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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**

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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 β -lactamase (ESBL)-producing and carbapenemase-producing
63 Enterobacteriaceae and *Pseudomonas aeruginosa*, is increasing worldwide.¹⁻³
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.^{1,4,5} 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.⁶
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- β -lactam β -lactamase inhibitor.^{7,8}
76 Avibactam has a broader spectrum of activity than currently available β -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 β -lactamases, including class A (including ESBLs, *Klebsiella pneumoniae*
80 carbapenemases [KPC]), class C (AmpC), and some class D enzymes
81 (e.g. OXA-48).⁹

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,¹⁰ 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,^{7,8} 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.¹¹

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.¹² 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,¹³
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 ≥ 48 h of therapy,
147 or lack of improvement after ≥ 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,¹⁴ or resistant using European Committee on Antimicrobial Susceptibility
162 Testing (EUCAST) criteria¹⁵ 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) ≥8 mg/L and
165 ≥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 ≥10⁵ 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.^{17,18} 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 ≥ 8 mg/L). In contrast, only 1.5% of Enterobacteriaceae were shown as non-
296 susceptible to ceftazidime-avibactam (MIC ≤ 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 MIC₅₀ and MIC₉₀ 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.¹⁹ 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 alone²⁰ 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.¹⁰ 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,^{21–23}
510 and two phase 2 trials of ceftazidime-avibactam in patients with cUTI and cIAI
511 caused by Gram-negative pathogens.^{7,8} The phase 2 trial in cUTI patients
512 demonstrated clinical response rates with ceftazidime-avibactam comparable to
513 those for imipenem-cilastatin.⁸ In cIAI patients, ceftazidime-avibactam (in
514 combination with metronidazole) achieved response rates comparable to those
515 achieved with meropenem.⁷ 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,²⁴ 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.¹⁰ 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

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553 on this study, including time to review and input to the publication.

554

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565

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Table 1: Baseline patient characteristics and infection type (mMITT population)

	cUTI		cIAI	
	Ceftazidime-avibactam (n=144)	BAT (n=137)	Ceftazidime-avibactam + metronidazole (n=10)	BAT (n=11)
Age, years; mean (SD)	64.3 (14.6)	61.3 (15.3)	49.9 (16.1)	68.4 (11.1)
75–90 years, n (%)	38 (26.4)	27 (19.7)	0	4 (36.4)
Female, n (%)	64 (44.4)	63 (46.0)	6 (60.0)	4 (36.4)
Race, n (%)				
White	136 (94.4)	131 (95.6)	9 (90.0)	11 (100)
Other†	8 (5.6)	6 (4.4)	1 (10.0)	0
Body mass index, kg/m ² ; mean (SD)	28.1 (5.5)	28.0 (5.8)	25.2 (6.3)	28.6 (4.6)
≥30 kg/m ² , n (%)	48 (33.3)	51 (37.2)	3 (30.0)	4 (36.4)
Renal status, creatinine clearance; mL/min, n (%)				
>50	118 (81.9)	113 (82.5)	10 (100)	6 (54.5)
31–50	19 (13.2)	18 (13.1)	0	3 (27.3)
16–30	4 (2.8)	5 (3.6)	0	2 (18.2)
6–15	3 (2.1)	1 (0.7)	0	0
Diagnosis cUTI, n (%)				
Acute pyelonephritis	57 (39.6)	70 (51.1)	N/A	N/A

cUTI without pyelonephritis	87 (60.4)	67 (48.9)	N/A	N/A
Complicating factors				
Partial obstructive uropathy	45 (31.3)	21 (15.3)	N/A	N/A
Abnormality of urogenital tract	39 (27.1)	38 (27.7)	N/A	N/A
Male with urinary retention	33 (22.9)	24 (17.5)	N/A	N/A
Catheterisation	30 (20.8)	25 (18.2)	N/A	N/A
Urogenital procedure within 7 days	27 (18.8)	21 (15.3)	N/A	N/A
Diagnosis cIAI, n (%)				
Cholecystitis	N/A	N/A	2 (20.0)	4 (36.4)
Diverticular disease	N/A	N/A	1 (10.0)	1 (9.1)
Appendiceal perforation or per-appendiceal abscess	N/A	N/A	2 (20.0)	0
Secondary peritonitis	N/A	N/A	3 (30.0)	2 (18.2)
Intra-abdominal abscess (≥1)	N/A	N/A	2 (20.0)	4 (36.4)
APACHE II score, mean (SD)‡	N/A	N/A	6.9 (5.8)	10.9 (4.4)
APACHE II score category	N/A	N/A		
≤10	N/A	N/A	8 (80.0)	6 (54.5)
>10–≤30	N/A	N/A	1 (10.0)	3 (27.3)
Prior antibiotic use, n (%)	72 (50.0)	63 (46.0)	10 (100)	11 (100)

