Results from REPRISE, a randomised, pathogen-directed phase 3 study of ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant *Enterobacteriaceae* and *Pseudomonas aeruginosa* complicated urinary tract infections or complicated intra-abdominal infections

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Link to the study protocol and synopsis of results:

27 http://www.astrazenecaclinicaltrials.com/Submission/View?id=695

Summary

Background Carbapenems are frequently the last line of defence in serious infections due to multi-drug-resistant Gram-negative bacteria but their use is threatened by the growing prevalence of carbapenemase-producing pathogens. Ceftazidime-avibactam represents a potential new agent for use in such infections.

Methods REPRISE (NCT01644643) was a prospective, pathogen-directed, international, randomised, open-label, phase 3 trial comparing the efficacy and safety of treatment with ceftazidime-avibactam 2000–500 mg versus best available therapy in adults with complicated urinary tract infections (cUTI) or complicated intra-abdominal infections (cIAI) due to ceftazidime-resistant Enterobacteriaceae or Pseudomonas aeruginosa. 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 (mMITT) population.

Findings Between January 2013 and August 2014, 333 patients were enrolled and randomised in 16 countries worldwide, of whom 302 (90·7%) were included in the mMITT population (281 cUTI, 21 cIAI). Most (97%) patients on best available therapy received a carbapenem, usually as monotherapy. The overall clinical cure rate at TOC in the mMITT population was similar with ceftazidime-avibactam (140/154 [90·9%; 95% confidence interval (CI), 85·6, 94·7]) and best available therapy (135/148 [91·2%; 95% CI, 85·9, 95·0]). The per-patient favourable microbiological response rate at TOC in cUTI patients was higher with ceftazidime-avibactam (118/144 [81·9%; 95% CI, 75·1, 87·6]) than with best available therapy (88/137 [64·2%; 95% CI, 56·0, 71·9]). No new safety concerns were identified for ceftazidime-avibactam.

Interpretation These results provide evidence of the efficacy of ceftazidime-avibactam as a potential alternative to carbapenems in patients with ceftazidime resistant Enterobacteriaceae and P. aeruginosa.

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Introduction

The prevalence of multi-drug resistant (MDR) Gram-negative pathogens, including extended-spectrum β-lactamase (ESBL)-producing and carbapenemase-producing Enterobacteriaceae and Pseudomonas aeruginosa, is increasing worldwide.[1–3] Contributing factors are the extensive use 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 carbapenem antibiotics – 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 alternative treatment options and carbapenem-sparing regimens 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 expanded-spectrum anti-pseudomonal cephalosporin, and avibactam, a novel non-β-lactam β-lactamase inhibitor.[7,8] Avibactam has a broader spectrum of activity than currently available β-lactamase inhibitors, and has been shown in vitro to restore the activity of ceftazidime against most MDR Enterobacteriaceae and P. aeruginosa by inhibiting a wide variety of β-lactamases, including class A (including ESBLs, Klebsiella pneumoniae carbapenemases [KPC]), class C (AmpC), and some class D enzymes (e.g. OXA-48).[9]

Two phase 3 studies of ceftazidime-avibactam in patients with complicated intra-abdominal infection (cIAI) (RECLAIM 1 and 2 [NCT01499290 and

NCT01500239]) have recently been reported,[10] and other phase 3 trials are ongoing, including patients with complicated urinary tract infections (cUTI) (RECAPTURE 1 and 2 [NCT01595438 and NCT01599806]), cIAI (RECLAIM 3 [NCT01726023]) and nosocomial pneumonia (REPROVE [NCT01808092]). However, based on data from phase 2 trials,[7,8] the United States Food and Drug Administration recently approved ceftazidime-avibactam for use in the treatment of adults with cIAI, in combination with metronidazole, and cUTI, including kidney infections (pyelonephritis), who have limited or no alternative treatment options.[11]

The phase 3 studies listed above enrolled patients with or without drug-resistant pathogens. Thus, although they can provide valuable information on safety, tolerability, and efficacy, they may not provide extensive information on efficacy against resistant pathogens. Given the need for new therapies to treat patients with drug-resistant infections, pathogen-directed studies have been recommended.[12] The international, randomised, phase 3 study (REPRISE; NCT01644643) reported here is the first MDR Gram-negative pathogen-directed study for ceftazidime-avibactam, focussing specifically on the efficacy, safety, and tolerability in patients with cUTI or cIAI due to ceftazidime-resistant Gram-negative pathogens.

Methods

Study design

REPRISE was a prospective, international, randomised, open-label, phase 3 trial. As summarised in figure S1 (appendix), eligible patients were randomised in a 1:1 ratio to receive 5–21 days of treatment with either ceftazidime-avibactam 2000–500 mg, administered together as a 2-h intravenous (IV) infusion every 8 h, or best available therapy. Randomisation codes were computer-generated using the AstraZeneca Global Randomization Scheme. Patients were stratified by entry diagnosis (cUTI and cIAI) and by region: (1) North America and Western Europe; (2) Eastern Europe; and (3) Rest of World. Best available therapy was determined by the investigator based on standard of care and local label recommendations, and was documented prior to randomisation. Preferred best available therapy options for cUTI and cIAI were meropenem, imipenem, doripenem, colistin, and (for cIAI) tigecycline, but any therapy, including combination treatment, was permitted. Patients with cUTI had two follow-up visits, at 21–25 days (FU1) and 28–32 days (FU2) from randomisation. Patients with cIAI had only one follow-up visit at 28–35 days from randomisation (FU1) (appendix).

As ceftazidime and avibactam are predominantly cleared renally,[13] ceftazidime-avibactam dose modifications were made for patients with moderate to severe renal impairment (estimated creatinine clearance 6–50 mL/min) (appendix). Patients with cIAI who were randomised to ceftazidime-avibactam also received IV metronidazole 500 mg, administered as a 60-min infusion every 8 h, immediately after the ceftazidime-avibactam infusion, for anaerobe coverage.

The study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and are consistent with International Conference on Harmonisation harmonised tripartite guideline E6(R1) Good Clinical Practice, applicable regulatory requirements, and the Sponsor's policy on Bioethics and Human Biological Samples. The final study protocol was approved by an independent Ethics Committee or institutional review board at each of the participating study sites.

