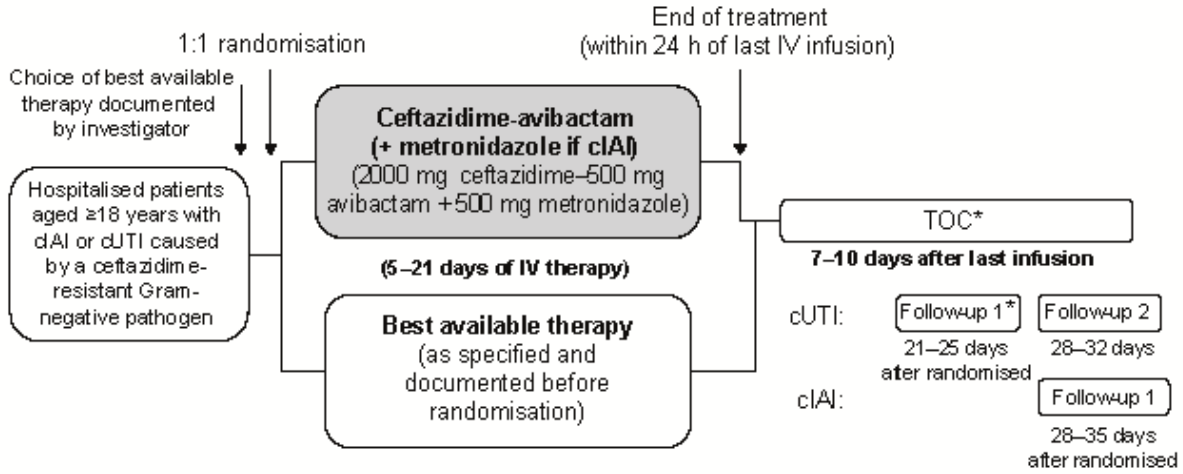
Supplementary webappendix

This webappendix formed part of the original submission and has been peer-reviewed. We post it as supplied by the authors.

Supplement to: Carmeli Y, Armstrong J, Laud PJ, Newell P, Stone G, Wardman A, Gasink LB. Efficacy and safety of ceftazidime-avibactam and best available therapy in the treatment of ceftazidime-resistant infections – results from a randomised phase 3 study. Lancet Infect Dis 2015 **[[publication date and doi to be added]]**

Contents

Figure S1: Study design



*Depending on the duration of study drug therapy, it was possible that the Follow-up 1 visit occurred prior to (or overlapped with) the TOC visit.

cIAI=complicated intra-abdominal infection; cUTI=complicated urinary tract infection; IV=intravenous; TOC=test of cure visit.

Table S1: Ceftazidime-avibactam dose regimens for patients with moderate to severe renal impairment

Estimated creatinine clearance (mL/min)[†]	Ceftazidime and avibactam dose, interval, duration
50–31	1000 mg ceftazidime and 250 mg avibactam every 12 h ± 30 min over 120 min at a constant rate of infusion
30–16	1000 mg ceftazidime and 250 mg avibactam every 24 h ± 30 min over 120 min at a constant rate of infusion
15–6	500 mg ceftazidime and 125 mg avibactam every 24 h ± 30 min over 120 min at a constant rate of infusion

[†]Estimated creatinine clearance using Cockcroft-Gault formula.

Note: Metronidazole infusion time = 60 min (for complicated intra-abdominal infection patients). Dose adjustments not needed.

