2. SYNOPSIS

Sponsor: Shionogi Inc.	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use only)***
Name of Finished Product Not applicable	**Volume:**	
Name of Active Ingredient: Cefiderocol (S-649266)	**Page:**	

Study Title: A Multicenter, Randomized, Open-label Clinical Study of S-649266 or Best Available Therapy for the Treatment of Severe Infections Caused by Carbapenem-resistant Gram-negative Pathogens

Investigators and Study Centers: [redacted]

Publication (reference): Bassetti M, Ariyasu M, Binkowitz B, Nagata TD, Echols R, Matsunaga Y, Toyoizumi K, Doi Y. 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.

Studied Period:

Study initiated (first subject enrolled): [redacted] Sep 2016

Study completed (last subject last visit): [redacted] Apr 2019

Phase of Development: 3

Objectives:

Primary:

- To assess, at Test of Cure (TOC), the clinical outcome of treatment with cefiderocol or best available therapy (BAT) in adult subjects with either hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP)/healthcare-associated pneumonia (HCAP) or bloodstream infection (BSI)/sepsis caused by carbapenem-resistant Gram-negative pathogens
- To assess, at TOC, the microbiological outcome of treatment with cefiderocol or BAT in adult subjects with complicated urinary tract infection (cUTI) caused by carbapenem-resistant Gram-negative pathogens

Notes: TOC was defined as End of Treatment (EOT) + 7 days (± 2 days); BSI was defined as documented bacteremia in a subject with a documented infection other than HAP/VAP/HCAP or cUTI; and sepsis was defined as an infection other than HAP/VAP/HCAP or cUTI associated with systemic inflammatory response syndrome (SIRS).

Secondary:

- To assess the safety of cefiderocol

The other secondary objectives of this study were as follows:

- To assess the clinical outcome of treatment with cefiderocol or BAT in subjects with either HAP/VAP/HCAP or BSI/sepsis at EOT and Follow-up (FU)
- To assess the clinical outcome of treatment with cefiderocol or BAT in subjects with cUTI at EOT, TOC, and FU
- To assess the microbiological outcome of treatment with cefiderocol or BAT in subjects with either HAP/VAP/HCAP or BSI/sepsis at EOT, TOC, and FU
- To assess the microbiological outcome of treatment with cefiderocol or BAT in subjects with cUTI at EOT and FU
- To assess the microbiological outcome of treatment with cefiderocol or BAT in subjects with bacteremia (regardless of the primary infection diagnosis) at EOT, TOC, and FU
- To assess the composite clinical and microbiological outcome of treatment with cefiderocol or BAT in subjects with cUTI at EOT, TOC, and FU
- To assess the all-cause mortality at Day 14 and Day 28 in subjects with HAP/VAP/HCAP and BSI/sepsis
- To compare cefiderocol with BAT in subjects with HAP/VAP/HCAP, cUTI, or BSI/sepsis based on the composite endpoint of survival and no change in antibiotic treatment due to either lack of therapeutic benefit or drug-related toxicity at TOC
- The secondary objectives shown below will not be included in the current Clinical Study Report (CSR); the results of these analyses will be presented in separate reports:
- To assess the relationship between the pharmacodynamic parameter % $fT_{>MIC}$ (fraction of time for which free drug concentration in plasma exceeds the minimum inhibitory concentration over the dosing interval) based on plasma drug concentrations at steady state and the clinical and microbiological outcomes of treatment with cefiderocol in subjects with HAP/VAP/HCAP, cUTI, or BSI/sepsis
- To assess the resource utilization required for the treatment of the study-qualifying infection

Note: EOT was defined as the last day of study therapy; FU was defined as EOT + 14 days (± 3 days).

Methodology: This was a Phase 3, multicenter (multinational), open-label, parallel-group, randomized, active-controlled study conducted in subjects with documented carbapenem-resistant Gram-negative bacterial infections (150 planned for entire study). Subjects meeting eligibility criteria and assessed by the investigator to require 7 to 14 days of intravenous (IV) treatment in a hospital were randomized (2:1) to either cefiderocol 2 g administered intravenously over 3 hours, every 8 hours (q8h), or BAT.

