2. SYNOPSIS

Sponsor: Shionogi Inc.	**Individual Study Table Referring to Part of the Dossier**	(***For National Authority Use only***)
Name of Finished Product: Cefiderocol (S-649266)	**Volume:**	
Name of Active Ingredient: Cefiderocol (S-649266)	**Page:**	
Study Title: A Study to Assess the Effect of S-649266 on the Pharmacokinetics of Furosemide, Metformin and Rosuvastatin in Healthy Adult Subjects		
Investigator and Study Center: [redacted]		
Publication (reference): None		
Study Period: [redacted] Nov 2016 (first subject enrolled) to Jan 2017 (last subject completed)		
Study Phase: Phase 1		
Objectives:		
Primary Objectives: **Part 1** To assess the effect of cefiderocol (S-649266) on the pharmacokinetics of furosemide, an OAT1 and OAT3 substrate, in healthy adult subjects. **Part 2** To assess the effect of cefiderocol on the pharmacokinetics of metformin, an OCT1, OCT2 and MATE2-K substrate, in healthy adult subjects. **Part 3** To assess the effect of cefiderocol on the pharmacokinetics of rosuvastatin, an OATP1B3 substrate, in healthy adult subjects.		
Secondary Objectives: **Part 1** To assess the safety and tolerability of cefiderocol after co-administration with furosemide in healthy adult subjects. **Part 2** To assess the safety and tolerability of cefiderocol after co-administration with metformin in healthy adult subjects. **Part 3** To assess the safety and tolerability of cefiderocol after co-administration with rosuvastatin in healthy adult subjects.		

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Study Design: A 3-part study (Part 1, Part 2, and Part 3), with each study part designed as an open-label, randomized, 2-sequence, 2-period crossover study

Number of Subjects (Planned and Analyzed):

Part 1

Number of subjects planned: 12 subjects

Number of subjects randomized: 12 subjects

Number of subjects analyzed for pharmacokinetics: 12 subjects

Number of subjects analyzed for safety: 12 subjects

Part 2

Number of subjects planned: 12 subjects

Number of subjects randomized: 13 subjects

Number of subjects analyzed for pharmacokinetics: 13 subjects (Treatment C) and 12 subjects (Treatment D)

Number of subjects analyzed for safety: 13 subjects (Treatment C) and 12 subjects (Treatment D)

Part 3

Number of subjects planned: 12 subjects

Number of subjects randomized: 13 subjects

Number of subjects analyzed for pharmacokinetics: 12 subjects (Treatment E) and 13 subjects (Treatment F)

Number of subjects analyzed for safety: 12 subjects (Treatment E) and 13 subjects (Treatment F)

Diagnosis and Main Criteria for Inclusion:

Healthy adult male or female subjects ≥ 18 to ≤ 50 years of age, with body mass index (BMI) ≥ 18.5 to ≤ 30.0 kg/m^2.

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

Cefiderocol (S-649266)

2 g, intravenous (IV) administration, infused over 3 hours, given every 8 hours (q8h) for a total of 3 doses (Part 1), 6 doses (Part 2) or 9 doses (Part 3)

Lot Number: [redacted]

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Substrate Drugs, Dose, and Mode of Administration, Lot Number:

Part 1:

Furosemide, 20-mg tablet, oral administration

Lot Number: [redacted]

Part 2: Metformin, 1000-mg tablet, oral administration

Lot Number: [redacted]

Part 3: Rosuvastatin, 10-mg tablet, oral administration

Lot Number: [redacted]

Duration of Treatment:

Part 1

Two days: One day of dosing in each treatment period (2-day washout interval between treatment periods)

Part 2

Three days: One day of dosing in one treatment period and two days of dosing in the other treatment period (6-day washout interval between treatment periods)

Part 3

Four days: One of dosing in one treatment period and three days of dosing in the other treatment period (6-day washout interval between treatment periods)

Criteria for Evaluation:

Pharmacokinetic Parameters for Co-administration of Furosemide, Metformin, and Rosuvastatin with Cefiderocol

C_{max}: Maximum observed plasma concentration

T_{max}: Time to maximum observed plasma concentration

$t_{1/2,z}$: Terminal elimination half-life, where $t_{1/2,z} = (\ln 2)/\lambda_z$. Terminal elimination rate constant, λ_z, is based on data points in the terminal phase.