Table S2: Additional inclusion criteria by diagnosis of cUTI and cIAI

cUTI	cIAI
Positive urine culture in the 5 days prior to screening, containing ≥105 colony-forming units (CFU)/mL of at least one Gram-negative uropathogen known to be ceftazidime-resistant, ie, the isolate from the study-qualifying culture)	Ceftazidime-resistant Gram-negative pathogen isolated from an abdominal source during a surgical intervention (open laparotomy, percutaneous drainage of an abscess, or laparoscopic surgery). Complete fascial closure was required but the skin incision may have been left open for the purposes of wound management
Pyuria in the 5 days prior to screening, as determined by a midstream clean catch or catheterised urine specimen with ≥10 white blood cells (WBC) per high-power field on standard examination of urine sediment, or ≥10 WBC/mm^3 in unspun urine	At least one of the following diagnoses:
Acute pyelonephritis criteria:	(i) Cholecystitis with gangrenous rupture or perforation or progression of the infection beyond the gall bladder wall
Flank pain (which must have onset or worsened within 7 day of enrolment) or costovertebral angle tenderness on examination, and at least one of the following:	(ii) Diverticular disease with perforation or abscess
• Fever (body temperature >38°C, with or without rigor, chills, or warmth) • Nausea and/or vomiting	(iii) Appendiceal perforation or peri-appendiceal abscess
Complicated lower UTI criteria:	(iv) Acute gastric and duodenal perforations, only if operated on >24 h after perforation occurred
At least two qualifying symptoms (at least one from Group A) and at least one complicating factor	(v) Traumatic perforation of the intestines, only if operated on >12 h after perforation occurred
• Group A qualifying symptoms: dysuria, urgency, frequency, and/or suprapubic pain	(vi) Secondary peritonitis (but not spontaneous bacterial peritonitis associated with cirrhosis or chronic ascites)
• Group B qualifying symptoms: fever (body temperature >38°C, with or without rigor, chills, or warmth), nausea and/or vomiting	(vii) Tertiary peritonitis
• Complicating factors:	(viii) Intra-abdominal abscess, including of the liver and spleen, provided that there is extension beyond the organ, with evidence of intraperitoneal involvement

– Documented history of urinary retention (male patients)	Patients were also required to have at least one of the signs/symptoms from Group A and B:
– Obstructive uropathy scheduled for medical or surgical relief during study therapy and before end of treatment	• Group A signs/symptoms: fever (defined as body temperature >38°C), hypothermia with a core body temperature <35°C, elevated WBC count (>12000 WBC/mm^3), and chills
– Functional or anatomical abnormality of the urogenital tract, including anatomic malformations or neurogenic bladder, or with a post-void residual urine volume of at least 100 mL	• Group B signs/symptoms: abdominal pain, nausea, vomiting, tenderness to palpation, rebound tenderness, and guarding
– Use of intermittent bladder catheterisation or presence of an indwelling bladder catheter for at least 48 h prior to obtainment of study-qualifying culture	
– Urogenital procedure (such as cystoscopy or urogenital surgery) within the 7 days before study entry prior to obtainment of study-qualifying culture	

Exclusion criteria – liver function test abnormalities

- Bilirubin >3× upper limit of normal (ULN), unless isolated hyperbilirubinaemia was directly related to the acute infection or due to known Gilbert's disease
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3× ULN values used by the laboratory performing the test. Patients with ALT or AST values >3× ULN and <5× ULN were eligible if this value was acute and directly related to the infectious process being treated. This had to be documented
- Alkaline phosphatase (AP) >3× ULN. Patients with AP values >3× ULN and <5× ULN were eligible if this value was acute and directly related to the infectious process being treated. This had to be documented

Additional exclusion criteria

cUTI patients

- More than two pathogens isolated from the patient's study-qualifying urine culture, regardless of colony count
- Renal transplant
- Suspected or known complete obstruction of any portion of the urinary tract, perinephric or intrarenal abscess, or prostatitis, or history of any illness that, in the opinion of the investigator, could have confounded the results of the study or posed additional risk in administering the study therapy to the patient
- Permanent urinary diversion (eg, ileal loops, cutaneous ureterostomy) or vesicoureteral reflux

cIAI patients

- Infections limited to the hollow viscus, such as simple cholecystitis, gangrenous cholecystitis without rupture, and simple appendicitis
- Acute suppurative cholangitis, infected necrotising pancreatitis, or pancreatic disease
- Abdominal wall abscess or small bowel obstruction without perforation, or ischaemic bowel without perforation
- Prior liver, pancreas, or small bowel transplant
- Surgery requiring staged abdominal repair, or 'open abdomen' technique, or marsupialisation. This criterion was intended to exclude patients in whom the abdomen was left open, particularly those for whom re-operation was planned
- History of serious allergy, hypersensitivity (eg, anaphylaxis), or any serious reaction to metronidazole

