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Efficacy and safety of ceftazidime-avibactam versus meropenem in patients with nosocomial pneumonia, including ventilator-associated pneumonia: Results from REPROVE, a randomised, double-blind, multicentre phase 3 non-inferiority trial

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Running header: REPROVE: ceftazidime-avibactam for NP

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Research in context

Evidence before this study

We searched PubMed with the search terms “randomized OR randomised” AND “ceftazidime AND avibactam” OR “ceftazidime AND avibactam AND Clinical Trial[ptyp]” for articles published up to 18 May 2017. These searches identified two phase 2 studies and four phase 3 studies that evaluated the efficacy and safety of ceftazidime-avibactam (± metronidazole as applicable for anaerobic coverage) in patients with serious Gram-negative infections, including complicated intra-abdominal infections (cIAI; NXL104/2002 [NCT00752219], RECLAIM 1 and 2 [NCT01499290], RECLAIM 3 [NCT01726023]), complicated urinary tract infections (cUTI; NXL104/2001 [NCT00690378], RECAPTURE 1 and 2 [NCT01595438 and NCT01599806]), or cIAI/cUTI caused by ceftazidime-non susceptible Gram-negative pathogens (REPRISE [NCT01644643]). Across these studies, ceftazidime-avibactam demonstrated similar efficacy and safety compared with predominantly carbapenem comparators. These clinical data, and a phase 1 study (NCT01395420) showing that both ceftazidime and avibactam penetrate dose-proportionally into epithelial lining fluid (ELF), supported the clinical investigation of ceftazidime-avibactam in nosocomial pneumonia (NP), including ventilator-associated pneumonia (VAP).

Added value of this study

The Phase 3 REPROVE trial is the first clinical study to evaluate ceftazidime-avibactam in adults with NP (including VAP). The patient population and pathogens isolated were consistent with those commonly observed in patients with NP. The results demonstrated that ceftazidime-avibactam was non-inferior to meropenem, a standard therapy for NP, in this setting. Efficacy of ceftazidime-avibactam was similar against infections caused by ceftazidime-susceptible and ceftazidime-resistant pathogens. The safety profile of

ceftazidime-avibactam was consistent with that previously observed with ceftazidime alone and with the known profile of ceftazidime-avibactam in cIAI and cUTI.

Implications of all the available evidence

The pathogens isolated in this study are consistent with those commonly observed in patients with NP, including VAP. NP is among the most serious bacterial infections, and β-lactams are frequently the cornerstone of antimicrobial therapy in this setting. These results add to the evidence base demonstrating the efficacy and safety of ceftazidime-avibactam in treating infections caused by Gram-negative pathogens, including those considered non-susceptible to ceftazidime. These findings collectively support a role for ceftazidime-avibactam as a potential alternative to carbapenems in patients with serious infections caused by Gram-negative pathogens, including NP/VAP.

Summary

Background: Nosocomial pneumonia (NP) is commonly associated with antimicrobial-resistant Gram-negative pathogens. The efficacy and safety of ceftazidime-avibactam in patients with NP, including ventilator-associated pneumonia (VAP), were evaluated in a multinational phase 3 double-blind, non-inferiority trial (REPROVE).

Methods: Adults with NP including VAP (enrolled at 136 centres in 23 countries) were randomised (1:1) to ceftazidime-avibactam 2000-500 mg (2-h intravenous [iv] infusions every 8 hours [q8h]) or meropenem 1000 mg (30-min iv infusions q8h) for 7–14 days (regimens adjusted for renal function). Computer-generated randomisation codes were stratified by infection type (VAP or non-VAP) and geographic region using a block size of 4. The primary endpoint was clinical cure at the test-of-cure visit (21–25 days post-randomisation). Non-inferiority was concluded if the lower limit of the 2-sided 95% CI for the treatment difference was greater than –12·5% in the co-primary clinically modified intention-to-treat (cMITT) and clinically evaluable (CE) populations. This trial is registered with ClinicalTrials.gov (NCT01808092) and EudraCT (2012-004006-96).

Findings: Between April 2013 and December 2015, 879 patients were randomised; 808, 726 and 527, respectively, were included in the safety, cMITT, and CE populations. Predominant Gram-negative baseline pathogens (microbiologically modified intent-to-treat population; n=355) were *Klebsiella pneumoniae* (36·6%) and *Pseudomonas aeruginosa* (29·6%); 28·2% were ceftazidime-non-susceptible. Clinical cure rates (ceftazidime-avibactam versus meropenem) were 245/356 (68·8%) versus 270/370 (73·0%; difference [95% CI], –4·2% [–10·76, 2·46]) and 199/257 (77·4%) versus 211/270 (78·1%; difference [95% CI], –0·7% [–7·86, 6·39]) in the cMITT and CE populations, respectively. Adverse events occurred in 302/405 (74·6%) versus 299/403 (74·2%) patients in the safety population; most were mild/moderate in intensity and unrelated to study treatment. Serious adverse events (SAEs)

and treatment-related SAEs occurred in 75/405 (18·5%) versus 54/403 (13·4%) and 4/405 (1·0%) versus 0/403 (0·0%) patients, respectively.

Interpretation: Ceftazidime-avibactam was non-inferior to meropenem in the treatment of NP.

Funding: AstraZeneca.

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Introduction

Nosocomial pneumonia (NP), also referred to as hospital-acquired pneumonia, remains among the most common hospital-acquired infections,[1] and is associated with high mortality and healthcare expenditure.[2,3] Gram-negative pathogens, particularly *Pseudomonas aeruginosa* and *Enterobacteriaceae*, predominate in NP.[4] These pathogens often harbour multiple antimicrobial resistance mechanisms (particularly extended-spectrum β-lactamases [ESBLs], and increasingly, carbapenemases).[5,6] Treatment options for ESBLs, and particularly carbapenemases, are extremely limited.[7] Mortality risk and costs of treatment are increased in patients receiving inappropriate or delayed appropriate antibiotics.[8,9]

Ceftazidime-avibactam combines the anti-pseudomonal cephalosporin ceftazidime, and the novel non-β-lactam β-lactamase inhibitor avibactam, which extends the *in vitro* activity of ceftazidime to include Gram-negative organisms producing Ambler class A (eg, ESBLs, *Klebsiella pneumoniae* carbapenemase), class C (AmpC) and some class D (OXA-48) β-lactamases.[10-12] This microbiological profile covers most carbapenem-non-susceptible *Enterobacteriaceae* and multidrug resistant (MDR) *P. aeruginosa* (excluding metallo-β-lactamase producers), and makes the combination a potential alternative to carbapenems for the treatment of serious Gram-negative infections, including those caused by some carbapenemase-producing bacteria.[13-15]

This paper reports the primary data from the international, randomised phase 3 REPROVE trial (NCT01808092) evaluating the efficacy and safety of ceftazidime-avibactam versus meropenem in the treatment of NP, including ventilator-associated pneumonia (VAP).

