Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial

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Summary

Background Nosocomial pneumonia is commonly associated with antimicrobial-resistant Gram-negative pathogens. We aimed to assess the efficacy and safety of ceftazidime-avibactam in patients with nosocomial pneumonia, including ventilator-associated pneumonia, compared with meropenem in a multinational, phase 3, double-blind, non-inferiority trial (REPROVE).

Methods Adults with nosocomial pneumonia (including ventilator-associated pneumonia), enrolled at 136 centres in 23 countries, were randomly assigned (1:1) to 2000 mg ceftazidime and 500 mg avibactam (by 2 h intravenous infusion every 8 h) or 1000 mg meropenem (by 30-min intravenous infusion every 8 h) for 7–14 days; regimens were adjusted for renal function. Computer-generated randomisation codes were stratified by infection type and geographical region with a block size of four. Participants and investigators were masked to treatment assignment. The primary endpoint was clinical cure at the test-of-cure visit (21–25 days after randomisation). Non-inferiority was concluded if the lower limit of the two-sided 95% CI for the treatment difference was greater than –12·5% in the coprimary clinically modified intention-to-treat and clinically evaluable populations. This trial is registered with ClinicalTrials.gov (NCT01808092) and EudraCT (2012-004006-96).

Findings Between April 13, 2013, and Dec 11, 2015, 879 patients were randomly assigned. 808 patients were included in the safety population, 726 were included in the clinically modified intention-to-treat population, and 527 were included in the clinically evaluable population. Predominant Gram-negative baseline pathogens in the microbiologically modified intention-to-treat population (n=355) were *Klebsiella pneumoniae* (37%) and *Pseudomonas aeruginosa* (30%); 28% were ceftazidime-non-susceptible. In the clinically modified intention-to-treat population, 245 (68·8%) of 356 patients in the ceftazidime-avibactam group were clinically cured, compared with 270 (73·0%) of 370 patients in the meropenem group (difference –4·2% [95% CI –10·8 to 2·5]). In the clinically evaluable population, 199 (77·4%) of 257 participants were clinically cured in the ceftazidime-avibactam group, compared with 211 (78·1%) of 270 in the meropenem group (difference –0·7% [95% CI –7·9 to 6·4]). Adverse events occurred in 302 (75%) of 405 patients in the ceftazidime-avibactam group versus 299 (74%) of 403 in the meropenem group (safety population), and were mostly mild or moderate in intensity and unrelated to study treatment. Serious adverse events occurred in 75 (19%) patients in the ceftazidime-avibactam group and 54 (13%) patients in the meropenem group. Four serious adverse events (all in the ceftazidime-avibactam group) were judged to be treatment related.

Interpretation Ceftazidime-avibactam was non-inferior to meropenem in the treatment of nosocomial pneumonia. These results support a role for ceftazidime-avibactam as a potential alternative to carbapenems in patients with nosocomial pneumonia (including ventilator-associated pneumonia) caused by Gram-negative pathogens.

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Introduction

Nosocomial pneumonia, which is also referred to as hospital-acquired pneumonia, is one of the most common hospital-acquired infections,[1] and is associated with high mortality and health-care expenditure.[2,3] Gram-negative pathogens—particularly *Pseudomonas aeruginosa* and Enterobacteriaceae—predominate in nosocomial pneumonia.[4] These pathogens often harbour several antimicrobial resistance mechanisms—particularly extended-spectrum β-lactamases, and increasingly, carbapenemases.[5,6] Very few treatment options are available for infections caused by pathogens with extended-spectrum β-lactamases, and especially for those with carbapenemases.[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

Research in context

Evidence before this study

We searched PubMed with the terms "randomized OR randomised" AND "ceftazidime AND avibactam" OR "ceftazidime AND avibactam AND Clinical Trial[ptyp]" for articles published in English up to May 18, 2017. We identified two phase 2 studies and four phase 3 studies in which the efficacy and safety of ceftazidime-avibactam (with or without metronidazole as applicable for anaerobic coverage) was assessed in patients with serious Gram-negative infections, including complicated intra-abdominal infections (NXL104/2002 [NCT00752219], RECLAIM 1 and 2 [NCT01499290], RECLAIM 3 [NCT01726023]), complicated urinary tract infections (NXL104/2001 [NCT00690378], RECAPTURE 1 and 2 [NCT01595438 and NCT01599806]), or either complicated intra-abdominal or urinary tract infections caused by ceftazidime-non-susceptible Gram-negative pathogens (REPRISE [NCT01644643]). Across these studies, ceftazidime-avibactam had similar efficacy and safety to 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, supported the clinical investigation of ceftazidime-avibactam in nosocomial pneumonia, including ventilator-associated pneumonia.

Added value of this study

The phase 3 REPROVE trial is the first clinical study, to our knowledge, of ceftazidime-avibactam in adults with nosocomial pneumonia (including ventilator-associated pneumonia). The patient population and pathogens isolated were consistent with those commonly observed in nosocomial pneumonia. Our results showed that ceftazidime-avibactam was non-inferior to meropenem, a standard therapy for nosocomial pneumonia, 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 noted with ceftazidime alone and with the known profile of ceftazidime-avibactam in patients with complicated intra-abdominal or urinary tract infections.

Implications of all the available evidence

Our results add to the evidence base showing the efficacy and safety of ceftazidime-avibactam in treating infections caused by Gram-negative pathogens, including those considered non-susceptible to ceftazidime, and support a role for ceftazidime-avibactam as a potential alternative to carbapenems in patients with nosocomial pneumonia (including ventilator-associated pneumonia) caused by Gram-negative pathogens.

β-lactamase inhibitor avibactam, which extends the in-vitro activity of ceftazidime to include Gram-negative organisms producing Ambler class A (eg, extended-spectrum β-lactamases, *Klebsiella pneumoniae* carbapenemase), class C (eg, AmpC), and some class D (eg, OXA-48) β-lactamases.[10–12] This microbiological profile covers most carbapenem-non-susceptible Enterobacteriaceae and multidrug-resistant *P aeruginosa* (excluding metallo-β-lactamase producers), and thus ceftazidime-avibactam is a potential alternative to carbapenems for the treatment of serious Gram-negative infections, including those caused by some carbapenemase-producing bacteria.[13–15] We did a randomised phase 3 trial to assess the non-inferiority of ceftazidime-avibactam to meropenem in terms of efficacy and safety in the treatment of nosocomial pneumonia.

Methods

Study design and participants

REPROVE was a prospective, international, multicentre, parallel-group, randomised, double-blind, double-dummy, phase 3 non-inferiority trial. REPROVE was done at 136 centres (general hospitals) in 23 countries (appendix p22). The study was done 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. The study protocol and amendments (available at www.astrazenecaclinicaltrials.com) were approved by local ethics committees or institutional review boards.

