Fetroja – Use in Patients with Renal Impairment or Augmented Renal Clearance

This medical response contains information in addition to that provided in the Fetroja® (cefiderocol) for injection, for intravenous use Full Prescribing Information approved by the U.S. Food and Drug Administration (FDA). Shionogi does not recommend the use of Fetroja in any manner other than as described in the Full Prescribing Information. **Please read the attached Fetroja Full Prescribing Information.**

1. SUMMARY

- The Phase 2 APEKS-cUTI study compared the efficacy and safety of cefiderocol with that of imipenem-cilastatin (IPM/CS) in patients with complicated urinary tract infection (cUTI). The primary efficacy endpoint of clinical cure and microbiologic response was achieved by 183 (73%) patients who received cefiderocol (modified intention-to-treat [mITT] population). When analyzed according to degree of renal impairment, the primary efficacy endpoint was achieved by 78.2%, 62.8%, 73.2% and 71.4% of patients with normal, mild, moderate and severe renal impairment, respectively. The incidence of treatment-emergent adverse events (TEAEs) in the cefiderocol group was consistent across all renal subgroups and did not increase with increasing degree of renal impairment[1,2]
- The Phase 3 non-inferiority APEKS-NP study compared all-cause mortality (ACM) rates at Day 14 as the primary endpoint between cefiderocol and high-dose, extended-infusion meropenem in patients with nosocomial pneumonia. The primary efficacy endpoint of Day 14 ACM was 12.4% in patients who received cefiderocol (modified intent-to-treat population [mITT]). When analyzed according to renal function, the primary efficacy endpoint was met by 14%, 12%, 7%, 7%, and 30%, of patients with creatine clearance (CrCL) of ≥120 mL/min, >80-120 mL/min, 50-80 mL/min, 30-50 mL/min, and <30 mL/min, respectively[3,4]
- The Phase 3 descriptive study (CREDIBLE-CR) assessed the efficacy and safety of cefiderocol to best-available therapy (BAT) in hospitalized patients with severe bacterial infections. The primary endpoint was clinical cure rate at the test of cure (TOC) visit for patients with hospital-acquired bacterial pneumonia, ventilator-associated bacterial pneumonia, and healthcare-associated bacterial pneumonia (HABP/VABP/HCABP) and bloodstream infection (BSI)/sepsis, and microbiological eradication rate at TOC for patients with cUTI in the carbapenem-resistant microbiological intent-to-treat population (CR-Micro-ITT)[5]
    - The clinical cure rates at TOC in the cefiderocol arm based on renal function were:[6]
        - CrCL ≥120 mL/min: 76.5%
        - CrCL >80-<120 mL/min: 40%
        - CrCL >50-80 mL/min: 53.3%
        - CrCL 30-50 mL/min: 50%
        - CrCL <30 mL/min: 40%
    - When analyzed according to degree of renal function, the microbiological eradication rates in the cefiderocol group at TOC were:[6]
        - CrCL ≥120 mL/min: 47.1%
        - CrCL >80-<120 mL/min: 20%
        - CrCL >50-80 mL/min: 46.7%
        - CrCL 30-50 mL/min: 22.2%
        - CrCL < 30 mL/min: 20%
    - Per renal function, the ACM rates in the safety population through end of study (EOS) were:[7]
        - CrCL ≥120 mL/min: 15%
        - CrCL >80-<120 mL/min: 22.2%

    - CrCL >50-80 mL/min: 45%
    - CrCL 30-50 mL/min: 43.5%
    - CrCL <30 mL/min: 40%
- The recommended cefiderocol dosing regimen for patients with impaired (or augmented) renal function was based on results from a pharmacokinetics (PK) model, which provided simulated cefiderocol exposures that were similar to patients with normal renal function following 2 g every 8 hours (q8h)[8,9]
    - The adjusted dosing regimens provided >90% probability of target attainment (PTA) for 75% fraction of time during the dosing interval, where the free drug concentration in plasma exceeded the minimum inhibitory concentration ($f_{T>MIC}$) against a minimum inhibitory concentration (MIC) of up to 4 µg/mL[9,10]
- An intrapulmonary PK model of cefiderocol was developed using plasma and epithelial lining fluid (ELF) concentration data from 20 healthy patients and seven patients with pneumonia requiring mechanical ventilation. Monte Carlo simulations calculated the PTA for 75% of time for which free ELF concentrations exceeded the MIC over the dosing interval ($f_{T>MIC,ELF}$) against an MIC range of 0.25 to 16 µg/mL. The PTA for 75% $f_{T>MIC,ELF}$ was 93.1% against MICs ≤4 µg/mL for all renal function groups[11]

2. OVERVIEW/BACKGROUND

Cefiderocol is mainly renally excreted, with approximately 90.6% of the administered dose found in the urine as unchanged parent drug.[12] Additionally, cefiderocol clearance correlates with creatinine clearance (CrCL), and thus with renal function.[13,14] The PK/pharmacodynamic (PD) parameter most closely correlated with efficacy of cefiderocol is the $f_{T>MIC}$.[9,13]

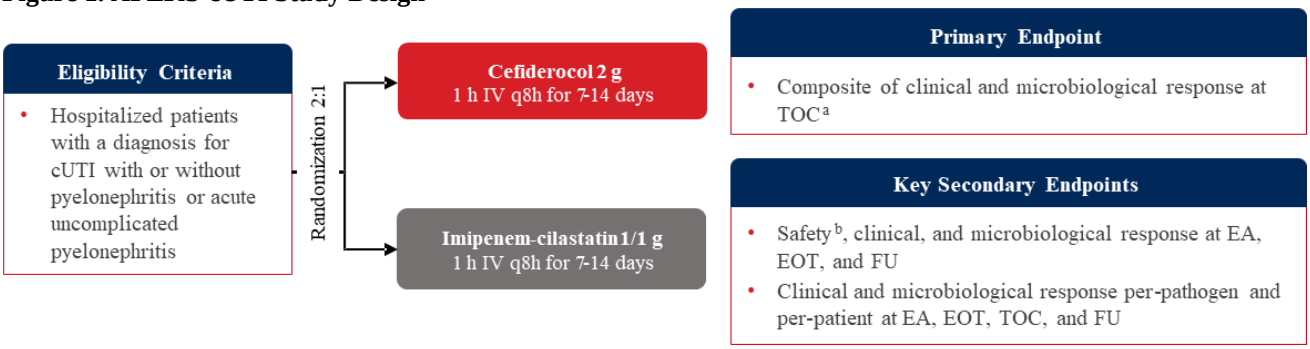
3. CLINICAL STUDIES

APEKS-cUTI

Methods

- APEKS-cUTI (NCT02321800) was a Phase 2, multicenter, randomized, double-blind, parallel-group, noninferiority study that assessed the efficacy and safety of cefiderocol in cUTI caused by suspected Gram-negative pathogens[1]