Table S3: Definitions of clinical response

Clinical response	Definition
Cure	Complete resolution or significant improvement of signs and symptoms of the index infection, such that no further antibacterial therapy (other than those allowed per protocol) was necessary; for cIAI patients, no drainage or surgical intervention after 96 h from randomisation was necessary
Failure	Patients who meet any one of the following criteria were considered a treatment failure: • Death related to the index infection • Received treatment with additional antibiotics (other than those allowed per protocol) for ongoing symptoms of index infection (including patients prematurely discontinued from study therapy due to an adverse event who require additional antibiotics for the index infection) • [For any visit following end of treatment visit] Previously met criteria for failure Additional failure criteria for complicated intra-abdominal infection patients: • Persistent or recurrent infection within the abdomen documented by the findings of reintervention, either percutaneously or operatively (after 96 h from randomisation) • Post-surgical wound infections defined as an open wound with signs of local infection, such as purulent exudates, erythema, or warmth, that required additional antibiotics, and/or non-routine wound care
Indeterminate	Study data were not available for evaluation of efficacy for any reason, including: • Patient lost to follow-up or assessment not undertaken, such that a determination of clinical response could not be made • Death where index infection was clearly non-contributory • Circumstances that precluded classification as a cure or failure

Table S4: Randomised patients by country

Region, country	cUTI		cIAI	
	Ceftazidime-avibactam (n=153)	**BAT (n=153)**	**Ceftazidime-avibactam + metronidazole (n=12)**	**BAT (n=15)**
Eastern Europe, n (%)	124 (81·0)	123 (80·4)	10 (83·3)	11 (73·3)
Bulgaria	44 (28·8)	46 (30·1)	0	1 (6·7)
Croatia	7 (4·6)	5 (3·3)	0	0
Czech Republic	0	0	3 (25·0)	3 (20·0)
Romania	15 (9·8)	14 (9·2)	1 (8·3)	1 (6·7)
Russian Federation	38 (24·8)	24 (15·7)	6 (50·0)	6 (40·0)
Turkey	6 (3·9)	17 (11·1)	0	0
Ukraine	14 (9·2)	17 (11·1)	0	0
North America and Western Europe, n (%)	8 (5·2)	7 (4·6)	0	1 (6·7)
France	2 (1·3)	1 (0·7)	0	0
Spain	1 (0·7)	2 (1·3)	0	1 (6·7)
United States of America	5 (3·3)	4 (2·6)	0	0
Rest of world, n (%)	21 (13·7)	23 (15·0)	2 (16·7)	3 (20·0)
Argentina	5 (3·3)	3 (2·0)	0	1 (6·7)
Israel	6 (3·9)	8 (5·2)	1 (8·3)	2 (13·3)
Republic of Korea	4 (2·6)	1 (0·7)	0	0
Mexico	3 (2·0)	4 (2·6)	0	0
Peru	2 (1·3)	7 (4·6)	0	0
South Africa	1 (0·7)	0	1 (8·3)	0

BAT=best available therapy; cIAI=complicated intra-abdominal infection; cUTI=complicated urinary tract infections.

Study sites and principal investigators

Eastern Europe

Bulgaria: Boris Bogov (University Multiprofile Hospital for Active Treatment "Aleksandrovska" EAD, Sofia); Margarita Velkova (Multiprofile Regional Hospital for Active Treatment "Dr Stefan Cherkezov" AD, Veliko Tarnovo); Rumen Kotsev (University Multiprofile Hospital for Active Treatment "Dr G Stranski" EAD, Pleven); Krassimir Yanev (University Multiprofile Hospital for Active Treatment "Aleksandrovaska" EAD, Sofia); Valentin Ignatov (Multiprofile Hospital for Active Treatment "Sv. Marina" EAD, Varna); Emil Dorosiev (University Multiprofile Hospital for Active Treatment and Emergency Medicine "N I Pirogov" EAD, Sofia); Ventsislav Georgiev (Multiprofile Hospital for Active Treatment, Ruse); Kaloyan Davidoff (Multiprofile Hospital for Active Treatment "Tokuda Hospital Sofia" AD, Sofia).

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Turkey: Neşe Saltoğlu (Istanbul University Cerrahpasa Medical Faculty, Faith, Istanbul); Mustafa Kemal Çelen (Dicle University Medical Faculty, Diyarbakir).

Ukraine: Igor Antonyan (#4 of MHI "Regional Clinical Centre of Urology and Nephrology n.a. V.I. Shapoval", Kharkiv); Olexiy Lyulko (Municipal Institute "Zaporizhzhya Regional Clinical Hospital" of Zaporizhzhya Regional Council, Zaporizhzhya); Viktor Stus (State Institution "Dnipropetrovsk State Medical Academy of MoH of Ukraine", Dnipropetrovsk); Petro Ivashchenko (Kyiv City Clinical Hospital, Kyiv).

