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

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Summary

Background Carbapenems are frequently the last line of defence in serious infections due to multidrug-resistant Gram-negative bacteria, but their use is threatened by the growing prevalence of carbapenemase-producing pathogens. Ceftazidime-avibactam is a potential new agent for use in such infections. We aimed to assess the efficacy, safety, and tolerability of ceftazidime-avibactam compared with best available therapy in patients with complicated urinary tract infection or complicated intra-abdominal infection due to ceftazidime-resistant Gram-negative pathogens.

Methods REPRISE was a pathogen-directed, international, randomised, open-label, phase 3 trial that recruited patients from hospitals across 16 countries worldwide. Eligible patients were aged 18–90 years with complicated urinary tract infection or complicated intra-abdominal infection caused by ceftazidime-resistant Enterobacteriaceae or *Pseudomonas aeruginosa*. Patients were randomised (1:1) to 5–21 days of treatment with either ceftazidime-avibactam (a combination of 2000 mg ceftazidime plus 500 mg avibactam, administered via a 2-h intravenous infusion every 8 h) or best available therapy. The primary endpoint was clinical response at the test-of-cure visit, 7–10 days after last infusion of study therapy, analysed in all patients who had at least one ceftazidime-resistant Gram-negative pathogen, as confirmed by the central laboratory, and who received at least one dose of study drug. Safety endpoints were assessed in all patients who received at least one dose of study drug. This study is registered with ClinicalTrials.gov, number NCT01644643.

Findings Between Jan 7, 2013, and Aug 29, 2014, 333 patients were randomly assigned, 165 to ceftazidime-avibactam and 168 to best available therapy. Of these, 154 assigned to ceftazidime-avibactam (144 with complicated urinary tract infection and ten with complicated intra-abdominal infection) and 148 assigned to best available therapy (137 with complicated urinary tract infection and 11 with complicated intra-abdominal infection) were analysed for the primary outcome. 163 (97%) of 168 patients in the best available therapy group received a carbapenem, 161 (96%) as monotherapy. The overall proportions of patients with a clinical cure at the test-of-cure visit were similar with ceftazidime-avibactam (140 [91%; 95% CI 85·6–94·7] of 154 patients) and best available therapy (135 [91%; 85·9–95·0] of 148 patients). 51 (31%) of 164 patients in the ceftazidime-avibactam group and 66 (39%) of 168 in the best available therapy group had an adverse event, most of which were mild or moderate in intensity. Gastrointestinal disorders were the most frequently reported treatment-emergent adverse events with both ceftazidime-avibactam (21 [13%] of 164 patients) and best available therapy (30 [18%] of 168 patients). 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 multidrug-resistant 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 human beings and animals, poor infection control, and the greatly increased global mobility of people, allowing the rapid spread of multidrug-resistant 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 multidrug-resistant Gram-negative bacteria, but now threatened by the growing prevalence of carbapenemase-producing pathogens.[6] Therefore, alternative treatment options and carbapenem-sparing regimens for patients with serious infections caused by multidrug-resistant Gram-negative pathogens are urgently needed.

Research in context

Evidence before this study

We searched PubMed with the search terms "ceftazidime-avibactam" AND "randomised", and the European Congress of Clinical Microbiology and Infectious Diseases 2015 abstracts with the search term "ceftazidime-avibactam", for articles published on or before July 16, 2015. No other restrictions were applied to the search, but we excluded preclinical and surveillance studies and reviews from the results. PubMed searches using the above terms identified three reports of phase 1 trials assessing the safety, tolerability, and pharmacokinetics of ceftazidime-avibactam, and two phase 2 trials of ceftazidime-avibactam in patients with complicated urinary tract infection and complicated intra-abdominal infection caused by Gram-negative pathogens. The phase 2 trial in patients with complicated urinary tract infection demonstrated clinical response rates with ceftazidime-avibactam similar to those for imipenem-cilastatin. In patients with complicated intra-abdominal infection, ceftazidime-avibactam (in combination with metronidazole) achieved a response that was similar to that achieved with meropenem. 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 here, and a single report of two identical phase 3 studies in complicated intra-abdominal infection (RECLAIM 1 and 2), which included some patients with ceftazidime-resistant Gram-negative infections. 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 complicated urinary tract infection, complicated intra-abdominal infection, 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 assess the efficacy of ceftazidime-avibactam and best available therapy in patients with ceftazidime-resistant Gram-negative complicated urinary tract infection or complicated intra-abdominal infection. The proportion of patients who were clinically cured were similar in both treatment groups, with a numerically higher proportion of patients achieving a favourable microbiological response 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 results support the further development of ceftazidime-avibactam as a potential alternative to carbapenems in patients with resistant Gram-negative infections.

Ceftazidime-avibactam could be an important new option for such cases, consisting of 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 available β-lactamase inhibitors, and has been shown in vitro to restore the activity of ceftazidime against most multidrug-resistant Enterobacteriaceae and *P aeruginosa* by inhibiting a wide variety of β-lactamases, including class A (such as ESBLs, *Klebsiella pneumoniae* carbapenemases), class C (AmpC), and some class D enzymes (eg, OXA 48).[9]

Two phase 3 studies of ceftazidime-avibactam in patients with complicated intra-abdominal infection (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 (RECAPTURE 1 and 2 [NCT01595438 and NCT01599806]), complicated intra-abdominal infection (RECLAIM 3 [NCT01726023]), and nosocomial pneumonia (REPROVE [NCT01808092]). However, on the basis of data from phase 2 trials,[7,8] the US Food and Drug Administration recently approved ceftazidime-avibactam for use in the treatment of adults with complicated intra-abdominal infection, in combination with metronidazole, and complicated urinary tract infection, 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 about safety, tolerability, and efficacy, they might not provide extensive information about 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 multidrug-resistant Gram-negative pathogen-directed study for ceftazidime-avibactam, focusing specifically on the efficacy, safety, and tolerability in patients with complicated urinary tract infection or complicated intra-abdominal infection due to ceftazidime-resistant Gram-negative pathogens.

Methods

Study design and participants

REPRISE was an international, randomised, open-label, phase 3 trial that recruited patients from hospitals worldwide. Male and female patients aged 18–90 years with complicated urinary tract infection or complicated intra-abdominal infection caused by ceftazidime-resistant Gram-negative pathogens were eligible for inclusion in the trial. Specified diagnoses for patients with complicated urinary tract infection were either confirmed acute pyelonephritis or complicated lower urinary tract infection without pyelonephritis with predefined signs and

symptoms (appendix). Patients with complicated intra-abdominal infection 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 complicated intra-abdominal infection (appendix).

