



This is a repository copy 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 (REPRISE): a randomised, pathogen-directed, phase 3 study.*

White Rose Research Online URL for this paper:  
<http://eprints.whiterose.ac.uk/131152/>

Version: Accepted Version

---

**Article:**

Carmeli, Y., Armstrong, J., Laud, P.J. [orcid.org/0000-0002-3766-7090](https://orcid.org/0000-0002-3766-7090) et al. (4 more authors) (2016) 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. *The Lancet Infectious Diseases*, 16 (6). pp. 661-673. ISSN 1473-3099

[https://doi.org/10.1016/S1473-3099\(16\)30004-4](https://doi.org/10.1016/S1473-3099(16)30004-4)

---

**Reuse**

Items deposited in White Rose Research Online are protected by copyright, with all rights reserved unless indicated otherwise. They may be downloaded and/or printed for private study, or other acts as permitted by national copyright laws. The publisher or other rights holders may allow further reproduction and re-use of the full text version. This is indicated by the licence information on the White Rose Research Online record for the item.

**Takedown**

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing [eprints@whiterose.ac.uk](mailto:eprints@whiterose.ac.uk) including the URL of the record and the reason for the withdrawal request.



[eprints@whiterose.ac.uk](mailto:eprints@whiterose.ac.uk)  
<https://eprints.whiterose.ac.uk/>

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

7 Yehuda Carmeli,MD, Jon Armstrong,MSc, Peter J Laud,MSc, Paul Newell,MBBS  
8 Greg Stone,PhD, Angela Wardman,MSc, Leanne B Gasink, MD

9 **Division of Epidemiology and the National Center for Antibiotic Resistance and**  
10 **Infection Control, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel (Prof Y**  
11 **Carmeli, MD, MPH); AstraZeneca, Infection GMed, Global Medicines**  
12 **Development, Alderley Park, UK (J Armstrong, MSc, Dr P Newell, MBBS, MRCP,**  
13 **MFPM, A Wardman, BPharm, MSc); Contracted to AstraZeneca from the**  
14 **Statistical Services Unit, University of Sheffield, Sheffield, UK (P J Laud, MSc);**  
15 **AstraZeneca, Infection GMed, Global Medicines Development, Waltham, MA,**  
16 **USA (Dr G Stone, PhD); AstraZeneca, Infection GMed, Global Medicines**  
17 **Development, Wilmington, DE, USA (Dr L B Gasink, MD, MSCE)**

18 Correspondence to:  
19 Prof Yehuda Carmeli, Division of Epidemiology, Tel Aviv Sourasky Medical Center,  
20 Tel Aviv, Israel

21 **Email: [yehudac@tlvmc.gov.il](mailto:yehudac@tlvmc.gov.il)**

22 **Prior publication**

23 These data were presented in part as a late breaker at the 25th European Congress  
24 of Clinical Microbiology and Infectious Diseases (ECCMID), 25–28 April 2015,  
25 Copenhagen, Denmark; abstract LBEV0061b

26 Link to the study protocol and synopsis of results:

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

## 28 **Summary**

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

33 **Methods** REPRISE (NCT01644643) was a prospective, pathogen-directed,  
34 international, randomised, open-label, phase 3 trial comparing the efficacy and  
35 safety of treatment with ceftazidime-avibactam 2000–500 mg versus best available  
36 therapy in adults with complicated urinary tract infections (cUTI) or complicated intra-  
37 abdominal infections (cIAI) due to ceftazidime-resistant Enterobacteriaceae or  
38 *Pseudomonas aeruginosa*. The primary endpoint was assessment of clinical  
39 response at test-of-cure (TOC) visit 7–10 days after last infusion of study therapy in  
40 the microbiologically modified intent-to-treat (mMITT) population.

41 **Findings** Between January 2013 and August 2014, 333 patients were enrolled and  
42 randomised in 16 countries worldwide, of whom 302 (90.7%) were included in the  
43 mMITT population (281 cUTI, 21 cIAI). Most (97%) patients on best available therapy  
44 received a carbapenem, usually as monotherapy. The overall clinical cure rate at  
45 TOC in the mMITT population was similar with ceftazidime-avibactam (140/154  
46 [90.9%; 95% confidence interval (CI), 85.6, 94.7]) and best available therapy  
47 (135/148 [91.2%; 95% CI, 85.9, 95.0]). The per-patient favourable microbiological  
48 response rate at TOC in cUTI patients was higher with ceftazidime-avibactam  
49 (118/144 [81.9%; 95% CI, 75.1, 87.6]) than with best available therapy (88/137  
50 [64.2%; 95% CI, 56.0, 71.9]). No new safety concerns were identified for  
51 ceftazidime-avibactam.

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

55

56 **Funding:** The REPRISE study was supported by AstraZeneca.

