Cefiderocol versus high-dose, extended-infusion meropenem for the treatment of Gram-negative nosocomial pneumonia (APEKS-NP): a randomised, double-blind, phase 3, non-inferiority trial

Richard G Wunderink, Yuko Matsunaga, Mari Ariyasu, Philippe Clevenbergh, Roger Echols, Keith S Kaye, Marin Kollef, Anju Menon, Jason M Pogue, Andrew F Shorr, Jean-Francois Timsit, Markus Zeitlinger, Tsutae D Nagata

Summary

Background Nosocomial pneumonia due to multidrug-resistant Gram-negative pathogens poses an increasing challenge. We compared the efficacy and safety of cefiderocol versus high-dose, extended-infusion meropenem for adults with nosocomial pneumonia.

Methods We did a randomised, double-blind, parallel-group, phase 3, non-inferiority trial in 76 centres in 17 countries in Asia, Europe, and the USA (APEKS-NP). We enrolled adults aged 18 years and older with hospital-acquired, ventilator-associated, or health-care-associated Gram-negative pneumonia, and randomly assigned them (1:1 by interactive response technology) to 3-h intravenous infusions of either cefiderocol 2 g or meropenem 2 g every 8 h for 7–14 days. All patients also received open-label intravenous linezolid (600 mg every 12 h) for at least 5 days. An unmasked pharmacist prepared the assigned treatments; investigators and patients were masked to treatment assignment. Only the unmasked pharmacist was aware of the study drug assignment for the infusion bags, which were administered in generic infusion bags labelled with patient and study site identification numbers. Participants were stratified at randomisation by infection type and Acute Physiology and Chronic Health Evaluation II (APACHE II) score (≤15 and ≥16). The primary endpoint was all-cause mortality at day 14 in the modified intention-to-treat (ITT) population (ie, all patients receiving at least one dose of study drug, excluding patients with Gram-positive monomicrobial infections). The analysis was done for all patients with known vital status. Non-inferiority was concluded if the upper bound of the 95% CI for the treatment difference between cefiderocol and meropenem groups was less than 12·5%. Safety was investigated to the end of the study in the safety population, which included all patients who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, NCT03032380, and EudraCT, 2016-003020-23.

Findings Between Oct 23, 2017, and April 14, 2019, we randomly assigned 148 participants to cefiderocol and 152 to meropenem. Of 292 patients in the modified ITT population, 251 (86%) had a qualifying baseline Gram-negative pathogen, including *Klebsiella pneumoniae* (92 [32%]), *Pseudomonas aeruginosa* (48 [16%]), *Acinetobacter baumannii* (47 [16%]), and *Escherichia coli* (41 [14%]). 142 (49%) patients had an APACHE II score of 16 or more, 175 (60%) were mechanically ventilated, and 199 (68%) were in intensive care units at the time of randomisation. All-cause mortality at day 14 was 12·4% with cefiderocol (18 patients of 145) and 11·6% with meropenem (17 patients of 146; adjusted treatment difference 0·8%, 95% CI −6·6 to 8·2; p=0·002 for non-inferiority hypothesis). Treatment-emergent adverse events were reported in 130 (88%) of 148 participants in the cefiderocol group and 129 (86%) of 150 in the meropenem group. The most common treatment-emergent adverse event was urinary tract infection in the cefiderocol group (23 patients [16%] of 148) and hypokalaemia in the meropenem group (23 patients [15%] of 150). Two participants (1%) of 148 in the cefiderocol group and two (1%) of 150 in the meropenem group discontinued the study because of drug-related adverse events.

Interpretation Cefiderocol was non-inferior to high-dose, extended-infusion meropenem in terms of all-cause mortality on day 14 in patients with Gram-negative nosocomial pneumonia, with similar tolerability. The results suggest that cefiderocol is a potential option for the treatment of patients with nosocomial pneumonia, including those caused by multidrug-resistant Gram-negative bacteria.

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Division of Pulmonary and Critical Care Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA (Prof R G Wunderink MD); **Shionogi, Florham Park, NJ, USA** (Y Matsunaga MD, A Menon PhD); **Shionogi & Co, Osaka, Japan** (M Ariyasu BPharm, T D Nagata MD); **Brugmann University Hospital, Brussels, Belgium** (P Clevenbergh MD); **Infectious Disease Drug Development Consulting, Easton, CT, USA** (R Echols MD); **Division of Infectious Diseases, Department of Medicine, University of Michigan Medical School, Ann Arbor, MI, USA** (Prof K S Kaye MD); **Division of Pulmonary and Critical Care Medicine, John T Milliken Department of Medicine, Washington University School of Medicine, St Louis, MO, USA** (Prof M Kollef MD); **Department of Clinical Pharmacy, College of Pharmacy, University of Michigan, Ann Arbor, MI, USA** (Prof J M Pogue PharmD); **Pulmonary and Critical Care Medicine, Medstar Washington Hospital Center, Washington DC, USA** (Prof A F Shorr MD); **Georgetown University, Washington DC, USA** (Prof A F Shorr); **UMR 1137, IAME Inserm/Université de Paris – Paris Diderot, Paris, France** (Prof J-F Timsit MD); **APHP, Bichat Hospital, Medical and Infectious Diseases ICU, F75018 Paris, France** (Prof J-F Timsit); **and Department of Clinical Pharmacology, Medical University of Vienna, Vienna, Austria** (Prof M Zeitlinger MD)

Introduction

Nosocomial pneumonia is one of the most common hospital-acquired infections.[1] Clinicians face a growing challenge from the rising number of infections caused by multidrug-resistant (MDR) pathogens,[2] which can lead to increases in mortality if treatment is delayed or

Correspondence to:
Dr Tsutae D Nagata,
Shionogi & Co, Osaka 530-0012,
Japan
tsutae.den.nagata@shionogi.co.jp

Research in context

Evidence before this study

Cefiderocol is a siderophore antibiotic that provides in-vitro activity against nearly all aerobic Gram-negative pathogens associated with nosocomial pneumonia, such as Enterobacterales, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Stenotrophomonas maltophilia*, including multidrug-resistant isolates. Following the streamlined clinical development programme, cefiderocol has demonstrated efficacy in complicated urinary tract infections in hospitalised patients (APEKS-cUTI) and has been investigated in a pathogen-focused study in patients with serious carbapenem-resistant infections (CREDIBLE-CR), which included patients with nosocomial pneumonia. The purpose of the APEKS-NP study was to investigate the efficacy of cefiderocol for the treatment of nosocomial pneumonia caused by a broad range of Gram-negative bacteria, which might have reduced susceptibility to standard of care antibiotics. Contemporary studies of new investigational agents in nosocomial pneumonia generally focused on causative pathogens that were susceptible to both the new and the comparator drugs. However, these agents are not consistently active against *A baumannii*, an important multidrug-resistant respiratory pathogen.
No systematic literature review was done before initiation of this study.

Added value of this study

This study showed that cefiderocol, initially approved in the USA for complicated urinary tract infections, was non-inferior to high-dose, extended-infusion meropenem in terms of the primary outcome, all-cause mortality at day 14, in patients with Gram-negative nosocomial pneumonia. Similar all-cause mortality rates between cefiderocol and meropenem groups were also shown at day 28. Additionally, similar mortality rates between groups were shown in cases where *A baumannii* (including a proportion of meropenem non-susceptible strains) or extended-spectrum β-lactamase-producing species were the causative pathogens. This study was the basis for a supplemental US Food and Drug Administration new drug application for use of cefiderocol in hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia, which has been approved.