Number of Subjects (Planned and Analyzed):

Planned for entire study: 150 subjects (~100 in cefiderocol group, ~50 in BAT group)

Randomized subjects: 152 subjects (101 in cefiderocol group, 51 in BAT group)

Analyzed for efficacy:

- Intent-to-treat (ITT) population: all randomized subjects who received at least 1 dose of study treatment; cefiderocol (N = 101), BAT (N = 49) (analyzed according to the treatment to which the subjects were randomized)
- Microbiological Intent-to-treat (Micro-ITT) population: all subjects in the ITT population who had a baseline Gram-negative pathogen from an appropriate clinical specimen; cefiderocol (N = 86), BAT (N = 44)
- Carbapenem-resistant Microbiological Intent-to-treat (CR Micro-ITT) population: all subjects in the Micro-ITT population whose baseline Gram-negative pathogen was carbapenem-resistant as confirmed by central laboratory testing (primary efficacy analysis population); cefiderocol (N = 80), BAT (N = 38)
- Carbapenem-resistant Microbiological Intent-to-treat 2 (CR Micro-ITT 2) population: all subjects in the CR Micro-ITT population who had at least 1 baseline Gram-negative pathogen that was carbapenem-resistant confirmed by local laboratory if there was no central laboratory; cefiderocol (N = 80), BAT (N = 39)
- Carbapenem-resistant Microbiologically Evaluable (CR-ME) population: includes all subjects in the CR Micro-ITT population who followed important components of the study as specified in the protocol with no major protocol violations; cefiderocol (N = 57), BAT (N = 23)

Analyzed for safety:

- Safety population: all randomized subjects who received at least 1 actual dose of the study treatment (identical to the ITT population); cefiderocol (N = 101), BAT (N = 49) (analyzed according to the treatment actually received)

Note: One subject [redacted] received cefiderocol via Shionogi's compassionate use program after completing and failing BAT (ie, after EOT). Because the subject completed BAT, the subject is included in the BAT group in this report, except where noted otherwise.

Analyzed for Pharmacokinetics (PK):

- PK Concentration population: all subjects who had plasma sampling and had at least 1 evaluable PK assay result for cefiderocol; cefiderocol (N = 91)

Diagnosis and Main Criteria for Inclusion:

Hospitalized male and female subjects, 18 years or older at the time of signing informed consent, with the following infections caused by a carbapenem-resistant Gram-negative pathogen were enrolled:

- HAP/VAP/HCAP
- BSI/sepsis (Note: BSI/sepsis was a group of subjects with documented carbapenem-resistant Gram-negative infections in the bloodstream (BSI) or in a

body site other than the urinary tract (cUTI) or lung (HAP/VAP/HCAP), and in case of sepsis, evidence of SIRS was required)

- cUTI

Notes: For the purposes of this study and for stratification at randomization, the infection sites were divided into 3 categories: 1) HAP/VAP/HCAP, which represented infections of the lung tissue (pneumonia); 2) cUTI, which represented infection of the upper and lower urinary tract; and 3) BSI/sepsis, which was an "other" category, ie, not HAP/VAP/HCAP or cUTI, whereby the subject had either a documented Gram-negative bacteremia (BSI) or another site of infection associated with SIRS, or both. Thus, most any documented infection caused by a carbapenem-resistant Gram-negative pathogen could have been enrolled in this study with certain exceptions (eg, meningitis, endocarditis, osteomyelitis).

Test Product, Dose and Mode of Administration, Lot Number:

Cefiderocol 2 g was administered intravenously q8h as a 3-hour infusion with/without adjunctive antibiotic therapy in subjects with normal renal function. Dose or schedule adjustment was provided for renal function and augmented renal clearance.

Lot numbers for cefiderocol: [redacted]

Duration of Treatment:

Planned: The recommended duration of treatment with IV study drugs was 7 to 14 days in the hospital, consistent with published treatment guidelines for serious infections (with a possible extension up to 21 days based on the investigator's clinical assessment of the subject). For subjects with cUTI only, the investigator could have chosen to stop treatment after a minimum of 5 days if it was in the best interests of the subject.

Actual: Subjects who received study treatment for more than 14 days represented 24.0% of the cefiderocol group and 28.2% of the BAT group. In subjects with HAP/VAP/HCAP or BSI/sepsis, the maximum treatment duration was 22 days in both treatment groups (some subjects received treatment on Day 22 if they had not completed all infusions on Day 1).

In subjects with cUTI, the maximum treatment duration was 29 days in the cefiderocol group and 14 days in the BAT group. One subject [redacted] in the cefiderocol group received study drug treatment for 29 days due to orchiepididymitis.

