Phase 3, randomised, multicentre study of ceftazidime-avibactam versus meropenem in adults with nosocomial pneumonia including ventilator-associated pneumonia (REPROVE)

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Disclosures

A Torres	Principal Investigator on the REPROVE study, funded by AstraZeneca
N Zhong	Institutional research grant funding from AstraZeneca for the conduct of the study
J Pachl	Institutional research grant funding from AstraZeneca for the conduct of the study
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M Kollef	Institutional research grant funding from AstraZeneca for the conduct of the study
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G Stone	Employee of and shareholder in AstraZeneca at the time of study completion; current employee of Pfizer
J Chow	Employee of and shareholder in AstraZeneca

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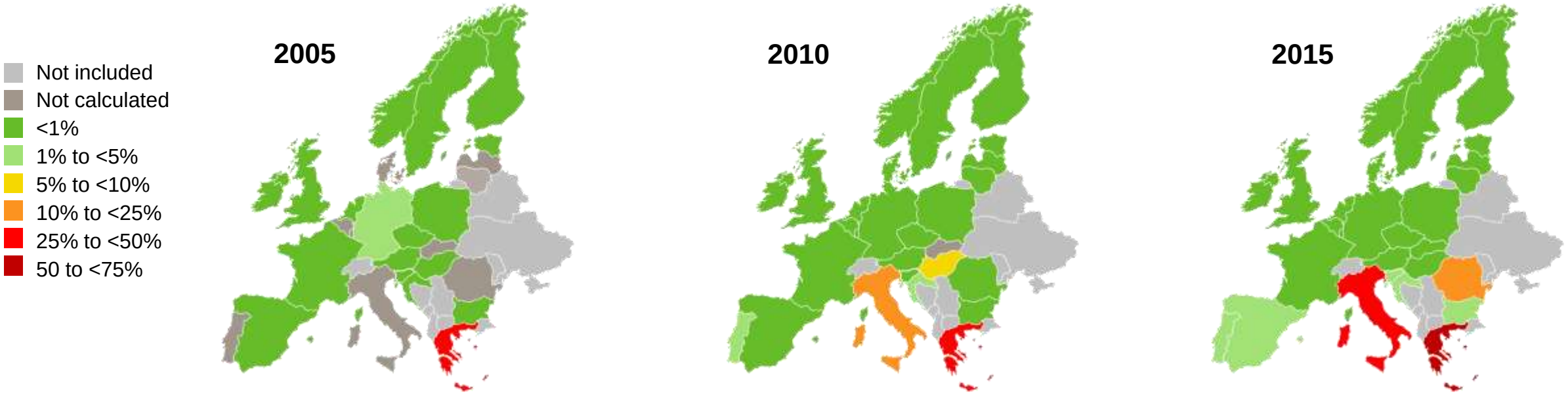
Background

- Nosocomial pneumonia remains among the most common hospital-acquired infections[1]
  - Gram-negative pathogens predominate with Enterobacteriaceae (notably *Klebsiella* spp.) and *Pseudomonas aeruginosa* commonly implicated[2–4]

Percentage *Klebsiella pneumoniae* isolates resistant to carbapenems (2005–2015)[5]

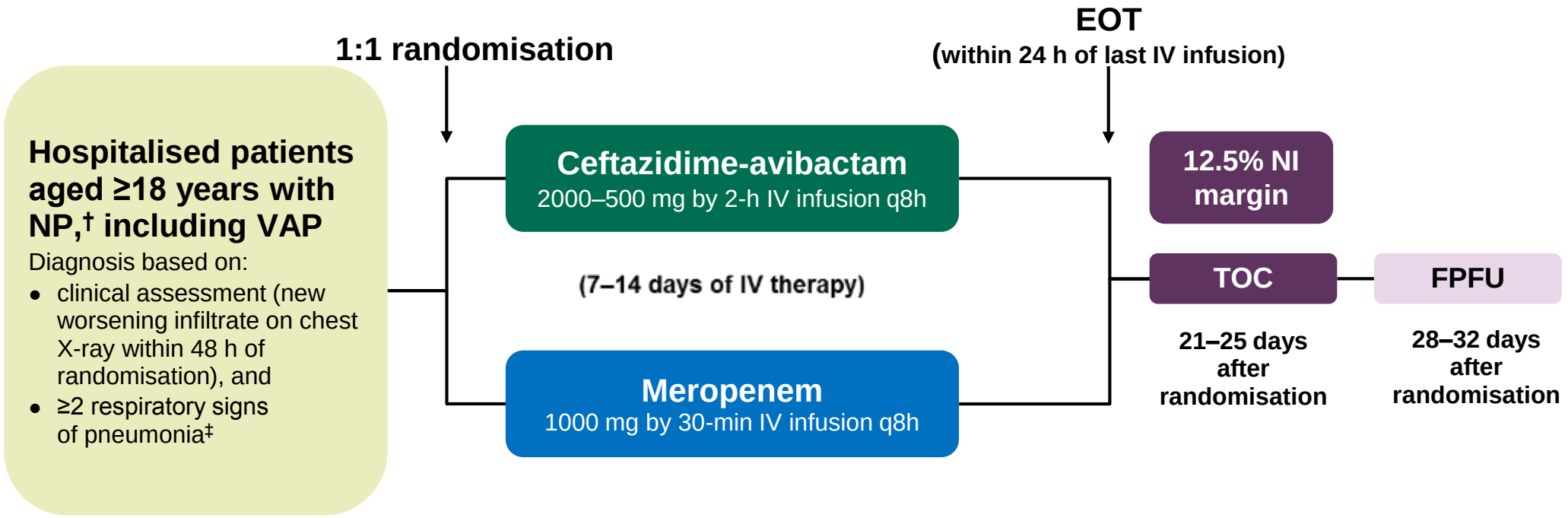


There is a need for new treatment options

1. Maggill SS et al. *N Engl J Med*. 2014;370:1198–1208.
2. Gaynes R, Edwards JR. *Clin Infect Dis.* 2005;41:848–854.
3. Jones RN. *Clin Infect Dis.* 2010;51 Suppl 1:S81–S87.
4. Peleg AY, Hooper DC. *N Engl J Med*. 2010;362:S81–S87.
5. http://atlas.ecdc.europa.eu/public/index.aspx?Instance=GeneralAtlas (accessed 20 April 2017).

