LBEV0061b

Efficacy and safety of ceftazidime-avibactam and best available therapy in the treatment of ceftazidime-resistant infections – results from a Phase III study

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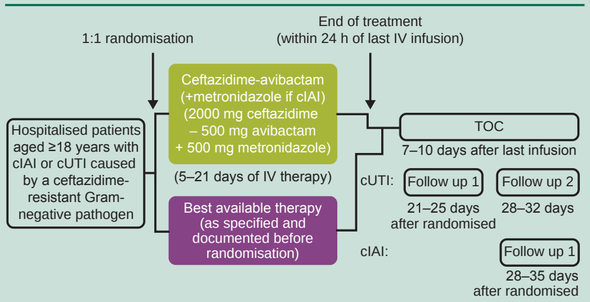
Introduction and purpose

- The prevalence of multi-drug resistant (MDR) Gram-negative pathogens is increasing worldwide, including extended-spectrum β-lactamase (ESBL)-producing and carbapenemase-producing *Enterobacteriaceae* and *Pseudomonas aeruginosa*.[1–3]
- Contributing factors are the overuse of antibiotics, both in humans and animals, poor infection control, and the greatly increased global mobility of people, allowing the rapid spread of MDR pathogens.[1,4,5]
- As the prevalence of ESBL-producing pathogens has increased, so has the use of carbapenems – frequently the last line of defence against MDR Gram-negative bacteria but now threatened by the growing prevalence of carbapenemase-producing pathogens.[6]
- There is therefore an urgent need to find alternatives to carbapenems for patients with serious infections caused by MDR Gram-negative pathogens.
- Ceftazidime-avibactam may represent an important new option for such cases, comprising ceftazidime, a widely used extended-spectrum anti-pseudomonal cephalosporin, and avibactam, a novel non-β-lactam β-lactamase inhibitor.
- The efficacy and safety of ceftazidime-avibactam in patients with serious ceftazidime-resistant Gram-negative bacterial infections have been evaluated in REPRISE, a prospective, international, randomised, open-label Phase III study (NCT01644643).

Methods

- The REPRISE study design is shown in Figure 1.

Figure 1. *Study Design*



- Male and female patients aged 18–90 years with complicated intra-abdominal infections (cIAI) or complicated urinary tract infections (cUTI) (including acute pyelonephritis) caused by ceftazidime-resistant Gram-negative pathogens (isolated from an appropriate culture within 5 days prior to study entry) were randomised 1:1 to receive 5–21 days of treatment with either:
  - Ceftazidime-avibactam 2000–500 mg administered as a 2-h intravenous (IV) infusion every 8 h (q8h), or
  - Best available therapy (BAT), as determined by the investigator based on standard of care, following label recommendations, and documented prior to randomisation.
- Dose modifications were made for patients with renal impairment.
- Patients with cIAI who were randomised to ceftazidime-avibactam also received IV metronidazole 500 mg administered as a 60-min infusion q8h, immediately after the ceftazidime-avibactam infusion, for anaerobe coverage.
- Ceftazidime-resistant *Enterobacteriaceae* and *P. aeruginosa* were defined as having ceftazidime minimum inhibitory concentrations ≥8 mg/L and ≥16 mg/L, respectively.
- The primary endpoint was assessment of clinical response at test of cure (TOC) visit 7–10 days after last infusion of study therapy in the microbiologically modified intent-to-treat population (mMITT).
- Secondary endpoints included per-patient favourable microbiological response rate in the mMITT population.
- Two-sided 95% CI for the treatment group response rates were calculated using the Jeffreys method.[7,8] Due to the infeasibility of recruiting larger numbers of patients infected with resistant Gram-negative pathogens, no formal statistical comparisons between the treatment groups were performed. Rather, the corresponding CIs for the efficacy of BAT were used to provide a context for estimates of ceftazidime-avibactam efficacy.
- Safety was assessed by monitoring adverse events (AEs) and laboratory parameters.

Results

- The following results are for the full dataset (whereas the submitted abstract showed results for first data cut-off).

