Efficacy of Ceftazidime-Avibactam against Multi-Drug Resistant *Enterobacteriaceae* and *Pseudomonas aeruginosa* from the Phase 3 Clinical Trial Program

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Introduction

- The prevalence of multi-drug resistant (MDR) Gram-negative pathogens, in particular *Enterobacteriaceae and Pseudomonas aeruginosa*, is increasing worldwide.[1]
- The clinical impact of infection with an MDR pathogen is substantial, as resistance can render commonly used antibiotic agents ineffective, leading to poorer clinical and economic outcomes.[1–3] The potential impact has been acknowledged for a range of infection types, including complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI).[3,4]
- Ceftazidime-avibactam is a combination of the established cephalosporin, ceftazidime, and the first-in-class, non-β-lactam β-lactamase inhibitor, avibactam, which inhibits extended-spectrum β-lactamases (ESBLs), *Klebsiella pneumoniae* carbapenemases (KPCs), AmpC and some OXA enzymes.[5]
- The efficacy and tolerability of ceftazidime-avibactam has been demonstrated in Phase 3 clinical trials for the treatment of patients with cIAI and cUTI.[6–8]
- Ceftazidime-avibactam is approved by the US Food and Drug Administration for the treatment of adults with cIAI (in combination with metronidazole) and cUTI including acute pyelonephritis (where patients have limited or no alternative treatment options), caused by designated susceptible microorganisms.[9] Ceftazidime-avibactam is also approved by the European Medicines Agency for the treatment of adults with cIAI, cUTI (including pyelonephritis), hospital-acquired pneumonia (including ventilator-associated pneumonia) and infections due to aerobic Gram-negative organisms in patients with limited treatment options.[10]
- This post-hoc analysis was performed to assess the efficacy of ceftazidime-avibactam against MDR *Enterobacteriaceae* and *P. aeruginosa* across the Phase 3 trials in patients with cIAI and cUTI.

Methods

- Data from five Phase 3 clinical trials were pooled for this analysis. In all studies, patients were treated with either ceftazidime-avibactam or comparators.
  - **RECLAIM 1 & 2** (NCT01499290, NCT01500239): Two prospective, multicenter, double-blind, randomized, comparative studies to determine the safety, tolerability, and efficacy of ceftazidime-avibactam plus metronidazole versus meropenem (5–14 days of treatment) in the treatment of cIAI in hospitalized adults.[6]
  - **RECAPTURE 1 & 2** (NCT01595438, NCT01599806): Two randomized, multicenter, double-blind, double-dummy, parallel-group, comparative studies to determine the efficacy, safety, and tolerability of ceftazidime-avibactam versus doripenem (5–10 days of treatment, or up to 14 days for patients with bacteremia) followed by appropriate oral therapy in the treatment of cUTI (including acute pyelonephritis) caused by a Gram-negative pathogen in hospitalized adults.[7]
  - **REPRISE** (NCT01644643): A prospective, open-label, randomized, multicenter study to evaluate the efficacy, safety, and tolerability of ceftazidime-avibactam compared with best available therapy (BAT) (5–21 days of treatment) in the treatment of hospitalized adults with cIAI or cUTI caused by ceftazidime-non-susceptible Gram-negative pathogens. In the BAT group, the majority of patients (approximately 97%) received a carbapenem.[8]
- In each trial, specimens obtained from patients were analyzed and MDR pathogens identified.
  - For cIAI, cultures from the site of infection (at time of surgery) and blood were collected. For cUTI, cultures were collected from urine and blood.
  - Identification of pathogens and antibiotic susceptibility testing were performed by both the local microbiology laboratory and a central microbiology reference laboratory (Covance Central Laboratory Services, Indianapolis, IN).
  - Susceptibility testing was performed and interpreted according to Clinical and Laboratory Standards Institute (CLSI) methodologies, using CLSI-defined breakpoints.[11,12]
  - MDR was defined as resistance to ≥3 categories of antimicrobials. These differed for *Enterobacteriaceae* and *P. aeruginosa*, and are defined in Table 1.