See Online for appendix

Eligible participants were aged 18–90 years, were in hospital, and had acquired nosocomial pneumonia, which was defined as pneumonia with an onset 48 h or longer after admission or less than 7 days after discharge from an inpatient care facility. Ventilator-associated pneumonia was defined as parenchymal lung infection with an onset 48 h or longer after endotracheal intubation and mechanical ventilation. The term non-ventilator-associated pneumonia was used to identify patients with nosocomial pneumonia who did not have ventilator-associated pneumonia. Diagnosis of nosocomial pneumonia was based on clinical assessment, including new or worsening infiltrate on chest radiographs within 48 h of randomisation, and at least one systemic and two respiratory signs or symptoms of pneumonia. A respiratory specimen for Gram stain and culture was required within 48 h before randomisation. Key exclusion criteria included infections caused by any Gram-positive pathogens only or by other pathogens not expected to respond to ceftazidime-avibactam or meropenem, or both (polymicrobial infections were permitted if they included a target Gram-negative pathogen), and infections expected to require more than 14 days' treatment. Patients without baseline culture data at randomisation could receive study therapy empirically. A full list of inclusion (pp 4–5) and exclusion criteria

(pp 5–6) are in the appendix. All participants provided written informed consent.

Randomisation and masking

Investigators enrolled eligible patients, and then used an an interactive voice web response system to randomly assign them (1:1) to either ceftazidime-avibactam or meropenem. Patients were stratified by infection type (ie, ventilator-associated or non-ventilator-associated) and geographical region (western Europe, eastern Europe, China, rest of the world) at randomisation. Randomisation codes were computer-generated by AstraZeneca with the AstraZeneca Global Randomization System (block size of four). To maintain the blinding of study treatments, patients received double-dummy matching placebos (ie, ceftazidime-avibactam plus meropenem placebo or ceftazidime-avibactam placebo plus meropenem). Patients, investigators, and all study centre personnel were masked to study treatment, except for an unblinded pharmacist designee, who was responsible for maintaining accountability and preparing blinded study treatments.

Procedures

Patients assigned to ceftazidime-avibactam (AstraZeneca, Södertälje, Sweden) received a fixed-dose combination of 2000 mg ceftazidime and 500 mg avibactam by 2 h intravenous infusion every 8 h. Patients in the meropenem (ACS Dobfar, Milan, Italy) group received 1000 mg meropenem by 30 min intravenous infusion every 8 h. Dosages of both treatments were adjusted for patients with moderate or severe renal impairment (ie, creatinine clearance 16–50 mL/min). After a protocol amendment (on Jan 9, 2015), ceftazidime-avibactam dosage adjustments in patients with renal impairment were modified (appendix pp 7–8), and the statistical analysis plan was updated to exclude patients with moderate or severe renal impairment at baseline who were randomly assigned before the protocol amendment from the main analyses to ensure the main efficacy and safety results were reflective of the approved ceftazidime-avibactam dosage regimens (data for excluded patients with moderate or severe renal impairment were summarised separately). Study treatment was discontinued after a minimum of 7 days (ie, 21 doses) and maximum of 14 days (ie, 42 doses).

Patients awaiting identification of causative pathogens or susceptibility results from the baseline culture at randomisation received open-label linezolid or vancomycin for Gram-positive pathogen coverage. Open-label amikacin (or another aminoglycoside) for additional Gram-negative coverage was given to all patients awaiting baseline culture results for a minimum of 48–72 h (extended depending on culture or susceptibility results) unless such treatment was contraindicated or patients were deemed at low risk of multidrug-resistant 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, mini-bronchoalveolar lavage, or protected brush specimen at baseline, the end-of- treatment visit (ie, within 24 h of the last dose of study treatment), and the test-of-cure visit (21–25 days after randomisation). Two sets of blood samples were collected from different sites for aerobic and anaerobic incubation within the 24 h before randomisation and as clinically indicated. If a previous culture was positive, repeat samples were taken at least every 3 days until bacteraemia cleared. Local laboratories did pathogen identification and susceptibility testing for all respiratory and blood isolates with Clinical Laboratory Standards Institute disk diffusion methods[16] against ceftazidime-avibactam, meropenem, and ceftazidime. Isolates identified by local laboratories and deemed 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, and at an end-of-treatment visit, a test-of-cure visit, and a final protocol follow-up visit 28–32 days after randomisation (appendix pp 9–12). Clinical outcomes at the end-of-treatment and test-of-cure visits (appendix pp 13–14) were classified by investigators as cure (defined at the test-of- cure visit as resolution of all signs and symptoms of pneumonia such that no antibacterial therapy for nosocomial pneumonia was taken between the end-of-treatment and test-of-cure visits, inclusive), indeterminate, or treatment 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, or presumed persistence), or indeterminate (per-pathogen responses only).

Outcomes

The primary endpoint was the proportion of patients clinically cured at the test-of-cure visit in the coprimary clinically modified intention-to-treat and clinically evaluable populations (appendix pp 16–17). The clinically modified intention-to-treat population comprised patients who met minimum disease criteria (on the basis of inclusion criteria; appendix pp 4–5) with one or more eligible Gram-negative pathogen, or those without any identifiable pathogen (patients with only non-target pathogens were excluded). The clinically evaluable population comprised patients in the clinically modified intention-to-treat population who received an adequate course of treatment and had an assessable clinical outcome within the assessment window, no protocol deviations that could affect the assessment of efficacy, and no unacceptable previous or concomitant antibiotics (appendix p 5).

Secondary endpoints included clinical response at the end-of-treatment visit in the clinically modified intention-to-treat and clinically evaluable populations; clinical response at the end-of-treatment and test-of-cure visits in

the microbiologically modified intention-to-treat, extended microbiologically evaluable, and microbiologically evaluable populations; all cause-mortality at the test-of-cure visit and at day 28 in the clinically evaluable and clinically modified and microbiologically modified intention-to-treat populations; clinical response at the end-of-treatment and test-of-cure visit in patients with ceftazidime-non-susceptible pathogens in the clinically evaluable, clinically modified intention-to-treat and microbiologically evaluable populations; and per-patient and per-pathogen microbiological responses at the end-of-treatment and test-of-cure visits in the microbiologically modified intention-to-treat, microbiologically evaluable, and extended microbiologically evaluable populations. A full list of secondary and exploratory analyses is in the appendix (pp 18–20). Safety assessments included monitoring of adverse events, clinical laboratory assessments, electrocardiograms, and mortality. Adverse events were summarised for events occurring from the first dose of study treatment to the final protocol follow-up visit. Adverse events 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 that power was sufficient (at least 85%) for the coprimary hypothesis tests against a 12·5% non-inferiority margin, in line with guidance from the European Medicines Agency.[17] We expected the underlying clinical cure rate at the test-of-cure visit to be around 78% in the clinically evaluable population and 70% in the clinically modified intention-to-treat population, which 50% and 85% of patients, respectively, would be eligible for inclusion in. The number of patients to be randomly assigned for the primary analysis for non-inferiority was approximately 790, to obtain around 394 and 670 evaluable patients in the clinically evaluable and clinically modified intention-to-treat populations, respectively. The estimated power with these numbers of assessable patients (with the previously described assumptions of cure rates and a one-sided α of 2·5%) was calculated with nQuery (version 7) via the Newcombe-Wilson score method (uncorrected).[18] Patients with ventilator-associated pneumonia were recruited in parallel with other patients.

