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Phase II, open-label REJUVENATE study of the pharmacokinetics and safety of aztreonam-avibactam plus metronidazole in hospitalised adults with complicated intra-abdominal infection

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Introduction and purpose

- Bacterial infections caused by multidrug-resistant (MDR) Gram-negative pathogens are increasing in prevalence and represent a serious threat to public health,[1,2] with strains expressing metallo-β-lactamases (MBLs) of particular concern due to a lack of effective treatment options.[3–5]
- Complicated intra-abdominal infections (cIAIs) are an important cause of morbidity and mortality, particularly if not adequately managed, and are frequently caused by MDR Gram-negative pathogens.[6]
- Aztreonam-avibactam is an investigational monobactam/β-lactamase inhibitor combination therapy for infections caused by MDR Gram-negative pathogens, including those that produce MBLs.
- A Phase I, double-blind study (NCT01689207) showed aztreonam-avibactam to be generally well tolerated and identified a dosing regimen for further evaluation.[7]
- The current Phase IIa study (REJUVENATE) was the first study of aztreonam-avibactam in a population of patients with cIAI, with the aim of providing dose selection for the Phase III aztreonam-avibactam development programme.
- The study is the first interventional clinical trial conducted within the Innovative Medicines Initiative (IMI)-supported COMBACTE-CARE project. IMI is a joint undertaking between the European Union and the pharmaceutical industry association EFPIA. COMBACTE-CARE is a consortium of 19 academic and 3 pharmaceutical partners focusing on carbapenem resistance in Europe with the aim of increasing the efficiency of antimicrobial drug development.

Methods

- This Phase IIa open-label, multicentre study (NCT02655419; EudraCT: 2015-002726-39) enrolled 40 adult patients with cIAI into sequential cohorts to receive intravenous (IV) aztreonam-avibactam (plus metronidazole) for 5–14 days. The primary objectives were to investigate the pharmacokinetics (PK) and safety of aztreonam-avibactam in patients with cIAI.
- Aztreonam-avibactam dosage regimen for Cohort 1 (for patients with estimated creatinine clearance [CrCl] >50 mL/min) was supported by population PK modelling and based on the final dosage regimen evaluated in the Phase I study.[7]
- Following an update of population PK/PD modelling (Poster #P1952 [Das et al, ECCMID 2019]) and a planned review of available safety and PK data from patients in Cohort 1, a protocol amendment was put in place for aztreonam-avibactam dosage regimens for evaluation in Cohort 2, including dose adjustments for patients with CrCl >30 to ≤50 mL/min (**Table 1**). Cohort 3 was an extension of Cohort 2 following further safety data review. All cohorts received metronidazole 500 mg every 8 h for anaerobic coverage.

Table 1. Dosing regimen for each cohort and renal function group

Cohort and CrCl threshold	Aztreonam-avibactam loading dose (30-min IV infusion)	Aztreonam-avibactam extended loading dose	Aztreonam-avibactam maintenance infusion (3-h IV infusion q6h)	Metronidazole (1-h IV infusion q8h)
Cohort 1 CrCl >50 mL/min	500/137 mg	Not applicable	*1500/410 mg	500 mg
Cohorts 2 and 3 CrCl >50 mL/min	500/167 mg	Not applicable	*1500/500 mg	500 mg
Cohorts 2 and 3 CrCl >30 to ≤50 mL/min	500/167 mg	**1500/500 mg by 3-h IV infusion	**750/250 mg	500 mg

*First maintenance dose administered immediately after completion of loading dose. **Extended loading dose administered immediately after completion of loading dose; first maintenance dose administered 3 h after completion of extended loading dose. CrCl, creatinine clearance; IV, intravenous; q6h, every 6 h; q8h, every 8 h.

- Blood samples for plasma PK analysis of aztreonam and avibactam were collected at pre-defined sampling times on Day 1 and Day 4 (±1 day).
  - All patients underwent sparse PK sampling (four samples per patient) on Day 1.
  - On Day 4 (±1 day), the first 25 patients enrolled were to undergo intensive PK sampling (11 samples per patient).
  - The remaining 15 patients were to undergo sparse PK sampling on Day 4 (±1 day).
- Plasma samples were analysed for aztreonam and avibactam concentrations at Covance Laboratories Ltd (Harrogate, UK) using validated analytical assays.
  - Aztreonam: sensitive and specific protein precipitation extraction/ liquid chromatography followed by tandem mass spectrometric detection (LC-MS/MS).
  - Avibactam: solid-phase extraction/LC-MS/MS.
- PK parameters were calculated for each patient with intensive plasma sampling collected on Day 4 using non-compartmental analysis of concentration–time data (Phoenix® WinNonlin 6.4 [Certara L.P., St. Louis, Missouri]).
- Safety assessments included monitoring of adverse events (AEs), laboratory assessments, vital signs, physical examinations and electrocardiograms.
- Hepatic and renal function were closely monitored throughout the treatment period, and intensified monitoring of liver-related laboratory parameters was initiated when specific safety criteria were attained.
- Efficacy assessments included the number and percentage of patients with investigator-determined clinical cure, clinical failure and indeterminate outcomes at the end-of-treatment (EOT), test-of-cure ([TOC], Day 25 ±3 days) and late follow-up ([LFU] Day 35 ±3 days) visits.

