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, Double-blind, Parallel-group, Clinical Study of S-649266 Compared with Meropenem for the Treatment of Hospital-acquired Bacterial Pneumonia, Ventilator-associated Bacterial Pneumonia, or Healthcare-associated Bacterial Pneumonia Caused by Gram-negative Pathogens (APEKS-NP)

Investigators and Study Centers: [redacted]

Publication (reference): Refer to Appendix 16.1.11

Studied Period:

Study initiated (first subject enrolled): [redacted] Oct 2017

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

Phase of Development: 3

Objectives:

Primary Objective:

- To compare the all-cause mortality at Day 14 of subjects who received cefiderocol with that of subjects who received the comparator, meropenem, in adults with hospital-acquired pneumonia (HABP), ventilator-associated bacterial pneumonia (VABP), or healthcare-associated bacterial pneumonia (HCABP) caused by Gram-negative pathogens

Secondary Objectives:

Key Secondary Objectives:

- To compare the clinical outcome of treatment with cefiderocol with that of meropenem in subjects at Test of Cure (TOC, defined as End of Treatment [EOT] + 7 days [± 2 days])
- To compare the microbiologic outcome of treatment with cefiderocol with that of meropenem at TOC
- To compare all-cause mortality at Day 14 of cefiderocol with that of meropenem for superiority of cefiderocol

Other Secondary Objectives:

Efficacy:

- To compare the clinical outcome of treatment with cefiderocol with that of meropenem in subjects at Early Assessment (EA; defined as start of treatment + 3 to 4 days), End of Treatment (EOT; defined as the last day of study

treatment), and Follow-up (FU)

- To compare the microbiologic outcome of treatment with cefiderocol with that of meropenem at EA, EOT, and FU
- To compare the all-cause mortality at Day 28 of subjects treated with cefiderocol with that of subjects treated with meropenem
- To compare the all-cause mortality during treatment and the follow-up period (until End of Study [EOS], defined as EOT + 28 days [± 3 days]) of cefiderocol with that of meropenem
- To compare the resource utilization required for the 2 study treatments for the study-qualifying infection. Note: This endpoint is not included in the clinical study report and will be filed in a separate report.

Safety:

- To assess the safety of cefiderocol

Methodology: This was a Phase 3, multicenter (multinational), double-blind, parallel-group, randomized, active-controlled study in approximately 300 subjects with documented nosocomial pneumonia caused by Gram-negative bacteria. Subjects meeting eligibility criteria and assessed by the investigator as requiring 7 to 14 days of intravenous (IV) treatment in the hospital were randomized (1:1) to either cefiderocol, 2 g, administered IV over 3 hours every 8 hours (q8h) or high-dose extended infusion meropenem, 2 g, administered IV over 3 hours, q8h. Linezolid was administered for at least 5 days to subjects in both arms to provide coverage for methicillin-resistant *Staphylococcus aureus* (MRSA), maintain the study blind, and, in the cefiderocol arm, provide coverage for Gram-positive bacteria.

Number of Subjects (Planned and Analyzed):

Planned: Approximately 300 subjects (150 in each treatment group)

Randomized: 300 subjects (148 in cefiderocol group, 152 in high-dose meropenem group)

Analyzed for efficacy:

- Intent-to-Treat (ITT) population: All randomized subjects who received at least 1 dose of a study treatment (cefiderocol [N = 148] and meropenem [N = 150)
- Modified Intent-to-Treat (mITT) population: All subjects in the ITT population who had evidence of a Gram-negative infection of the lower respiratory tract based on either a culture, Gram stain, or other diagnostic test OR who had evidence of a lower respiratory infection, but culture or other diagnostic tests did not provide a microbiological diagnosis (cefiderocol [N = 145] and meropenem [N = 147])
- Micro-evaluable Per-Protocol (ME-PP) population: All subjects in the mITT who did not have a major protocol violations and had a culture-confirmed diagnosis of a Gram-negative bacterium (cefiderocol [N = 105] and meropenem [N = 101])

Analyzed for safety:

- Safety population: All randomized subjects who received at least 1 dose of the

study treatment (identical to the ITT population) (cefiderocol [N = 148] and meropenem [N = 150])

Analyzed for Pharmacokinetics:

- Pharmacokinetic (PK) Concentration population: All subjects who had plasma sampling and who had at least 1 evaluable PK assay result for cefiderocol (cefiderocol [N = 128])

Diagnosis and Main Criteria for Inclusion:

Male or female subjects 18 years of age or older who had a documented nosocomial pneumonia (HABP/VABP/HCABP) caused by an aerobic Gram-negative pathogen only or in combination with an aerobic Gram-positive or anaerobic pathogen who required hospitalization for the parenteral (IV) treatment of the infection and who met all inclusion criteria were enrolled.

