Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial

Matteo Bassetti, Roger Echols, Yuko Matsunaga, Mari Ariyasu, Yohei Doi, Ricard Ferrer, Thomas P Lodise, Thierry Naas, Yoshihito Niki, David L Paterson, Simon Portsmouth, Julian Torre-Cisneros, Kiichiro Toyoizumi, Richard G Wunderink, Tsutae D Nagata

Lancet Infect Dis 2021; 21: 226–40

Published Online October 12, 2020 https://doi.org/10.1016/S1473-3099(20)30796-9

See Comment page 153

Infectious Diseases Clinic, Department of Health Sciences, University of Genoa, Genoa and Hospital Policlinico San Martino IRCCS, Genoa, Italy (Prof M Bassetti MD); **Infectious Disease Drug Development Consulting, Easton, CT, USA** (R Echols MD); **Shionogi, Florham Park, NJ, USA** (Y Matsunaga MD, S Portsmouth MD); **Shionogi, Osaka, Japan** (M Ariyasu BPharm, K Toyoizumi PhD, T D Nagata MD); **Division of Infectious Diseases, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA** (Y Doi MD); **Department of Intensive Care Medicine and SODIR-VHIR Research Group, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain** (R Ferrer MD); **Albany College of Pharmacy and Health Sciences, Albany, NY, USA** (Prof T P Lodise PharmD); **Department of Medical Microbiology, Bicêtre Hospital, Paris, France** (Prof T Naas MD); **Department of Clinical Infectious Diseases, Showa University School of Medicine, Tokyo, Japan** (Prof Y Niki MD); **UQ Centre for Clinical Research, Faculty of Medicine, The University of Queensland, Herston, QLD, Australia** (Prof D L Paterson MD); **Maimonides Institute for Biomedical Research, Reina Sofia University Hospital, University of Córdoba, Córdoba, Spain** (Prof J Torre-Cisneros MD);

Summary

Background New antibiotics are needed for the treatment of patients with life-threatening carbapenem-resistant Gram-negative infections. We assessed the efficacy and safety of cefiderocol versus best available therapy in adults with serious carbapenem-resistant Gram-negative infections.

Methods We did a randomised, open-label, multicentre, parallel-group, pathogen-focused, descriptive, phase 3 study in 95 hospitals in 16 countries in North America, South America, Europe, and Asia. We enrolled patients aged 18 years or older admitted to hospital with nosocomial pneumonia, bloodstream infections or sepsis, or complicated urinary tract infections (UTI), and evidence of a carbapenem-resistant Gram-negative pathogen. Participants were randomly assigned (2:1 by interactive web or voice response system) to receive either a 3-h intravenous infusion of cefiderocol 2 g every 8 h or best available therapy (pre-specified by the investigator before randomisation and comprised of a maximum of three drugs) for 7–14 days. For patients with pneumonia or bloodstream infection or sepsis, cefiderocol treatment could be combined with one adjunctive antibiotic (excluding polymyxins, cephalosporins, and carbapenems). The primary endpoint for patients with nosocomial pneumonia or bloodstream infection or sepsis was clinical cure at test of cure (7 days [plus or minus 2] after the end of treatment) in the carbapenem-resistant microbiological intention-to-treat population (ITT; ie, patients with a confirmed carbapenem-resistant Gram-negative pathogen receiving at least one dose of study drug). For patients with complicated UTI, the primary endpoint was microbiological eradication at test of cure in the carbapenem-resistant microbiological ITT population. Safety was evaluated in the safety population, consisting of all patients who received at least one dose of study drug. Mortality was reported through to the end of study visit (28 days [plus or minus 3] after the end of treatment). Summary statistics, including within-arm 95% CIs calculated using the Clopper-Pearson method, were collected for the primary and safety endpoints. This trial is registered with ClinicalTrials.gov (NCT02714595) and EudraCT (2015-004703-23).

Findings Between Sept 7, 2016, and April 22, 2019, we randomly assigned 152 patients to treatment, 101 to cefiderocol, 51 to best available therapy. 150 patients received treatment: 101 cefiderocol (85 [85%] received monotherapy) and 49 best available therapy (30 [61%] received combination therapy). In 118 patients in the carbapenem-resistant microbiological ITT population, the most frequent carbapenem-resistant pathogens were *Acinetobacter baumannii* (in 54 patients [46%]), *Klebsiella pneumoniae* (in 39 patients [33%]), and *Pseudomonas aeruginosa* (in 22 patients [19%]). In the same population, for patients with nosocomial pneumonia, clinical cure was achieved by 20 (50%, 95% CI 33·8–66·2) of 40 patients in the cefiderocol group and ten (53%, 28·9–75·6) of 19 patients in the best available therapy group; for patients with bloodstream infection or sepsis, clinical cure was achieved by ten (43%, 23·2–65·5) of 23 patients in the cefiderocol group and six (43%, 17·7–71·1) of 14 patients in the best available therapy group. For patients with complicated UTIs, microbiological eradication was achieved by nine (53%, 27·8–77·0) of 17 patients in the cefiderocol group and one (20%, 0·5–71·6) of five patients in the best available therapy group. In the safety population, treatment-emergent adverse events were noted for 91% (92 patients of 101) of the cefiderocol group and 96% (47 patients of 49) of the best available therapy group. 34 (34%) of 101 patients receiving cefiderocol and nine (18%) of 49 patients receiving best available therapy died by the end of the study; one of these deaths (in the best available therapy group) was considered to be related to the study drug.

Interpretation Cefiderocol had similar clinical and microbiological efficacy to best available therapy in this heterogeneous patient population with infections caused by carbapenem-resistant Gram-negative bacteria. Numerically more deaths occurred in the cefiderocol group, primarily in the patient subset with *Acinetobacter* spp infections. Collectively, the findings from this study support cefiderocol as an option for the treatment of carbapenem-resistant infections in patients with limited treatment options.

Funding Shionogi.

and Division of Pulmonary and Critical Care Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA
(Prof R G Wunderink MD)

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

Introduction

The need for novel treatments for carbapenem-resistant Gram-negative infections is clear, especially for metallo-β-lactamase-producing or OXA carbapenemase-producing organisms. WHO, the Infectious Diseases Society of America, and the European Commission have warned about the shortage of effective antibiotics and urged pharmaceutical companies to develop new drugs.[1–5]

Cefiderocol, a novel siderophore cephalosporin designed to treat carbapenem-resistant bacteria, has shown potent in-vitro activity against carbapenem-resistant Enterobacterales, carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Pseudomonas aeruginosa*, and *Stenotrophomonas maltophilia*.[6,7] Cefiderocol has also shown in-vitro activity against strains that are carbapenemase producers, including those that produce metallo-β-lactamases such as imipenemase, New Delhi metallo-β-lactamase (NDM), and Verona integron-encoded metallo-β-lactamase, and those with porin channel mutations or upregulated efflux pumps.[7–10] The multinational SIDERO surveillance studies showed the broad spectrum of activity of cefiderocol, with minimum

Research in context

Evidence before this study

Despite the approval of several new antibiotics to treat carbapenem-resistant Gram-negative infections, randomised clinical trials including the target pathogens have been limited generally to carbapenem-resistant Enterobacterales and carbapenem-resistant *Pseudomonas aeruginosa*. Randomised trials for the treatment of carbapenem-resistant infections including *Acinetobacter baumannii* have been limited to mostly colistin-based generic antibiotics. Cefiderocol is a siderophore cephalosporin with in vitro activity against carbapenem-resistant Gram-negative bacteria, including carbapenem-resistant Enterobacterales and non-fermenters (eg, *P aeruginosa* and *A baumannii*). Cefiderocol has been approved in the USA for the treatment of complicated urinary tract infections, and hospital-acquired and ventilator-associated bacterial pneumonia, and in Europe for the treatment of infections caused by aerobic Gram-negative bacteria in adults with limited treatment options. The broad-spectrum activity of cefiderocol, irrespective of mechanism of carbapenem resistance, makes cefiderocol a good candidate for investigation in serious infections involving multiple infection sites. No systematic literature review was done before initiation of the study.

Added value of this study

We provide descriptive evidence of the efficacy and safety of cefiderocol for the treatment of life-threatening carbapenem-resistant infections. A novel aspect of this open-label study (CREDIBLE-CR) was the pathogen-focused design, with the aim to investigate cefiderocol in carbapenem-resistant infections caused by any Gram-negative species, with any carbapenem resistance mechanism, at different infection sites. Evidence of carbapenem resistance was based on five different criteria, including direct specimen testing by PCR to identify carbapenemase-producing pathogens. Patients were enrolled with few exclusion criteria and had multiple risk factors for poor outcomes. The study showed similar clinical and microbiological outcomes between cefiderocol and best available therapy, which could include up to three antibiotics. In patients with infections caused by carbapenem-resistant Enterobacterales, 19 (66%) of 29 in the cefiderocol group and five patients (45%) of 11 in the best available therapy group achieved a clinical cure. In patients with infections caused by organisms producing metallo-β-lactamases, clinical cure was achieved by 12 (75%) of 16 with cefiderocol and two (29%) of seven with best available therapy. Numerically more patients died in the cefiderocol group than in the best available therapy group by the end of the study (34 [34%] of 101 *vs* nine [18%] of 49). This difference was mainly noted in patients with pneumonia or bloodstream infections or sepsis caused by *Acinetobacter* spp. There was no mortality difference among patients with carbapenem-resistant Enterobacterales infections, including a few due to metallo-β-lactamase-producing bacteria.