Patients

Male and female patients aged 18–90 years with cUTI or cIAI caused by ceftazidime-resistant Gram-negative pathogens were eligible for inclusion in the trial. Specified diagnoses for cUTI patients were either confirmed acute pyelonephritis or complicated lower UTI without pyelonephritis with pre-defined signs and symptoms (appendix). Patients with cIAI had to have a ceftazidime-resistant Gram-negative pathogen isolated from an abdominal source during a surgical intervention, at least one of eight specified diagnoses during surgical intervention, and specified signs or symptoms of cIAI (appendix).

Patients with ongoing symptoms of either cUTI/pyelonephritis or cIAI at the time of screening and an isolated causative Gram-negative ceftazidime-resistant pathogen could be included regardless of prior antibiotic therapy. Patients who had received prior antibacterial agents that were effective in vitro against the isolated pathogen (based on the known susceptibility profile of the organism) were required to have worsening of objective symptoms or signs of infection after ≥48 h of therapy, or lack of improvement after ≥72 h of therapy.

Key exclusion criteria for both cUTI and cIAI patients included estimated creatinine clearance (CrCL) <6 mL/min by Cockcroft-Gault formula; evidence of abnormal liver function (including bilirubin, alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase levels >3× the upper limit of normal); infection due to a Gram-negative bacterial species that was unlikely to respond to ceftazidime-avibactam treatment (eg, Acinetobacter spp. and Stenotrophomonas spp.); and infection considered unlikely to respond to 5–21 days of study treatment. Patients with cIAI were also excluded from the trial if they had Acute Physiology and Chronic Health Evaluation (APACHE) II score >30; prior liver, pancreas, or small-bowel transplant. Detailed exclusion criteria are summarised in the appendix.

For patients to be entered into the study, ceftazidime-resistant isolates were defined as Enterobacteriaceae and P. aeruginosa with susceptibility results that were intermediate or resistant using Clinical and Laboratory Standards Institute (CLSI) criteria,[14] or resistant using European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria[15] when tested at the local microbiology laboratory. Specifically, for Enterobacteriaceae and P. aeruginosa, ceftazidime resistance was defined as a ceftazidime minimum inhibitory concentration (MIC) ≥8 mg/L and ≥16 mg/L, respectively. The causative Gram-negative ceftazidime-resistant pathogen had to be from an abdominal source obtained during a surgical intervention in cIAI patients, and from a positive urine culture at $\geq 10^5$ colony-forming units (CFU)/mL in cUTI patients, within 5 days prior to screening. All isolates were sent to a central laboratory for culture, identification, and susceptibility testing using CLSI criteria, and the results were used for all analyses except where unavailable, in which case local laboratory results were used. For cUTI patients, a supplementary urine culture was also taken prior to the first dose of study therapy.

All patients, or their legally acceptable representatives, were required to provide written informed consent prior to any study-specific procedures.

Study endpoints

The primary endpoint was assessment of clinical response (cure, failure, or indeterminate) at test-of-cure (TOC) visit 7–10 days after last infusion of study therapy in the microbiologically modified intent-to-treat population (mMITT). Definitions of clinical cure, treatment failure, and indeterminate response are summarised in the appendix. Briefly, clinical cure was defined as complete resolution or significant improvement of signs and symptoms of the index infection, such that no further antibacterial therapy (other than those allowed per protocol) was necessary. In addition, for cIAI patients, cure also required that no drainage or surgical intervention was needed after 96 h from randomisation.

The mMITT population included all patients who had a diagnosis of cUTI or cIAI with at least one ceftazidime-resistant Gram-negative pathogen, as confirmed by the central laboratory, and who received at least one dose of study drug.

Key secondary endpoints in the mMITT population included clinical response at other time points (end of treatment [EOT], FU1 and FU2 [cUTI only]); clinical response at TOC by (i) baseline Gram-negative pathogen isolated, and (ii) entry diagnosis; ~~and~~ per-patient favourable microbiological response rate at EOT, TOC, FU1, and FU2 (cUTI only) and per-pathogen favourable microbiological response rate at TOC. Other secondary outcomes ~~not reported here due to space limitations are listed in the appendix.~~in the mMITT population were clinical cure at TOC by previously failed antibiotic treatment class, per-patient favourable microbiological response rate at the other visits (EOT, FU1 and FU2), favourable per-pathogen

microbiological response at the other visits (EOT, FU1 and FU2), favourable per-pathogen microbiological response by ceftazidime-avibactam MIC, clinical and microbiological response by resistance mechanism, reasons for treatment change and/or discontinuation, and 28-day all-cause mortality rate. All outcomes as listed for the mMITT population were also evaluated for the extended microbiologically evaluable population, as well as clinical cure by previously failed antibiotic treatment class at the EOT, TOC, FU1 and FU2 visits. Finally, pharmacokinetic evaluation was performed for the individual components of ceftazidime-avibactam.

Favourable microbiological response was defined as eradication or presumed eradication. Eradication was defined as absence (or urine quantification $<10^4$ CFU/mL for cUTI patients) of the causative pathogen from the site of infection. In addition, if the patient was bacteraemic at screening, the bacteraemia had also resolved. As is usual for this type of cIAI study, presumed eradication was specifically used for cIAI patients where repeat cultures were not performed/clinically indicated and therefore microbiological response was presumed from clinical response.

Safety and tolerability were assessed by monitoring adverse events (AEs), serious adverse events (SAEs) and laboratory parameters, including liver function tests. Patients underwent 12-lead electrocardiogram (ECG) at days 1 and 3 of study treatment (and as clinically indicated) and at the EOT visit, and vital signs checks and physical examinations were performed at each study visit.

Statistical analysis

Two-sided 95% confidence intervals (CI) for the treatment group response rates were calculated using the Jeffreys method.[17,18] Due to the unfeasibility of recruiting

large numbers of patients infected with resistant Gram-negative pathogens, no formal power calculations were performed for this study, nor any formal statistical comparisons between the treatment groups. Rather, the corresponding CIs for the efficacy of best available therapy were used to provide a context for descriptive estimates of ceftazidime-avibactam efficacy.

It was planned to recruit approximately 200 patients per treatment group, which was expected to provide sufficient data such that the 95% CI would extend at most ~7% on either side of the observed proportion in the overall summary, or at most 17% on either side for each separate pathogen infecting at least 30 patients, or at most 13% on either side for pathogens infecting at least 60 patients.