Patients with ongoing symptoms of either complicated urinary tract infection or pyelonephritis or complicated intra-abdominal infection at the time of screening and an isolated causative Gram-negative ceftazidime-resistant pathogen could be included regardless of previous antibiotic therapy. Patients who had received previous 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 or longer of therapy, or absence of improvement after 72 h or longer of therapy.

Key exclusion criteria for both patients with complicated urinary tract infection and those with complicated intra-abdominal infection included estimated creatinine clearance of less than 6 mL/min by Cockcroft-Gault formula; evidence of abnormal liver function (including bilirubin, alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase levels more than three times 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 complicated intra-abdominal infection were also excluded from the trial if they had an Acute Physiology and Chronic Health Evaluation (APACHE) II score of greater than 30 or had previously undergone a 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,[13] or resistant using European Committee on Antimicrobial Susceptibility Testing criteria[14] when tested at the local microbiology laboratory. Specifically, for Enterobacteriaceae and *P aeruginosa,* ceftazidime resistance was defined as a ceftazidime minimum inhibitory concentration (MIC) of 8 mg/L or greater and 16 mg/L or greater, respectively. The causative Gram-negative ceftazidime-resistant pathogen had to be from an abdominal source obtained during a surgical intervention in patients with complicated intra-abdominal infection, and from a positive urine culture at at least 10^5 colony-forming units (CFU) per mL in patients with complicated urinary tract infection, within 5 days before 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 when unavailable, in which case local laboratory results were used. For patients with complicated urinary tract infection, a supplementary urine culture was also taken before the first dose of study therapy. All patients, or their legally acceptable representatives, were required to provide written informed consent before any study-specific procedures.

See Online for appendix

The study was done 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 AstraZeneca'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, and is available online. This study was not overseen by a data monitoring committee.

For the **trial protocol** see http://www.astrazenecaclinicaltrials.com/Submission/View?id=695

Randomisation

Eligible patients were randomised in a 1:1 ratio to either ceftazidime-avibactam or best available therapy (appendix). Randomisation codes were computer-generated using the AstraZeneca Global Randomization Scheme. Patients were stratified by entry diagnosis (complicated urinary tract infection and complicated intra-abdominal infection) and by region: North America and western Europe; eastern Europe; and rest of world. Participants, people administering the treatment, those assessing outcomes at the sites, and those analysing the data were not masked to group assignment.

Procedures

Patients assigned to ceftazidime-avibactam received 5–21 days of treatment with ceftazidime-avibactam (a combination of 2000 mg ceftazidime plus 500 mg avibactam), administered together as a 2-h intravenous (IV) infusion every 8 h. Best available therapy was determined by the investigator on the basis of standard of care and local label recommendations, and was documented before randomisation. Preferred best available therapy options for complicated urinary tract infection and complicated intra-abdominal infection were 5–21 days of treatment with meropenem, imipenem, doripenem, colistin, and (for complicated intra-abdominal infection) tigecycline, administered intravenously, but any therapy, including combination treatment, was permitted.

Because ceftazidime and avibactam are predominantly cleared renally,[15] ceftazidime-avibactam dose modifications were made for patients with moderate to severe renal impairment (estimated creatinine clearance 6–50 mL/min; appendix). Patients with complicated intra-abdominal infection who were randomly assigned 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.

Patients with complicated urinary tract infection had two follow-up visits, at 21–25 days (follow-up visit 1) and 28–32 days (follow-up visit 2) from randomisation. Patients with complicated intra-abdominal infection had only one follow-up visit at 28–35 days from randomisation (follow-up visit 1; appendix). Assessments done at follow-up visits 1 and 2 were a review of concomitant medications and antibiotics, complete physical examination, assessment of infection signs and symptoms, urinary device status (patients with complicated urinary tract infection only), temperature, heart rate, blood pressure, respiratory rate, 12-lead electrocardiogram (ECG), serum and urine β-human chorionic gonadotropin for women of childbearing age, quantitative urine culture (patients with complicated urinary tract infection only), clinical response assessment, mortality, blood and urine tests for safety analysis, and adverse events. Follow-up blood culture and intra-abdominal culture (patients with complicated intra-abdominal infection only) were done as clinically indicated.

Outcomes

The primary endpoint was assessment of clinical response (cure, failure, or indeterminate) at the test-of-cure visit, 7–10 days after last infusion of study therapy in the microbiologically modified intention-to-treat population (mMITT). The mMITT population included all patients who had a diagnosis of complicated urinary tract infection or complicated intra-abdominal infection 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. Definitions of clinical cure, treatment failure, and indeterminate response are summarised in the appendix. Briefly, clinical cure was defined as complete resolution or substantial improvement of signs and symptoms of the index infection, such that no further antibacterial therapy (other than those allowed per protocol) was necessary. Additionally, for patients with complicated intra-abdominal infection, cure also required that no drainage or surgical intervention was needed after 96 h from randomisation.

Key secondary endpoints in the mMITT population included clinical response at other timepoints (end of treatment, follow-up visit 1, and follow-up visit 2 [complicated urinary tract infection only]); clinical response at the test-of-cure visit by baseline Gram-negative pathogen isolated, and entry diagnosis; per-patient favourable microbiological response at end of treatment, test-of-cure visit, follow-up visit 1, and follow-up visit 2 (complicated urinary tract infection only); and per-pathogen favourable microbiological response at test-of-cure visit. Other secondary outcomes in the mMITT population were clinical cure at test-of-cure visit by previously failed antibiotic treatment class, per-pathogen favourable microbiological response at the other visits (end of treatment, follow-up visit 1, and follow-up visit 2), per-pathogen favourable microbiological response by ceftazidime-avibactam MIC, clinical and microbiological response by resistance mechanism, reasons for treatment change or discontinuation, and 28-day all-cause mortality. All outcomes as listed for the mMITT population were also assessed in the extended microbiologically evaluable population; this population was defined as all patients who were included in the mMITT population who received at least 5 days of treatment, or less than 48 h of therapy before discontinuing as a result of an adverse event, had no important protocol deviations that would affect assessment of efficacy, received no additional systemic Gram-negative antibacterial treatment (other than study treatment as designated at randomisation) for treatment of infections other than complicated urinary tract and intra-abdominal infection, and (in patients with complicated urinary tract infection only) had a microbiological assessment from a quantitative urine culture at the end of therapy, test-of-cure, follow-up visit 1 and 2, with a microbiological response other than indeterminate (patients with complicated urinary tract infection only), and had a microbiological response other than indeterminate at the end of treatment, test-of-cure and follow-up visit 1 (patients with complicated intra-abdominal infection only). Clinical cure by previously failed antibiotic treatment class at the end of treatment, test-of-cure visit, follow-up visit 1, and follow-up visit 2 was also assessed. Finally, we did a pharmacokinetic evaluation for the individual components of ceftazidime-avibactam.