Implications of all the available evidence

CREDIBLE-CR assessed the efficacy and safety of cefiderocol treatment in a high-risk, severely ill patient population with carbapenem-resistant infections, including *Acinetobacter* spp infections and metallo-β-lactamase expressing organisms. The findings showed that clinical and microbiological outcomes by site of infection or causative pathogen were similar between cefiderocol and best available therapy groups. Numerically more patients died in the cefiderocol group than in the best available therapy group. By contrast, in the randomised, double-blind APEKS-NP study, there was no mortality difference between cefiderocol and the comparator high-dose, extended-infusion meropenem in patients with nosocomial pneumonia caused by suspected Gram-negative pathogens, including *Acinetobacter* spp. This study showed cefiderocol to be effective in the treatment of life-threatening, carbapenem-resistant infections in a few patients and, along with pharmacokinetic findings, was the basis for the European approval of cefiderocol for the treatment of infections caused by aerobic Gram-negative bacteria in adults with limited treatment options. Additional studies are needed to assess the relative benefits and risks of cefiderocol for this patient population.

inhibitory concentrations (MICs) of 4 µg/mL or less against more than 99% of all tested Gram-negative isolates[11,12] and more than 97% of isolates non-susceptible to carbapenems.[13] Preclinical infection models showed that the in-vitro activity of cefiderocol correlated with its in-vivo effectiveness and described the target plasma exposure for the treatment of carbapenem-resistant infections, which was further characterised in phase 1 pharmacokinetic studies.[14]

Following discussions with the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), cefiderocol was investigated under a streamlined development programme.[15] The APEKS-cUTI study[16] was the pivotal study for approval by the FDA, whereas a pathogen-focused, open-label study (CREDIBLE-CR) targeting serious carbapenem-resistant infections was required for approval by the EMA.[15] APEKS-NP, a third study, was initiated after APEKS-cUTI and CREDIBLE-CR to broaden the indications to include nosocomial pneumonia in the USA.[15] APEKS-cUTI showed that cefiderocol was non-inferior, with a post-hoc analysis showing superiority to imipenem–cilastatin in patients with complicated urinary tract infections (UTIs) caused by carbapenem-susceptible Gram-negative bacteria. The study also established the safety profile of the 2 g dose of cefiderocol infused over 1 h every 8 h, in a population at risk of multidrug-resistant Gram-negative infections.[16] Another study, APEKS-NP showed that cefiderocol was non-inferior to high-dose, extended-infusion meropenem for the outcome of all-cause mortality on day 14 in critically ill patients with nosocomial pneumonia caused by Gram-negative pathogens (patients were excluded if the baseline Gram-negative pathogens were known at the time of randomisation to be carbapenem-resistant).[17] All-cause mortality on day 28 in APEKS-NP[17] was similar between treatment groups, and the safety and tolerability of cefiderocol were similar to high-dose, extended-infusion meropenem. APEKS-NP led to approval of cefiderocol for the treatment of nosocomial pneumonia in the USA on Sept 25, 2020.

The need for new antibiotics in carbapenem-resistant infections has been recognised globally.[1–5] Inclusion of such patients in traditional infection-site studies has been problematic because the prevalence of carbapenem resistance is low relative to the total burden of Gram-negative infections.[1,3] Furthermore, regulatory requirements for traditional double-blind, infection site-specific studies limit the ability to enrol a substantial number of patients with carbapenem-resistant infections.[1,15] Therefore pathogen-focused studies, which specifically include carbapenem-resistant infections without restriction by infection site, better represent the patient population for which a new antibiotic is intended to be used in clinical practice.[1,15,18]

For approval of cefiderocol by the EMA, a pathogen-focused, open-label study targeting serious carbapenem-resistant infections was required.[15] We therefore designed the CREDIBLE-CR study to assess the efficacy and safety of cefiderocol or best available therapy for the treatment of patients admitted to hospital with a range of serious carbapenem-resistant Gram-negative infections who required intravenous antibiotic therapy.[18]

Methods

Study design and participants

CREDIBLE-CR was a randomised, open-label, parallel-group, pathogen-focused, descriptive, phase 3 study done in 95 hospitals in 16 countries in North America, South America, Europe, and Asia (appendix p 11).[18] The study design was approved by the EMA Committee for Medicinal Products for Human Use (CHMP), and the protocol was approved by relevant national authorities and institutional review boards or independent ethics committees (appendix p 52).[18]

Eligible participants were adult patients (≥18 years) with a diagnosis of hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), health care-associated pneumonia (HCAP), bloodstream infection or sepsis (in whom the primary source of infection was not pneumonia or complicated UTIs), or complicated UTIs, with evidence of carbapenem-resistant Gram-negative infection (appendix p 52).[18] The list of enrolling investigators is in the appendix (p 11). Evidence of carbapenem-resistance could be based on any of the following criteria. (1) Documented treatment failure (both clinically and microbiologically) while on empirical antibiotic therapy, with a carbapenem-resistant Gram-negative pathogen confirmed by culture at least 2 days after the start of the empirical antibiotic regimen, or in-vitro susceptibility testing within 72 h before randomisation. (2) Rapid diagnostics (either selective media or PCR test, which could be locally available or the GeneXpert system (Cepheid, Sunnyvale, CA, USA) provided to laboratories to test the presence of carbapenemase enzymes) on an appropriate clinical biospecimen to confirm a carbapenem-resistant pathogen. (3) Identification of a pathogen for which the local susceptibility antibiogram showed more than a 90% rate of non-susceptibility or resistance to carbapenems. (4) The pathogen was confirmed as *S maltophilia*, which has intrinsic resistance to carbapenems. (5) The patient was confirmed to be colonised with carbapenem-resistant Gram-negative bacteria in the primary infection site within 72 h before enrolment and randomisation and later developed an infection at the same site of colonisation.[18] Inclusion and exclusion criteria were established for each infection type (appendix p 6). Key exclusion criteria were receipt of potentially effective antibiotics for the current carbapenem-resistant infection within 72 h before randomisation (with a continuous duration of >24 h for complicated UTIs or >36 h for other infections), requirement for more than three systemic Gram-negative antibiotics as best available therapy at the time of

See Online for appendix

randomisation, an Acute Physiology and Chronic Health Evaluation (APACHE) II score of more than 30, and refractory septic shock (ie, the patient not responding to fluid resuscitation). Concomitant inhaled antibiotics with Gram-negative activity was an additional exclusion criterion for patients with nosocomial pneumonia (appendix p 6).[18] All patients, or their legal representatives, provided written informed consent.

Randomisation and masking

We randomly assigned participants (2:1) to either cefiderocol or best available therapy. Randomisation was done via an interactive web or voice response system. At randomisation, patients were stratified by infection type (HAP, VAP, HCAP, bloodstream infection or sepsis, and complicated UTI), APACHE II score (≤15 and ≥16), and geographical region (North America, South America, Europe, and Asia). Best-available therapy was not a uniform, protocol-defined single agent or combination regimen, and was provided on the basis of individual patient assessment by the investigator of the infection site, pathogen identification, and antibiotic availability. Therefore, the study was open label.[18]

Procedures

Patients received either cefiderocol 2 g every 8 h as a 3-h intravenous infusion adjusted on the basis of renal function, or best available therapy.[18] For cefiderocol-treated patients with a creatinine clearance of more than 120 mL/min, a regimen of 2 g every 6 h was used. For patients with pneumonia, or bloodstream infection or sepsis, cefiderocol treatment could be combined with one adjunctive antibiotic, excluding polymyxins, cephalosporins (including β-lactamase inhibitor combinations), and carbapenems. The treatment duration in both groups was expected to be 7–14 days (a minimum of 5 days for patients with complicated UTIs), which could be extended to 21 days at the discretion of the investigator. Best-available therapy had to be pre-specified before randomisation and comprised a maximum of three systemic antibiotics, dosed according to the country's label. EMA guidance was recommended for colistin dosing when colistin was selected.[18] De-escalation of adjunctive therapy (in the cefiderocol group) or best available therapy agents (if combination therapy was initiated at randomisation) was allowed on the basis of local susceptibility-testing results at the early assessment timepoint (day 3–4). Escalation of antibiotics in either treatment group was not permitted; any treatment escalation was considered a protocol violation. If patients did not respond to the study drugs, a change of antibiotic treatment from the early assessment timepoint was considered as rescue therapy.

Patients were monitored clinically for treatment effect, safety, and protocol-defined assessments, including Sequential Organ Failure Assessment (SOFA) scores. Clinical signs and symptoms of infection were assessed for each clinical diagnosis at early assessment (day 3–4), end of treatment (last day of study drug), test of cure (7 days [plus or minus 2] after the end of treatment), and follow-up (14 days [plus or minus 3] after the end of treatment). Additionally, chest radiographs and Clinical Pulmonary Infection Scores (CPIS) were assessed in patients with HAP, VAP, or HCAP at the same timepoints.

For microbiological assessments, appropriate clinical specimens, obtained within 48 h before the first dose of study treatment, along with two blood cultures from separate venepunctures, were processed locally for culture and susceptibility testing. All clinical samples required a Gram stain, including a description of both inflammatory cells and bacteria to confirm the quality of the sample at randomisation. Additional appropriate samples were collected at early assessment, end of treatment, test of cure, and follow-up visits. If it was not possible to obtain an appropriate clinical specimen after randomisation, the reason had to be documented. All isolated pathogens were frozen and sent to the central microbiology laboratory (International Health Management Associates, Schaumburg, IL, USA) for confirmation of species identification, antibiotic susceptibility, and molecular mechanisms of carbapenem resistance (appendix p 4). Blood samples were collected (ie, sparse sampling) at steady state (day 3) to confirm cefiderocol pharmacokinetics;[18] results of the pharmacokinetic analysis will be published separately.

Outcomes

The primary endpoint in patients with nosocomial pneumonia, or a bloodstream infection or sepsis was the proportion achieving a clinical cure at test of cure. In patients with complicated UTIs, the primary endpoint was the proportion achieving microbiological eradication at test of cure. Secondary endpoints included assessments of clinical and microbiological outcomes at end of treatment, test of cure, and follow-up visits, including changes in SOFA scores for all indications and CPIS scores for patients with pneumonia. The pre-specified secondary efficacy endpoint of all-cause mortality was evaluated at days 14 and 28 for each diagnosis. Overall survival by Kaplan-Meier analysis was analysed up to the end of study visit (28 days [plus or minus 3] after the end of treatment for all patients). The composite endpoint of survival and no change in antibiotic treatment because of drug-related toxicity or absence of therapeutic benefit at test of cure was assessed and compared between treatment groups. Full definitions of outcomes are in the appendix (pp 8–10).