$AUC_{0\text{-last}}$: Area under the plasma concentration-time curve from zero to the timepoint of the last quantifiable postdose plasma concentration, calculated by using the linear trapezoidal method when concentrations were increasing and by using the logarithmic trapezoidal method when concentrations were decreasing (linear up/log down trapezoidal method).

$AUC_{0\text{-inf}}$: Area under the plasma concentration-time curve extrapolated from time zero to infinity, defined as $AUC_{0\text{-last}}+C_{last}/\lambda_z$, where C_{last} is the last quantifiable plasma concentration.

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CL/F: Apparent total clearance, calculated as Dose/AUC_{0-inf}

λ_z : Terminal elimination rate constant

V_z/F: Apparent volume of distribution in the terminal elimination phase, where $V_z/F = CL/F/\lambda_z$

Pharmacokinetic Parameters for Cefiderocol

C_{max}: Maximum observed plasma concentration

T_{max}: Time to maximum observed plasma concentration

AUC_{0-8}: Area under the concentration-time curve from time zero to 8 hours, after the first infusion of that part, calculated by using the trapezoidal method (Linear Up/Log Down Trapezoidal Method)

Safety

Safety was monitored by physical examinations, vital sign measurements, 12-lead electrocardiograms (ECGs), clinical laboratory tests, and reporting of adverse events (AEs).

Statistical Methods:

Pharmacokinetics

The effect of cefiderocol on the pharmacokinetics (PK) of furosemide (Part 1), metformin (Part 2), and rosuvastatin (Part 3) were assessed by an analysis of variance (ANOVA) which was performed by using SAS Proc Mixed, which includes terms for Treatment, Sequence and Period as fixed effects and Subject Within Sequence as a random effect for the following parameters of furosemide, metformin, and rosuvastatin: the ln-transformed values for C_{max}, AUC_{0-last}, AUC_{0-inf}, λ_z, $t_{1/2,z}$, CL/F, and V_z/F. The analysis was to be performed separately for each part. The following linear mixed effects model was used:

Parameter = Treatment + Sequence + Period + Subject Within Sequence + Random error where Parameter was the given PK parameter, Treatment was a fixed treatment effect, Sequence was a fixed sequence effect, Period was a fixed period effect, Subject Within Sequence was a random subject effect, and Random error is a random error.

The treatment comparisons between co-administration of cefiderocol and each substrate (furosemide [Part 1], metformin [Part 2], or rosuvastatin [Part 3]) and each substrate alone were made. The point estimates and 90% confidence intervals (CIs) were generated for the differences between treatments for ln-transformed PK parameters. The point estimates and 90% CIs were back-transformed to obtain the corresponding geometric least squares mean ratios and 90% CIs. In the case of unbalanced data, the Kenward-

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Roger method was to be used to compute the denominator degrees of freedom for the tests of fixed effects in this analysis.

If the 90% CIs of the geometric least-squares mean ratios (co-administration cefiderocol + substrate/substrate alone) for the primary PK parameters, C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$ of each substrate were completely contained within the range of 80.00% to 125.00%, then it was concluded that co-administration of cefiderocol did not affect the PK of each substrate. The PK parameters of substrates were graphically presented for comparisons between treatments.

Statistical Analysis of Safety

All safety assessments of quantitative data summarized the absolute value and change from baseline values by timepoint. The number of treatment-emergent adverse events reported and the number and percentage of subjects who experienced a TEAE were summarized by study part and treatment. The same summarization and calculation were performed for treatment-related AEs.

Summary of Results:

Pharmacokinetics:

Part 1: Co-administration of Furosemide and Cefiderocol

The mean (SD) plasma concentration-time profiles for furosemide after administration of furosemide alone (Treatment A) and the co-administration of furosemide and cefiderocol (Treatment B) are displayed using a linear scale in Figure S-1. Furosemide was rapidly absorbed after administration of both treatments, though associated with considerable variability. After co-administration of furosemide and cefiderocol, a small second peak was observed. After 4 hours post dose, the concentration-time profiles of furosemide were nearly superimposable.