Role of the funding source

The funder of the study was responsible for study design and data collection. Together with YC, the authors employed (JA, PN, GS, AW, and LBG) or contracted (PJL) by the funder were responsible for data interpretation and writing of this report. JA, PJL, PN, GS, AW, and LBG had full access to all the data in the study, and these were discussed with YC. All authors had final responsibility for the decision to submit for publication.

Results

Patients

Between January 2013 and August 2014, 333 patients were enrolled and randomised at 53 centres in 16 countries worldwide: ceftazidime-avibactam n=165 (153 with cUTI and 12 with cIAI); best available therapy n=168 patients (153 with cUTI and 15 with cIAI). Although 400 patients were planned for inclusion, recruitment was ended early as it was considered that a sufficient number of patients with a suitable range of pathogens had been recruited. 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%. A table of randomised patients by country and a full list of study sites and principal investigators are shown in the appendix.

Most (97%) patients in the best available therapy group received a carbapenem antibiotic and the majority received this as monotherapy, with imipenem and meropenem being the most frequently prescribed agents in cUTI (50% and 37%, respectively) and cIAI patients (33% and 60%). A summary of best available therapy agents administered, and dosing information for imipenem and meropenem, are provided in the appendix. Doses of drugs used in best available therapy were generally in accordance with those recommended in product labelling. One patient randomised to ceftazidime-avibactam did not receive treatment. Therefore, 332 (99·7%) patients were included in the safety population. A total of 302 (90·7%) patients were eligible for inclusion in the mMITT population (ceftazidime-avibactam, n=154; best available therapy, n=148) (figure 1). The main reason for exclusion from the mMITT population was that the ceftazidime resistance of the baseline Gram-

negative study-qualifying isolate, as evaluated at the local microbiology laboratory, was not confirmed by the central laboratory.

For cUTI patients, the urine culture taken at screening (documenting the presence of at least one ceftazidime-resistant Gram-negative pathogen) made the patient eligible for the trial, and for the mMITT analysis set, providing the other criteria were met (see study endpoints). The majority of cUTI patients in the mMITT analysis set had at least one ceftazidime-resistant Gram-negative pathogen in the screening urine culture that was also confirmed in the supplementary baseline urine culture, and the numbers were balanced across the treatment groups (119 patients (82.6%) in the ceftazidime-avibactam group and 112 patients (81.2%) in the best available therapy group).

Baseline patient and disease characteristics, and baseline pathogen distribution, were generally similar between the treatment groups, This was true both in cUTI and cIAI, although patient numbers in the latter group were small (table 3). The majority of patients were infected with Enterobacteriaceae, most commonly K. pneumoniae and Escherichia coli (table 1). Ten cUTI patients also had bacteraemia, in nine of whom the isolates were E. coli or K. pneumoniae (the same pathogens as were isolated in their urine). None of the cIAI patients had bacteraemia.

Of the 55 cUTI patient with a catheter at baseline, 24 patients (43.6%) had a catheter in place for the duration of study therapy or the catheter was only removed 1 to 2 days prior to the end of study therapy (table 1). cUTI patients without pyelonephritis were required to have at least one complicating factor present at baseline. For the 127 patients with acute pyelonephritis, 17 of the 57 patients on ceftazidime-avibactam (29.8%) and 19 of the 70 patients on best available therapy

(27.1%) had at least one complicating factor at baseline. The most common complicating factors present in these 36 patients were partial obstructive uropathy (19 patients) and urogenital procedure within 7 days prior to study entry (13 patients).

Figure 2 shows ceftazidime and ceftazidime-avibactam MICs for baseline Gram-negative pathogens isolated from urine in cUTI patients, including study-qualifying ceftazidime-resistant pathogens, and any other (ceftazidime-susceptible) pathogens isolated. As determined by the central microbiology laboratory, 99·2% of all Enterobacteriaceae isolated from urine in the ceftazidime-avibactam group and 95·7% of those in the best available therapy group were ceftazidime-resistant (MIC ≥8 mg/L). In contrast, only 1·5% of Enterobacteriaceae were shown as non-susceptible to ceftazidime-avibactam (MIC ≤8 mg/L was considered provisionally susceptible and MIC >8 mg/L as provisionally resistant to ceftazidime-avibactam). In each treatment group, the ceftazidime-avibactam MIC_{50} and MIC_{90} were 0·25 and 1 mg/L, respectively, for E. coli, and 0·5 and 1 mg/L for K. pneumoniae. With the exception of one isolate, all P. aeruginosa isolated from the urine of cUTI patients were resistant to ceftazidime (MIC >16 mg/L). In the mMITT analysis set, nine of the 14 baseline P. aeruginosa isolates in the ceftazidime-avibactam group for cUTI patients had a ceftazidime-avibactam MIC >8 mg/L – that is, were provisionally resistant.

Four cUTI patients in the ceftazidime-avibactam group had Gram-negative bacteraemia at baseline, with all blood isolates identified as K. pneumoniae or E coli. All the K. pneumoniae blood isolates and four of five E. coli were resistant to

ceftazidime, but all were within the provisional range of susceptibility for ceftazidime-avibactam (MIC ≤8 mg/L).

In all except seven cUTI patients in the best available therapy group, MIC values to the relevant best available therapy were in the susceptible range according to the central laboratory for all baseline pathogens isolated from urine. In all six cUTI patients in the best available therapy group who had Gram-negative bacteraemia at baseline (K. pneumoniae or E. coli), MICs were in the susceptible range to the best available therapy received. For one E. coli blood isolate in the best available therapy group, the ceftazidime MIC was 4 mg/L.

In the cIAI population, 95.5% of Enterobacteriaceae isolated from the intra-abdominal site were resistant to ceftazidime (MIC ≥8 mg/L), and 100% had ceftazidime-avibactam MICs within the provisional range of susceptibility. Only one cIAI patient in the ceftazidime-avibactam group had a P. aeruginosa isolate and this was provisionally resistant to ceftazidime-avibactam (MIC >8 mg/L).