Methods

Study design

REPROVE was a prospective, international, multicentre, parallel-group, randomised, double-blind, double-dummy, Phase 3 non-inferiority trial in patients with NP, including VAP. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki, and are consistent with the ICH Harmonised Tripartite Guideline E6(R1) for Good Clinical Practice, and applicable regulatory requirements. All participants provided written informed consent. The study protocol and amendments (available at www.astrazenecaclinicaltrials.com) were approved by local ethics committees and/or institutional review boards.

Participants

Hospitalised adult patients (aged 18–90 years) with NP were eligible for inclusion (see appendix pp 4–5). NP was defined as pneumonia with an onset ≥48 hours after admission or <7 days after discharge from an inpatient care facility. VAP was defined as parenchymal lung infection with an onset ≥48 hours after endotracheal intubation and mechanical ventilation. The term 'non-VAP' was used to identify patients with NP who did not have VAP. Diagnosis of NP was based on clinical assessment, including new/worsening infiltrate on chest X-ray within 48 hours of randomisation, and at least one systemic and at least two respiratory signs or symptoms of pneumonia. A respiratory specimen for Gram stain and culture was required within 48 hours prior to randomisation. Key exclusion criteria included: infections caused by any Gram-positive pathogens only or other pathogens not expected to respond to ceftazidime-avibactam and/or meropenem (polymicrobial infections were permitted if they included a target Gram-negative pathogen); patients expected to require >14 days' treatment (appendix

pp 5–6). Patients without baseline culture data at the time of randomisation could receive study therapy empirically.

Randomisation and masking

Eligible patients were randomised 1:1 using an interactive voice/web response system to receive either ceftazidime-avibactam or meropenem. Patients were stratified by infection type (VAP and non-VAP) and geographic region (Western Europe, Eastern Europe, China, rest of the world) at randomisation. Randomisation codes were computer-generated by AstraZeneca using the AstraZeneca Global Randomization System with a block size of 4. To maintain blinding of study treatments, patients received double-dummy matching placebos (ceftazidime-avibactam plus meropenem placebo or ceftazidime-avibactam placebo plus meropenem). Patients, investigators and all study centre personnel remained blinded to study treatment, except for an unblinded pharmacist/designee, who was responsible for maintaining accountability and preparing blinded study treatment.

Procedures

Patients assigned to ceftazidime-avibactam (AstraZeneca AB; Södertälje, Sweden) received a fixed-dose combination of ceftazidime-avibactam (2000 mg-500 mg) by 2-hour intravenous infusion every 8 hours. Patients assigned to the comparator arm received meropenem (ACS Dobfar SpA, Milano, Italy) 1000 mg by 30-min intravenous infusion every 8 hours. Dosages of both treatments were adjusted for patients with moderate or severe renal impairment (CrCL 16–50 mL/min); following a protocol amendment, ceftazidime-avibactam dosage adjustments in patients with renal impairment were modified (see appendix pp 7–8), and the statistical analysis plan was updated to exclude patients with moderate/severe renal impairment at baseline who were randomised before the protocol amendment ($MSRIB_{orig}$) from the main analyses to ensure the main efficacy and safety results were reflective of the

approved ceftazidime-avibactam dosage regimens; data for $MSRIB_{orig}$ patients were summarised separately. Study treatment was discontinued after a minimum of 7 days (21 doses) and maximum of 14 days (42 doses).

Patients awaiting identification of aetiologic pathogen(s) and/or susceptibility results from the baseline culture at randomisation received open-label linezolid or vancomycin for Gram-positive pathogen coverage. Open-label amikacin (or other aminoglycoside) for additional Gram-negative coverage was given to all patients awaiting baseline culture results for a minimum of 48–72 hours (extended depending on culture/susceptibility results) unless contraindicated or considered at low risk of MDR Gram-negative pathogens.

Respiratory specimens for Gram stain and culture were obtained via endotracheal aspirate (ventilated patients), expectorated or induced sputum (non-ventilated patients), bronchoalveolar lavage (BAL), mini-BAL or protected brush specimen at baseline, end of treatment (EOT, within 24 hours after the last dose of study treatment) and at the test-of-cure (TOC) visit (21–25 days after randomisation). Two sets of blood samples were collected from different sites for aerobic and anaerobic incubation within 24 hours prior to randomisation and as clinically indicated. If a previous culture was positive, repeat samples were collected at least every three days until clearance of bacteraemia was documented.

Local laboratories performed pathogen identification and susceptibility testing for all respiratory and blood isolates using Clinical Laboratory Standards Institute (CLSI) disk diffusion methods[16] against ceftazidime-avibactam, meropenem and ceftazidime. Isolates identified by local laboratories and considered pathogens by investigators were sent to a central reference laboratory for confirmation of identification and susceptibility testing.

Patients had daily assessments from Days 2–14, as well as at an EOT visit within 24 hours after completion of the last infusion of study treatment, a TOC visit 21–25 days from

randomisation, and a final protocol follow-up (FPFU) visit 28–32 days from randomisation. The schedule of procedures and assessments is shown in the appendix (pp 9–12).

Clinical outcomes at EOT and TOC (appendix pp 13–14) were classified by investigators as cure (defined at TOC as resolution of all signs and symptoms of pneumonia such that no antibacterial therapy for NP was taken between EOT and TOC inclusive), indeterminate or failure. Per-pathogen and per-patient microbiological responses (appendix p 15) were assessed as favourable (eradication or presumed eradication); unfavourable (persistence, persistence with increasing minimum inhibitory concentration [MIC], or presumed persistence); or indeterminate (per-pathogen responses only).

Outcomes

The primary endpoint was the proportion of patients clinically cured at the TOC visit in co-primary clinically modified intention-to-treat (cMITT) and clinically evaluable (CE) populations (see appendix pp 16–17 for definitions of analysis populations). Key secondary endpoints included: clinical response at EOT in the cMITT and CE populations and clinical response at EOT and TOC in the microbiologically modified intention-to-treat (mMITT), extended microbiologically evaluable (eME) and microbiologically evaluable (ME) populations; all cause-mortality at TOC and at Day 28 in the CE, cMITT and mMITT populations; clinical response at EOT and TOC in patients with ceftazidime-non-susceptible pathogens in the CE, cMITT and ME populations; per-patient and per-pathogen microbiological responses at EOT and TOC in the mMITT, ME and eME populations (see appendix p 18–20 for secondary and exploratory analyses). Safety evaluations included monitoring of adverse events (AEs), clinical laboratory assessments, electrocardiograms, and mortality. AEs were summarised for events occurring from the first dose of study treatment to the FPFU visit. AEs occurring from the time when informed consent was obtained to the

first dose of study treatment were recorded, but are not reported here.