57 **Keywords:** Ceftazidime-avibactam; ceftazidime-resistant, carbapenem-resistant,  
58 MDR Gram-negative, pathogen-directed study, complicated urinary tract infections,  
59 complicated intra-abdominal infections

## 60 **Introduction**

61 The prevalence of multi-drug resistant (MDR) Gram-negative pathogens, including  
62 extended-spectrum  $\beta$ -lactamase (ESBL)-producing and carbapenemase-producing  
63 Enterobacteriaceae and *Pseudomonas aeruginosa*, is increasing worldwide.<sup>1-3</sup>  
64 Contributing factors are the extensive use of antibiotics, both in humans and  
65 animals, poor infection control, and the greatly increased global mobility of people,  
66 allowing the rapid spread of MDR pathogens.<sup>1,4,5</sup> As the prevalence of ESBL-  
67 producing pathogens has increased, so has the use of carbapenem antibiotics –  
68 frequently the last line of defence against MDR Gram-negative bacteria but now  
69 threatened by the growing prevalence of carbapenemase-producing pathogens.<sup>6</sup>  
70 There is therefore an urgent need to find alternative treatment options and  
71 carbapenem-sparing regimens for patients with serious infections caused by MDR  
72 Gram-negative pathogens.

73 Ceftazidime-avibactam may represent an important new option for such  
74 cases, comprising ceftazidime, a widely used expanded-spectrum anti-pseudomonal  
75 cephalosporin, and avibactam, a novel non- $\beta$ -lactam  $\beta$ -lactamase inhibitor.<sup>7,8</sup>  
76 Avibactam has a broader spectrum of activity than currently available  $\beta$ -lactamase  
77 inhibitors, and has been shown in vitro to restore the activity of ceftazidime against  
78 most MDR Enterobacteriaceae and *P. aeruginosa* by inhibiting a wide variety of  
79  $\beta$ -lactamases, including class A (including ESBLs, *Klebsiella pneumoniae*  
80 carbapenemases [KPC]), class C (AmpC), and some class D enzymes  
81 (e.g. OXA-48).<sup>9</sup>

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

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

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

101

## 102 **Methods**

### 103 **Study design**

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

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



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

### 132 **Patients**

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

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

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

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

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

### 175 **Study endpoints**

176 The primary endpoint was assessment of clinical response (cure, failure, or  
177 indeterminate) at test-of-cure (TOC) visit 7–10 days after last infusion of study  
178 therapy in the microbiologically modified intent-to-treat population (mMITT).

179 Definitions of clinical cure, treatment failure, and indeterminate response are  
180 summarised in the appendix. Briefly, clinical cure was defined as complete resolution  
181 or significant improvement of signs and symptoms of the index infection, such that  
182 no further antibacterial therapy (other than those allowed per protocol) was  
183 necessary. In addition, for cIAI patients, cure also required that no drainage or  
184 surgical intervention was needed after 96 h from randomisation.

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

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

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

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

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

## 218 **Statistical analysis**

219 Two-sided 95% confidence intervals (CI) for the treatment group response rates  
220 were calculated using the Jeffreys method.<sup>17,18</sup> Due to the unfeasibility of recruiting

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

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

### 231 **Role of the funding source**

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

## 238 **Results**

### 239 **Patients**

240 Between January 2013 and August 2014, 333 patients were enrolled and  
241 randomised at 53 centres in 16 countries worldwide: ceftazidime-avibactam n=165  
242 (153 with cUTI and 12 with cIAI); best available therapy n=168 patients (153 with  
243 cUTI and 15 with cIAI). Although 400 patients were planned for inclusion, recruitment  
244 was ended early as it was considered that a sufficient number of patients with a  
245 suitable range of pathogens had been recruited. The proportions of randomised  
246 patients by region were: Eastern Europe 80.5%, North America and Western Europe  
247 4.8%, and rest of world 14.7%. A table of randomised patients by country and a full  
248 list of study sites and principal investigators are shown in the appendix.

249 Most (97%) patients in the best available therapy group received a  
250 carbapenem antibiotic and the majority received this as monotherapy, with imipenem  
251 and meropenem being the most frequently prescribed agents in cUTI (50% and 37%,  
252 respectively) and cIAI patients (33% and 60%). A summary of best available therapy  
253 agents administered, and dosing information for imipenem and meropenem, are  
254 provided in the appendix. Doses of drugs used in best available therapy were  
255 generally in accordance with those recommended in product labelling. One patient  
256 randomised to ceftazidime-avibactam did not receive treatment. Therefore, 332  
257 (99.7%) patients were included in the safety population. A total of 302 (90.7%)  
258 patients were eligible for inclusion in the mMITT population (ceftazidime-avibactam,  
259 n=154; best available therapy, n=148) (figure 1). The main reason for exclusion from  
260 the mMITT population was that the ceftazidime resistance of the baseline Gram-

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

263 For cUTI patients, the urine culture taken at screening (documenting the  
264 presence of at least one ceftazidime-resistant Gram-negative pathogen) made the  
265 patient eligible for the trial, and for the mMITT analysis set, providing the other  
266 criteria were met (see study endpoints). The majority of cUTI patients in the mMITT  
267 analysis set had at least one ceftazidime-resistant Gram-negative pathogen in the  
268 screening urine culture that was also confirmed in the supplementary baseline urine  
269 culture, and the numbers were balanced across the treatment groups (119 patients  
270 (82.6%) in the ceftazidime-avibactam group and 112 patients (81.2%) in the best  
271 available therapy group).