Safety investigations included assessments of treatment-emergent adverse events (TEAEs), according to the Medical Dictionary for Regulatory Activities (version 18.1), and clinical laboratory safety tests (haematology, blood chemistry, and specialised tests related to iron homoeostasis) up to the end of study visit. The relationship to treatment, severity, and seriousness

of adverse events were determined by the investigator. Mortality through to the end of the study was considered a safety endpoint.

Statistical analysis

CREDIBLE-CR was designed as a descriptive study without hypothesis testing.[18] No formal inferential analyses were planned for any outcomes and the analyses are descriptive. Following discussions with EMA CHMP and feasibility considerations, approximately 100 patients treated with cefiderocol and 50 treated with best available therapy were required (with a 2:1 randomisation ratio); thus, randomisation of 150 patients was planned.

The primary analysis was done in the carbapenem-resistant microbiological intention-to-treat (ITT) population, which consisted of patients with a confirmed carbapenem-resistant Gram-negative pathogen who received at least one dose of study drug (appendix p 3).[18] Sensitivity analyses of clinical and microbiological outcomes and mortality were done in the microbiological ITT and carbapenem-resistant microbiologically evaluable populations (data not shown). The microbiological ITT population included all patients who had a Gram-negative pathogen at baseline isolated from an appropriate clinical specimen. The carbapenem-resistant microbiologically evaluable population included all patients from the carbapenem-resistant microbiological ITT population who had no major protocol violations, had no violations of restrictions on concomitant therapy, had an assessment at test of cure, and received at least 5 days intravenous antibiotic treatment if not considered failure. All-cause mortality was evaluated in the carbapenem-resistant microbiological ITT population or the ITT population (ie, all randomly assigned participants who received at least one dose of study drug). Overall survival by Kaplan-Meier analysis was reported in the ITT and safety populations, which were the same (the safety population consisted of all randomly assigned participants who received at least one dose of study drug and were assessed for the actual study treatment they received). Safety variables were analysed in the safety population. The composite endpoint of survival and no change in antibiotic treatment was assessed in the carbapenem-resistant microbiological ITT population.

Summary statistics are provided for outcomes, as per protocol and statistical analysis plan, including the number of patients, arithmetic mean and SD, and median and range. For the primary and secondary endpoints, the proportion of patients achieving a clinical and microbiological cure by treatment group and within-group 95% CIs were calculated by the Clopper-Pearson method. The composite survival endpoint was compared using the Cochran–Mantel–Haenszel method, stratified by infection site. For probability of survival, a Kaplan–Meier analysis was planned. For analysis of adverse events, incidence by System Organ Class and Preferred Term by treatment group was calculated. MIC_{90} (ie, the MIC required to inhibit the growth of 90% of the organisms) was calculated for the carbapenem-resistant microbiological ITT population and the microbiological ITT population (ie, all patients with an appropriate baseline Gram-negative pathogen).

Subgroup analyses of clinical and microbiological outcomes were planned for the subgroups of age, sex, race, clinical diagnosis, baseline carbapenem-resistant pathogen, APACHE II score, and region. Post-hoc analyses were done to evaluate the mortality difference and intra-group 95% CIs by the end of study, to do multivariate logistic regression analysis to investigate the relationship between mortality and baseline patient factors (including the parameters used for the subgroup analyses), and to calculate treatment differences and 95% CIs between treatment groups with the Miettinen-Nurminen method for all-cause mortality data at day 28, the end of study visit, and day 49 (an FDA regulatory timepoint) for regulatory reviews by the FDA and the EMA (appendix p 3). Missing data were not replaced. All analyses were done with SAS version 9.2.[18]

An independent data safety monitoring board (DSMB) was formally established for this study after observation of a mortality difference between treatment groups (when approximately 30% of patients were enrolled). The DSMB reviewed patient-level information on a continuing basis and judged that the deaths were not due to a safety issue with cefiderocol; therefore, the study continued without protocol change. This trial is registered with ClinicalTrials.gov (NCT02714595) and EudraCT (2015-004703-23).

Role of the funding source

The sponsor of the study provided cefiderocol to enrolling sites, and had a role in study design, protocol development, writing 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 Sept 7, 2016, and April 22, 2019, we randomly assigned 152 patients to treatment (101 to cefiderocol and 51 to best available therapy; figure). Of the randomised population, 150 patients received at least one dose of study drug and comprised the ITT and safety populations.

Demographic and baseline clinical characteristics were generally similar between the two treatment groups in the identical ITT and safety populations (table 1). 45% (67/150) of patients had nosocomial pneumonia, 31% (47/150) had bloodstream infection or sepsis, and 24% (36/150) had complicated UTIs. There were numerically more patients aged 65 years or older (table 1), with moderate or severe renal impairment, or in an intensive care unit (ICU) at randomisation in the cefiderocol group than in the best available therapy group. The

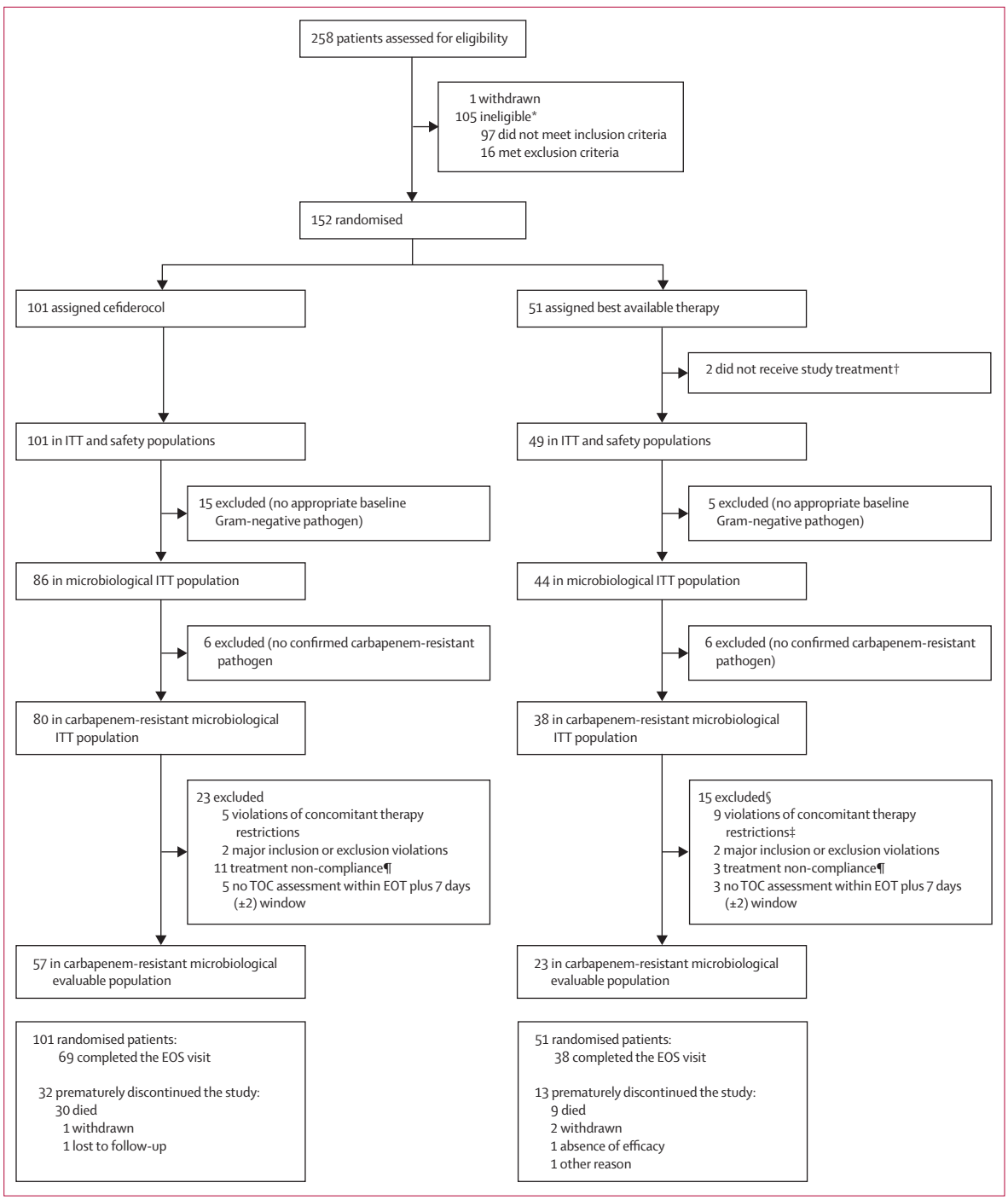

Figure: **Trial profile**
ITT=intention to treat. TOC=test of cure. EOT=end of treatment. EOS=end of study. *Patients could have had more than one reason for being ineligible. †One patient withdrew consent before infusion of the first dose of study drug; one patient was ineligible at screening but was randomly assigned to treatment by error. ‡Includes violations of concomitant antibiotic therapy with activity against Gram-negative bacteria (appendix p 13). §Patients could have had more than one reason for exclusion. ¶Patients could have had more than one reason for non-compliance (appendix p 14).

proportions of patients with previous antibiotic treatment, empirical treatment failure, and positive blood cultures at baseline were similar in both treatment groups. Chronic pulmonary disease, renal disease, diabetes, and cancer were frequent comorbid conditions (table 1). Baseline data were similar between the carbapenem-resistant microbiological ITT population (appendix p 15) and the ITT population.