Statistical analyses

The study was sized to ensure there was sufficient power (at least 85%) for the co-primary hypothesis tests against a 12·5% non-inferiority margin, in line with EMA guidance.[17] It was expected that the underlying clinical cure rate at TOC would be approximately 78% in the CE population and 70% in the cMITT population, and that 50% and 85% of patients, respectively, would be eligible for inclusion in the CE and cMITT populations.

The number of patients to be randomised for the primary analysis for non-inferiority was approximately 790 patients, to obtain approximately 394 and 670 evaluable patients in the CE and cMITT populations, respectively. The estimated power with these numbers of evaluable patients (with the above described cure rate assumptions, and with one-sided α=2·5%) was calculated using nQuery® Version 7 (Statistical Solutions Ltd Cork, Ireland) using the Newcombe-Wilson score method (uncorrected).[18] VAP patients were recruited in parallel with non-VAP patients (ensuring ≥25% with VAP in the total study population).

The primary endpoint was clinical response at the TOC visit. Statistical analyses and the non-inferiority assessment were based on the difference in clinical cure rates between treatment groups. The primary efficacy outcome was analysed in the co-primary cMITT and CE populations (see appendix pp 16–17). The cMITT population comprised patients who met minimum disease criteria (based on inclusion criteria 4 to 7; see appendix pp 4–5) with ≥1 eligible Gram-negative pathogen, or those without any identifiable pathogen; patients with only non-target pathogens were excluded. The CE population comprised patients in the cMITT population who received an adequate course of treatment, had an evaluable clinical outcome within the assessment window, no protocol deviations that could affect the assessment of efficacy, and no unacceptable prior or concomitant antibiotics as defined in

exclusion criterion 3 (see appendix p 5). The safety population comprised all patients who received any amount of study therapy. An independent Data Monitoring Committee (IDMC) was established with an IDMC charter to ensure the safety of patients was not compromised.

Two-sided 95% confidence intervals (CI) for difference between treatments in proportion of patients with clinical cure were computed using the unstratified method of Miettinen and Nurminen.[19] For primary efficacy endpoints, non-inferiority of ceftazidime-avibactam to meropenem was considered demonstrated if lower limit of the two-sided 95% CI for the treatment difference (ceftazidime-avibactam minus meropenem) was greater than –12·5% and the p value was calculated for the corresponding one-sided non-inferiority hypothesis test. All statistical analyses were conducted using SAS version 9.1 or higher (SAS Institute Inc., Cary, NC, USA).

The following sensitivity analyses were performed for the primary efficacy variable: (1) adjusting for the effect of pre-specified stratification factors, type of infection (VAP or non-VAP), and geographical region; (2) considering patients who had received potentially effective concomitant antibiotics as having indeterminate clinical response at TOC; and (3) considering patients who died after TOC and up to FPFU visit as clinical failures at TOC. Pre-specified subgroup analyses evaluated impact of baseline patient and disease characteristics, including infection type (ie, non-VAP or VAP), study region, Acute Physiology and Chronic Health Evaluation II (APACHE II) category, prior systemic antibiotic use, presence of bacteraemia, and baseline renal function (including moderate/severe impairment [CrCL 16–50 mL/min] and augmented renal clearance [CrCL >151 mL/min]). Concomitant aminoglycoside use was evaluated as an exploratory *post hoc* subgroup analysis with patients assigned to categories of concomitant aminoglycoside exposure defined before study database lock by blinded review of post-baseline data. This

trial is registered with ClinicalTrials.gov (NCT01808092) and EudraCT (2012-004006-96).

Role of the funding source

The study sponsor was involved in study design, collection, analysis and interpretation of data, as well as data checking of information provided in the manuscript. Responsibility for opinions, conclusions, and data interpretation lies with the authors. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between April 2013 and December 2015, 879 patients were randomised; 62 patients with $MSRIB_{orig}$ (randomised before the protocol amendment) were excluded from the main analyses. Of the remaining 817 patients (enrolled at 136 centres in 23 countries; see appendix p 22 for patient recruitment by region and country), 409 and 408, respectively, were randomised to ceftazidime-avibactam and meropenem, and 405 and 403, respectively, received study treatment and comprised the safety population (figure 1). The cMITT and CE populations comprised, respectively, 356 and 257 patients in the ceftazidime-avibactam group and 370 and 270 patients in the meropenem group. Baseline and disease characteristics were generally well balanced (Table 1 and appendix pp 76–77). Main reason for exclusion from the cMITT population was isolation of only Gram-positive pathogens at baseline (46 [11·2%] and 31 [7·6%] patients in the ceftazidime-avibactam and meropenem groups, respectively). Overall, 131 patients (70[17·3%] and 61 [15·1%] respectively) had important protocol deviations leading to exclusion from the CE population; main reasons for exclusion (patients could be excluded for more than one reason) were receipt of concomitant non-protocolled antibiotics with potential impact on efficacy up to TOC (ceftazidime-avibactam 43 [10·5%], and meropenem 46 [11·3%]) and not having response of cure or failure at TOC (40 [9·8%] and 37 [9·1%] patients, respectively).