We defined favourable microbiological response as eradication or presumed eradication. Eradication was defined as absence (or urine quantification $<10^4$ CFU per mL for patients with complicated urinary tract infection) of the causative pathogen from the site of infection. Additionally, if the patient was bacteraemic at screening, the bacteraemia had also resolved. As is usual for this type of complicated intra-abdominal infection study, presumed eradication was specifically used for patients with complicated intra-abdominal infection for whom repeat cultures were not done or clinically indicated and therefore microbiological response was presumed from clinical response.

We assessed safety and tolerability by monitoring adverse events, serious adverse events, and laboratory parameters, including liver function tests. Adverse events were assessed according to their severity (mild, moderate, or severe). Patients underwent 12-lead ECG at days 1 and 3 of study treatment (and as clinically indicated) and at the end of treatment, and vital signs checks and physical examinations were done at each study visit. The safety population was defined as all patients who received at least one dose of study drug.

Statistical analysis

We planned to recruit about 200 patients per treatment group, which was expected to provide sufficient data

such that the 95% CI for the proportion of patients who were cured within each treatment group would extend at most by about 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.

Two-sided 95% CIs for the treatment group response were calculated using the Jeffreys method.[16,17] Because of the unfeasibility of recruiting large numbers of patients infected with resistant Gram-negative pathogens, we did not do any formal power calculations for this study, or any formal statistical comparisons between the treatment groups. Rather, we used the corresponding CIs for the efficacy of best available therapy to provide a context for descriptive estimates of ceftazidime-avibactam efficacy. We did all analyses using SAS version 9.1.3.

This study is registered with ClinicalTrials.gov, number NCT01644643.

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

Between Jan 7, 2013, and Aug 29, 2014, 333 patients were enrolled and randomised at 53 hospitals in 16 countries worldwide: 165 to ceftazidime-avibactam (153 with complicated urinary tract infection and 12 with complicated intra-abdominal infection), and 168 to best available therapy (153 with complicated urinary tract infection and 15 with complicated intra-abdominal infection; figure 1). Although we had planned to include 400 patients, recruitment was ended early because the funder considered that a sufficient number of patients with a suitable range of pathogens had been recruited. 268 (80%) randomly assigned patients were recruited from eastern Europe, 16 (5%) from North America and western Europe, and 49 (15%) from the rest of world. A table of randomised patients by country and a full list of study sites and principal investigators are shown in the appendix.

163 (97%) of 168 patients in the best available therapy group received a carbapenem antibiotic and 161 (96%) received this as monotherapy, with imipenem and meropenem being the most frequently prescribed agents in complicated urinary tract infection (76 [50%] of 153 patients and 57 [37%] of 153 patients, respectively) and patients with complicated intra-abdominal infection (five [33%] of 15 and nine [60%] of 15, respectively). A summary of best available therapy agents administered, and dosing information for imipenem and meropenem, is provided in the appendix. Doses of drugs used in best available therapy were generally in accordance with those recommended on the product labelling. One patient randomly assigned to ceftazidime-avibactam did not