Results

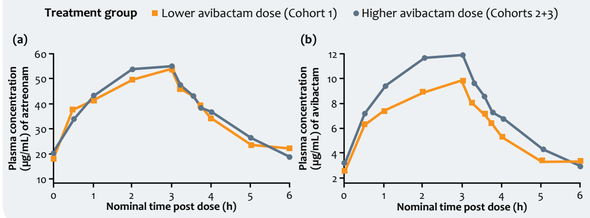
Patients

- In total, 40 patients were enrolled; of these, four did not fulfil eligibility criteria, and a further two did not receive treatment due to difficulties with IV access. A total of 34 patients received treatment and were included in the modified intent-to-treat (MITT) population (Cohort 1, n=16; Cohorts 2 and 3, n=18).
- Patient demographics and baseline characteristics were generally well balanced across cohorts.
- Median (range) age was 51.5 (19–71) years and 76.5% were male.
- cIAI relating to appendiceal perforation or peri-appendiceal abscess was the most frequent primary diagnosis (41.2% of patients).
- Median (range) CrCl at baseline was 96.5 (54.1, 165.0) mL/min in Cohort 1 and 110.1 (40.2, 182.4) mL/min in Cohorts 2 and 3.
- Only one patient (Cohorts 2 and 3) had CrCl 31–50 mL/min at baseline.
  - This patient had acquired acute kidney injury prior to study inclusion and was withdrawn from study treatment on Day 2, owing to further deterioration in renal function meeting the discontinuation criterion.
- In total, 23/34 (67.6%) patients had a pathogen identified at baseline and comprised the microbiological MITT (mMITT) population. The baseline pathogen profile was balanced across cohorts and was consistent with the cIAI population.
  - *Escherichia coli*, *Klebsiella pneumoniae* and *Klebsiella oxytoca* were the most commonly isolated Enterobacteriaceae species.

Pharmacokinetics

- 21 of the 25 planned patients completed intensive PK sampling on Day 4.
- Following maximum plasma concentration near the end of the 3-h infusion, both aztreonam and avibactam plasma concentrations declined in an apparent monophasic manner up to 6 h post start of infusion (**Figure 1**).

Figure 1. Geometric mean plasma concentration–time curves for aztreonam **(a)** and avibactam **(b)** following 3-h IV infusion of aztreonam-avibactam on Day 4



- On Day 4, geometric mean (% coefficient of variation) steady-state aztreonam area under the plasma concentration–time curve (AUC_{0-6}) was 235.2 μg*h/mL (60.6%) in Cohort 1, and 234.7 μg*h/mL (54.6%) in Cohorts 2 and 3, whereas that of avibactam was 40.4 μg*h/mL (74.0%) in Cohort 1 and 47.5 μg*h/mL (79.2%) in Cohorts 2 and 3, in proportion to the increased avibactam dose (**Table 2**).
- High between-patient variability in systemic exposure was observed for aztreonam and avibactam.

Table 2. Summary of steady-state aztreonam and avibactam PK parameters following IV infusion of aztreonam-avibactam

PK parameter		Aztreonam Cohort 1 (N=16)	Aztreonam Cohort 2+3 (N=18)	Avibactam Cohort 1 (N=16)	Avibactam Cohort 2+3 (N=18)
$AUC_{(0-6)}$ (h*μg/mL)	n	13	8	13	8
	Geometric mean (CV%)	235.2 (60.6)	234.7 (54.6)	40.4 (74.0)	47.5 (79.2)
C_{max} (μg/mL)	n	13	8	13	8
	Geometric mean (CV%)	62.5 (146.9)	55.4 (42.6)	11.6 (164.5)	12.1 (61.2)
t_{max} (h)	n	13	8	13	8
	Median (range)	2.9 (0.5–3.5)	2.4 (2.0–3.0)	2.9 (0.5–3.8)	2.8 (2.0–3.3)
$t_{1/2}$ (h)	n	11	8	11	8
	Mean (SD)	2.3 (1.06)	2.8 (2.05)	1.8 (0.59)	2.2 (1.85)
CL (L/h)	n	13	8	13	8
	Geometric mean (CV%)	6.4 (35.4)	6.4 (35.5)	10.1 (42.6)	10.5 (41.4)
V_{ss} (L)	n	11	8	11	8
	Geometric mean (CV%)	20.3 (16.9)	19.6 (31.8)	26.0 (22.0)	23.7 (29.7)
Vz (L)	n	11	8	11	8
	Geometric mean (CV%)	21.4 (15.3)	21.6 (24.1)	28.2 (20.4)	27.4 (20.6)

$AUC_{(0-6)}$, area under plasma concentration–time curve from time point zero to 6 h post; CL, clearance; C_{max}, maximum plasma concentration; CV, geometric coefficient of variance; IV, intravenous; n, number of patients with an observation; N, number of patients enrolled; PK, pharmacokinetic; SD, standard deviation; t_{max}, time of observed maximum concentration; $t_{1/2}$, plasma elimination half-life; V_{ss}, apparent volume of distribution at steady state after IV administration; Vz, volume of distribution during the terminal phase after IV administration.