Of 817 randomised patients, 355 (43·5%) were included in the mMITT population. Baseline pathogens were similar between groups and as expected for patients with NP (appendix pp 23–26). Predominant Gram-negative pathogens isolated from respiratory site or blood were *K. pneumoniae* (n=130; 36·6%) and *P. aeruginosa* (n=105; 29·6%); 100 patients (28·2%) had ≥1 ceftazidime-non-susceptible Gram-negative pathogen, including 79 with *Enterobacteriaceae* and 25 with *P. aeruginosa*. *Staphylococcus aureus* (58 patients; 16·3%) was the only Gram-positive pathogen to be isolated in ≥10 patients. Ceftazidime and ceftazidime-avibactam MIC_{90} values were >32 mg/L and 0·5 mg/L, respectively, against 317 isolates of *Enterobacteriaceae*, and >32 mg/L and 8 mg/L, respectively, against 101 isolates of *P. aeruginosa* tested at the central laboratory. Among these isolates, 79/317 (24·9%) *Enterobacteriaceae* and 25/101 (24·8%) *P. aeruginosa* were non-susceptible to ceftazidime by CLSI criteria (MIC >4 mg/L for *Enterobacteriaceae* and MIC >8 mg/L for *P. aeruginosa*); thus, the ceftazidime-avibactam MIC distribution was left-shifted compared with that of ceftazidime alone (appendix p 84). Meropenem MIC_{90} values against the same isolates were 0·12 mg/L for *Enterobacteriaceae* and >8 mg/L for *P. aeruginosa*. Two isolates of *K. pneumoniae* and nine isolates of *P. aeruginosa* were resistant to ceftazidime-avibactam (MIC >8 mg/L), and six isolates of *Enterobacteriaceae* (five *K. pneumoniae* and one *Serratia marcescens*) and 31 isolates of *P. aeruginosa* were non-susceptible to meropenem (MIC >2 mg/L); among these isolates, two *K. pneumoniae* and eight *P. aeruginosa* were non-susceptible to both study drugs.

In the mMITT population, 203 (57·2%) patients had monomicrobial infections and 152 (42·8%) patients had polymicrobial infections; 66 (18·6%) patients had a mixture of Gram-negative and Gram-positive pathogens. These results were balanced between treatment groups and were generally similar for the extended-ME and the ME populations.

Non-inferiority of ceftazidime-avibactam to meropenem was demonstrated in both co-primary analysis populations (figure 2). Clinical cure rates at TOC were 245/356 (68·8%) for ceftazidime-avibactam and 270/370 (73·0%) for meropenem (difference [95% CI], –4·2 [–10·76, 2·46], p=0·007) in the cMITT population and 199/257 (77·4%) and 211/270 (78·1%), respectively (difference [95% CI], –0·7 [–7·86, 6·39], p<0·001) in the CE population. Similar results were observed in secondary analysis populations (appendix p85).

Sensitivity analyses that adjusted for stratification factors, or considered patients who died after TOC as clinical failures at TOC, were consistent with the primary analysis (data not shown). In the cMITT population, 24/356 (6·7%) ceftazidime-avibactam and 33/370 (8·9%) meropenem patients with clinical cure at TOC received potentially effective concomitant antibiotics. Sensitivity analysis adjusted for treatment with potentially effective concomitant antibiotics (cMITT population) accounted for a 2·2% shift in treatment difference, with clinical cure rates of 221/356 (62·1%) for ceftazidime-avibactam and 237/370 (64·1%) for meropenem (difference [95% CI], –2·0 [–8·99, 5·04]).

Subgroup analyses of the primary endpoint (figure 3) revealed no trends associated with various patient factors, including baseline renal status (including moderate/severe renal impairment and augmented renal function), prior systemic antibiotic use, type of infection (ie, non-VAP or VAP and early *vs* late VAP), and APACHE II score category. Cure rates were generally comparable across treatment groups and similar in both co-primary populations in each subgroup, including among non-VAP and VAP patients. Clinical cure rates were similar across treatment groups in the exploratory analysis of patients who received concomitant aminoglycosides (either ≤72 hours or >72 hours; appendix pp 274–28) and those who did not.

Per-pathogen clinical cure rates at TOC were generally comparable between treatment groups, with numerical differences containing wide CIs among individual bacterial species

(Table 2). Results of other secondary efficacy analyses are presented in the appendix (pp 296–72, 85). Per-pathogen clinical cure rates at TOC among patients infected with ceftazidime-non-susceptible pathogens (appendix pp 64–66) were comparable between groups (29/36 [80·6%] for ceftazidime-avibactam and 32/41 [78·0%] for meropenem; difference [95% CI] 2·5% [–16·42, 20·74]), and were similar to those in patients with only ceftazidime-susceptible pathogens isolated at baseline (63/84 [75·0%] *vs* 69/88 [78·4%]; difference [95% CI] –3·4% [–16·18, 9·30]).

Of the 62 $MSRIB_{orig}$ patients, 58 were included in the cMITT population and 44 were included in the CE population. Clinical cure rates at TOC among these patients were 18/30 (60·0%) *vs.* 16/28 (57·1%), and 15/21 (71·4%) *vs*. 13/23 (56·5%), respectively.

All-cause mortality rates were similar across treatment groups at both TOC and Day 28. In the cMITT population, mortality rates at TOC were 29/356 (8·1%) in the ceftazidime-avibactam group and 25/370 (6·8%) in the meropenem group (difference [95% CI], 1·4 [–2·48, 5·35]), and were 30/356 (8·4%) and 27/370 (7·3%), (difference [95% CI], 1·1 [–2·84, 5·18]), respectively at Day 28. Respective rates in the CE population were 11/257 (4·3%) and 8/270 (3·0%; difference [95% CI], 1·3 [–2·01, 4·89]) at TOC and 12/257 (4·7%) and 9/270 (3·3%; difference [95% CI], 1·3 [–2·14, 5·04]) at Day 28.

Per-patient favourable microbiological response rates at TOC were generally lower than clinical cure rates, but were similar across treatment groups and consistent across the mMITT (ceftazidime-avibactam 95/171 [55·6%] *vs* meropenem 118/184 [64·1%]; difference [95% CI], –8·6 [–18·65, 1·64]), eME (80/125 [64·0%] *vs* 89/131 [67·9%]; difference [95% CI], –3·9 [–15·49, 7·66]) and ME (70/107 [65·4%] *vs* 83/118 [70·3%]; difference [95% CI], –4·9 [–17·10, 7·28]) populations. In patients infected with ceftazidime-non-susceptible pathogens, per-patient favourable microbiological response rates were similar between groups at EOT

and TOC in the mMITT, eME and ME populations (appendix p 67), and were similar to the overall per-patient favourable microbiological response rates.

Favourable per-pathogen microbiological response (eradication or presumed eradication) rates at TOC were similar between groups, with numerical differences containing wide CIs among individual bacterial species (Table 2). Per-pathogen eradication rates at TOC (eME population) for common *Enterobacteriaceae* ranged from 75·0% to 90·9% for ceftazidime-avibactam and from 60·0% to 88·9% for meropenem; respective eradication rates for *P. aeruginosa* were 42·9% and 40·0% (Table 2).