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Spain: Javier Cobo Reinoso (Hospital Ramon y Cajal, Madrid).

United States of America: Ravi K Kamepalli (St Rita's Medical Center, Lima, OH); Loren Smith (Willis-Knighton Physician Network/Urology at Pierremont, Shreveport, LA).

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South Africa: Guy Anthony Richards (Charlotte Maxeke Johannesburg Academic Hospital, Parktown, Johannesburg).

Table S5: Best available therapy (safety population)

	cUTI n (%)	cIAI n (%)
Any preferred monotherapy, n (%)[†]	146 (95·4)	14 (93·3)
Any other monotherapy, n (%)[‡]	6 (3·9)	0
BAT single therapy, n (%)		
Amikacin	1 (0·7)	0
Colistin	2 (1·3)	0
Doripenem	11 (7·2)	0
Ertapenem	1 (0·7)	0
Ertapenem sodium	2 (1·3)	0
Gentamicin	1 (0·7)	0
Imipenem[¶]	76 (49·7)	5 (33·3)
Meropenem[¶]	57 (37·3)	9 (60·0)
Piperacillin/tazobactam	1 (0·7)	0
Any combination therapy, n (%)		
Ciprofloxacin + meropenem	0	1 (6·7)
Colistin + imipenem	1 (0·7)	0

[†]Preferred BAT options as specified in the protocol for cUTI were meropenem, imipenem, doripenem, and colistin; for cIAI, they were meropenem, imipenem, doripenem, tigecycline, and colistin.

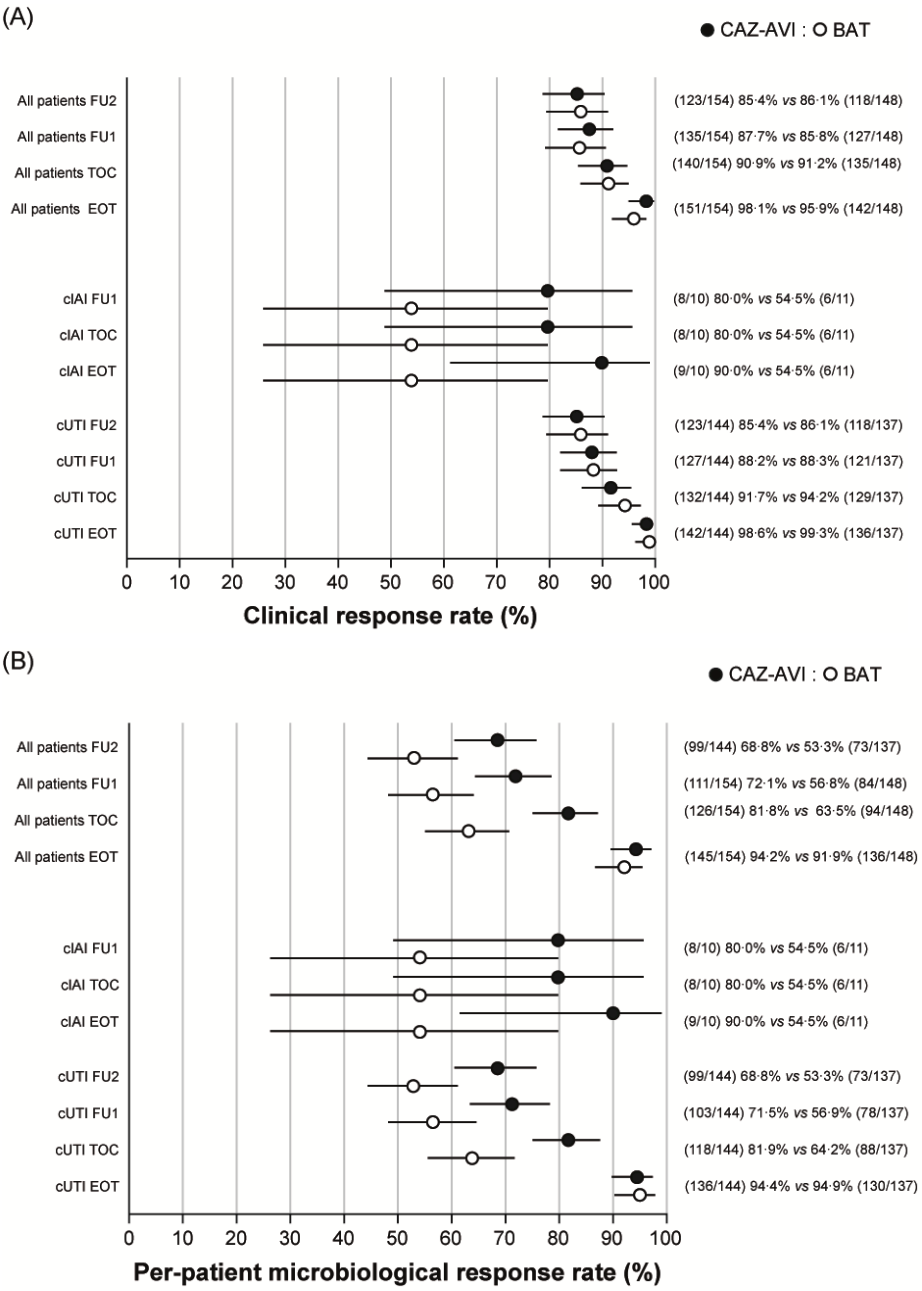
[‡]BAT other than any of the preferred BAT options specified in the protocol.