Safety

- AEs occurred with similar frequency and pattern between cohorts in the MITT population (**Table 3**).

Table 3. Summary of treatment-emergent AEs and AEs occurring in ≥2 patients, by system organ class and preferred term (modified intent-to-treat population)

	Cohort 1 (n=16)	Cohorts 2+3 (n=18)	Total (N=34)
Patients with any AE	11 (68.8)	12 (66.7)	23 (67.6)
Patients with outcome of death (related and not related)	0	1 (5.6)	1 (2.9)*
Patients with SAEs	4 (25.0)	5 (27.8)	9 (26.5)
Patients discontinued from study drug due to AEs	2 (12.5)	2 (11.1)	4 (11.8)
Any AE with severe intensity	3 (18.8)	2 (11.1)	5 (14.7)
Any AE related to aztreonam-avibactam	8 (50.0)	2 (11.1)	10 (29.4)
Any AE related to metronidazole	1 (6.3)	0	1 (2.9)
AEs by system organ class/preferred term, n (%)			
Blood and lymphatic system disorders	2 (12.5)	2 (11.1)	4 (11.8)
Anaemia	1 (6.3)	2 (11.1)	3 (8.8)
Gastrointestinal disorders	3 (18.8)	8 (44.4)	11 (32.4)
Abdominal pain lower	0	2 (11.1)	2 (5.9)
Diarrhoea	2 (12.5)	3 (16.7)	5 (14.7)
Nausea	0	2 (11.1)	2 (5.9)
General disorders/administration site conditions	1 (6.3)	2 (11.1)	3 (8.8)
Oedema	0	2 (11.1)	2 (5.9)
Investigations	7 (43.8)	2 (11.1)	9 (26.5)
Hepatic enzyme increased	7 (43.8)	2 (11.1)	9 (26.5)

AE, adverse event; SAE, serious adverse event. Values are displayed as n (%).
*This event was a post-late follow-up event.

- The most common AE (Medical Dictionary for Regulatory Activities preferred terms) was 'hepatic enzyme increased' (n=9; 26.5%).
  - Of these nine cases, seven (20.6%) were considered related to aztreonam-avibactam, one related to metronidazole, and one not drug-related.
- Potentially clinically significant increases in alanine transaminase and/or aspartate transaminase (>3 x upper limit of normal and 100% change from baseline) occurred in six patients (17.6%).
- Serious AEs were reported in a total of nine (26.5%) patients (Cohort 1, four [25.0%]; Cohorts 2 and 3, five [27.8%]). None were considered treatment-related.
- Four patients (11.8%) were discontinued from the study drug owing to AEs, of which three were due to liver enzyme disorders (two of these were 'hepatic enzyme increased' and considered treatment-related, and one was an event of hypertransaminasaemia that was assessed as being unrelated to the study drug). The fourth was a patient with unrelated worsening of kidney failure.

Efficacy

- Clinical responses at TOC are summarised in **Table 4**. Approximately 60% of patients overall were assessed as being clinically cured at TOC (58.8% in the MITT population and 60.9% in the mMITT population). The clinical response to study treatment was similar in the lower and the higher avibactam dose groups.

Table 4. Investigator assessment of clinical responses at the test-of-cure visit (modified intent-to-treat and microbiological modified intent-to-treat populations)

Response n (%)	MITT population Cohort 1 (N=16)	MITT population Cohorts 2+3 (N=18)	MITT population Total (N=34)	mMITT population Cohort 1 (N=12)	mMITT population Cohorts 2+3 (N=11)	mMITT population Total (N=23)
Cure	10 (62.5) 95% CI [35.4, 84.8]	10 (55.6) 95% CI [30.8, 78.5]	20 (58.8)	8 (66.7) 95% CI [34.9, 90.1]	6 (54.5) 95% CI [23.4, 83.3]	14 (60.9)
Failure	3 (18.8)	5 (27.8)	8 (23.5)	2 (16.7)	2 (18.2)	4 (17.4)
Indeterminate	3 (18.8)	3 (16.7)	6 (17.6)	2 (16.7)	3 (27.3)	5 (21.7)

CI, confidence interval; MITT, modified intent-to-treat; mMITT, microbiologically modified intent-to-treat; n, number of patients with an observation; TOC, test of cure.

Conclusions

- Observed AEs following aztreonam-avibactam plus metronidazole treatment in patients with cIAIs were in line with the known safety profile of aztreonam monotherapy, with a favourable risk–benefit profile in the treatment of cIAI and no new safety concerns identified.
- The data from this study support selection of the aztreonam-avibactam 1500/500 mg (3-h infusions) q6h dosing regimen for the Phase III development programme.

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Disclosures

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