Statistical analyses and the non-inferiority assessment for the primary endpoint were based on the difference in clinical cure rates between treatment groups. The safety population comprised all patients who received any amount of study therapy. An independent data monitoring committee was established with a charter to ensure that the safety of patients was not compromised.

Two-sided 95% CIs for difference between treatments in the proportion of patients with clinical cure were computed with the unstratified method of Miettinen and Nurminen.[19] For primary efficacy endpoints, non-inferiority of ceftazidime-avibactam to meropenem was deemed to be shown if the 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.

Three sensitivity analyses were done for the primary efficacy variable: adjustment for the effect of prespecified stratification factors, type of infection (ie ventilator-associated or non-ventilator-associated), and geographical region; analysis of patients who had received potentially effective concomitant antibiotics as having indeterminate clinical response at the test-of-cure visit; and analysis of patients who died after the test-of-cure visit and up to the final protocol follow-up visit as clinical failures at the test-of-cure visit. Prespecified subgroup analyses assessed the effect of baseline patient and disease characteristics, including infection type, study region, Acute Physiology and Chronic Health Evaluation II (APACHE II) category, previous systemic antibiotic use, presence of bacteraemia, and baseline renal function (including moderate or severe impairment and augmented renal clearance [creatinine clearance >151 mL/min]). Concomitant aminoglycoside use was assessed 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. All statistical analyses were done in SAS (version 9.1 or higher). 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; data collection, analysis, and interpretation; and data checking of information provided in the Article. Responsibility for opinions, conclusions, and data interpretation lies with the authors. All authors had full access to all study data and final responsibility for the decision to submit for publication.

Results

Between April 13, 2013, and Dec 15, 2015, 879 patients were randomly assigned (table 1). After 62 patients with moderate or severe renal impairment (who were randomly assigned before the protocol amendment) were excluded from the main analyses, 409 patients were assigned to ceftazidime-avibactam and 408 to meropenem, of whom 405 and 403, respectively, received study treatment and comprised the safety population (figure 1). Baseline and disease characteristics were generally well balanced (table 1; appendix pp 76–77). Main reason for exclusion from the clinically modified intention-to-treat population was isolation of only Gram-positive pathogens at baseline (46 [11%] in the ceftazidime-avibactam group and 31 [8%] patients in the meropenem group). 70 (17%) in the ceftazidime-avibactam

group and 61 (15%) in the meropenem group had important protocol deviations leading to exclusion from the clinically evaluable population; the main reasons for exclusion were receipt of concomitant non-protocolled antibiotics with potential effects on efficacy up to the test-of-cure visit (43 (11%) in the ceftazidime-avibactam group and 46 [11%] in the meropenem group) and not having a response of cure or failure at the test-of-cure visit (40 [10%] in the ceftazidime-avibactam group and 37 [9%] in the meropenem group).

Of 817 randomly assigned patients, 355 (44%) were included in the microbiologically modified intention-to-treat population. Baseline pathogens were similar between groups and as expected for patients with nosocomial pneumonia (appendix pp 23–26). Prominent Gram-negative pathogens isolated from respiratory site or blood were *K pneumoniae* and *P aeruginosa* (appendix p 23). 100 patients (28%) had one or more ceftazidime-non-susceptible Gram-negative pathogen, including 79 with Enterobacteriaceae and 25 with *P aeruginosa*. *Staphylococcus aureus* (detected in 58 patients [16%]) was the only Gram-positive pathogen to be isolated in ten or more patients.

The minimum inhibitory concentrations required to inhibit the growth of at least 90% of isolates (MIC_{90}) with ceftazidime and ceftazidime-avibactam were greater than 32 mg/L and 0·5 mg/L, respectively, against 317 isolates of Enterobacteriaceae, and greater than 32 mg/L and 8 mg/L, respectively, against 101 isolates of *P aeruginosa* tested at the central laboratory. 79 (25%) Enterobacteriaceae isolates and 25 (24·8%) *P aeruginosa* isolates were non-susceptible to ceftazidime by Clinical Laboratory Standards Institute criteria (minimum inhibitory concentration >4 mg/L for Enterobacteriaceae and >8 mg/L for *P aeruginosa*). Thus, the ceftazidime-avibactam minimum inhibitory concentration 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 greater than 8 mg/L for *P aeruginosa*. Two isolates of *K pneumoniae* and nine isolates of *P aeruginosa* were resistant to ceftazidime-avibactam, and six isolates of Enterobacteriaceae (five *K pneumoniae* and one *Serratia marcescens*) and 31 isolates of *P aeruginosa* were not susceptible to meropenem (minimum inhibitory concentration >2 mg/L). Overall, two *K pneumoniae* isolates and eight *P aeruginosa* were non-susceptible to either study drug.

Of the 355 patients in the microbiologically modified intention-to-treat population, 203 (57%) had monomicrobial infections and 152 (43%) had polymicrobial infections. 66 (19%) had a mixture of Gram-negative and Gram-positive pathogens. These results were balanced between treatment groups and were generally similar for the extended microbiologically evaluable and the microbiologically evaluable populations (data not shown).