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

279 Of the 55 cUTI patient with a catheter at baseline, 24 patients (43.6%) had a  
280 catheter in place for the duration of study therapy or the catheter was only removed  
281 1 to 2 days prior to the end of study therapy (table 1). cUTI patients without  
282 pyelonephritis were required to have at least one complicating factor present at  
283 baseline. For the 127 patients with acute pyelonephritis, 17 of the 57 patients on  
284 ceftazidime-avibactam (29.8%) and 19 of the 70 patients on best available therapy

285 (27.1%) had at least one complicating factor at baseline. The most common  
286 complicating factors present in these 36 patients were partial obstructive uropathy  
287 (19 patients) and urogenital procedure within 7 days prior to study entry (13  
288 patients).

289 Figure 2 shows ceftazidime and ceftazidime-avibactam MICs for baseline  
290 Gram-negative pathogens isolated from urine in cUTI patients, including study-  
291 qualifying ceftazidime-resistant pathogens, and any other (ceftazidime-susceptible)  
292 pathogens isolated. As determined by the central microbiology laboratory, 99.2% of  
293 all Enterobacteriaceae isolated from urine in the ceftazidime-avibactam group and  
294 95.7% of those in the best available therapy group were ceftazidime-resistant (MIC  
295  $\geq 8$  mg/L). In contrast, only 1.5% of Enterobacteriaceae were shown as non-  
296 susceptible to ceftazidime-avibactam (MIC  $\leq 8$  mg/L was considered provisionally  
297 susceptible and MIC  $> 8$  mg/L as provisionally resistant to ceftazidime-avibactam). In  
298 each treatment group, the ceftazidime-avibactam MIC<sub>50</sub> and MIC<sub>90</sub> were 0.25 and 1  
299 mg/L, respectively, for *E. coli*, and 0.5 and 1 mg/L for *K. pneumoniae*. With the  
300 exception of one isolate, all *P. aeruginosa* isolated from the urine of cUTI patients  
301 were resistant to ceftazidime (MIC  $> 16$  mg/L). In the mMITT analysis set, nine of the  
302 14 baseline *P. aeruginosa* isolates in the ceftazidime-avibactam group for cUTI  
303 patients had a ceftazidime-avibactam MIC  $> 8$  mg/L – that is, were provisionally  
304 resistant.

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



308 ceftazidime, but all were within the provisional range of susceptibility for ceftazidime-  
309 avibactam (MIC  $\leq$ 8 mg/L).

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

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

## 322 **Clinical cure rates**

323 The overall clinical cure rate at TOC in the mMITT population (cUTI and cIAI  
324 combined) was similar with ceftazidime-avibactam (140/154 [90.9%; 95% CI, 85.6,  
325 94.7]) and best available therapy (135/148 [91.2%; 95% CI, 85.9, 95.0]).

## 326 **cUTI patients**

327 In the cUTI group, clinical cure rates at TOC were similar between treatment groups  
328 (ceftazidime-avibactam: 132/144 [91.7%; 95% CI, 86.3, 95.4] and best available  
329 therapy: 129/137 [94.2%; 95% CI 89.3, 97.2]) (figure 3A). Among those with acute  
330 pyelonephritis, clinical cure rates at TOC were 91.2% (52/57) with ceftazidime-

331 avibactam and 90.0% (63/70) with best available therapy. Among those without  
332 acute pyelonephritis, clinical cure rates at TOC were 92.0% (80/87) and 98.5%  
333 (66/67), respectively. In terms of later time points, clinical cure rates decreased  
334 slightly over time in both treatment groups, but remained  $\geq 85\%$  with ceftazidime-  
335 avibactam, generally achieving similar clinical cure rates to best available therapy at  
336 each visit (appendix, figure S2A).

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

### 339 **cIAI patients**

340 The proportion of cIAI patients with clinical cure at TOC was 80.0% (8/10; 95% CI  
341 47.9, 95.6) in the ceftazidime-avibactam plus metronidazole group, and 54.5% (6/11;  
342 95% CI 27.0, 80.0) in the best available therapy group (figure 3A). The CIs were  
343 very wide due to the small number of cIAI patients. Clinical cure rates remained the  
344 same at FU1 (last follow-up in cIAI patients) in both treatment groups (appendix).

### 345 **Per-patient microbiological response rates**

#### 346 **cUTI patients**

347 Per-patient favourable microbiological response rates at TOC in the cUTI population  
348 were higher with ceftazidime-avibactam (118/144 [81.9%; 95% CI, 75.1, 87.6]) than  
349 with best available therapy (88/137 [64.2%; 95% CI, 56.0, 71.9]) (figure 3B). Among  
350 patients with acute pyelonephritis, per-patient favourable microbiological response  
351 rates at TOC were 87.7% (50/57) with ceftazidime-avibactam and 70.0% (49/70)  
352 with best available therapy; corresponding rates in patients without pyelonephritis  
353 were 78.2% (68/87) and 58.2% (39/67), respectively. In the mMITT analysis set, the

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

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

365 Favourable microbiological response rates for *E. coli* and *K. pneumoniae*  
366 isolated from urine in cUTI patients were higher in the ceftazidime-avibactam group  
367 than in the best available therapy group (88.1% vs 66.7%, respectively for *E. coli*,  
368 and 83.6% vs 66.2% for *K. pneumoniae* [figure 4B]).