Figure 1. APEKS-cUTI Study Design[1]



Abbreviations: CFU, colony-forming unit; cUTI, complicated urinary tract infection; EA, early assessment; EOT, end of treatment; FU, follow-up; IV, intravenous; g, grams; h, hours; mITT, modified intention-to-treat; q8h, every 8 hours; TOC, test of cure.

[a]In the mITT population (noninferiority margin, -15%), defined as all randomly assigned individuals who received at least one dose of study drug and had qualifying Gram-negative uropathogen (≥1×10^5 CFU/mL).

[b]Safety assessed in all randomly assigned individuals who received at least one dose of study drug, according to the treatment they received.

- Dose adjustments were made for both cefiderocol and IPM/CS based on body weight and renal function (**Table 1**)
- Patients with CrCL <20 mL/min at baseline were excluded from the study[2]
- The primary endpoint (composite of clinical and microbiological response) at test of cure (TOC; 7 days after the end of antibiotic treatment) was analyzed by CrCL subgroup[2]

Table 1. Dosing Adjustments for Renal Impairment and/or Body Weight to Cefiderocol and IPM/CS[2]

Body Weight[a] (kg)	Cefiderocol Nominal Dose 6.0 g/day[b]			Imipenem-cilastatin nominal dose 3.0 g/day[b]		
	Creatinine clearance (mL/min)[c]			Creatinine clearance (mL/min)[c]		
	≥71	41 to 70	21 to 40	≥71	41 to 70	21 to 40
	Then the reduced dose regimen was:			Then the reduced dose regimen was:		
≥70	2.0 g q8h	1.0 g q6h	1.0 g q8h	1.0 g q8h	0.5 g q6h	0.5 g q8h
60	2.0 g q8h	1.5 g q8h	1.0 g q8h	0.75 g q8h	0.5 g q8h	0.5 g q8h
50	1.5 g q6h	1.5 g q8h	0.75 g q6h	0.5 g q6h	0.5 g q8h	0.25 g q6h
40	2.0 g q8h	1.0 g q6h	1.0 g q8h	0.5 g q8h	0.25 g q6h	0.25 g q8h
30	1.5 g q6h	1.5 g q8h	1.0 g q8h	0.25 g q6h	0.25 g q8h	0.25 g q8h

Abbreviations: IPM/CS, imipenem-cilastatin; g, grams; q6h, every 6 hours; q8h, every 8 hours.
[a]The body weight on the far left that was closest to the patient's body weight (kg) was selected.
[b]There were two possible dosing intervals, i.e., q6h and q8h
[c]Values are whole numbers without rounding.

Results

- A total of 371 patients were included in the mITT population; the primary efficacy endpoint was achieved by 183 (73%) patients in the cefiderocol group and 65 (55%) patients in the IPM/CS group (adjusted treatment difference 18.58% [95% CI: 8.23-28.92] *P*=0.0004)[1]
- Consistent with the results observed in the overall mITT population, treatment differences in the composite outcome at TOC in favor of cefiderocol compared with IPM/CS were observed across all renal subgroups (**Table 2**), with the largest differences in those with moderate or severe renal impairment[2]

Table 2. Efficacy Outcomes of Cefiderocol vs IPM/CS in Patients with cUTI according to Renal Function[2]

Composite outcome at TOC (mITT Population)			
Renal subgroup, CrCL mL/min	**Cefiderocol (n=250)**	**IPM/CS (n=119)**	**Difference (95% CI)**
>80 (Normal)	97/124 (78.2)	31/51 (60.8)	17.4 (2.2; 32.7)
>50-80 (Mild)	49/78 (62.8)	22/41 (53.7)	9.2 (-9.5; 27.8)
30-50 (Moderate)	30/41 (73.2)	11/23 (47.8)	25.3 (0.8; 49.9)
<30 (Severe)	5/7 (71.4)	1/4 (25)	46.4 (na)

Abbreviations: CI, confidence interval; CrCL, creatinine clearance; cUTI, complicated urinary tract infection; IPM/CS, imipenem-cilastatin; mITT, microbiological intent-to-treat population; na, not available; TOC, test of cure.

- A total of 448 patients were included in the safety population. The incidence of TEAEs in the cefiderocol group was consistent across all renal subgroups and did not increase with increasing degree of renal impairment[2]
- This was in contrast to the IPM/CS group, in which the TEAE incidence increased with increasing renal impairment (**Table 3**)[2]

Table 3. Safety Outcomes of Cefiderocol vs IPM/CS in Patients with cUTI according to Renal Function[2]

TEAEs (Safety Population)		
Renal subgroup, CrCL mL/min	**Cefiderocol (n=298)**	**IMP/CS (n=148)**
>80 (Normal)	62/152 (40.8)	26/63 (41.3)
>50-80 (Mild)	35/89 (39.3)	27/50 (54)
30-50 (Moderate)	22/49 (44.9)	18/28 (64.3)
<30 (Severe)	3/8 (37.5)	5/7 (71.4)

Abbreviations: CrCL, creatinine clearance; cUTI, complicated urinary tract infection; IPM/CS, imipenem–cilastatin; TEAE, treatment-emergent adverse event.