Table 1. Antibiotics included in susceptibility testing of *Enterobacteriaceae* and *P. aeruginosa*

Pathogen	Antibiotic class	Antibiotics
Enterobacteriaceae	Aminoglycosides	Gentamicin, amikacin
	Anti-MRSA	Ceftaroline (only approved for *Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca*)
	Antipseudomonal penicillins & β-lactamases	Ticarcillin-clavulanic acid, piperacillin-tazobactam
	Carbapenems	Imipenem, meropenem, doripenem
	Extended-spectrum cephalosporins; 3rd and 4th generation cephalosporins	Cefotaxime or ceftriaxone, ceftazidime, cefepime
	Fluoroquinolones	Ciprofloxacin
	Folate pathway inhibitors	Trimethoprim-sulphamethoxazole
	Monobactams	Aztreonam
	Penicillins	Ampicillin
P. aeruginosa	Aminoglycosides	Gentamicin, amikacin
	Antipseudomonal carbapenems	Imipenem, meropenem, doripenem
	Antipseudomonal cephalsporins	Ceftazidime, cefepime
	Antipseudomonal fluoroquinolones	Ciprofloxacin, levofloxacin
	Antipseudomonal penicillins & β-lactamase inhibitors	Ticarcillin-clavulanic acid, piperacillin-tazobactam
	Monobactams	Aztreonam

- In this analysis, outcome was assessed according to infection by MDR *Enterobacteriaceae* or *P. aeruginosa* and treatment.
  - Microbiological responses were classified as favorable or unfavorable, and are defined in Table 2.
  - Favorable per-pathogen microbiological response rates, measured at the test-of-cure visit, were determined for the pooled microbiologically modified intent-to-treat (mMITT) analysis set.

Table 2. Definitions of favorable or unfavorable microbiological responses

Disease	Response		Definition
cIAI	Favorable	Eradication	Absence of causative organism. If bacteremic at Screening, resolved
		Presumed eradication	Repeat cultures not performed if clinical response of cure
	Unfavorable	Persistence	Causative organism still present at/beyond end-of-treatment visit
		Persistence with increasing MIC	As above, with ≥4-fold higher MIC
		Presumed persistence	Repeat cultures not performed if patient previously assessed as clinical failure
		Indeterminate outcome	Information insufficient to determine outcome
cUTI	Favorable	Eradication	Urine quantification of causative organism $<10^4$ CFU/mL. If bacteremic at Screening, resolved
	Unfavorable	Persistence	Urine quantification of causative organism at/beyond end-of-treatment visit $\geq 10^4$ CFU/mL or (for RECAPTURE) death related to cUTI
		Persistence with increasing MIC	As above, with ≥4-fold higher MIC
		Indeterminate outcome	Information insufficient to determine outcome

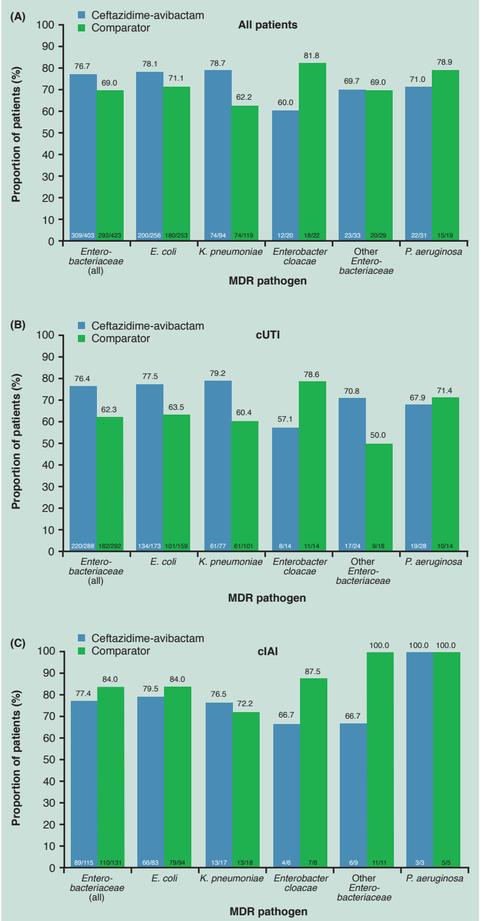
CFU, colony forming units; MIC, minimum inhibitory concentration

  - mMITT definition varied by study, but generally included all patients with appropriate diagnosis and at least one study-qualifying pathogen. Species not expected to respond to study drugs, such as *Acinetobacter* or *Stenotrophomonas* species, were excluded.
  - The test-of-cure visit was Day 28–35 for RECLAIM, 7–10 days after end of treatment for REPRISE, and Day 21–25 for RECAPTURE.