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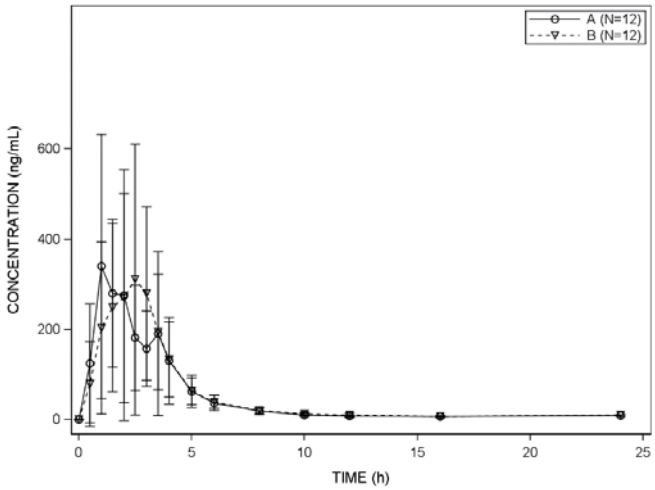
Figure S-1 **Part 1: Arithmetic Mean (± SD) Plasma Concentration-Time Profiles for Furosemide after Administration of Furosemide Alone (Treatment A) and Co-administration of Furosemide and Cefiderocol (Treatment B) in Healthy Adult Subjects**

Linear Scale



Treatment A: Administration of a single 20-mg dose of furosemide;

Treatment B: Co-administration of a single 20-mg dose of furosemide with a 2-g dose of cefiderocol (3 hour intravenous infusion), given q8h for a total of 3 doses.

Source: Table 14.2.1 and Table 14.2.2

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Part 1: Co-administration of Furosemide and Cefiderocol (continued)

The mean (SD) PK parameter values after administration of furosemide alone and upon co-administration of furosemide and cefiderocol were similar (Table S-1).

Table S-1 Part 1: Summary of Plasma Pharmacokinetic Parameters of Furosemide after Administration of Furosemide Alone (Treatment A) and Co-administration of Furosemide and Cefiderocol (Treatment B) in Healthy Adult Subjects

	Furosemide Alone (Treatment A)			Co-administration of Furosemide + Cefiderocol (Treatment B)		
PK Parameters	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
C_{max}, ng/mL	12	553	256	12	528	225
T_{max}, hr	12	1.50 (1.00, 3.50)		12	2.00 (1.00, 3.50)	
$AUC_{0\text{-last}}$, ng·hr/mL	12	1058	311.9	12	1087	376.6
$AUC_{0\text{-inf}}$, ng·hr/mL	10 [a]	1128	309.9	11 [a]	1052	312.6
$t_{1/2,\,z}$, hr	10 [a]	2.52	0.719	11 [a]	3.20	1.21
λ_z, 1/hr	10 [a]	0.2979	0.0913	11 [a]	0.2522	0.1151
CL/F, L/hr	10 [a]	18.8	4.68	11 [a]	20.9	7.39
V_z/F, L	10 [a]	68.2	24.7	11 [a]	100	56.5

a $AUC_{0\text{-inf}}$, λ_z, $t_{1/2,\,z}$, CL/F, and V_z/F were excluded from the statistical analysis for 2 subjects after administration of furosemide alone (Treatment A) and 1 subject after co-administration of furosemide and cefiderocol (Treatment B) due to the adjusted $R^2 < 0.80$;

T_{max} is presented as Median (Minimum, Maximum); N, The number of non-missing observations; Mean, Arithmetic mean; SD, Standard deviation.

Source: Table 14.2.10 and Table 14.2.11

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Part 1: Co-administration of Furosemide and Cefiderocol (continued)

Statistical comparisons of the $C_{max,}$ $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ of furosemide after administration of furosemide alone and upon co-administration of furosemide and cefiderocol are presented in Table S-2. The geometric least squares mean ratio (GMR; co-administration [furosemide+cefiderocol]/furosemide alone) and 90% CI for the $C_{max,}$ $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ of furosemide were 100.38 (70.86, 142.20), 100.60 (87.83, 115.24) and 91.69 (72.78, 115.52), respectively. These small numerical differences in the exposure to furosemide after co-administration of furosemide with cefiderocol are considered not to be clinically meaningful.