- Similar cefiderocol exposures depicted by the area under the curve (AUC), were observed across renal function groups although slightly lower exposure was seen in patients with augmented renal clearance (**Table 4**)[2]

Table 4. Cefiderocol Exposure in Relation to Creatinine Clearance[2]

Exposure		
Renal subgroup	**N**	**AUC (µg·h/mL)**
Augmented (CrCL ≥120 mL/min)	23	824 (46.9)
Normal (CrCL 90 to <120 mL/min)	76	1032 (45)
Mild (CrCL 60 to <90 mL/min)	76	1104 (36.5)
Moderate (CrCL 30 to <60 mL/min)	58	1140 (28.1)
Severe (CrCL 15 to <30 mL/min)	5	1086 (13)

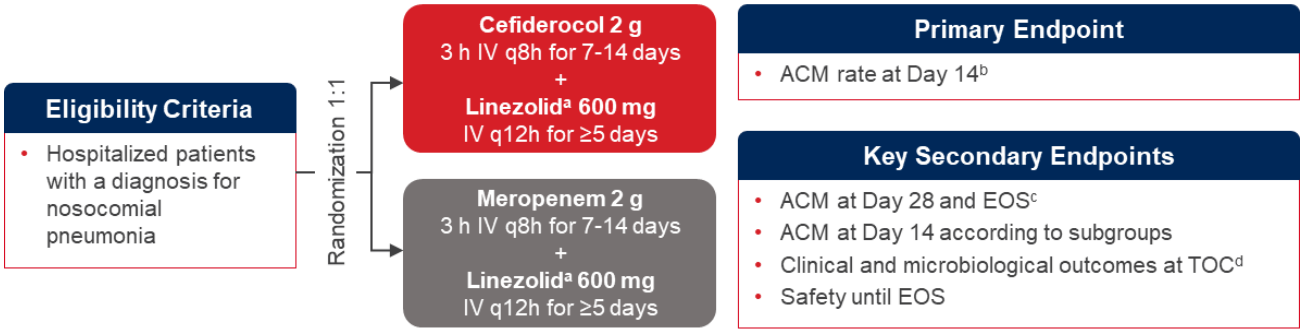
Data are expressed as geometric mean (coefficient of variance, %).
Abbreviations: AUC, area under the curve; CrCl, creatinine clearance.

APEKS-NP

Methods

- APEKS-NP (NCT03032380) was a Phase 3, multicenter, randomized, double-blind, parallel-group, noninferiority study that assessed the efficacy and safety of cefiderocol in HABP, HCABP, or VABP caused by suspected Gram-negative pathogens[3]

Figure 2. APEKS-NP Study Design[3]



Abbreviations: ACM, all-cause mortality; EOS, end of study; IV, intravenous; g, grams; h, hours; mITT, modified intention-to-treat; q8h, every 8 hours; q12h, every 12 hours; RTI, respiratory tract infection; TOC, test of cure.
[a]Administered to cover Gram-positive bacteria.
[b]In the mITT population (noninferiority margin, -12.5%), defined as all randomized patients who received ≥1 dose of a study drug and had evidence of a Gram-negative lower RTI.
[c]EOT + 28 days (±3 days).
[d]EOT + 7 days (±2 days).

Results

- A total of 300 patients were randomly assigned to cefiderocol (n=148) or meropenem (n=152), of whom 298 patients (n=148 cefiderocol; n=150 meropenem) received study treatment (ITT and safety populations)[3]
- 3 patients in each arm with Gram-positive pathogens only were excluded, so that the mITT population comprised 292 patients (n=145 cefiderocol; n=147 meropenem)[3]
- Cefiderocol was shown to be non-inferior to meropenem in the primary endpoint. The ACM at Day 14 was 12.4% in the cefiderocol arm and 11.6% in the meropenem arm (treatment difference: 0.8; 95% CI: -6.6, 8.2; *P*-value for non-inferiority=0.002)[3]
    - Please see **Table 5** for the primary endpoint, ACM at Day 14, based on renal function

Table 5. ACM at Day 14 of Cefiderocol vs Meropenem in Patients with HABP/VABP/HCABP according to Renal Function (mITT Population)[3]

Renal Subgroup, CrCL mL/min	Cefiderocol, n/N (%)	Meropenem n/N(%)	Treatment Difference (95% CI)
≥120	3/22 (14%)	2/25 (8%)	5.6 (-12.2 to 23.5)
>80-120	4/33 (12%)	3/35 (9%)	3.5 (-10.9 to 18.0)
>50-80	3/43 (7%)	2/35 (6%)	1.3 (-9.6 to 12.1)
30-50	2/27 (7%)	6/31 (19%)	-11.9 (29.0 to 5.1)
<30	6/20 (30%)	4/20 (20%)	10.0 (-16.7 to 36.7)

Abbreviations: ACM, all-cause mortality; CI, confidence interval; CrCL, creatinine clearance; HABP, hospital-acquired bacterial pneumonia; HCABP, healthcare-associated bacterial pneumonia; mITT, modified intent-to-treat; VABP, ventilator-associated bacterial pneumonia.

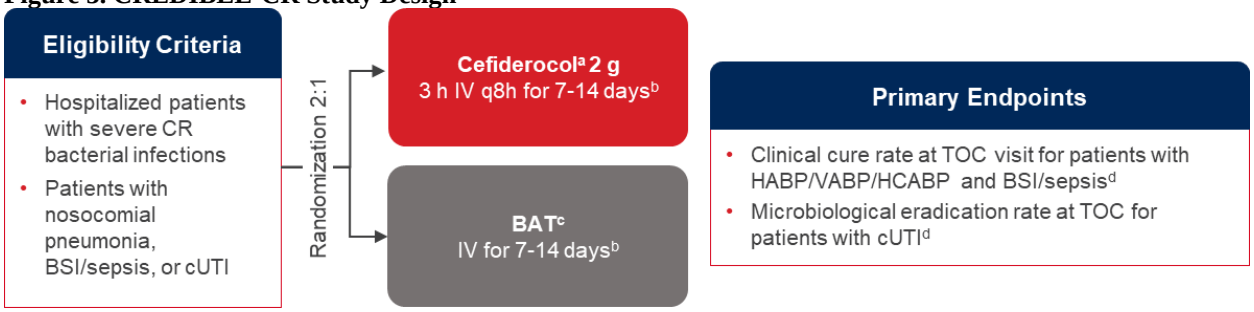
- An analysis of safety based on renal function has not been conducted[4]