Persistence with increasing MIC (≥4-fold MIC increase) at EOT and/or TOC was observed in 2/125 (1·6%) patients in the ceftazidime-avibactam group and 11/131 (8·4%) patients in the meropenem group. Multi-Locus Sequence Typing showed that organisms with increasing MIC with the same genotype as the baseline isolate occurred in one patient in the ceftazidime-avibactam group (*K. pneumoniae*), and 11 patients in the meropenem group (nine *P. aeruginosa*, one *K. pneumoniae*, one with both *P. aeruginosa* and *K. pneumoniae*). Rates of emergent infections (eME population; appendix p 73) were low across both treatment groups. New infections were identified in 5/125 (4·0%) and 6/131 (4·6%) patients treated with ceftazidime-avibactam and meropenem, respectively. Three (2·3%) superinfections and three (2·3%) new infections were identified with *P. aeruginosa*, all in the meropenem group.

Rates of AEs and serious AEs (SAEs) are shown in Table 3. Overall, ≥1 AE occurred in 302/405 (74·6%) and 299/403 (74·2%) patients in the ceftazidime-avibactam and meropenem groups, respectively; AEs were considered treatment-related in 66/405 (16·3%) and 54/403 (13·4%) patients, and were of severe intensity in 66/405 (16·3%) and 51/403 (12·7%) patients, respectively. Few AEs resulted in discontinuation of the study drug (ceftazidime-avibactam 16/405 [4·0%], meropenem 11/403 [2·7%]; appendix p 74). AEs reported in ≥5%

of patients in either group comprised diarrhoea (see appendix p 83 for narrative of diarrhoea AEs), hypokalaemia, anaemia, constipation and vomiting. No clinically meaningful trends or changes in haematological values, clinical chemistry parameters, coagulation results or urinalysis results were identified, and no clinical changes of concern were noted for vital signs or electrocardiograms in either treatment group.

SAEs occurred in 75/405 (18·5%) and 54/403 (13·4%) patients in the ceftazidime-avibactam and meropenem groups, respectively. The most commonly reported SAEs were in the system organ classes of infections and infestations; respiratory, thoracic, and mediastinal disorders; and cardiac disorders. Four patients (1·0%) in the ceftazidime-avibactam group (and none in the meropenem group) had an SAE that was considered by investigators as possibly related to the study drug, and two of these led to study drug discontinuation. These SAEs comprised diarrhoea in a male aged 22 years, acute coronary syndrome in a male aged 79, subacute hepatic failure in a female aged 33, and liver function test abnormal in a male aged 22; all were recovered/resolved or recovering/resolving at the time of the FPFU visit. Safety data for the 62 $MSRIB_{orig}$ patients are presented in the appendix (p 80).

Discussion

REPROVE is the first phase 3 study of ceftazidime-avibactam in adults with NP (including VAP), and the first randomised controlled trial to our knowledge to demonstrate non-inferiority of a new antimicrobial therapy versus a carbapenem targeting Gram-negative pathogens in this setting. The results demonstrate non-inferiority of ceftazidime-avibactam versus meropenem for the treatment of NP (including VAP) caused by ceftazidime-non-susceptible or ceftazidime-susceptible Gram-negative aerobic pathogens. The safety profile of ceftazidime-avibactam was comparable to that of the well-established safety profile of ceftazidime alone and consistent with the known profile of ceftazidime-avibactam.[20-24] No new safety concerns were identified; the overall pattern of AEs and SAEs was reflective of the underlying disease and co-morbidities in this patient population. Although there was a numerical difference in the reported incidence of SAEs, most were unrelated to study treatment. There were no new trends in SAEs compared with previous trials of ceftazidime-avibactam.[20-24]

Baseline pathogens were as expected for NP,[3,4] and balanced between treatment groups. In the mMITT population, 73·0% of patients were infected with *Enterobacteriaceae* (36·6% *K. pneumoniae*, 13·5% *Enterobacter cloacae*), and 29·6% with *P. aeruginosa*. Overall, 28·2% of patients had Gram-negative isolates that were non-susceptible to ceftazidime. Two *K. pneumoniae* and nine *P. aeruginosa* isolates at baseline were resistant to ceftazidime-avibactam, and five *K. pneumoniae* and 31 *P. aeruginosa* were non-susceptible to meropenem.

Per-patient favourable microbiological response rates were generally lower than clinical cure rates, but similar across treatment groups. Perhaps surprisingly, and in contrast to previous antibiotic trials, albeit in community-acquired pneumonia,[25,26] no improvement was observed

in clinical cure rates for patients who received ≤24 hours of prior antibiotics compared with patients who did not receive prior antibiotics in either treatment group. These findings may have implications for future NP clinical trial design, such as potentially extending permitted prior antibiotic use to a period greater than the current convention of ≤24 h.

All randomised patients were to receive concomitant aminoglycoside for a minimum of 48–72 hours unless they were known to have a carbapenem-susceptible Gram-negative pathogen or low risk of infection with a resistant pathogen. Interestingly, the exploratory analysis of clinical cure rates among patients who received concomitant aminoglycoside (either ≤72 hours or >72 hours exposure) revealed no differences compared with patients not receiving concomitant aminoglycosides. The favourable clinical outcomes observed with either ceftazidime-avibactam or meropenem without aminoglycoside should be interpreted with caution, however, since REPROVE was not designed to evaluate monotherapy (β-lactam alone) versus combination therapy (β-lactam plus aminoglycoside).

The observation that persistence of an organism with increasing MIC with the same genotype as the baseline isolate occurred in 11 patients in the meropenem group (*vs* one patient in the ceftazidime-avibactam group) may have an impact on clinicians' choice of empiric antibiotic therapy in the future for patients deemed to be at higher risk of NP recurrence, particularly for those with *P. aeruginosa* infections.

Subgroup analyses of the primary endpoint revealed no trends in treatment differences across various patient subgroups. Despite initial expectations, no difference was observed in clinical cure rates among non-VAP versus VAP patients. This might be related to continuing improvements over time in care of VAP patients, and possibly to the use of a standard comparator (meropenem) in this trial. Also, some patients diagnosed as non-VAP subsequently required mechanical ventilation. Clinical cure rates were similar between

groups for patients with augmented renal clearance, normal renal function/mild impairment or moderate to severe impairment.