Table S-2 Part 1: Statistical Comparisons of Plasma Pharmacokinetic Parameters of Furosemide after Administration of Furosemide Alone (Treatment A) and Co-administration of Furosemide and Cefiderocol (Treatment B) in Healthy Adult Subjects

	Furosemide Alone (Treatment A)		**Co-administration of Furosemide + Cefiderocol (Treatment B)**		**(Co-administration of Furosemide + Cefiderocol)/ Furosemide Alone (Treatment B/A)**
PK Parameters	**N**	**Geometric Mean**	**N**	**Geometric Mean**	**GMR (90% CI)**
C_{max}† (ng/mL)	12	488	12	490	100.38 (70.86, 142.20)
$AUC_{0\text{-last}}$† (ng·hr/mL)	12	1019	12	1025	100.60 (87.83, 115.24)
$AUC_{0\text{-inf}}$† (ng·hr/mL)	10[a]	1087	11[a]	996.8	91.69 (72.78, 115.52)

a $AUC_{0\text{-inf}}$ was excluded from the statistical analysis for 2 subjects after administration of furosemide alone (Treatment A) and 1 subject after co-administration of furosemide and cefiderocol (Treatment B) due to the adjusted $R^2 < 0.80$;

† Back-transformed least-squares mean ratio and its 90% confidence interval from ANOVA model were performed on log-transformed values;

GMR=Geometric least-squares mean ratio; CI=Confidence interval;

GMR and 90% CI were reported as percentage.

Source: Appendix 16.2.6.4

Sponsor: Shionogi Inc.	**Individual Study Table Referring to Part of the Dossier**	**(*For National Authority Use only*)**
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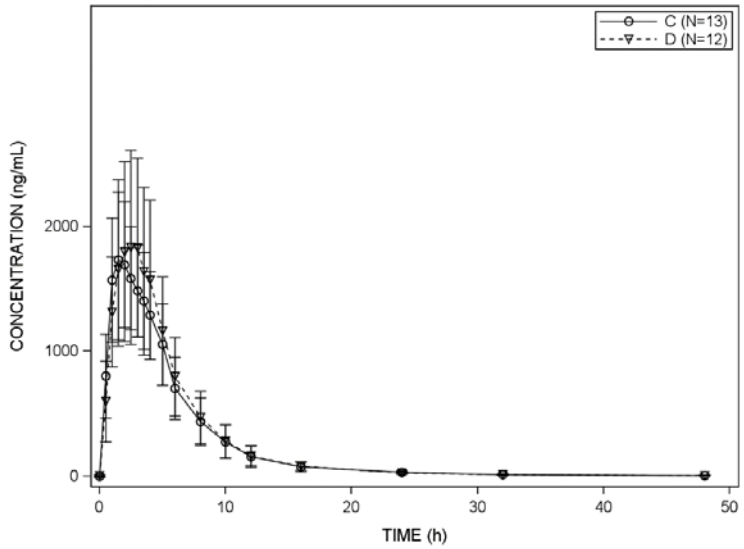
Part 2: Co-administration of Metformin and Cefiderocol

The mean (SD) plasma concentration-time profiles for metformin after administration of metformin alone and upon co-administration of metformin and cefiderocol are shown using linear scale in Figure S-2. Metformin was rapidly absorbed after administration of both treatments; the T_{max} after co-administration of metformin and cefiderocol occurred slightly later compared with after administration of metformin alone. However, the concentration-time profiles for both treatments were nearly superimposable, especially from 2 to 48 hours postdose.

Figure S-2 **Part 2: Arithmetic Mean (± SD) Plasma Concentration-Time Profiles for Metformin after Administration of Metformin Alone (Treatment C) and Co-administration of Metformin and Cefiderocol (Treatment D) in Healthy Adult Subjects**

Linear Scale



Treatment C: Administration of a single 1000-mg dose of metformin

Treatment D: Co-administration of a single 1000-mg dose of metformin with a 2-g dose of cefiderocol (3-hour intravenous infusion), given q8h for a total of 6 doses.

Source: Table 14.2.4 and Table 14.2.5

Sponsor: Shionogi Inc.	**Individual Study Table Referring to Part of the Dossier**	**(*For National Authority Use only*)**
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Part 2: Co-administration of Metformin and Cefiderocol (Continued)

The mean (SD) plasma PK parameters of metformin after administration of metformin alone and upon co-administration of metformin and cefiderocol were similar (Table S-3).