CREDIBLE-CR

Methods

- CREDIBLE-CR (NCT02714595) was a Phase 3, prospective, open-label, multicenter, randomized, parallel-group, descriptive study that assessed the efficacy and safety of cefiderocol and BAT in hospitalized patients with severe CR bacterial infections[5]
- CREDIBLE-CR was a descriptive study with no hypothesis testing or formal inferential analyses[5]

Figure 3. CREDIBLE-CR Study Design[5]



Abbreviations: BAT, best available therapy; BSI, bloodstream infection; CR, carbapenem-resistant; cUTI, complicated urinary tract infection; IV, intravenous; g, grams; h, hours; HABP, hospital-acquired bacterial pneumonia; HCABP, healthcare-associated bacterial pneumonia; q8h, every 8 hours; TOC, test of cure; VABP, ventilator-associated bacterial pneumonia.
[a]Could be complemented with one adjunctive antibiotic therapy, excluding polymyxins, cephalosporins, and carbapenems and combinations with a β-lactamase inhibitor.
[b]Could be extended up to 21 days at the discretion of the investigator.
[c]Selected before randomization and could consist of up to 3 systemic antibiotics.
[d]Defined as all patients with a confirmed CR Gram-negative pathogen who received at least 1 dose of study drug.

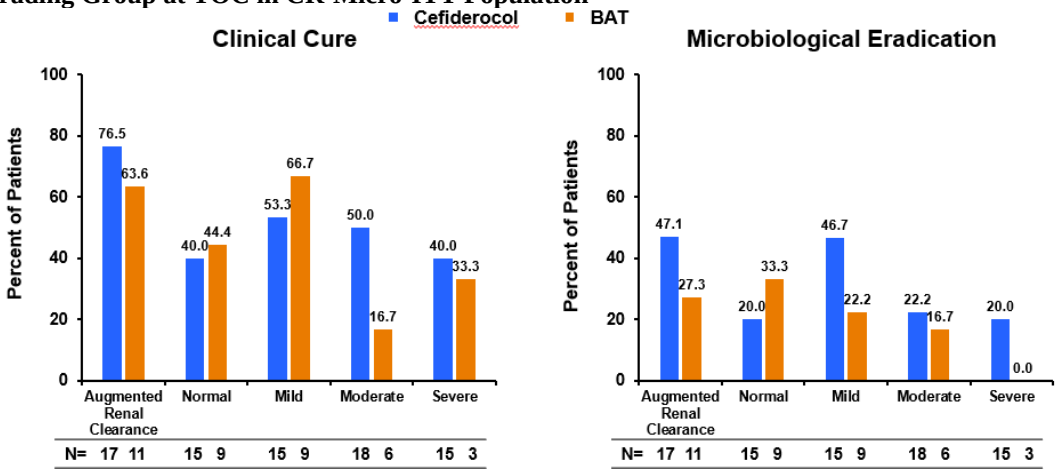
- A total of 152 patients were randomly assigned to cefiderocol or BAT, of whom 150 patients (n=101 cefiderocol; n=49 BAT) received treatment (ITT and safety population)[5]
- Efficacy was evaluated in the CR-Micro-ITT group; defined as all patients with a confirmed CR Gram-negative pathogen who received ≥1 dose of study drug[5]

Results

Efficacy

- Clinical cure (overall) at TOC was achieved by 42 (53%) patients and 19 (50%) patients in the cefiderocol and BAT groups, respectively (CR-Micro-ITT population)[5]
    - Clinical cure (HABP/HCABP/VABP) was achieved by 20 (50%) and 10 (53%) patients in the cefiderocol and BAT groups, respectively
    - Clinical cure (BSI/sepsis) was achieved by 10 (43%) and 6 (43%) patients in the cefiderocol and BAT groups, respectively
- Microbiological eradication (overall) at TOC was achieved by 25 (31%) and 9 (24%) patients in the cefiderocol and BAT groups, respectively[5]
    - Microbiological eradication (cUTI) was achieved by 9 (53%) and 1 (20%) patient in the cefiderocol and BAT groups, respectively
- The microbiological eradication rates in patients with cUTI were 53% (9/17) and 20% (1/5) in the cefiderocol and BAT groups, respectively[5]
- Clinical and microbiological outcomes were also assessed according to renal function **(Figure 4)**

Figure 4. Summary of Clinical and Microbiological Outcome by Creatine Clearance Renal Grading Group at TOC in CR-Micro-ITT Population[6]



Augmented renal clearance: ≥120 mL/min; Normal: >80 mL/min to <120 mL/min; Mild: >50 mL/min to 80 mL/min; Moderate: 30 mL/min to 50 mL/min; Severe: <30 mL/min.

Mortality

- All-cause mortality through EOS was higher in the cefiderocol group compared to BAT (34 [34%] vs 9 [18%], respectively). None of the deaths were considered to be related to cefiderocol (eg. drug toxicity).[5] The ACM was analyzed based on renal function (see **Table 6**).

Table 6. ACM (Safety Population) according to Renal Function at EOS[7]

Renal subgroup, CrCL mL/min	Cefiderocol (n=101)	BAT (n=49)
≥120 (Augmented renal clearance)	3/20 (15)	2/12 (16.7)
>80-<120 (Normal)	4/18 (22.2)	1/10 (10)
>50-80 (Mild)	9/20 (45)	2/12 (16.7)
30-50 (Moderate)	10/23 (43.5)	2/8 (25)
<30 (Severe)	8/20 (40)	2/7 (28.6)

All-cause mortality through end of study was defined as deaths that occurred through the end of study visit (EOT + 28 [±3] days) and fatal outcomes of SAEs with an onset before or on the EOS visit (followed until resolution, stabilization, the subject was lost to follow-up, or the outcome was fatal).
Abbreviations: ACM, all-cause mortality; EOS, end of study; EOT, end of treatment; BAT, best-available therapy; CrCL, creatinine clearance; SAEs, serious adverse events.

