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Pharmacokinetics, Safety and Tolerability of Pilabactam (formerly ANT3310) Combined with Meropenem in Participants with Impaired Renal Function

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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. As both drugs are predominantly excreted unchanged in urine, their profile was further investigated in participants with impaired renal function in the present study.

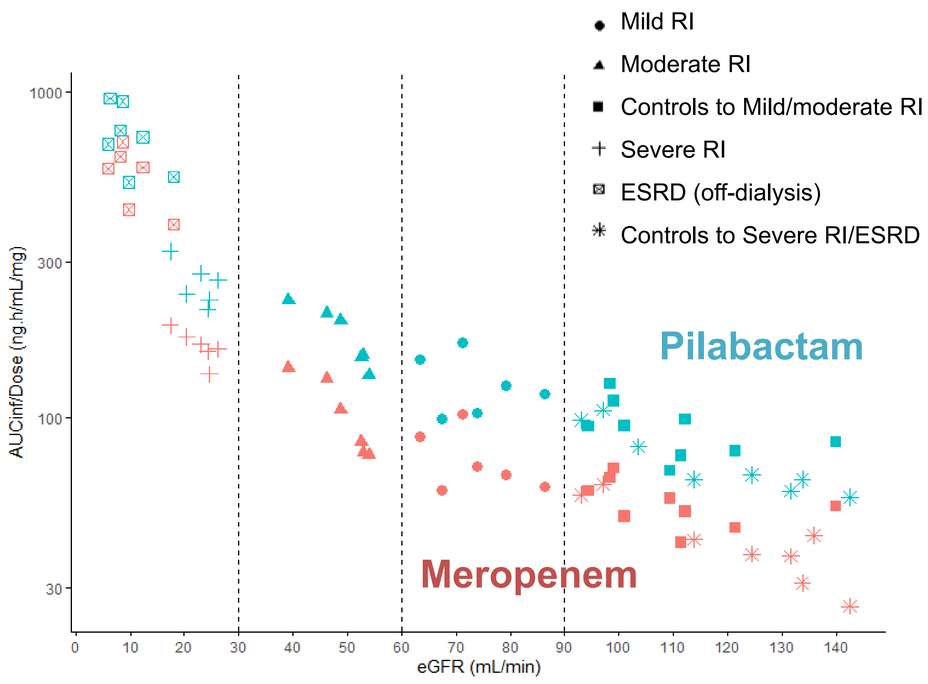
OBJECTIVES

The objectives of this study were to assess the pharmacokinetics (PK), safety, and tolerability of MEM-PIL as intravenous (i.v.) infusion over 3 hours, in participants with varying degrees of renal impairment (RI).
The Primary endpoints were the dose normalized C_{max} and AUC_{inf}.

METHODS

- This Phase 1 trial was conducted according to an open-label, non-randomized, single-center, single i.v. dose study design, in participants with different degrees of renal function impairment, including end-stage renal disease (ESRD), and matching control participants with normal renal function (NCT06527677).
- Participants: males and females aged ≥ 18 to ≤ 80 years with body mass index (BMI) ≥ 18.0 to ≤ 36.0 kg/m²
- Participants enrolled were stratified according to the estimated absolute glomerular filtration rate (eGFR):
  - Mild RI: 60 to <90 mL/min
  - Moderate RI: 30 to <60 mL/min
  - Severe RI: <30mL/min not requiring dialysis
  - ESRD: requiring dialysis for ≥3 months prior to dosing
  - Controls: ≥90 mL/min, matched to 1 or 2 participants with RI by sex, age ± 10 years, and BMI ± 15%.
- All participants received 1 single dose of the combination of MEM-PIL as a 3-hour i.v. infusion , except participants with ESRD who received a single dose in 2 dosing periods: dialysis-free interval period ("off-dialysis") and dialysis period ("on-dialysis").

Figure 2. Dose normalized AUC versus eGFR (semi-log scale)



RESULTS

42 participants (10 women, 32 men) between 34 and 80 years (mean: 61 years) with a BMI between 21.4 and 35.8 kg/m² (mean: 27.7 kg/m²) were enrolled.

- Pilabactam and meropenem showed slower elimination in plasma concentrations in renally impaired participants compared to controls (**Figure 1**).
- With decreasing renal function, overall exposure (AUC_{inf}) of pilabactam increased substantially, by 1.35x (mild RI), 1.75x (moderate RI), 3.94x (severe RI) and >10x (ESRD) compared to the control participants. Increase in exposure to meropenem was of the same magnitude (**Figure 2**).
- Peak concentrations of PIL and MEM also increased, but in a less pronounced manner than the overall exposure (**Table 1**).
- The reduced renal clearance resulted in a prolongation of the elimination half-life of both PIL and MEM from ~1 h in healthy participants up to ~3 h in participants with severe RI and ~8 h in ESRD participants.
- Both PIL and MEM are removed by dialysis, with drug recovery in dialysate of 44% and 38% of the respective dose.
- 12 Treatment-Emergent Adverse Events (TEAEs) were observed in 9 participants (21.4%), including 1 serious TEAE of moderate gastroenteritis.
- Drug-related TEAEs were reported by 6 participants (14.3%), related headache being the most frequent one with 3 TEAEs in 3 participants.