Bacteraemia, yes; n (%) [¶]	4 (2.8)	6 (4.4)	0	0
Infection type, n (%)				
Monomicrobial	139 (96.5)	131 (95.6)	4 (40.0)	4 (36.4)
Polymicrobial (2 pathogens)	4 (2.8)	6 (4.4)	4 (40.0)	5 (45.5)
Polymicrobial (≥3 pathogens) [§]	1 (0.7)	0	2 (20.0)	2 (18.2)
Baseline pathogen in urine (cUTI) or intra-abdominal site (cIAI), n (%)				
Enterobacteriaceae	131 (91.0)	132 (96.4)	9 (90.0)	11 (100)
Escherichia coli	59 (41.0)	57 (41.6)	4 (40.0)	6 (54.5)
Klebsiella pneumoniae	55 (38.2)	65 (47.4)	5 (50.0)	3 (27.3)
Enterobacter cloacae	8 (5.6)	6 (4.4)	3 (30.0)	1 (9.1)
Pseudomonas aeruginosa	14 (9.7)	5 (3.6)	1 (10.0)	1 (9.1)

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

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

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

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

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

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

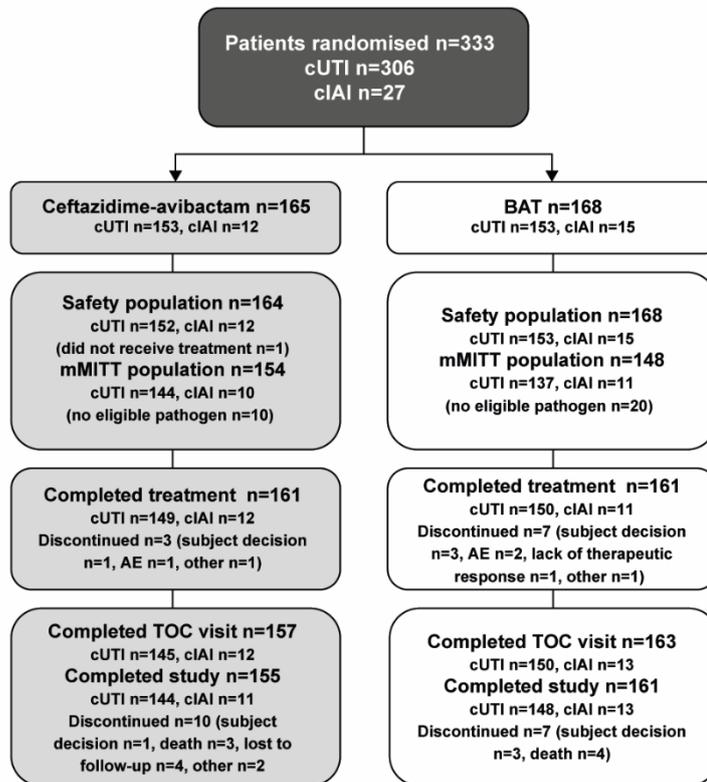
Table 2: Adverse events* (safety population)

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 ≥ 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.