REPROVE
Phase 3 study in patients with nosocomial pneumonia

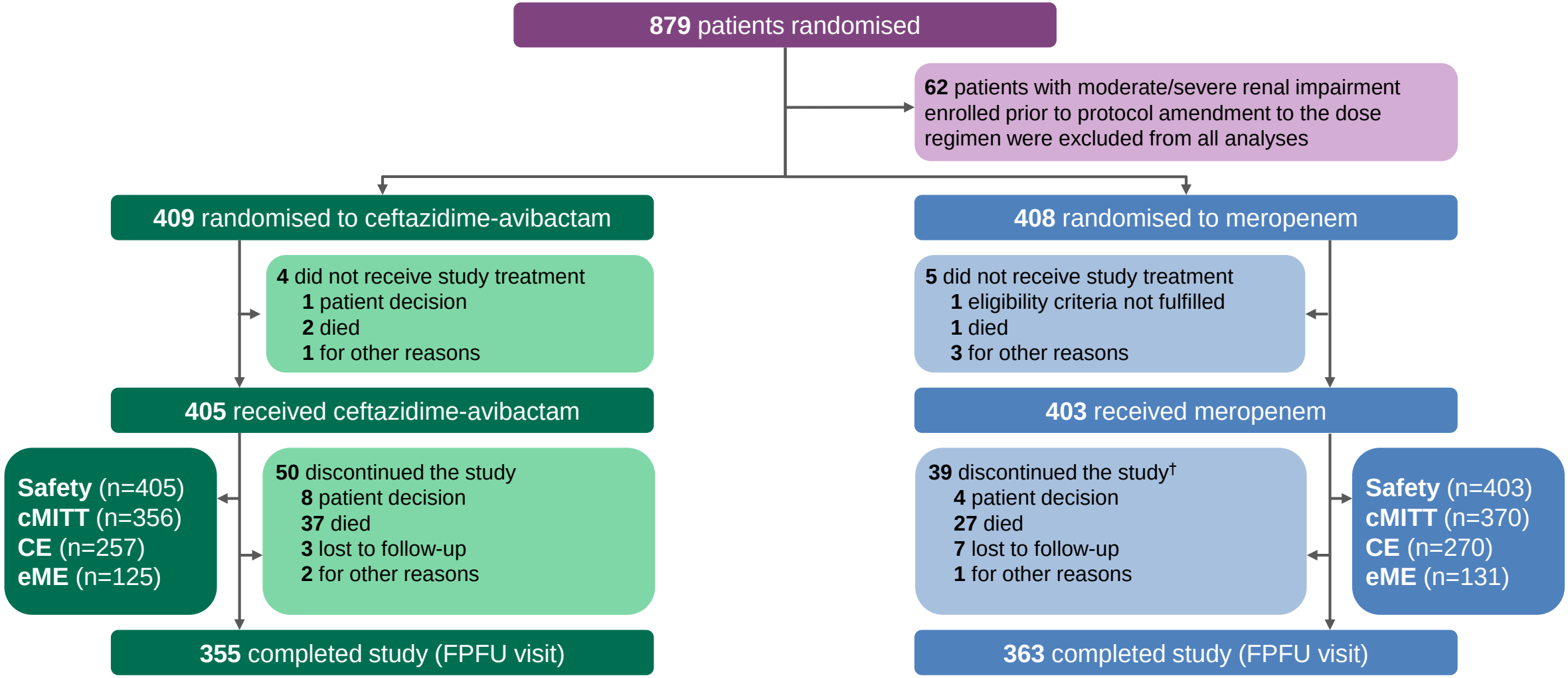
- **REPROVE (NCT01808092)** was a prospective, multicentre, international, randomised, double-blind, double-dummy, Phase 3 study, evaluating efficacy and safety of ceftazidime-avibactam compared with meropenem
- **Primary endpoint:** clinical cure at the TOC visit in the co-primary cMITT and CE populations



†Defined as pneumonia with onset ≥48 h after admission or <7 days after discharge from an inpatient acute or chronic care facility; ‡A respiratory specimen for Gram stain and culture was required within 48 h of randomisation. Open-label linezolid (or vancomycin) was given for Gram-positive coverage, and/or open-label amikacin (or other aminoglycoside) for Gram-negative coverage for a minimum of 48–72 h in patients awaiting identification or susceptibility results from the baseline culture at randomisation

CE, clinically evaluable; cMITT, clinically modified intent-to-treat; EOT, end-of-treatment; FPFU, final protocol follow-up; IV, intravenous; NI, non-inferiority; NP, nosocomial pneumonia; q8h, every 8 h; TOC, test-of-cure; VAP, ventilator-associated pneumonia from an inpatient acute or chronic care facility

Patient disposition



†One meropenem patient completed the TOC visit (outside the window) and the FPFU visit on the same day, and was neither recorded as having completed the study nor as having discontinued the study
CE, clinically evaluable; cMITT, clinically modified intent-to-treat; eME, extended microbiologically evaluable; FPFU, final patient follow-up; ME, microbiologically evaluable; TOC, test of cure

Key patient and disease characteristics at baseline (cMITT population)

Parameter	Ceftazidime-avibactam (N=356)	Meropenem (N=370)
Age, years, mean (SD)	62.1 (16.6)	61.9 (17.4)
Male, n (%)	268 (75.3)	274 (74.1)
Race, n (%)		
White	150 (42.1)	163 (44.1)
Black or African American	1 (0.3)	2 (0.5)
Asian	201 (56.5)	199 (53.8)
Other	4 (1.1)	6 (1.6)
Body mass index, kg/m^2, mean (SD)	24.0 (6.1)	23.9 (5.2)
APACHE II score category, n (%)		
<10	1 (0.3)	1 (0.3)
10–19	309 (86.8)	316 (85.4)
20–30	46 (12.9)	53 (14.3)
Estimated CrCL, mL/min, mean (SD)	102.6 (67.5)	100.1 (53.1)
Renal status, n (%)		
Normal renal function or mild impairment (CrCL >50–150 mL/min)	286 (80.3)	292 (78.9)
Moderate or severe impairment (CrCL 16–50 mL/min)	18 (5.1)	18 (4.9)
Augmented (CrCL >150 mL/min)	50 (14.0)	58 (15.7)
NP subtype, n (%)		
VAP	118 (33.1)	128 (34.6)
Non-VAP	238 (66.9)	242 (65.4)
Mechanical ventilation at baseline, n (%)		
Ventilated	154 (43.3)	159 (43.0)
Non-ventilated	202 (56.7)	211 (57.0)
Prior systemic antibiotic use (in the 48-h before randomisation), n (%)		
None	122 (34.3)	117 (31.6)
>0 to ≤24 h	185 (52.0)	209 (56.5)
>24 to ≤48 h	49 (13.8)	44 (11.9)