Clinical cure rates

The overall clinical cure rate at TOC in the mMITT population (cUTI and cIAI combined) was similar with ceftazidime-avibactam (140/154 [90·9%; 95% CI, 85·6, 94·7]) and best available therapy (135/148 [91·2%; 95% CI, 85·9, 95·0]).

cUTI patients

In the cUTI group, clinical cure rates at TOC were similar between treatment groups (ceftazidime-avibactam: 132/144 [91·7%; 95% CI, 86·3, 95·4] and best available therapy: 129/137 [94·2%; 95% CI 89·3, 97·2]) (figure 3A). Among those with acute pyelonephritis, clinical cure rates at TOC were 91·2% (52/57) with ceftazidime-

avibactam and 90·0% (63/70) with best available therapy. Among those without acute pyelonephritis, clinical cure rates at TOC were 92·0% (80/87) and 98·5% (66/67), respectively. In terms of later time points, clinical cure rates decreased slightly over time in both treatment groups, but remained ≥85% with ceftazidime-avibactam, generally achieving similar clinical cure rates to best available therapy at each visit (appendix, figure S2A).

Clinical cure rates at TOC by baseline Gram-negative pathogen isolated from urine were generally high and similar in both treatment groups (figure 4A).

cIAI patients

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 best available therapy group (figure 3A). The CIs were very wide due to the small number of cIAI patients. Clinical cure rates remained the same at FU1 (last follow-up in cIAI patients) in both treatment groups (appendix).

Per-patient microbiological response rates

cUTI patients

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 best available therapy (88/137 [64·2%; 95% CI, 56·0, 71·9]) (figure 3B). Among patients with acute pyelonephritis, per-patient favourable microbiological response rates at TOC were 87·7% (50/57) with ceftazidime-avibactam and 70·0% (49/70) with best available therapy; corresponding rates in patients without pyelonephritis were 78·2% (68/87) and 58·2% (39/67), respectively. In the mMITT analysis set, the

per-patient favourable microbiological response rate at TOC in patients receiving best available therapy with acute pyelonephritis was similar whether at least 1 complicating factor was present at baseline or not (68.4% and 70.6%, respectively). For patients with acute pyelonephritis in the ceftazidime-avibactam arm, the favourable microbiological response rate at TOC was 94.1% and 85.0%, respectively. However, the number of acute pyelonephritis patients with at least 1 complicating factor was small.

Consistent with the natural history of cUTI, the per-patient microbiological response was slightly lower at subsequent visits after TOC (appendix, figure S2B). However, at each subsequent visit, the response rates were consistently higher for ceftazidime-avibactam than for best available therapy.

Favourable microbiological response rates for E. coli and K. pneumoniae isolated from urine in cUTI patients were higher in the ceftazidime-avibactam group than in the best available therapy group (88·1% vs 66·7%, respectively for E. coli, and 83·6% vs 66·2% for K. pneumoniae [figure 4B]).

Favourable microbiological responses to ceftazidime-avibactam at TOC in cUTI patients were demonstrated at ceftazidime-avibactam MICs of 8 mg/L for all Enterobacteriaceae and P. aeruginosa isolates (i.e. just within the provisional range of susceptibility).. Seven of nine cUTI patients in the ceftazidime-avibactam group with provisionally resistant P. aeruginosa isolates (ceftazidime-avibactam MIC >8 mg/L) had a favourable microbiological response at TOC. Two of the 132 baseline Enterobacteriaceae isolates from cUTI patients were provisionally resistant to ceftazidime-avibactam (MIC >8 mg/L), and both patients had an unfavourable microbiological response at TOC.

Given the small number of patients in the study, no other sub-group analyses for the per-patient microbiological response in cUTI patients were planned. However, catheter use at baseline, and by best available therapy received, were investigated post-hoc. Per-patient favourable microbiological response rates at TOC were similar in the ceftazidime-avibactam group whether a catheter was present at baseline or not (25 out of 30 patients (83.3%) and 93 out of 114 patients (81.6%), respectively). For patients receiving best available therapy, the favourable microbiological response rate at TOC was lower in those patients with a catheter at baseline (13 out of 25 patients (52.0%)) compared to those without a catheter at baseline (75 out of 112 patients (67.0%)). However, the number of patients with a catheter at baseline was small (30 patients on ceftazidime-avibactam and 25 patients on best available therapy).

With regards to best available therapy, imipenem or meropenem monotherapy were the most common antibiotics used for cUTI patients (72 patients and 46 patients respectively (in the mMITT analysis set)). Other best available therapy options (monotherapy or combination therapy) were used in the remaining 19 patients. In the mMITT analysis set, the favourable per-patient microbiological response at TOC for cUTI patients was lower for patients receiving imipenem monotherapy (39 out of 72 patients (54.2%) compared to meropenem monotherapy (37 out of 46 patients (80.4%)) or other best available therapy (12 out of 19 patients (63.2%)).

cIAI patients

For cIAI patients, per-patient microbiological outcomes at TOC, and per-pathogen favourable microbiological response among Gram-negative pathogens isolated from the intra-abdominal site, were presumed from the clinical response (figure 3B and figure 4C, respectively). One cIAI patient in the ceftazidime-avibactam plus metronidazole group had a P. aeruginosa isolate with a ceftazidime-avibactam MIC >8 mg/L at baseline. This patient had a favourable microbiological response at TOC.

Other secondary outcomes

The results for all other secondary outcomes are summarised in the appendix.

Safety

The median (range) duration of treatment with ceftazidime-avibactam and best available therapy was 10 (2 to 21) and 10 (2 to 21) days, respectively, in cUTI, and 10·5 (6 to 21) and 12 (4 to 23) 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 best available therapy group had experienced AEs, the majority of which were mild or moderate in intensity. Gastrointestinal disorders were the most frequently reported treatment-emergent AEs with both ceftazidime-avibactam (21/164 patients, 12·8%) and best available therapy (30/168 patients,17·9%) (table 2).

Three AEs leading to discontinuation of study drug occurred: one patient (0·6%) in the ceftazidime-avibactam group and two (1·2%) in the best available therapy group. Seven patients experienced an AE with an outcome of death, none of which were considered related to study drug by the investigator. In the ceftazidime-avibactam group, the AEs with an outcome of death (occurring in one cUTI patient

each) were: cardiorespiratory arrest, cardiac arrest and renal failure. For patients on best available therapy, the events with an outcome of death were cardiac arrest (two cUTI patients), acute respiratory failure (one cUTI patient) and lobar pneumonia (one cIAI patient).