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

378           Given the small number of patients in the study, no other sub-group analyses  
379 for the per-patient microbiological response in cUTI patients were planned. However,  
380 catheter use at baseline, and by best available therapy received, were investigated  
381 post-hoc. Per-patient favourable microbiological response rates at TOC were similar  
382 in the ceftazidime-avibactam group whether a catheter was present at baseline or  
383 not (25 out of 30 patients (83.3%) and 93 out of 114 patients (81.6%), respectively).  
384 For patients receiving best available therapy, the favourable microbiological  
385 response rate at TOC was lower in those patients with a catheter at baseline (13 out  
386 of 25 patients (52.0%)) compared to those without a catheter at baseline (75 out of  
387 112 patients (67.0%)). However, the number of patients with a catheter at baseline  
388 was small (30 patients on ceftazidime-avibactam and 25 patients on best available  
389 therapy).

390           With regards to best available therapy, imipenem or meropenem monotherapy  
391 were the most common antibiotics used for cUTI patients (72 patients and 46  
392 patients respectively (in the mMITT analysis set)). Other best available therapy  
393 options (monotherapy or combination therapy) were used in the remaining 19  
394 patients. In the mMITT analysis set, the favourable per-patient microbiological  
395 response at TOC for cUTI patients was lower for patients receiving imipenem  
396 monotherapy (39 out of 72 patients (54.2%)) compared to meropenem monotherapy  
397 (37 out of 46 patients (80.4%)) or other best available therapy (12 out of 19 patients  
398 (63.2%)).

399

400 **cIAI patients**

401 For cIAI patients, per-patient microbiological outcomes at TOC, and per-pathogen  
402 favourable microbiological response among Gram-negative pathogens isolated from  
403 the intra-abdominal site, were presumed from the clinical response (figure 3B and  
404 figure 4C, respectively). One cIAI patient in the ceftazidime-avibactam plus  
405 metronidazole group had a *P. aeruginosa* isolate with a ceftazidime-avibactam MIC  
406 >8 mg/L at baseline. This patient had a favourable microbiological response at TOC.

407 **Other secondary outcomes**

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

409 **Safety**

410 The median (range) duration of treatment with ceftazidime-avibactam and best  
411 available therapy was 10 (2 to 21) and 10 (2 to 21) days, respectively, in cUTI, and  
412 10.5 (6 to 21) and 12 (4 to 23) days in cIAI. By the last follow-up visit (28–35 days  
413 post-randomisation), 51/164 patients (31.1%) in the ceftazidime-avibactam group  
414 and 66/168 (39.3%) in the best available therapy group had experienced AEs, the  
415 majority of which were mild or moderate in intensity. Gastrointestinal disorders were  
416 the most frequently reported treatment-emergent AEs with both ceftazidime-  
417 avibactam (21/164 patients, 12.8%) and best available therapy (30/168  
418 patients, 17.9%) (table 2).

419 Three AEs leading to discontinuation of study drug occurred: one patient  
420 (0.6%) in the ceftazidime-avibactam group and two (1.2%) in the best available  
421 therapy group. Seven patients experienced an AE with an outcome of death, none of  
422 which were considered related to study drug by the investigator. In the ceftazidime-  
423 avibactam group, the AEs with an outcome of death (occurring in one cUTI patient

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

428           The incidence of AEs considered related to study drug by the investigator was  
429 low (ceftazidime-avibactam 14/164 patients, 8.5%, best available therapy 11/168  
430 patients, 6.5%). Overall, nine patients in the ceftazidime-avibactam group and ten  
431 patients in the best available therapy group experienced SAEs, but none were  
432 considered related to study drug. There were no new safety concerns identified for  
433 ceftazidime-avibactam, including for any of the clinical laboratory, ECG, physical  
434 examination, or vital signs assessments.

435

## 436 **Discussion**

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

447         The REPRISE study met its primary endpoint, demonstrating a similar overall  
448 clinical cure rate at TOC with ceftazidime-avibactam and best available therapy in  
449 the mMITT population (90.9% vs 91.2%, respectively). The majority of ceftazidime-  
450 resistant pathogens were in the provisionally susceptible MIC range for ceftazidime-  
451 avibactam, and further analysis is ongoing to evaluate those that were not. Molecular  
452 characterisation of the isolates from the study is also ongoing. Seven of nine cUTI  
453 patients in the ceftazidime-avibactam group with provisionally resistant *P.*  
454 *aeruginosa* isolates (ceftazidime-avibactam MIC >8 mg/L) had a favourable  
455 microbiological response at TOC. This observation of an apparent response to an  
456 agent to which pathogens are non-susceptible is well known and not unique to this  
457 study. A review of antibacterial clinical trials spanning 30 years characterized the  
458 “90-60 rule”, whereby infections due to susceptible isolates respond to therapy  
459 ~90% of the time, whereas infections due to resistant isolates respond ~60% of the

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

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



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

492 In conclusion, treatment of serious ceftazidime-resistant Gram-negative cUTI  
493 with ceftazidime-avibactam results in similar clinical cure rates to treatment with best  
494 available therapy and numerically higher per-patient favourable microbiological  
495 response rates. In cIAI, clinical and microbiological response rates were also high for  
496 ceftazidime-avibactam and in line with those observed with best available therapy.  
497 However, the number of cIAI patients in this study was small, limiting the  
498 interpretation of the findings in this population. The safety and tolerability profile of  
499 ceftazidime-avibactam reported here is broadly similar to the recognised profile of  
500 ceftazidime alone. These promising results support the use of ceftazidime-avibactam  
501 as a potential alternative to carbapenems in patients with resistant Gram-negative  
502 infections.

