2. SYNOPSIS

Sponsor:

For all countries except Japan:
Shionogi, Inc.
[redacted]

For Japan:
Shionogi & Co., Ltd.
[redacted]

Name of Finished Product:

Cefiderocol (S-649266)

Name of Active Ingredient:

Cefiderocol

Study Title:

A Multicenter, Double-blind, Randomized, Clinical Study to Assess the Efficacy and Safety of Intravenous S-649266 in Complicated Urinary Tract Infections With or Without Pyelonephritis or Acute Uncomplicated Pyelonephritis Caused by Gram-negative Pathogens in Hospitalized Adults in Comparison with Intravenous Imipenem/Cilastatin

Investigators and Study Centers: [redacted]

Publication (reference): Refer to Appendix 16.1.11

Studied Period:

[redacted] Feb 2015 (first subject first visit [signed informed consent form (ICF)]) to Aug 2016 (last subject completed)

Phase of Development: 2

Objectives:

The primary objective of the study was:

- To compare the composite outcome of microbiological eradication and clinical response of cefiderocol with that of imipenem/cilastatin (IPM/CS) in a subject population at risk for multidrug resistant (MDR) Gram-negative pathogens originating from complicated urinary tract infections (cUTIs) with or without pyelonephritis or acute uncomplicated pyelonephritis. The primary efficacy assessment was performed at the Test of Cure (TOC) (approximately 7 days following the End of Treatment [EOT]).

The secondary objectives of the study were:

- To assess the safety of cefiderocol in a subject population with the potential to have MDR bacterial infections
- To compare the clinical and microbiological response of cefiderocol with

IPM/CS in a subject population at risk for MDR Gram-negative pathogens at Early Assessment (EA) (Day 4 ± 1 day), EOT (last day of study drug; same calendar day), and Follow-up (FUP) (EOT +14 ± 3 days)

- To assess microbiological response per pathogen at EA, EOT, TOC, and FUP
- To assess microbiological response per subject at EA, EOT, TOC, and FUP
- To assess clinical response per pathogen at EA, EOT, TOC, and FUP
- To assess clinical response per subject at EA, EOT, TOC, and FUP
- To determine plasma and urine drug concentrations at specified times postdose in a population of subjects with acute infection

Methodology:

This was a Phase 2, multicenter (multinational), double-blind, randomized, active-controlled, parallel-group study in subjects diagnosed with cUTI with or without pyelonephritis or acute uncomplicated pyelonephritis. Subjects were randomized (2:1) to either an intravenous (IV) 2-g dose of cefiderocol or a 1-g dose of IPM/CS administered 3 times daily over 1 hour, at 8-hour intervals, for 7 to 14 days in the hospital. This was the recommended treatment duration. If it became in the subject's best interest to be discharged from the hospital earlier, then treatment was stopped after a minimum of 5 days of treatment and EOT assessments, including a urinary culture, were completed. Dosage adjustment for subjects with reduced renal function (estimated creatinine clearance [CrCl] ≤ 70 mL/minute) and/or body weight (< 70 kg) was made by an unblinded pharmacist or qualified designee and included every 6-hour dosing intervals and/or reduced doses. No sequential oral antibiotic (step-down) therapy was permitted. Subjects were evaluated daily for clinical response and safety during hospitalization and periodically during follow-up for approximately 42 days starting from the time of randomization. An evaluation of safety by a Data Safety Monitoring Board (DSMB) was performed after approximately 100 subjects completed the study, and recommendations were communicated to the sponsor. The DSMB continuously reviewed blinded safety data throughout the conduct of the trial. Electrocardiograms (ECGs) were reviewed locally by sites and then reanalyzed centrally to improve accuracy of interpretation, and a summary of the results of centrally reviewed ECGs was reviewed by the DSMB.