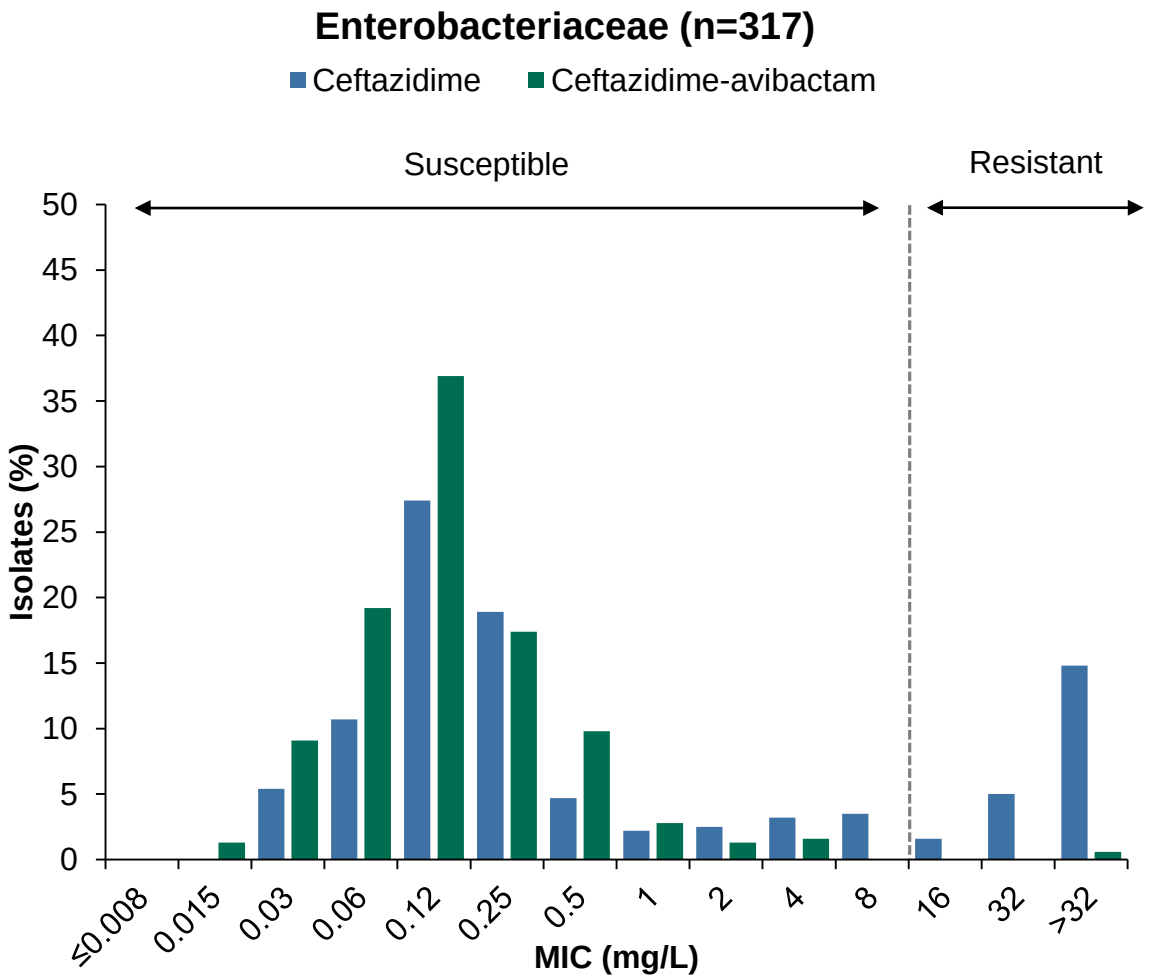
APACHE, Acute Physiology and Chronic Health Evaluation; cMITT, clinically modified intent-to-treat; CrCL, creatinine clearance; n, number of patients in subgroup; N, number of patients in treatment group; NP, nosocomial pneumonia; SD, standard deviation; VAP, ventilator-associated pneumonia from an inpatient acute or chronic care facility

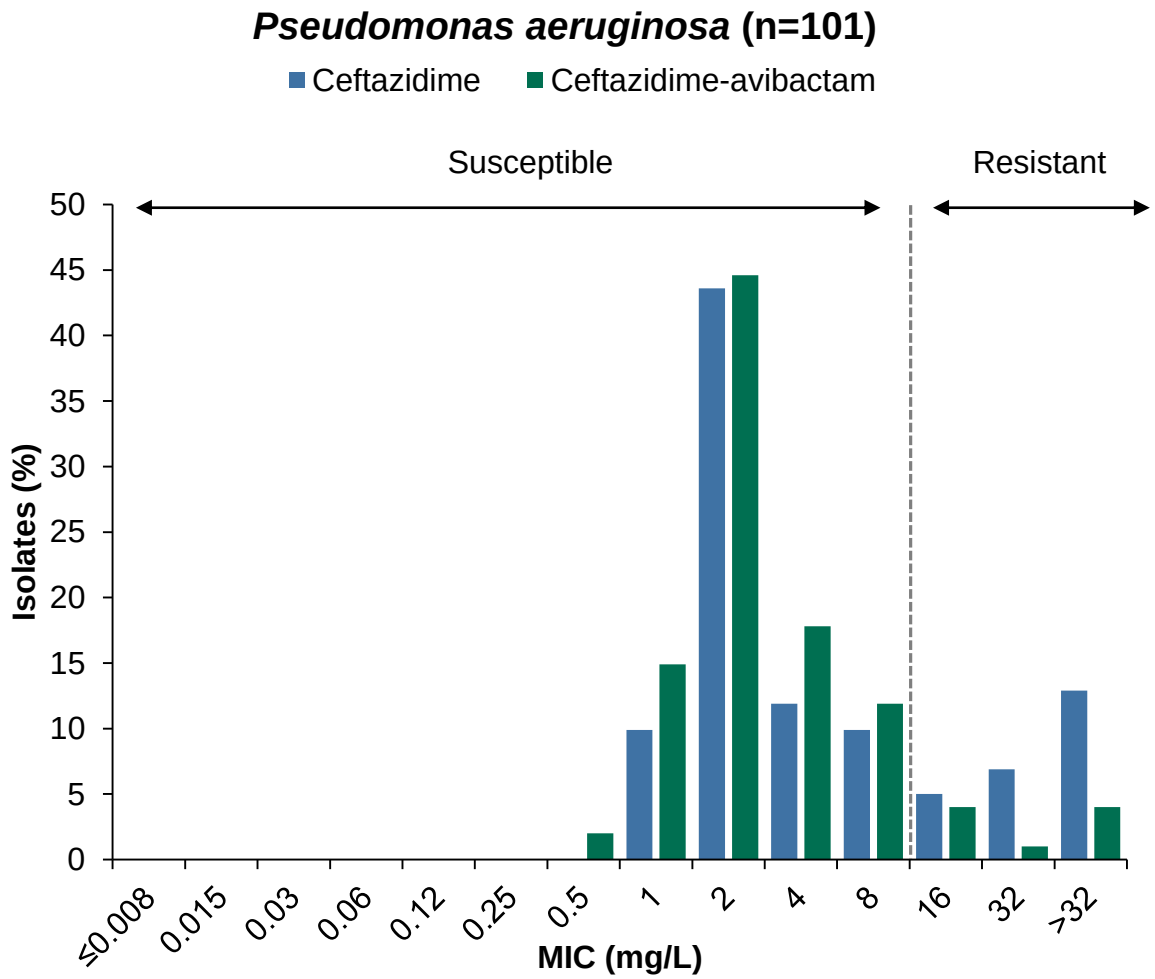
Gram-negative pathogens identified at baseline with a combined frequency of ≥10 (mMITT population)

