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: An Open-label, Multicenter, Single-arm, Phase 1 Study to Assess the Intrapulmonary Concentrations of Cefiderocol at Steady State in Hospitalized Subjects with Known or Suspected Bacterial Pneumonia on Treatment with Standard of Care Antibiotics and Requiring Mechanical Ventilation

Investigators and Study Centers: [redacted]

Publication (reference): None

Studied Period:

Study initiated (first subject enrolled): [redacted] February 2019

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

Study Phase: Phase 1b

Objectives:

The primary objectives of the study were as follows:

- To estimate the concentration of cefiderocol in epithelial lung fluid (ELF) at steady state in hospitalized subjects with known or suspected bacterial pneumonia receiving treatment with standard of care (SOC) antibiotics and requiring mechanical ventilation
- To estimate the ratio of the concentration for cefiderocol in ELF relative to plasma ($R_{C,E/P}$) in hospitalized subjects with known or suspected bacterial pneumonia receiving treatment with SOC antibiotics and requiring mechanical ventilation

Methodology: This was a multicenter, single-arm, open-label Phase 1b study to assess the intrapulmonary and plasma concentrations of cefiderocol at steady state after multiple-dose administration in hospitalized subjects with known or suspected bacterial pneumonia on treatment with SOC antibiotics and requiring mechanical ventilation. Subjects meeting eligibility criteria received 2-g doses of cefiderocol (or renally adjusted doses), administered intravenously over 3 hours, every 8 hours (q8h), or every 6 hours (q6h) if augmented renal function. Cefiderocol was to be administered for a minimum of 3 doses and up to a total of 6 doses in subjects with normal or augmented renal function and subjects with mild or moderate renal impairment, and for a minimum of 6 doses and up to a total of 9 doses in subjects with severe renal impairment. Bronchoalveolar lavage (BAL) procedure (Mini-BAL was not allowed in this study) was conducted at the third dosing (or sixth dosing for subjects with severe renal impairment). If the third dosing was not convenient for the subject or the institution to perform the BAL procedure (or sixth dosing for subjects with severe renal impairment), the fourth, fifth, or sixth dosing could have been considered as the timing for the BAL procedure (or the seventh,

eighth, or ninth dosing for subjects with severe renal impairment).

Number of Subjects (Planned and Analyzed):

Number of subjects planned: up to approximately 18 subjects (minimum of 3 subjects)

Number of subjects enrolled: 8

Number of subjects analyzed for pharmacokinetics: 7

Number of subjects analyzed for safety: 7

Diagnosis and Main Criteria for Inclusion: Hospitalized male or female subjects, 18 to 80 years of age (inclusive), with known or suspected bacterial pneumonia who were being treated with SOC antibiotics and were mechanically ventilated and expected to remain mechanically ventilated for at least 48 hours (or 72 hours for subjects with severe renal impairment) after first dose of cefiderocol were enrolled.

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

Cefiderocol 2 g was administered intravenously q8h as a 3-hour infusion in subjects with normal, mild, moderate, or severe renal function. Dose or schedule adjustment was provided for renal function, including augmented renal clearance.

Lot Number: [redacted]

Duration of Treatment:

Planned: The dosing duration for cefiderocol was anticipated to be 3 to 4 days, depending on the subject's renal function.

Actual: One subject with normal renal function and 1 subject with mild renal impairment received cefiderocol 2 g q8h (total of 3 doses each, over 2 days). Two subjects with augmented renal function received cefiderocol 2 g q6h (1 subject received a total of 3 doses and 1 subject received a total of 4 doses; over 2 days). Of the 3 subjects with moderate renal function at the start of the study, 2 subjects received cefiderocol 1.5 g q8h (total of 3 doses each, over 2 days) and 1 subject received cefiderocol 1.5 g q8h for 3 doses followed by cefiderocol 1 g q8h for 3 doses (dose adjusted due to an AE of acute kidney injury) over 3 days.

Reference Therapy: Not applicable

Criteria for Evaluation:

***Pharmacokinetic Assessments*:**

The ELF sample for determination of cefiderocol concentration was collected by BAL procedure at 3, 5, or 7 hours (depending on the ELF cefiderocol concentration data obtained) after administration of at least 3 doses of cefiderocol in subjects with normal or augmented renal function and in subjects with mild or moderate renal impairment, and after administration of at least 6 doses of cefiderocol in subjects with severe renal impairment. A total of 4 blood samples for determination of plasma cefiderocol concentrations were collected at prespecified time points corresponding to the time point at which the ELF sample was collected. Pharmacokinetic assessment of concentration data from both ELF and plasma samples was performed for every 3 subjects to determine if modifications to the ELF sampling time point were needed in subsequent subjects.

Blood and ELF samples were also used for determination of urea concentration. Urea was used as an endogenous marker of ELF because urea is small and relatively nonpolar and can travel across membranes freely to reach the outer surfaces of alveoli. The calculated volume of ELF (V_{ELF}) was adjusted for excess

exogenous volume using the concentration of urea in blood and BAL.

Cefiderocol concentrations in ELF were calculated using cefiderocol concentrations in BAL and urea concentrations in blood and BAL.

***Bioanalytic Assessment*:**

- Measurement method: Liquid chromatography/tandem mass spectrometry (LC/MS/MS)
- Lower limit of quantification of cefiderocol in plasma and ELF: 0.1 µg/mL and 0.005 µg/mL

***Safety Assessment*:**

Subject safety was assessed by the identification of adverse events (AEs) from the time of informed consent to the end of the study, up to 7 days (±3 days) after the last dose of cefiderocol. Additional safety assessments included physical examinations, vital sign measurements, chest x-rays, and clinical laboratory tests.