Number of Subjects (Planned and Analyzed):

Planned: 450

Randomized: 452 (303 [cefiderocol], 149 [IPM/CS])

Analyzed for Efficacy:

- Intent-to-treat (ITT) Population: 290 (cefiderocol), 147 (IPM/CS)
- Microbiological ITT (Micro-ITT) Population: 252 (cefiderocol), 119 (IPM/CS)
- Microbiological Evaluable (ME) Population: 228 (cefiderocol), 106 (IPM/CS)

Analyzed for Safety:

- Safety Population: 300 (cefiderocol), 148 (IPM/CS)

Analyzed for Pharmacokinetics:

- Pharmacokinetic Concentration Population: 293 (cefiderocol)

Diagnosis and Main Criteria for Inclusion:

Male or female subjects 18 years of age or greater who had symptomatic cUTIs were eligible. There were 3 groups of subjects with cUTI that were eligible for inclusion in the study. These were subjects with cUTIs with pyelonephritis, subjects with cUTIs without pyelonephritis, and subjects with acute uncomplicated pyelonephritis.

Symptomatic cUTI was defined as a clinical syndrome characterized by pyuria and a documented or suspected microbial pathogen on culture of urine or blood, accompanied by local and systemic signs and symptoms, including fever (ie, temperature ≥ 38ºC), chills, malaise, flank pain, back pain, and/or costovertebral angle pain or tenderness. This clinical syndrome occurred in the presence of a functional or anatomical abnormality of the urinary tract or in the presence of catheterization, except for subjects with acute uncomplicated pyelonephritis.

Subjects with acute uncomplicated pyelonephritis were limited to no more than 30% of subject enrollment (~ 135 subjects based on a total enrollment of 450 subjects). Because this population may have responded more readily to treatment, clinical diagnosis was a stratification factor for randomization into 1 of 2 strata (cUTI with or without pyelonephritis and acute uncomplicated pyelonephritis).

Hospitalized subjects who had a clinical diagnosis of either cUTI with or without pyelonephritis or acute uncomplicated pyelonephritis were eligible for enrollment.

The specific clinical diagnosis of cUTI included:

cUTI with or without pyelonephritis with a history of at least 1 of the following:

- Indwelling urinary catheter or recent instrumentation of the urinary tract (within 14 days prior to Screening)
- Urinary retention caused by benign prostatic hypertrophy
- Urinary retention of at least 100 mL or more of residual urine after voiding (neurogenic bladder)
- Obstructive uropathy (nephrolithiasis, fibrosis, etc)
- Azotemia caused by intrinsic renal disease (blood urea nitrogen [BUN] and creatinine values greater than normal laboratory values)

OR

Acute uncomplicated pyelonephritis (pyelonephritis and normal urinary tract anatomy)

AND

All subjects had to have at least 2 of the following signs or symptoms:

- Chills or rigors or warmth associated with fever (temperature ≥ 38ºC)
- Flank pain (pyelonephritis) or suprapubic/pelvic pain (cUTI)
- Nausea or vomiting
- Dysuria, urinary frequency, or urinary urgency
- Costovertebral angle tenderness on physical examination

AND

All subjects had to have urinalysis evidence of pyuria demonstrated by 1 of the following:

- Dipstick analysis positive for leukocyte esterase
- ≥ 10 white blood cells (WBCs) per µL in unspun urine or ≥ 10 WBCs per high power field in spun urine

Subjects who had a positive urine culture obtained within 48 hours prior to randomization containing ≥ 10^5 colony-forming units (CFUs)/mL of a Gram-negative uropathogen likely to be susceptible to imipenem were eligible for the study. Subjects who had been treated previously with an empiric antibiotic other than the study drugs, but failed treatment, both clinically and microbiologically, were eligible for the study if they had an identified Gram-negative uropathogen that was not susceptible to the previously used empiric treatment and likely to be susceptible to imipenem.

Subjects were excluded if they had a history of hypersensitivity reactions to carbapenems, cephalosporins, penicillins, or other β-lactam antibiotics; a urine culture at study entry that isolated more than 2 uropathogens, regardless of colony count; a confirmed fungal urinary tract infection; asymptomatic bacteriuria; or were receiving hemodialysis or peritoneal dialysis.