Reference Therapy, Dose and Mode of Administration, Lot Number:

The control population was treated with BAT, locally sourced by study sites, within the local standard of care determined by the investigator for each infection diagnosis prior to randomization. This consisted of 1 to 3 antibiotic agents selected specifically for the carbapenem-resistant Gram-negative pathogen.

Criteria for Evaluation:

Efficacy Assessments: Both clinical and microbiological outcomes were assessed by the investigator at Early Assessment (EA), EOT, TOC, and FU. In cases in which treatment duration was extended beyond 14 days, additional clinical and microbiological outcomes were assessed on Day 14.

- Results of general assessments were also collected: vital status, Glasgow Coma

Scale (GCS), Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, ventilator parameters (mechanically ventilated subjects), oxygenation status (for subjects receiving oxygen inhalation therapy), chest radiographs (for subjects with HAP/VAP/HCAP), Clinical Pulmonary Infection Score (CPIS) (for subjects with HAP/VAP/HCAP), and clinical signs and/or symptoms of infection.
Safety Assessment: Adverse event (AE) assessments, clinical laboratory safety tests (hematology, chemistry, and specialized tests [hepcidin, total iron-binding capacity (TIBC), iron, and transferrin iron saturation]), vital sign measurements, and 12-lead electrocardiography (ECG) examinations
Pharmacokinetics Assessment: Ninety-one of 101 subjects (90.1%) treated with cefiderocol had blood drawn for sparse PK sampling of plasma concentrations of study drug. Pharmacokinetic blood sampling occurred on Day 3 (after at least 6 doses of drug) at 4 time points: (1) just prior to the start of the infusion, (2) 1 hour after the start of the infusion, (3) at the end of the infusion, and (4) 1 hour after the end of the infusion. The date, actual time, and site of the PK sampling were recorded in the electronic case report form. Subjects with nonstable renal function resulting in a dosage adjustment (dose or interval) at EA underwent another blood PK sampling (4 samples at the above specified time points) within 24 to 72 hours after their dosing adjustment. The timing for PK blood draws was the same as the above timing on Day 3. If possible, a single blood sampling was performed as soon as possible at EOT in case of premature EOT (within 24 hours of last dose).
Statistical Methods: Descriptive statistics for all parameters were provided. For the primary endpoint, which was the clinical response at TOC for subjects with HAP/VAP/HCAP or BSI/sepsis and the microbiological response at TOC for subjects with cUTI, each response rate was provided with the 95% confidence interval (CI) by treatment group. For the secondary efficacy endpoints of clinical response and microbiological response, each response rate was also provided with 95% CI by treatment group per infection site.
Efficacy: Descriptive statistics were provided for the primary efficacy analyses. For the subjects with HAP/VAP/HCAP or BSI/sepsis, the clinical response rates by treatment group and the 95% CIs were calculated. For the subjects with cUTI, the microbiological response rates by treatment group and the 95% CIs were calculated. The secondary endpoints of clinical and microbiological response rates per subject and per baseline pathogen by treatment group and the 95% CIs were calculated. Composite clinical and microbiological response rates by treatment group and the 95% CIs were calculated. Summary statistics and CIs are provided for the response rate of a composite endpoint of survival and no change in antibiotic treatment due to either lack of therapeutic benefit or drug-related toxicity at TOC. The SOFA scores and CPIS (HAP/VAP/HCAP only) parameters by infection site as relevant were summarized by time point.

Safety:

Safety analyses were performed for the Safety population. Adverse events were collected and tabulated by treatment group. Safety assessment results were summarized as changes from baseline values in vital signs and clinical laboratory safety tests (hematology, chemistry, and specialized tests [hepcidin, TIBC, iron, and transferrin iron saturation]). Electrocardiogram data were listed.

All-cause mortality at Day 14 and Day 28 were prespecified as secondary efficacy endpoints, while mortality through End of Study (EOS) was a safety endpoint. However, given the mortality results observed in this study, Shionogi acknowledges the importance of a complete assessment of mortality; therefore, the mortality results were treated as safety data.

Pharmacokinetics:

Individual plasma concentrations of cefiderocol were listed and summarized by nominal sampling time window, and dosage based on renal function.