The incidence of AEs considered related to study drug by the investigator was low (ceftazidime-avibactam 14/164 patients, 8·5%, best available therapy 11/168 patients, 6·5%). Overall, nine patients in the ceftazidime-avibactam group and ten patients in the best available therapy group experienced SAEs, but none were considered related to study drug. There were no new safety concerns identified for ceftazidime-avibactam, including for any of the clinical laboratory, ECG, physical examination, or vital signs assessments.

Discussion

Serious infections due to resistant Gram-negative pathogens are difficult to treat and have few treatment options. Thus, patients with these infections have adverse outcomes. Most clinical trials are limited in their ability to provide evidence of efficacy against infections caused by resistant organisms, since their design does not favour the inclusion of large number of patients with such organisms. The REPRISE study is the first pathogen-directed clinical trial for ceftazidime-avibactam examining its effectiveness against ceftazidime-resistant Gram-negative pathogens. Therefore, this study provides valuable information for clinicians and represents an important addition to the ceftazidime-avibactam trial programme, providing supporting data for the pivotal phase 3 trials in cIAI and cUTI.

The REPRISE study met its primary endpoint, demonstrating a similar overall clinical cure rate at TOC with ceftazidime-avibactam and best available therapy in the mMITT population (90·9% vs 91·2%, respectively). The majority of ceftazidime-resistant pathogens were in the provisionally susceptible MIC range for ceftazidime-avibactam, and further analysis is ongoing to evaluate those that were not. Molecular characterisation of the isolates from the study is also ongoing. Seven of nine cUTI patients in the ceftazidime-avibactam group with provisionally resistant P. aeruginosa isolates (ceftazidime-avibactam MIC >8 mg/L) had a favourable microbiological response at TOC. This observation of an apparent response to an agent to which pathogens are non-susceptible is well known and not unique to this study. A review of antibacterial clinical trials spanning 30 years characterized the "90-60 rule", whereby infections due to susceptible isolates respond to therapy ~90% of the time, whereas infections due to resistant isolates respond ~60% of the

time.[19] In addition, ceftazidime-avibactam is excreted in the urine to high levels, potentially contributing to a favourable microbiological response in these patients with a provisionally resistant isolate. A higher microbiological response rate was observed for ceftazidime-avibactam compared with best available therapy in cUTI patients, the reason for which not clear. Imipenem was the most common antibiotic used as best available therapy for cUTI patients, and there were more with an unfavourable microbiological response at TOC in those who received imipenem compared with other best available therapy. Although dosing of imipenem was in line with labelling, a variety of doses were used and some patients received doses at the lower end of the recommended range. However, given that the baseline MICs of study treatment received were low, and generally well within the susceptible range for the antibiotic administered, it is difficult to draw any conclusions from this observation. No new safety signals for ceftazidime-avibactam were identified, and the overall safety profile was similar to that reported previously for ceftazidime alone[20] and the cephalosporin class.

The main limitation to the REPRISE study was the open-label nature of the trial. Open label administration was mandated in order to allow choice of best available therapy against resistant organisms with variable susceptibility patterns. This limitation was offset partly by the requirement for the individual investigators to define their choice of best available therapy prior to randomisation. Furthermore, the study found high rates of microbiological response compared with best available therapy, which is an objective assessment and therefore unlikely to have been affected by the study design. Another potential limitation was the predominance of patient recruitment from Eastern Europe compared with the other regions, but recruitment was generally well balanced between the treatment groups with regard

to geographic distribution. The small number of cIAI patients enrolled meant that the study results only allowed for general descriptions of treatment-related trends for this population. However, the RECLAIM 1 and 2 studies in cIAI (reported as a single study database) included 529 patients treated with ceftazidime-avibactam plus metronidazole, which was shown to be non-inferior to meropenem.[10] Results in the subset of patients with infections due to ceftazidime-resistant Gram-negative pathogens were consistent with the primary results of this study.

In conclusion, treatment of serious ceftazidime-resistant Gram-negative cUTI with ceftazidime-avibactam results in similar clinical cure rates to treatment with best available therapy 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 best available therapy. However, the number of cIAI patients in this study was small, limiting the interpretation of the findings in this population. The safety and tolerability profile of ceftazidime-avibactam reported here is broadly similar to the recognised profile of ceftazidime alone. These promising results support the use of ceftazidime-avibactam as a potential alternative to carbapenems in patients with resistant Gram-negative infections.

Research in context

Evidence before this study

PubMed search terms: [ceftazidime-avibactam AND randomised]

ECCMID 2015 search term: [ceftazidime-avibactam]

PubMed searches using the above terms identified three reports of phase 1 trials assessing the safety, tolerability and pharmacokinetics of ceftazidime-avibactam,[21–23] and two phase 2 trials of ceftazidime-avibactam in patients with cUTI and cIAI caused by Gram-negative pathogens.[7,8] The phase 2 trial in cUTI patients demonstrated clinical response rates with ceftazidime-avibactam comparable to those for imipenem-cilastatin.[8] In cIAI patients, ceftazidime-avibactam (in combination with metronidazole) achieved response rates comparable to those achieved with meropenem.[7] Both studies included some patients with ceftazidime-resistant infections, but this was not an inclusion criterion in either trial.

The ECCMID 2015 search identified the results of some phase 3 studies of ceftazidime-avibactam: the REPRISE study reported in this paper,[24] and a single report of two identical phase 3 studies in cIAI (RECLAIM 1 and 2), which included some patients with ceftazidime-resistant Gram-negative infections.[10] Ceftazidime-avibactam plus metronidazole was shown to be non-inferior to meropenem.

Other ongoing or recently completed (but not yet published) phase 3 trials of ceftazidime-avibactam, including patients with cUTI, cIAI, or nosocomial pneumonia, also included all-comers rather than specifically recruiting patients with ceftazidime-resistant infections.

Added value of this study

The REPRISE study was specifically designed to evaluate the efficacy of ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant Gram-negative cUTI and cIAI. Clinical cure rates were similar in both treatment groups, with numerically higher per-patient favourable microbiological response rates in the ceftazidime-avibactam group. The observed safety and tolerability ceftazidime-avibactam was similar to the recognised profile of ceftazidime alone.

Implications of all the available evidence

These promising results support the further development of ceftazidime-avibactam as a potential alternative to carbapenems in patients with resistant Gram-negative infections.

Contributors

YC obtained the data, as International Coordinating Investigator.

JA, PJL, PN, GS, AW, and LBG analysed the data.

YC, JA, PJL, PN, GS, AW, and LBG wrote the first draft and all authors reviewed and edited the final manuscript.