- All subjects must have fulfilled at least 1 of the following clinical criteria at screening: new onset or worsening of pulmonary symptoms or signs, such as cough, dyspnea, tachypnea (eg, respiratory rate > 25 breaths/minute), expectorated sputum production, or requirement for mechanical ventilation; hypoxemia (eg, a partial pressure of oxygen [PaO_2] < 60 mm Hg while the subject is breathing room air, as determined by arterial blood gas [ABG], or worsening of the ratio of the PaO_2 to the fraction of inspired oxygen [PaO_2/FiO_2]); need for acute changes in the ventilator support system to enhance oxygenation, as determined by worsening oxygenation (ABG or PaO_2/FiO_2) or needed changes in the amount of positive end-expiratory pressure; or new onset of or increase in (quantity or characteristics) suctioned respiratory secretions, demonstrating evidence of inflammation and absence of contamination.
- All subjects must have had at least 1 of the following signs at screening: documented fever (ie, core body temperature [tympanic, rectal, esophageal] ≥ 38°C [100.4°F], oral temperature ≥ 37.5°C, or axillary temperature ≥ 37°C), hypothermia (ie, core body temperature [tympanic, rectal, esophageal] ≤ 35°C [95.0°F], oral temperature ≤ 35.5°C, and axillary temperature ≤ 36°C), leukocytosis with a total peripheral white blood cell (WBC) count ≥ 10,000 cells/mm^3, leukopenia with total peripheral WBC count ≤ 4500 cells/mm^3, or > 15% immature neutrophils (bands) noted on peripheral blood smear.
- All subjects must have had a chest radiograph during screening or have had a previous chest radiograph within 48 hours prior to randomization showing the presence of new or progressive infiltrate(s) suggestive of bacterial pneumonia. A computed tomography scan in the same time window showing the same findings was also acceptable.
- All subjects must have had a suspected Gram-negative infection involving the lower respiratory tract by 1 or more of the following: Gram stain of lower respiratory secretions showing Gram-negative bacteria, either alone or mixed with Gram-positive bacteria at or within 72 hours prior to randomization; microbiologic culture of respiratory tract secretions within 72 hours prior to randomization identifying Gram-negative aerobic bacteria; other diagnostic

tests, including molecular tests, which provide evidence of Gram-negative bacterial infection of the lower respiratory tract; or pneumonia highly suspected to be due to Gram-negative bacteria based on prior antibiotic use or local epidemiologic evidence of Gram-negative infection outbreak.

- Subjects who failed empiric therapy were allowed in the study; however, confirmation of both clinical and microbiological failure was necessary.

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

Cefiderocol, 2 g, administered IV q8h as a 3-hour infusion in subjects with normal renal function; dose adjustment for renal function or dialysis was required; and lot numbers used were [redacted]

Duration of Treatment:

The recommended duration of treatment with IV study treatments was 7 to 14 days in the hospital, but treatment could have been extended up to 21 days based on the investigator's clinical assessment of the subject.

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

Meropenem, 2 g, administered IV q8h as a 3-hour infusion in subjects with normal renal function. Dose adjustment for renal function was required.

Concomitant Linezolid Treatment, Dose, and Mode of Administration:

Linezolid, 600 mg, was administered IV every 12 hours (q12h) over 30 minutes to 2 hours concomitantly for at least 5 days to provide coverage for Gram-positive bacteria in the cefiderocol arm, to provide coverage for MRSA in both study arms, and to maintain the study blind. Dose adjustment for renal function was not required

Criteria for Evaluation:

Efficacy Assessments:

All-cause mortality at Day 14 (primary efficacy endpoint), at Day 28, and at EOS; clinical and microbiological outcomes per subject and per pathogen as assessed by the investigator at EA, EOT, TOC, and FU. If treatment was extended beyond 14 days, additional clinical and microbiological outcomes were assessed on Day 14.