Ceftazidime-avibactam was non-inferior to meropenem in both coprimary analysis populations (figure 2). In the clinically modified intention-to-treat population, 245 (68·8%) of 356 people in the ceftazidime-avibactam group were clinically cured at the test-of-cure visit, compared with 270 (73·0%) of 370 in the meropenem group (difference –4·2 [95% CI –10·76 to 2·46]; p=0·0066). 199 (77·4%) of 257 in the ceftazidime-avibactam

	Ceftazidime-avibactam (n=356)	Meropenem (n=370)
Age (years)	62·1 (16·6)	61·9 (17·4)
Male sex	268 (75%)	274 (74%)
Body-mass index (kg/m²)*	23·97 (6·11)	23·94 (5·17)
Race		
White	150 (42%)	163 (44%)
Black or African American	1 (<1%)	2 (1%)
Asian	201 (56%)	199 (54%)
Other	4 (1%)	6 (2%)
APACHE II		
Score	14·5 (4·01)	14·9 (4·05)
<10	1 (<1%)	1 (<1%)
10–19	309 (87%)	316 (85%)
20–30	46 (13%)	53 (14%)
Renal status†		
Estimated creatinine clearance (mL/min)	102·6 (67·5)	100·1 (53·1)
Normal renal function or mild impairment (51–150 mL/min)	286 (80%)	292 (79%)
Moderate or severe impairment (16–50 mL/min)	18 (5%)	18 (5%)
Augmented (>151 mL/min)	50 (14%)	58 (16%)
Type of nosocomial pneumonia		
Ventilator-associated pneumonia	118 (33%)	128 (35%)
Non-ventilator-associated pneumonia	238 (67%)	242 (65%)
Type of ventilator-associated pneumonia infection		
Early	29 (8%)	47 (13%)
Late	89 (25%)	81 (22%)
Mechanical ventilation at baseline		
Ventilated	154 (43%)	159 (43%)
Not ventilated	202 (57%)	211 (57%)
Bacteraemic	19 (5%)	15 (4%)
Infection type		
Monomicrobial	104 (29%)	105 (28%)
Polymicrobial	69 (19%)	83 (22%)
No study-qualifying pathogen identified	183 (51%)	182 (49%)
Previous systemic antibiotic use‡		
None	122 (34%)	117 (32%)
≤24 h	185 (52%)	209 (56%)
>24 to ≤48 h	49 (14%)	44 (12%)
Concomitant aminoglycoside use§		
None	72 (20%)	68 (18%)
>0 to ≤72 h	199 (56%)	225 (61%)
>72 h	85 (24%)	77 (21%)

Data are mean (SD) or n (%). APACHE=Acute Physiology and Chronic Health Evaluation. *Data were missing for ten patients in the ceftazidime-avibactam group and nine patients in the meropenem group. †As reported by the site from the Cockcroft-Gault method on the basis of local laboratory data; data were missing for two patients in each group. ‡In the 48 h 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 1: **Baseline patient demographics and disease characteristics in clinically modified intention-to-treat population**

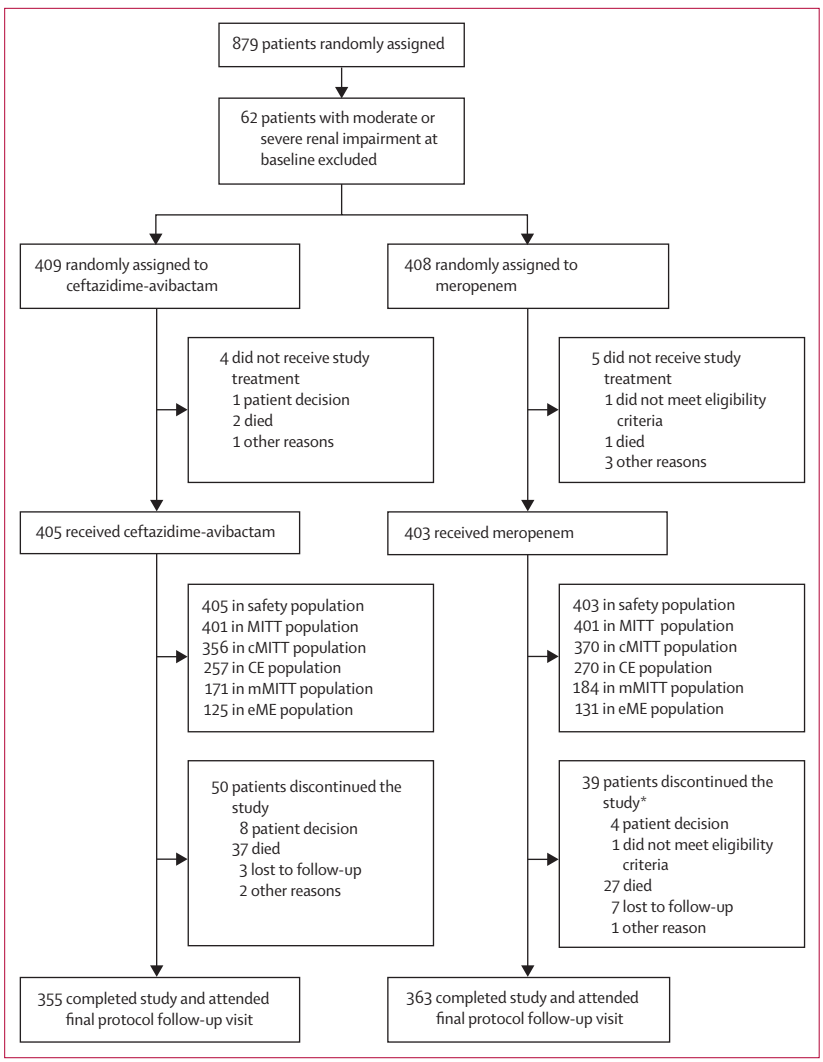

Figure 1: **Trial profile**
CE=clinically evaluable. cMITT=clinically modified intention-to-treat population. eME=extended microbiologically evaluable. MITT=modified intention-to-treat. mMITT=microbiologically modified intention-to-treat.
*One patient in the meropenem group completed the test-of-cure visit (which was out of window) and the final protocol follow-up visit on the same day, and was treated as having neither completed nor discontinued the study.

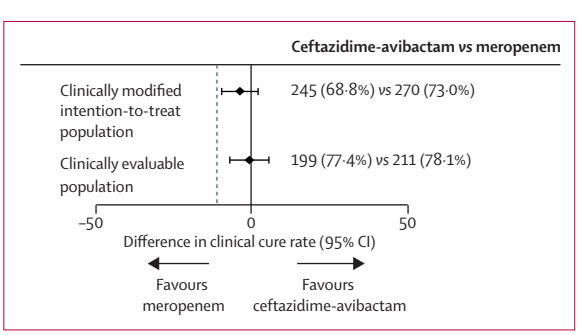

Figure 2: **Clinical cure rates at test-of-cure visit**
Data are number of patients with clinical cure (%). Dashed line indicates non-inferiority margin of –12·5%.

group and 211 (78·1%) of 270 in the meropenem group were cured in the clinically evaluable population (difference –0·7 [95% CI –7·86 to 6·39]; p=0·0007). Similar results were noted in secondary analysis populations (appendix p 85).