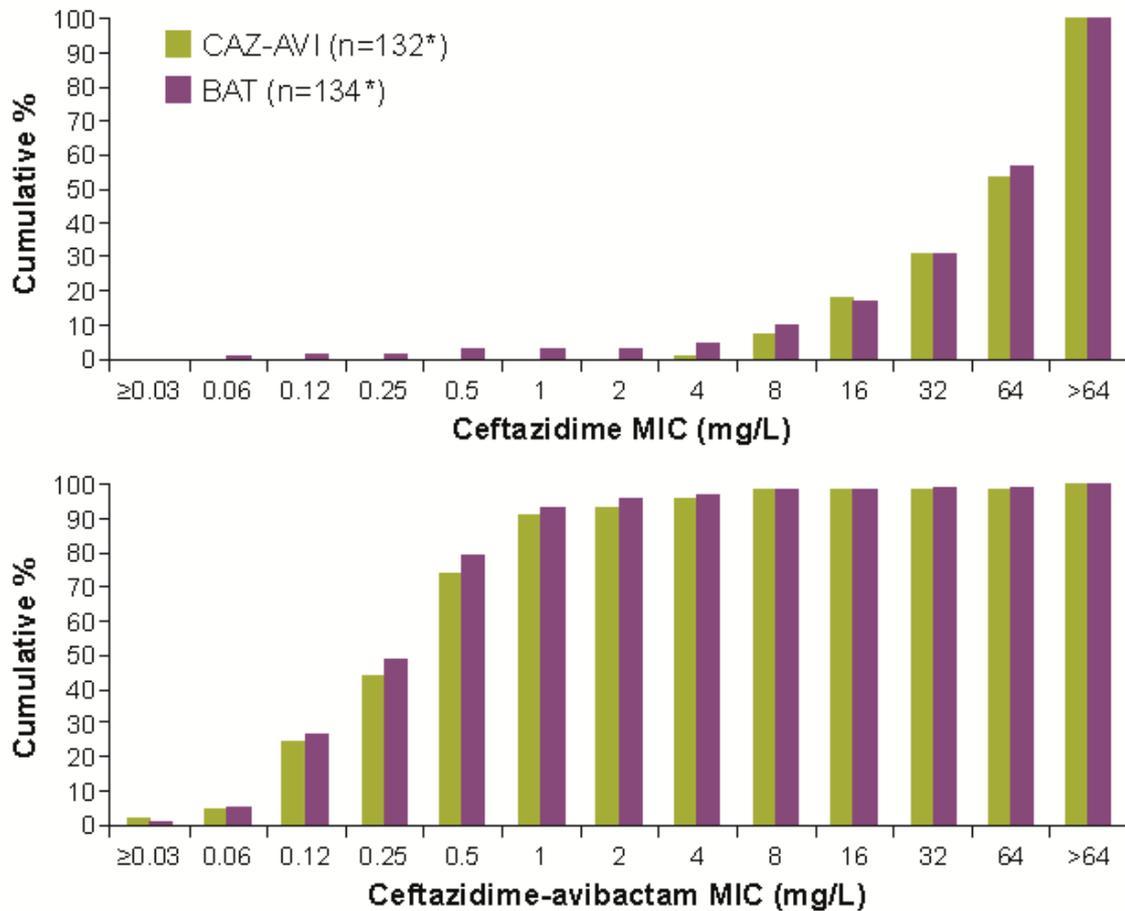
AE=adverse events; BAT=best available therapy; cIAI=complicated intra-abdominal infection; cUTI=complicated urinary tract infection; FU1=follow-up 1; FU2=follow-up 2.

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.

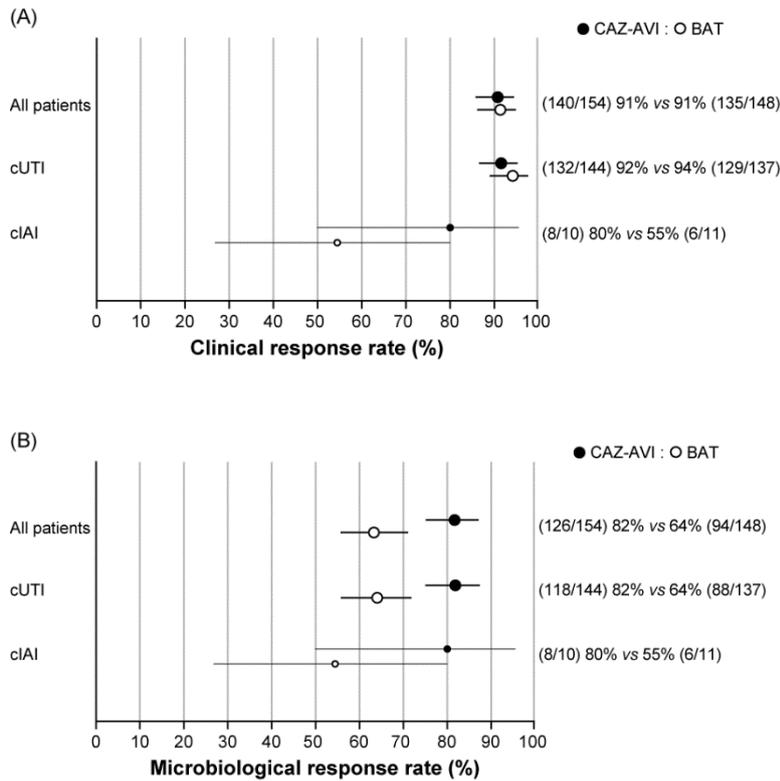
Figure 2: Ceftazidime and ceftazidime-avibactam MIC for all Enterobacteriaceae isolated from urine at baseline in cUTI patients (mMITT population)