Safety Assessments:

Adverse event (AE) assessments, clinical laboratory tests (hematology, blood chemistry, and urinalysis), specialized chemistry tests (hepcidin, total iron-binding capacity [TIBC], iron, and transferrin iron saturation), and vital sign measurements

Pharmacokinetic Assessment:

Plasma concentrations of cefiderocol on Days 3 or 4 at 4 time points: (1) just prior to the start of the 3-hour infusion, (2) 1 hour after the start of infusion, (3) before the end of infusion, and (4) 1 hour after the end of infusion

Statistical Methods:

Protocol-defined statistical analyses are listed below. Statistical testing was performed at the 2-sided significance level of 0.05 unless stated otherwise.

Efficacy:

The primary efficacy analysis was performed for the mITT population

For the primary efficacy endpoint, the adjusted estimates of the difference in the all-cause mortality at Day 14 between cefiderocol and high-dose meropenem groups were calculated along with 95% confidence intervals (CIs) based on a stratified analysis using Cochran-Mantel-Haenszel (CMH) weights. The CMH weights were calculated with the Acute Physiology and Chronic Health Evaluation (APACHE) II score (≤ 15 and ≥ 16) as the stratification factor. Noninferiority was concluded if the upper bound of a 2-sided 95% CI for the difference in mortality at Day 14 between the 2 treatment groups (cefiderocol minus meropenem) was smaller than a noninferiority margin of 12.5%. A 2-sided p-value was also calculated for noninferiority testing.

Analysis of the primary endpoint was performed for the ITT and ME-PP populations as sensitivity analyses.

The key secondary endpoints were compared between treatment groups. A fixed-sequence approach was applied for multiplicity adjustment with the primary efficacy analyses. If the primary noninferiority hypothesis was satisfied, the following key secondary endpoints were tested in this order:

- To compare the microbiologic outcome of treatment with cefiderocol with that of meropenem in subjects at TOC
- To compare the clinical outcome of treatment with cefiderocol with that of meropenem at TOC
- To compare all-cause mortality at Day 14 of cefiderocol with that of meropenem for superiority of cefiderocol

The other following secondary endpoints were compared between treatment groups:

- To compare the clinical outcome of treatment with cefiderocol with that of meropenem in subjects at EA, EOT, and FU
- To compare the microbiologic outcome of treatment with cefiderocol with that of meropenem in subjects at EA, EOT and FU
- To compare the all-cause mortality at Day 28 of subjects treated with cefiderocol with that of subjects treated with meropenem
- To compare the all-cause mortality during treatment and the follow-up period (until EOS) of cefiderocol with that of meropenem.

Sequential Organ Failure Assessment (SOFA) and Clinical Pulmonary Infection Score (CPIS) scores were also evaluated. In addition, efficacy evaluations were performed per baseline pathogen for clinical and microbiological outcomes.

Safety:

Adverse events were classified by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities Version 18.1 or higher; treatment-emergent adverse events (TEAEs) were used for the safety analyses. The number and percentage of subjects who experienced TEAEs were summarized by treatment group. The summary by severity and by relationship to study treatment is presented by SOC and PT. All AEs, including AEs not considered treatment-emergent, are listed. Summary statistics are presented for laboratory test data and vital sign measurements for each scheduled time point and for the change from baseline to each time point.

Pharmacokinetics:

Individual plasma concentrations of cefiderocol are listed and summarized by nominal sampling time window and by dosage based on renal function. Summary statistics are presented. Population PK and PK/pharmacodynamic analyses were performed and reported separately.

Summary of Results

Efficacy:

- Demographic and baseline disease characteristics were generally similar between the treatment groups. Similar age, sex, weight, and race characteristics were observed in subjects randomized to either cefiderocol or high-dose extended infusion meropenem treatment groups. The percentage of subjects with severe disease was 49.0% in the cefiderocol group and 33.3% in the meropenem group. In the cefiderocol group, 49.7% of subjects had a CPIS of < 6, and 40.7% had a score of 6 to 7; in the meropenem group, 59.9% of subjects had a CPIS of < 6, and 27.2% had a score of 6 to 7.
- At Baseline, *Klebsiella pneumoniae* (31.5% of subjects), *Pseudomonas aeruginosa* (16.4% of subjects), *Acinetobacter baumannii* (16.1% of subjects), *Escherichia coli* (14.0% of subjects), and *Enterobacter cloacae* (5.1% of subjects) were the 5 most commonly observed Gram-negative pathogens.

The protocol prespecified multiplicity strategy included the primary and 3 key secondary endpoints.

- For the primary endpoint of all-cause mortality assessed at Day 14, cefiderocol demonstrated noninferiority to high-dose meropenem (all-cause mortality was 12.4% for cefiderocol vs 11.6% for meropenem; 95% CI: -6.6, 8.2).