118 patients (80 assigned cefiderocol and 38 best available therapy) had at least one carbapenem-resistant pathogen at baseline and comprised the carbapenem-resistant microbiological ITT population (figure, table 2; appendix pp 13–14). *A baumannii*, *Klebsiella pneumoniae*, and *P aeruginosa* were the most frequent carbapenem-resistant pathogens in both treatment groups (*A baumannii* in 54 patients [46%],

	Cefiderocol (n=101)	Best available therapy (n=49)
Sex		
Male	66 (65%)	35 (71%)
Female	35 (35%)	14 (29%)
Age (years)		
Mean (SD)	63·1 (19·0)	63·0 (16·7)
Median (range; IQR)	69 (19–92; 52–77)	62 (19–92; 51–76)
<65	37 (37%)	27 (55%)
≥65	64 (63%)	22 (45%)
<75	72 (71%)	35 (71%)
≥75	29 (29%)	14 (29%)
BMI (kg/m²)*	25·0 (12·0–52·4; 21·3–27·8)	23·5 (14·3–48·9; 20·3–29·2)
Region		
Europe	57 (56%)	28 (57%)
Asia-Pacific	29 (29%)	14 (29%)
North America	6 (6%)	3 (6%)
South America	9 (9%)	4 (8%)
Race		
White	63 (62%)	32 (65%)
Asian	29 (29%)	14 (29%)
Black or African American	0	0
Other	9 (9%)	3 (6%)
Clinical diagnosis		
Nosocomial pneumonia	45 (45%)	22 (45%)
HAP	20 (20%)	7 (14%)
VAP	24 (24%)	13 (27%)
HCAP	1 (1%)	2 (4%)
Bloodstream infections or sepsis†	30 (30%)	17 (35%)
Bloodstream infection	22 (22%)	9 (18%)
Complicated intra-abdominal infection	3 (3%)	2 (4%)
Skin and skin structure infection	1 (1%)	0
Intravenous line infection	4 (4%)	2 (4%)
Other‡	5 (5%)	1 (2%)
Unknown	9 (9%)	4 (8%)
Sepsis	8 (8%)	8 (16%)
Complicated intra-abdominal infection	2 (2%)	1 (2%)
Skin and skin structure infection	4 (4%)	3 (6%)
Intravenous line infection	0	3 (6%)
Other‡	2 (2%)	1 (2%)
Complicated urinary tract infection	26 (26%)	10 (20%)
Ventilation at randomisation	50 (50%)	26 (53%)

(Table 1 continues in next column)

	Cefiderocol (n=101)	Best available therapy (n=49)
(Continued from previous column)		
Creatinine clearance (mL/min)		
Mean (SD),	85·8 (79·3)	88·9 (64·2)
Median (range; IQR)	59·2 (9·4–539·26; 33·9–107·9)	69·4 (4·6–270·8; 47·6–119·8)
≥120	20 (20%)	12 (24%)
>80 to <120	18 (18%)	10 (20%)
>50 to ≤80	20 (20%)	12 (24%)
≥30 to ≤50	23 (23%)	8 (16%)
<30	20 (20%)	7 (14%)
Empirical treatment failure	58 (57%)	27 (55%)
Previous therapy§		
Antibiotics¶	93 (92%)	49 (100%)
Carbapenems	60 (59%)	26 (53%)
Systemic corticosteroids	44 (44%)	17 (35%)
ICU at randomisation	57 (56%)	21 (43%)
Shock	19 (19%)	6 (12%)
Immunocompromised	27 (27%)	10 (20%)
Positive blood culture	25 (25%)	13 (27%)
APACHE II score		
Mean (SD)	15·3 (6·5)	15·4 (6·2)
Median (range; IQR)	15 (2–29; 11–20)	14 (2–28; 11–20)
≤15	55 (54%)	27 (55%)
16–19	17 (17%)	9 (18%)
≥20	29 (29%)	13 (27%)
CPIS score‖		
Mean (SD)	4·9 (1·7)	4·6 (1·5)
Median (range; IQR)	5 (2–9; 4–6)	5 (0–7; 4–5)
≤5	30/45 (67%)	16/22 (73%)
≥6	14/45 (31%)	5/22 (23%)
Missing	1/45 (2%)	1/22 (5%)
SOFA score**		
Mean (SD)	5·1 (4·0)	5·1 (3·8)
Median (range)	4 (0–17; 2–8)	4 (0–16; 2–8)
≤6	67 (66%)	32 (65%)
≥7	33 (33%)	17 (35%)
≤9	84 (83%)	43 (88%)
≥10	16 (16%)	6 (12%)
Missing	1 (1%)	0
CCI score		
Mean (SD)	5·5 (3·1)	5·4 (3·1)
Median (range; IQR)	5 (0–12; 3–8)	6 (0–13; 3–7)
Medical history based on CCI components	101 (100%)	49 (100%)
Renal disease	40 (40%)	20 (41%)
Chronic pulmonary disease	40 (40%)	16 (33%)
Diabetes	35 (35%)	17 (35%)

(Table 1 continues in next column)

	Cefiderocol (n=101)	Best available therapy (n=49)
(Continued from previous column)		
Cancer	24 (24%)	13 (27%)
Congestive heart failure	12 (12%)	10 (20%)
Peripheral vascular disease	11 (11%)	5 (10%)
Moderate or severe liver disease	11 (11%)	4 (8%)
Hepatitis	12 (12%)	2 (4%)
Severity of infection††		
Mild	5 (5%)	4 (8%)
Moderate	41 (41%)	22 (45%)
Severe	55 (55%)	23 (47%)

Data are n (%), n/N (%), mean (SD), or median (range; IQR). BMI=body-mass index. HAP=hospital-acquired pneumonia. VAP=ventilator-associated 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. CCI=Charlson Comorbidity Index. *Data available for 99 patients assigned cefiderocol and 49 assigned best available therapy. †Definitions of bloodstream infection and sepsis are in the appendix (p 6). Sepsis diagnoses were based on Systemic Inflammatory Response Syndrome criteria that were valid at the time of study design. ‡Including biliary tract infection, pelvic infection, respiratory tract infections other than infection sites identified as HAP, VAP, HCAP (eg, community-acquired pneumonia, lung abscess, pleural space, or empyema). §A patient taking two or more medications was counted only once within a treatment classification; however, the same patient might have contributed to two or more Preferred Terms in the same classification, according to the Medical Dictionary for Regulatory Activities (version 18.1). ¶Previous antimicrobial therapy taken within 2 weeks before randomisation. ||Shown only for patients with nosocomial pneumonia; data available for 44 patients assigned cefiderocol and 21 assigned best available therapy. **Data available for 100 patients assigned cefiderocol and 49 assigned best available therapy. ††Based on the investigators' clinical judgement (ie, there were no pre-defined criteria for infection severity).

Table 1: **Baseline characteristics of the intention-to-treat and safety populations**

	Cefiderocol (n=80)	Best available therapy (n=38)
Number of carbapenem-resistant Gram-negative pathogens from appropriate specimens*		
One	62 (78%)	30 (79%)
Two	13 (16%)	8 (21%)
Three	4 (5%)	0
Four	1 (1%)	0
Type of carbapenem-resistant Gram-negative pathogen		
All patients	N=87†	N=40‡
Acinetobacter baumannii	37 (46%)	17 (45%)
Klebsiella pneumoniae	27 (34%)	12 (32%)
Pseudomonas aeruginosa	12 (15%)	10 (26%)
Stenotrophomonas maltophilia	5 (6%)	0
Acinetobacter nosocomialis	2 (3%)	0
Enterobacter cloacae	2 (3%)	0
Escherichia coli	2 (3%)	1 (3%)
Nosocomial pneumonia		
A baumannii	26/40 (65%)	10/19 (53%)
P aeruginosa	6/40 (15%)	5/19 (26%)
K pneumoniae	6/40 (15%)	5/19 (26%)
S maltophilia	5/40 (13%)	0
A nosocomialis	2/40 (5%)	0
E cloacae	2/40 (5%)	0
E coli	0	1/19 (5%)
Bloodstream infections or sepsis		
K pneumoniae	10/23 (44%)	4/14 (29%)
A baumannii	10/23 (44%)	7/14 (50%)
P aeruginosa	2/23 (9%)	3/14 (21%)
E coli	1/23 (4%)	0
Complicated urinary tract infections		
K pneumoniae	11/17 (65%)	3/5 (60%)
P aeruginosa	4/17 (24%)	2/5 (40%)
A baumannii	1/17 (6%)	0
E coli	1/17 (6%)	0

Data are n (%) or n/N (%), where N is the total number of patients with at least one Gram-negative pathogen at baseline. *Based on data from the central microbiology laboratory if available. Polymicrobial infections could include carbapenem-resistant and carbapenem-susceptible bacteria present at the primary infection site. †Total number of baseline carbapenem-resistant Gram-negative pathogens in the cefiderocol group. ‡Total number of baseline carbapenem-resistant Gram-negative pathogens in the best available therapy group.

Table 2: **Baseline carbapenem-resistant Gram-negative pathogen distribution in the carbapenem-resistant microbiological intention-to-treat population**

K pneumoniae in 39 patients [33%], and *P aeruginosa* in 22 patients [19%]; table 2, appendix p 17). The distribution of the most frequent Gram-negative pathogens was similar in the carbapenem-resistant microbiological ITT and microbiological ITT populations (table 2; appendix p 17). Cefiderocol MIC_{90} values were 1 µg/mL for carbapenem-resistant *A baumannii*, 4 µg/mL for carbapenem-resistant *K pneumoniae*, and 2 µg/mL for carbapenem-resistant *P aeruginosa* in the carbapenem-resistant microbiological ITT population, with similar values in the microbiological ITT population (appendix p 18). Four pathogens had cefiderocol MICs of greater than 4 µg/mL (ie, the provisional Clinical and Laboratory Standards Institute breakpoint), and an additional six pathogens had MICs of 4 µg/mL, in both the carbapenem-resistant microbiological ITT and microbiological ITT populations (appendix p 18).