Implications of all the available evidence

This randomised, double-blind trial confirms the clinical efficacy and safety of cefiderocol in a patient population with serious respiratory tract infections caused by a broad range of Gram-negative bacteria, including *A baumannii*. The results support cefiderocol as a potential treatment option for critically ill patients with nosocomial pneumonia who are at risk of infection from multidrug-resistant Gram-negative pathogens.

ineffective.[3] Mortality in clinical practice remains high for both ventilated and non-ventilated patients with nosocomial pneumonia (from 30% to >70%).[3,4] Frequent causative Gram-negative pathogens include *Escherichia coli*, *Klebsiella pneumoniae*, and the non-fermenters *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Stenotrophomonas maltophilia*.[2–7] Among the most difficult-to-treat pathogens are extended-spectrum β-lactamase (ESBL) Enterobacterales or carbapenemase-producing Enterobacterales[8] and *A baumannii*, which frequently show resistance to most antibiotic therapies.[6]

Crucial to the successful treatment of patients with nosocomial pneumonia at risk for MDR pathogens is the use of appropriate empirical antibiotic therapy at doses capable of achieving pharmacokinetic–pharmacodynamic targets.[1,5,9] For many years, β-lactam antibiotics (eg, carbapenems) have been the backbone of antibiotic therapy for critically ill patients admitted to intensive care units (ICUs).[3,10] However, increased use of these agents has resulted in a global surge in carbapenem-resistant *K pneumoniae*, *P aeruginosa*, and *A baumannii* isolates.[11] Additionally, in critically ill patients an increased volume of distribution and augmented renal clearance might lead to suboptimal drug exposure when β-lactam antibiotics are selected for treatment.[12] Administering higher doses and prolonging infusion times according to pharmacokinetic–pharmacodynamic principles have been identified as ways of optimising the effectiveness of β-lactam antibiotics in this setting.[3,9,10,12,13] Studies show that extended infusion of high-dose (2 g) meropenem provides sufficient exposure even against isolates with higher minimum inhibitory concentrations (MICs).[10,14–17] The European Committee on Antimicrobial Susceptibility Testing (EUCAST) has established a susceptibility breakpoint of 8 μg/mL or less for this high-dose regimen of meropenem.[18]

Cefiderocol is a novel siderophore cephalosporin with broad activity and low MIC_{90} (ie, the MIC required to inhibit the growth of 90% of the organisms) values against Gram-negative bacteria susceptible and non-susceptible to carbapenems, including ESBL-producing or carbapenemase-producing Enterobacterales, *P aeruginosa*, and *A baumannii*, and other MDR Gram-negative pathogens.[19–21] Cefiderocol has no activity against Gram-positive or anaerobic pathogens.[19] Cefiderocol has linear pharmacokinetics and is excreted almost entirely via the kidneys, with an elimination half-life of 2–3 h.[22] Target concentrations are achieved with a 2 g infusion over 3 h every 8 h for most patients and with dose adjustments for patients with moderate or severe renal impairment or augmented renal clearance.[22] The streamlined clinical development of cefiderocol incorporated studies investigating its efficacy and safety in complicated urinary tract infections (APEKS-cUTI),[23] as well as in serious infections caused by carbapenem-resistant Gram-negative pathogens (CREDIBLE-CR),[24,25] involving multiple infection sites.

The objective of the phase 3 APEKS-NP study was to compare the efficacy and safety of cefiderocol versus high-dose, extended-infusion meropenem in patients with hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), or health-care-associated pneumonia (HCAP) caused by Gram-negative bacteria.

Methods

Study design and participants

We did a randomised, controlled, double-blind, parallel-group, phase 3 trial at 76 centres in 17 countries in Asia, Europe, and the USA (appendix p 4). The study design followed US regulatory considerations that were valid in 2016.[26] The study protocol was approved by relevant institutional review boards and independent ethics committees (appendix p 55).

Eligible patients were adults (≥18 years old) admitted to hospital with acute bacterial pneumonia in the form of HAP, VAP, or HCAP. HCAP was included as a subset clinical diagnosis to enrich the patient population for Gram-negative pathogens. Inclusion criteria for HAP and VAP were in accordance with the US Food and Drug Administration (FDA) guidelines (appendix p 6).[26] Eligibility required Gram-negative bacterial infection of the lower respiratory tract suspected on the basis of Gram stain or microbiological culture of respiratory secretions within 72 h before randomisation, or both. Eligibility included patients with pneumonia that was highly suspected to be due to Gram-negative bacteria on the basis of previous antibiotic use or local epidemiological evidence of a Gram-negative outbreak and those who did not respond to empirical antibiotic therapy within 2 calendar days for pneumonia caused by a Gram-negative pathogen. Key exclusion criteria included community-acquired, atypical, or viral pneumonia; chemical pneumonitis; pneumonia caused by a known carbapenem-resistant pathogen at the time of randomisation (patients who had a carbapenem-resistant pathogen confirmed after randomisation based on local susceptibility testing with relevant breakpoints had to be evaluated clinically, and continuation of therapy was at the investigator's discretion); an Acute Physiology and Chronic Health Evaluation II (APACHE II) score of more than 35; refractory septic shock; concomitant mould infection; cystic fibrosis, bronchiectasis, and concomitant CNS infection. Full inclusion and exclusion criteria are in the appendix (p 6). All patients or their legal guardians provided written informed consent.

Randomisation and masking

We randomly assigned participants (1:1) to treatment with either cefiderocol or meropenem. Randomisation was done via interactive response technology to identification numbers to which treatment had already been randomly assigned by the system provider. At randomisation, patients were stratified by infection type (HAP, VAP, and HCAP) and APACHE II scores (≤15 and ≥16). The proportion of ventilated participants in the study was anticipated to be approximately 50%.

An unmasked pharmacist prepared the allocated treatments according to the study pharmacy manual. Only the unmasked pharmacist was aware of the study drug assignment for the infusion bags, which were administered in generic infusion bags labelled with patient and study site identification numbers according to local regulatory requirements. The investigator, site personnel, sponsor, and the sponsor's designees involved in monitoring, data management, or other aspects of the study (except for those involved in obtaining and preparing the drugs), and patients were masked to treatment assignment. Cefiderocol and meropenem were prepared in physiological saline solution and administration for both had to be completed within 4 h of preparation, including duration of infusion.

See Online for appendix

Procedures

Patients received 3-h intravenous infusions of either cefiderocol 2 g or meropenem 2 g (each in at least 100 mL saline solution) every 8 h for 7–14 days. Treatment could be extended to 21 days based on the investigator's clinical assessment of the patient. The meropenem dosing regimen was selected in consultation with clinical and medical experts and agreed with the FDA because it is not included in the product label. EUCAST has designed breakpoints for this meropenem regimen (susceptible: MIC ≤8 μg/mL).[18] The initial dose of study drugs was modified based on estimated creatinine clearance, and was adjusted to 2 g every 6 h for cefiderocol in patients with a creatinine clearance of more than 120 mL/min (appendix p 8). Such dose modifications were carried out by the unmasked hospital pharmacist or qualified designee. In agreement with the FDA, a double-dummy study design was not adopted to avoid the risk of fluid overload for such patients. All patients also received open-label intravenous linezolid (600 mg every 12 h) for at least 5 days to ensure coverage of Gram-positive bacteria in the cefiderocol group and of meticillin-resistant *Staphylococcus aureus* in both treatment groups.

Systemic adjunctive antibiotics for Gram-negative pathogens and aerosolised antibiotics were not permitted from randomisation until test of cure. Sequential step-down oral antibiotic treatment was not permitted in the study. Patients who were assessed as having had treatment failure could be switched to rescue therapy with an alternative systemic antibacterial agent, and an end of therapy assessment for study drug had to be completed. The rescue therapy was recorded until end of study.