Results

- In the mMITT population, 2019 *Enterobacteriaceae* and *P. aeruginosa* isolates were identified at baseline across the five studies. Among these, 43.4% (876/2019) were defined as MDR.
  - In the ceftazidime-avibactam arm, there were 434 MDR pathogens (118 from patients with cIAI and 316 from patients with cUTI [including 11 cIAI and 145 cUTI pathogens from REPRISE]), 547 non-MDR pathogens, and 16 pathogens where MDR status could not be calculated due to missing or no susceptibility data.
  - In the comparator arms, there were 442 MDR pathogens (136 from patients with cIAI and 306 from patients with cUTI [including 11 cIAI and 139 cUTI pathogens from REPRISE]), 559 non-MDR pathogens, and 21 pathogens where MDR status could not be calculated due to missing or no susceptibility data.
- Overall, 10.5% (92/876) of MDR pathogens were non-susceptible to carbapenems: 12.2% (53/434) in the ceftazidime-avibactam arm and 8.8% (39/442) in the comparator arm.
- Favorable per-pathogen microbiological response rates by MDR pathogen for all patients and for different indications (cUTI or cIAI) are shown in Figure 1. For the *Enterobacteriaceae* (all) group, the favorable per-pathogen response rates for patients with cUTI and cIAI treated with ceftazidime-avibactam were similar to each other and consistent with the all patient group (>76%) (Figure 1).

Figure 1. Favorable per-pathogen microbiological response rates at test-of-cure in the pooled mMITT by MDR pathogen, for (A) all patients, (B) patients with cUTI or (C) patients with cIAI



- Favorable per-pathogen microbiological response rates for MDR pathogens in the *Enterobacteriaceae* (all) group were high (76.7% for the ceftazidime-avibactam arm vs 69.0% for the comparator arm) and similar to results for *Enterobacteriaceae* (all) in the overall mMITT population (79.1% for the ceftazidime-avibactam arm vs 76.2% for the comparator arm).
- Similarly, the favorable per-pathogen microbiological response rates for MDR *P. aeruginosa* were high (71% for the ceftazidime-avibactam arm vs 78.9% for the comparator arm), and comparable to results for *P. aeruginosa* in the overall mMITT population (79.4% for the ceftazidime-avibactam arm vs 85.5% for the comparator arm).
- The minimum inhibitory concentration (MIC) range, MIC_{50} and MIC_{90} for ceftazidime-avibactam, for pathogens of key interest, are shown in Table 3. The MIC_{90} for *Enterobacteriaceae* (1 μg/mL) was below the susceptibility breakpoint of ≤8 mg/L.[9,10] Many of the *P. aeruginosa* isolates in this analysis had resistance mechanisms that were not susceptible to avibactam, such as Class B metallo-β-lactamases for which avibactam has no inhibitory effect, and Class D β-lactamases (other than OXA-48) for which avibactam is not expected to provide additional benefit; this accounts for the high MIC_{90} (64 μg/mL) observed for *P. aeruginosa*.

Table 3. Ceftazidime-avibactam MIC range, MIC_{50} and MIC_{90} for MDR pathogens of key interest (pooled mMITT for ceftazidime-avibactam arm)

Pathogen	Number of pathogens	Number of patients	MIC (μg/mL)	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)
Enterobacteriaceae (all)	403	394	0.008–256	0.12	1
E. cloacae	20	20	0.25–256	1.00	4
E. coli	256	256	0.008–8	0.12	0.5
K. pneumoniae	94	94	0.06–256	0.50	1
P. aeruginosa	31	31	2–256	8.00	64

Conclusions

- Among the bacterial pathogens isolated in Phase 3 clinical trials of ceftazidime-avibactam, a large proportion were MDR.
- Ceftazidime-avibactam was effective in the treatment of patients with cIAI and cUTI caused by MDR pathogens.

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Disclosures

GGS, PN, HB and AW are employees and shareholders of AstraZeneca. LG is a former employee and shareholder of AstraZeneca. KY is a contractor for AstraZeneca and received consulting fees from AstraZeneca. Ceftazidime-avibactam is marketed by AstraZeneca and Allergan.

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