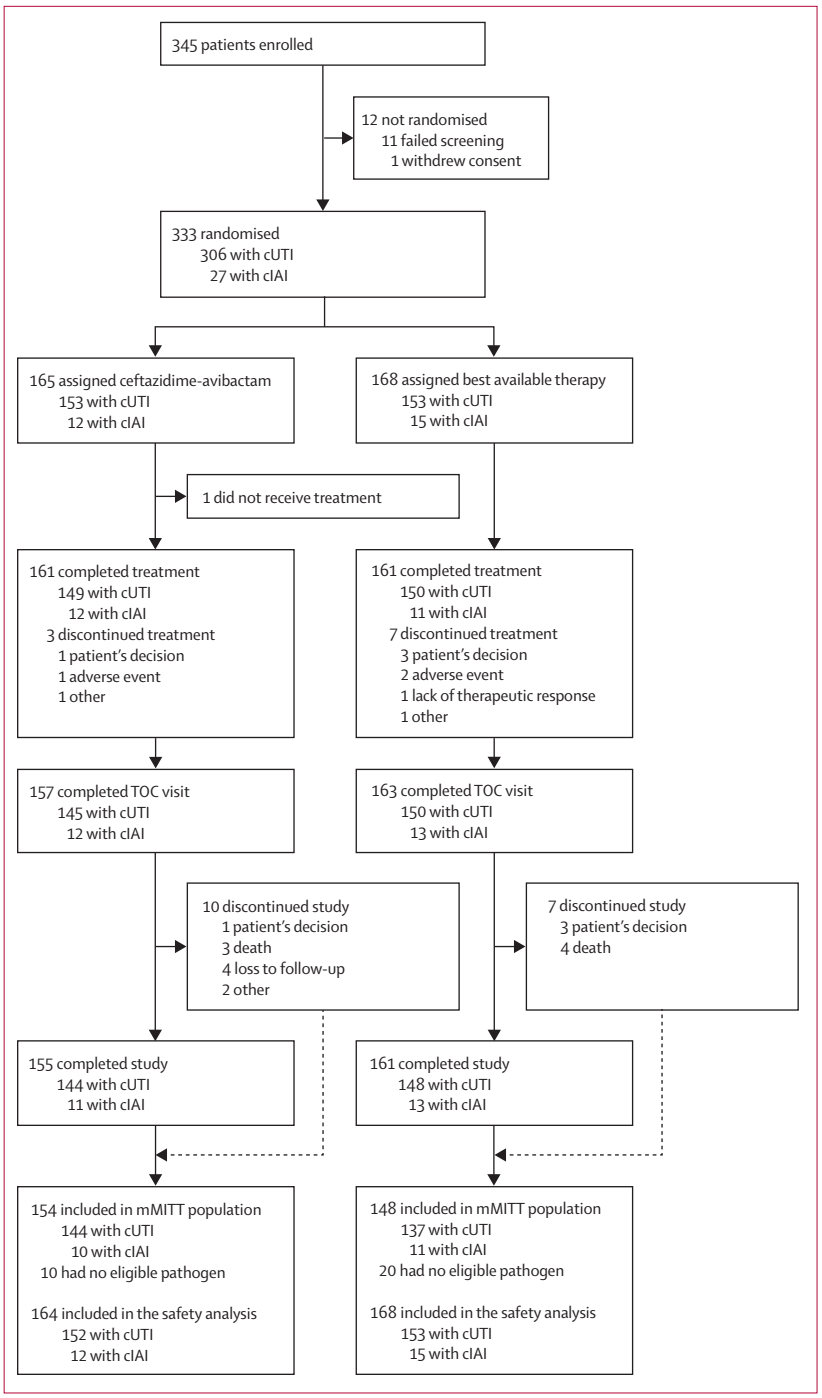

Figure 1: **Trial profile**
cIAI=complicated intra-abdominal infection. cUTI=complicated urinary tract infection. mMITT=microbiologically modified intention-to-treat. TOC=test-of-cure visit.

receive treatment; therefore, 332 (>99%) patients were included in the safety population. 302 (91%) of 333 patients were eligible for inclusion in the mMITT population (154 assigned to ceftazidime-avibactam, and 148 assigned to best available therapy; 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 assessed at the local microbiology laboratory, was not confirmed by the central laboratory (for 11 [100%] of 11 patients excluded in the ceftazidime-avibactam group [one was also excluded because they did not receive treatment] and 20 [100%] of 20 patients excluded in the best available therapy group).

For patients with complicated urinary tract infection, the urine culture taken at screening (documenting the presence of at least one ceftazidime-resistant Gram-negative pathogen) confirmed each patient's eligibility for the trial and their eligibility for the mMITT analysis set, providing the other criteria were met. 231 (82%) of 281 patients with complicated urinary tract infection 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 [83%] of 144 patients in the ceftazidime-avibactam group and 112 [82%] of 137 patients in the best available therapy group).

Baseline patient and disease characteristics, and baseline pathogen distribution, were generally similar between the treatment groups (table 1), for both

	Complicated urinary tract infection		Complicated intra-abdominal infection	
	Ceftazidime-avibactam (n=144)	Best available therapy (n=137)	Ceftazidime-avibactam plus metronidazole (n=10)	Best available therapy (n=11)
Age, years	64·3 (14·6)	61·3 (15·3)	49·9 (16·1)	68·4 (11·1)
75–90 years	38 (26%)	27 (20%)	0	4 (36%)
Female	64 (44%)	63 (46%)	6 (60%)	4 (36%)
Race				
White	136 (94%)	131 (96%)	9 (90%)	11 (100%)
Other*	8 (6%)	6 (4%)	1 (10%)	0
Body-mass index, kg/m²	28·1 (5·5)	28·0 (5·8)	25·2 (6·3)	28·6 (4·6)
≥30 kg/m²	48 (33%)	51 (37%)	3 (30%)	4 (36%)
Renal status, creatinine clearance				
>50 mL/min	118 (82%)	113 (82%)	10 (100%)	6 (55%)
31–50 mL/min	19 (13%)	18 (13%)	0	3 (27%)
16–30 mL/min	4 (3%)	5 (4%)	0	2 (18%)
6–15 mL/min	3 (2%)	1 (1%)	0	0
cUTI diagnosis				
Acute pyelonephritis	57 (40%)	70 (51%)	NA	NA
cUTI without pyelonephritis	87 (60%)	67 (49%)	NA	NA
Complicating factors				
Partial obstructive uropathy	45 (31%)	21 (15%)	NA	NA
Abnormality of urogenital tract	39 (27%)	38 (28%)	NA	NA
Male with urinary retention	33 (23%)	24 (18%)	NA	NA
Catheterisation	30 (21%)	25 (18%)	NA	NA
Urogenital procedure within 7 days	27 (19%)	21 (15%)	NA	NA
cIAI diagnosis				
Cholecystitis	NA	NA	2 (20%)	4 (36%)
Diverticular disease	NA	NA	1 (10%)	1 (9%)
Appendiceal perforation or perappendiceal abscess	NA	NA	2 (20%)	0
Secondary peritonitis	NA	NA	3 (30%)	2 (12%)
Intra-abdominal abscess (≥1)	NA	NA	2 (20%)	4 (36%)
APACHE II score†	NA	NA	6·9 (5·8)	10·9 (4·4)
APACHE II score category				
≤10	NA	NA	8 (80%)	6 (55%)
>10–≤30	NA	NA	1 (10%)	3 (27%)
Previous antibiotic use	72 (50%)	63 (46%)	10 (100%)	11 (100%)

(Table 1 continues on next page)

	Complicated urinary tract infection		Complicated intra-abdominal infection	
	Ceftazidime-avibactam (n=144)	Best available therapy (n=137)	Ceftazidime-avibactam plus metronidazole (n=10)	Best available therapy (n=11)
(Continued from previous page)				
Bacteraemia‡	4 (3%)	6 (4%)	0	0
Infection type				
Monomicrobial	139 (97%)	131 (96%)	4 (40%)	4 (36%)
Polymicrobial (2 pathogens)	4 (3%)	6 (4%)	4 (40%)	5 (45%)
Polymicrobial (≥3 pathogens)§	1 (1%)	0	2 (20%)	2 (18%)
Baseline pathogen in urine (cUTI) or intra-abdominal site (cIAI)¶				
Enterobacteriaceae	131 (91%)	132 (96%)	9 (90%)	11 (100%)
Escherichia coli	59 (41%)	57 (42%)	4 (40%)	6 (55%)
Klebsiella pneumoniae	55 (38%)	65 (47%)	5 (50%)	3 (27%)
Enterobacter cloacae	8 (6%)	6 (4%)	3 (30%)	1 (9%)
Pseudomonas aeruginosa	14 (10%)	5 (4%)	1 (10%)	1 (9%)
Other identified pathogens‖	12 (8%)	10 (7%)	5 (50%)	8 (73%)