Declaration of interests

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Table 1: Baseline patient characteristics and infection type (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)
75–90 years, n (%)	38 (26·4)	27 (19·7)	0	4 (36·4)
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)
≥30 kg/m^2, n (%)	48 (33·3)	51 (37·2)	3 (30·0)	4 (36·4)
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
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
Complicating factors				
Partial obstructive uropathy	45 (31·3)	21 (15·3)	N/A	N/A
Abnormality of urogenital tract	39 (27·1)	38 (27·7)	N/A	N/A
Male with urinary retention	33 (22·9)	24 (17·5)	N/A	N/A
Catheterisation	30 (20·8)	25 (18·2)	N/A	N/A
Urogenital procedure within 7 days	27 (18·8)	21 (15·3)	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)
APACHE II score, mean (SD)‡	N/A	N/A	6·9 (5·8)	10·9 (4·4)
APACHE II score category	N/A	N/A		
≤10	N/A	N/A	8 (80·0)	6 (54·5)
>10–≤30	N/A	N/A	1 (10·0)	3 (27·3)
Prior antibiotic use, n (%)	72 (50·0)	63 (46·0)	10 (100)	11 (100)

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)
Baseline pathogen in urine (cUTI) or intra-abdominal site (cIAI), n (%)[‖]				
Enterobacteriaceae	131 (91·0)	132 (96·4)	9 (90·0)	11 (100)
Escherichia coli	59 (41·0)	57 (41·6)	4 (40·0)	6 (54·5)
Klebsiella 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)
Pseudomonas aeruginosa	14 (9·7)	5 (3·6)	1 (10·0)	1 (9·1)

[†]Black or African American, Asian, or other.

[‡]Data available for nine patients in each group.

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

[§]Maximum of two uropathogens permitted for study entry; however, one cUTI patient in the ceftazidime-avibactam group had one Gram-negative pathogen (Proteus mirabilis) in the urine and two anaerobes in the blood.

[‖]Other pathogens identified in urine were: Citrobacter freundii complex (5 patients), Proteus mirabilis (6 patients), Serratia marcescens (2 patients), and (in 1 patient each) Enterobacter aerogenes, Klebsiella oxytoca, Klebsiella ozaenae, Morganella morganii, Proteus rettgeri, Providencia stuartii, Raoultella terrigena, and Ochrobactrum anthropi. Other pathogens identified in intra-abdominal site were: Citrobacter freundii complex (2 patients), Gram-positive aerobes (7 patients), and anaerobes (4 patients).

APACHE=Acute Physiology and Chronic Health Evaluation; BAT=best available therapy; cIAI=complicated intra-abdominal infection; cUTI=complicated urinary tract infection; mMITT=microbiologically modified intent-to-treat; SD=standard deviation.

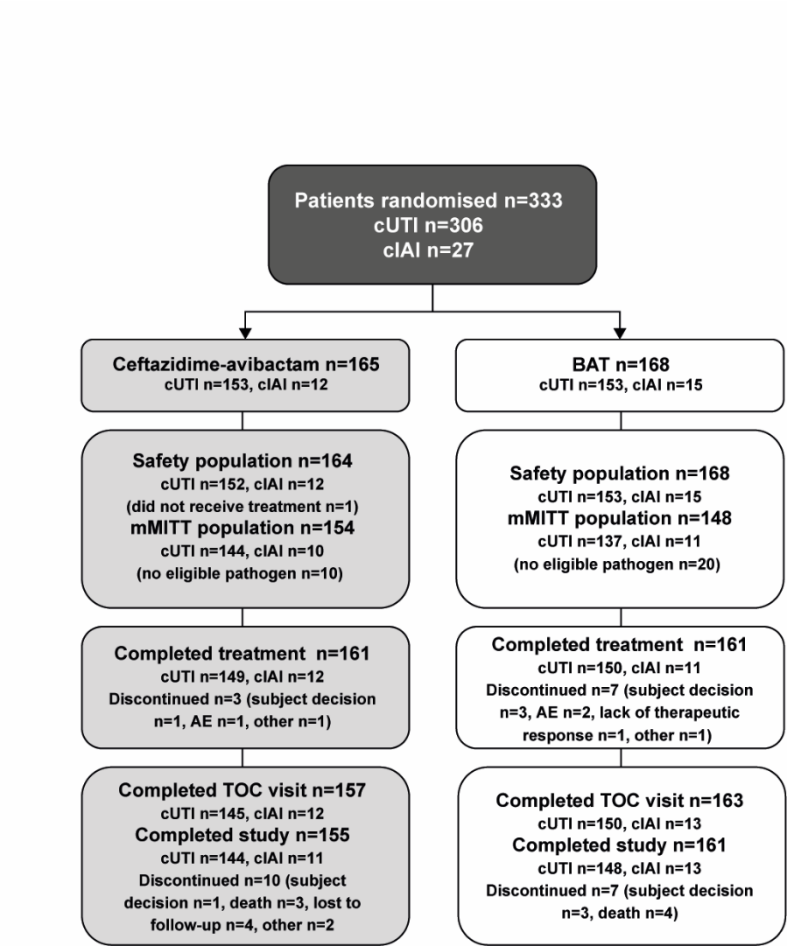
Table 2: Adverse events* (safety population)

	cUTI		cIAI	
Preferred term, n (%)	**Ceftazidime-avibactam (n=152)**	**BAT (n=153)**	**Ceftazidime-avibactam + metronidazole (n=12)**	**BAT (n=15)**
Patients with any AE	43 (28·3)	54 (35·3)	8 (66·7)	12 (80·0)
Nausea	5 (3·3)	9 (5·9)	3 (25·0)	1 (6·7)
Vomiting	4 (2·6)	2 (1·3)	2 (16·7)	1 (6·7)
Diarrhoea	3 (2·0)	8 (5·2)	2 (16·7)	0
Pyrexia	4 (2·6)	2 (1·3)	0	0
Abdominal pain	3 (2·0)	4 (2·6)	0	1 (6·7)
Dyspepsia	2 (1·3)	5 (3·3)	0	0
Headache	1 (0·7)	11 (7·2)	2 (16·7)	1 (6·7)
Oedema peripheral	3 (2·0)	1 (0·7)	0	0
Vulvovaginal candidiasis	3 (2·0)	0	0	0
Insomnia	2 (1·3)	0	2 (16·7)	4 (26·7)
Nasal congestion	1 (0·7)	0	2 (16·7)	0
Phlebitis	1 (0·7)	2 (1·3)	2 (16·7)	1 (6·7)
Back pain	0	0	2 (16·7)	0
Paraesthesia	0	0	2 (16·7)	0
Respiratory failure	0	0	0	2 (13·3)

*AEs occurring in ≥2% patients for cUTI and/or ≥2 patients for cIAI (ceftazidime-avibactam or BAT), and with onset time on or after time of first dose and up to and including last follow-up visit (FU2 for cUTI, FU1 for cIAI), irrespective of relationship to study drug.