Patients

- A total of 333 patients were enrolled and randomized in 53 centres in 16 countries worldwide between January 2013 and August 2014:
  - Ceftazidime-avibactam: 165 patients
    - 153 with cUTI and 12 with cIAI
  - BAT: 168 patients
    - 153 with cUTI and 15 with cIAI.
- The proportions of randomised patients by region were: Eastern Europe 80.5%, North America and Western Europe 4.8%, and rest of world 14.7%.
- Most (97%) patients in the BAT group received a carbapenem antibiotic and the majority received this as monotherapy.
- A total of 302 (90.7%) patients were included in the mMITT population (ceftazidime-avibactam, n=154; BAT, n=148). Baseline characteristics were generally similar between the treatment groups in cUTI, and also broadly similar in cIAI, although patient numbers were small (Table 1).

Table 1. *Baseline patient characteristics (mMITT population)*

	cUTI		cIAI	
	Ceftazidime-avibactam (n=144)	BAT (n=137)	Ceftazidime-avibactam + metronidazole (n=10)	BAT (n=11)
Age, years; mean (SD)	64.3 (14.6)	61.3 (15.3)	49.9 (16.1)	68.4 (11.1)
Female; n (%)	64 (44.4)	63 (46.0)	6 (60.0)	4 (36.4)
Race; n (%)				
White	136 (94.4)	131 (95.6)	9 (90.0)	11 (100)
Other†	8 (5.6)	6 (4.4)	1 (10.0)	0
Body mass index, kg/m^2; mean (SD)	28.1 (5.5)	28.0 (5.8)	25.2 (6.3)	28.6 (4.6)
Renal status, creatinine clearance, mL/min; n (%)				
>50	118 (81.9)	113 (82.5)	10 (100)	6 (54.5)
31–50	19 (13.2)	18 (13.1)	0	3 (27.3)
16–30	4 (2.8)	5 (3.6)	0	2 (18.2)
6–15	3 (2.1)	1 (0.7)	0	0

†Black or African American, Asian, or other

- Baseline disease characteristics were similar between the two treatment groups (Table 2). The majority of patients were infected with *Enterobacteriaceae*, most commonly *Klebsiella pneumoniae* and *Escherichia coli*. In 9 of the 10 cUTI patients with bacteraemia, the isolates were *E. coli* or *K. pneumoniae* (the same pathogens as were isolated in their urine).

Efficacy

Overall clinical cure rates at TOC in the mMITT population (cUTI and cIAI combined):
- Ceftazidime-avibactam: 140/154 (90.9%; 95% CI, 85.6, 94.7).
- BAT: 135/148 (91.2%; 95% CI, 85.9, 95.0).

cUTI

- Clinical cure rates at TOC were similar between treatment groups in patients with cUTI (ceftazidime-avibactam: 132/144 [91.7%; 95% CI, 86.3, 95.4]; BAT: 129/137 [94.2%; 95% CI 89.3, 97.2]) (Figure 2).
- Per-patient favourable microbiological response rates at TOC in the cUTI population were higher with ceftazidime-avibactam (118/144 [81.9%; 95% CI, 75.1, 87.6]) than with BAT (88/137 [64.2%; 95% CI, 56.0, 71.9]) with the 95% CI in each treatment group not overlapping (Figure 3).
- In terms of later time points, clinical cure rates decreased over time in both treatment groups, but remained ≥85% with ceftazidime-avibactam, generally achieving similar clinical cure rates to BAT at each visit.

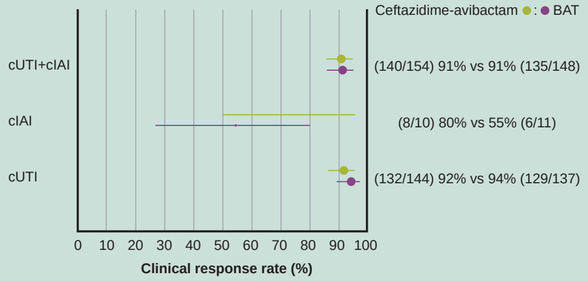
Table 2. *Baseline disease characteristics (mMITT population)*