Data are mean (SD) and n (%). cUTI=complicated urinary tract infection. NA=not applicable. cIAI=complicated intra-abdominal infection. APACHE=Acute Physiology and Chronic Health Evaluation. mMITT=microbiologically modified intention-to-treat. *Black or African American, Asian, or other. †Data available for nine patients in each group. ‡Pathogens identified in blood were *Klebsiella pneumoniae* (in two patients in the ceftazidime-avibactam group and two patients in the best available therapy group), *Escherichia coli* (one and four patients, respectively), *Bacteroides fragilis* (one and zero patients, respectively), and *Clostridium ramosum* (one and zero patients, respectively); one patient had more than one bacteria identified in their blood. §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. ¶One patient in the ceftazidime-avibactam group was infected with both Enterobacteriaceae and *Pseudomonas aeruginosa*. ‖Other pathogens identified in urine were: *Citrobacter freundii* complex (three patients in the ceftazidime-avibactam group and two patients in the best available therapy group), *Klebsiella oxytoca* (zero and two patients, respectively), *Serratia marcescens* (zero and two patients), and (in one patient each) *Enterobacter aerogenes* (in the ceftazidime-avibactam group), *Klebsiella ozaenae* (in the best available therapy group), *Morganella morganai* (ceftazidime-avibactam), *Proteus rettgeri* (best available therapy), *Providencia stuartii* (ceftazidime-avibactam), *Raoultella terrigena* (best available therapy), and *Ochrobactrum anthropic* (ceftazidime-avibactam); other pathogens identified in intra-abdominal site were: *C freundii* complex (zero patients in the ceftazidime-avibactam group and two patients in the best available therapy group), Gram-positive aerobes (three and four patients, respectively), and anaerobes (two and two patients, respectively).

Table 1: **Baseline patient characteristics and infection type in the mMITT population**

complicated urinary tract infection and complicated intra-abdominal infection, although patient numbers in the intra-abdominal infection group were small. Most patients were infected with Enterobacteriaceae, most commonly *Escherichia coli* and *K pneumoniae* (table 1). Ten (4%) of 281 patients with complicated urinary tract infection also had bacteraemia; in nine of these patients, the isolates were *E coli* or *K pneumoniae* (the same pathogens as were isolated in their urine). None of the patients with complicated intra-abdominal infection had bacteraemia.

Of the 55 patients with complicated urinary tract infection with a catheter at baseline, 14 (47%) of 30 patients in the ceftazidime-avibactam group and ten (40%) of 25 patients in the best available therapy group had a catheter in place for the duration of study therapy or until 1–2 days before the end of study treatment. Patients with complicated urinary tract infection without pyelonephritis were required to have at least one complicating factor present at baseline. For the 127 patients with acute pyelonephritis, 17 (30%) of the 57 patients assigned to ceftazidime-avibactam and 19 (27%) of the 70 patients assigned to best available therapy had at least one complicating factor at baseline. The most common complicating factors present were partial obstructive uropathy (in 12 [21%] of 57 patients in the ceftazidime-avibactam group and seven [10%] of 70 patients in the best available therapy group) and urogenital procedure within 7 days before study entry (eight [14%] and five [7%] patients, respectively).

Figure 2 shows ceftazidime and ceftazidime-avibactam MICs for baseline Gram-negative pathogens isolated from urine in patients with complicated urinary tract infection, including study-qualifying ceftazidime-resistant pathogens, and any other (ceftazidime-susceptible) isolated pathogens. As determined by the central microbiology laboratory, 132 (99%) of all 133 Enterobacteriaceae isolated from urine in the ceftazidime-avibactam group and 132 (96%) of 138 isolated in the best available therapy group were ceftazidime-resistant (MIC ≥8 mg/L). By contrast, only two (2%) of 132 Enterobacteriaceae tested in the ceftazidime-avibactam group, and two (1%) of 134 tested in the best available therapy group, were shown to be 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 both treatment groups, the ceftazidime-avibactam MIC that inhibited 50% of bacterial isolates (MIC_{50}) was 0·25 mg/L, and the MIC that inhibited 90% of isolates (MIC_{90}) was 1 mg/L, for *E coli*, and 0·5 mg/L and 1 mg/L, respectively, for *K pneumoniae*. With the exception of one isolate, all *P aeruginosa* isolated from the urine of patients with

complicated urinary tract infection 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 patients with complicated urinary tract infection had a ceftazidime-avibactam MIC of greater than 8 mg/L—ie, were provisionally resistant.

Four patients with complicated urinary tract infection in the ceftazidime-avibactam group had Gram-negative bacteraemia at baseline, with all blood isolates identified as *K pneumoniae* or *E coli*. All four *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 130 (95%) of 137 patients with complicated urinary tract infection 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 patients with complicated urinary tract infection 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 complicated intra-abdominal infection population, 21 (95%) of 22 Enterobacteriaceae isolated from the intra-abdominal site were resistant to ceftazidime (MIC ≥8 mg/L), and 22 (100%) had ceftazidime-avibactam MICs within the provisional range of susceptibility. Only one patient with complicated intra-abdominal infection in the ceftazidime-avibactam group had a *P aeruginosa* isolate, and this isolate was provisionally resistant to ceftazidime-avibactam (MIC >8 mg/L).

The overall proportions of patients with a clinical cure at the test-of-cure visit (7–10 days after last infusion of study therapy) in the mMITT population (complicated urinary tract infection and complicated intra-abdominal infection combined) were similar with ceftazidime-avibactam (140 [91%; 95% CI 85·6–94·7] of 154 patients) and best available therapy (135 [91%; 85·9–95·0] of 148 patients).

In the complicated urinary tract infection group, the proportions of patients with a clinical cure at the test-of-cure visit were similar between treatment groups (132 [92%; 95% CI 86·3–95·4] of 144 patients in the ceftazidime-avibactam group *vs* 129 [94%; 89·3–97·2] of 137 in the best available therapy group; figure 3A). In patients with acute pyelonephritis, 91% (52 of 57) of patients in the ceftazidime-avibactam group were clinically cured at test-of-cure visit compared with 90% (63 of 70) in the best available therapy group. In patients without acute pyelonephritis, the proportions who were