Table S-3 Part 2: Summary of Plasma Pharmacokinetic Parameters of Metformin after Administration of Metformin Alone (Treatment C) and Co-administration of Metformin and Cefiderocol (Treatment D) in Healthy Adult Subjects

	Metformin Alone (Treatment C)			Co-administration of Metformin and Cefiderocol (Treatment D)		
PK Parameters	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
C_{max}, ng/mL	13	1870	576	12	2060	719
T_{max}, hr	13	1.50 (1.00, 3.50)		12	2.25 (1.00, 4.00)	
$AUC_{0\text{-last}}$, ng·hr/mL	13	10920	2930	12	11630	3873
$AUC_{0\text{-inf}}$, ng·hr/mL	13	11050	2885	12	11730	3855
$t_{1/2,\,z}$, hr	13	11.6	8.07	12	9.23	3.91
λ_z, 1/hr	13	0.0805	0.0361	12	0.0852	0.0286
CL/F, L/hr	13	96.9	27.4	12	93.5	29.2
V_z/F, L	13	1690	1360	12	1250	663

T_{max}, Presented as Median (Minimum, Maximum); N, The number of non-missing observations; Mean, Arithmetic mean; SD, Standard deviation.

Source Table 14.2.13 and Table 14.2.14

Statistical comparisons of the C_{max}, $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ of metformin after administration of metformin alone and upon co-administration of metformin with cefiderocol are presented in Table S-4. The GMR (co-administration [metformin + cefiderocol]/metformin alone) and 90% CI for the C_{max}, $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ of metformin were 108.58 (92.16, 127.93), 103.65 (93.35, 115.09) and 103.37 (93.23, 114.61), respectively. The small numerical differences in exposure to metformin after co-administration of metformin with cefiderocol are considered not to be clinically meaningful.

Sponsor: Shionogi Inc.	**Individual Study Table Referring to Part of the Dossier**	**(*For National Authority Use only*)**
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Table S-4 Part 2: Statistical Comparisons of Plasma Pharmacokinetic Parameters of Metformin after Administration of Metformin Alone (Treatment C) and Co-administration of Metformin and Cefiderocol (Treatment D) in Healthy Adult Subjects

	Metformin Alone (Treatment C)		**Co-administration of Metformin and Cefiderocol (Treatment D)**		**(Co-administration of Metformin and Cefiderocol)/ Metformin Alone (Treatment D/C)**
PK Parameters	**N**	**Geometric Mean**	**N**	**Geometric Mean**	**GMR (90% CI)**
C_{max}†, ng/mL	13	1790	12	1940	108.58 (92.16, 127.93)
$AUC_{0\text{-}last}$†, ng·hr/mL	13	10570	12	10950	103.65 (93.35, 115.09)
$AUC_{0\text{-}inf}$†, ng·hr/mL	13	10710	12	11070	103.37 (93.23, 114.61)

† Back-transformed least-squares mean ratio and its 90% confidence interval from ANOVA model were performed on log-transformed values;

N, The number of non-missing observations; GMR, Geometric least-squares mean ratio; CI, Confidence interval;

GMR and 90% CI were reported as percentage

Source: Appendix 16.2.6.4

Sponsor: Shionogi Inc.	**Individual Study Table Referring to Part of the Dossier**	**(*For National Authority Use only*)**
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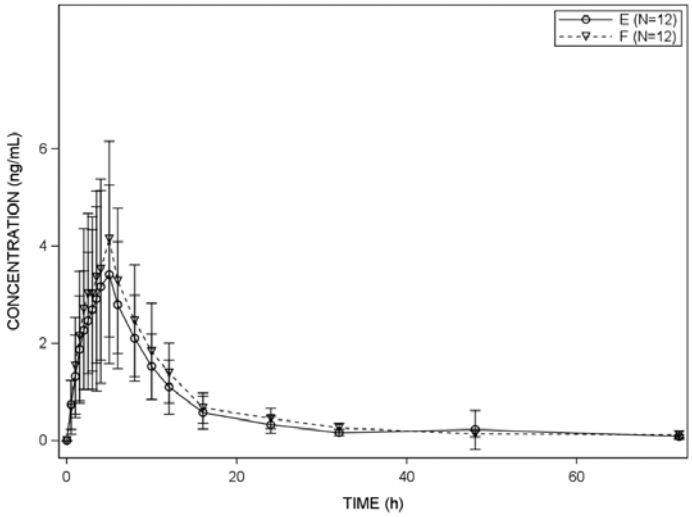
Part 3: Co-administration of Rosuvastatin and Cefiderocol

The mean (SD) plasma concentration-time profiles for rosuvastatin after administration of rosuvastatin alone and upon co-administration of rosuvastatin and cefiderocol using a linear scale are shown in Figure S-3. The concentration-time profiles for rosuvastatin were nearly superimposable.