4. PHARMACOKINETIC STUDIES

Population PK Model (Renal Function Dose Adjustments)

- A population-PK model was developed to determine the recommended dose adjustment of cefiderocol in patients with impaired renal function, patients requiring intermittent HD, and patients with augmented renal function[9]

Methods

- Population PK models were developed using plasma, urine and dialysate concentration data for cefiderocol from two Phase 1 studies[9]
- A healthy subject model was developed from a study in 49 Japanese and 5 Caucasian healthy subjects. Data used for the modeling were from 1348 plasma and 276 urine concentration data points for cefiderocol following single (100 to 2000 mg) or multiple (1000 and 2000 mg q8h) 1 h IV infusions[9]
    - A total of 633 plasma and 30 dialysate concentrations were used to develop the PK models
- Covariate modeling to describe the effect of renal impairment on cefiderocol PK was performed using the healthy subject data and PK from subjects with renal impairment. A separate hemodialysis model accounting for clearance due to hemodialysis was also developed[13]
- The dosing regimens for patients with renal impairment or augmented renal function were adjusted to provide an AUC that was similar to patients with normal renal function after receiving the standard dose of 2 g q8h (3 h infusion). In addition, Monte Carlo simulations were conducted to determine the PTA of 75% $f_{T>MIC}$ against a MIC of 0.25-16 µg/mL[9]

Results

- The dose-adjusted regimens based on the modeling provided daily AUCs for patients with renal impairment that were comparable to patients with normal renal function who received cefiderocol 2 g q8h (please see **Table 7**)

Table 7. Simulated Exposure of Cefiderocol at Adjusted Dose Regimens by Renal Function Group Using the Covariate Model with MDRD-eGFR[9]

	Median (90% Prediction Interval)[a]				
PK parameter	**Normal 2 g q8h**	**Mild 2 g q8h**	**Moderate 1.5 g q8h**	**Severe 1 g q8h**	**ESRD 0.75 g q12h**
C_{max}, µg/mL	90 (71.8-111.6)	105.4 (83.4-133.5)	104.1 (78.8-134.3)	95.4 (73.7-122.3)	77.5 (61.6-97.5)
Daily AUC, µg•h/mL	1070 (814-1410)	1344 (972-1855)	1522 (1046-2154)	1599 (1136-2231)	1187 (857-1671)

Abbreviations: AUC, area under the plasma concentration-time curve from 0 to infinity; $C_{max,}$ peak plasma concentration; ESRD, end-stage renal disease; MDRD-eGFR, estimated glomerular filtration by the modification of diet in renal disease equation; PK, pharmacokinetic; q8h, every8 hours; q12h, every 12 hours.
[a]Renal function group defined according to the following MDRD-eGFR categories: Normal: ≥90 mL/min/1.73 m^2; Mild: 60 to <90 mL/min/1.73 m^2; Moderate: 30 to <60 mL/min/1.73 m^2; Severe: 15 to <30 mL/min/1.73 m^2; ESRD: <15 mL/min/1.73 m^2. The infusion time was 3 hours.

- The PTA for 75% $f_{T>MIC}$ was >90% against pathogens with an MIC up to 4 µg/mL for all renal function groups using the dose-adjusted regimens[9]
- For patients requiring HD, the adjusted dosing regimen of cefiderocol 0.75 g q12h with a supplemental dose of 0.75 g provided AUC and C_{max} values that were similar to patients with normal renal function following the administration of 2 g q8h (**Table 8**)
- Without the supplemental dose, the PTA for 75% $f_{T>MIC}$ was >90% against a MIC of up to 8 µg/mL (non-HD days) and against an MIC up to 1 µg/mL on HD days. When a supplemental dose of 0.75 g was administered, the PTA for 75% $f_{T>MIC}$ was >90% against a MIC of up to 16 µg/mL on HD days[9]

Table 8. Simulated Exposure of Cefiderocol following the Adjusted Dosing Regimen for Patients Requiring Hemodialysis[9]

	Median (90% Prediction Interval)		
	Non Dialysis Day	**Dialysis Day**	
		0.75 g q12h with 0.75 g supplemental dose	**0.75 g q12h without 0.75 g supplemental dose**
C_{max} (µg/mL)	77.2 (60.4-98.3)	89.1 (72.8-109)	59.3 (49.2-72.3)
Daily AUC (µg•h/mL)	1189 (841.8-1659)	1211 (941-1515)	783.2 (608.1-998.7)

Infusion time was 3 hours.
Abbreviations: AUC, area under the plasma concentration–time curve from 0 to infinity; $C_{max,}$ peak plasma concentration; q12h, every 12 hours.

- For patients with augmented renal function, the adjusted dose of 2 g q6h (3 h infusion) provided a daily AUC that was similar to patients with normal renal function (**Table 9**)
- The PTA for 75% $f_{T>MIC}$ at the adjusted dose of 2 g q6h (3 h infusion) was >90% for MIC values of up to 4 µg/mL even for the inflated interindividual variability (to take into account the increased PK variability in clearance and volume of distribution that has been reported in critically ill patients)[9]

Table 9. Simulated Exposure of Cefiderocol for Patients with Normal and Augmented Renal Function (Using Covariate Model with CrCL)[9]

	Median (90% Prediction Interval) for the Following CrCL and Adjusted Dosing Regimen[a]		
	90 to <120 mL/min (2 g q8h) 3 h infusion	**120 to <150 mL/min (2 g q 6h) 3 h infusion**	**150 to 200 mL/min (2 g q6h) 3 h infusion**
C_{max} (µg/mL)	99.1 (84.4-117)	95.1 (81.2-112)	87 (72.6-102)
Daily AUC (µg•h/mL)	1238 (1007-1535)	1450 (1196-1776)	1278 (1037-1560)

Abbreviations: AUC, area under the plasma concentration–time curve from 0 to infinity; $C_{max,}$ peak plasma concentration; CrCL, creatinine clearance determined by Cockcroft-Gault formula; h, hours; q6h, every 6 hours; q8h, every 8 hours.
[a]With original interindividual pharmacokinetic variability of 10%–20%.