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

Cefiderocol, 2 g, was administered IV over 1 hour, at 8-hour intervals. Dose adjustment was required based on renal impairment and/or body weight. Lot numbers used were [redacted]

Duration of Treatment:

The recommended duration of treatment with IV study drugs was 7 to 14 days in the hospital. If in the opinion of the investigator it became in the subject's best interest to be discharged from the hospital earlier, then treatment could have been stopped after a minimum of 5 days. No sequential oral antibiotic step-down treatment was allowed.

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

Imipenem/cilastatin, 1 g, was administered IV over 1 hour at 8-hour intervals. Dose adjustment was required based on renal impairment and/or body weight. Lot numbers used were [redacted]

Prohibited Concomitant Therapy:

Concurrent use of nonstudy antibacterial drug therapy with a Gram-negative spectrum of activity before TOC was prohibited. Coadministration of valproic acid, probenecid, methotrexate, or procainamide was prohibited during the treatment phase of this study. These nonantibiotic medications could be restarted after EOT, if indicated.

Criteria for Evaluation:

Efficacy Assessment:

Both clinical and microbiological responses were assessed at EA (Day 4 ± 1), EOT, TOC (7 days ± 2 days following EOT), and FUP (approximately 14 days ± 3 days after EOT). The presence and severity of the subject's symptoms were determined, and microbiological assessment (quantitative culture) of the urine was conducted at each evaluation time point.

Clinical response was determined by improvement or resolution of clinical signs and symptoms of cUTI assessed by the investigator. Microbiological response was determined by quantitative microbiological assessments (defined as a negative urine culture or urine culture with $< 10^4$ CFUs/mL). Clinical resolution assessed by the investigator was based in part on the graded response to the Structured Patient Interview about the current status of the subject's symptoms that had been recorded at the time of randomization and at each study visit and the absence of any new symptoms related to the cUTI.

Safety Assessment:

Safety was assessed daily while the subject was hospitalized and specifically at EOT, TOC, and FUP. Safety assessments extended up to 28 days after the last dose of the study drug. Subjects were assessed for adverse events (AEs) daily. Vital signs (including body temperature) were measured 3 times daily. Clinical laboratory tests (including specialized tests) of blood chemistry, hematology, and urinalysis were performed at Screening, EA, EOT, TOC, and FUP. Safety laboratory tests were also performed on Day 1.

Electrocardiograms were performed at Screening and at EA at the end of 1 of the study drug infusions. The ECG results were initially reported by study centers, and subsequently all ECGs were manually reanalyzed by an independent cardiologist to improve diagnostic accuracy.

Pharmacokinetic Assessment:

All subjects had sparse blood sampling to determine the plasma concentrations of study drug. In addition, timed spot urine samples were collected for the determination of drug concentration. Pharmacokinetic blood samples were drawn on Day 3 (+ 2 days); 1 draw just prior to the infusion of study drug, 1 draw -0.25 to 0 hours before the end of the infusion, and 1 draw 2 ± 0.5 hours after the start of infusion (for subjects enrolled in the original protocol dated 25 Mar 2014), and 1 draw 1 ± 0.5 hours after the end of the infusion (added in Protocol Version 2, Amendment 1, dated 05 Aug 2015). A single blood draw was performed as soon as possible if EOT occurred before Day 7 of treatment or for subjects withdrawn or discontinued from the study. The PK urine samples were collected 2 and 6 hours (± 0.5 hours) after the start of infusion of study drug on Day 3.

Statistical Methods:

Efficacy:

For the assessment of the primary objective, a 2-sided 95% confidence interval (CI) of the difference of response rate between the treatment groups (cefiderocol minus

IPM/CS) for the composite of microbiological eradication and clinical response was constructed based on a stratified analysis using Cochran-Mantel-Haenszel weights in the Micro-ITT Population (subjects having taken at least 1 dose of study drug and with a Gram-negative uropathogen causing the cUTI). The stratification factor for the 2 strata was baseline diagnosis (cUTI with or without pyelonephritis versus acute uncomplicated pyelonephritis).

The study design and primary objectives were based on a 20% noninferiority margin for the response rate of composite of microbiological eradication and clinical response at TOC. If the study hypothesis to exclude the possibility that cefiderocol was more than 20% inferior to IPM/CS were to have been accepted, the hypothesis based on the 15% noninferiority margin would have been tested.