Summary of Results:

Demographics and Baseline Characteristics:

- In the CR Micro-ITT population, at baseline, the percentage of subjects ≥ 65 years old (62.5% [50/80] and 44.7% [17/38]), with moderate or severe renal impairment (41.3% [33/80] and 23.7% [9/38]), and with severe disease (62.5% [50/80] and 52.6% [20/38]) was greater (> 5% difference) in the cefiderocol group than in the BAT group, respectively. The incidence of the following characteristics was greater (> 5% difference) in the BAT group than in the cefiderocol group: BSI/sepsis diagnosis at baseline (36.8% [14/38] and 28.8% [23/80], respectively), sepsis diagnosis at baseline (15.8% [6/38] and 8.8% [7/80], respectively), IV line subgroup of sepsis at baseline (7.9% [3/38] and 0.0% [0/80], respectively), moderate severity of disease (39.5% [15/38] and 32.5% [26/80], respectively), prior treatment (100.0% [38/38] and 91.3% [73/80], respectively), and mechanical ventilation at randomization in subjects with HAP/VAP/HCAP (78.9% [15/19] and 72.5% [29/40], respectively). Other demographic and baseline disease characteristics were broadly similar between the treatment groups.
- Subjects with HAP/VAP/HCAP represented 50.0% (59/118) of subjects in the CR Micro-ITT population; 31.4% (37/118) of subjects had BSI/sepsis, and 18.6% (22/118) had cUTI.
- In the CR Micro-ITT population, for all infection sites combined, carbapenem-resistant *Acinetobacter baumannii, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa* were the 3 most frequently occurring pathogens in both treatment groups (46.3% [37/80] and 44.7% [17/38] of subjects had *A. baumannii*, 40.0% [32/80] and 31.6% [12/38] of subjects had *K. pneumoniae*, and 21.3% [17/80] and 28.9% [11/38] had *P. aeruginosa* in the cefiderocol and BAT groups, respectively). In subjects with HAP/VAP/HCAP, 65.0% (26/40) and 52.6% (10/19) of subjects in the cefiderocol and BAT groups, respectively, had *A. baumannii* as the baseline pathogen.
- In the CR Micro-ITT population, in the cefiderocol group, 82.5% (66/80) of

subjects received monotherapy, while 28.9% (11/38) of subjects in the BAT group received monotherapy. A colistin-based regimen was given to 65.8% (25/38) of the subjects in the BAT group. Other than colistin monotherapy (received by 6 subjects in the BAT group), 5 subjects in the BAT group received other monotherapy (amikacin, ceftazidime-avibactam, doripenem, fosfomycin, and gentamicin).

- Baseline subject characteristics for the Micro-ITT (N = 130), CR-ME (N = 80), and Safety (N = 150) populations were broadly similar to the CR Micro-ITT population (N = 118).

Efficacy (in the CR Micro-ITT population, unless specified otherwise):

Primary Efficacy Endpoints:

- In subjects with HAP/VAP/HCAP and BSI/sepsis, the clinical cure rate at TOC was the primary efficacy endpoint. For subjects with HAP/VAP/HCAP, the clinical cure rate at TOC was 50.0% (20/40) and 52.6% (10/19) in the cefiderocol and BAT groups, respectively. For subjects with BSI/sepsis, the clinical cure rate at TOC was 43.5% (10/23) and 42.9% (6/14) in the cefiderocol and BAT groups, respectively.
- In subjects with cUTI, the eradication rate at TOC was 52.9% (9/17) in the cefiderocol group and 20.0% (1/5) in the BAT group.

Secondary Efficacy Endpoints: Secondary efficacy clinical and microbiological outcomes per subject at TOC are presented below. Additional secondary efficacy clinical and microbiological outcomes per subject at other timepoints and per pathogen by timepoint are provided in the study report.