- In summary, the following dosing regimens based on impaired or augmented renal function provide similar cefiderocol exposure compared with patients with normal renal function following the 2 g q8h dose (3 h infusion) and 90% PTA for 75% $f_{T>MIC}$ against a MIC ≤4 µg/mL (**Table 10**)[9]

Table 10. Cefiderocol Dose Regimen according to Renal Function[9]

Renal function	**Dose Regimen (All as 3 h infusion)**
Augmented (CrCL, ≥120 mL/min/1.73m^2)	2 g q6h
Normal (MDRD-eGFR, ≥90 mL/min/1.73m^2)	2 g q8h
Mild impairment (MDRD-eGFR, 60 to <90 mL/min/1.73m^2)	2 g q8h
Moderate impairment (MDRD-eGFR, 30 to <60 mL/min/1.73m^2)	1.5 g q8h
Severe impairment (MDRD-eGFR, 15 to <30 mL/min/1.73m^2)	1 g q8h
ESRD (MDRD-eGFR, <15 mL/min/1.73m^2)	0.75 g q12h
Requiring intermittent HD	0.75 g q12h[a]

Abbreviations: CrCL, creatinine clearance determined by Cockcroft-Gault formula; HD, hemodialysis; MDRD-eGFR, estimated glomerular filtration determined by the modification of diet in renal disease equation; q6h, every 6 hours; q8h, every 8 hours; q12h, every 12 hours.
[a]The Fetroja (cefiderocol) Prescribing Information recommends administering Fetroja immediately after HD for patients receiving intermittent HD.

Population PK Model (Phase 1 studies, APEKS-NP, APEKS-cUTI, and CREDIBLE-CR)

Methods

- A population PK model was developed using plasma concentration data from the cefiderocol clinical development program (Phase 1 studies, APEKS-NP, APEKS-cUTI, and CREDILBE-CR)[10]
- Data from 6854 plasma concentration data points for cefiderocol from 425 patients with an infection and 91 uninfected subjects following single (100 to 2000 mg) or multiple (1000 and 2000 mg q8h) 1 h to 3 h IV infusions were used for the analysis[10,15]
- Covariate modeling was utilized to identify covariates on the total clearance of cefiderocol such as CrCL (Cockcroft-Gault equation), body weight, age, sex, aspartate aminotransferase, alanine aminotransferase, total bilirubin, albumin, race, infection site, and ventilation[10]
- The recommended dosage adjustments for cefiderocol (based on renal function) was evaluated using Monte Carlo simulations (1000 virtual patients for each infection site and renal function group) to determine the PTA of 75% $f_{T>MIC}$ and 100% $f_{T>MIC}$ against a MIC of 0.25-16 µg/mL[10]

Results

- Given the renal excretion of cefiderocol, CrCL was the most significant covariate for cefiderocol PK[10]
- Total clearance in patients with cUTI (CREDIBLE-CR), pneumonia, and BSI/sepsis was similar to healthy volunteers without infections. Patients with cUTI/AUP (APEKs-cUTI) demonstrated a total clearance that was 27% higher compared with healthy volunteers without infection[10]
- The estimated C_{max} and daily AUC overlapped among the various infection sites. For patients with pneumonia, the estimated C_{max} and AUC was similar between patients with mechanical ventilation and patients without mechanical ventilation[10]
- The PTA for 75% $fT_{>MIC}$ exceeded 95% against an MIC of up to 4 μg/mL (please see **Table 11**). Meanwhile, the PTA for 100% $fT_{>MIC}$ exceeded 90% against MICs ≤4 μg/mL across all infection sites and renal groups, with the exception of patients with normal renal function and BSI/sepsis (85%)[10]

Table 11. Probability of Target Attainment for 75% $fT_{>MIC}$ by Infection Site and Renal Function Group[10, a]

Renal function group and infection site	CrCl ranges	Dose regimens with 3-h infusion	PTA(%) for MIC (μg/mL) of:						
			0.25	0.5	1	2	4	8	16
Pneumonia									
Augmented renal function	>120 mL/min (120 to <150 = 50%; >150 = 50%)	2 g q6h	100	100	100	100	99.7	94.5	60.4
Normal renal function	90 to <120 mL/min	2 g q8h	100	100	100	99.9	98.9	87.1	43.4
Mild renal impairment	60 to <90 mL/min	2 g q8h	100	100	100	100	99.8	97	69.7
Moderate renal impairment	30 to <60 mL/min	1.5 g q8h	100	100	100	100	99.9	98.7	83.3
Severe renal impairment	15 to <30 mL/min	1 g q8h	100	100	100	100	100	99.9	90.7
ESRD	5 to <15 mL/min	0.75 g q12h	100	100	100	100	100	99.6	86.3
BSI/sepsis[b]									
Augmented renal function		2 g q6h	100	100	100	100	99.4	91.3	49.6
Normal renal function		2 g q8h	100	100	100	99.9	97.3	80.6	32.6
Mild renal impairment		2 g q8h	100	100	100	99.9	99.6	94.4	57.7
Moderate renal impairment		1.5 g q8h	100	100	100	100	99.9	98	74.8
Severe renal impairment		1 g q8h	100	100	100	100	100	99.8	84.8
ESRD		0.75 g q12h	100	100	100	100	100	99.2	79.2
cUTI[b]									
Augmented renal function		2 g q6h	100	100	100	100	99.9	96.9	73.3
Normal renal function		2 g q8h	100	100	100	100	99.6	93.6	56.3
Mild renal impairment		2 g q8h	100	100	100	100	99.8	98.4	81.2
Moderate renal impairment		1.5 g q8h	100	100	100	100	100	99.6	90.4
Severe renal impairment		1 g q8h	100	100	100	100	100	100	95.9
ESRD		0.75 g q12h	100	100	100	100	100	100	91.6

Abbreviations: BSI, bloodstream infection; CrCl, creatine clearance; cUTI, complicated urinary tract infection; ESRD, end-stage renal disease; h, hours; MIC, minimum inhibitory concentration; PK, pharmacokinetic; PTA, probability of target attainment; q6h, every 6 hours; q8h, every 8 hours; q12h, every 12 hours.