Clinical assessments are described in detail in the appendix (pp 10–11). Clinical signs and symptoms of pneumonia, such as sputum production, increase or thickening of tracheal secretions, cough, dyspnoea (including retractions), chest pain, wheezing, rales,

rhonchi, aegophony, dullness to percussion, and bronchial breath sounds were assessed at baseline as absent, mild, moderate, severe, or unknown. Signs and symptoms present at baseline were similarly assessed at specified timepoints. For microbiological assessments at all timepoints, appropriate respiratory specimens, collected by mini bronchoalveolar lavage, protected specimen brush, and endotracheal aspirate or as expectorated sputum, and two blood samples from separate venepunctures were obtained within 48 h before the first dose of study treatment and processed at the local laboratory for identification and susceptibility testing of all causative species. All baseline respiratory specimens required a Gram stain, and quality of the sample was ascertained at low-power microscopic view (report of both inflammatory cells and bacteria was required). Specimens were grown semi-quantitatively or quantitatively with appropriate method-specific dilutions. All isolated pathogens were frozen and stored for shipping to the central laboratory (International Health Management Associates, Schaumburg, IL, USA) for confirmation of species, their susceptibility pattern, and molecular characterisation of resistance to β-lactam antibiotics, where applicable (appendix p 3).

Blood samples were collected from all patients on days 3–4. Following study completion and unblinding, the samples from the cefiderocol group underwent pharmacokinetic analysis, the results of which will be published elsewhere. Meropenem concentrations and pharmacokinetics were not investigated.

Outcomes

The primary endpoint was all-cause mortality at day 14. Between-treatment differences in all-cause mortality at day 14 were analysed for predefined subgroups, comprising clinical diagnosis, sex, race, age, geographical region, and baseline clinical characteristics (ie, APACHE II score, Clinical Pulmonary Infection Score [CPIS], concomitant bacteraemia, renal function, empirical treatment failure, in ICU at randomisation, ventilation status at randomisation, and the five most common baseline Gram-negative pathogens). Superiority of cefiderocol over meropenem in terms of all-cause mortality on day 14 was a secondary endpoint.

Key secondary endpoints included clinical and microbiological outcomes per treatment group at test of cure (7 days [plus or minus 2 days] after the end of treatment). Other secondary endpoints consisted of clinical and microbiological outcomes per patient or per baseline pathogen at early assessment (days 3–4 of treatment), end of treatment (last day of treatment), and follow-up (14 days [plus or minus 3 days] after the end of treatment. All-cause mortality at day 28, overall and according to the same subgroups used for day 14 all-cause mortality analyses, was assessed as a secondary endpoint. Other secondary analyses also included clinical and microbiological outcomes by baseline pathogen at each timepoint, and changes from baseline in the Sequential Organ Failure Assessment (SOFA) score and CPIS. Definitions of clinical and microbiological outcomes are in the appendix (pp 13–14).

Post-hoc subgroup analyses of all-cause mortality and clinical and microbiological outcomes were done according to meropenem non-susceptibility based on two criteria: Clinical and Laboratory Standards Institute breakpoints,[27] which are species-dependent (including intermediate and resistant: MIC ≥4 μg/mL for *P aeruginosa,* ≥8 μg/mL for *Acinetobacter spp,* and ≥2 μg/mL for Enterobacterales), and EUCAST's susceptibility breakpoint (ie, resistance when MIC >8 μg/mL and susceptibility when MIC ≤8 μg/mL for high-dose extended-infusion meropenem, which is species-independent).[18] Meropenem non-susceptibility was confirmed by the central laboratory. Additionally, post-hoc analyses of mortality at day 14 and day 28 were done for pathogen type, in *Acinetobacter* spp cases according to EUCAST's susceptibility breakpoint for meropenem, for pathogens expressing ESBL enzymes, and at least four-fold increases in MICs from baseline were also assessed.

The safety of the study drugs was assessed during the period from the time of informed consent to the end of study (ie, 28 days [plus or minus 3 days] after the end of treatment). Treatment-emergent adverse events (TEAEs) were assessed using the Medical Dictionary for Regulatory Activities (version 18.1). The relationship of TEAEs to treatment was determined by the investigator. All patients were followed up after discharge from hospital until their follow-up visit, and those with a TEAE or a serious adverse event were followed up until resolution of the adverse event (including death) after the end of study visit. Additional safety assessments and routine laboratory investigations included hepatic enzyme elevations, iron homoeostasis parameters, and *Clostridioides difficile*-related adverse events.

Statistical analysis

The study was designed to test the hypothesis that cefiderocol is non-inferior to meropenem for day 14 all-cause mortality based on a 12·5% non-inferiority margin, as agreed with the FDA as part of cefiderocol's streamlined development. Non-inferiority could be concluded if the upper boundary of the two-sided 95% CI for the adjusted difference in mortality (defined as all-cause mortality for cefiderocol minus all-cause mortality for meropenem) was smaller than 12·5% (appendix p 15). Assuming all-cause mortality for 10% of participants in both groups at day 14,[7,28] the 12·5% non-inferiority margin would achieve 90% power with a one-sided significance level of 0·025, for which a sample size of 244 evaluable patients (122 in each group) was required. With an estimated non-evaluable rate of 20% of randomly assigned patients, a target of 300 randomised patients was set.

The primary endpoint was assessed in the modified intention-to-treat (ITT) population, which consisted of all randomly assigned patients who met inclusion criteria

and received at least one dose of study drug, excluding patients with Gram-positive monomicrobial infections. The ITT population consisted of all randomly assigned patients who received at least one dose of study drug (appendix p 12). Sensitivity analyses of all-cause mortality on day 14 were done in the microbiologically evaluable per-protocol (ME-PP) population, which included all randomly assigned patients in the modified ITT population without a major protocol violation and with a culture-confirmed diagnosis of a Gram-negative bacterium. Safety endpoints were assessed in the safety population, which consisted of randomly assigned patients who received at least one dose of study drug and were assessed for the actual study treatment they received.

The adjusted estimates of the difference in mortality between cefiderocol and meropenem groups are presented with two-sided 95% CIs that were calculated based on a stratified analysis using Cochran–Mantel–Haenszel weights and calculated with APACHE II scores (≤15 and ≥16). We included the APACHE II score, which has been shown to be a predictor of mortality (appendix), as the only stratification factor in the analysis because a low number of deaths was expected. The analysis was done for all patients with known vital status.

For subgroup analyses, unadjusted estimates of the difference in all-cause mortality at day 14 between the cefiderocol and meropenem groups overall and within each subgroup were calculated along with two-sided 95% CIs using a normal approximation to the difference between two binomial proportions (Wald method) if data warranted (ie, at least ten patients in each subgroup were available for analysis to present the 95% Wald CIs). The widths of the CIs for subgroup analyses were not adjusted for multiplicity and therefore cannot be used to infer treatment effects.

For clinical and microbiological outcomes per patient, the Cochran–Mantel–Haenszel method used both clinical diagnosis and APACHE II score as stratification factors. For key secondary analyses, a fixed-sequence multiplicity strategy included the primary endpoint and three key secondary endpoints (microbiological outcome at test of cure, clinical outcome at test of cure, and superiority based on all-cause mortality at day 14). Such a strategy, designed to avoid type 1 error inflation associated with testing multiple hypotheses, is applied by performing stepwise testing on a prespecified sequence of hypotheses. The testing proceeds in sequence until a hypothesis tests as not significant, at which point none of the remaining subsequent tests in the sequence are done.

Continuous variables are summarised using the number of non-missing observations, the arithmetic mean, and SD as summary statistics. Categorical variables are summarised using the frequency count and percentage of patients in each category. Missing data were not replaced or imputed. All analyses were done using SAS version 9.2 or higher.