Figure S-3 **Part 3: Arithmetic Mean (± SD) Plasma Concentration-Time Profiles for Rosuvastatin after Administration of Rosuvastatin Alone (Treatment E) and Co-administration of Rosuvastatin and Cefiderocol (Treatment F) in Healthy Adult Subjects**

Linear Scale



Treatment E: Administration of a single 10-mg dose of rosuvastatin

Treatment F: Co-administration of a single 10-mg dose of rosuvastatin with a 2-g dose of cefiderocol (3 hour intravenous infusion), given q8h for a total of 9 doses.

Source Table 14.2.7 and 14.2.8

Sponsor: Shionogi Inc.	**Individual Study Table Referring to Part of the Dossier**	**(*For National Authority Use only*)**
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Part 3: Co-administration of Rosuvastatin and Cefiderocol (Continued)

A summary of the mean (SD) plasma pharmacokinetic parameters of rosuvastatin after administration of rosuvastatin alone and upon co-administration of rosuvastatin and cefiderocol were similar (Table S-5).

Table S-5 Part 3: Summary of Plasma Pharmacokinetic Parameters of Rosuvastatin after Administration of Rosuvastatin Alone (Treatments E) and Co-administration of Rosuvastatin and Cefiderocol (Treatment F) in Healthy Adult Subjects

	Rosuvastatin Alone (Treatment E)			**Co-administration of Rosuvastatin and Cefiderocol (Treatment F)**		
PK Parameters	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
C_{max}, ng/mL	12	3.49	1.82	12 [b]	4.31	2.01
T_{max}, hr	12	5.00 (2.00, 6.00)		12 [b]	5.00 (2.00, 5.00)	
$AUC_{0\text{-last}}$, ng·hr/mL	12	38.78	17.31	12 [b]	45.42	20.74
$AUC_{0\text{-inf}}$, ng·hr/mL	10 [a]	41.11	17.99	12 [b]	49.28	24.30
$t_{1/2,\,z}$, hr	10 [a]	15.2	7.72	12 [b]	18.5	11.0
λ_z, 1/hr	10 [a]	0.0575	0.0282	12 [b]	0.0465	0.0191
CL/F, L/hr	10 [a]	274	83.6	12 [b]	237	87.2
V_z/F, L	10 [a]	5920	3580	12 [b]	5810	2760

a $AUC_{0\text{-inf}}$, λ_z, $t_{1/2,\,z}$, CL/F, and V_z/F were excluded from the statistical analysis for 2 subjects after administration of rosuvastatin alone (Treatment E) due to the adjusted $R^2 < 0.80$;

b All parameters were excluded from the statistical analysis for 1 subject in Treatment F due to the pre-dose value greater than 5% of C_{max};

T_{max} is presented as Median (Minimum, Maximum); N, The number of non-missing observations; Mean, Arithmetic mean; SD, Standard deviation.

Source: Table 14.2.16 and 14.2.17

Sponsor: Shionogi Inc.	**Individual Study Table Referring to Part of the Dossier**	**(*For National Authority Use only*)**
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Part 3: Co-administration of Rosuvastatin and Cefiderocol (Continued)

Statistical comparisons of the C_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$ of rosuvastatin after administration of rosuvastatin alone and upon co-administration of rosuvastatin with cefiderocol are presented in Table S-6. The GMR (co-administration [rosuvastatin+cefiderocol]/rosuvastatin alone) and 90% CI for the C_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$ of rosuvatstatin) were 127.87 (111.70, 146.37), 124.30 (109.99, 140.47) and 120.80 (107.83, 135.32), respectively. However, the increases in exposure to rosuvastatin after co-administration of rosuvastatin with cefiderocol are considered not to be clinically meaningful.