Since the outcome of the primary endpoint was noninferiority, the first key secondary endpoint in the multiplicity strategy could then be tested.

- Microbiological eradication at TOC was 47.6% (59/124) with cefiderocol and was 48.0% (61/127) with meropenem, with a difference of -1.4% (95% CI: -13.5, 10.7).

This result was not statistically significant. Therefore, the other key secondary endpoints could not be tested for statistical significance.

- Clinical cure at TOC was 64.8% (94/145) with cefiderocol and was 66.7% (98/147) with meropenem, with a difference of -2.0% (95% CI: -12.5, 8.5).
- Superiority testing for all-cause mortality at Day 14 was not performed, and the associated 2-sided p-value was not calculated

For other secondary efficacy endpoints, results are as follows:

- The clinical cure rate with cefiderocol was 82.8% (120/145) at EA, 77.2% (112/145) at EOT, and 57.9% (84/145) at FU, and with meropenem was 83.0% (122/147) at EA, 81.0% (119/147) at EOT, and 57.8% (85/147) at FU.
- The clinical cure rate at TOC with cefiderocol was 64.6% (31/48) for *K. pneumoniae*, 66.7% (16/24) for *P. aeruginosa*, 52.2% (12/23) for *A. baumannii*, and 63.2% (12/19) for *E. coli*; with meropenem, these values

were 65.9% (29/44), 70.8% (17/24), 58.3% (14/24), and 59.1% (13/22), respectively.

- Microbiological eradication with cefiderocol was 41.9% (55/124) at EA, 63.7% (79/124) at EOT, and 43.5% (54/124) at FU, and with meropenem was 53.5% (68/127) at EA, 66.9% (85/127) at EOT, and 38.6% (49/127) at FU.
- Microbiological eradication at TOC with cefiderocol was 45.8% (22/48) for *K. pneumoniae*, 37.5% (9/24) for *P. aeruginosa*, 39.1% (9/23) for *A. baumannii*, and 52.6% (10/19) for *E. coli*; with meropenem, these values were 54.5% (24/44), 45.8% (11/24), 33.3% (8/24), and 50.0% (11/22), respectively.
- In the cefiderocol group, the all-cause mortality rate was 21.0% (30/143) at Day 28 and 26.8% (38/142) at the EOS visit; in the meropenem group, the all-cause mortality rate was 20.5% (30/146) at Day 28 and 23.3% (34/146) at the EOS visit.

Safety:

- Adverse events occurred in 87.8% (130/148) of subjects in the cefiderocol group and 86.0% (129/150) of subjects in the high-dose extended infusion meropenem group. The most frequently (≥ 10% of subjects in either group) reported AEs were urinary tract infection and hypokalemia. Adverse events of hypotension occurred more frequently in the meropenem group than in the cefiderocol group. The incidences of all other reported AEs differed between the treatment groups by < 5%.
- The percentage of subjects who experienced treatment-related AEs was 9.5% (14/148) in the cefiderocol group and 11.3% (17/150) in the meropenem group. The only treatment-related AE that occurred in > 2 subjects in either treatment group was diarrhea (2.0% [3/148] and 3.3% [5/150] of subjects in the cefiderocol and meropenem groups, respectively).
- The percentage of subjects with AEs leading to death was 26.4% (39/148) in the cefiderocol group and 23.3% (35/150) in the meropenem group. Treatment-related AEs leading to death were reported for 1 subject (sepsis [secondary to HABP]) in the cefiderocol group and 2 subjects (pseudomonas infection in 1 subject and disseminated intravascular coagulation and multiple organ dysfunction syndrome [both noted to be related to linezolid] in 1 subject) in the meropenem group. None of the other deaths in either treatment group were considered related to the study treatment by either the investigator or the sponsor.
- The percentage of subjects who experienced SAEs was 36.5% (54/148) in the cefiderocol group and 30.0% (45/150) in the meropenem group. Each SAE occurred in < 5% of subjects in either treatment group. Three subjects in the cefiderocol group and 5 subjects in the meropenem group were reported with treatment-related SAEs.
- Overall, 8.1% (12/148) of subjects in cefiderocol group and 9.3% (14/150) of subjects in the meropenem group experienced AEs leading to discontinuation of study treatment. Four subjects had AEs leading to discontinuation of study treatment that were considered by the investigator as related to study treatment

(alanine aminotransferase [ALT] increased in 1 subject and ALT increased, aspartate aminotransferase increased, and hepatic failure in 1 subject in the cefiderocol group; hepatic enzyme increased in 1 subject [considered to be caused by RBC transfusion] and disseminated intravascular coagulation and multiple organ dysfunction syndrome in 1 subject in the meropenem group).