During the early stages of REPROVE, results from the RECLAIM 1 and 2 studies became available,[20] suggesting the potential for underdosing of ceftazidime-avibactam with the protocolled dosage regimen in patients with moderate/severe renal impairment. Thus, the REPROVE protocol was amended to increase the ceftazidime-avibactam dose for such patients, and the 62 patients with $MSRIB_{orig}$ were excluded from the main analyses. Efficacy and safety results in these patients were consistent with the overall population; however, the small number of patients in this subgroup prevents definitive conclusions. The amended dosage modifications are supported by pharmacokinetic-pharmacodynamic analyses[27] and reflect the approved product labelling.[28,29]

Mortality rates for NP are influenced by multiple factors, and reported rates vary substantially. All-cause mortality rates at Day 28 (cMITT population) were 8·4% in the ceftazidime-avibactam group and 7·3% in the meropenem group, somewhat lower than some other investigators have reported;[3] however, REPROVE recruited a representative patient population in terms of VAP/non-VAP, APACHE II score and prior antibiotics use within the confines of a clinical study. Patients were not enrolled if they had concurrent morbidities preventing accurate disease assessment, or if they had a high likelihood of dying within the treatment period despite delivery of adequate antibiotics for NP; this is likely to be reflected in the overall mortality rates. A key limitation of this trial is that it is unable to determine the optimum duration of treatment with either ceftazidime-avibactam or meropenem (as noted above it is also unable to determine the relative benefits and risks of adding aminoglycosides to either regimen), and hence it does not provide any additional information that impacts on the current standard of care with respect to these aspects of patient management. Moreover,

various aspects of the design, particularly the duration of study treatment of 7–14 days, while consistent with guidelines available at the start of the study,[30] may be unrepresentative of current real-life practice and guidelines, which typically involve antibiotic de-escalation based on culture results. Similarly, the mode of meropenem administration (30 minute infusions every 8 hours), although consistent with the approved label and guidelines,[3,30] may not reflect current practice (some institutions employ prolonged or continuous infusions). Such design constraints are common in non-inferiority trials where careful efforts to avoid confounding the results and falsely concluding non-inferiority are required. Moreover, the small numbers of patients with bacteraemia limits the applicability of the results to septic patients.

In summary, these results confirm the efficacy and safety of ceftazidime-avibactam for the treatment of NP, including VAP. Consistent with other phase 3 trial results in patients with complicated intra-abdominal or urinary tract infections, which have consistently demonstrated the non-inferiority of ceftazidime-avibactam to carbapenem comparators,[20-22] the data also support a role for ceftazidime-avibactam as a carbapenem-sparing strategy for serious Gram-negative infections (including NP).

Contributors

Study concept and design: AT, NZ, JP, J-FT, MK and JWC. Acquisition, analysis or interpretation of data: AT, NZ, JP, J-FT, DT, PJL, GGS and JWC. Drafting of the manuscript: ZC, JS, DT, PJL, GGS and JWC. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: PJL. Administrative, technical, or material support: DT, ZC, JS, PJL, and JWC. Study supervision: AT, DT, NZ, JP, J-FT, MK, ZC, and JS. All authors approved the final version of the manuscript for publication. All authors had full access to all trial data and take responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of interests

AT received a consultancy fee from AstraZeneca for participating as Principal Investigator of the study. NZ is an employee of The First Affiliated Hospital of Guangzhou Medical University, which received institutional research grant funding from AstraZeneca for the conduct of the study. JP is an employee of Charles University, which received institutional research grant funding from AstraZeneca for the conduct of the study. J-FT is an employee of APHP Hôpital Bichat-Claude Bernard, Paris-Diderot University, which received institutional research grant funding from AstraZeneca for the conduct of the study. MK is an employee of the Washington University School of Medicine, which received institutional research grant funding from AstraZeneca for the conduct of the study. JWC and GGS were employees of and shareholders in AstraZeneca at the time of study completion, and are currently employees of Pfizer. JS and ZC are employees of AstraZeneca. PL is contracted to AstraZeneca from the Statistical Services Unit, University of Sheffield. DT is contracted to AstraZeneca from Taylormade Health Ltd, Cheshire, and is a shareholder in AstraZeneca.

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Table 1: Baseline patient demographic and disease characteristics (cMITT population)

Parameter	Ceftazidime-avibactam (n=356)	Meropenem (n=370)
Age (years)	62·1 (16·6)	61·9 (17·4)
Male	268 (75·3%)	274 (74·1%)
Race		
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*	23·97 (6·11)	23·94 (5·17)
APACHE II score	14·5 (4·01)	14·9 (4·05)
APACHE II score category		
<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†		
Normal renal function or mild impairment (CrCL 51–150 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 >151 mL/min)	50 (14·0%)	58 (15·7%)
NP subtype		
VAP	118 (33·1%)	128 (34·6%)
Non-VAP	238 (66·9%)	242 (65·4%)
Type of VAP infection		
Early	29 (8·1%)	47 (12·7%)
Late	89 (25·0%)	81 (21·9%)
Mechanical ventilation at baseline		
Ventilated	154 (43·3%)	159 (43·0%)
Non-ventilated	202 (56·7%)	211 (57·0%)
Bacteraemic	19 (5·3%)	15 (4·1%)
Infection type		
Monomicrobial	104 (29·2%)	105 (28·4%)
Polymicrobial	69 (19·4%)	83 (22·4%)
No study qualifying pathogen identified	183 (51·4%)	182 (49·2%)
Prior systemic antibiotic use‡		
None	122 (34·3%)	117 (31·6%)
>0 to ≤24 hours	185 (52·0%)	209 (56·5%)
>24 to ≤48 hours	49 (13·8%)	44 (11·9%)
Concomitant aminoglycoside use§		
None	72 (20·2%)	68 (18·4%)
>0 to ≤72 hours	199 (55·9%)	225 (60·8%)
>72 hours	85 (23·9%)	77 (20·8%)

APACHE=Acute Physiology and Chronic Health Evaluation. cMITT=clinically modified intent-to-treat. CrCL=creatinine

clearance. NP=nosocomial pneumonia. SD=standard deviation. VAP=ventilator-associated pneumonia. Data are mean (SD) and n (%). *Body mass index data were missing for ten patients in the ceftazidime-avibactam group and nine patients in the meropenem group. †As reported by the site using the Cockcroft-Gault method based on local laboratory data; CrCL data were missing for two patients in the ceftazidime-avibactam group and two patients in the meropenem group. ‡In the previous 48 hours before randomisation. §Exploratory analysis (not defined a priori in the clinical study protocol). The concomitant aminoglycoside subgroups are not based on a baseline patient characteristic, but were defined by blinded review of post-baseline data.