Statistical Methods:

***Pharmacokinetics*:**

Individual ELF and plasma concentrations of cefiderocol were summarized descriptively by nominal sampling time, including N, mean, SD, median, minimum, maximum, CV% (calculated by SD/Mean × 100), geometric mean, and CV% geometric mean values. The CV% geometric mean was calculated according to a formula: CV% geometric mean = $(\exp[sd^2]-1)^{1/2} \times 100$, where sd was the standard deviation for natural log (ln)-transformed data. $R_{C,E/P}$ concentration ratios were also calculated and summarized descriptively for each subject. The time courses of individual and mean plasma and ELF concentrations and individual and mean $R_{C,E/P}$ were presented graphically.

Safety:

Due to the small number of subjects enrolled in the study, all safety data (AEs, physical examination findings, vital sign results, chest x-ray findings, and clinical laboratory parameter values) were listed by subject and time point.

Summary of Results:

Disposition:

Of the 8 subjects enrolled, 1 subject was a screen failure and 7 subjects were administered cefiderocol and completed the study as scheduled. The 7 subjects who received cefiderocol were included in the Safety and PK Populations.

Demographics and Baseline Characteristics:

The majority of subjects (5/7) were white. Four subjects were female and 3 subjects were male. All 7 subjects had a diagnosis of pneumonia, including 4 subjects with healthcare associated pneumonia (HAP), 2 subjects with community acquired pneumonia (CAP), and 1 subject with ventilator associated pneumonia (VAP). The majority of subjects (5/7) had signs and symptoms at baseline (eg, dyspnea, rales, and/or other signs and symptoms). Of 5 subjects with microbiology test results, 3 subjects had a pathogen identified (1 with *Staphylococcus aureus*, 1 with *Serratia marcescens* and *Staphylococcus aureus*, and 1 with *Pseudomonas aeruginosa*) and 2 subjects did not have a pathogen identified.

Pharmacokinetics:

Geometric mean (minimum, maximum) plasma concentrations of cefiderocol were 60.3 (25.2, 104), 80.8 (43.6, 116), 56.3 (20.7, 102), and 44.6 (12.9, 99.3) µg/mL at

1 hour after start of infusion, 3 hours after start of infusion, 2 hours after end of infusion, and 4 hours after end of infusion, respectively (PK Concentration Population, N = 7).

Geometric mean (minimum, maximum) ELF concentration of cefiderocol was 7.63 (3.10, 20.7) µg/mL at 3 hours after start of infusion (N = 4) and was 10.4 (7.19, 15.9) µg/mL at 2 hours after end of infusion (N = 3) (PK Concentration Population).

Geometric mean (minimum, maximum) cefiderocol $R_{C,E/P}$ ratios were 0.0893 (0.0379, 0.178) at 3 hours after start of infusion (N = 4) and 0.231 (0.187, 0.347) at 2 hours after end of infusion (N = 3) (PK Concentration Population).

Safety:

All 7 subjects (100%) in the Safety Population reported at least 1 AE. All of the AEs were either mild or moderate in severity, and all were considered not related to cefiderocol. There were no notable trends in the types of AEs reported.

Adverse events of special interest included mild anemia reported in 2 of 7 subjects and mild thrombocytopenia reported in 1 of 7 subjects. All of these AEs of special interest were considered by the investigator as mild in severity and not related to cefiderocol.

No deaths, SAEs, or AEs leading to withdrawal from the study occurred during the study. Two deaths occurred after the End of Study (EOS) visit (1 subject died due to respiratory failure, secondary to his underlying hepatic encephalopathy, cirrhosis of the liver, and hepatitis C, 6 days after completing the study; and 1 subject died due to bowel/cecal ischemia, resulting in sepsis, septic shock, and multiorgan failure, 4 days after completing the study). These deaths were considered by the investigator as not related to cefiderocol.

As expected for this population of hospitalized subjects with known or suspected bacterial pneumonia, who were requiring mechanical ventilation, all subjects had abnormal physical examination findings during the study.

There were no notable trends in clinical laboratory or vital signs results during the study.

CONCLUSIONS

Pharmacokinetics:

- Geometric mean (minimum, maximum) ELF concentration of cefiderocol was 7.63 (3.10, 20.7) µg/mL at 3 hours after start of infusion (N = 4) and was 10.4 (7.19, 15.9) µg/mL at 2 hours after end of infusion (N = 3) (PK Concentration Population). The individual ELF concentrations achieved would be sufficient to inhibit pathogens with minimum inhibitory concentrations (MICs) of ≤ 4 µg/mL for cefiderocol.
- Geometric mean (minimum, maximum) cefiderocol $R_{C,E/P}$ ratios were 0.0893 (0.0379, 0.178) at 3 hours after start of infusion (N = 4) and 0.231 (0.187, 0.347) at 2 hours after end of infusion (N = 3) (PK Concentration Population). The ratio at 3 hours after the start of infusion was comparable to the ELF/total plasma AUC-based ratio in healthy subjects (0.101; N = 20; Study R2112), and the ratio at 2 hours after the end of infusion was higher. Pharmacokinetic lag in ELF was suggested compared with plasma in subjects with known or suspected bacterial pneumonia receiving treatment with SOC antibiotics and requiring mechanical ventilation.

Safety: • All 7 subjects (100%) in the Safety Population reported at least 1 AE. All of the AEs were mild or moderate in severity, and all were considered not related to cefiderocol. No deaths, SAEs, or AEs leading to withdrawal occurred during the study.
Final Report Date: 29 Apr 2020