[a]PK steady state was assumed. Shaded area indicates >90%. There were 1000 simulated patients in each simulation scenario. Body weight was assumed to be log-normal distributed with mean of 72.6 kg and CV of 30%. Albumin was assumed to be log-normal distributed with mean of 2.8 g/dL and CV of 30%. [b]CrCl ranges are similar to those shown for pneumonia.

- The study results demonstrate that adequate plasma exposure of cefiderocol can be attained with the recommended dosing regimen for patients with infections[10]

Intrapulmonary PK Model (Phase 1 studies)

- An intrapulmonary PK model was developed for cefiderocol using plasma and ELF concentration data from patients with pneumonia and healthy patients. To evaluate the dosing regimens of cefiderocol, Monte Carlo simulations were used to consider for PK variability when calculating the PTA for the targeted $\%fT_{>MIC}$ in ELF ($\%fT_{>MIC,ELF}$)[11]

Methods

- Concentration data for cefiderocol, consisting of 168 plasma and 27 ELF concentrations, were collected from seven patients with pneumonia on mechanical ventilation from a Phase 1b study and 20 healthy patients a Phase 1 study[11]
- Monte Carlo simulations (1000 virtual patients with pneumonia by renal function group) were performed to determine the PTA for 75% $f_{T>MIC,ELF}$ against a MIC of 0.25-16 µg/mL by renal function[11]

Results

- Based on Monte Carlo simulations, the PTA for 75% $fT>_{MIC,ELF}$ was at least 91.8% overall against MIC ≤4 µg/mL and at least 87.0% for patients with normal renal function against MIC ≤4 µg/mL (**Table 12**)[11]

Table 12. Probability of Target Attainment for 75% $fT_{>MIC,ELF}$ by Renal Function Group[11]

Renal function group	CrCl ranges	Dose regimens with 3-h infusion	MIC (µg/mL)						
			0.25	0.5	1	2	4	8	16
Augmented renal function	>120 mL/min (120 to <150 = 50%; >150 = 50%)	2 g every 6 h	100	100	100	99.8	91.8	54	10.2
Normal renal function	90 to <120 mL/min	2 g every 8 h	100	100	100	99.6	87.7	42.9	6.2
Mild renal impairment	60 to <90 mL/min	2 g every 8 h	100	100	100	99.8	93.8	59.8	14.9
Moderate renal impairment	30 to <60 mL/min	1.5 g every 8 h	100	100	100	100	95.9	66	17.5
Severe renal impairment	15 to <30 mL/min	1 g every 8 h	100	100	100	99.9	97.7	74.6	24.8
ESRD	5 to <15 mL/min	0.75 g every 12 h	100	100	100	99.9	94.3	63.1	20.8

Pharmacokinetics at steady state was assumed. Probability of target attainment is shown in percent (%).
1000 simulated patients in each simulation scenario.
Body weight was assumed to be log-normal distributed with mean of 72.6 kg and CV of 30%.
Albumin was assumed to be log-normal distributed with mean of 2.8 g/dL and CV of 30%.
Abbreviations: CV, coefficient of variation; ELF, epithelial lining fluid; ESRD, end-stage renal disease; fT>MIC,ELF, percentage of time for which free epithelial lining fluid concentrations exceed MIC over the dosing interval; g, gram; h, hour; MIC, minimum inhibitory concentration.

5. RELEVANT PRESCRIBING INFORMATION

Fetroja® is indicated in patients 18 years of age or older for the treatment of:[8]

- Complicated urinary tract infections (cUTIs), including pyelonephritis caused by the following susceptible Gram-negative microorganisms: *Escherichia coli, Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Enterobacter cloacae* complex

- Hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP), caused by the following susceptible Gram-negative microorganisms: *Acinetobacter baumannii* complex, *Escherichia coli*, *Enterobacter cloacae* complex, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Serratia marcescens*[8]

Fetroja is contraindicated in:[8]

- Patients with a known history of severe hypersensitivity to cefiderocol or other beta-lactam antibacterial drugs, or any other component of Fetroja.

As described in **Dosage and Administration, Sections 2.1** and **2.2** of the Fetroja **Full Prescribing Information:**[8]

> Dosage adjustment of Fetroja is recommended for patients with CLcr less than 60 mL/min, including patients receiving intermittent hemodialysis (HD) or continuous renal replacement therapy (CRRT), and for patients with CLcr 120 mL/min or greater.
>
> **Dosage Adjustments in Patients With CLcr Less Than 60 mL/min (Including Patients Undergoing Intermittent HD or CRRT), and CLcr 120 mL/min or Greater**
>
> Dosage Adjustments in Patients with CLcr Less Than 60 mL/min Including Patients Receiving Intermittent HD
>
> Dosage adjustment of Fetroja is recommended in patients with CLcr less than 60 mL/min (**Table 1**). For patients undergoing intermittent HD, start the dosing of Fetroja immediately after the completion of HD. For patients with fluctuating renal function, monitor CLcr and adjust dosage accordingly.

Table 1. Recommended Dosage of Fetroja for Patients with CLcr Less Than 60 mL/min Including Patients Receiving Intermittent HD

Estimated Creatinine Clearance (CLcr)[a]	Dose	Frequency	Infusion Time
CLcr 30 to 59 mL/min	1.5 grams	Every 8 hours	3 hours
CLcr 15 to 29 mL/min	1 gram	Every 8 hours	3 hours
CLcr less than 15 mL/min, with or without intermittent HD[b]	0.75 grams	Every 12 hours	3 hours

[a]CLcr = creatinine clearance estimated by Cockcroft-Gault equation.
[b]Cefiderocol is removed by HD; administer FETROJA immediately after HD for patients receiving intermittent HD.
HD = hemodialysis.

> Dosage Adjustments in Patients Receiving CRRT
>
> For patients receiving CRRT, including continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD) and continuous venovenous hemodiafiltration (CVVHDF), the dosage of Fetroja should be based on the effluent flow rate in CRRT (see **Table 2**). These recommendations are intended to provide initial dosing in patients receiving CRRT. Dosing regimens may need to be tailored based on residual renal function and patient's clinical status.