In the cefiderocol group, 83% (66/80) of patients received monotherapy; in the best available therapy group, 71% (27/38) received combination therapy. 25 patients (66%) of 38 in the best available therapy group received colistin-based treatment (appendix pp 19–20). For patients with HAP, VAP, HCAP, or bloodstream infection or sepsis (who generally have more severe disease than patients with complicated UTIs), median treatment duration was 11·0 days (IQR 8·0–14·0) with cefiderocol and 13·0 days (10·0–15·0) with best available therapy, with a maximum duration of 22 days in each group. In patients with complicated UTIs, median treatment duration was 10·5 days (IQR 8·0–15·0) with cefiderocol and 6·5 days (6·0–11·0) with best available therapy, with a maximum duration of 29 days in the cefiderocol group and 14 days in the best available therapy group (appendix p 21).

	Nosocomial pneumonia		Bloodstream infections or sepsis		Complicated urinary tract infections		Overall	
	Cefiderocol (n=40)	Best available therapy (n=19)	Cefiderocol (n=23)	Best available therapy (n=14)	Cefiderocol (n=17)	Best available therapy (n=5)	Cefiderocol (n=80)	Best available therapy (n=38)
Clinical outcomes								
End of treatment								
Clinical cure	24 (60%; 43·3–75·1)	12 (63%; 38·4–83·7)	16 (70%; 47·1–86·8)	7 (50%; 23·0–77·0)	13 (77%; 50·1–93·2)	3 (60%; 14·7–94·7)	53 (66%; 54·8–76·4)	22 (58%; 40·8–73·7)
Clinical failure	13 (33%)	7 (37%)	6 (26%)	7 (50%)	1 (6%)	1 (20%)	20 (25%)	15 (40%)
Indeterminate	3 (8%)	0	1 (4%)	0	3 (18%)	1 (20%)	7 (9%)	1 (3%)
Test of cure								
Clinical cure*	20 (50%; 33·8–66·2)	10 (53%; 28·9–75·6)	10 (43%; 23·2–65·5)	6 (43%; 17·7–71·1)	12 (71%; 44·0–89·7)	3 (60%; 14·7–94·7)	42 (53%; 41·0–63·8)	19 (50%; 33·4–66·6)
Clinical failure	16 (40%)	6 (32%)	9 (39%)	7 (50%)	2 (12%)	1 (20%)	27 (34%)	14 (37%)
Indeterminate	4 (10%)	3 (16%)	4 (17%)	1 (7%)	3 (18%)	1 (20%)	11 (14%)	5 (13%)
Follow-up								
Sustained clinical cure	20 (50%; 33·8–66·2)	6 (32%; 12·6–56·6)	9 (39%; 19·7–61·5)	4 (29%; 8·4–58·1)	9 (53%; 27·8–77·0)	3 (60%; 14·7–94·7)	38 (48%; 36·2–59·0)	13 (34%; 19·6–51·4)
Relapse	0	3 (16%)	1 (4%)	1 (7%)	1 (6%)	0	2 (3%)	4 (11%)
Clinical failure	16 (40%)	6 (32%)	9 (39%)	7 (50%)	2 (12%)	1 (20%)	27 (34%)	14 (37%)
Indeterminate	4 (10%)	4 (21%)	4 (17%)	2 (14%)	5 (29%)	1 (20%)	13† (16%)	7† (18%)
Microbiological outcomes								
End of treatment								
Eradication	12 (30%; 16·6–46·5)	5 (26%; 9·1–51·2)	14 (61%; 38·5–80·3)	4 (29%; 8·4–58·1)	12 (71%; 44·0–89·7)‡	1 (20%; 0·5–71·6)‡	38 (48%; 36·2–59·0)	10 (26%; 13·4–43·1)
Persistence	15 (38%)	9 (47%)	1 (4%)	1 (7%)	0	0	16 (20%)	10 (26%)
Indeterminate	13 (33%)	5 (26%)	8 (35%)	9 (64%)	5 (29%)	4 (80%)	26 (33%)	18 (47%)
Test of cure								
Eradication§	9 (23%; 10·8–38·5)	4 (21%; 6·1–45·6)	7 (30%; 13·2–52·9)	4 (29%; 8·4–58·1)	9 (53%; 27·8–77·0)‡	1 (20%; 0·5–71·6)‡	25 (31%; 21·3–42·6)	9 (24%; 11·4–40·2)
Persistence	8 (20%)	7 (37%)	3 (13%)	2 (14%)	5 (29%)	1 (20%)	16 (20%)	10 (26%)
Indeterminate	23 (58%)	8 (42%)	13 (57%)	8 (57%)	3 (18%)	3 (60%)	39 (49%)	19 (50%)
Follow-up								
Sustained eradication	8 (20%; 9·1–35·6)	3 (16%; 3·4–39·6)	6 (26%; 10·2–48·4)	3 (21%; 4·7–50·8)	7 (41%; 18·4–67·1)‡	1 (20%; 0·5–71·6)‡	21 (26%; 17·0–37·3)	7 (18%; 7·7–34·3)
Recurrence	0	1 (5%)	0	0	0	0	0	1 (3%)
Persistence	8 (20%)	7 (37%)	3 (13%)	2 (14%)	5 (29%)	1 (20%)	16 (20%)	10 (26%)
Indeterminate	24 (60%)	8 (42%)	14 (61%)	9 (64%)	5 (29%)	3 (60%)	43¶ (54%)	20¶ (53%)

Data are n (%) or n (%, 95% CI), categorised by clinical diagnosis and visit. *Primary endpoint for patients with nosocomial pneumonia, or bloodstream infections or sepsis. †Indeterminate clinical responses were reported as either deaths (for seven patients assigned cefiderocol and three assigned best available therapy), or missing (for six patients assigned cefiderocol and four assigned best available therapy [definitions in the appendix, p 8]). ‡Eradication was defined as reduction of urine culture Gram-negative uropathogens from at least 10^5 colony forming units (CFU) per mL at baseline to less than 10^3 CFU per mL. §Primary endpoint for patients with complicated urinary tract infections. ¶Indeterminate microbiological responses were reported as deaths (21 patients assigned cefiderocol and six assigned best available therapy); additional therapy required (for ten patients assigned cefiderocol and seven assigned best available therapy); or missing (for 12 patients assigned cefiderocol and seven assigned best available therapy [definitions in the appendix, p 10]).

Table 3: **Clinical and microbiological secondary outcomes in the carbapenem-resistant microbiological intention-to-treat population**

In the carbapenem-resistant microbiological ITT population, the proportions of patients with HAP, VAP, or HCAP achieving a clinical cure at test of cure were 50% (95% CI 33·8–66·2; 20 of 40) of the cefiderocol group and 53% (28·9–75·6; ten of 19) of the best available therapy group (table 3). For patients with bloodstream infection or sepsis, a clinical cure at test of cure was achieved by 43% (23·2–65·5; ten of 23) of the cefiderocol group and 43% (17·7–71·1; six of 14) of the best available therapy group (table 3). For patients with complicated UTIs, microbiological eradication at test of cure was achieved by 53% (27·8–77·0; nine of 17) of the cefiderocol group and 20% (0·5–71·6; one of five) of the best available therapy group (table 3). In subgroup analyses of clinical and microbiological outcomes at test of cure, numerical differences were noted by age (ie, <65 years or ≥65 years), pathogen group (ie, Enterobacterales), region (ie, North America and South America), race (ie, white, other, etc), and APACHE II score (ie, ≤15; appendix p 22).

Similar proportions of patients with HAP, VAP, HCAP, or bloodstream infection or sepsis achieved microbiological eradication in either treatment group at all timepoints (table 3). A numerically higher proportion of patients with complicated UTIs in the cefiderocol group than in the best available therapy group achieved a clinical cure at test of cure (table 3). Relapse occurred in 3% (two of 80) of patients in the cefiderocol group and 11% (four of 38) of patients in the best available therapy group, and overall persistence rates at follow-up were 20% (16 patients of 80) in the cefiderocol group and 26% (ten patients of 38) in the best available therapy group (table 3). Clinical and microbiological outcomes by baseline carbapenem-resistant pathogen at test of cure were generally similar between treatment groups (appendix p 23). A numerically higher proportion of patients with carbapenem-resistant Enterobacterales infections achieved a clinical cure in the cefiderocol group (66% [19 of 29]) than in the best available therapy group (45% [five of 11]), whereas similar proportions of patients with non-fermenters achieved a clinical cure in either group (cefiderocol 45% [22 of 49], best available therapy 52% [13 of 25]; appendix p 23). Rates of clinical cure and microbiological eradication were not associated with baseline cefiderocol MIC values for the most frequent carbapenem-resistant pathogens (appendix p 25). Of patients with infections due to metallo-β-lactamase producers, the proportions achieving a clinical cure and microbiological eradication at test of cure were higher in the cefiderocol group than in the best available therapy group (appendix p 26).

The composite endpoint of survival without the need to change antibiotic due to toxicity or absence of efficacy was achieved in 63% (50/80) of the cefiderocol group and 61% (23/38) of the best available therapy group (treatment difference 1·1%, 95% CI –17·7 to 20·0). Changes in SOFA scores for each diagnosis and in CPIS scores for pneumonia patients were generally similar between the two treatment groups at end of treatment, test of cure, and follow-up visits (appendix pp 27–28).

In the carbapenem-resistant microbiological ITT population, all-cause mortality at day 14 in patients with nosocomial pneumonia was 25% (ten of 40) for the cefiderocol group and 11% (two of 19) for the best available therapy group; at day 28, all-cause mortality was 33% (13 of 40) for the cefiderocol group and 16% (three of 19) for the best available therapy group (appendix p 42). Higher mortality rates were also noted in the cefiderocol group than in the best available therapy group at days 14 and 28 for patients with bloodstream infection or sepsis (cefiderocol 22% [five of 23] on day 14 and 30% [seven of 23] on day 28; best available therapy 7% [one of 14] on day 14 and 21% [three of 14] on day 28), but not for patients with complicated UTIs (cefiderocol 12% [two of 17] on day 14 and 12% [two of 17] on day 28; best available therapy 40% [two of five] on day 14 and 40% [two of five] on day 28; appendix p 42).