Table 2: Per-pathogen clinical cure rates at TOC (CE population) and favourable microbiological response rates at TOC (eME population)

	Patients with clinical cure (CE population)			Patients with favourable microbiological response[†] (eME population)		
	Ceftazidime-avibactam (n=257)	Meropenem (n=270)	Difference	Ceftazidime-avibactam (n=125)	Meropenem (n=131)	Difference
Enterobacteriaceae						
Klebsiella pneumoniae	31/37 (83·8%)	39/49 (79·6%)	4·2 (–13·49, 20·50)	29/37 (78·4%)	39/49 (79·6%)	–1·2 (–19·60, 15·96)
Enterobacter cloacae	20/21 (95·2%)	7/11 (63·6%)	31·6 (4·79, 61·30)	18/21 (85·7%)	7/11 (63·6%)	22·1 (–8·07, 53·69)
Escherichia coli	8/11 (72·7%)	14/18 (77·8%)	–5·1 (–39·26, 25·79)	10/11 (90·9%)	16/18 (88·9%)	2·0 (–29·11, 26·44)
Proteus mirabilis	11/11 (100·0%)	7/8 (87·5%)	12·5 (–16·54, 48·07)	9/11 (81·8%)	6/8 (75·0%)	6·8 (–30·73, 46·51)
Serratia marcescens	10/12 (83·3%)	8/8 (100·0%)	–16·7 (–45·58, 19·48)	9/12 (75·0%)	5/8 (62·5%)	12·5 (–27·47, 51·82)
Enterobacter aerogenes	4/6 (66·7%)	2/5 (40·0%)	26·7 (–31·92, 70·73)	5/6 (83·3%)	3/5 (60·0%)	23·3 (–31·30, 68·33)
Gram-negative pathogens other than *Enterobacteriaceae*						
Pseudomonas aeruginosa	27/42 (64·3%)	27/35 (77·1%)	–12·9 (–32·25, 8·01)	18/42 (42·9%)	14/35 (40·0%)	2·9 (–19·13, 24·32)
Haemophilus influenzae	10/11 (90·9%)	11/13 (84·6%)	6·3 (–26·19, 36·09)	11/11 (100·0%)	12/13 (92·3%)	7·7 (–20·08, 34·00)
Gram-positive aerobes						
Staphylococcus aureus	11/14 (78·6%)	16/22 (72·7%)	5·8 (–25·24, 32·67)	5/14 (35·7%)	17/22 (77·3%)	–41·6 (–67·04, –8·36)

CE=clinically evaluable. CI=confidence interval. eME=extended microbiologically evaluable. TOC=test of cure. Data are number of patients with clinical cure/number of patients in subgroup (%) and % difference (95% CI). [†]Favourable microbiologic response comprised eradication or presumed eradication of the baseline pathogen(s).

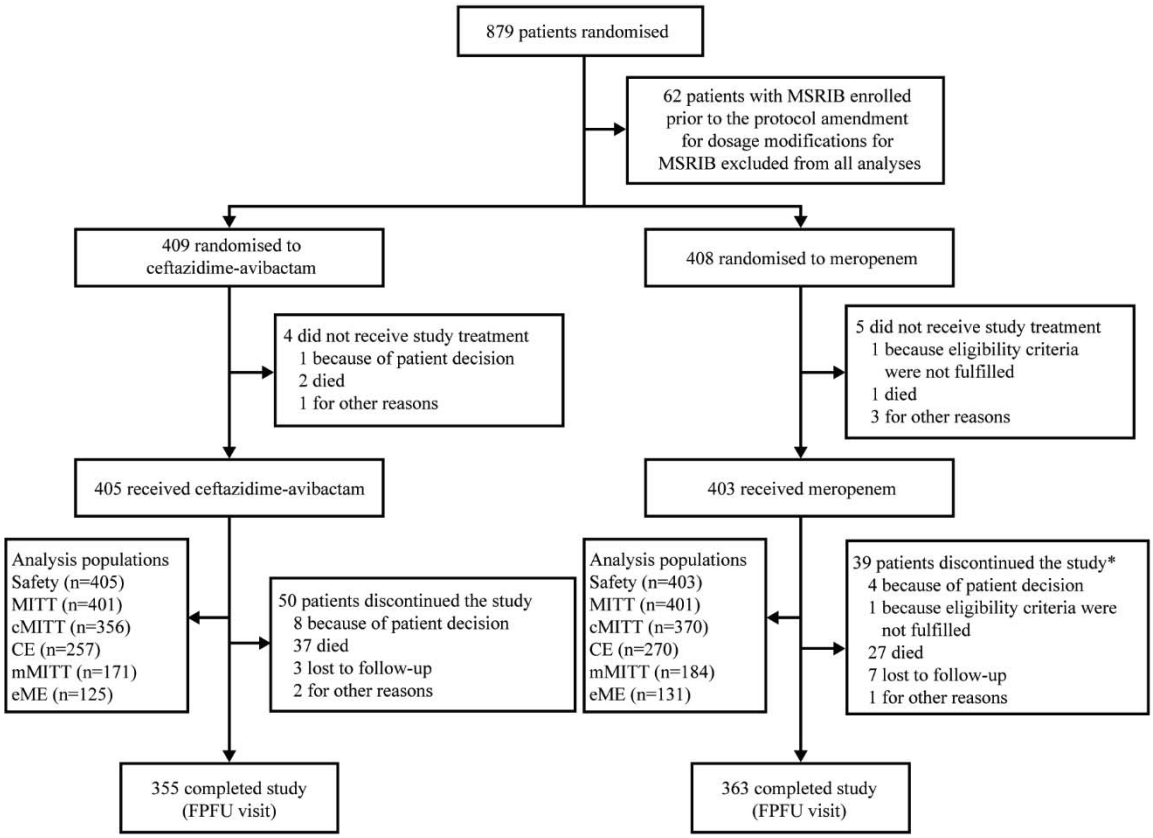
Table 3: Mortality and adverse events up to the final follow-up visit (safety population)

	Ceftazidime-avibactam (N=405)	Meropenem (N=403)
All-cause mortality	38 (9·4%)	30 (7·4%)
Deaths due to disease progression	13 (3·2%)	8 (2·0%)
AEs[*]		
Any AE	302 (74·6%)	299 (74·2%)
Any AE with outcome of death[†]	25 (6·2%)[‡]	22 (5·5%)[‡]
Any SAE[§]	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 ≥2% of patients*		
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%)
Alanine aminotransferase increased	16 (4·0%)	19 (4·7%)
Aspartate aminotransferase increased	16 (4·0%)	17 (4·2%)
Oedema peripheral	17 (4·2%)	15 (3·7%)
Hypertension	14 (3·5%)	15 (3·7%)
Nausea	13 (3·2%)	7 (1·7%)
Decubitus ulcer	9 (2·2%)	6 (1·5%)
Pyrexia	10 (2·5%)	13 (3·2%)
Hyponatremia	10 (2·5%)	6 (1·5%)
Hypotension	10 (2·5%)	8 (2·0%)
Urinary tract infection	11 (2·7%)	15 (3·7%)
Abdominal pain	10 (2·5%)	8 (2·0%)
Pneumonia	10 (2·5%)	12 (3·0%)
Respiratory failure	10 (2·5%)	5 (1·2%)
Pleural effusion	9 (2·2%)	9 (2·2%)
Rash	8 (2·0%)	13 (3·2%)
Tachycardia	8 (2·0%)	5 (1·2%)
Cardiac failure	8 (2·0%)	6 (1·5%)
Atrial fibrillation	5 (1·2%)	9 (2·2%)
Insomnia	4 (1·0%)	11 (2·7%)