	cUTI		cIAI	
	Ceftazidime-avibactam (n=144)	BAT (n=137)	Ceftazidime-avibactam + metronidazole (n=10)	BAT (n=11)
Diagnosis cUTI, n (%)				
Acute pyelonephritis	57 (39.6)	70 (51.1)	N/A	N/A
cUTI without pyelonephritis	87 (60.4)	67 (48.9)	N/A	N/A
Diagnosis cIAI, n (%)				
Cholecystitis	N/A	N/A	2 (20.0)	4 (36.4)
Diverticular disease	N/A	N/A	1 (10.0)	1 (9.1)
Appendiceal perforation or per-appendiceal abscess	N/A	N/A	2 (20.0)	0
Secondary peritonitis	N/A	N/A	3 (30.0)	2 (18.2)
Intra-abdominal abscess (≥1)	N/A	N/A	2 (20.0)	4 (36.4)
Bacteraemia, yes; n (%)†	4 (2.8)	6 (4.4)	0	0
Infection type, n (%)				
Monomicrobial	139 (96.5)	131 (95.6)	4 (40.0)	4 (36.4)
Polymicrobial (2 pathogens)	4 (2.8)	6 (4.4)	4 (40.0)	5 (45.5)
Polymicrobial (≥3 pathogens)	1 (0.7)	0	2 (20.0)	2 (18.2)
Prior antibiotic use, n (%)	72 (50.0)	63 (46.0)	10 (100)	11 (100)
Baseline pathogen in urine (cUTI) or intra-abdominal site (cIAI), n (%)‡				
Enterobacteriaceae	131 (91.0)	132 (96.4)	9 (90.0)	11 (100)
E. coli	59 (41.0)	57 (41.6)	4 (40.0)	6 (54.5)
K. pneumoniae	55 (38.2)	65 (47.4)	5 (50.0)	3 (27.3)
Enterobacter cloacae	8 (5.6)	6 (4.4)	3 (30.0)	1 (9.1)
P. aeruginosa	14 (9.7)	5 (3.6)	1 (10.0)	1 (9.1)

†Pathogens identified in blood were *Klebsiella pneumoniae* (4), *Escherichia coli* (5), *Bacteroides fragilis* (1) and *Clostridium ramosum* (1).

‡Other pathogens identified in urine were: *Citrobacter freundii* complex, *Enterobacter aerogenes, Klebsiella oxytoca, Klebsiella ozaenae, Morganella morganii, Proteus mirabilis, Proteus rettgeri, Providencia stuartii, Raoultella terrigena, Serratia marcescens* and *Ochrobactrum anthropi*. Other pathogens identified in intra-abdominal site were: *C. freundii*, Gram-positive aerobes and anaerobes. N/A, not applicable

Figure 2. *Clinical response rate (95% CI) at TOC (mMITT population)*

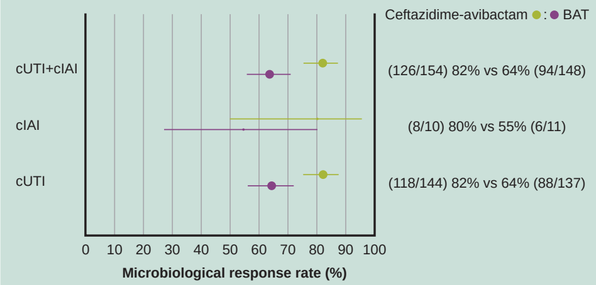


- Consistent with the natural history of cUTI, the microbiological response was lower at subsequent visits after TOC. However, at each subsequent visit, the response rates were consistently higher for ceftazidime-avibactam than for BAT.

cIAI

- The proportion of cIAI patients with clinical cure at TOC was 80.0% (8/10; 95% CI 47.9, 95.6) in the ceftazidime-avibactam plus metronidazole group, and 54.5% (6/11; 95% CI 27.0, 80.0) in the BAT group (Figure 2). Per-patient microbiological outcomes for cIAI patients were presumed from clinical response (Figure 3). The CIs were very wide due to the small number of cIAI patients.

