosing and PK sampling. In the dosing phase, the nominal amikacin dose to the lungs, whereas standard nebulizers deliver less than 10% of the nominal dose if attached to ventilator circuits.5

Pharmacokinetic Parameters
Pharmacokinetic parameters for amikacin in the BAL/ELF samples were calculated using non-compartmental analysis with the support of Phoenix software (Certara). The pharmacokinetic population was defined as all treated patients who had any evaluable pharmacokinetic data for any of the four PK sampling time points.

Safety Results
A total of 355 adverse events (AEs) were collected during the study, most were expected and independent of study medication. A total of 10 AEs were considered possibly related to the study medication, including one case of cavoatrial fistula and one case of cavoatrial fistula.

Conclusions
Delivery of aerosolized AMK using PDDS Clinical achieved very high antibiotic concentrations in the tracheal aspirates and the BAL, but the effects of prolonged nebulization remain to be defined. Phase I dose-finding studies conducted on a larger scale may further elucidate these findings.

References