Results of sensitivity analyses that adjusted for stratification factors, or in which patients who died after the test-of-cure visit were deemed clinical failures at the test-of-cure visit, were consistent with those of the primary analysis (data not shown). In the clinically modified intention-to-treat population, 24 (7%) of 356 participants in the ceftazidime-avibactam group and 33 (9%) of 370 in the meropenem group with clinical cure at the test-of-cure visit received potentially effective concomitant antibiotics. Sensitivity analysis adjusted for treatment with potentially effective concomitant antibiotics (in the clinically modified intention-to-treat population) accounted for a 2·2% shift in treatment difference, with clinical cure rates of 221 (62·1%) in the ceftazidime-avibactam group and 237 (64·1%) in the meropenem group (difference –2·0 [95% CI –8·99 to 5·04]).

Subgroup analyses of the primary endpoint (figure 3) showed no trends associated with various patient factors, including baseline renal status (including moderate or severe renal impairment and augmented renal function), previous systemic antibiotic use, type of infection (ie, non-ventilator-associated *vs* ventilator-associated and early *vs* late ventilator-associated pneumonia), and APACHE II score category. Cure rates were generally similar across treatment groups and in both coprimary populations in each subgroup. Clinical cure rates were similar across treatment groups in the exploratory analysis of patients who received concomitant aminoglycosides (either ≤72 h or >72 h; appendix pp 27–28) and those who did not.

Per-pathogen clinical cure rates at the test-of-cure visit were generally similar between treatment groups, with numerical differences with wide CIs among individual bacterial species (table 2). Results of other secondary efficacy analyses are presented in the appendix (pp 29–72, 85). Per-pathogen clinical cure rates at the test-of-cure visit among patients infected with ceftazidime-non-susceptible pathogens in the clinically evaluable population were similar between groups (29 [80·6%] of 36 in the ceftazidime-avibactam group *vs* 32 [78·0%] of 41 in the meropenem group; difference 2·5% [95% CI –16·42 to 20·74]), and were also similar to those in patients in whom only ceftazidime-susceptible pathogens were isolated at baseline (63 [75·0%] of 84 *vs* 69 [78·4%] of 88; difference –3·4% [95% CI –16·18 to 9·30]).

Of the 62 patients with moderate or severe renal impairment at baseline, 58 were included in the clinically modified intention-to-treat population and 44 were included in the clinically evaluable population. At the test-of-cure visit, 18 (60%) of 30 patients in the ceftazidime-avibactam group and 16 (57%) of 28 in the

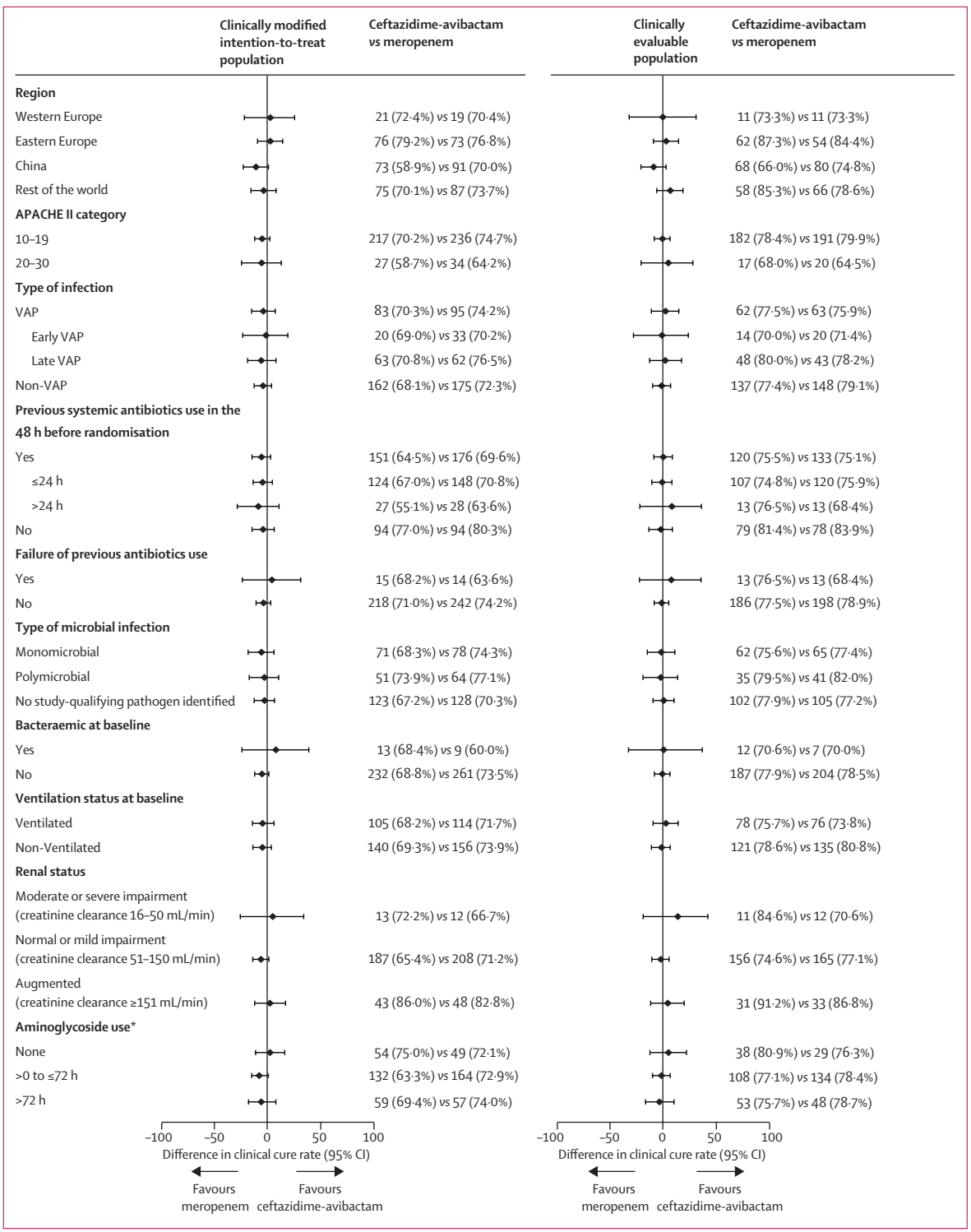

Figure 3: **Subgroup analysis of clinical cure rates at test-of-cure visit**

Data are number of patients with clinical cure (%) or number of patients in subgroup (%). APACHE II=Acute Physiology and Chronic Health Evaluation II. VAP=ventilator-associated pneumonia. *Exploratory analysis (not defined a priori in the clinical study protocol); all other subgroup analyses were prespecified 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.