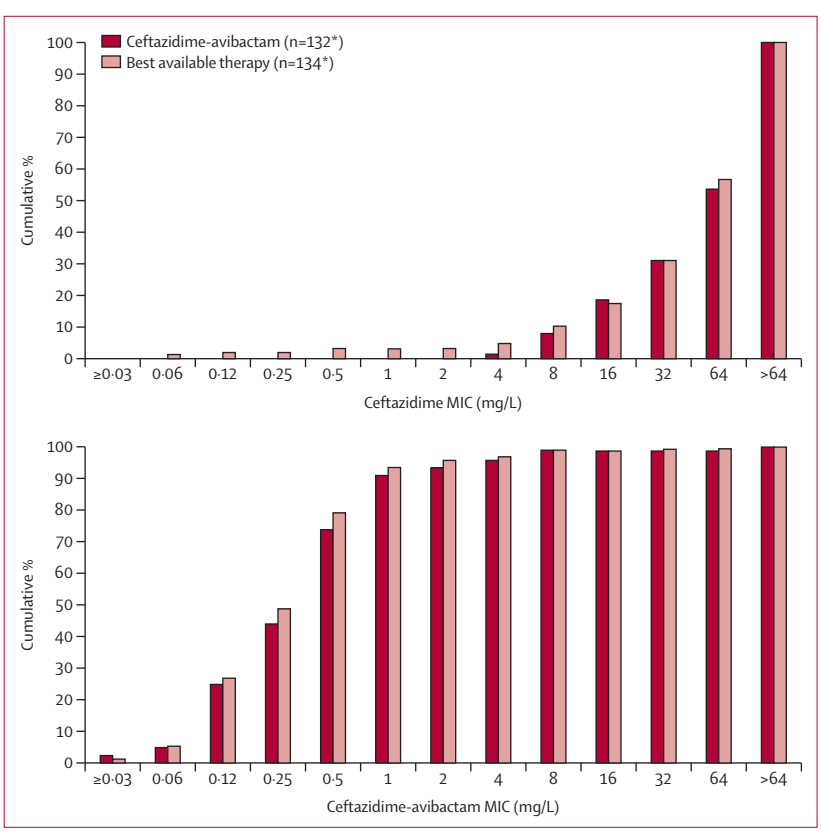

***Figure 2*: Baseline ceftazidime and ceftazidime-avibactam MICs for all Enterobacteriaceae isolated from urine in patients with complicated urinary tract infection (mMITT population)**
MIC=minimum inhibitory concentration. mMITT=microbiologically modified intention-to-treat. *Number of pathogens; some patients had more than one baseline Gram-negative pathogen and one of those may have been ceftazidime-susceptible.

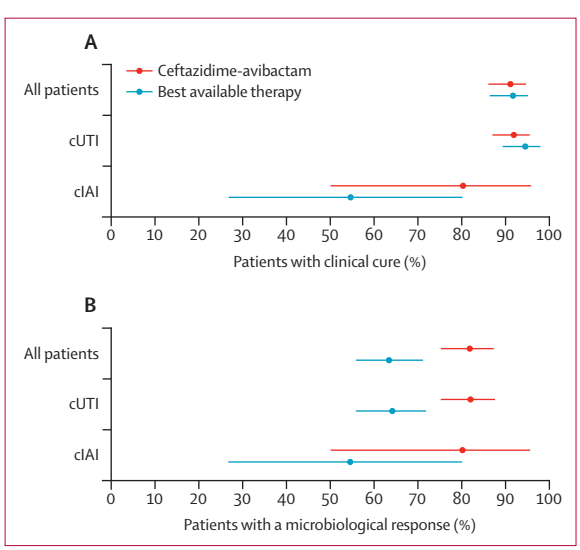

***Figure 3*: Patients with a clinical cure and favourable microbiological response at test-of-cure visit (mMITT population)**
Proportion of patients with a clinical cure at the test-of-cure visit (A), and proportion of patients with a favourable microbiological response at the test-of-cure visit (B). Per-patient microbiological outcomes for patients with complicated intra-abdominal infection were presumed from clinical response. Datapoints show the proportion of patients; error bars show 95% CI. cIAI=complicated intra-abdominal infection. cUTI=complicated urinary tract infection. mMITT=microbiologically modified intention-to-treat.