	Cefiderocol (n=101)	Best available therapy (n=49)
All TEAEs	92 (91%)	47 (96%)
Mild	23 (23%)	9 (18%)
Moderate	26 (26%)	16 (33%)
Severe	43 (43%)	22 (45%)
Drug-related TEAEs	15 (15%)	11 (22%)
Discontinuation due to TEAEs	10 (10%)	3 (6%)
Discontinuation due to drug-related TEAEs	3 (3%)	2 (4%)
SAEs	50 (50%)	23 (47%)
Drug-related SAEs	1 (1%)	5 (10%)
Death due to SAEs*	34 (34%)	9 (18%)

Data are n (%). Adverse events that started after the first dose of the study drug and up to end of study visit were defined as treatment emergent. A patient could have two or more adverse events but would be counted only once within a System Organ Class category according to the Medical Dictionary for Regulatory Activities (version 18.1). One patient who received cefiderocol after completion of best available therapy is included in the best available therapy group in this table. TEAE=treatment-emergent adverse event. SAE=serious adverse event. *Patients could have had one or more SAE that led to death.

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

Nearly all patients had at least one TEAE; most were moderate or severe (table 4). Drug-related TEAEs led to study drug discontinuation in three patients in the cefiderocol group (ie, due to pyrexia, aminotransferase increase, or skin rash) and in two patients in the best available therapy group (ie, due to anaphylactic reaction or status epilepticus). The most frequently reported TEAEs were diarrhoea (19 [19%] of 101 in the cefiderocol group *vs* six [12%] of 49 in the best available therapy group), pyrexia (14 [14%] *vs* six [12%]), septic shock (13 [13%] *vs* seven [14%]), and vomiting (13 [13%] *vs* seven [14%]; appendix pp 31–33). Nearly half the patients in each group had serious adverse events (table 4), most frequently infections and infestations (cefiderocol 29% [29/101]; best available therapy 22% [11/49]; appendix p 34). One (1%) of 101 patients in the cefiderocol group and five (10%) of 49 patients in the best available therapy group had serious adverse events that were considered to be related to a study drug (appendix p 36). No remarkable findings in laboratory investigations with respect to iron homoeostasis were noted (data not shown). Liver-related TEAEs, including liver enzyme increases or clotting abnormalities, occurred more frequently in the cefiderocol group (30% [30 of 101]) than in the best available therapy group (14% [seven of 49]). No cases met the clinical and biochemical criteria for Hy's law or drug-induced liver injury.

Across all diagnoses, 34 (34%) of 101 patients receiving cefiderocol and nine (18%) of 49 patients receiving best available therapy died by the end of the study in the safety population (table 5, appendix p 44). No death was considered to be related to cefiderocol (ie, drug toxicity) but one death was considered to be related to best available therapy (acute kidney injury, metabolic acidosis, and respiratory arrest following treatment with colistin plus fosfomycin). Details of all 43 deaths up to the end of the study visit are in the appendix (p 37).

	Nosocomial pneumonia		Bloodstream infections or sepsis		Complicated urinary tract infections		Overall	
	Cefiderocol (n=45)	Best available therapy (n=22)	Cefiderocol (n=30)	Best available therapy (n=17)	Cefiderocol (n=26)	Best available therapy (n=10)	Cefiderocol (n=101)	Best available therapy (n=49)
Day 14	11 (24%; 12·9—39·5)	3 (14%; 2·9–34·9)	5 (17%; 5·6–34·7)	1 (6%; 0·1–28·7)	3 (12%; 2·4–30·2)	2 (20%; 2·5–55·6)	19 (19%; 11·7–27·8)	6 (12%; 4·6–24·8)
Day 28	14 (31%; 18·2–46·6)	4 (18%; 5·2–40·3)	7 (23%; 9·9–42·3)	3 (18%; 3·8–43·4)	4 (15%; 4·4–34·9)	2 (20%; 2·5–55·6)	25 (25%; 16·7–34·3)	9 (18%; 8·8–32·0)
End of study	19 (42%; 27·7–57·8)	4 (18%; 5·2–40·3)	11 (37%; 19·9–56·1)	3 (18%; 3·8–43·4)	4 (15%; 4·4–34·9)	2 (20%; 2·5–55·6)	34 (34%; 24·6–43·8)	9 (18%; 8·8–32·0)

Data are n (%; 95% CI) by clinical diagnosis and overall. Percentages were calculated using n as the denominator, where n was the number of patients in the safety population who had the specified clinical diagnosis and known vital status at each timepoint.

Table 5: **All-cause mortality in the safety population**

	Cefiderocol (n=101)	Best available therapy (n=49)
Acinetobacter spp*	21/42 (50%)	3/17 (18%)
Acinetobacter baumannii	19/39 (49%)	3/17 (18%)
Klebsiella pneumoniae	8/34 (24%)	4/16 (25%)
Without *Acinetobacter* spp	6/28 (21%)	4/15 (27%)
Pseudomonas aeruginosa	6/17 (35%)	2/12 (17%)
Without *Acinetobacter* spp	2/11 (18%)	2/11 (18%)
Escherichia coli	1/6 (17%)	0/3
Without *Acinetobacter* spp	0/3	0/1
Stenotrophomonas maltophilia	4/5 (80%)	NA
Without *Acinetobacter* spp	2/3 (67%)	NA

Data are n/N (%). NA=not available. *Includes *Acinetobacter baumannii* (for 39 patients assigned cefiderocol and 17 assigned best available therapy), *Acinetobacter nosocomialis* (for two patients assigned cefiderocol), and *Acinetobacter radioresistens* (for one patient assigned cefiderocol).

Table 6: **All-cause mortality at the end of study by most frequent baseline pathogen in the safety population**

In the safety population, there were numerically more deaths in the cefiderocol group than in the best available therapy group for patients with nosocomial pneumonia or bloodstream infection or sepsis at day 14, day 28, and the end of the study (table 5). Numbers of deaths were similar between treatment groups for patients with complicated UTIs (table 5). In an exploratory analysis to investigate the timing of all-cause mortality difference in patients across all diagnoses, we found that more deaths occurred in the cefiderocol group up to day 3 (cefiderocol 4% [four of 101], best available therapy 0% [none of 49]) and from day 29 to the end of study visit (cefiderocol 9% [nine of 101], best available therapy 0%), but a similar proportion of patients in either group died between days 4 and 28 (cefiderocol 21% [21 of 101], best available therapy 18% [nine of 49]; appendix p 43). The Kaplan–Meier analysis showed similar results (appendix p 51).

Following the end of the study timepoint, the investigators spontaneously reported deaths for two patients in the cefiderocol group and for five patients in the best available therapy group (details not available). Thus, all-cause mortality was 36% (36/101) in the cefiderocol group and 29% (14/49) in the best available therapy group. The masked adjudication committee found that 47% (16 of 34) of deaths in the cefiderocol group and 44% (four of nine) of deaths in the best available therapy group that were documented by the end of study visit occurred from causes other than the underlying Gram-negative infection (appendix p 37). A post-hoc logistic regression analysis for day 28 all-cause mortality did not identify any baseline variable that could explain the mortality difference (appendix p 45).

All-cause mortality differences between the groups appeared to be largely driven by *Acinetobacter* spp infections (table 6). A mortality difference was noted for polymicrobial infections of *P aeruginosa* and *Acinetobacter* spp, whereas there was no difference when patients had no *Acinetobacter* spp co-infections at baseline (table 6).

For patients with *Acinetobacter* spp infections, moderate or severe renal dysfunction (33% [14 of 42] and 18% [three of 17]), ICU at randomisation (81% [34 of 42] and 47% [eight of 17]), ongoing shock (19% [eight of 42] and 6% [one of 17]), or shock within 31 days before randomisation (26% [11 of 42] and 6% [one of 17]) occurred more frequently at baseline in the cefiderocol group than in the best available therapy group, respectively (appendix p 47). In patients without *Acinetobacter* spp infection, there were no differences in mortality rates for any of the variables between the cefiderocol and best available therapy groups (appendix p 47).

Post-hoc analysis of all-cause mortality for regulatory purposes in the safety population showed that in the cefiderocol group there were 6·4% more deaths (95% CI –8·6 to 19·2) at day 28, 15·3% more deaths (–0·2 to 28·6) at the end of study visit, and 13·3% more deaths (–2·5 to 26·9) at day 49 compared with the best available therapy group (appendix p 44).

In post-hoc analyses in the carbapenem-resistant microbiological ITT population, proportions of patients with clinical cure and microbiological eradication at test of cure were similar between patients treated with cefiderocol monotherapy and those treated with cefiderocol combination therapy (appendix p 29). In the

safety population up to the end of study visit, patients in the best available therapy group received rescue therapy more frequently (22% [11/49] vs 13% [13/101]) and earlier than those in the cefiderocol arm (appendix p 50).

In post-hoc analysis of MICs, in the cefiderocol group, 12 isolates (from 12 patients [15%]) had at least a four-fold increase in cefiderocol MIC from baseline (ie, five for *A baumannii*, one for *S maltophilia*, three for *K pneumoniae*, and three for *P aeruginosa*). For these 12 isolates, the increased MIC remained low and would be considered susceptible; only four isolates had an MIC that increased to more than 2 µg/mL, of which three isolates had an MIC of more than 4 µg/mL (appendix p 30). In the best available therapy group, six isolates (from five patients [13%]) had at least a four-fold increase in MIC to the active agents used for treatment, all of which met criteria for resistance (appendix p 30).