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

*Eradication or presumed eradication of the baseline pathogens.

Table 2: **Per-pathogen clinical cure rates and favourable microbiological response rates at test-of-cure visit**

meropenem group were clinically cured in the clinically modified intention-to-treat population, whereas in the clinically evaluable population, 15 (71%) of 21 patients in the ceftazidime-avibactam group and 13 (57%) of 23 in the meropenem group were clinically cured.

All-cause mortality was similar across treatment groups at both the test-of-cure visit and day 28. In the clinically modified intention-to-treat population, 29 (8·1%) of 356 died in the ceftazidime-avibactam and 25 (6·8%) of 370 in the meropenem group died by the test-of-cure visit (difference 1·4 [95% CI –2·48 to 5·35]), whereas 30 (8·4%) and 27 (7·3%), respectively, died by day 28 (difference 1·1 [95% CI –2·84 to 5·18]). In the clinically evaluable population, 11 (4·3%) of 257 died in the ceftazidime-avibactam group and eight (3·0%) of 270 died in the meropenem group by the test-of-cure visit (difference 1·3 [95% CI –2·01 to 4·89]), whereas 12 (4·7%) and nine (3·3%), respectively, died by day 28 (difference 1·3 [95% CI –2·14 to 5·04]).

Per-patient favourable microbiological response rates at the test-of-cure visit were generally lower than clinical cure rates, but were similar between the ceftazidime-avibactam and meropenem groups and consistent across the microbiologically modified intention-to-treat (95 [55·6%] of 171 *vs* 118 [64·1%] of 184; difference –8·6 [95% CI –18·65 to 1·64]), extended microbiologically evaluable (80 [64·0%] of 125 *vs* 89 [67·9%] of 131; difference –3·9 [95% CI –15·49 to 7·66]), and microbiologically evaluable (70 [65·4%] of 107 *vs* 83 [70·3%] of 118; difference –4·9 [95% CI –17·10 to 7·28]) populations. In patients infected with ceftazidime-non-susceptible pathogens, per-patient favourable microbiological response rates were similar between groups at the end-of-treatment and test-of-cure visits in the microbiologically modified intention-to-treat, extended microbiologically evaluable, and microbiologically evaluable 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 the test-of-cure visit were similar between groups, with numerical differences with wide CIs among individual bacterial species (table 2). Per-pathogen eradication rates at the test-of-cure visit in the extended microbiologically evaluable population for common Enterobacteriaceae ranged from 75·0% to 90·9% for ceftazidime-avibactam, and from 60·0% to 88·9% for meropenem; the corresponding eradication rates for *P aeruginosa* were 42·9% and 40·0%, respectively (table 2).

In the extended microbiologically evaluable population, persistence with increasing minimum inhibitory concentrations (≥four-times increase) at the end-of-treatment or test-of-cure visit was noted in two (2%) patients in the ceftazidime-avibactam group and 11 (8%) patients in the meropenem group. Multi-locus sequence typing showed that organisms with increasing minimum inhibitory concentrations 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 with *P aeruginosa*, one with *K pneumoniae*, one with both *P aeruginosa* and *K pneumoniae*). Rates of emergent infections in the extended microbiologically evaluable population were low across both treatment groups (appendix p 73). New infections were identified in five (4%) patients in the ceftazidime-avibactam group and six (5%) patients in the meropenem group. Three (2%) superinfections and three (2%) new infections were identified with *P aeruginosa*, all in the meropenem group.

Overall, one or more adverse events occurred in 302 (75%) patients in the ceftazidime-avibactam group and 299 (74%) patients in the meropenem groups

(table 3). Adverse events were judged to be treatment related in 66 (16%) patients in the ceftazidime-avibactam group and 54 (13%) patients in the meropenem group. Few adverse events resulted in discontinuation of the study drug (table 3; appendix p 74). Diarrhoea (appendix p 83), hypokalaemia, anaemia, constipation, and vomiting occurred in 5% or more of patients in one or both groups (table 3). 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.

Serious adverse events occurred in 75 (19%) patients in the ceftazidime-avibactam group and 54 (13%) patients in the meropenem group. The most commonly reported serious adverse events were in the system organ classes of infections and infestations; respiratory, thoracic, and mediastinal disorders; and cardiac disorders. Four patients (1%) in the ceftazidime-avibactam group (and none in the meropenem group) had a serious adverse event that was considered by investigators as possibly related to the study drug: diarrhoea in a 22-year-old man, acute coronary syndrome in a 79-year-old man, subacute hepatic failure in a 33-year-old woman, and abnormal liver function test results in a 22-year-old man. Two of these events led to discontinuation of study drug. All patients had recovered (or the event had resolved) or were recovering at the time of the final protocol follow-up visit. Safety data for the 62 patients with moderate or severe renal impairment excluded after the protocol amendment are in the appendix (p 80).

	Ceftazidime-avibactam (n=405)	Meropenem (n=403)
All-cause mortality	38 (9%)	30 (7%)
Deaths due to disease progression	13 (3%)	8 (2%)
Adverse events*		
Any	302 (75%)	299 (74%)
Any with outcome of death†	25 (6%)‡	22 (5%)‡
Any serious adverse events§	75 (19%)	54 (13%)
Any leading to discontinuation of study drug	16 (4%)	11 (3%)
Any of severe intensity	66 (16%)	51 (13%)
Adverse events in ≥2% of patients*		
Diarrhoea	61 (15%)	62 (15%)
Hypokalaemia	43 (11%)	33 (8%)
Anaemia	25 (6%)	18 (4%)
Constipation	25 (6%)	31 (8%)
Vomiting	23 (6%)	22 (5%)
Alanine aminotransferase increased	16 (4%)	19 (5%)
Aspartate aminotransferase increased	16 (4%)	17 (4%)
Oedema peripheral	17 (4%)	15 (4%)
Hypertension	14 (3%)	15 (4%)
Nausea	13 (3%)	7 (2%)
Decubitus ulcer	9 (2%)	6 (1%)
Pyrexia	10 (2%)	13 (3%)
Hyponatraemia	10 (2%)	6 (1%)
Hypotension	10 (2%)	8 (2%)
Urinary tract infection	11 (3%)	15 (4%)
Abdominal pain	10 (2%)	8 (2%)
Pneumonia	10 (2%)	12 (3%)
Respiratory failure	10 (2%)	5 (1%)
Pleural effusion	9 (2%)	9 (2%)
Rash	8 (2%)	13 (3%)
Tachycardia	8 (2%)	5 (1%)
Cardiac failure	8 (2%)	6 (1%)
Atrial fibrillation	5 (1%)	9 (2%)
Insomnia	4 (1%)	11 (3%)

Data are n (%). Terms defined according to the Medical Dictionary for Regulatory Activity (version 18.1). *Patients with multiple adverse events in the same category were counted only once in that category; patients with adverse events in more than one category were counted once in each of those categories. †Excludes patients who died as a result of disease progression. ‡One patient in each group had an adverse event that began before final protocol follow-up and resulted in death after final protocol follow-up; these patients were excluded from this summary. §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 or 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 could jeopardise the patient or require medical intervention to prevent one of the outcomes listed above; deaths resulting from disease progression were not counted as serious adverse events.