Table S-6 Part 3: Statistical Comparisons of Plasma Pharmacokinetic Parameters of Rosuvastatin after Administration of Rosuvastatin Alone (Treatment E) and Co-administration of Rosuvastatin and Cefiderocol (Treatment F) in Healthy Adult Subjects

	Rosuvastatin Alone (Treatment E)		Co-administration of Rosuvastatin and Cefiderocol (Treatment F)		Co-administration of Rosuvastatin and Cefiderocol/ Rosuvastatin Alone (Treatment F/E)
PK Parameters	**N**	**Geometric Mean**	**N**	**Geometric Mean**	**GMR (90% CI)**
C_{max}†, ng/mL	12	3.12	12 [b]	3.99	127.87 (111.70, 146.37)
$AUC_{0\text{-}last}$†, ng·hr/mL	12	35.42	12 [b]	44.02	124.30 (109.99, 140.47)
$AUC_{0\text{-}inf}$†, ng·hr/mL	10 [a]	38.13	12 [b]	46.06	120.80 (107.83, 135.32)

a $AUC_{0\text{-}inf}$ was excluded from the statistical analysis for 2 subjects after administration of rosuvastatin alone (Treatment E) due to the adjusted $R^2 < 0.80$;

b All parameters were excluded from the statistical analysis for one 1 subject in Treatment F due to the pre-dose value greater than 5% of C_{max};

† Back-transformed least-squares mean ratio and its 90% confidence interval from ANOVA model were performed on log-transformed values;

N, The number of non-missing observations; GMR, Geometric least-squares mean ratio; CI, Confidence interval.

GMR and 90% CI were reported as percentage

Source: Appendix 16.2.6.4

Sponsor: Shionogi Inc.	**Individual Study Table Referring to Part of the Dossier**	**(*For National Authority Use only*)**
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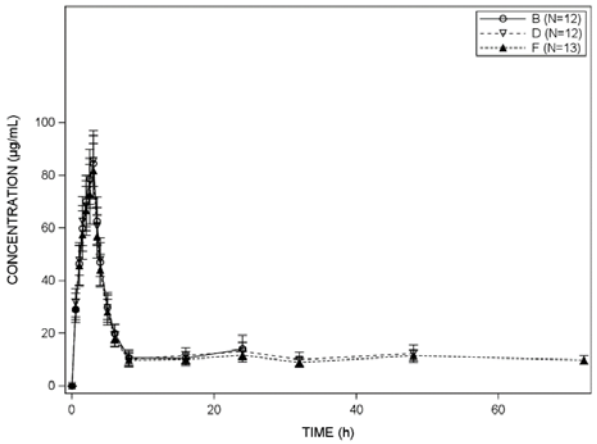
PK Cefiderocol Results

The mean plasma concentration-time profiles for cefiderocol after co-administration of cefiderocol and a single 20-mg dose of furosemide (Part 1), a 1000-mg dose of metformin (Part 2) ora 10-mg dose of rosuvastatin (Part 3) were super-imposable, as shown in Figure S-4.

Figure S-4 Arithmetic Mean Cefiderocol Plasma Concentration-Time Profiles after Co-administration of Furosemide and Cefiderocol (Treatment B), Co-administration of Metformin and Cefiderocol (Treatment D), and Co-administration of Rosuvastatin and Cefiderocol (Treatment F) in Healthy Adult Subjects

Linear Scale



Note:

Treatment B: Co-administration of a single 20-mg dose of furosemide with a 2-g dose of cefiderocol (3 hour intravenous infusion), given q8h for a total of 3 doses;

Treatment D: Co-administration of a single 1000-mg dose of metformin with a 2-g dose of cefiderocol (3 hour intravenous infusion), given q8h for a total of 6 doses;

Treatment F: Co-administration of a single 10-mg dose of rosuvastatin with a 2-g dose of cefiderocol (3 hour intravenous infusion), given q8h for a total of 9 doses.