	Patients, n (%)		
	Ceftazidime-avibactam (N=171)	Meropenem (N=184)	Total (N=355)
Enterobacteriaceae	121 (70.8)	138 (75.0)	259 (73.0)
Klebsiella pneumoniae	59 (34.5)	71 (38.6)	130 (36.6)
Enterobacter cloacae	26 (15.2)	22 (12.0)	48 (13.5)
Escherichia coli	17 (9.9)	20 (10.9)	37 (10.4)
Serratia marcescens	15 (8.8)	13 (7.1)	28 (7.9)
Proteus mirabilis	14 (8.2)	12 (6.5)	26 (7.3)
Enterobacter aerogenes	8 (4.7)	8 (4.3)	16 (4.5)
Gram-negative pathogens other than Enterobacteriaceae	79 (46.2)	80 (43.5)	159 (44.8)
Pseudomonas aeruginosa	58 (33.9)	47 (25.5)	105 (29.6)
Haemophilus influenzae	16 (9.4)	25 (13.6)	41 (11.5)

mMITT, microbiologically modified intent-to-treat; n, number of patients in subgroup; N, number of patients in treatment group

Ceftazidime and ceftazidime-avibactam MIC distributions of pathogens isolated at baseline (mMITT population)

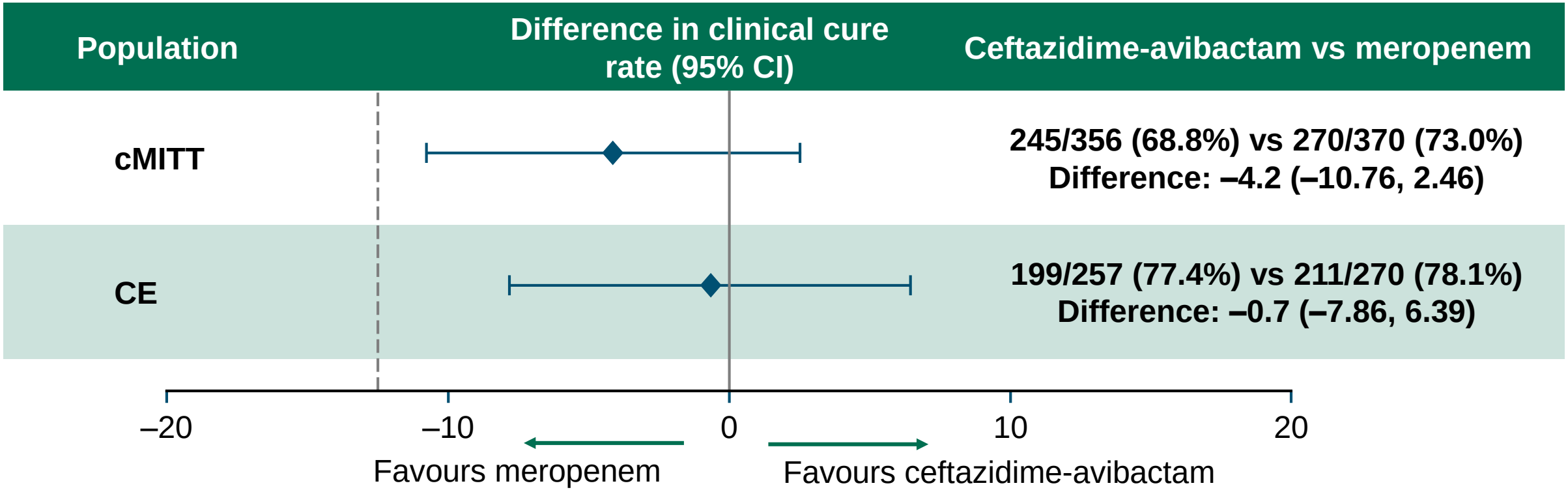




Vertical line between MIC 8 and 16 mg/L represents the EUCAST/FDA susceptible breakpoint for ceftazidime-avibactam against Enterobacteriaceae and *Pseudomonas aeruginosa* (i.e. susceptible ≤8 mg/L; resistant >8 mg/L). EUCAST breakpoints for ceftazidime alone against Enterobacteriaceae: susceptible ≤1 mg/L; resistant >4 mg/L, and against *P. aeruginosa*: susceptible ≤8 mg/L; resistant >8 mg/L

MIC, minimum-inhibitory concentration; mMITT, microbiologically modified intent-to-treat; n, number of isolates in subgroup