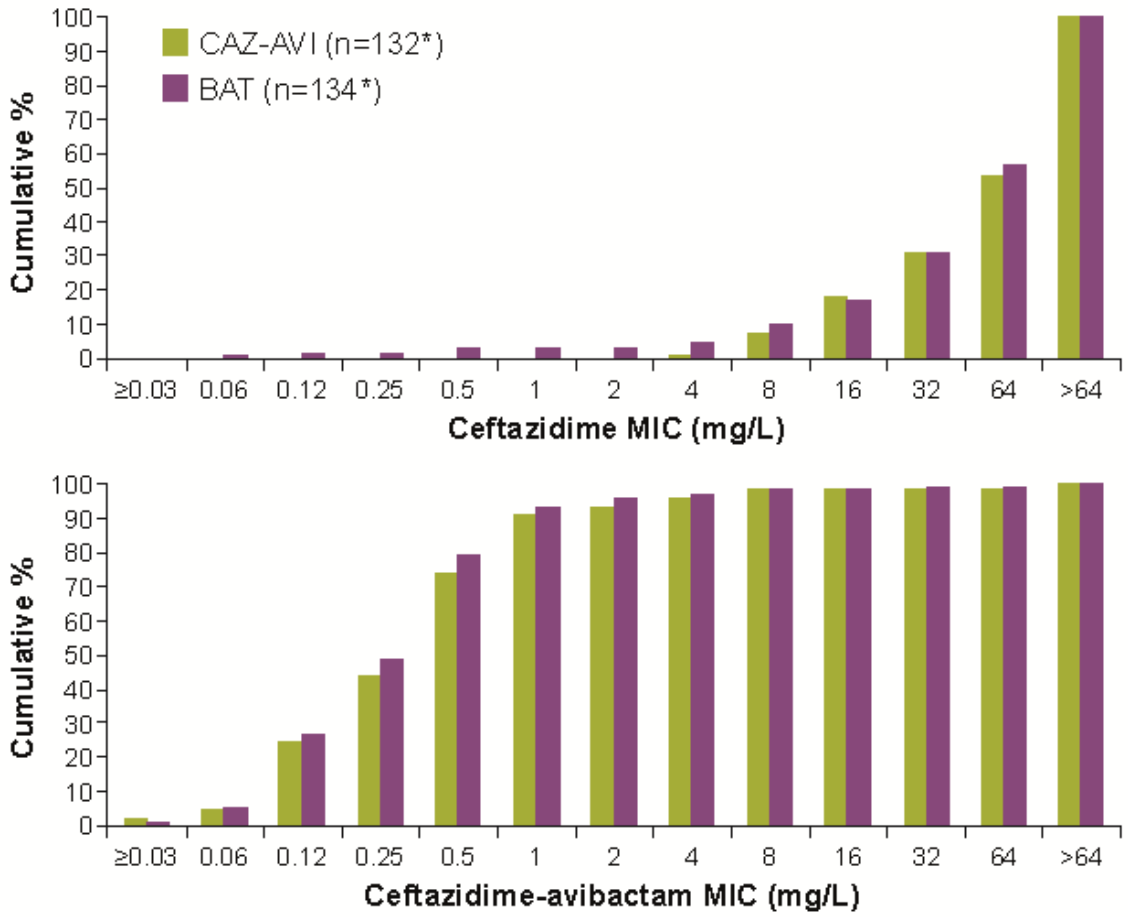
AE=adverse events; BAT=best available therapy; cIAI=complicated intra-abdominal infection; cUTI=complicated urinary tract infection; FU1=follow-up 1; FU2=follow-up 2.

Figure 1: Study flow



AE=adverse event; BAT=best available therapy; cIAI=complicated intra-abdominal infection; cUTI=complicated urinary tract infection; mMITT=microbiologically modified intent-to-treat; TOC=test of cure visit.

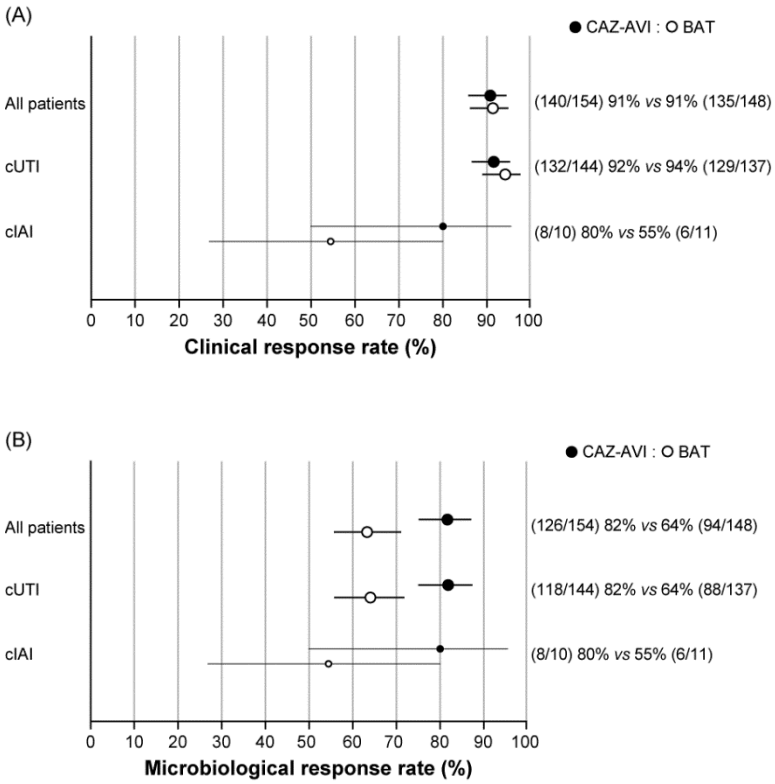
Figure 2: Ceftazidime and ceftazidime-avibactam MIC for all Enterobacteriaceae isolated from urine at baseline in cUTI patients (mMITT population)



*Number of pathogens. Some patients had more than one baseline Gram-negative pathogen and one of those may have been ceftazidime-susceptible.