- Overall, the incidence of AEs related to *Clostridium difficile* (now referred to as *Clostridioides difficile* by the Clinical and Laboratory Standards Institute, but previously called *Clostridium difficile* at the time that the study was conducted) was low, with only 4 subjects in each treatment group experiencing *C. difficile*-related AEs. Seven subjects (4 in the cefiderocol group and 3 in the meropenem group) had AEs of *C. difficile* infection and 1 subject (meropenem group) had an AE of *C. difficile* colitis. Adverse events of diarrhea occurred in 8.8% (13/148) of subjects in the cefiderocol group and 8.7% (13/150) of subjects in the meropenem group. All of the AEs of diarrhea were mild or moderate in severity. None of the AEs of diarrhea were SAEs, and none led to discontinuation of study treatment. All but 2 of the AEs of diarrhea resolved, resolved with sequelae (1 case), or were resolving.
- The incidence of AEs characteristic of the β-lactam class of antibiotics was low in the cefiderocol group and did not reveal any previously unexpected events.
  - No SAEs related to rash/hypersensitivity were reported. The occurrence, nature, and severity of rash in this study do not indicate that cefiderocol has any important differences in this regard compared with other antibiotics.
  - Adverse events of seizure were reported for 2 subjects in each treatment group. All of the events of seizure were of mild or moderate severity and were considered not serious and not related to study treatment.
  - No notable differences between the treatment groups were identified in the occurrence of liver-related AEs, including biochemistry and clotting tests, or liver-related laboratory test results. None of the cases met the clinical and biochemical criteria for Hy's law or drug-induced liver injury.
  - Overall, the incidences of AEs that could suggest bone marrow suppression were low, and no differences were noted between the 2 treatment groups.
- Mean values for the blood chemistry, hematology, and specialized laboratory parameters evaluated were generally similar between the 2 treatment groups at baseline, and mean changes from baseline for each parameter were generally similar between the treatment groups during the study. The percentage of subjects meeting each predefined laboratory outlier category for hematology and biochemistry parameters (not including liver-related parameters) was generally similar (< 5% difference) between the treatment groups, with 2 exceptions. The percentage of subjects who had a decrease of ≥ 1.5 g/dL in hemoglobin at EOT was 29.4% (37/126) in the cefiderocol group and 21.8% (31/142) in the meropenem group. The percentage of subjects who had an increase of ≥ 50% and value > upper limit of normal (ULN) for ALP at TOC was 13.4% (15/112) in the cefiderocol group and 20.3% (24/118) in the meropenem group. No notable differences between the treatment groups were identified in the occurrence of liver-related AEs, including biochemistry and

clotting tests, or in the occurrence of liver-related laboratory test results, with the exception of the percentage of subjects who had AST or ALT values > 3 × ULN (13.1% [19/145] in the cefiderocol group and 23.6% [35/148] in the meropenem group). No subjects met the clinical and biochemical criteria for Hy's law or drug-induced liver injury.

- Cefiderocol, which as a siderophore complexes with free iron to facilitate sequestration into bacterial cell walls, did not have an effect on hemoglobin, hematocrit, iron, TIBC, transferrin saturation, or hepcidin values over time.
- There were no clinically meaningful differences between the treatment groups in vital signs (at baseline and postbaseline).

Pharmacokinetics: For the total PK Concentration population (all dose groups), geometric mean (range) plasma concentrations of cefiderocol on Day 3 or Day 4 were 30.7 (0 to 267) µg/mL just prior to infusion, 67.9 (12.6 to 325) µg/mL 1 hour after the start of infusion, 80.2 (14 to 1900) µg/mL at the end of infusion, and 58.1 (10.5 to 231) µg/mL 1 hour after the end of infusion.

CONCLUSIONS

Efficacy Conclusions:

Cefiderocol is noninferior to high-dose extended infusion meropenem in the treatment of subjects with documented nosocomial pneumonia caused by Gram-negative bacteria (HABP, VABP, or HCABP) for all-cause mortality at Day 14.

Safety Conclusions:

The observed safety profile of cefiderocol was as expected for a cephalosporin. The safety profile was comparable between the cefiderocol and high-dose meropenem groups.

Report Date: 24 Jan 2020

Date of Amendment 1: 10 Feb 2020