- In subjects with cUTI, the clinical cure rate at TOC was 70.6% (12/17) in the cefiderocol group and 60.0% (3/5) in the BAT group.
- In subjects with HAP/VAP/HCAP, the eradication rate at TOC was 22.5% (9/40) in the cefiderocol group and 21.1% (4/19) in the BAT group. In subjects with BSI/sepsis, the eradication rate at TOC was 30.4% (7/23) in the cefiderocol group and 28.6% (4/14) in the BAT group.
- For the combined group of subjects with HAP/VAP/HCAP or BSI/sepsis, the clinical response rate at TOC was 47.6% (30/63) in the cefiderocol group and 48.5% (16/33) in the BAT group, and the eradication rate at TOC was 25.4% (16/63) in the cefiderocol group and 24.2% (8/33) in the BAT group.
- For all infection types combined, the clinical cure rate at TOC was 52.5% (42/80) and 50.0% (19/38) and the eradication rate at TOC was 31.3% (25/80) and 23.7% (9/38) in the cefiderocol and BAT groups, respectively.
- For all subjects with bacteremia from all infection sites combined, the eradication rate at TOC was 31.8% (7/22) and 30.8% (4/13), the persistence rate was 4.5% (1/22) and 7.7% (1/13), and the indeterminate rate was 63.6% (14/22) and 61.5% (8/13) for the cefiderocol and BAT groups, respectively.
- In subjects with cUTI, the composite response rate of clinical cure and eradication at TOC was 47.1% (8/17) in the cefiderocol group and 20.0% (1/5)

in the BAT group.

- For all infection sites combined, the composite response rate of clinical cure and eradication at TOC was 30.0% (24/80) in the cefiderocol group and 21.1% (8/38) in the BAT group.
- Clinical and microbiological outcomes in the Micro-ITT (N = 130), CR-Micro ITT2 (N = 119), and CR-ME (N = 80) populations were generally consistent with those in the CR Micro-ITT population (N = 118).
- In subgroup analyses of clinical and microbiological outcomes at TOC for the CR Micro-ITT population, the following were noted:
  - The clinical response rate at TOC was > 10% higher in the cefiderocol group than in the BAT group for the following subgroups: subjects with cUTI, subjects who were ≥ 65 years of age, and subjects with an Enterobacteriaceae CR pathogen at baseline. The clinical response rate at TOC was > 10% lower in the cefiderocol group than in the BAT group for subjects < 65 years of age.
  - The eradication rate at TOC was > 10% higher in the cefiderocol group than in the BAT group for the following subgroups: subjects with cUTI, subjects who were ≥ 65 years of age, white subjects, subjects with an Enterobacteriaceae CR pathogen at baseline, and subjects with a total APACHE II score ≤ 15.
- Results of supplementary analyses performed using modified definitions for clinical and microbiological outcomes (to further classify indeterminate outcomes) were generally consistent with and supported the predefined analyses.
- For all infection sites combined, the response rate at TOC for the composite endpoint of survival and no change in antibiotic treatment due to either lack of therapeutic benefit or drug-related toxicity was 62.5% (50/80 subjects) in the cefiderocol group and 60.5% (23/38 subjects) in the BAT group (difference [95% CI]: 1.1 [-17.7, 20.0]).
- For subjects with HAP/VAP/HCAP only, the mean CPIS value at baseline was 5.1 and 5.0 in the cefiderocol and BAT groups, respectively; and the median CPIS value at baseline was 5.0 in both treatment groups. The CPIS was decreased from baseline at EOT, TOC, and FU in both treatment groups. At TOC, the mean change from baseline in CPIS was -3.1 and -2.7 and the median change from baseline in CPIS was -4.0 and -2.5 in the cefiderocol and BAT groups, respectively.
- For all infection sites combined (all subjects), the mean SOFA score was the same for both treatment groups at baseline (5.6) and the median SOFA score at baseline was 4.0 in the cefiderocol group and 5.5 in the BAT group. At EOT, TOC, and FU, both treatment groups had a decrease from baseline in mean SOFA score (change from baseline of -0.9 to -1.9) and in median SOFA score (change from baseline of -0.5 to -1.0).

Safety:

- Greater than 90% of subjects in each treatment group in the Safety population

had at least 1 AE. Adverse events reported in ≥ 10% of subjects in either group were diarrhea, pyrexia, septic shock, vomiting, hypokalemia, acute kidney injury, and hyperkalemia. Adverse events reported more frequently (> 5% difference) in the cefiderocol group than in the BAT group were diarrhea, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, pleural effusion, and chest pain. Adverse events reported more frequently (> 5% difference) in the BAT group than in the cefiderocol group were hypokalemia, hyperkalemia, rash, and depression.