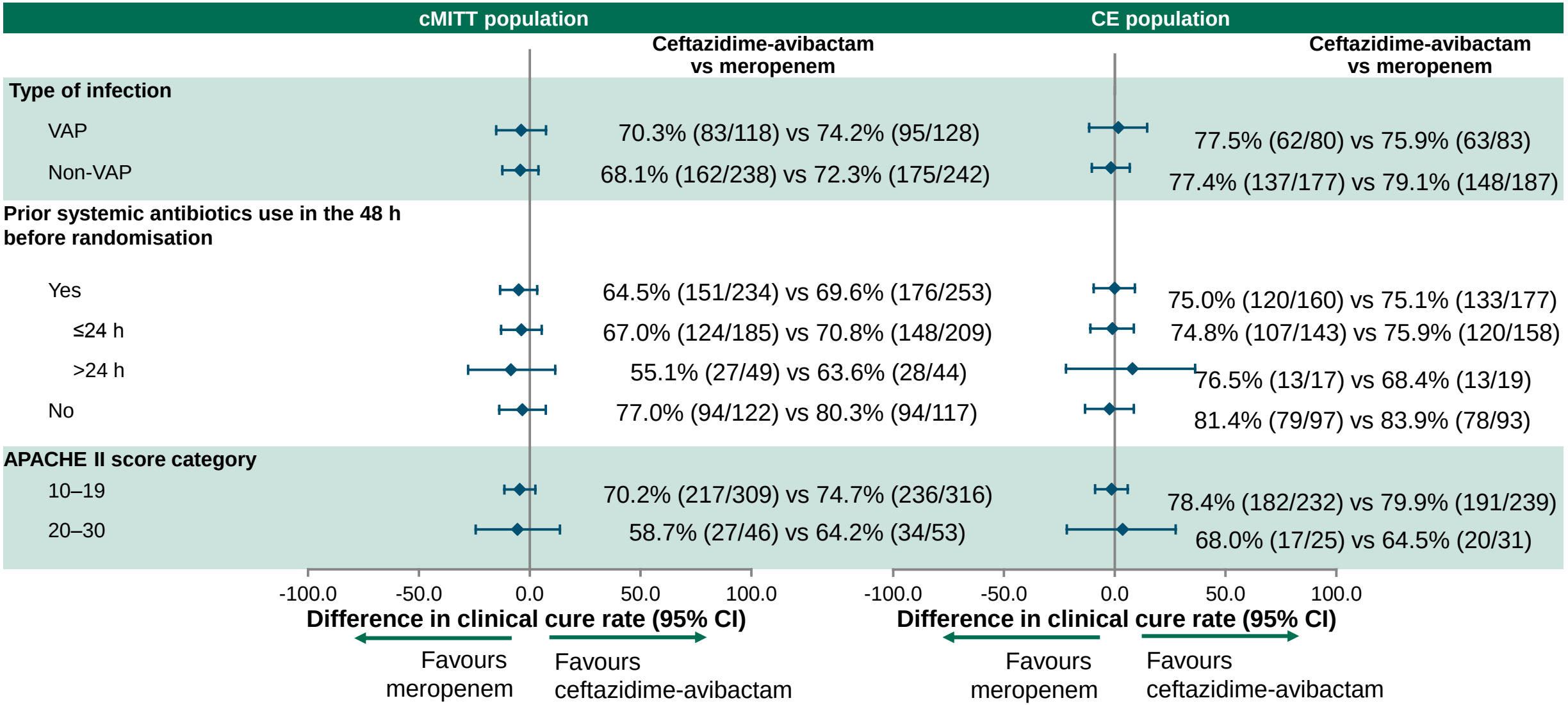
Primary efficacy results
Clinical cure rates at TOC visit (cMITT and CE populations)



- **The primary endpoint was met:**
  - ceftazidime-avibactam was non-inferior to meropenem in both co-primary populations

CE, clinically evaluable; CI, confidence interval; cMITT, clinically modified intent-to-treat; TOC, test-of-cure

Subgroup analysis
Clinical cure rates at TOC visit (cMITT and CE populations)



CE, clinically evaluable at TOC visit; CI, confidence interval; cMITT, clinically modified intent-to-treat; TOC, test-of-cure

Per-pathogen clinical cure rate at TOC according to Gram-negative pathogen isolated (CE population)

	Patients, m/n (%)		
	Ceftazidime-avibactam (N=257)	Meropenem (N=270)	Difference (95% CI)
Enterobacteriaceae			
Klebsiella pneumoniae	31/37 (83.8)	39/49 (79.6)	4.2 (–13.49, 20.50)
Enterobacter cloacae	20/21 (95.2)	7/11 (63.6)	31.6 (4.79, 61.30)
Escherichia coli	8/11 (72.7)	14/18 (77.8)	–5.1 (–39.26, 25.79)
Serratia marcescens	10/12 (83.3)	8/8 (100)	–16.7 (–45.58, 19.48)
Proteus mirabilis	11/11 (100)	7/8 (87.5)	12.5 (–16.54, 48.07)
Enterobacter aerogenes	4/6 (66.7)	2/5 (40.0)	26.7 (–31.92, 70.73)
Gram-negative pathogens other than Enterobacteriaceae			
Pseudomonas aeruginosa	27/42 (64.3)	27/35 (77.1)	–12.9 (–32.25, 8.01)
Haemophilus influenzae	10/11 (90.9)	11/13 (84.6)	6.3 (–26.19, 36.09)

CE, clinically evaluable; CI, confidence interval; m, number of patients with clinical cure; n, number of patients in subgroup; N, number of patients in treatment group; TOC, test-of-cure

Per-pathogen favourable microbiological response rate at TOC according to Gram-negative pathogen isolated (eME population)

	Patients, m/n (%)		
	Ceftazidime-avibactam (N=125)	Meropenem (N=131)	Difference (95% CI)
Enterobacteriaceae			
Klebsiella pneumoniae	29/37 (78.4)	39/49 (79.6)	–1.2 (–19.60, 15.96)
Enterobacter cloacae	18/21 (85.7)	7/11 (63.6)	22.1 (–8.07, 53.69)
Escherichia coli	10/11 (90.9)	16/18 (88.9)	2.0 (–29.11, 26.44)
Serratia marcescens	9/12 (75.0)	5/8 (62.5)	12.5 (–27.47, 51.82)
Proteus mirabilis	9/11 (81.8)	6/8 (75.0)	6.8 (–30.73, 46.51)
Enterobacter aerogenes	5/6 (83.3)	3/5 (60.0)	23.3 (–31.30, 68.33)
Gram-negative pathogens other than Enterobacteriaceae			
Pseudomonas aeruginosa	18/42 (42.9)	14/35 (40.0)	2.9 (–19.13, 24.32)
Haemophilus influenzae	11/11 (100)	12/13 (92.3)	7.7 (–20.08, 34.00)

CI, confidence interval; eME, extended microbiologically evaluable; m, number of patients with favourable microbiological response; n, number of patients in subgroup; N, number of patients in treatment group; TOC, test-of-cure

Per-patient favourable microbiological response rates at TOC in patients with ceftazidime-non-susceptible Gram-negative pathogens isolated at baseline

Analysis population	Patients, n/N (%)		
	Ceftazidime-avibactam	Meropenem	Difference (95% CI)
mMITT	27/46 (58.7)	27/54 (50.0)	8.7 (–10.91, 27.56)
eME	23/37 (62.2)	21/41 (51.2)	10.9 (–11.14, 31.90)
ME	21/30 (70.0)	18/32 (56.3)	13.8 (–10.49, 36.38)

Ceftazidime-non-susceptible includes both the CLSI-breakpoint-defined categories for ceftazidime-non-susceptible and intermediate pathogens, i.e., MIC ≥8 mg/L for Enterobacteriaceae and ≥16 mg/L for *Pseudomonas aeruginosa*

CI, confidence interval; CLSI, Clinical Laboratory Standards Institute; eME, extended microbiologically evaluable; ME, microbiologically evaluable; MIC, minimum inhibitory concentration; n, number of patients in subgroup; N, number of patients in treatment group; mMITT, microbiologically modified intent-to-treat; TOC; test-of-cure

All-cause mortality (cMITT and CE populations)