Figure 3. *Per-patient favourable microbiological response rate (95% CI) at TOC (mMITT population)**



*Per-patient microbiological outcomes for cIAI patients were presumed from clinical response

Safety

- The median duration of ceftazidime-avibactam and BAT exposure was 10 and 10 days, respectively, in cUTI, and 10.5 and 12 days in cIAI.
- By the last follow-up visit (28–35 days post-randomisation), 51/164 patients (31.1%) in the ceftazidime-avibactam group and 66/168 (39.3%) in the BAT group had experienced AEs, with serious AEs in 5.5% and 6.0%, respectively. Gastrointestinal disorders were the most frequently reported AEs with both ceftazidime-avibactam (12.8%) and BAT (17.9%).
- Three AEs leading to discontinuation of study drug occurred: one patient (0.6%) in the ceftazidime-avibactam group and two (1.2%) in the BAT group.
- Seven patients experienced an AE with an outcome of death, three in the ceftazidime-avibactam group and four in the BAT group, none of which were considered related to study drug by the investigator.
- The incidence of AEs considered related to study drug by the investigator was low (ceftazidime-avibactam 8.5%, BAT 6.5%).
- There were no new safety concerns identified from the safety topics of interest (liver disorders, diarrhoea, hypersensitivity/anaphylaxis, haematological disorders, and renal disorders), nor for any of the clinical laboratory, electrocardiogram, physical examination or vital signs assessments.

Conclusions

- Treatment of serious ceftazidime-resistant Gram-negative cUTI with ceftazidime-avibactam results in similar clinical cure rates to treatment with BAT, and numerically higher per-patient favourable microbiological response rates. In cIAI, clinical and microbiological response rates were also high for ceftazidime-avibactam and in line with those observed with BAT. The number of cIAI patients in this study was small.
- The safety and tolerability profile of ceftazidime-avibactam is broadly similar to ceftazidime alone.
- In two recently completed studies in cIAI (RECLAIM 1 and 2 [NCT01499290 and NCT01500239]), ceftazidime-avibactam plus metronidazole was shown to be non-inferior to meropenem, including in infections due to ceftazidime-resistant Gram-negative pathogens (see Abstract 1731). Ceftazidime-avibactam is currently being investigated in ongoing Phase III trials* in cUTI (RECAPTURE 1 and 2 [NCT01595438 and NCT01599806]) cIAI (RECLAIM 3 [NCT01726023]) and nosocomial pneumonia (REPROVE [NCT01808092]).

*While ceftazidime-avibactam is still in clinical development, the United States Food and Drug Administration, based on the data from the Phase II programme, approved the drug on 25 February 2015 for use in the treatment of adults with complicated intra-abdominal infections, in combination with metronidazole, and complicated urinary tract infections, including kidney infections (pyelonephritis), who have limited or no alternative treatment options (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm435629.htm).

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Disclosures

YC has received grants, honoraria, travel support, consulting fees, and other forms of financial support from Achaogen Inc, Allecra Therapeutics, AstraZeneca, Basilea Pharmaceutica LTD, Biomerieux SA, Cepheid, DaVolterra, Durata Therapeutics, Inc, Intercell AG, Merck & Co. Inc, PPD, Proteologics, Rempex Pharmaceuticals, Rib-X Pharmaceuticals, Syntezza Bioscience LTD, Takeda Pharmaceutical Company Limited. LG, PN, JA, GS and AW are employees of AstraZeneca. PL was contracted to AstraZeneca from the Statistical Services Unit, University of Sheffield, Sheffield, UK, and as such received fees for services in relation to statistical analysis on this study, including time to review and input to the publication.

This study was supported by AstraZeneca and Actavis. Medical writing support was provided by Liz Anfield of Prime Medica Ltd, Knutsford, Cheshire, UK, funded by AstraZeneca. Poster typesetting support was provided by Prime Medica Ltd, Knutsford, Cheshire, UK, funded by AstraZeneca.
Presented at the 25th European Congress of Clinical Microbiology and Infectious Diseases, 25–28 April 2015, Copenhagen, Denmark.