*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)*



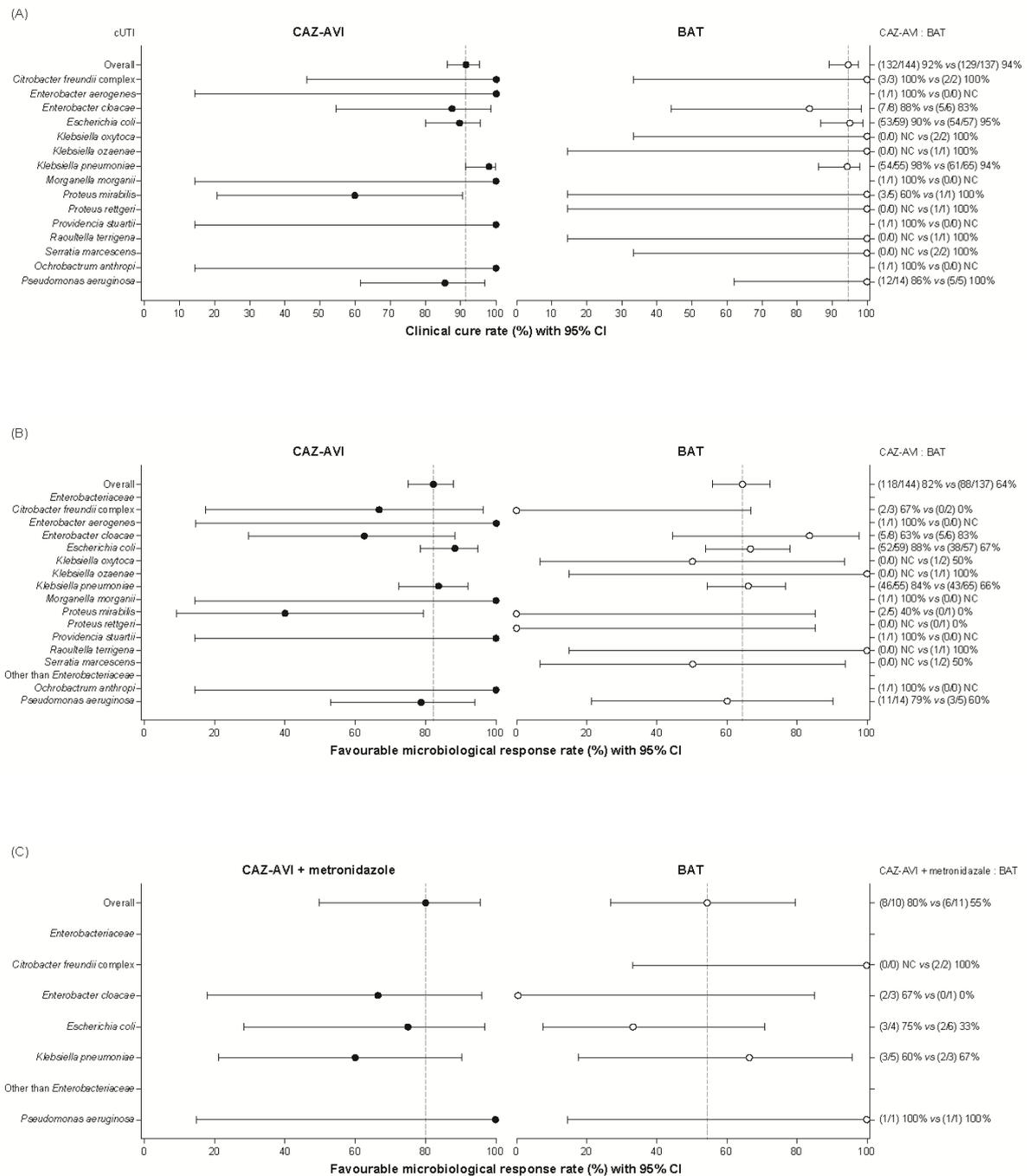
*Per-patient microbiological outcomes for cIAI patients were presumed from clinical response.

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.