- The incidence of treatment-related AEs was 14.9% (15/101 subjects) in the cefiderocol group and 22.4% (11/49 subjects) in the BAT group. Treatment-related AEs occurring in > 2 subjects included ALT increased and AST increased (each occurred in 3.0% [3/101] of subjects in the cefiderocol group only), and acute kidney injury (8.2% [4/49] of subjects in the BAT group only).
- Adverse events of interest included antibiotic-related AEs (*C. difficile*-related AEs and diarrhea), β-lactam antibiotic class effects (rash/hypersensitivity reactions; liver-related AEs, including liver biochemistry and clotting tests; seizures/epilepsy; and bone marrow suppression), and iron transport/metabolism considerations.
  - Overall, the incidence of AEs related to *C. difficile* was low, with only 4 subjects (3 in the cefiderocol group and 1 in the BAT group) experiencing *C. difficile*-related AEs. Adverse events of diarrhea occurred in 18.8% (19/101) of subjects in the cefiderocol group and 12.2% (6/49) of subjects in the BAT group. All of the AEs of diarrhea were mild or moderate in severity. None of these AEs of diarrhea were serious adverse events (SAEs) and none led to discontinuation of study drug. All but 2 of the AEs of diarrhea were considered not related to study treatment.
  - The incidence of AEs characteristic of the β-lactam class of antibiotics (seizure and bone marrow suppression) was low in the cefiderocol group and no unexpected events were reported. In the cefiderocol group, 1 subject experienced 3 AEs of seizure, which were considered mild in severity and not related to the study drug. Overall, the incidences of AEs that could suggest bone marrow suppression were low and no differences were noted between the 2 treatment groups.
  - Liver-related AEs, including liver biochemistry and clotting tests, occurred more frequently in the cefiderocol group (29.7% [30/101 subjects]) than in the BAT group (14.3% [7/49 subjects]). The percentage of subjects who had AST or ALT values > 3 × upper limit of normal (ULN) during the study was 26.0% (25/96) in the cefiderocol group and 16.7% (8/48) in the BAT group. The percentage of subjects who had ALT and/or AST > 3 × ULN and total bilirubin (TBL) > 2 × ULN or prothrombin time-international normalized ratio (PT-INR) > 1.5 was 12.4% (12/97) in the cefiderocol group and 8.3% (4/48) in the BAT group. There were no cases meeting the clinical and biochemical criteria for Hy's law or drug-induced liver injury. Confounders were present in the majority of cases.

  - Cefiderocol did not have an effect on hemoglobin, hematocrit, iron, TIBC, transferrin saturation, or hepcidin values over time.

- The incidence of subjects who experienced SAEs was 49.5% (50/101 subjects) in the cefiderocol group and 46.9% (23/49 subjects) in the BAT group. Septic shock was the most frequently reported SAE in both the cefiderocol (11.9% [12/101] of subjects) and BAT (12.2% [6/49] of subjects) groups. One subject (1.0%) in the cefiderocol group and 5 subjects in the BAT group (10.2%) experienced SAEs considered treatment related by the investigator.
- The incidence of subjects that experienced AEs leading to discontinuation was 9.9% (10/101) in the cefiderocol group and 6.1% (3/49) in the BAT group. The only reported AE leading to discontinuation of study treatment occurring in > 1 subject was septic shock, which occurred in 4 subjects in the cefiderocol group and 0 subjects in the BAT group; all 4 events were considered not related to the study drug by the investigator.
- Overall, 5 subjects had AEs leading to discontinuation of study treatment that were considered related to study treatment (pyrexia, transaminases increased, and drug eruption in 1 subject each in the cefiderocol group; and anaphylactic reaction and status epilepticus in 1 subject each in the BAT group).
- The incidence of subjects with AEs leading to death (including fatal outcomes of SAEs that were ongoing as of the EOS visit) was 33.7% (34/101) in the cefiderocol group and 18.4% (9/49) in the BAT group. None of the deaths in the cefiderocol group were considered related to study treatment. One death in the BAT group was due to SAEs (metabolic acidosis, respiratory arrest, and acute kidney injury) considered related to study treatment (colistin and fosfomycin). There were 20.8% (21/101) of subjects in the cefiderocol group and 6.1% (3/49) of subjects in BAT group with AEs leading to death classified in the system organ class (SOC) of infections and infestations.
- In the Safety population, all-cause mortality at Day 14 for all subjects (ie, all infection sites combined) was 18.8% (19/101 subjects) in the cefiderocol group and 12.2% (6/49 subjects) in the BAT group. All-cause mortality at Day 28 for all subjects was 24.8% (25/101 subjects) in the cefiderocol group and 18.4% (9/49 subjects) in the BAT group. Through EOS (EOT + 28 days, unless there was an ongoing SAE at the EOS visit, in which case EOS was defined as the time of resolution of the SAE), mortality for all subjects was 33.7% (34/101 subjects) in the cefiderocol group and 18.4% (9/49 subjects) in the BAT group.
- A higher proportion of subjects in the BAT group received rescue therapy and received it sooner during the study than those in the cefiderocol group, which may indicate that there was an ascertainment bias in subject assessment in this open-label randomized study.
- All-cause mortality at Day 49 for both treatment groups combined was higher for subjects with *Acinetobacter* spp. infections (42.4% [25/59]) than for subjects without *Acinetobacter* spp. (20.9% [19/91]).
- Among those infected with *Acinetobacter* spp., cefiderocol-treated subjects had