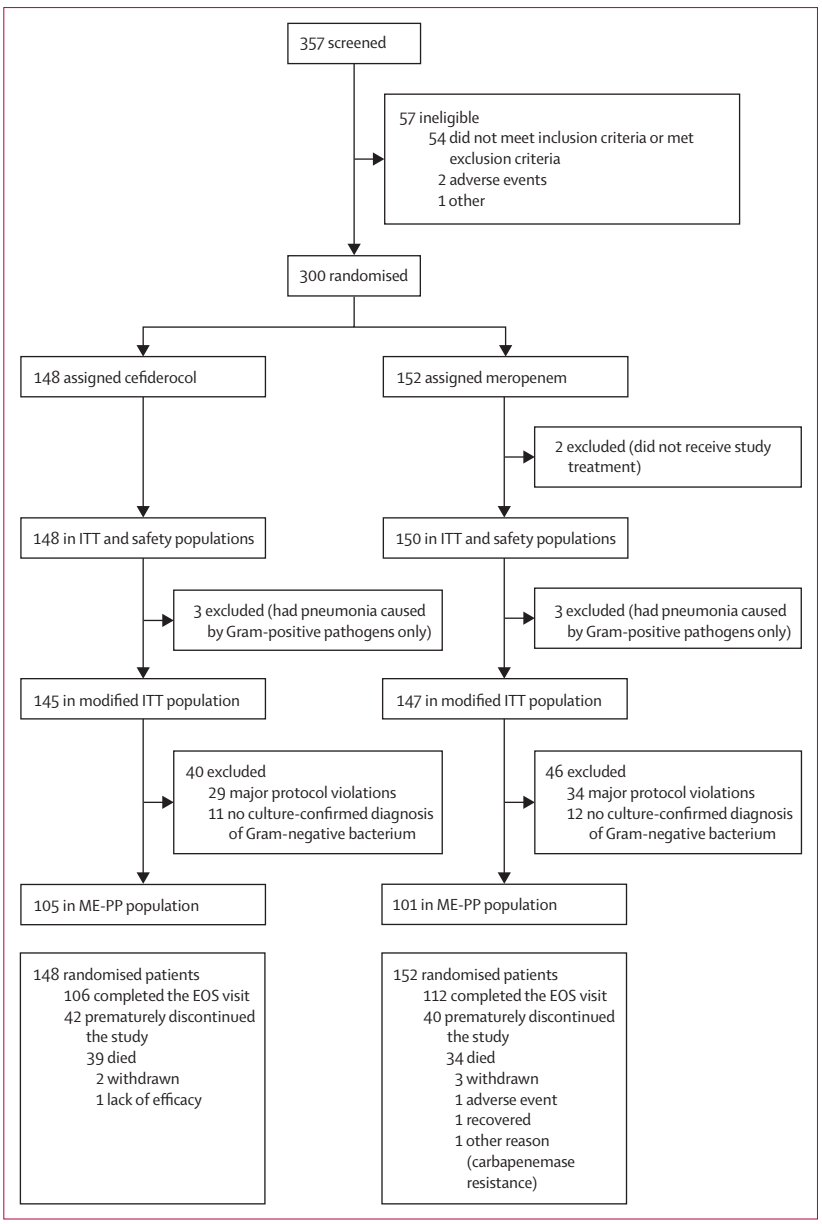

Figure 1: **Trial profile**
Details of major protocol violations are in the appendix (p 16). EOS=end of study. ITT=intention-to-treat. ME-PP=microbiologically evaluable per-protocol.

An unblinded evaluation of safety and efficacy data was done by an independent data safety monitoring board (DSMB) for the first 50 and 100 patients who completed the study. The DSMB supported the study's continuation without protocol modification. This trial is registered with ClinicalTrials.gov, NCT03032380 and EudraCT, 2016-003020-23.

Role of the funding source

The funder of the study provided the study drugs and had a role in the study design, protocol development,

	Cefiderocol (n=145)	Meropenem (n=147)
Sex		
Male	99 (68%)	101 (69%)
Female	46 (32%)	46 (31%)
Age (years)		
Mean (SD)	64·6 (14·6)	65·4 (15·1)
≥65	80 (55%)	89 (61%)
≥75	40 (28%)	44 (30%)
Body-mass index (kg/m²)	26·4 (6·1)	26·7 (6·9)
Region		
Europe	99 (68%)	98 (67%)
Asia-Pacific	40 (28%)	43 (29%)
North America	6 (4%)	6 (4%)
Race		
White	102 (70%)	98 (67%)
Asian	41 (28%)	43 (29%)
Other or missing	2 (1%)	6 (4%)
Clinical diagnosis		
VAP	59 (41%)	64 (44%)
HAP	59 (41%)	60 (41%)
HCAP	27 (19%)	23 (16%)
Ventilated at randomisation		
VAP*	58/59 (98%)	63/64 (98%)
HAP	22/59 (37%)	21/60 (35%)
HCAP	9/27 (33%)	2/23 (9%)
Creatinine clearance (mL/min)		
Mean (SD)	78·5 (55·4)	82·7 (56·6)
>120	22 (15%)	26 (18%)
>80 to 120	33 (23%)	35 (24%)
>50 to 80	43 (30%)	35 (24%)
30–50	27 (19%)	31 (21%)
<30	20 (14%)	20 (14%)
Empirical treatment failure	48 (33%)	47 (32%)
Previous therapy		
Antibiotics†	105 (72%)	101 (69%)
Carbapenems	11 (8%)	10 (7%)
Systemic corticosteroids	61 (42%)	39 (27%)
Medical history by preferred term, ≥15% in either treatment group‡		
Diabetes	46 (32%)	36 (24%)
Chronic obstructive pulmonary disease	39 (27%)	31 (21%)
Hypertension	94 (65%)	102 (69%)
Atrial fibrillation	33 (23%)	38 (26%)
Cardiac failure	32 (22%)	41 (28%)
Coronary artery disease	24 (17%)	18 (12%)
Myocardial ischaemia	18 (12%)	26 (18%)
Hypokalaemia	26 (18%)	24 (16%)
Anaemia	28 (19%)	27 (18%)
In ICU at randomisation	102 (70%)	97 (66%)
APACHE II score		
Mean (SD)	16·0 (6·1)	16·4 (6·9)
≤15	74 (51%)	76 (52%)
16–19	31 (21%)	25 (17%)
≥20	40 (28%)	46 (31%)
CPIS score		
Overall	5·4 (1·7)	5·2 (1·9)§
Ventilated patients¶	5·9 (1·6)	5·8 (1·9)
Non-ventilated patients¶	4·7 (1·7)	4·2 (1·4)
SOFA score		
Overall	4·7 (3·0)	4·9 (3·4)§
Ventilated patients‖	6·1 (2·8)	6·3 (3·1)
Non-ventilated patients‖	2·6 (2·0)	2·8 (2·6)
Severity of disease**		
Mild	4 (3%)	7 (5%)
Moderate	70 (48%)	91 (62%)
Severe	71 (49%)	49 (33%)

The modified intention-to-treat population included all randomly assigned patients who met inclusion criteria and received at least one dose of study drug, excluding patients with Gram-positive monomicrobial infections. Data are n (%), n/N (%), or mean (SD). VAP=ventilator-associated pneumonia. HAP=hospital-acquired pneumonia. HCAP=health care-associated pneumonia. ICU=intensive care unit. APACHE II=Acute Physiology and Chronic Health Evaluation II. CPIS=Clinical Pulmonary Infection Score. SOFA=Sequential Organ Failure Assessment.
*Two patients with VAP (one in each treatment group) were removed from the ventilator at randomisation. †Previous antibiotic therapy to treat another infection or as prophylaxis taken within the 2 weeks before randomisation. ‡Medical history was reported by investigators (appendix p 55) and coded by the sponsor to Preferred Terms and System Organ Classes according to the Medical Dictionary for Regulatory Activities (version 18.1) hierarchy. §Data available for 146 patients. ¶For ventilated patients, data were available for 89 patients assigned cefiderocol and 86 assigned meropenem; for non-ventilated patients, data were available for 56 patients assigned cefiderocol and 61 assigned meropenem. ‖For ventilated patients, data were available for 89 patients assigned cefiderocol and 85 assigned meropenem (missing baseline value for one patient); for non-ventilated patients, data were available for 56 patients assigned cefiderocol and 61 assigned meropenem.
**Disease severity was based on the investigator's clinical judgement and according to local practice (clinical signs and symptoms listed in the Methods).