BAT=best available therapy; CAZ-AVI=ceftazidime-avibactam; cUTI=complicated urinary tract infection; MIC=minimum inhibitory concentration; mMITT=microbiologically modified intent-to-treat.

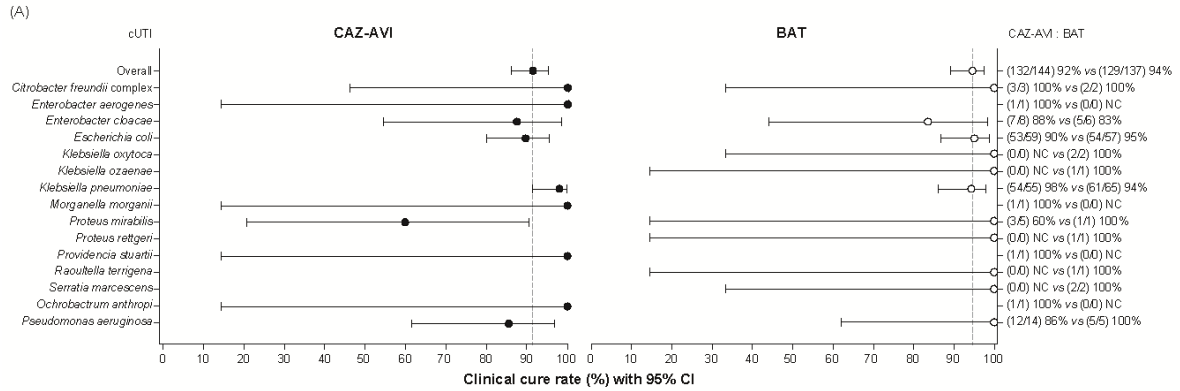
Figure 3: (A) Clinical response rate (95% CI) at TOC (mMITT population); (B) per-patient favourable microbiological response rate (95% CI) at TOC (mMITT population)*

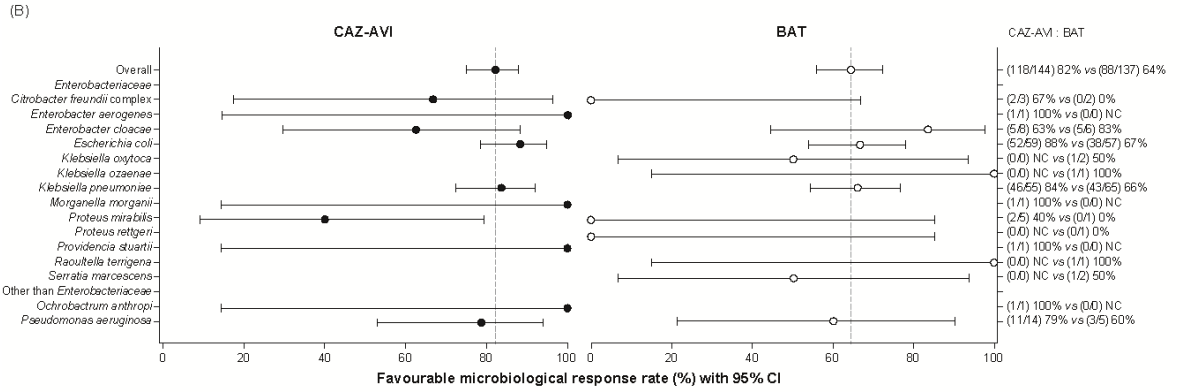


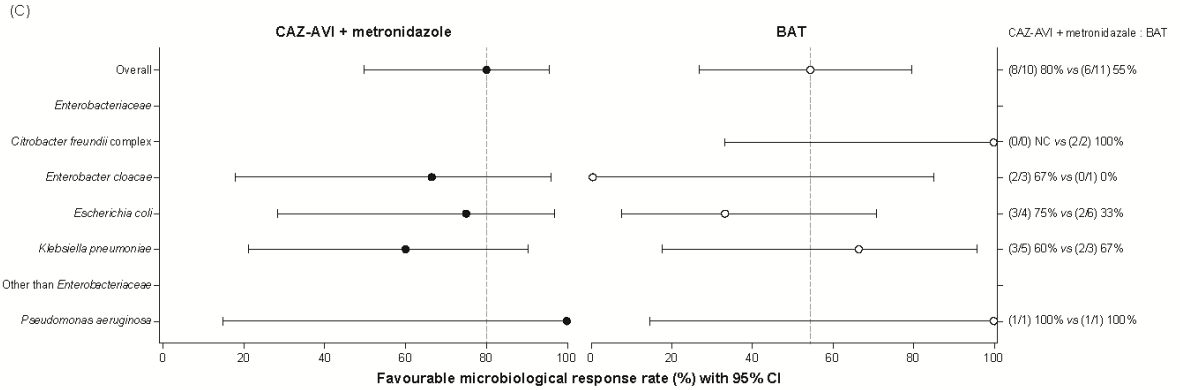
*Per-patient microbiological outcomes for cIAI patients were presumed from clinical response.

BAT=best available therapy; CAZ-AVI=ceftazidime-avibactam; CI=confidence interval; cIAI=complicated intra-abdominal infection; cUTI=complicated urinary tract infection; mMITT=microbiologically modified intent-to-treat; TOC=test of cure visit.

Figure 4: Per-pathogen response rates at TOC among Gram-negative pathogens isolated at baseline: (A) clinical response rates per pathogen isolated from urine in cUTI patients; (B) favourable microbiological response rates per pathogen isolated from urine in cUTI patients; (C) favourable microbiological response rates per pathogen isolated from intra-abdominal site in cIAI patients (mMITT population)*







*Some patients had more than one baseline Gram-negative pathogen.

BAT=best available therapy; CAZ-AVI=ceftazidime-avibactam; cIAI=complicated intra-abdominal infection; cUTI=complicated urinary tract infection; mMITT=microbiologically modified intent-to-treat; NC=not calculated; TOC=test of cure visit.