503

## 504 **Research in context**

### 505 **Evidence before this study**

506 PubMed search terms: [ceftazidime-avibactam AND randomised]

507 ECCMID 2015 search term: [ceftazidime-avibactam]

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

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

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

526 **Added value of this study**

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

533 **Implications of all the available evidence**

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

537

538 **Contributors**

539 YC obtained the data, as International Coordinating Investigator.

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

541 YC, JA, PJL, PN, GS, AW, and LBG wrote the first draft and all authors reviewed

542 and edited the final manuscript.

543

544 **Declaration of interests**

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

554

555 **Acknowledgments**

556 This study was supported by AstraZeneca and Forest Laboratories. Ceftazidime-  
557 avibactam is now being developed by AstraZeneca and Forest Laboratories Inc., a  
558 subsidiary of Actavis plc. The sponsors collected, managed, and analysed the data.  
559 The corresponding author had full access to the data and vouches for the accuracy  
560 and completeness of the data and all analyses.

561 Medical writing support was provided by Liz Anfield of Prime Medica Ltd,  
562 Knutsford, Cheshire, UK, funded by AstraZeneca. The design and conduct of the  
563 study, analysis of the study data, and opinions, conclusions, and interpretation of the  
564 data are the responsibility of the authors.

565

## 566 **References**

- 567 1 Carlet J, Jarlier V, Harbarth S, Voss A, Goossens H, Pittet D. Ready for a world  
568 without antibiotics? The Penalties Antibiotic Resistance Call to Action.  
569 Antimicrob Resist Infect Control 2012; **1** 11–
- 570 2 Tangden T, Giske CG. Global dissemination of extensively drug-resistant  
571 carbapenemase-producing Enterobacteriaceae: clinical perspectives on  
572 detection, treatment and infection control. J Intern Med 2015; **277** 501–512.
- 573 3 Poole K. Pseudomonas aeruginosa: resistance to the max. Front Microbiol  
574 2011; **2** 65–
- 575 4 Lerner A, Adler A, Abu-Hanna J, Cohen PS, Kazma MM, Carmeli Y. Spread of  
576 KPC-producing carbapenem-resistant Enterobacteriaceae: the importance of  
577 super-spreaders and rectal KPC concentration. Clin Microbiol Infect 2015; **21**  
578 470.e1–470.e7.
- 579 5 Hawkey PM. Multidrug-resistant Gram-negative bacteria: a product of  
580 globalization. J Hosp Infect 2015; **89** 241–247.
- 581 6 Temkin E, Adler A, Lerner A, Carmeli Y. Carbapenem-resistant  
582 Enterobacteriaceae: biology, epidemiology, and management. Ann N Y Acad  
583 Sci 2014; **1323** 22–42.
- 584 7 Lucasti C, Popescu I, Ramesh MK, Lipka J, Sable C. Comparative study of the  
585 efficacy and safety of ceftazidime/avibactam plus metronidazole versus  
586 meropenem in the treatment of complicated intra-abdominal infections in

- 587 hospitalized adults: results of a randomized, double-blind, Phase II trial. J  
588 Antimicrob Chemother 2013; **68** 1183–1192.
- 589 8 Vazquez JA, Gonzalez Patzan LD, Stricklin D, et al. Efficacy and safety of  
590 ceftazidime-avibactam versus imipenem-cilastatin in the treatment of  
591 complicated urinary tract infections, including acute pyelonephritis, in  
592 hospitalized adults: results of a prospective, investigator-blinded, randomized  
593 study. Curr Med Res Opin 2012; **28** 1921–1931.
- 594 9 Zhanel GG, Lawson CD, Adam H, et al. Ceftazidime-avibactam: a novel  
595 cephalosporin/beta-lactamase inhibitor combination. Drugs 2013; **73** 159–177.
- 596 10 Mazuski JE, Gasink L, Armstrong J, et al. Efficacy and safety of ceftazidime-  
597 avibactam plus metronidazole versus meropenem in the treatment of  
598 complicated intra-abdominal infection - results from from a randomized,  
599 controlled, double-blind, phase 3 program. Clin Infect Dis 2016; **In press**
- 600 11 U.S.Food and Drug Administration. FDA approves new antibacterial drug  
601 Avycaz. 2015.  
602 [http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm435629.](http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm435629.htm)  
603 [htm](http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm435629.htm) (accessed May 11, 2015).
- 604 12 Spellberg B, Blaser M, Guidos RJ, et al. Combating antimicrobial resistance:  
605 policy recommendations to save lives. Clin Infect Dis 2011; **52 (suppl 5)** S397–  
606 S428.
- 607 13 Merdjan H, Tarral A, Haazen W, Evene E, Robertson M, Sable C.  
608 Pharmacokinetics and tolerability of NXL104 in normal subjects and in patients



609 with varying degrees of renal insufficiency. Clin Microbiol Infect 2010; **16 (suppl**  
610 **2)**: S333 (abstract P1598).