Sample Size:

Based on the noninferiority margin of 20%, 249 evaluable subjects were required for the Micro-ITT Population to provide 90% power with a 1-sided significance level of 2.5%, assuming a 70% composite response rate for both the cefiderocol group and the IPM/CS group. In addition, based on a 15% noninferiority margin, 330 evaluable subjects were required to provide 80% power under the same assumptions. However, in order to meet Food and Drug Administration (FDA) requirements (ie, 300 subjects exposed to cefiderocol) for a safety database large enough for registration, the sample size of randomized subjects had to be at least 450 subjects. Assuming 80% of the randomized subjects were evaluable, 450 randomized subjects provided 360 evaluable subjects for the Micro-ITT Population, which had a power of 83% to demonstrate noninferiority of cefiderocol to IPM/CS under the 15% margin. The number of evaluable subjects also ensured > 90% power to demonstrate noninferiority based on the 20% noninferiority margin. The proportion of the Micro-ITT Population was monitored in a blinded fashion during the conduct of the study to ensure the adequacy of the design assumptions.

Randomization:

Each subject was randomized to either the cefiderocol group or the IPM/CS group in a 2:1 ratio. The randomization was stratified according to the subject's clinical diagnosis, (cUTI with or without pyelonephritis and acute uncomplicated pyelonephritis) and region (North America, European Union [EU], Russia, and Japan plus the rest of world). This resulted in 8 strata based on the combination of clinical diagnosis and region: 1 to 4 = cUTI with or without pyelonephritis + region, 5 to 8 = acute uncomplicated pyelonephritis + region.

Safety:

For the safety assessments including AEs, clinical laboratory safety tests (hematology, chemistry, endocrinology, and urinalysis), physical examination findings, vital sign measurements, and 12-lead ECGs, the number and percentage for the AEs or outliers, and summary statistics (observations, mean, standard deviation [SD], median, minimum, and maximum) for the continuous values were provided by treatment group.

Pharmacokinetics:

Individual plasma concentrations of cefiderocol were listed and summarized by nominal sampling time window, by dosing regimen and nominal sampling time, and, if

possible, by dosing regimen based on estimated CrCl and body weight and nominal sampling time with the number of nonmissing observations (N), arithmetic mean (Mean), SD, and coefficient of variation (CV%, calculated by SD/Mean × 100), geometric mean and coefficient of variation for geometric mean (CV% Geometric Mean), and median, minimum, and maximum values. The CV% Geometric Mean was calculated according to a formula CV% Geometric Mean = $[\exp(sd^2)-1]^{1/2} \times 100$, where sd is the standard deviation for natural log -transformed data. Individual urine concentrations of cefiderocol were listed and summarized by nominal sampling time with the same summary statistics as plasma concentrations.

Summary of Results

A total of 452 subjects were randomized. Of these, 448 subjects (300 in the cefiderocol group and 148 in the IPM/CS group) received blinded study drug and met the definition for the Safety Population, 371 subjects (252 in the cefiderocol group and 119 in the IPM/CS group) met the definition for the Micro-ITT Population (82.1%), and 293 subjects in the cefiderocol group met the definition for the PK Population.

In the Micro-ITT Population, 25.8% (65/252) of subjects in the cefiderocol group had a diagnosis of acute uncomplicated pyelonephritis compared with 29.4% (35/119) of subjects in the IPM/CS group; 74.2% (187/252) of subjects in the cefiderocol group had a clinical diagnosis at baseline of cUTI with or without pyelonephritis compared with 70.6% (84/119) of subjects in the IPM/CS group. Factors contributing to this difference between treatment groups were the exclusion of approximately 18% of randomized subjects from the Micro-ITT Population and the correction of the clinical diagnosis at baseline for 15 subjects after randomization (based on a confirmed diagnosis). This resulted in a lower proportion of subjects (25.8% [65/252] of subjects) in the cefiderocol group than in the IPM/CS group (29.4% [35/119] of subjects) with acute uncomplicated pyelonephritis. This difference between treatment groups in clinical diagnosis in the Micro-ITT Population was also reflected in minor differences in gender and age between the treatment groups. A larger proportion of males (47.2% [119/252] of subjects) and a slightly older population (mean age 62.3 years) was observed in the cefiderocol group compared with the IPM/CS group (40.3% [48/119] of subjects were male, mean age 61.3 years).

