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Penetration of Pilabactam (formerly ANT3310) and Meropenem into Pulmonary Epithelial Lining Fluid in Healthy Adult Participants

J. Dao[1], C. Zwingelstein[1], A.C. Benichou[1], L. Fabre[1], K. Rodvold[2], M. Gotfried[3], J. Burr Ross[3]

[1]Antabio - Labège, France; [2]University of Illinois - Chicago (United States), [3]Pulmonary Associates PA - Phoenix (United States)

INTRODUCTION

Pilabactam (PIL), formerly ANT3310, is a novel diazabicyclooctanone (DBO) serine β-lactamase inhibitor, in clinical development in combination with Meropenem (MEM) for the treatment of severe infections caused by Gram-negative pathogens in hospitalized patients. MEM-PIL has a broader spectrum of coverage than current marketed antibiotics, including carbapenem-resistant Enterobacterales (CRE) and *A. baumannii* (CRAB), as well as *P. aeruginosa*.

MEM-PIL demonstrated a favourable safety profile in the First-in-Human study. Intrapulmonary penetration is a key determinant of antibiotic efficacy in lower respiratory tract infections. Pulmonary epithelial lining fluid (ELF) is an important site of infection for common extracellular respiratory pathogens, and bronchoscopy with bronchoalveolar lavage (BAL) has been widely used to assess the antibiotic penetration into ELF.