a higher mortality rate during the study than BAT-treated subjects. Subjects with *Acinetobacter* spp. infections who had shock at or within 1 month of randomization (prior to treatment initiation) and were in the ICU at randomization or who were unlikely to survive regardless of treatment represented a higher percentage of the cefiderocol group than the BAT group. These differences may explain the difference in all-cause mortality between the 2 groups. Such differences were not present in those infected with non-*Acinetobacter* spp. The mortality difference between the treatment groups did not appear to be due to lack of clinical or microbiological efficacy, which were similar for the 2 treatments.

Pharmacokinetics:

The geometric mean (minimum, maximum) plasma concentrations of cefiderocol on Day 3 for the total PK Concentration population (all dose groups) were 42.4 (7.28, 224) µg/mL prior to infusion, 80.5 (19.3, 1110) µg/mL 1 hour after start of infusion, 91.2 (16.4, 1220) µg/mL at the end of infusion, and 74.0 (13.3, 303) µg/mL 1 hour after the end of infusion. The mean peak plasma concentration was observed at the end of infusion, as expected.

For subjects with nonstable renal function who had dosage adjustment (all dose groups), geometric mean (minimum, maximum) plasma concentrations of cefiderocol from repeated sampling was 49.2 (16.9, 131) µg/mL prior to infusion, 77.3 (41.5, 166) µg/mL 1 hour after start of infusion, 88.0 (68.3, 135) µg/mL at the end of infusion, and 83.8 (19.6, 166) µg/mL 1 hour after the end of infusion. The ranges of plasma concentrations at the adjusted dose regimens were narrow compared to those on Day 3.

The geometric mean (minimum, maximum) plasma concentration of cefiderocol at premature EOT for all dose groups (total) was 33.8 (13.6, 80.3) µg/mL (PK Concentration population). The extremely high plasma concentrations were not observed at premature EOT.

The geometric mean plasma concentrations prior to infusion (C_{min}) were 42.4 to 49.2 µg/mL. The mean free drug concentrations in plasma calculated based on unbound fraction of 0.422 were 17.9 to 20.8 µg/mL, which exceeded the minimum inhibitory concentration (MIC) of 16 µg/mL.

CONCLUSIONS

1. The CREDIBLE-CR study was an open-label, randomized study to collect information on the activity of cefiderocol in subjects with heterogenous backgrounds with carbapenem-resistant bacterial infection. It was not designed for inferential hypothesis testing for all-cause mortality, as the study was not large enough to stratify for multiple prognostic factors, although the APACHE II score was used for stratification. A higher proportion of subjects in the BAT group received rescue therapy and received it sooner during the study than those in the cefiderocol group, which may indicate that there was an ascertainment bias in subject assessment in this open-label randomized study.

2. The primary endpoints of the study, ie, the clinical and microbiological outcomes, were comparable between the cefiderocol and BAT groups, despite the fact that

treatment was largely monotherapy in the cefiderocol group (82.5%) and combination therapy of approved drugs in the BAT group (71.1%).

3. The safety profile other than all-cause mortality was comparable between the cefiderocol and BAT groups, and it was comparable to that of existing cephalosporins.

4. A difference was observed in all-cause mortality between the cefiderocol and BAT groups, with a higher rate in the cefiderocol group. The all-cause mortality difference shown in this study is not believed to be due to cefiderocol, either as a direct drug-related adverse effect or due to lack of efficacy; the difference was considered to be due to imbalances in the baseline characteristics of subsets of those infected with *Acinetobacter* spp. A difference in all-cause mortality from the comparator group was not seen in a double-blind comparative study of cefiderocol in nosocomial pneumonia (APEKS-NP study).

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