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

Discussion

REPROVE is the first phase 3 study of ceftazidime-avibactam in adults with nosocomial pneumonia (including ventilator-associated pneumonia). To our knowledge it is the first randomised controlled trial to show non-inferiority, compared with a carbapenem, of a new antimicrobial therapy targeting Gram-negative pathogens in this setting. Our results show non-inferiority for the treatment of nosocomial pneumonia caused by ceftazidime-non-susceptible or ceftazidime-susceptible Gram-negative aerobic pathogens.

The safety profile of ceftazidime-avibactam in this trial was similar to that of ceftazidime alone and consistent with the profile of ceftazidime-avibactam.[20–24] No new safety concerns were identified, and the overall pattern of adverse and serious adverse events was reflective of the underlying disease and comorbidities in this patient population. Although a numerical difference in the incidence of serious adverse events was noted between the ceftazidime-avibactam and meropenem groups, most were unrelated to study treatment.

Per-patient favourable microbiological response rates were generally lower than clinical cure rates, but similar across treatment groups. By contrast with previous antibiotic trials (albeit in community-acquired pneumonia),[25,26] no improvement was noted in clinical cure rates for patients who received 24 h or less of

previous antibiotics compared with those who did not receive previous antibiotics in either treatment group. These findings might have implications for design of future trials of nosocomial pneumonia, such as potentially extending permitted previous antibiotic use to a period greater than 24 h.

An exploratory analysis showed no difference in clinical cure rates between patients who received concomitant aminoglycosides (either ≤72 h or >72 h of exposure) and those who did not. The favourable clinical outcomes noted with either ceftazidime-avibactam or meropenem without aminoglycoside should be interpreted with caution, however, because REPROVE was not designed to evaluate monotherapy (ie, β-lactam alone) versus combination therapy (ie, a β-lactam plus aminoglycoside).

The persistence of an organism with increasing minimum inhibitory concentration with the same genotype as the baseline isolate occurred in 11 patients in the meropenem group (compared with one patient in the ceftazidime-avibactam group), which could affect clinicians' choice of empirical antibiotic therapy in the future for patients deemed to be at high risk of recurrence of nosocomial pneumonia, particularly for those with *P aeruginosa* infections.

Subgroup analyses of the primary endpoint showed no treatment differences across various patient subgroups. Despite initial expectations, no difference was observed in clinical cure rates between those with ventilator-associated and non-ventilator-associated penumonia. This finding might be related to improvements in care of patients with ventilator-associated infection, or possibly to the use of a standard comparator (meropenem) in this trial. Furthermore, some patients in whom non-ventilator-associated pneumonia was diagnosed subsequently required mechanical ventilation. Clinical cure rates were similar in patients with augmented renal clearance, normal renal function or mild impairment, or moderate to severe impairment.

During the early stages of REPROVE, results from RECLAIM 1 and 2 became available,[20] suggesting the potential that the per-protocol regimen of ceftazidime-avibactam could be an underdose in patients with moderate or severe renal impairment. Thus, the REPROVE protocol was amended to increase the ceftazidime-avibactam dose in such patients, and patients with moderate or severe renal impairment who received the original dosing regimen were excluded from the main analyses. Efficacy and safety results in these patients were consistent with those in the overall population, but the small size of this subgroup prevents definitive conclusions. The amended dosage modifications are supported by pharmacokinetic–pharmacodynamic analyses,[27] and reflect the approved product labelling.[28,29]

The mortality associated with nosocomial pneumonia is affected by several factors, and reported frequency varies substantially. All-cause mortality at day 28 (clinically modified intention-to-treat population) were 8% in the ceftazidime-avibactam group and 7% in the meropenem group—somewhat lower than some other investigators have reported.[3] However, REPROVE had a representative patient population in terms of ventilator-associated and non-ventilator-associated pneumonia, APACHE II score, and previous 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; these exclusions are likely to be reflected in the overall mortality rates.

A key limitation of this trial is that we could not establish optimum duration of treatment with either ceftazidime-avibactam or meropenem, and thus it does not provide any additional information that affects the standard of care with respect to these aspects of patient management. Furthermore, various aspects of the design, particularly the duration of study treatment of 7–14 days, although consistent with guidelines available at the start of the study,[30] might not be representative of clinical practice and guidelines, which typically involve antibiotic de-escalation based on culture results. Similarly, the mode of meropenem administration (30 min infusions every 8 h) we used was consistent with the approved label and guidelines,[3,30] but might not reflect how the drug is given now (some institutions give prolonged or continuous infusions). Such design constraints are common in non-inferiority trials, in which careful efforts to avoid confounding the results and falsely concluding non-inferiority are required. Furthermore, the small numbers of patients with bacteraemia limits the applicability of the results to patients with sepsis.

In summary, our data support a role for ceftazidime-avibactam as a carbapenem-sparing strategy for nosocomial pneumonia.

Contributors

AT, NZ, JP, J-FT, MK, and JWC designed and conceived the study. AT, NZ, JP, J-FT, DT, PJL, GGS, and JWC had roles in acquisition, analysis, or interpretation of data. PJL did the statistical analysis. ZC, JS, DT, PJL, and JWC provided administrative, technical, or material support. AT, DT, NZ, JP, J-FT, MK, ZC, and JS supervised the study. ZC, JS, DT, PJL, GGS, and JWC wrote the Article, which was critically revised for important intellectual content by all authors. All authors approved the final version of the Article.

Declaration of interests

AT received a consultancy fee from AstraZeneca for participating as principal investigator of the study. NZ, JP, J-FT, and MK's institutions received research grant funding from AstraZeneca for the conduct of the study. ZC and JS are employees of AstraZeneca. GGS and JWC were employees of, and shareholders in, AstraZeneca at the time of study completion, and are currently employees of Pfizer. DT was contracted to AstraZeneca from Taylormade Health at the time of study completion, and is a shareholder in AstraZeneca. PJL is contracted to AstraZeneca from the Statistical Services Unit, University of Sheffield.

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References

1 Magill SS, Edwards JR, Bamberg W, et al. Multistate point-prevalence survey of health care-associated infections. *N Engl J Med* 2014; **370:** 1198–208.