611 14 Clinical and Laboratory Standards Institute. Performance standards for  
612 antimicrobial susceptibility testing. Twenty-second informational supplement.  
613 Wayne, PA: CLSI; 2012.

614 15 EUCAST. Clinical breakpoints - bacteria v 2.0. 2012.  
615 [http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST\\_files/Breakpoint\\_tables/Breakpoint\\_table\\_v\\_2.0\\_120221.pdf](http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/Breakpoint_table_v_2.0_120221.pdf) (accessed Jul 15, 2015).  
616

617 16 Data on File, AstraZeneca. 2016.

618 17 Brown LD, Cai TT, DasGupta A. Interval estimation for a binomial proportion.  
619 Statistical Science 2001; **16** 101–117.

620 18 Cai TT. One-sided confidence intervals in discrete distributions. J Stat Plan  
621 Inference 2005; **131** 63–88.

622 19 Rex JH, Pfaller MA. Has antifungal susceptibility testing come of age? Clin  
623 Infect Dis 2002; **35** 982–989.

624 20 GlaxoSmithKline. FORTAZ Prescribing Information. 2007.  
625 [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2007/050578s053,050634s020lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/050578s053,050634s020lbl.pdf) (accessed May 11, 2015).  
626

627 21 Das S, Armstrong J, Mathews D, Li J, Edeki T. Randomized, placebo-controlled  
628 study to assess the impact on QT/QTc interval of suprathreshold doses of  
629 ceftazidime-avibactam or ceftaroline fosamil-avibactam. J Clin Pharmacol 2014;  
630 **54** 331–340.

- 631 22 Merdjan H, Rangaraju M, Tarral A. Safety and pharmacokinetics of single and  
632 multiple ascending doses of avibactam alone and in combination with  
633 ceftazidime in healthy male volunteers: results of two randomized, placebo-  
634 controlled studies. *Clin Drug Investig* 2015; **35** 307–317.
- 635 23 Tominaga N, Edeki T, Li J, Learoyd M, Bouw MR, Das S. Phase I study  
636 assessing the safety, tolerability, and pharmacokinetics of avibactam and  
637 ceftazidime-avibactam in healthy Japanese volunteers. *J Infect Chemother*  
638 2015; **21** 551–558.
- 639 24 Carmeli Y, Armstrong J, Laud PJ, et al. Efficacy and safety of ceftazidime-  
640 avibactam and best available therapy in the treatment of ceftazidime-resistant  
641 infections - results from a Phase III study. 25th European Congress of Clinical  
642 Microbiology and Infectious Diseases (ECCMID), 25-28 April 2015,  
643 Copenhagen, Denmark (abstract LBEV0061b).;
- 644
- 645
- 646

**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 <sup>2</sup> ; mean (SD)	28.1 (5.5)	28.0 (5.8)	25.2 (6.3)	28.6 (4.6)
≥30 kg/m <sup>2</sup> , 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 (%) <sup>¶</sup>	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) <sup>§</sup>	1 (0.7)	0	2 (20.0)	2 (18.2)
Baseline pathogen in urine (cUTI) or intra-abdominal site (cIAI), n (%) <sup>  </sup>				
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)

<sup>†</sup>Black or African American, Asian, or other.

<sup>‡</sup>Data available for nine patients in each group.

<sup>¶</sup>Pathogens identified in blood were *Klebsiella pneumoniae* (4), *Escherichia coli* (5), *Bacteroides fragilis* (1), and *Clostridium ramosum* (1).

<sup>§</sup>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.

<sup>||</sup>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)**

Preferred term, n (%)	cUTI		cIAI	
	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)

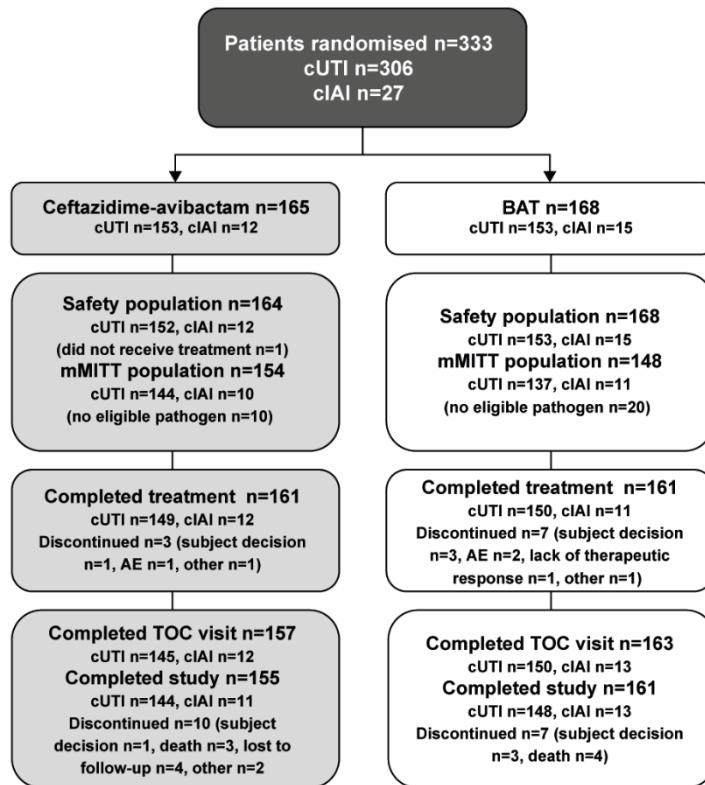
\*AEs occurring in  $\geq 2\%$  patients for cUTI and/or  $\geq 2$  patients for cIAI (ceftazidime-avibactam or BAT), and with onset time on or after time of first dose and up to and including last follow-up visit (FU2 for cUTI, FU1 for cIAI), irrespective of relationship to study drug.