Efficacy:

Primary Efficacy Endpoint:

In the Micro-ITT Population, the response rate for the primary endpoint of the composite of microbiological eradication and clinical response at TOC was 72.6% (183/252) of subjects in the cefiderocol group and 54.6% (65/119) of subjects in the IPM/CS group. The adjusted treatment difference (cefiderocol minus IPM/CS) of 18.58% (95% CI; 8.23%, 28.92%) met the criterion for noninferiority at the prespecified 20% margin, since the lower limit of the 95% CI exceeded -20%. Noninferiority at the prespecified 15% margin was also demonstrated since the lower limit of 8.23% exceeded −15%. In addition, the lower limit of 8.23% exceeded zero, which is consistent with superiority of cefiderocol compared with IPM/CS.

In the ME Population (used as a sensitivity analysis and defined as any subjects in the Micro-ITT Population meeting per-protocol criteria), the response rate for the

cefiderocol group was noninferior to the IPM/CS group at both the prespecified 20% and 15% margins, and since the lower limit of the 95% CI exceeded zero, it was also consistent with superiority of cefiderocol compared with IPM/CS.

Secondary Efficacy Endpoints:

At TOC in the Micro-ITT Population, the microbiological eradication rate was 73.0% (184/252) of subjects in the cefiderocol group and 56.3% (67/119) of subjects in the IPM/CS group. The adjusted treatment difference of 17.25% (95% CI; 6.92%, 27.58%) in favor of cefiderocol was statistically significant and clinically meaningful. The sustained eradication rate at FUP was 57.1% (144/252) of subjects in the cefiderocol group and 43.7% (52/119) of subjects in the IPM/CS group; the adjusted treatment difference of 13.92% (95% CI; 3.21%, 24.63%) in favor of cefiderocol was also statistically significant and clinically meaningful. The microbiological eradication rates at EA and EOT were similar between treatment groups.

At TOC, the clinical response rate was similar between the treatment groups: 89.7% (226/252) of subjects in the cefiderocol group and 87.4% (104/119) of subjects in the IPM/CS group. The clinical response rates at EA and EOT were similar between treatment groups. The sustained clinical response rate at FUP was 81.3% (205/252) of subjects in the cefiderocol group and 72.3% (86/119) of subjects in the IPM/CS group. The adjusted treatment difference of 9.02% (95% CI, -0.37%, 18.41%) favored the cefiderocol group, though the difference was not statistically significant.

In the Micro-ITT Population, the response rates for the composite of microbiological eradication and clinical response at EA and EOT were similar between the treatment groups. At FUP, response rate was 54.4% (137/252) of subjects in the cefiderocol group and 39.5% (47/119) of subjects in the IPM/CS group; the adjusted treatment difference of 15.31% (95% CI; 4.69%, 25.92%) favoring cefiderocol was statistically significant and clinically meaningful.

The microbiological and clinical response rates per pathogen at TOC, EA, EOT, and FUP in the Micro-ITT Population are described for *Escherichia coli* and *Klebsiella pneumoniae*, the 2 most frequently occurring uropathogens.

For both uropathogens, microbiological eradication at EA and EOT was similar between the treatment groups. For *E. coli* at TOC and FUP, adjusted treatment differences of 16.77% and 18.10%, respectively, were demonstrated, and these differences are consistent with the microbiological response in the overall population. For *K. pneumoniae,* an adjusted treatment difference of 23.00% at TOC was observed, followed by a treatment difference of 6.33% at FUP. These results demonstrate the microbiological efficacy of cefiderocol, which is consistently better than IPM/CS for these uropathogens.

For *E. coli*, rates of clinical response at TOC, EA, and EOT were similar between treatment groups. At FUP, sustained clinical response was higher in the cefiderocol group compared with the IPM/CS group (difference between the 2 treatment groups: 10.15%). For *K. pneumoniae*, rates of clinical response at TOC, EA, and EOT were similar between treatment groups. At FUP, sustained clinical response was higher in the cefiderocol group compared with the IPM/CS group (difference between the 2 treatment groups: 14.61%).