Table 1: **Baseline characteristics of the modified intention-to-treat population**

writing of the statistical analysis plan, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Oct 23, 2017, and April 14, 2019, we randomly assigned 300 patients to treatment: 148 to cefiderocol and 152 to meropenem (figure 1, appendix p 16). Three patients in each group had Gram-positive only pneumonia and were excluded from the modified ITT population; additionally, two patients were excluded from the meropenem group analyses because they did not receive study treatment. Thus, the modified ITT population included 292 patients (98% of the ITT population).

	Cefiderocol (n=145)	Meropenem (n=147)
Type of baseline pathogen		
Gram-negative only	113 (78%)	105 (71%)
Mixed*	11 (8%)	22 (15%)
Fungal only	1 (1%)	1 (1%)
None (contaminant or coloniser only, or culture negative)	15 (10%)	13 (9%)
No respiratory sample	3 (2%)	4 (3%)
Missing	2 (1%)	2 (1%)
Baseline Gram-negative pathogen (all patients)		
Klebsiella pneumoniae	48 (33%)	44 (30%)
Pseudomonas aeruginosa	24 (17%)	24 (16%)
Acinetobacter baumannii	23 (16%)	24 (16%)
Escherichia coli	19 (13%)	22 (15%)
Enterobacter cloacae	7 (5%)	8 (5%)
Other†	38 (26%)	42 (29%)
Baseline Gram-negative pathogen (HAP only)		
K pneumoniae	19/59 (32%)	17/60 (28%)
P aeruginosa	10/59 (17%)	5/60 (8%)
A baumannii	8/59(14%)	11/60 (18%)
E coli	6/59 (10%)	7/60 (12%)
E cloacae	2/59 (3%)	3/60 (5%)
Other†	15/59 (25%)	16/60 (27%)
Baseline Gram-negative pathogen (VAP only)		
K pneumoniae	19/59 (32%)	19/64 (30%)
P aeruginosa	11/59 (19%)	14/64 (22%)
A baumannii	12/59 (20%)	10/64 (16%)
E coli	12/59 (20%)	12/64 (19%)
Serratia marcescens	7/59 (12%)	4/64 (6%)
E cloacae	2/59 (3%)	5/64 (8%)
Other†	11/59 (19%)	15/64 (23%)
Baseline Gram-negative pathogen (HCAP only)		
K pneumoniae	10/27 (37%)	8/23 (35%)
P aeruginosa	3/27 (11%)	5/23 (22%)
A baumannii	3/27 (11%)	3/23 (13%)
E coli	1/27 (4%)	3/23 (13%)
S marcescens	1/27 (4%)	0
E cloacae	3/27 (11%)	0
Other†	4/27 (15%)	7/23 (30%)
(Table 2 continues in next column)		
(Continued from previous column)		
ESBL producers‡§	45/145 (31%)	42/147 (29%)
Enterobacterales	36/69 (52%)	25/67 (37%)
P aeruginosa	1/24 (4%)	3/24 (13%)
A baumannii	10/23 (43%)	16/24 (67%)
Carbapenemase producers§¶		
Enterobacterales	9/69 (13%)	3/67 (4%)
P aeruginosa	2/24 (8%)	2/24 (8%)
A baumannii	16/23 (70%)	15/24 (63%)
Number of Gram-negative pathogens isolated at baseline		
0	21 (14%)	20 (14%)
1	95 (66%)	96 (65%)
2	25 (17%)	26 (18%)
≥3	4 (3%)	5 (3%)
Gram-negative bacteraemia	8 (6%)	10 (7%)

The modified intention-to-treat population included all randomly assigned patients who met inclusion criteria and received at least one dose of study drug, excluding patients with Gram-positive monomicrobial infections. Data are n (%) or n/N (%), where N is the number of patients with the respective infection type or number of patients with the respective pathogen. HAP=hospital-acquired pneumonia. VAP=ventilator-associated pneumonia. HCAP=health care-associated pneumonia. ESBL=extended-spectrum β-lactamase. *Mixed infections included Gram-negative and Gram-positive pathogens at randomisation. †Other included *Stenotrophomonas maltophilia*: one patient assigned cefiderocol (HCAP), and three assigned meropenem (one each for HAP, VAP, and HCAP). ‡ESBLs were examined when isolates proved to be either resistant to meropenem or susceptible to meropenem but resistant to cefepime or aztreonam, based on Clinical and Laboratory Standards Institute breakpoints. §Patients could have one or more baseline pathogen. ¶Carbapenemases were examined when isolates proved to be resistant to meropenem.

Table 2: **Baseline pathogen distribution in the modified intention-to-treat population**

Baseline demographic and clinical characteristics were balanced between the two treatment groups in the modified ITT population (table 1) and the ITT and safety populations (appendix p 17). 42% (123/292) of patients were diagnosed with VAP, 41% (119/292) with HAP, and 17% (50/292) with HCAP. 60% (175/292) of patients required mechanical ventilation, with similar proportions between treatment groups for VAP and HAP. Fewer patients with HCAP in the meropenem group required mechanical ventilation than in the cefiderocol group. Renal function and mean APACHE II, CPIS, and SOFA scores were also similar between the two treatment groups (table 1, appendix pp 17–19).

124 (86%) of 145 patients in the cefiderocol group and 127 (86%) of 147 patients in the meropenem group had a culture-documented Gram-negative infection (table 2). Monomicrobial Gram-negative infections were present in 66% (95/145) and 65% (96/147) of patients in the cefiderocol and meropenem groups, respectively. The most commonly detected pathogen was *K pneumoniae*, followed by *P aeruginosa* and *A baumannii*, in all three pneumonia types. ESBLs were frequently found in Enterobacterales spp, and carbapenemases were most common in *A baumannii* (table 2).

Cefiderocol MIC_{90} values for the most frequent pathogens in the modified ITT population ranged between 0·5 µg/mL and 2·0 µg/mL (appendix p 20). Cefiderocol MIC values of 4 µg/mL or higher were infrequent (two *A baumannii* and two *K pneumoniae* in the cefiderocol group, and two *K pneumoniae*, eight *A baumannii*, and one *Rhizobium radiobacter* in the meropenem group). According to the central laboratory test results, which became available after randomisation, meropenem MIC_{90} values were high for