	Patients, n/N (%)		
	Ceftazidime-avibactam	Meropenem	Difference, % (95% CI)
cMITT population			
TOC	29/356 (8.1)	25/370 (6.8)	1.4 (–2.48, 5.35)
FPFU (Day 28)	30/356 (8.4)	27/370 (7.3)	1.1 (–2.84, 5.18)
CE population			
TOC	11/257 (4.3)	8/270 (3.0)	1.3 (–2.01, 4.89)
FPFU (Day 28)	12/257 (4.7)	9/270 (3.3)	1.3 (–2.14, 5.04)

CE, clinically evaluable at TOC; CI, confidence interval; cMITT, clinically modified intent-to-treat; FPFU, final protocol follow-up; n, number of patients in subgroup; N, number of patients in treatment group; TOC, test-of-cure

Adverse events up to final follow-up visit (safety population)

Patients, n (%)†	Ceftazidime-avibactam (N=405)	Meropenem (N=403)
Any AE	302 (74.6)	299 (74.2)
Any AE with outcome of death‡	26 (6.4)	23 (5.7)
Any serious AE	75 (18.5)	54 (13.4)
Any AE leading to discontinuation of study drug	16 (4.0)	11 (2.7)
Any AE of severe intensity	66 (16.3)	51 (12.7)
AEs in ≥3% of patients in either treatment group (MedDRA preferred terms)		
Diarrhoea	61 (15.1)	62 (15.4)
Hypokalaemia	43 (10.6)	33 (8.2)
Anaemia	25 (6.2)	18 (4.5)
Constipation	25 (6.2)	31 (7.7)
Vomiting	23 (5.7)	22 (5.5)
Peripheral oedema	17 (4.2)	15 (3.7)
Alanine aminotransferase increased	16 (4.0)	19 (4.7)
Aspartate aminotransferase increased	16 (4.0)	17 (4.2)
Hypertension	14 (3.5)	15 (3.7)
Nausea	13 (3.2)	7 (1.7)
Urinary tract infection	11 (2.7)	15 (3.7)
Pyrexia	10 (2.5)	13 (3.2)
Pneumonia	10 (2.5)	12 (3.0)
Rash	8 (2.0)	13 (3.2)

†Patients with multiple AEs in the same category were counted only once in that category. Patients with AEs in more than one category were counted once in each of those categories. ‡Excludes patients who died due to disease progression

AE, adverse event; MedDRA, medical dictionary for regulatory activities; n, number of patients in subgroup; N, number of patients in treatment group

Summary and conclusions

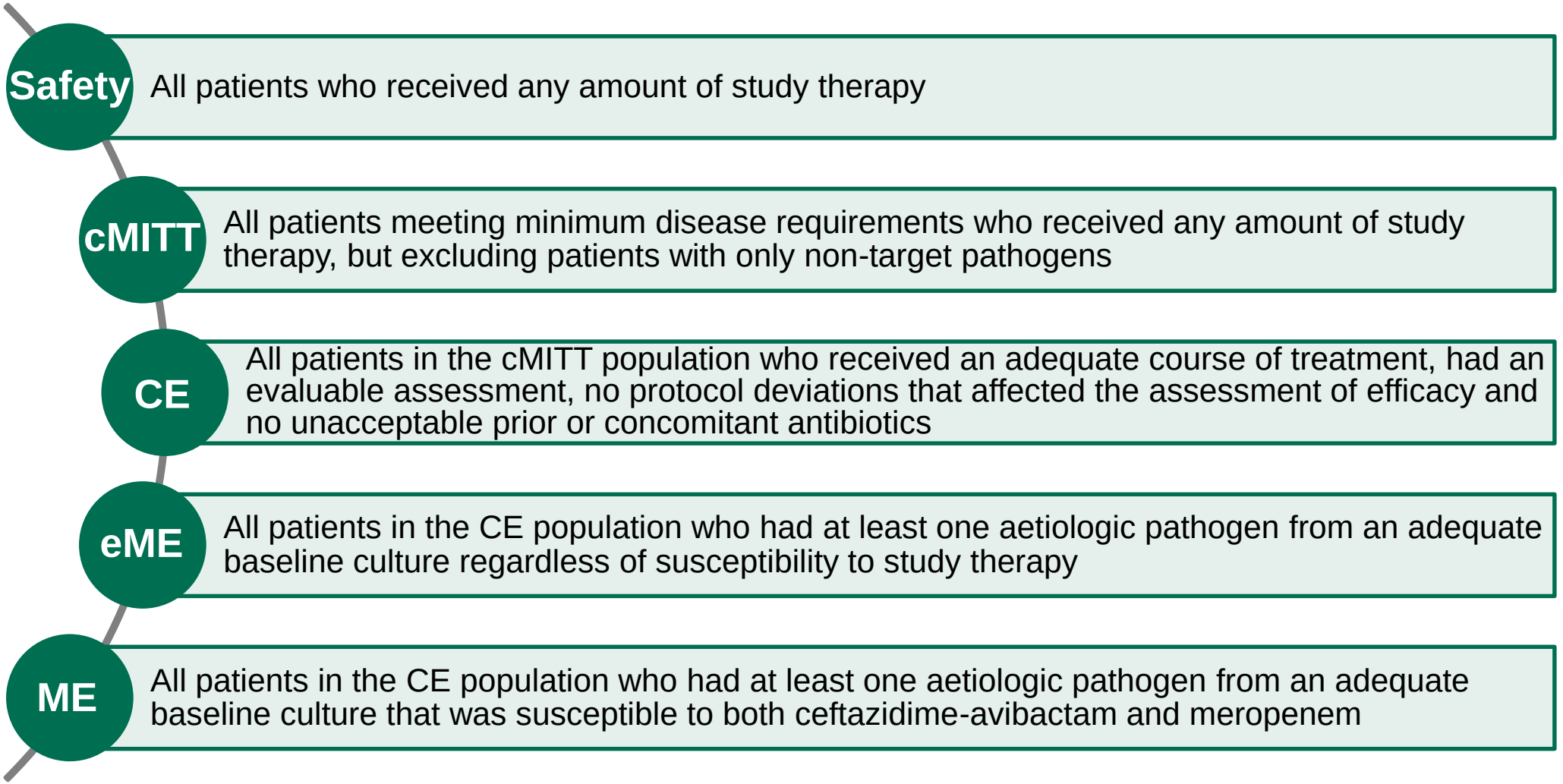
- REPROVE is the first Phase 3 study to assess the efficacy and safety of ceftazidime-avibactam in the treatment of adults with NP
- Ceftazidime-avibactam was effective in the treatment of NP, including VAP, as demonstrated by non-inferiority to meropenem in both co-primary cMITT and CE populations
  - All-cause mortality rates were similar in the two treatment groups
- Safety and tolerability findings were consistent with the known profile for ceftazidime-avibactam
- Results are consistent with other ceftazidime-avibactam Phase 3 trials in patients with cIAI[1–3] and cUTI,[1,4] supporting a role for ceftazidime-avibactam as an alternative treatment option for serious Gram-negative infections, including NP