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.



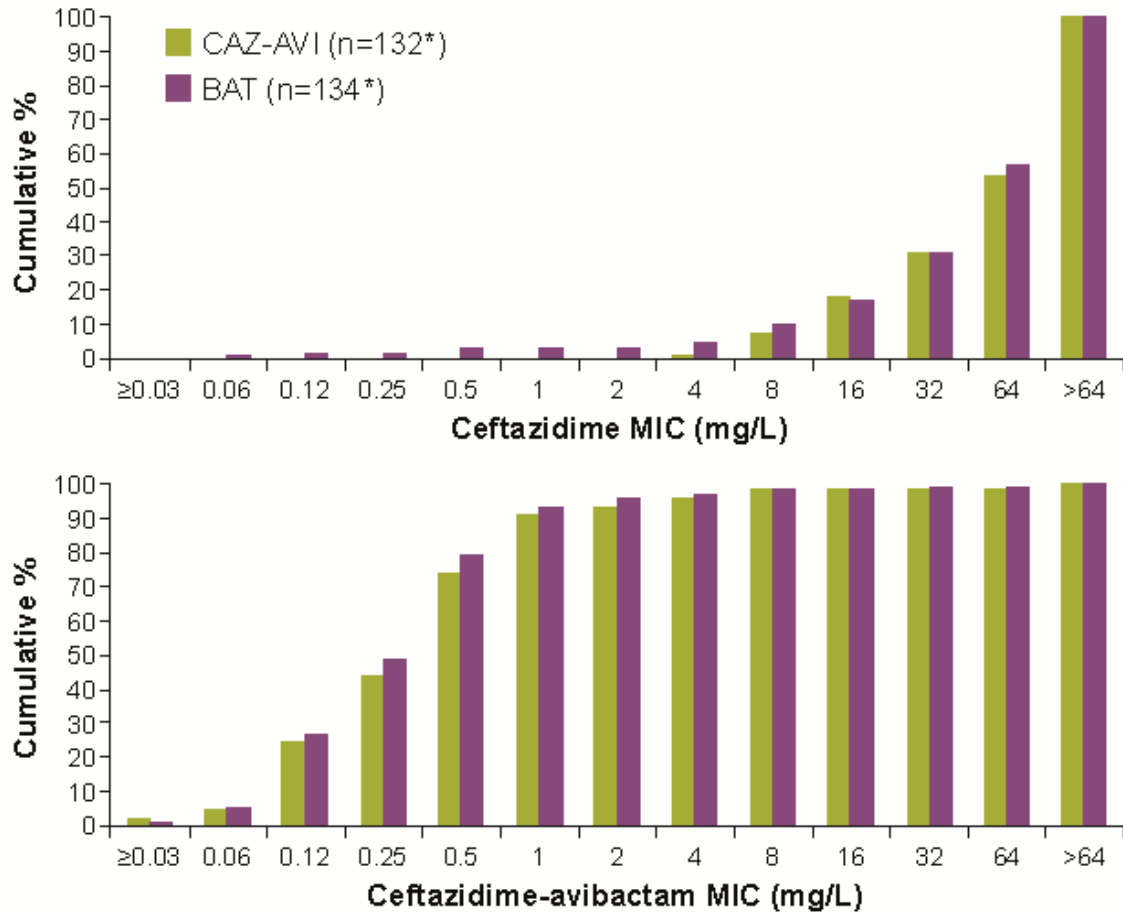


**Figure 1: Study flow**



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.