[¶]In cUTI patients, the most common total daily dose of imipenem was 1·5–4·0 g (64 patients [84·2%]), the most common total daily dose of meropenem patients was 1·5–3·0 g (54 patients [94·7%], the most common dose regimens for initiation of imipenem were 500 mg q8h (38 patients [50.0%]) and 500 mg q6h (20 patients [26.3%]), and the most common dose regimens for initiation of meropenem were 1000 mg q8h (31 patients [54.4%]) and 500 mg q8h (15 patients [26.3%]). In cIAI patients, dose regimens for initiation of imipenem were 1 g every 6 h (n=2), 500 mg every 6 h (n=2), and 1 g every 8 h (n=1), and dose regimens for initiation of meropenem were 1 g every 8 h (n=6), 2 g every 8 h (n=2), and 1 g every 12 h (n=1). The remaining patients had varying degrees of renal impairment at baseline and received lower doses of imipenem or meropenem.

Metronidazole is not summarised here. Any BAT regimens listed could have been with or without metronidazole.

BAT=best available therapy; cIAI=complicated intra-abdominal infection; cUTI=complicated urinary tract infections.

Figure S2: A) Clinical response and B) per-patient microbiological response at all-time points (mMITT population)



cUTI: CAZ-AVI (n=144), BAT (n=137).

cIAI: CAZ-AVI (n=10), BAT (n=11).

All patients: CAZ-AVI (n=154), BAT (n=148).

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

BAT=best available therapy; CAZ-AVI=ceftazidime-avibactam; cIAI=complicated intra-abdominal infection; cUTI=complicated urinary tract infection; EOT=end of treatment; FU1=follow-up 1; FU2=follow-up 2; mMITT=microbiologically modified intent-to-treat; TOC=test of cure visit.