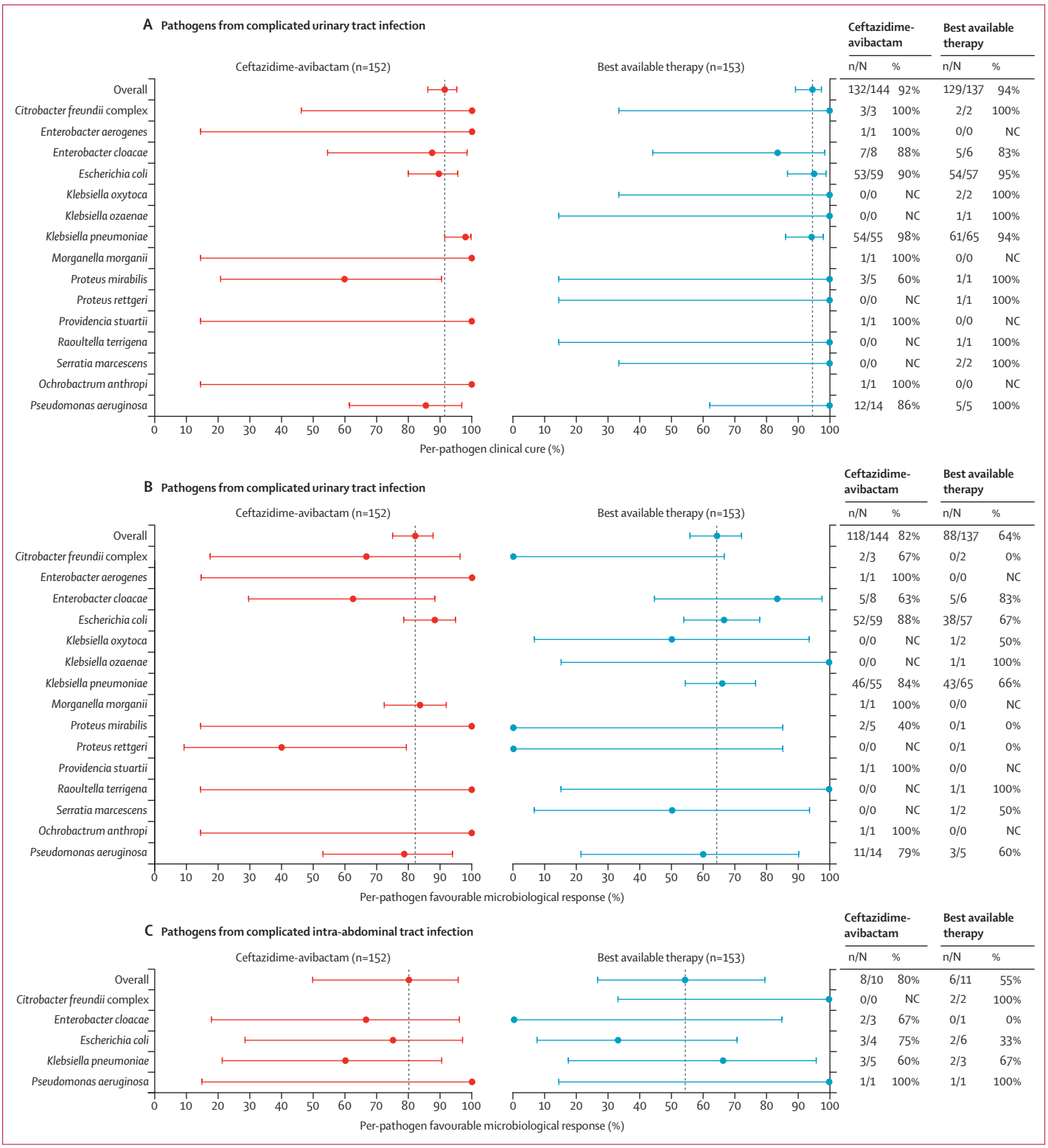

Figure 4: **Per-pathogen response at test-of-cure visit for Gram-negative pathogens isolated at baseline (mMITT population)***

(A) Clinical response per pathogen isolated from urine in patients with complicated urinary tract infection; (B) favourable microbiological response rates per pathogen isolated from urine in patients with complicated urinary tract infection; and (C) favourable microbiological response per pathogen isolated from intra-abdominal site in patients with complicated intra-abdominal infection. Datapoints show the proportion of patients; error bars show 95% CI. cIAI=complicated intra-abdominal infection. cUTI=complicated urinary tract infection. mMITT=microbiologically modified intention-to-treat. NC=not calculated. *Some patients had more than one baseline Gram-negative pathogen.

	Complicated urinary tract infection		Complicated intra-abdominal infection	
	Ceftazidime-avibactam (n=152)	Best available therapy (n=153)	Ceftazidime-avibactam + metronidazole (n=12)	Best available therapy (n=15)
Patients with any AE	43 (28%)	54 (35%)	8 (67%)	12 (80%)
Nausea	5 (3%)	9 (6%)	3 (25%)	1 (7%)
Vomiting	4 (3%)	2 (1%)	2 (17%)	1 (7%)
Diarrhoea	3 (2%)	8 (5%)	2 (17%)	0
Pyrexia	4 (3%)	2 (1%)	0	0
Abdominal pain	3 (2%)	4 (3%)	0	1 (7%)
Dyspepsia	2 (1%)	5 (3%)	0	0
Headache	1 (1%)	11 (7%)	2 (17%)	1 (7%)
Oedema peripheral	3 (2%)	1 (1%)	0	0
Vulvovaginal candidiasis	3 (2%)	0	0	0
Insomnia	2 (1%)	0	2 (17%)	4 (27%)
Nasal congestion	1 (1%)	0	2 (17%)	0
Phlebitis	1 (1%)	2 (1%)	2 (17%)	1 (7%)
Back pain	0	0	2 (17%)	0
Paraesthesia	0	0	2 (17%)	0
Respiratory failure	0	0	0	2 (13%)

Data are number of patients with at least one event (% of patients). AE=adverse event. *Occurring in ≥2% patients with complicated urinary tract infection and/or two or more patients with complicated intra-abdominal infection (ceftazidime-avibactam or best available therapy), and with onset on or after first dose of treatment, and up to and including last follow-up visit (follow-up visit 2 for complicated urinary tract infection, follow-up visit 1 for complicated intra-abdominal infection), irrespective of relation to study drug.

Table 2: **Adverse events* in the safety population**

clinically cured at test-of-cure visit were 92% (80 of 87) and 99% (66 of 67), respectively. The proportion of patients with a clinical cure decreased slightly over subsequent follow-up visits in both treatment groups, but remained at 85% or greater with ceftazidime-avibactam, generally achieving similar clinical cure rates to best available therapy at each visit (appendix).

The proportion of patients with complicated intra-abdominal infection with a clinical cure at test-of-cure visit was eight (80% [95% CI 47·9–95·6]) of ten in the ceftazidime-avibactam plus metronidazole group, and six (55% [27·0–80·0]) of 11 in the best available therapy group (figure 3A). The CIs were very wide due to the small number of patients with complicated intra-abdominal infection. The proportion of patients who had a clinical cure remained the same at follow-up visit 1 (the last follow-up in patients with complicated intra-abdominal infection) in both treatment groups (appendix).

The proportion of patients with a favourable microbiological response at the test-of-cure visit in the complicated urinary tract infection population was higher with ceftazidime-avibactam (118 [82%, 95% CI 75·1–87·6] of 144 patients) than with best available therapy (88 [64%; 56·0–71·9] of 137 patients; figure 3B). In patients with acute pyelonephritis, 50 (88%) of 57 patients in the ceftazidime-avibactam group had a favourable microbiological response at the test-of-cure visit compared with 49 (70%) of 70 in the best available therapy group; corresponding proportions in patients without pyelonephritis were 68 (78%) of 87 and 39 (58%) of 67, respectively. In the mMITT analysis set, a similar number of patients with acute pyelonephritis in the best available therapy group had a favourable microbiological response at the test-of-cure visit, irrespective of whether at least one complicating factor was present at baseline or not (13 [68%] of 19 patients with a complicating factor and 36 [71%] of 51 patients without). For patients with acute pyelonephritis in the ceftazidime-avibactam group, 16 [94%] of 17 and 34 [85%] of 40 had a favourable microbiological response rate at test-of-cure visit, respectively. However, the number of patients with acute pyelonephritis with at least one complicating factor was small.

Consistent with the natural history of complicated urinary tract infection, the proportion of patients with a microbiological response was slightly lower at subsequent visits after the test-of-cure visit (appendix). However, at each subsequent visit, the response rates were consistently higher for ceftazidime-avibactam than for best available therapy.