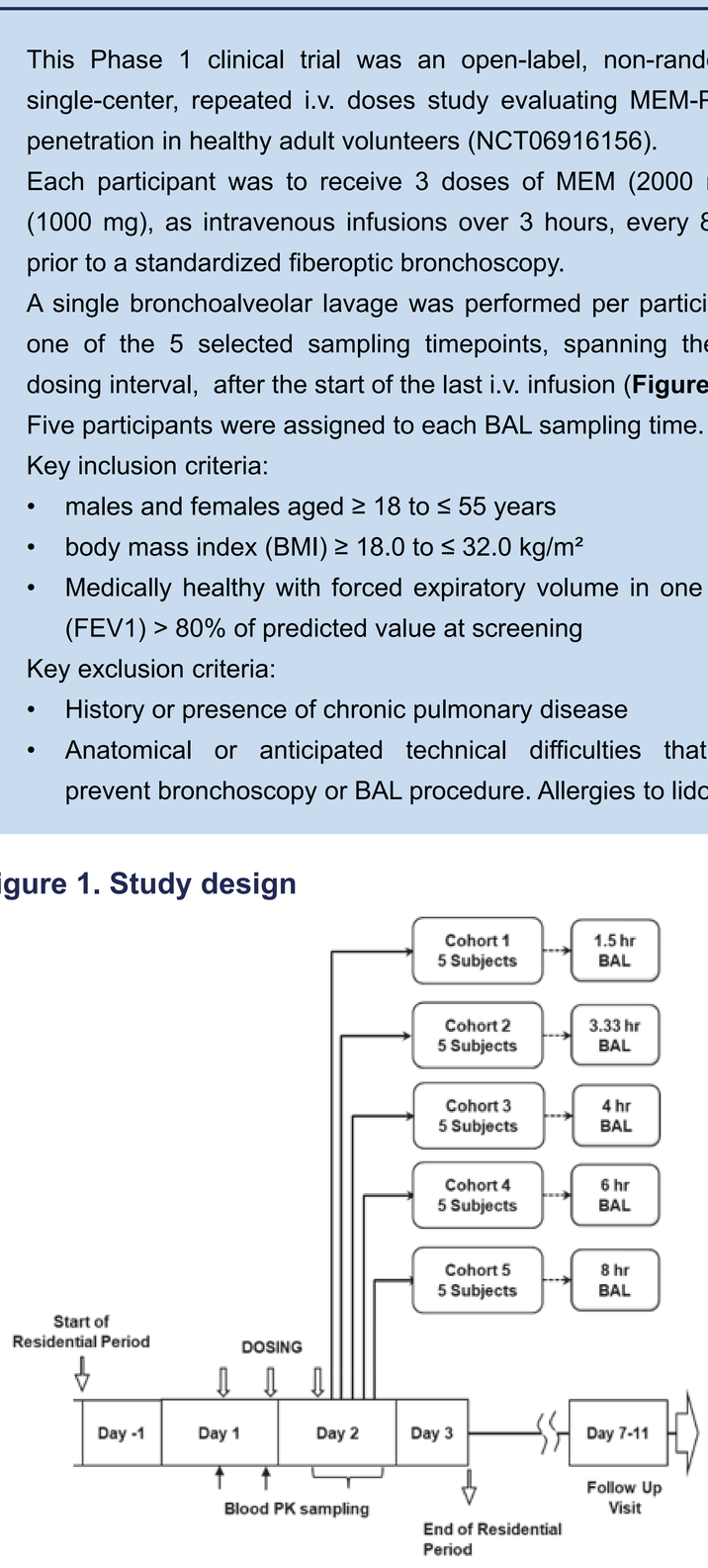
OBJECTIVES

The primary objective of this study was to determine lung penetration of pilabactam and meropenem at steady state following repeated intravenous (i.v.) infusions of MEM-PIL in healthy adult participants. Safety and tolerability were also assessed.

METHODS

- This Phase 1 clinical trial was an open-label, non-randomized, single-center, repeated i.v. doses study evaluating MEM-PIL lung penetration in healthy adult volunteers (NCT06916156).
- Each participant was to receive 3 doses of MEM (2000 mg)-PIL (1000 mg), as intravenous infusions over 3 hours, every 8 hours, prior to a standardized fiberoptic bronchoscopy.
- A single bronchoalveolar lavage was performed per participant, at one of the 5 selected sampling timepoints, spanning the entire dosing interval, after the start of the last i.v. infusion (**Figure 1**).
- Five participants were assigned to each BAL sampling time.
- Key inclusion criteria:
  - males and females aged ≥ 18 to ≤ 55 years
  - body mass index (BMI) ≥ 18.0 to ≤ 32.0 kg/m²
  - Medically healthy with forced expiratory volume in one second (FEV1) > 80% of predicted value at screening
- Key exclusion criteria:
  - History or presence of chronic pulmonary disease
  - Anatomical or anticipated technical difficulties that would prevent bronchoscopy or BAL procedure. Allergies to lidocaine.

Figure 1. Study design



RESULTS

26 participants were enrolled: 8 women and 18 men, aged between 21 and 55 years (mean: 37.5 years) with a BMI between 20.0 and 31.3 kg/m² (mean: 26.4 kg/m²). 25 participants completed dosing and scheduled assessments, including bronchoscopy.

- Intravenous infusions of meropenem given concurrently with pilabactam achieved similar time courses and patterns of concentrations for both analytes in plasma and ELF (**Figure 2**).
- Exposure to pilabactam and meropenem in plasma and ELF, and the penetration ratio are displayed in **Table 1.**
- Mean and median AUC values were similar for both analytes, suggesting generally consistent exposures among participants.
- For pilabactam, the ELF-to-total plasma $AUC_{0\text{-}8h}$ ratios were approximately 0.37 and 0.38, using mean and median concentrations respectively, and the ELF-to-unbound plasma $AUC_{0\text{-}8h}$ ratios were approximately 0.39 and 0.41 using mean and median concentrations, respectively.
- For meropenem, the ELF-to-plasma $AUC_{0\text{-}8h}$ ratios were approximately 0.24 and 0.25, using total or unbound mean and median concentrations.
- The penetration ratios observed are within the expected range for β-lactam/β-lactamase inhibitor antibiotics and confirm that both pilabactam and meropenem attain clinically meaningful concentrations in ELF following intravenous administration.
- Eight participants (30.8%) experienced a total of 10 treatment-emergent adverse events (TEAEs) of mild to moderate severity which resolved during the study. Half of TEAEs were minor infusion site reactions.
- No deaths, serious AEs, or discontinuations due to AEs were reported.

Figure 2. Mean (± SD) concentration profile for Pilabactam (left) and Meropenem (right) in plasma and ELF after the third meropenem (2g) – pilabactam (1g) i.v. infusion (semi-log scale).