CE, clinically evaluable; cIAI, complicated intra-abdominal infection; cMITT, clinically modified intent-to-treat; cUTI, complicated urinary tract infection; NP, nosocomial pneumonia; VAP, ventilator-associated pneumonia from an inpatient acute or chronic care facility

1. Carmeli Y et al. *Lancet Infect Dis*. 2016;16:661–673
2. Mazuski JE et al. *Clin Infect Dis*. 2016;62:1380–1389
3. Qin X et al. *Int J Antimicrob Agents.* 2017; (Epub ahead of print)
4. Wagenlehner FM et al. *Clin Infect Dis*. 2016;63:754–762

Backup Slides

Analysis populations

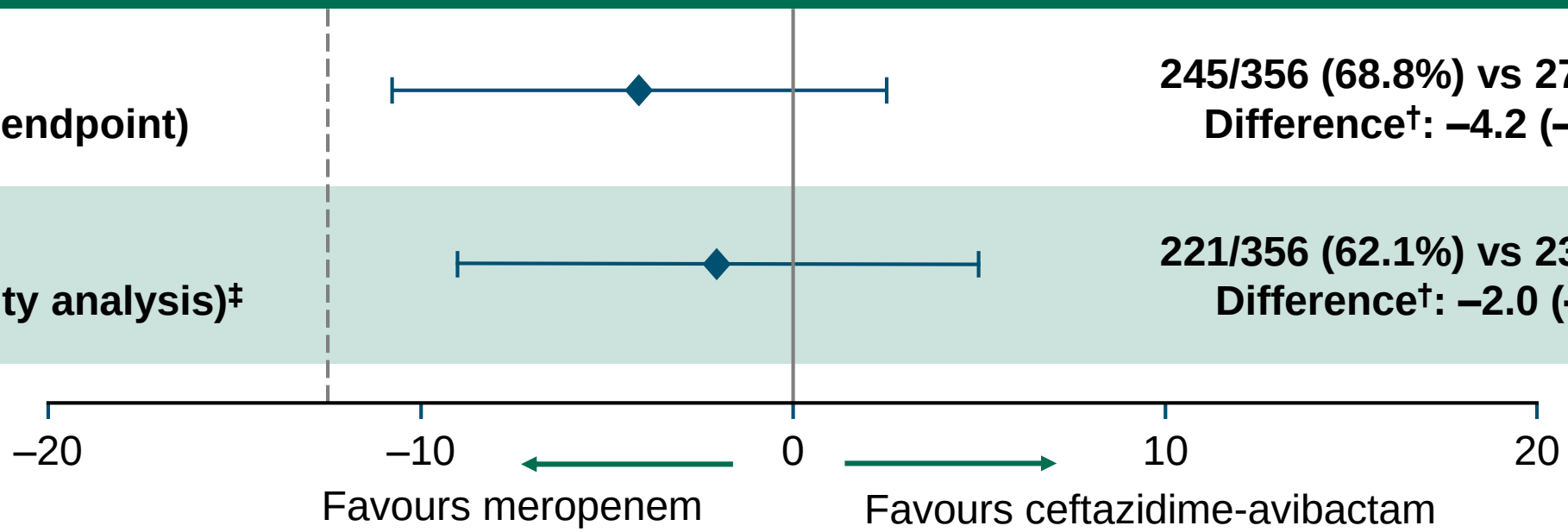


Patients with moderate/severe renal impairment enrolled prior to protocol amendment to the new dosing regimen were excluded from all analysis populations

CE, clinically evaluable; cMITT, clinically modified intent-to-treat; eME, extended microbiologically evaluable; ME, microbiologically evaluable

Sensitivity analysis: Clinical cure rates at TOC visit in patients receiving additional potentially effective antibiotics before TOC (cMITT)

Population	Difference in clinical cure rate (95% CI)	Ceftazidime-avibactam vs meropenem
cMITT (primary endpoint)		**245/356 (68.8%) vs 270/370 (73.0%) Difference†: –4.2 (–10.76, 2.46)**
cMITT (sensitivity analysis)‡		**221/356 (62.1%) vs 237/370 (64.1%) Difference†: –2.0 (–8.99, 5.04)**



- In the sensitivity analysis adjusted for patients receiving potentially effective concomitant antibiotics, there was a 2.2% shift in the difference between treatments
  - 24/245 (9.8%) ceftazidime-avibactam and 33/270 (12.2%) meropenem-treated cured patients received potentially effective concomitant antibiotics

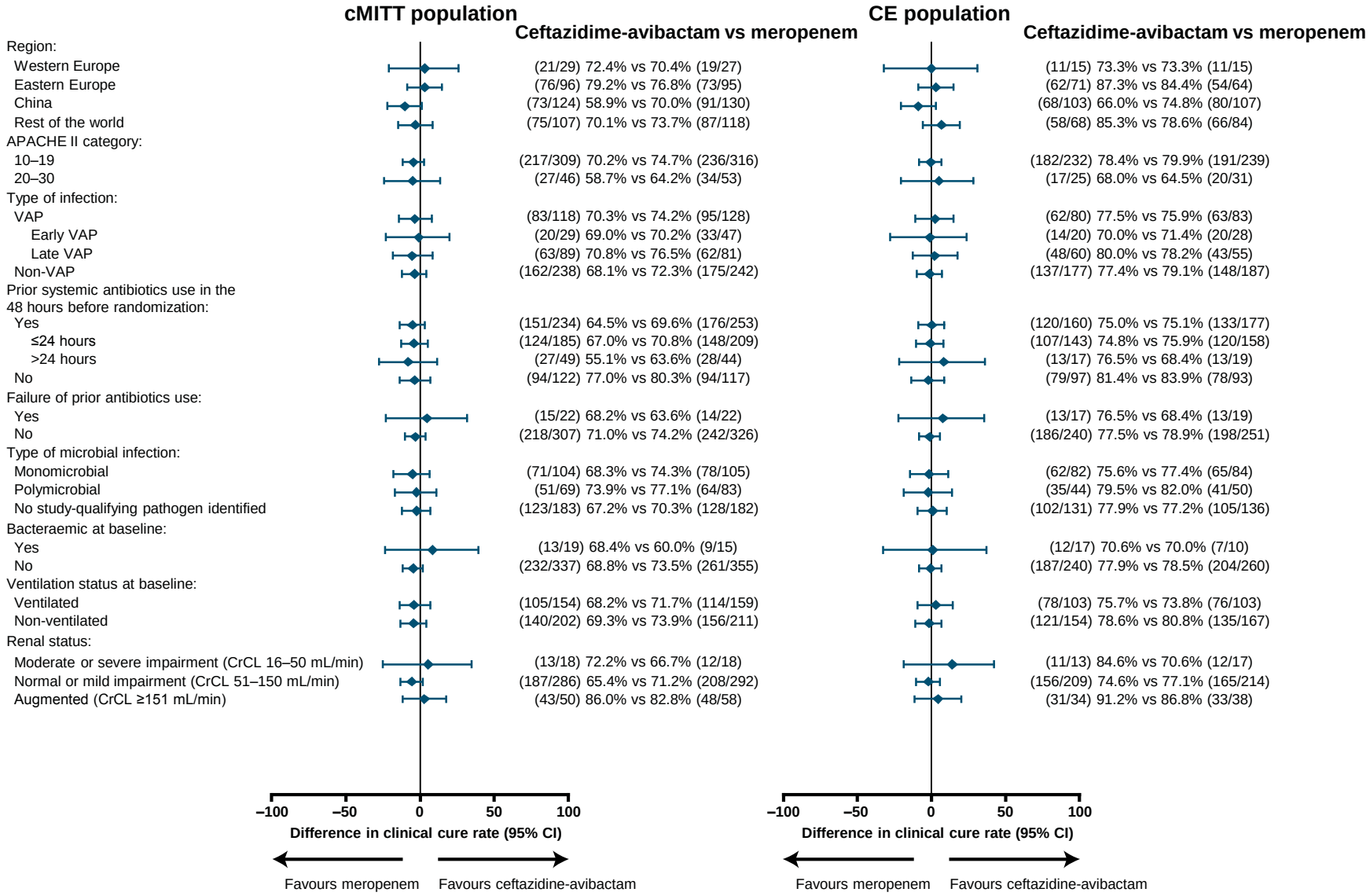
†Difference ceftazidime-avibactam minus meropenem (95% confidence interval); ‡Patients who received concomitant therapy before TOC with potential activity against any of the baseline pathogens were counted as indeterminate
CE, clinically evaluable; CI, confidence interval; cMITT, clinically modified intent-to-treat; TOC, test-of-cure