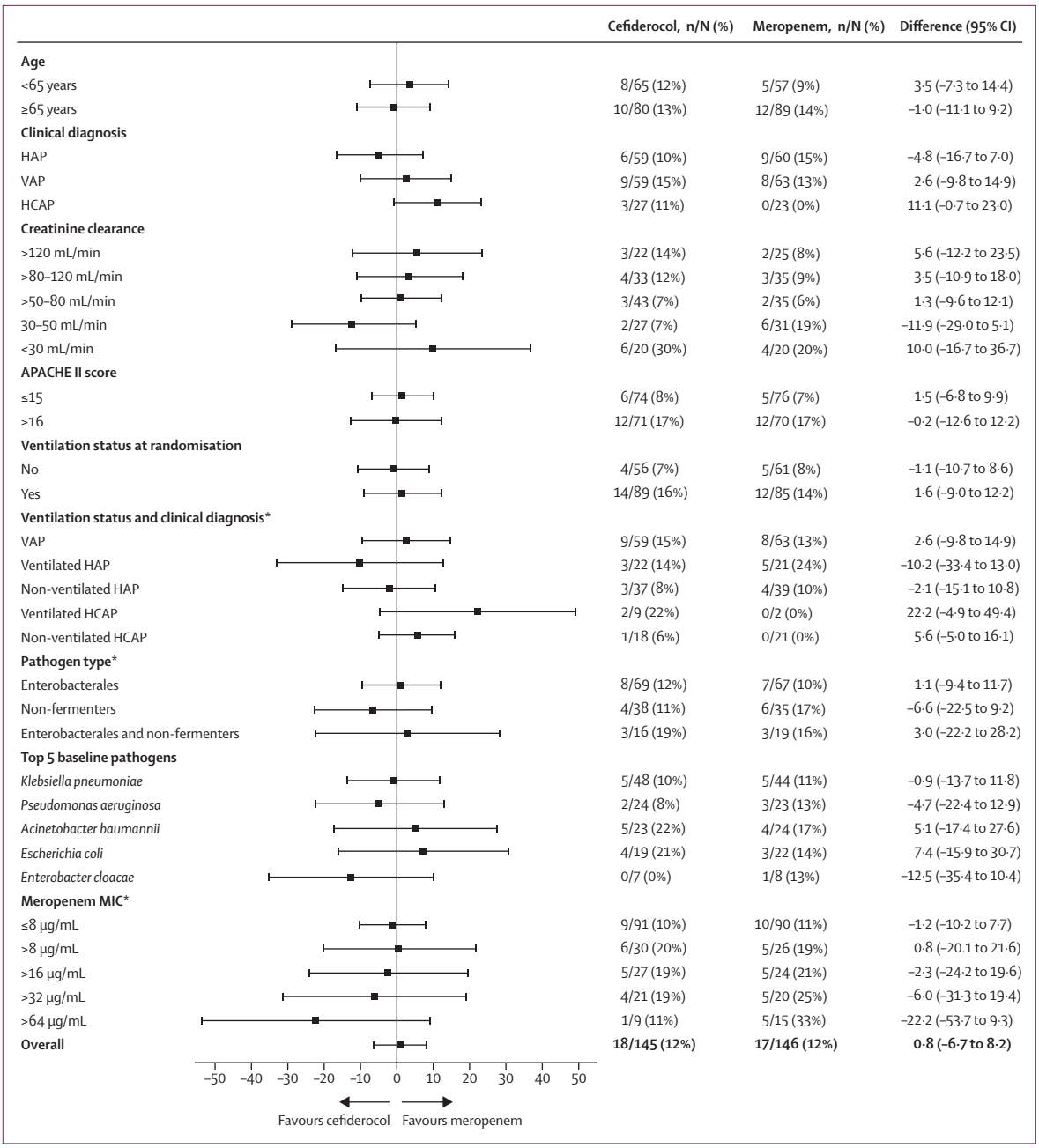

Figure 2: **All-cause mortality at day 14**

Data are shown for selected subgroups in the modified intention-to-treat population (appendix p 21). The widths of the 95% CIs for the subgroup analyses were not adjusted for multiplicity and therefore cannot be used to infer treatment effects. Percentages for overall and subgroup analyses were calculated as the number of patients who died from any cause at or before day 14 divided by the total number of patients in the analysis populations or within subgroups with known survival status at day 14. HAP=hospital-acquired pneumonia. VAP=ventilator-associated pneumonia. HCAP=health care-associated pneumonia. APACHE II=Acute Physiology and Chronic Health Evaluation II. MIC=minimum inhibitory concentration. *Post-hoc analysis categories.

some species, and central laboratory testing revealed that 30 (24%) of 124 patients in the cefiderocol group and 26 (20%) of 127 patients in the meropenem group had a pathogen with a meropenem MIC of more than 8 µg/mL; most of these organisms were *A baumannii*.

The mean duration of treatment was similar in both groups in the ITT and safety populations: 10·4 days (SD 4·1) for cefiderocol and 10·1 days (4·0) for meropenem, with 21% (31/148) and 16% (24/150) of patients, respectively, receiving more than 14 days of treatment. Dose adjustments based on renal function were required in 26%

(38/148) of cefiderocol-treated patients and 23% (34/150) of meropenem-treated patients. The mean duration of linezolid treatment was 7·2 days (SD 3·2) in the cefiderocol group and 6·8 days (2·8) in the meropenem group.

The primary endpoint of all-cause mortality at day 14 in the modified ITT population was 12·4% for the cefiderocol group (18 patients of 145) and 11·6% for the meropenem group (17 patients of 146; adjusted treatment difference 0·8%, 95% CI –6·6 to 8·2; p=0·002 for the non-inferiority hypothesis). Statistical analysis for superiority in the primary endpoint could not be tested according to results in the protocol-specified multiplicity strategy. All-cause mortality was also similar between groups at day 28 (21·0% [30 patients of 143 in the cefiderocol group *vs* 20·5% [30 patients of 146] in the meropenem group; adjusted treatment difference 0·5%, 95% CI –8·7 to 9·8). Predefined subgroup analyses in the modified ITT population of day 14 all-cause mortality showed no clinically important differences between the cefiderocol and meropenem groups, except for the subgroup of patients with HCAP in which numerically more patients died in the cefiderocol group than in the meropenem group (nine *vs* two; figure 2; appendix p 21). All-cause mortality findings at day 28 were similar between treatment groups in patients with higher risk scores (eg, APACHE II scores ≥20 and SOFA scores ≥7), with previous empirical treatment failure, and in the ICU at randomisation (appendix pp 22–23). At the end of study visit, 38 (27%) of 142 patients in the cefiderocol group and 34 (23%) of 146 in the meropenem group had died (denominators here are the number of patients for whom vital status was known at the end of study visit). The findings for all-cause mortality at days 14 and 28 in the modified ITT population were supported by sensitivity analyses in the ME-PP population (appendix p 24).

The proportions of patients with clinical cure at test of cure in the modified ITT population were 94 patients (65%) of 145 in the cefiderocol group and 98 (67%) of 147 in the meropenem group (adjusted treatment difference –2·0, 95% CI –12·5 to 8·5; appendix p 25). The proportions with microbiological eradication at test of cure were 59 patients (48%) of 124 in the cefiderocol group and 61 (48%) of 127 in the meropenem group (adjusted treatment difference –1·4, 95% CI –13·5 to 10·7; appendix p 26).

In a subgroup analysis, the proportions of patients with clinical cure and microbiological eradication at test of cure were highest in both groups in patients with HCAP (table 3). Ten (7%) of 145 patients in the cefiderocol group and 13 (9%) of 147 in the meropenem group received rescue therapy. Prespecified sensitivity analyses of the clinical and microbiological outcomes in the ME-PP population supported the findings in the modified ITT population (appendix pp 28–29).

The clinical and microbiological outcomes at test of cure were generally similar in both groups for each of the most common baseline pathogens (table 3; appendix pp 30–32).

	Cefiderocol (n=145)	Meropenem (n=147)	Treatment difference (95% CI)
Clinical cure			
All patients	94/145 (65%)	98/147 (67%)	–1·8 (–12·7 to 9·0)
HAP	33/59 (56%)	41/60 (68%)	–12·4 (–29·7 to 4·9)
VAP	39/59 (66%)	36/64 (56%)	9·9 (–7·3 to 27·0)
HCAP	22/27 (82%)	21/23 (91%)	–9·8 (–28·5 to 8·8)
Top five baseline pathogens			
Klebsiella pneumoniae	31/48 (65%)	29/44 (66%)	–1·3 (–20·8 to 18·1)
Pseudomonas aeruginosa	16/24 (67%)	17/24 (71%)	–4·2 (–30·4 to 22·0)
Acinetobacter baumannii	12/23 (52%)	14/24 (58%)	–6·2 (–34·5 to 22·2)
Escherichia coli	12/19 (63%)	13/22 (59%)	4·1 (–25·8 to 33·9)
Enterobacter cloacae	5/7 (71%)	4/8 (50%)	21·4 (NA)
Microbiological eradication			
All patients	59/145 (41%)	61/147 (42%)	–0·8 (–12·1 to 10·5)
HAP	21/59 (36%)	27/60 (45%)	–9·4 (–26·9 to 8·1)
VAP	25/59 (42%)	22/64 (34%)	8·0 (–9·2 to 25·2)
HCAP	13/27 (48%)	12/23 (52%)	–4·0 (–31·8 to 23·8)
Top five baseline pathogens			
K pneumoniae	21/48 (44%)	22/44 (50%)	–6·3 (–26·6 to 14·1)
P aeruginosa	9/24 (38%)	11/24 (46%)	–8·3 (–36·1 to 19·5)
A baumannii	9/23 (39%)	8/24 (33%)	5·8 (–21·7 to 33·2)
E coli	10/19 (53%)	11/22 (50%)	2·6 (–28·0 to 33·3)
E cloacae	4/7 (57%)	3/8 (38%)	19·6 (NA)

The modified intention-to-treat population included all randomly assigned patients who met inclusion criteria and received at least one dose of study drug, excluding patients with Gram-positive monomicrobial infections. Data are n/N (%) unless stated otherwise. The treatment difference (cefiderocol minus meropenem) is the estimate of the difference in clinical cure or microbiological eradication rate at test of cure between the two treatment groups. HAP=hospital-acquired pneumonia. VAP=ventilator-associated pneumonia. HCAP=health care-associated pneumonia. NA=not available.