2 Kollef MH, Hamilton CW, Ernst FR. Economic impact of ventilator-associated pneumonia in a large matched cohort. *Infect Control Hosp Epidemiol* 2012; **33:** 250–56.

3 Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis* 2016; **63:** e61–111.

4 Jones RN. Microbial etiologies of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia. *Clin Infect Dis* 2010; **51** (suppl 1)**:** S81–87.

5 MacVane SH. Antimicrobial resistance in the intensive care unit: a focus on Gram-negative bacterial infections. *J Intensive Care Med* 2016; **32:** 25–37.

6 Kaye KS, Pogue JM. Infections caused by resistant gram-negative bacteria: epidemiology and management. *Pharmacotherapy* 2015; **35:** 949–62.

7 Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2013. http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf (accessed March 23, 2017).

8 Luna CM, Aruj P, Niederman MS, et al. Appropriateness and delay to initiate therapy in ventilator-associated pneumonia. *Eur Respir J* 2006; **27:** 158–64.

9 Zilberberg MD, Nathanson BH, Sulham K, Fan W, Shorr AF. Carbapenem resistance, inappropriate empiric treatment and outcomes among patients hospitalized with Enterobacteriaceae urinary tract infection, pneumonia and sepsis. *BMC Infect Dis* 2017; **17:** 279.

10 Lagace-Wiens P, Walkty A, Karlowsky JA. Ceftazidime-avibactam: an evidence-based review of its pharmacology and potential use in the treatment of Gram-negative bacterial infections. *Core Evid* 2014; **9:** 13–25.

11 Lahiri SD, Mangani S, Durand-Reville T, et al. Structural insight into potent broad-spectrum inhibition with reversible recyclization mechanism: avibactam in complex with CTX-M-15 and *Pseudomonas aeruginosa* AmpC beta-lactamases. *Antimicrob Agents Chemother* 2013; **57:** 2496–505.

12 Falcone M, Paterson D. Spotlight on ceftazidime/avibactam: a new option for MDR Gram-negative infections. *J Antimicrob Chemother* 2016; **71:** 2713–22.

13 De Jonge BL, Karlowsky JA, Kazmierczak KM, Biedenbach DJ, Sahm DF, Nichols WW. *In vitro* susceptibility to ceftazidime-avibactam of carbapenem-nonsusceptible Enterobacteriaceae isolates collected during the INFORM Global Surveillance Study (2012 to 2014). *Antimicrob Agents Chemother* 2016; **60:** 3163–69.

14 Hackel M, Kazmierczak KM, Hoban DJ, et al. Assessment of the in vitro activity of ceftazidime-avibactam against multidrug-resistant *Klebsiella* spp collected in the INFORM Global Surveillance Study, 2012 to 2014. *Antimicrob Agents Chemother* 2016; **60:** 4677–83.

15 Karlowsky JA, Biedenbach DJ, Kazmierczak KM, Stone GG, Sahm DF. Activity of ceftazidime-avibactam against extended-spectrum- and AmpC beta-lactamase-producing enterobacteriaceae collected in the INFORM Global Surveillance Study from 2012 to 2014. *Antimicrob Agents Chemother* 2016; **60:** 2849–57.

16 Clinical Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing. Twenty-second informational supplement. Wayne, PA: Clinical Laboratory Standards Institute, 2012.

17 European Medicines Agency. Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/11/WC500153953.pdf (accessed June 23, 2017).

18 Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. *Stat Med* 1998; **17:** 873–90.

19 Miettinen O, Nurminen M. Comparative analysis of two rates. *Stat Med* 1985; **4:** 213–26.

20 Mazuski JE, Gasink L, Armstong J, et al. Efficacy and safety of ceftazidime-avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infection: results from a randomised, controlled, double-blind, phase 3 program. *Clin Infect Dis* 2016; **62:** 1380–89.

21 Wagenlehner FM, Sobel JD, Newell P, et al. Ceftazidime-avibactam versus doripenem for the treatment of complicated urinary tract infections, including acute pyelonephritis: RECAPTURE, a phase 3 randomized trial program. *Clin Infect Dis* 2016; **63:** 754–62.

22 Carmeli Y, Armstrong J, Laud PJ, et al. Ceftazidime-avibactam or best available therapy in patients with ceftazidime-resistant Enterobacteriaceae and *Pseudomonas aeruginosa* complicated urinary tract infections or complicated intra-abdominal infections (REPRISE): a randomised, pathogen-directed, phase 3 study. *Lancet Infect Dis* 2016; **16:** 661–73.

23 Lucasti C, Popescu I, Ramesh MK, Lipka J, Sable C. Comparative study of the efficacy and safety of ceftazidime/avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infections in hospitalized adults: results of a randomized, double-blind, phase II trial. *J Antimicrob Chemother* 2013; **68:** 1183–92.

24 Vazquez JA, Gonzalez Patzan LD, Stricklin D, et al. Efficacy and safety of ceftazidime-avibactam versus imipenem-cilastatin in the treatment of complicated urinary tract infections, including acute pyelonephritis, in hospitalized adults: results of a prospective, investigator-blinded, randomized study. *Curr Med Res Opin* 2012; **28:** 1921–31.

25 Pertel PE, Bernardo P, Fogarty C, et al. Effects of prior effective therapy on the efficacy of daptomycin and ceftriaxone for the treatment of community-acquired pneumonia. *Clin Infect Dis* 2008; **46:** 1142–51.

26 File TM Jr, Low DE, Eckburg PB, et al. Integrated analysis of FOCUS 1 and FOCUS 2: randomized, doubled-blinded, multicenter phase 3 trials of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in patients with community-acquired pneumonia. *Clin Infect Dis* 2010; **51:** 1395–405.

27 Li J, Zhou D, Das S, et al. PK/PD target attainment analyses and assessment of dose adjustments for renal insufficiency for ceftazidime-avibactam (CAZ-AVI) in patients with complicated intra-abdominal infection (cIAI), complicated urinary tract infection (cUTI) or nosocomial pneumonia (NP). American Association of Pharmaceutical Scientists Annual Meeting and Exposition; Orlando, FL, USA; Oct 25, 2015; abstr 2459.

28 AstraZeneca. Summary of product characteristics: Zavicefta. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004027/WC500210234.pdf (accessed May 18, 2017).

29 Allergan. AVYCAZ (ceftazidime-avibactam) for injection, for intravenous use: prescribing information. http://pi.actavis.com/data_stream.asp?product_group=1957&p=pi&language=E (accessed May 18, 2017).

30 American Thoracic Society. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005; **171:** 388–416.

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