Pathogens identified at baseline with a combined frequency of ≥10 (mMITT population)

	Patients, n (%)		
	Ceftazidime-avibactam (N=171)	Meropenem (N=184)	Total (N=355)
Enterobacteriaceae	121 (70.8)	138 (75.0)	259 (73.0)
Enterobacter aerogenes	8 (4.7)	8 (4.3)	16 (4.5)
Enterobacter cloacae	26 (15.2)	22 (12.0)	48 (13.5)
Escherichia coli	17 (9.9)	20 (10.9)	37 (10.4)
Klebsiella pneumoniae	59 (34.5)	71 (38.6)	130 (36.6)
Proteus mirabilis	14 (8.2)	12 (6.5)	26 (7.3)
Serratia marcescens	15 (8.8)	13 (7.1)	28 (7.9)
Gram-negative pathogens other than Enterobacteriaceae	79 (46.2)	80 (43.5)	159 (44.8)
Pseudomonas aeruginosa	58 (33.9)	47 (25.5)	105 (29.6)
Haemophilus influenzae	16 (9.4)	25 (13.6)	41 (11.5)
Gram-positive aerobes	25 (14.6)	41 (22.3)	66 (18.6)
Staphylococcus aureus	24 (14.0)	34 (18.5)	58 (16.3)

mMITT, microbiologically modified intent-to-treat; n, number of patients in subgroup; N, number of patients in treatment group.

Subgroup analysis of clinical cure rates at TOC



Per-pathogen clinical cure rate at TOC by ceftazidime-susceptibility of baseline isolates (CE population)

	Ceftazidime-Susceptible			Ceftazidime-Non-susceptible[†]		
	Ceftazidime-avibactam	Meropenem	Difference, % (95% CI)	Ceftazidime-avibactam	Meropenem	Difference, % (95% CI)
All	63/84 (75.0)	69/88 (78.4)	–3.4 (–16.2, 9.3)	29/36 (80.6)	32/41 (78.0)	2.5 (–16.4, 20.7)
Enterobacteriaceae	44/58 (75.9)	50/62 (80.6)	–4.8 (–19.8, 10.1)	23/27 (85.2)	22/30 (73.3)	11.9 (–10.2, 32.8)
Enterobacter aerogenes	1/2 (50.0)	2/5 (40.0)	10.0 (–56.3, 70.3)	3/4 (75.0)	0/0 (N/A)	N/A
Enterobacter cloacae	12/13 (92.3)	4/5 (80.0)	12.3 (–20.3, 57.6)	5/5 (100)	3/5 (60.0)	40.0 (–16.3, 78.2)
Escherichia coli	4/6 (66.7)	10/12 (83.3)	–16.7 (–58.7, 23.0)	4/5 (80)	3/4 (75.0)	5.0 (–49.6, 59.8)
Klebsiella pneumoniae	18/22 (81.8)	21/25 (84.0)	–2.2 (–25.6, 20.3)	12/14 (85.7)	17/22 (77.3)	8.4 (–21.3, 33.2)
Other Gram-negative pathogens	28/40 (70.0)	26/34 (76.5)	–6.5 (–26.2, 14.3)	6/9 (66.7)	12/13 (92.3)	–25.6 (–59.6, 8.5)
Pseudomonas aeruginosa	18/28 (64.3)	14/18 (77.8)	–13.5 (–37.7, 14.8)	6/9 (66.7)	12/13 (92.3)	–25.6 (–59.6, 8.5)

[†]Includes both the Clinical and Laboratory Standards Institute-breakpoint-defined ceftazidime-non-susceptible and ceftazidime-intermediate categories
Table includes pathogens isolated in ≥5 patients in both treatment arms.

CE, clinically evaluable; CI, confidence interval; N/A, not applicable; TOC, test-of-cure

Emergent infections at TOC (eME population)

	Patients, n (%)	
	Ceftazidime-avibactam (N=125)	Meropenem (N=131)
Patients with a superinfection, n (%)	0 (0.0)	3 (2.3)
Pseudomonas aeruginosa	0 (0.0)	3 (2.3)
Patients with a new infection, n (%)	5 (4.0)	6 (4.6)
Burkholderia cepacia complex	0 (0.0)	1 (0.8)
Enterobacter cloacae	0 (0.0)	4 (3.1)
Enterobacter faecalis	0 (0.0)	1 (0.8)
Klebsiella pneumoniae	3 (2.4)	1 (0.8)
Proteus mirabilis	0 (0.0)	1 (0.8)
Providencia spp.	1 (0.8)	0 (0.0)
Pseudomonas aeruginosa	0 (0.0)	3 (2.3)
Pseudomonas luteola	1 (0.8)	0 (0.0)
Staphylococcus aureus	2 (1.6)	1 (0.8)

eME, extended microbiologically evaluable; n, number of patients in subgroup; N, number of patients in treatment group; TOC, test-of-cure