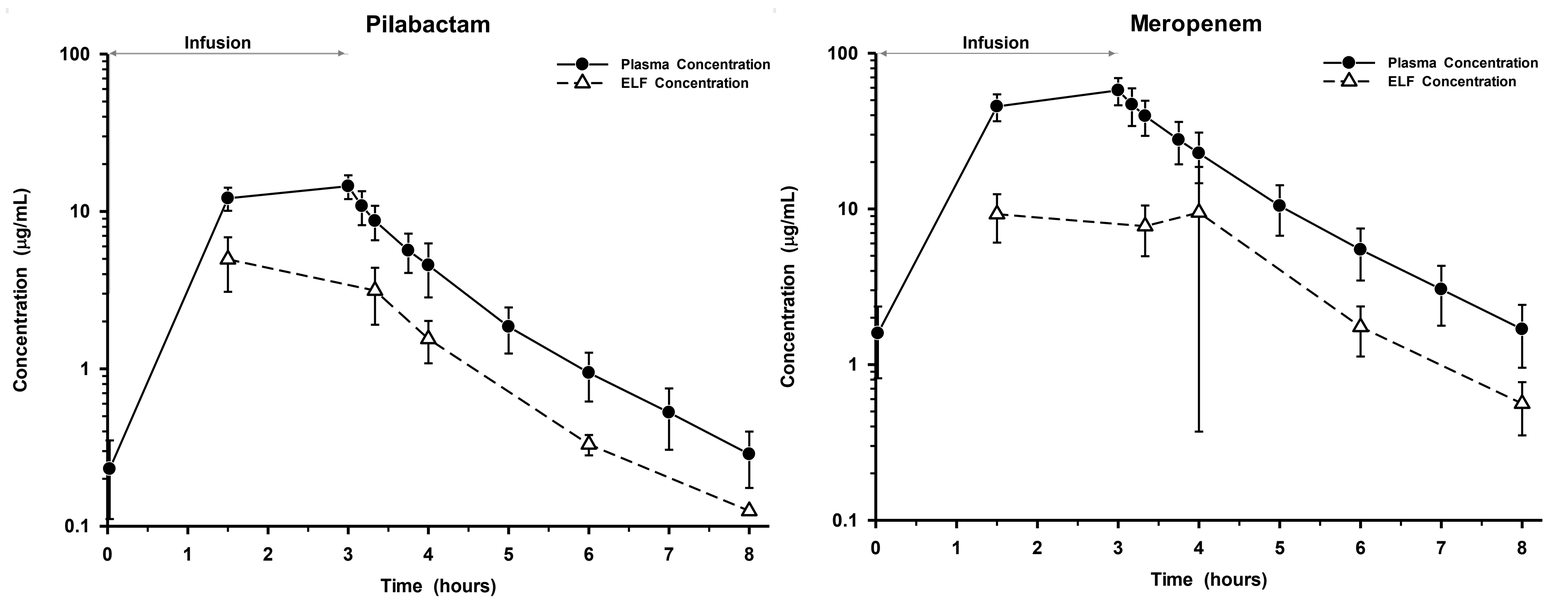


Table 1. Exposure and penetration ratios for Pilabactam and Meropenem in plasma and ELF

Parameter	Pilabactam (1g)		Meropenem (2g)	
	Mean Value	Median Value	Mean Value	Median Value
$AUC_{0\text{-}8h}$ plasma (total)	39.82[a]	38.14[b]	162.3[a]	155.6[b]
$AUC_{0\text{-}8h}$ plasma (unbound)[c]	37.83	36.23	159.0	152.4
$AUC_{0\text{-}8h}$ ELF	14.64[a]	14.66[b]	39.93[a]	37.05[b]
Ratio of $AUC_{0\text{-}8h}$ of ELF-to-Total Plasma	0.368	0.384	0.246	0.238
Ratio of $AUC_{0\text{-}8h}$ of ELF-to-Unbound Plasma	0.387	0.405	0.251	0.243
$t_{1/2\text{-}ELF}$ (hours)	1.102	1.162	0.980	1.280

AUC0-8h as ug.h/mL; BAL = bronchoalveolar lavage; ELF = epithelial lining fluid
[a] Mean concentration value at each BAL sampling time were determined and combined into a single dataset to calculate the $AUC_{0\text{-}8h}$ value of each matrix
[b] Median concentration value at each BAL sampling time were determined and combined into a single dataset to calculate the $AUC_{0\text{-}8h}$ value of each matrix
[c] Value used for the unbound fraction of pilabactam and meropenem in plasma were 0.95 and 0.98, respectively.

CONCLUSIONS

- Repeated intravenous administration of MEM-PIL was safe and generally well tolerated in healthy volunteers.
- The penetration ratios of pilabactam and meropenem confirm the intrapulmonary penetration of both drugs.
- These results support further clinical evaluation of the MEM–PIL combination in patients with lower respiratory tract infections caused by multidrug-resistant Gram-negative pathogens.

Contact Information
www.antabio.com
info@antabio.com
Biostep, 436 rue Pierre et Marie Curie, 31670 Labège, France