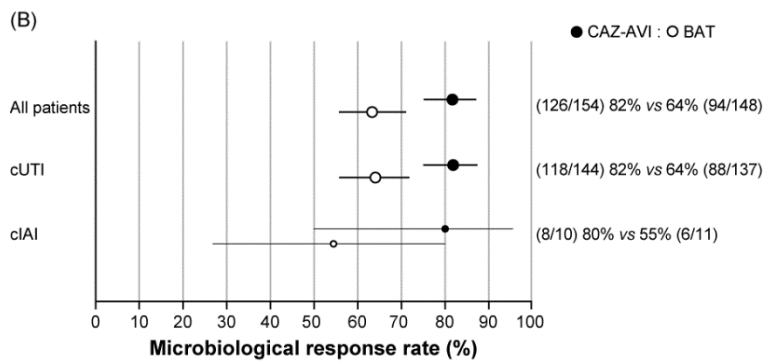
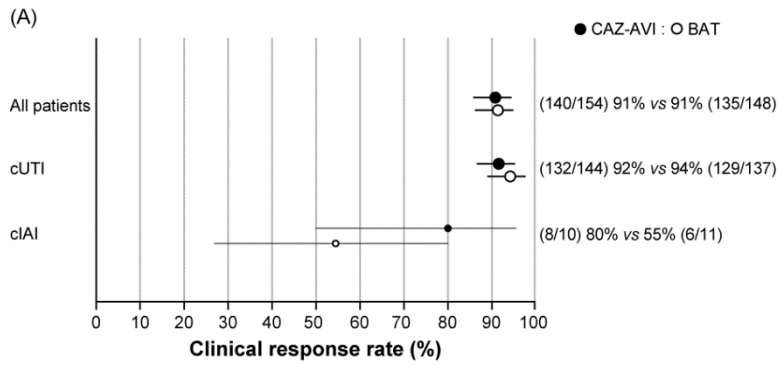
**Figure 2: Ceftazidime and ceftazidime-avibactam MIC for all Enterobacteriaceae isolated from urine at baseline in cUTI patients (mMITT population)**



\*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)\***



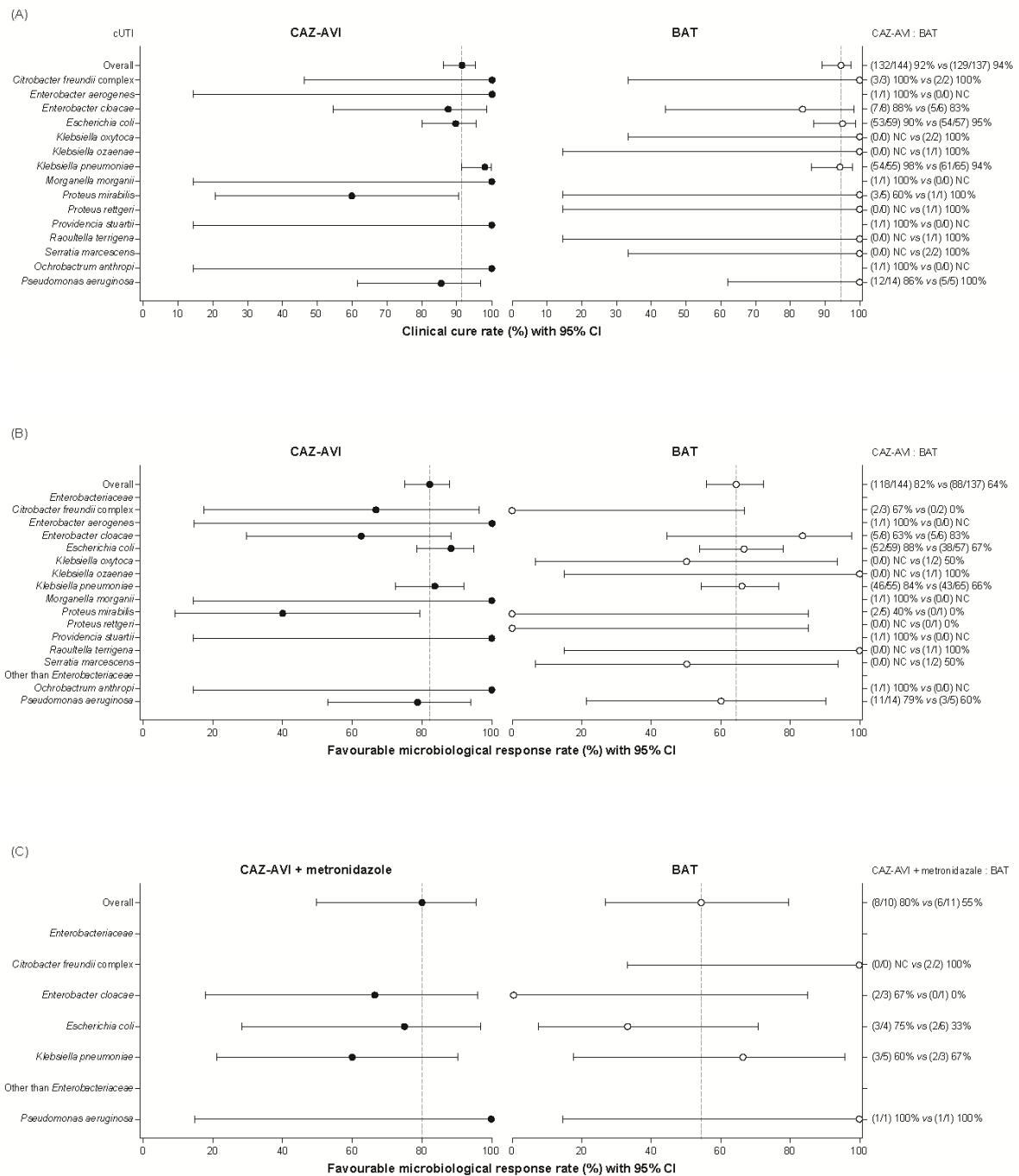
\*Per-patient microbiological outcomes for cIAI patients were presumed from clinical response.

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.