Results of secondary outcomes not reported in the main manuscript

Type	Description	Summary of results
Efficacy	Proportion of patients with clinical cure at the EOT, TOC, FU1and FU2 visits in the extended ME analysis sets*	Data for the mMITT analysis set shown in the main manuscript and figure S2. Extended ME analysis set. Overall clinical cure rates (cUTI and cIAI): EOT: 100.0% (95% CI 98.3 to 100.0) in the ceftazidime-avibactam group and 100.0% (95% CI 98.1 to 100.0) in the Best Available Therapy group. FU1: 96.9% (95% CI 92.9 to 99.0) in the ceftazidime-avibactam group and 93.5% (95% CI 88.1 to 96.9) in the Best Available Therapy group. FU2 (cUTI only): 91.4% (95% CI 85.2 to 95.5) in the ceftazidime-avibactam group and 89.5% (95% CI 82.9 to 94.1) in the Best Available Therapy group.
Efficacy	Proportion of patients with clinical cure at the TOC visit by entry diagnosis in the extended ME analysis set*	Data for the mMITT analysis set shown in the main manuscript. Extended ME at TOC analysis set: cUTI: 98.4% (95% CI 95.1 to 99.7) in the ceftazidime-avibactam group and 98.4% (95% CI 94.8 to 99.7) in the Best Available Therapy group. cIAI: 8 patients (100.0%) (95% CI 73.8 to 100.0) in the ceftazidime-avibactam group and 5 patients (100.0%) (95% CI 62.1 to 100.0) in the Best Available Therapy group.
Efficacy	Proportion of patients with clinical cure at the TOC visit by pathogen in the extended ME analysis set*	Data for the mMITT analysis set shown in the main manuscript. Data for the 2 most common pathogens (E.coli and K.pneumoniae) in the extended ME at TOC analysis set: **cUTI (urine):** E. coli: 98.1% (95% CI 91.4 to 99.8) in the ceftazidime-avibactam group and 97.9% (95% CI 90.7 to 99.8) in the Best Available Therapy group. K.pneumoniae: 100.0% (95% CI 95.4 to 100.0) in the ceftazidime-avibactam group and 100.0% (95% CI 95.8 to 100.0) in the Best Available Therapy group. **cIAI (intra-abdominal site):** E. coli:3 patients (100.0%) (95% CI 46.4 to 100.0) in the ceftazidime-avibactam group and 2 patients (100.0%) (95% CI 33.3 to 100.0) in the Best Available Therapy group. K. pneumoniae: 3 patients (100.0%) (95% CI 46.4 to 100.0) in the ceftazidime-avibactam group and 2 patients (100.0%) (95% CI 33.3 to 100.0) in the Best Available Therapy group.

Efficacy	Proportion of favourable per pathogen microbiological response at the EOT, FU1 and FU2 visits in the mMITT analysis set, and at the EOT, TOC, FU1, and FU2 visits in the extended ME analysis sets*	mMITT analysis set: Favourable per-pathogen microbiological response rate at TOC shown in the main manuscript. Data for the 2 most common pathogens at other visits (E. coli and K. pneumoniae): **cUTI (urine):** E. coli: EOT: 96.6% (95% CI 89.6 to 99.3) in the ceftazidime-avibactam group and 93.0% (95% CI 84.2 to 97.6) in the Best Available Therapy group FU1: 76.3% (95% CI 64.3 to 85.7) in the ceftazidime-avibactam group and 57.9% (95% CI 45.0 to 70.1) in the Best Available Therapy group FU2: 72.9% (95% CI 60.6 to 82.9) in the ceftazidime-avibactam group and 56.1% (95% CI 43.2 to 68.5) in the Best Available Therapy group K.pneumoniae: EOT: 94.5% (95% CI 86.2 to 98.4) in the ceftazidime-avibactam group and 93.8% (95% CI 86.0 to 97.9) in the Best Available Therapy group FU1: 76.4% (95% CI 64.0 to 86.1) in the ceftazidime-avibactam group and 60.0% (95% CI 47.9 to 71.3) in the Best Available Therapy group FU2: 70.9% (95% CI 58.1 to 81.6) in the ceftazidime-avibactam group and 53.8% (95% CI 41.8 to 65.6) in the Best Available Therapy group **cIAI (intra-abdominal site):** E.coli: EOT: 3 patients (75.0%) (95% CI 28.4 to 97.2) in the ceftazidime-avibactam group and 2 patients (33.3%) (95% CI 7.7 to 71.4) in the Best Available Therapy group FU1: 3 patients (75.0%) (95% CI 28.4 to 97.2) in the ceftazidime-avibactam group and 2 patients (33.3%) (95% CI 7.7 to 71.4) in the Best Available Therapy group K. pneumoniae: EOT: 4 patients (80.0%) (95% CI 37.1 to 97.7) in the ceftazidime-avibactam group and 2 patients (66.7%) (95% CI 17.7 to 96.1) in the Best Available Therapy group FU1: 3 patients (60.0%) (95% CI 20.9 to 90.6) in the ceftazidime-avibactam group and 2 patients (66.7%) (95% CI 17.7 to 96.1) in the Best Available Therapy group For the extended ME analysis set, the results were similar to those observed in the mMITT analysis set.