Source: Table 14.2.3, Table 14.2.6 and Table 14.2.9

Sponsor: Shionogi Inc.	**Individual Study Table Referring to Part of the Dossier**	**(*For National Authority Use only*)**
Name of Finished Product: Cefiderocol (S-649266)	**Volume:**	
Name of Active Ingredient: Cefiderocol (S-649266)	**Page:**	

The mean (SD) plasma pharmacokinetic parameters (C_{max}, $T_{max,}$ and AUC_{0-8}) of cefiderocol after co-administration of cefiderocol and furosemide (Part 1), metformin (Part 2) or rosuvastatin (Part 3) were similar (Table S-7).

Table S-7 Summary of Plasma Pharmacokinetic Parameters of Cefiderocol after Co-Administration of Cefiderocol and Furosemide (Treatment B), Metformin and Cefiderocol (Treatment D), and Rosuvastatin and Cefiderocol (Treatment F) in Healthy Adult Subjects

	Co-administration of Furosemide + Cefiderocol (Treatment B)			**Co-administration of Metformin and Cefiderocol (Treatment D)**			**Co-administration of Rosuvastatin and Cefiderocol (Treatment F)**		
PK Parameters	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
C_{max}, µg/mL	12	84.6	12.7	12	85.7	9.12	13	81.6	10.4
T_{max}, hr	12	2.95 (2.50, 2.98)		12	2.95 (2.50, 3.03)		13	2.95 (2.95, 2.95)	
AUC_{0-8}, µg·hr/mL	12	317.8	46.25	12	317.8	29.98	13	299.6	37.51

T_{max}, Median (Minimum, Maximum); N, The number of non-missing observations; Mean, Arithmetic mean; SD, Standard deviation.

Source: Table 14.2.12, Table 14.2.15 and Table 14.2.18

Safety: There were no TEAEs reported in Part 1 or Part 2 of the study. In Part 3 of the study, a total of 5 TEAEs were reported in 3 of the 13 subjects. One subject had 1 TEAE (headache) after administration of rosuvastatin alone (Treatment E) in Treatment Period 2. The other 4 TEAEs were reported in 3 subjects after co-administration of rosuvastatin and cefiderocol (Treatment F) in Treatment Period 1: nausea and dizziness, reported by the same subject, and mechanical phlebitis reported once each in 2 different subjects, one of which was reported by the same subject who reported headache for Treatment E, as mentioned above. No deaths, serious adverse events (SAEs), or AEs leading to withdrawal were reported in any subject. There were no clinically significant abnormal findings for ECG parameters, vital sign measurements, or clinical laboratory test results observed in the study.

CONCLUSIONS

Part 1:

- The PK of furosemide, an OAT1 and OAT3 substrate, were not clinically meaningfully altered after co-administration of furosemide and cefiderocol, indicating that cefiderocol will not affect the PK of other substrates for these transporters.

Sponsor: Shionogi Inc.	**Individual Study Table Referring to Part of the Dossier**	**(*For National Authority Use only*)**
Name of Finished Product: Cefiderocol (S-649266)	**Volume:**	
Name of Active Ingredient: Cefiderocol (S-649266)	**Page:**	

- Administration of a single 20-mg dose of furosemide alone or after co-administration with cefiderocol was generally safe and well tolerated in healthy adult subjects.

Part 2:

- The PK of metformin, an OCT1, OCT2 and MATE2-K substrate, were not clinically meaningfully altered after co-administration of metformin and cefiderocol, indicating that cefiderocol will not affect the PK of other substrates for these transporters.
- Administration of a single 1000-mg dose of metformin alone or after co-administration with cefiderocol was generally safe and well tolerated in healthy adult subjects.

Part 3:

- The C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$ of rosuvastatin, an OATP1B3 substrate, were increased by 28%, 24%, and 21%, respectively, after co-administration of rosuvastatin and cefiderocol; the GMR (co-administration [rosuvastatin+cefiderocol]/rosuvastatin alone) and 90% CI for the C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$ of rosuvastatin were 127.87 (111.70, 146.37), 124.30 (109.99, 140.47) and 120.80 (107.83, 135.32), respectively. The increases in exposure to rosuvastatin after co-administration of rosuvastatin with cefiderocol were considered not to be clinically meaningful indicating that cefiderocol will not affect the PK of other OATP1B3 substrates for this transporter.
- Administration of a single 10-mg dose of rosuvastatin alone or after co-administration with cefiderocol was generally safe and well tolerated in healthy adult subjects.

Final Report Date: 16 Nov 2017

Amendment 1 Report Date: 26 Jan 2018