Figure 1. Mean (± SD) dose normalized concentration-time profiles (A) Mild to severe renal impairment groups and controls (B) ESRD participants on- and off-dialysis (semi-log scale)

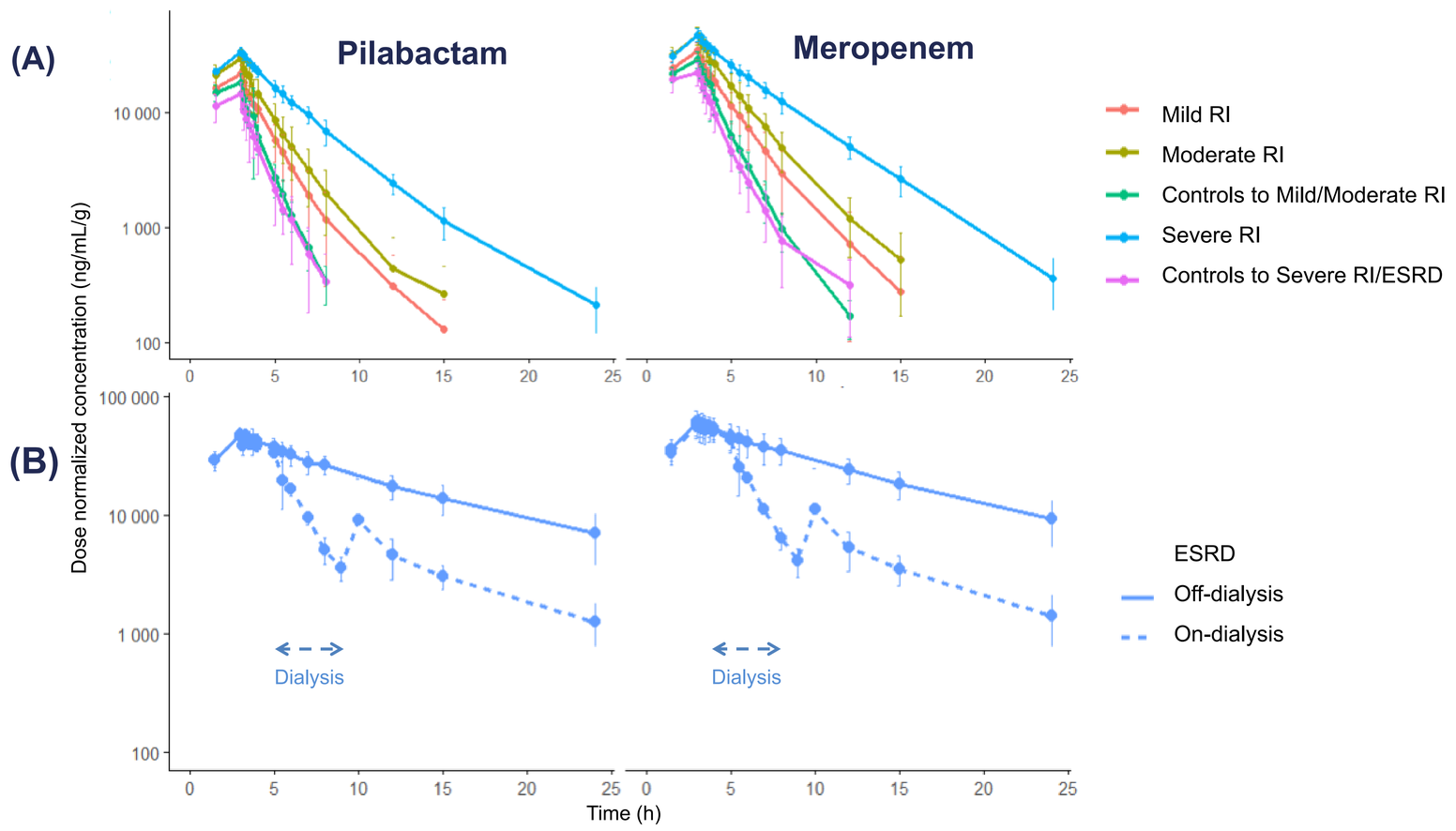


Table 1. Mean (SD) Pharmacokinetics Parameters

		Meropenem (2g) + Pilabactam (1g)			Meropenem (1g) + Pilabactam (0.5g)		
	Parameter [unit]	Mild RI N=6	Moderate RI N=6	Normal renal function N=9	Severe RI N=6	ESRD off-dialysis N=6	Normal renal function N=8
Pilabactam	C_{max}/Dose [ng/mL/mg]	21.4 (17.8)	28.7 (19.6)	18.3 (21.8)	33.3 (9.44)	49.2 (10.6)	14.0 (26.9)
	AUC_{0-inf}/Dose [ng.h/mL/mg]	73.1 (21.4)	99.7 (27.4)	54.0 (16.8)	165 (11.6)	544 (22.9)	40.7 (29.6)
	CL [L/h]	13.7 (21.4)	10.0 (37.2)	18.5 (16.8)	6.07 (11.6)	1.84 (22.9)	24.5 (29.6)
Meropenem	C_{max}/Dose [ng/mL/mg]	34.0 (18.5)	45.5 (18.7)	28.6 (18.5)	46.2 (13.2)	62.1 (19.5)	22.5 (17.9)
	AUC_{0-inf}/Dose [ng.h/mL/mg]	125 (21.2)	177 (21.2)	91.0 (19.6)	256 (14.9)	718 (23.6)	72.8 (23.6)
	CL [L/h]	7.98 (21.2)	5.66 (21.2)	11.0 (19.6)	3.91 (14.9)	1.39 (23.6)	13.7 (23.6)

CONCLUSIONS

- MEM-PIL was safe and well tolerated by study participants.
- Exposure to pilabactam and meropenem increased to a comparable degree with increasing renal impairment.
- Both drugs are substantially removed by dialysis.
- Study results support development of a fixed dose combination as similar dosing adjustments of MEM and PIL will be necessary in patients with impaired renal function.

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