Discussion

Generally, clinical and microbiological outcomes were similar between the cefiderocol and best available therapy groups, overall and by clinical diagnosis and carbapenem-resistant pathogen. Although one adjunctive agent was permitted for the treatment of pneumonia or bloodstream infection or sepsis, most patients in the cefiderocol group received monotherapy; by contrast, best available therapy drugs were administered in combination for more than half of the group. Clinical cure rates were higher with cefiderocol than with best available therapy among patients with infections caused by carbapenem-resistant Enterobacterales, including metallo-β-lactamase producing organisms. Overall, the proportion of patients with clinical cure did not change substantially from test of cure to follow-up in the cefiderocol group (53% to 48%), whereas in the best available therapy group, more patients relapsed (cefiderocol 3%, best available therapy 11%). The cefiderocol group had a higher rate of all-cause mortality than the best available therapy group, particularly in patients with nosocomial pneumonia or bloodstream infection or sepsis with *Acinetobacter* spp at baseline.

Data from randomised clinical studies investigating carbapenem-resistant infections are scarce.[19–21] Conventional, randomised, double-blind, phase 3 studies are unsuitable to address carbapenem-resistant infections, since their prevalence is low compared with the prevalence of all Gram-negative infections, thus enrolment of patients is not feasible within a reasonable amount of time. Patients who are at highest risk of being infected by resistant pathogens are often excluded from these trials.[22] By permitting the use of best available therapy as a comparator in an open-label study design in different geographical locations, this study could directly assess the efficacy and safety of cefiderocol in patients with evidence of carbapenem-resistant Gram-negative infections caused by any Gram-negative pathogen, including *Acinetobacter* spp.[18] Thus, patients were enrolled irrespective of infection type, comorbidities, pathogen species, or carbapenem resistance mechanism, resulting in a heterogeneous patient population.

The three most frequent carbapenem-resistant pathogens in this study were *A baumannii*, *P aeruginosa*, and *K pneumoniae*. Across these difficult-to-treat carbapenem-resistant pathogens, 95% had cefiderocol MICs of 4 µg/mL or less, consistent with large surveillance studies.[11–13] Between treatment groups, similar rates of persistence were noted, and the proportion of patients who had pathogen isolates with an MIC that had increased more than four-fold from baseline was also similar between groups. The true proportions of patients with microbiological eradication were difficult to calculate because indeterminate microbiological responses (due to deaths, administration of additional antibiotics, or missing samples) occurred frequently in both treatment groups. In a small proportion of carbapenem-resistant infections caused by pathogens expressing metallo-β-lactamases, including infections with NDM-producing isolates with cefiderocol MICs of 4 or 16 µg/mL, clinical cure rates were higher in the cefiderocol group than in the best available therapy group. Collectively, data from this study provide evidence that cefiderocol is efficacious in the treatment of patients with carbapenem-resistant infections.

The safety profile of cefiderocol was similar to that of other β-lactams, consistent with previous cefiderocol studies.[16,17] Liver-related adverse events (more specifically increased concentrations of liver enzymes) were reported more frequently in patients treated with cefiderocol than with best available therapy in this study. Most of these adverse events were mild or moderate and emerged in patients with confounding factors such as a medical history of viral hepatitis or concomitant medications. None were considered treatment related and all events had alternative causes. Cefiderocol is an iron-chelating molecule;[10] however, there was no evidence of alterations in iron homoeostasis variables. Additionally, no unexpected safety signals emerged.

Despite the similarities in clinical and microbiological outcomes, the all-cause mortality rate in the cefiderocol group was higher than in the best available therapy group. It is unclear whether the difference in all-cause mortality is a chance finding in this heterogeneous population or truly reflects a deficit in the activity of cefiderocol. There was no cefiderocol-related toxicity that could potentially explain the difference in all-cause mortality rates. For regulatory reviews, the difference in all-cause mortality between treatment groups, with 95% CIs, was calculated in a post-hoc analysis using the Miettinen-Nurminen method (appendix p 44) with coverage probablity known to be close to nominal confidence level, which was 95% in this case. These treatment differences and 95% CIs are included in the cefiderocol US Prescribing Information and the European Summary of Product Characteristics.[23,24]

A closer inspection of all-cause mortality indicated that the timing of the deaths was different in the two treatment groups and that higher mortality in the cefiderocol group than in the best available therapy group was found primarily in the subset of patients infected by *Acinetobacter* spp. A higher percentage of deaths in the cefiderocol group than in the best available therapy group in early (up to day 3) and late (from day 29 to the end of study visit) phases was noted, whereas between days 4 and 28, a similar proportion of patients died in both groups. This finding required a careful evaluation of potential acute exacerbating factors present at the time of randomisation, and factors related to underlying conditions or subsequent infections that might have caused late deaths. The most severely ill patients with a short life expectancy (eg, 48–72 h) were frequently excluded from previous clinical studies at randomisation or from the primary efficacy analysis because of their high mortality risk.[25] However, the few exclusion criteria in the CREDIBLE-CR study allowed such patients to be enrolled and included in the analysis. Nevertheless, no individual baseline factor was identified as an independent predictor of increased mortality in logistic regression analysis. Because all-cause mortality was not the primary endpoint of the study, stratification based on factors of severity of illness (eg, ICU or shock) other than APACHE II score at randomisation was not feasible.

The all-cause mortality difference was primarily found in patients with nosocomial pneumonia or bloodstream infection or sepsis who were infected with *Acinetobacter* spp, with or without co-infection with another pathogen. In *Acinetobacter*-infected patients, a higher proportion had shock within 31 days before or at randomisation in the cefiderocol group than in the best available therapy group (26% and 6%, respectively) or were in an ICU at randomisation (81% and 47%, respectively), suggesting a higher baseline mortality risk in the cefiderocol group. The effect of baseline septic shock on outcomes has been exemplified in a propensity-matched cohort study[26] of 9000 patients with extensively drug-resistant infections, which showed a nine-fold higher increased infection-attributable mortality for patients with severe sepsis or septic shock.

In this study, twice as many patients with *Acinetobacter* spp died by day 28 in the cefiderocol group than in the best available therapy group. In other randomised, controlled, pathogen-focused studies in patients with HAP, VAP, bloodstream infections, or sepsis, in which colistin monotherapy was compared with combination regimens of colistin plus either rifampicin, fosfomycin, or meropenem, the all-cause mortality rate in patients with *Acinetobacter* spp infections was more than 40%.[25,27,28] In all six treatment groups in these studies, the day 28 all-cause mortality rate was similar to that in the cefiderocol group in this study.[25,27–29] The low mortality rate in the best available therapy group in patients with *Acinetobacter* spp infections in this study, which occurred in a few patients, seems an outlier when compared with other larger studies.[25,27–29] Unexpectedly, in the best available therapy group, overall all-cause mortality did not correlate with APACHE II score (ie, 19% for APACHE II ≤15 and 18% for APACHE II ≥16, respectively [data not shown]) and was also unchanged over time (ie, 18% at day 28 and 18% at the end of study visit).

Between-treatment differences in mortality were not noted in the APEKS-NP study[17] in critically ill patients with *Acinetobacter* spp nosocomial pneumonia. In APEKS-NP, all-cause mortality rates were similar at day 28 between the cefiderocol group (32%) and the comparator group assigned meropenem (30%).[17] The APEKS-NP patient population was better balanced between treatment groups in terms of risk factors in patients with *Acinetobacter* spp pneumonia (unpublished). Altogether, these findings suggest that the risk of all-cause mortality might not increase with cefiderocol, even for *Acinetobacter* spp infections; such an increased risk is most often seen in the presence of multiple confounding factors.[30–32]

Limitations of CREDIBLE-CR include the use of descriptive statistics only without inferential hypothesis testing, inclusive of the primary endpoints, which was planned owing to the small sample size. The small sample size and heterogeneous patient population limited the possible number of stratification factors for randomisation, increasing the potential for imbalances in baseline factors that might have contributed to the difference in all-cause mortality. We used only the APACHE II score as a stratification factor to balance the severity of illness. Future studies could consider other factors, such as ICU admission at baseline or sepsis or septic shock before randomisation to better balance the risk of all-cause mortality. The open-label design of this study was necessary because of the variability in the best available therapy regimen, which was mostly given as a combination of two or three antibiotics. Best available therapy was tailored to each patient's pathogens and site of infection and represented the best therapy prescribed for each patient. Despite the optimised regimen used in this group, however, more frequent and earlier administration of rescue therapy was required than in the cefiderocol group, suggesting insufficient therapeutic effect of existing drugs. One limitation of the composite endpoint was that it seemed to be confounded by its individual components—ie, the higher mortality rate in the cefiderocol group than in the best available therapy group and the more frequent need for a change in antibiotics for rescue or because of toxicity in the best available therapy group than in the cefiderocol group. Further limitations of the composite endpoint are that the endpoint did not incorporate the time to the additional treatment, survival or mortality data could not be adjusted for factors that affect these outcomes, such as APACHE II scores, and it used a mixture of safety and efficacy evaluations.

The strengths of this study include the novel pathogen-focused design and enrolment of patients with a broad range of carbapenem-resistant Gram-negative pathogens, including *Acinetobacter* spp and metallo-β-lactamase-producing pathogens.

In conclusion, the patient population in this study represents a real clinical scenario with a high unmet need, and the study findings provide evidence of the efficacy and safety of cefiderocol for physicians treating such patients.

Contributors

TDN, RE, and MA conceived and designed the study. MA, TDN, and RE developed the protocol. YM, KT, SP, TDN, RE, MA, RGW, RF, JT-C, YN, YD, and MB collected the data. MA, YM, KT, RE, SP, and TDN analysed the data. All authors interpreted the data, drafted and reviewed the manuscript, and approved the final draft.