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

The per-pathogen favourable microbiological response for *E coli* and *K pneumoniae* isolated from urine in patients with complicated urinary tract infection was higher in the ceftazidime-avibactam group than in the best available therapy group (52 [88%; 95% CI 78·1–94·5] of 59 *vs* 38 [67%; 53·8–77·8] of 57, respectively, for *E coli*, and 46 [84%; 72·3–91·6] of 55 *vs* 43 [66%; 54·1–76·8] of 65, respectively, for *K pneumoniae*; figure 4B).

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

Given the small number of patients in the study, no other subgroup analyses for the per-patient microbiological response in patients with complicated urinary tract infection were planned. However, we did post-hoc investigations by catheter use at baseline and by best available therapy received. The proportions of patients

with a favourable microbiological response at the test-of-cure visit were similar in the ceftazidime-avibactam group, irrespective of whether a catheter was present at baseline or not (25 [83%] of 30 patients and 93 [82%] of 114 patients, respectively). For patients in the best available therapy group, 13 (52%) of 25 patients with a catheter at baseline had a favourable microbiological response at test-of-cure visit compared with 75 (67%) of 112 patients without a catheter at baseline. However, the number of patients with a catheter at baseline was small.

With regards to best available therapy used, imipenem or meropenem monotherapy were the most common antibiotics used for patients with complicated urinary tract infection (used in 72 [53%] and 46 [34%] of 137 patients, respectively). Other best available therapy options (monotherapy or combination therapy) were used in the remaining 19 patients. In the mMITT analysis set, the proportion of patients with complicated urinary tract infection with a favourable microbiological response at the test-of-cure visit was lower for patients receiving imipenem monotherapy (39 [54%] of 72 patients) than in those receiving meropenem monotherapy (37 [80%] of 46 patients) or other best available therapy (12 [63%] of 19 patients).

For patients with complicated intra-abdominal infection, per-patient microbiological outcomes at the test-of-cure visit (figure 3B), and per-pathogen favourable microbiological response in Gram-negative pathogens isolated from the intra-abdominal site (figure 4C), were presumed from the clinical response. One patient with complicated intra-abdominal infection in the ceftazidime-avibactam plus metronidazole group had a *P aeruginosa* isolate with a ceftazidime-avibactam MIC of greater than 8 mg/L at baseline. This patient had a favourable microbiological response at the test-of-cure visit.

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

The median duration of treatment was 10 days (range 2–21) with ceftazidime-avibactam and 10 days (2–21) with best available therapy in patients with complicated urinary tract infection, and 10·5 days (6–21) and 12 days (4–23), respectively, in those with complicated intra-abdominal infection. By the last follow-up visit (28–35 days after randomisation), 51 (31%) of 164 patients in the ceftazidime-avibactam group and 66 (39%) of 168 in the best available therapy group had reported an adverse event, most of which were mild or moderate in intensity (appendix). Gastrointestinal disorders were the most frequently reported treatment-emergent adverse events with both ceftazidime-avibactam (21 [13%] of 164 patients) and best available therapy (30 [18%] of 168 patients; table 2).

Three adverse events led to discontinuation of study drug: one patient (1%) in the ceftazidime-avibactam group and two (1%) in the best available therapy group. Seven patients had an adverse event that resulted in death (three in the ceftazidime-avibactam group and four in the best available therapy group), none of which were considered related to study drug by the investigator. In the ceftazidime-avibactam group, the adverse events with an outcome of death (occurring in one patient with complicated urinary tract infection 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 patients with complicated urinary tract infection), acute respiratory failure (one patient with complicated urinary tract infection), and lobar pneumonia (one patient with complicated intra-abdominal infection).

The incidence of adverse events considered related to study drug by the investigator was low (14 [9%] of 164 patients in the ceftazidime-avibactam group, and 11 [7%] of 168 patients in the best available therapy group). Overall, nine patients in the ceftazidime-avibactam group and ten patients in the best available therapy group had serious adverse events, 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

The REPRISE study is the first pathogen-directed clinical trial for ceftazidime-avibactam examining its efficacy 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 complicated intra-abdominal infection and complicated urinary tract infection.

The study showed that ceftazidime-avibactam and best available therapy led to the same proportion of patients achieving an overall clinical cure at the test-of-cure visit in the mMITT population (91% in both groups). Most 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 patients with complicated urinary tract infection in the ceftazidime-avibactam group with provisionally resistant *P aeruginosa* isolates (ceftazidime-avibactam MIC >8 mg/L) had a favourable microbiological response at test-of-cure visit. 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 characterised the so-called 90–60 rule, whereby infections due to susceptible isolates respond to therapy about 90% of the time, whereas infections due to resistant isolates respond about 60% of the time.[18] Additionally, high concentrations of ceftazidime-avibactam are excreted in the urine, potentially contributing to a favourable microbiological response in

these patients with a provisionally resistant isolate. A higher proportion of patients achieved a microbiological response in the ceftazidime-avibactam group than in the best available therapy group in patients with complicated urinary tract infection, the reason for which was not clear. Imipenem was the most common antibiotic used as best available therapy for complicated urinary tract infection, and more patients who received imipenem had an unfavourable microbiological response at test-of-cure visit than did those who received other best available therapy. Although dosing of imipenem was in line with labelling, various 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[19] and the cephalosporin class.

The main limitation of the REPRISE study was the open-label nature of the trial. Open-label administration was mandated 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 before randomisation. Furthermore, the study found a high proportion of microbiological responses 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 geographical distribution. The small number of patients with complicated intra-abdominal infection 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 complicated intra-abdominal infection (reported as a single study database) included 529 patients given 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 complicated urinary tract infection with ceftazidime-avibactam results in similar clinical cure rates to treatment with best available therapy and a numerically higher per-patient favourable microbiological response rate. In complicated intra-abdominal infection, the proportion of patients with a clinical and microbiological response was also high for ceftazidime-avibactam and in line with that observed with best available therapy. However, the number of patients with complicated intra-abdominal infection 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.

Contributors

YC obtained the data, as international coordinating investigator. JA, PJL, PN, GS, AW, and LBG analysed the data. All authors wrote the first draft and reviewed and edited the final manuscript.

Declaration of interests

YC has received grants, honoraria, travel support, consulting fees, and other forms of financial support from Achaogen, Allecra Therapeutics, AstraZeneca, Basilea Pharmaceutica, Biomerieux SA, DaVolterra, Durata Therapeutics, Intercell AG, Merck & Co, PPD, Proteologics, Rempex Pharmaceuticals, and Rib-X Pharmaceuticals. LBG, PN, JA, GS, and AW are employees of AstraZeneca. PJL 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.

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