Table 3: **Clinical cure and microbiological eradication at test of cure in the modified intention-to-treat population**

The findings for clinical outcomes in the modified ITT population were supported by similar inter-group post-baseline changes in CPIS and SOFA scores (appendix p 34). 56 patients had isolates with meropenem MIC values that were higher than 8 µg/mL (30 with cefiderocol and 26 with meropenem). For patients with Gram-negative pathogens with meropenem MIC values greater than 8 µg/mL at baseline, all-cause mortality rates at day 14 and day 28 were similarly higher in both groups compared with rates for patients with MIC values of 8 µg/mL or less (appendix pp 35–36). At test of cure in the subgroup of patients with meropenem MIC greater than 8 µg/mL, clinical cure was reported in 17 patients (57%) of 30 in the cefiderocol group and in 15 (58%) of 26 in the meropenem group (appendix p 37). For the same subgroup, microbiological eradication was reported in 12 patients (40%) of 30 in the cefiderocol group and in eight (31%) of 26 in the meropenem group (appendix p 38). Two patients for whom meropenem-resistant species were reported based on local susceptibility testing for the baseline pathogen discontinued the study because of the investigator's concern regarding a potential absence of response to treatment.

	Cefiderocol (n=148)	Meropenem (n=150)
All TEAEs	130 (88%)	129 (86%)
Mild*	33 (22%)	37 (25%)
Moderate†	41 (28%)	47 (31%)
Severe‡	56 (38%)	45 (30%)
Drug-related TEAEs	14 (9%)	17 (11%)
Treatment-emergent SAEs	54 (36%)	45 (30%)
SAEs leading to death	39 (26%)	35 (23%)
Drug-related SAEs	3 (2%)	5 (3%)
Discontinuation due to TEAEs	12 (8%)	14 (9%)
Discontinuation due to drug-related TEAEs	2 (1%)	2 (1%)

Data are n (%). SAEs were events with the following outcomes: death, life-threatening condition, admission to hospital or prolongation of hospital stay, persistent or significant disability or incapacity, congenital anomaly or birth defect, or other medically important conditions. TEAE=treatment-emergent adverse event. SAE=serious adverse event. *Mild was defined as a finding or symptom that was minor and did not interfere with usual daily activities. †Moderate was defined as an event that caused discomfort and interfered with usual daily activity or affected clinical status. ‡Severe was defined as an event that interrupted the patient's usual daily activities or had a clinically significant effect (appendix p 47).

Table 4: **TEAEs by patient in the safety population**

In patients with *Acinetobacter* spp pneumonia, all-cause mortality at day 14 was 19% (five of 26) in the cefiderocol group and 22% (six of 27) in the meropenem group (treatment difference −3·0%, 95% CI −24·8 to 18·8; appendix pp 39, 53–54). All-cause mortality at days 14 and 28 was similar between treatment groups for subgroups of patients with meropenem MICs greater than 8 µg/mL (appendix pp 39, 53–54). For 16 patients with *Acinetobacter spp* with meropenem MICs higher than 64 µg/mL, all-cause mortality at day 14 was 0% (none of five) in the cefiderocol group and 46% (five of 11) in the meropenem group, and at day 28 was 20% (one of five) in the cefiderocol group and 64% (seven of 11) in the meropenem group (appendix pp 53–54). In patients with *Acinetobacter* spp infections, clinical and microbiological outcomes overall and according to whether the meropenem MIC was greater than 8 µg/mL at baseline were similar between treatment groups (appendix pp 40–41). In patients with ESBL-producing pathogens, all-cause mortality at days 14 and 28 and clinical and microbiological outcomes at each timepoint were similar between groups and in line with those for the overall population (appendix pp 42–44).

During therapy, increases of at least four-fold in cefiderocol MIC values occurred in six patients in the cefiderocol group: for *K pneumoniae* in three patients, *Enterobacter aerogenes* in two patients, and *Enterobacter cloacae* plus *Serratia marcescens* in one patient. Despite this increase, MICs remained at 1 µg/mL or less for all isolates, except for *E cloacae* in one patient at end of treatment (MIC 4 µg/mL; appendix p 45). Five patients in the meropenem group had at least four-fold increases in meropenem MIC values during treatment, including *K pneumoniae* in one patient, *P aeruginosa* in three patients, and *Citrobacter freundii* in one patient (appendix p 45). None of these 11 patients had died by day 14.

The overall occurrences of TEAEs, drug-related TEAEs, serious adverse events, and TEAEs leading to study drug discontinuation were similar between treatment groups (table 4, appendix pp 46–50). TEAEs reported in at least 5% of patients in either treatment group were generally balanced across treatment groups (appendix p 46). The two most common TEAEs were urinary tract infection (16% [23 patients of 148] in the cefiderocol group and 11% [16 patients of 150] in the meropenem group) and hypokalaemia (11% [16 patients of 148] in the cefiderocol group and 15% [23 patients of 150] in the meropenem group). The most common treatment-emergent gastrointestinal adverse events in both groups were diarrhoea (in 13 [9%] of 148 patients in the cefiderocol group and 13 [9%] of 150 in the meropenem group) and constipation (in seven [5%] patients in the cefiderocol group and six [4%] in the meropenem group).

Serious adverse events occurred in 54 (36%) of 148 patients in the cefiderocol group (three drug-related) and in 45 (30%) of 150 patients in the meropenem group (five drug-related; table 4; appendix p 48). Numbers of drug-related TEAEs and TEAEs leading to discontinuation of study drugs were low (table 4; appendix pp 49–50). Four (3%) of 148 patients in the cefiderocol group and four (3%) of 150 patients in the meropenem group developed *C difficile* infection or colitis. No differences were found between treatment groups for variables related to iron homoeostasis (ie, hepcidin level, iron concentration, total iron binding capacity, transferrin concentration, and transferrin saturation), or adverse events related to anaemia (data not shown). The number of TEAEs reported for β-lactam antibiotics were low in both groups (data not shown). No notable differences between the treatment groups were identified in the occurrence of liver-related adverse events (data not shown).

Discussion

This study showed that cefiderocol 2 g (given as a 3-h infusion every 8 h) was non-inferior compared with meropenem given as a high-dose (2 g every 8 h), extended infusion (3 h) for the outcome of all-cause mortality at day 14. This primary objective result was complemented by clinical and microbiological secondary outcomes that were within the ranges expected in critically ill patients with pneumonia. All-cause mortality at day 28 was also similar between the two groups. Subgroup analyses of all-cause mortality at days 14 and 28 suggested that cefiderocol and meropenem were effective across the subgroups investigated, including age, renal function, clinical diagnosis, ventilation status, disease severity, APACHE II score, baseline pathogens, and pathogen groups. These analyses were not powered for conclusive treatment comparisons (ie, patient numbers were small);

therefore, results should be interpreted with caution. Notably, objective reductions in SOFA and CPIS scores in both groups over the course of the study supported investigator-recorded clinical responses.