Declaration of interests

YM, TDN, MA, SP, and KT are employees of Shionogi. RE is a consultant for Shionogi and received a consultancy fee. MB has participated in advisory boards or received speaker honoraria from Achaogen, Angelini, Astellas, Bayer, Basilea, bioMérieux, Cidara, Gilead, Menarini, Merck Sharpe & Dohme (MSD), Nabriva, Paratek, Pfizer, Roche, Melinta, Shionogi, Tetraphase, VenatoRx, and Vifor; and has received study grants from Angelini, Basilea, Astellas, Shionogi, Cidara, Melinta, Gilead, Pfizer, and MSD. YD has received research grants from Astellas, Janssen, Kanto Chemical, Merck, Pfizer, and Shionogi; speaker honoraria from Beckton-Dickinson, Merck, Pfizer, and Shionogi; and has served on advisory boards for bioMérieux, Entasis, Gilead, Janssen, and VenatoRx. TN has received honoraria from Pfizer and Shionogi. RF has received honoraria from Toray, Thermofisher, Grifols, Pfizer, MSD, Beckton-Dickinson, and Shionogi. JT-C has received honoraria from Menarini, Merck, Pfizer, and Shionogi. RGW received consulting fees from Shionogi and Merck during the study. DLP has received research grants from Shionogi and Merck; speaker honoraria from Accelerate, bioMérieux, Merck, Pfizer; and participated at advisory boards for Entasis, Merck, and VenatoRx. TPL has received research grants from Merck and Motif Bio, and consultancy fees from DoseME, Melinta, Merck, Motif Bio, Nabriva, Paratek, Spero, and Sunovion. YN declares no competing interests.

Data sharing

Data from this study might be available on reasonable request 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.

Acknowledgments

This study was funded by Shionogi. We thank all patients, investigators, and study personnel who participated in the study. We thank Masahiro Kinoshita, Takamichi Baba, Yoshinori Yamano, and Miki Takemura (Shionogi, Osaka, Japan) for their valuable support in the preparation of the manuscript. Medical writing assistance and editorial support was provided by Adrienn Kis and Joanne Shrewsbury-Gee (Highfield, Oxford, UK). This assistance was sponsored by Shionogi (Florham Park, NJ, USA).

References

1 Boucher HW, Ambrose PG, Chambers HF, et al. White paper: developing antimicrobial drugs for resistant pathogens, narrow-spectrum indications, and unmet needs. *J Infect Dis* 2017; **216:** 228–36.

2 WHO. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. Geneva: World Health Organization, 2017. https://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf (accessed Aug 9, 2019).

3 Gutiérrez-Gutiérrez B, Sojo-Dorado J, Bravo-Ferrer J, et al. European prospective cohort study on enterobacteriaceae showing resistance to carbapenems (EURECA): a protocol of a European multicentre observational study. *BMJ Open* 2017; **7:** e015365.

4 Doi Y. Treatment options for carbapenem-resistant Gram-negative bacterial infections. *Clin Infect Dis* 2019; **69** (suppl 7)**:** S565–75.

5 Paterson DL, Isler B, Stewart A. New treatment options for multiresistant Gram negatives. *Curr Opin Infect Dis* 2020; **33:** 214–23.

6 Ito A, Kohira N, Bouchillon SK, et al. In vitro antimicrobial activity of S-649266, a catechol-substituted siderophore cephalosporin, when tested against non-fermenting Gram-negative bacteria. *J Antimicrob Chemother* 2016; **71:** 670–77.

7 Ito A, Sato T, Ota M, et al. In vitro antibacterial properties of cefiderocol, a novel siderophore cephalosporin, against Gram-negative bacteria. *Antimicrob Agents Chemother* 2017; **62:** e01454–17.

8 Ito-Horiyama T, Ishii Y, Ito A, et al. Stability of novel siderophore cephalosporin S-649266 against clinically relevant carbapenemases. *Antimicrob Agents Chemother* 2016; **60:** 4384–86.

9 Ito A, Nishikawa T, Ota M, et al. Stability and low induction propensity of cefiderocol against chromosomal AmpC β-lactamases of *Pseudomonas aeruginosa* and *Enterobacter cloacae*. *J Antimicrob Chemother* 2018; **73:** 3049–52.

10 Sato T, Yamawaki K. Cefiderocol: discovery, chemistry, and pharmacological profiles of a novel siderophore cephalosporin. *Clin Infect Dis* 2019; **69** (suppl 7)**:** S538–43.

11 Hackel MA, Tsuji M, Yamano Y, et al. In vitro activity of the siderophore cephalosporin, cefiderocol, against a recent collection of clinically relevant Gram-negative bacilli from North America and Europe, including carbapenem-nonsusceptible isolates (SIDERO-WT-2014 Study). *Antimicrob Agents Chemother* 2017; **61:** e00093-17.

12 Karlowsky JA, Hackel MA, Tsuji M, et al. In vitro activity of cefiderocol, a siderophore cephalosporin, against Gram-negative bacilli isolated by clinical laboratories in North America and Europe in 2015-2016: SIDERO-WT-2015. *Int J Antimicrob Agents* 2019; **53:** 456–66.

13 Kazmierczak KM, Tsuji M, Wise MG, et al. In vitro activity of cefiderocol, a siderophore cephalosporin, against a recent collection of clinically relevant carbapenem-non-susceptible Gram-negative bacilli, including serine carbapenemase- and metallo-β-lactamase-producing isolates (SIDERO-WT-2014 Study). *Int J Antimicrob Agents* 2019; **53:** 177–84.

14 Katsube T, Echols R, Wajima T. Pharmacokinetic and pharmacodynamic profiles of cefiderocol, a novel siderophore cephalosporin. *Clin Infect Dis* 2019; **69** (suppl 7)**:** S552–58.

15 Echols R, Ariyasu M, Nagata TD. Pathogen-focused clinical development to address unmet medical need: cefiderocol targeting carbapenem resistance. *Clin Infect Dis* 2019; **69** (suppl 7)**:** S559–64.

16 Portsmouth S, van Veenhuyzen D, Echols R, et al. Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by Gram-negative uropathogens: a phase 2, randomised, double-blind, non-inferiority trial. *Lancet Infect Dis* 2018; **18:** 1319–28.

17 Wunderink RG, Matsunaga Y, Ariyasu M, et al. 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. *Lancet Infect Dis* 2020; published online Oct 12. https://doi.org/10.1016/S1473-3099(20)30731-3.

18 Bassetti M, Ariyasu M, Binkowitz B, et al. Designing a pathogen-focused study to address the high unmet medical need represented by carbapenem-resistant Gram-negative pathogens—the international, multicenter, randomized, open-label, phase 3 CREDIBLE-CR study. *Infect Drug Resist* 2019; **12:** 3607–23.

19 Wunderink RG, Giamarellos-Bourboulis EJ, Rahav G, et al. Effect and safety of meropenem–vaborbactam versus best-available therapy in patients with carbapenem-resistant Enterobacteriaceae infections: the TANGO II randomized clinical trial. *Infect Dis Ther* 2018; **7:** 439–55.

20 McKinnell JA, Dwyer JP, Talbot GH, et al. Plazomicin for infections caused by carbapenem-resistant Enterobacteriaceae. *N Engl J Med* 2019; **380:** 791–93.

For **data sharing** see https://www.shionogi.com/global/en/company/policies/clinical-trial-data-transparency-policy.html

21 Motsch J, Murta de Oliveira C, Stus V, et al. RESTORE-IMI 1: a multicenter, randomized, double-blind trial comparing the efficacy and safety of imipenem/relebactam versus colistin plus imipenem in patients with imipenem-non-susceptible bacterial infections. *Clin Infect Dis* 2020; **70:** 1799–808.

22 Mehta M, Uhlemann AC. Beware of broad-spectrum generalizations: ceftazidime-avibactam compared to meropenem for the treatment of gram-negative pneumonia. *J Emerg Crit Care Med* 2018; **2:** 45.

23 Shionogi. Fetroja (cefiderocol) for injection, for intravenous use. Prescribing information. Shionogi, Florham Park, NJ, USA. 2020.

24 Shionogi. Fetcroja (cefiderocol). 1 g powder for concentrate for solution for infusion. Summary of product characteristics. Shionogi BV, Amsterdam, Netherlands. 2020.

25 Paul M, Daikos GL, Durante-Mangoni E, et al. Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial. *Lancet Infect Dis* 2018; **18:** 391–400.

26 Kadri SS, Strich JR, Swihart BJ, et al. Attributable mortality from extensively drug-resistant gram-negative infections using propensity-matched tracer antibiotic algorithms. *Am J Infect Control* 2019; **47:** 1040–47.

27 Durante-Mangoni E, Signoriello G, Andini R, et al. Colistin and rifampicin compared with colistin alone for the treatment of serious infections due to extensively drug-resistant *Acinetobacter baumannii*: a multicenter, randomized clinical trial. *Clin Infect Dis* 2013; **57:** 349–58.

28 Sirijatuphat R, Thamlikitkul V. Preliminary study of colistin versus colistin plus fosfomycin for treatment of carbapenem-resistant *Acinetobacter baumannii* infections. *Antimicrob Agents Chemother* 2014; **58:** 5598–601.

29 Lodise TP, Bassetti M, Ferrer Roca R, et al. Comparison of 28-day mortality rates of recently completed prospective, randomised treatment studies of adult patients with carbapenem-resistant Gram-negative bacterial infections (CR-GNBIs). 30th European Congress of Clinical Microbiology and Infectious Diseases; Paris, France; April 18–21, 2020 (abstr 2497).

30 Leão AC, Menezes PR, Oliveira MS, Levin AS. *Acinetobacter* spp are associated with a higher mortality in intensive care patients with bacteremia: a survival analysis. *BMC Infect Dis* 2016; **16:** 386.

31 Garnacho-Montero J, Timsit JF. Managing *Acinetobacter baumannii* infections. *Curr Opin Infect Dis* 2019; **32:** 69–76.

32 Du X, Xu X, Yao J, et al. Predictors of mortality in patients infected with carbapenem-resistant *Acinetobacter baumannii*: a systematic review and meta-analysis. *Am J Infect Control* 2019; **47:** 1140–45.