Other uropathogens occurred at a low frequency (in less than 10 subjects in at least 1 of the groups) and therefore a statistical comparison could not be made for either clinical or microbiological eradication.

Safety:

In the Safety Population, 40.7% (122/300) of subjects in the cefiderocol group reported at least 1 AE compared with 51.4% (76/148) of subjects in the IPM/CS group. Serious adverse events (SAEs) were reported in 4.7% (14/300) of subjects in the cefiderocol group compared with 8.1% (12/148) of subjects in the IPM/CS group. Treatment-related SAEs were reported for 0.3% (1/300) of subjects in the cefiderocol group compared with 0.7% (1/148) of subjects in the IPM/CS group. Discontinuations due to AEs were reported for 1.7% (5/300) of subjects in the cefiderocol group compared with 2.0% (3/148) of subjects in the IPM/CS group.

There were no clinically important differences in laboratory evaluations or vital signs.

One death (cardiorespiratory arrest, considered by the investigator to be unrelated to study drug) was reported in a subject treated with cefiderocol.

The ECG analyses did not demonstrate a clinically significant effect of study drug on QT interval corrected for heart rate using Fridericia's formula (QTcF) duration or other ECG parameters.

Pharmacokinetics:

The mean (range) plasma concentrations of cefiderocol in total were 18.0 (0 to 147), 141 (6.70 to 1930), and 70.2 (11.7 to 235) μg/mL at the time points of preinfusion (−1 to 0 hours), at the end of infusion (-0.25 to 0 hours), and 1 ± 0.5 hours after the end of infusion, respectively. The mean (range) urine concentration of cefiderocol in all 8 subjects in all dose groups was 2710 (953 to 5520) μg/mL at 2 hours postinfusion. At the time point of 6 hours postinfusion, mean (range) urine concentration of cefiderocol in all 8 subjects in all dose groups was 1520 (336 to 4220) μg/mL.

CONCLUSIONS

Efficacy Conclusions:

Cefiderocol met the prespecified criteria for noninferiority to IPM/CS for the response rate of the composite of microbiological eradication and clinical response at TOC. The lower limit of 95% CI for the between-group difference (cefiderocol minus IPM/CS) exceeded −20% (prespecified 20% margin), and it also exceeded −15% (prespecified 15% margin). In addition, it exceeded zero, which is consistent with superiority of cefiderocol compared with IPM/CS in a subject population at risk for MDR Gram-negative pathogens originating from cUTI with or without pyelonephritis or acute uncomplicated pyelonephritis. The magnitude of the observed differences is considered clinically important. The results were consistent between the primary efficacy population (Micro-ITT Population) and the ME Population used for the sensitivity analysis.

The rate of microbiological eradication of infection with cefiderocol was higher than with IPM/CS at TOC, and the difference between treatments was statistically significant and clinically meaningful. The majority of infections were due to *E. coli* and *K. pneumoniae*; however, there were a substantial number of other organisms,

many with a significant degree of fluoroquinolone and fourth-generation cephalosporin resistance. Cefiderocol was consistently favored over IPM/CS in subjects with *E. coli* in microbiological eradication of this uropathogen, and the eradication rate at EOT and the sustained eradication rate at FUP were higher in the cefiderocol group with statistically significant differences compared with the IPM/CS group.

Safety Conclusions:

Cefiderocol was generally well tolerated, with more than 90% of subjects completing treatment. Adverse event rates were generally similar between the 2 treatment groups, particularly for mild AEs, but a greater proportion of subjects in the IPM/CS group had moderate or severe AEs compared with the cefiderocol group; the between-group difference was considered clinically meaningful. This may reflect the enhanced efficacy of cefiderocol in resolving the underlying infection and confirms that the safety profile of cefiderocol is comparable to a well-established antibiotic therapy. The observed safety profile of cefiderocol is as expected for β-lactam antibiotic, and no unexpected safety concerns were identified.

Final Report Date: 02 Oct 2017