Efficacy	Proportion of patients with clinical cure at the TOC visit by resistance mechanism in the mMITT and extended ME analysis set*	Data analysis ongoing
Efficacy	Proportion of patients with favorable per-patient microbiological response at the TOC visit by resistance mechanism in the mMITT and extended ME analysis set*	Data analysis ongoing
Efficacy	Proportion of patients with clinical cure by previously failed antibiotic treatment class at the TOC visit in the mMITT analysis set, and at EOT, TOC, FU1 and FU2 visits in the extended ME analysis set*	mMITT analysis set: Overall clinical cure rates (cUTI and cIAI) at TOC for patients with at least 1 failed antibiotic treatment class: 92.9% (95% CI 71.2 to 99.2) in the ceftazidime-avibactam group and 93.8% (95% CI 74.3 to 99.3) in the Best Available Therapy group For the extended ME analysis set, the results were similar to those observed at TOC in the mMITT analysis set.
Efficacy	Proportion of patients with favourable per-patient microbiological response at the EOT, TOC, FU1 and FU2 visits in the extended ME analysis set*	Data for the mMITT analysis set shown in the main manuscript and figure S2. Extended ME analysis set. Overall favourable per-patient microbiological response rates (cUTI and cIAI): EOT: 99.3% (95% CI 96.8 to 99.9) in the ceftazidime-avibactam group and 100.0% (95% CI 98.1 to 100) in the Best Available Therapy group. FU1: 78.9% (95% CI 71.4 to 85.2) in the ceftazidime-avibactam group and 64.0% (95% CI 55.3 to 72.0) in the Best Available Therapy group. FU2 (cUTI only): 72.6% (95% CI 64.1 to 80.1) in the ceftazidime-avibactam group and 59.1% (95% CI 50.0 to 67.8) in the Best Available Therapy group.
Efficacy	Proportion of patients with favourable per-pathogen microbiological response at the EOT, TOC, FU1 and FU2 visits, by ceftazidime-avibactam minimum inhibitory concentration (MIC) categories in the mMITT and extended ME analysis sets*	Data for the mMITT analysis set for the most common pathogens at TOC are shown in the main manuscript. For other visits and the extended ME analysis set, the results were similar to those observed at TOC in the mMITT analysis set.
Efficacy	Reasons for treatment change and/or discontinuation in the mMITT analysis set	Only a small number of patients required a treatment change or discontinuation and these were generally balanced across the treatment groups. Nineteen patients with cUTI required a treatment change during the study period: 11 patients (7.6%) in the ceftazidime-avibactam group and 8 patients (5.8%) in the Best Available Therapy group. Only 1 cIAI patient (in

		the Best Available Therapy group) required a treatment change during the study period. The most common reason for a treatment change was a change in creatinine clearance during the study.
Efficacy	28-day mortality rate in the mMITT analysis set and extended ME at TOC analysis set*	In the mMITT analysis set, 6 cUTI patients (3 patients in each treatment group [2.1% for ceftazidime-avibactam and 2.2% for Best Available Therapy) and 1 cIAI patient (in the Best Available Therapy group [9.1%]) died on or before Day 28. In the extended ME at TOC analysis set, 2 cUTI patients (1 in each treatment group (0.8%)) died on or before Day 28.
Pharmacokinetics	Pharmacokinetics of the individual components of ceftazidime-avibactam	Exposure data for both ceftazidime and avibactam were as expected from previous studies.

*Extended microbiologically evaluable (ME) analysis set at the EOT, TOC, FU1 and FU2 (cUTI patients only) visits includes all patients meeting the following criteria:

- Were included in the mMITT analysis set
- Received at least 5 days of therapy or received <48 hours of therapy before discontinuing due to an AE
- Had no important protocol deviations that would affect the assessment of efficacy
- Received no additional systemic, Gram-negative antibacterial therapy (other than study therapy as designated at randomisation) for treatment of a non-cIAI or non-cUTI infection. This does not include antibiotic therapy taken for the treatment of cIAI or cUTI by patients who were considered failures.
- For cUTI patients only, had a microbiological assessment from a quantitative urine culture at the EOT, TOC, FU1, and FU2 (cUTI only) visits, respectively, with a microbiological response other than indeterminate.
- For cIAI patients, at the EOT, TOC, FU1 visits had a microbiological response other than indeterminate.

Further details of these additional secondary outcomes are available at ClinicalTrials.gov (Identifier: NCT01644643).