Terms defined according to the Medical Dictionary for Regulatory Activity (version 18.1). AE=adverse event. FPFU=Final Protocol Follow Up. SAE=serious adverse event. Data are n (%). *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. [‡]Excludes one patient in each group with an AE with onset before FPFU, that had an outcome of death post-FPFU. [§]An SAE was defined as any event occurring during any study phase that fulfilled one or more of the following criteria: resulted in death; was immediately life-threatening; required in-

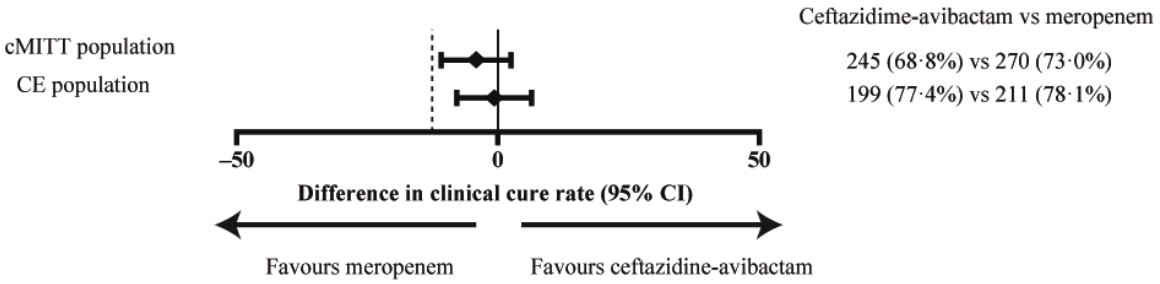
patient hospitalisation or prolongation of existing hospitalisation; resulted in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions; was a congenital abnormality or birth defect; was an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above. Deaths due to disease progression were not counted as SAEs.

Figure 1. Patient disposition



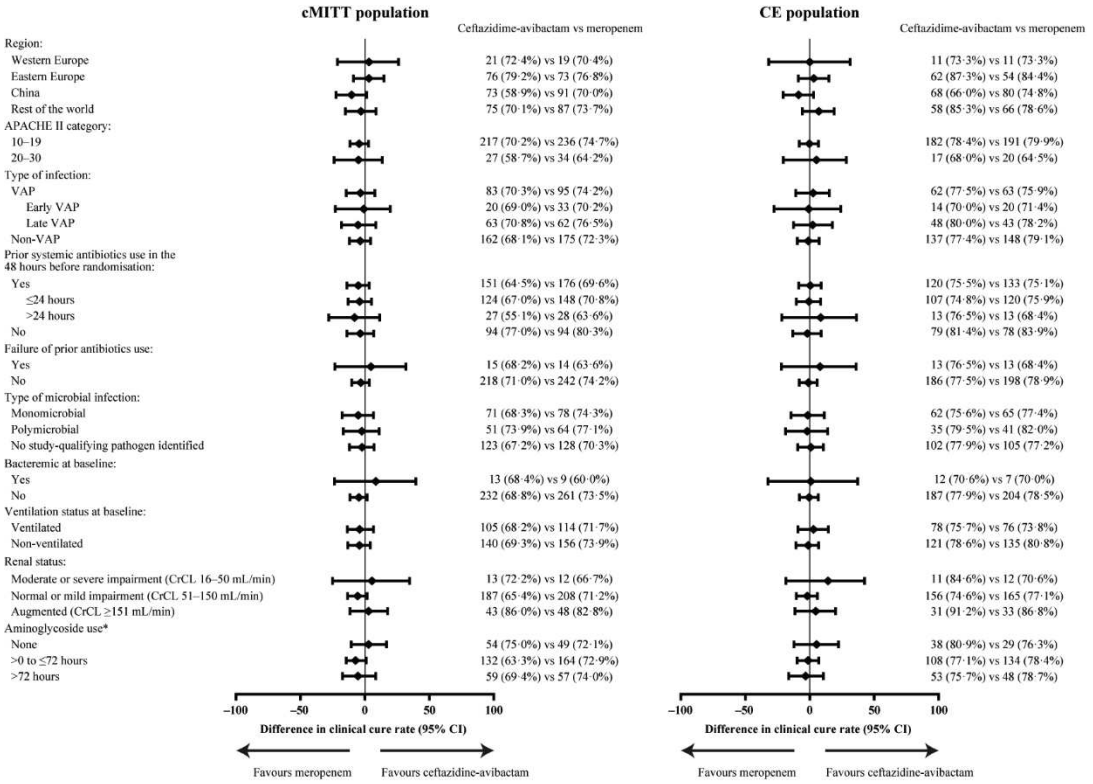
CE=clinically evaluable. cMITT=clinically modified intent-to-treat. eME=extended microbiologically evaluable. FPFU=final protocol follow-up. MITT=modified intent-to-treat. mMITT= microbiologically modified intent-to-treat. MSRIB=moderate/severe renal impairment at baseline. TOC=test-of-cure. *One patient in the meropenem group completed the TOC visit (which was out of window) and the FPFU visit on the same day, and was treated as having neither completed nor discontinued the study.

Figure 2. Clinical cure rates at TOC (primary efficacy analysis)



CE=clinically evaluable. CI=confidence interval. cMITT=clinically modified intent-to-treat. TOC=test of cure. Data are number of patients with clinical cure (%). Dashed line indicates NI margin of –12·5%.

Figure 3. Subgroup analysis of clinical cure rates at TOC



CE=clinically evaluable. CI=confidence interval. cMITT=clinically modified intent-to-treat. TOC=test of cure. Data are number of patients with clinical cure/number of patients in subgroup (%). *Exploratory analysis (not defined *a priori* in the clinical study protocol); all other subgroup analyses were pre-specified in the study protocol. The concomitant aminoglycoside subgroups are not based on a baseline patient characteristic, and were defined before the study database lock and assigned by blinded review of post-baseline data.