For the APEKS-NP study, discussions with the FDA led to the selection of day 14 all-cause mortality with a 12·5% non-inferiority margin as the primary endpoint under streamlined clinical development. This endpoint with a 12·5% non-inferiority margin required fewer patients than the conventional guidance for a primary endpoint of all-cause mortality at day 28 with a 10% non-inferiority margin (about 300 compared with 540).[26] However, our results also showed non-inferiority for all-cause mortality within the standard FDA guidance margin of 10%, although the 10% margin was not prespecified for this study.

The decision to include patients with HCAP in the study, as a way of enriching the study population with Gram-negative pneumonia, was also made in agreement with the FDA. Patients with HCAP had similar profiles to those with HAP or VAP in terms of the most common causative pathogens involved and severity of illness, as assessed by SOFA and CPIS. However, there was little information for the subgroup of ventilated patients with HCAP receiving meropenem as it comprised only two patients.

The safety profile comparability of cefiderocol with high-dose imipenem (3 g per day) has been established previously.[23] In this study, no remarkable new safety findings emerged for cefiderocol, and proportions of patients with serious adverse events and drug-related adverse events were similar to those with meropenem treatment.

The APEKS-NP study has several strengths. It was undertaken in a high-risk, critically ill patient population, representing the current epidemiology and aetiology of nosocomial pneumonia, including *A baumannii*. Nearly half of the patients had an APACHE II score of at least 16, 60% required mechanical ventilation, and approximately 70% were in an ICU at randomisation.

The all-cause mortality rate at day 28 (21·0%) was similar to the 25% reported in the phase 3 ASPECT-NP study, which compared ceftolozane–tazobactam with meropenem (1 g, every 8 h, 0·5-h infusion) in mechanically ventilated patients with nosocomial pneumonia.[13] Similarly to this study, ASPECT-NP enrolled critically ill patients at high risk of MDR pathogens, all of whom were ventilated and nearly all of whom were in the ICU. The phase 3 REPROVE study, which compared ceftazidime–avibactam with meropenem (1 g, every 8 h, 0·5-h infusion) in patients with nosocomial pneumonia, reported lower all-cause mortality at day 28 (<10%) than either APEKS-NP or ASPECT-NP.[29,30] In the REPROVE study,[31] only about 35% of patients required mechanical ventilation; thus, patients were probably less seriously ill than those enrolled in APEKS-NP. Both ASPECT-NP and REPROVE allowed adjunctive Gram-negative coverage,[13,29] making APEKS-NP the only study with results not confounded by adjunctive Gram-negative therapy.

The broad spectrum of activity of cefiderocol against aerobic Gram-negative bacteria[19] allowed the APEKS-NP pneumonia study to enrol patients with any suspected Gram-negative species, including those at risk of MDR infections, such as ESBL-producing bacteria. Because of the in-vitro activity of cefiderocol against a broad range of MDR Gram-negative pathogens,[21] including non-fermenters, this is the only contemporary study assessing a new investigational antibiotic for nosocomial pneumonia to include *A baumannii* or pneumonia cases with other, less frequent *Acinetobacter* spp.[13,29]Most (98%) of the randomly assigned patients were included in the primary efficacy analysis, and about 85% of these patients had culture-documented Gram-negative pneumonia.

Another strength of this study was the use of the high-dose, prolonged-infusion meropenem regimen (2 g infused over 3 h every 8 h), which is preferred to the approved regimen (1 g infused over 30 min every 8 h) for severe pneumonia caused by Gram-negative pathogens with higher meropenem MIC values.[9,16,18] Such high-dose, extended-duration regimens might help to achieve pharmacokinetic–pharmacodynamic targets in epithelial lining fluid[15,16] and provide activity against some meropenem-resistant strains.[17,32]

A limitation of this study is that we did not mandate the use of bronchoalveolar lavage for the diagnosis of pneumonia, which, had it been done, might have improved the identification of the causative pathogens. The microbiological outcome could include eradication, persistence, or indeterminate responses (due to missing data, or administration of additional antibiotics before test of cure). We found that persistence rates were relatively low at end of treatment (15% in both groups) and test of cure visits (21% in both groups), whereas the rates of indeterminate response (22% in the cefiderocol group and 18% in the meropenem group at the end of treatment, and 31% and 32%, respectively, at test of cure) were relatively high in both groups. Finally, although subgroup analyses might have provided some interesting signals, they were not powered for conclusive treatment comparisons and so the results should be interpreted with caution.

Although we planned to exclude patients with pathogens with known non-susceptibility to meropenem at randomisation, 56 (19%) patients were found to have carbapenem-resistant pathogens based on EUCAST breakpoints after randomisation. These cases were included in the primary efficacy population and involved mostly *A baumannii* or other *Acinetobacter* spp, which are frequently MDR.[6] More than 60% of *Acinetobacter* spp expressed carbapenemases (mainly OXA enzymes; data not shown), against which cefiderocol showed similar clinical and microbiological outcomes to pharmacokinetic-optimised meropenem treatment. Although

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investigators had local susceptibility data available identifying meropenem non-susceptible pathogens, the treatment was masked and these patients were evaluated clinically by the investigator before discontinuation of the study drug or switch to rescue therapy. In this subset of patients, only two were withdrawn because of the presence of a meropenem-resistant pathogen at baseline. We found that day 14 and day 28 all-cause mortality data were similar between cefiderocol and meropenem for patients with meropenem-resistant pathogens, and proportions only increased in the meropenem group for infections with very high meropenem MICs (ie, >64 µg/mL). Additionally, the number of pathogens with cefiderocol MIC values of more than 4 µg/mL at baseline was low, and on-therapy elevated cefiderocol MIC values remained 1 µg/mL or less for nearly all pathogens that demonstrated a four-fold MIC increase or more. In addition to the current data collected, further studies are required to understand antibiotic pressures leading to cefiderocol resistance. The finding that cefiderocol was effective against carbapenem non-susceptible pathogens suggests that cefiderocol might be useful in treating the type of challenging pathogens commonly encountered in clinical practice.

In conclusion, cefiderocol monotherapy was non-inferior to high-dose, extended-infusion meropenem monotherapy for the outcome of day 14 all-cause mortality in critically ill patients with nosocomial pneumonia caused by a broad range of Gram-negative bacteria, including *A baumannii*, *P aeruginosa*, and Enterobacterales. Secondary clinical and microbiological outcomes were consistent with the study mortality findings. Cefiderocol was well tolerated; its safety profile is consistent with that of other cephalosporins or carbapenems. These results suggest that cefiderocol might be an appropriate option for the treatment of nosocomial pneumonia in patients at risk of MDR Gram-negative infections.

Contributors

TDN, RE, and MA designed the study and developed the protocol. YM, AM, MA, PC, RGW, and J-FT collected the data. MA, YM, AM, TDN, and RE analysed the data. All authors interpreted the data, drafted and reviewed the manuscript, and approved the final draft.

Declaration of interests

MA, YM, AM, and TDN are employees of Shionogi. RE is a consultant for Shionogi and received a consultancy fee for his services. RGW has served as a consultant for Shionogi and Merck. MK is supported by the Barnes-Jewish Hospital Foundation and has received consultancy fees from Shionogi. J-FT has received honoraria for participating in advisory boards for Pfizer, Merck, MedImmune, Paratek, Nabriva, Bayer, and Gilead, and for lectures for Pfizer, Merck, Biomérieux, and Brahms; and has also received research grants from Merck, Pfizer, 3M, and Gilead. JMP has served as a consultant for Shionogi, Merck, and Qpex. KSK has served as a consultant for Shionogi, Melinta, Merck, and Qpex. MZ has received honoraria from Shionogi. AFS has received research grants from Merck and Tetraphase, and speaker or consultancy fees from Merck, Pfizer, Melinta, Shionogi, and Tetraphase. PC declares no competing interests.

Data sharing

Data from this study might be available for reasonable requests by health-care providers, investigators, and researchers to address specific scientific or clinical objectives. Shionogi is committed to reviewing requests from researchers for access to clinical trial protocols, de-identified patient-level clinical trial data, and study-level clinical trial data.

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