Table 2. Recommended Dosage of Fetroja for Patients Receiving CRRT

Effluent Flow Rate[a]	Recommended Dosage of Fetroja
2 L/hr or less	1.5 grams every 12 hours
2.1 to 3 L/hr	2 grams every 12 hours
3.1 to 4 L/hr	1.5 grams every 8 hours
4.1 L/hr or greater	2 grams every 8 hours

[a]Ultrafiltrate flow rate for CVVH, dialysis flow rate for CVVHD, ultrafiltrate flow rate plus dialysis flow rate for CVVHDF.
CRRT=continuous renal replacement therapy

Dosage Adjustments in Patients with CLcr 120 mL/min or Greater

For patients with CLcr greater than or equal to 120 mL/min, Fetroja 2 grams administered every 6 hours by IV infusion over 3 hours is recommended.

Please also see **Sections 8.6 Renal Impairment** and **12.3 Pharmacokinetics** in the Fetroja **Full Prescribing Information.**[8]

Please read the attached Fetroja **Full Prescribing Information**.

6. LITERATURE SEARCH

As of February 2026, a computerized search of the published medical literature using internal and external databases (i.e., Medline® and Embase®) has identified the following relevant references regarding the use of cefiderocol in patients with renal impairment or augmented renal clearance. For your review, these references are listed in the bibliography that follows:

Müller-Kühnle J, Rittershofer B, Schanz M, Allgäuer S, Muerdter T, Schricker S. Cefiderocol elimination during peritoneal dialysis: a short report. *Cureus*. 2025;17(12):e99579. doi:10.7759/cureus.99579

Kawaguchi N, Katsube T, Echols R, Wajima T. Population pharmacokinetic analysis of cefiderocol, a parenteral siderophore cephalosporin, in healthy subjects, subjects with various degrees of renal function, and patients with complicated urinary tract infection or acute uncomplicated pyelonephritis. *Antimicrob Agents Chemother* 2018;62(2). doi:10.1128/AAC.01391-17.

Katsube T, Echols R, Ferreira JCA, Krenz HK, Berg JK, Galloway C. Cefiderocol, a siderophore cephalosporin for Gram-negative bacterial infections: pharmacokinetics and safety in subjects with renal impairment. *J Clin Pharmacol* 2017;57(5):584-591.

Please keep in mind that medical literature databases, while considered a major source of biomedical information, are selective in their sources, and the information derived from it should not be considered all-inclusive.

REFERENCES

1. Portsmouth S, van Veenhuyzen D, Echols R, et al. Cefiderocol versus imipenem-cilastatin for the treatment of complicated urinary tract infections caused by Gram-negative uropathogens: a phase 2, randomised, double-blind, non-inferiority trial. *Lancet Infect Dis*. 2018;18(12):1319-1328. doi:10.1016/s1473-3099(18)30554-1
2. Portsmouth S, Echols R, Machida M, et al. Efficacy and Safety of Cefiderocol According to Renal Impairment in Patients with Complicated Urinary Tract Infection (cUTI) in a Phase 2 Study. Poster presented at: ID Week. October 2-6, 2019. Washington, DC
3. Wunderink RG, Matsunaga Y, Ariyasu M, et al. Cefiderocol versus high-dose, extended-infusion meropenem for the treatment of Gram-negative nosocomial pneumonia (APEKS-NP): a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Infect Dis*. 2021;21(2):213-225. doi:10.1016/s1473-3099(20)30731-3
4. Data on File 3. Shionogi Inc.
5. Bassetti M, Echols R, Matsunaga Y, et al. Efficacy and safety of cefiderocol or best available therapy for the treatment of serious infections caused by carbapenem-resistant Gram-negative bacteria (CREDIBLE-CR): a randomised, open-label, multicentre, pathogen-focused, descriptive, phase 3 trial. *Lancet Infect Dis*. 2021;21(2):226-240. doi:10.1016/s1473-3099(20)30796-9

6. Data on File 25. Shionogi Inc.
7. Data on File 18. Shionogi Inc.
8. Fetroja® (cefiderocol) for injection, for intravenous use [Prescribing Information]. Shionogi Inc.
9. Katsube T, Wajima T, Ishibashi T, et al. Pharmacokinetic/pharmacodynamic modeling and simulation of cefiderocol, a parenteral siderophore cephalosporin, for dose adjustment based on renal function. *Antimicrob Agents Chemother*. 2016;61(1)doi:10.1128/AAC.01381-16
10. Kawaguchi N, Katsube T, Echols R, et al. Population pharmacokinetic and pharmacokinetic/pharmacodynamic analyses of cefiderocol, a parenteral siderophore cephalosporin, in patients with pneumonia, bloodstream infection/sepsis, or complicated urinary tract infection. *Antimicrob Agents Chemother*. 2021;65(3):e01437-20. doi:10.1128/AAC.01437-20.
11. Kawaguchi N, Katsube T, Echols R, et al. Intrapulmonary pharmacokinetic modeling and simulation of cefiderocol, a parenteral siderophore cephalosporin, in patients with pneumonia and healthy subjects. *J Clin Pharmacol*. 2022;62(5):670-680. doi:10.1002/jcph.1986.
12. Miyazaki S, Katsube T, Shen H, et al. Metabolism, excretion, and pharmacokinetics of [(14) C]-cefiderocol (S-649266), a siderophore cephalosporin, in healthy subjects following intravenous administration. *J Clin Pharmacol*. 2019;59(7):958-967. doi:10.1002/jcph.1386
13. Zhanel GG, Golden AR, Zelenitsky S, et al. Cefiderocol: a siderophore cephalosporin with activity against carbapenem-resistant and multidrug-resistant Gram-negative bacilli. *Drugs*. 2019;79(3):271-289. doi:10.1007/s40265-019-1055-2
14. Katsube T, Echols R, Arjona Ferreira JC, et al. Cefiderocol, a siderophore cephalosporin for Gram-negative bacterial infections: pharmacokinetics and safety in subjects with renal impairment. *J Clin Pharmacol*. 2017;57(5):584-591. doi:10.1002/jcph.841
15. Kawaguchi N, Katsube T, Echols R, et al. Population pharmacokinetic and pharmacokinetic/pharmacodynamic analyses of cefiderocol, a parenteral siderophore cephalosporin, in patients with pneumonia, bloodstream infection/sepsis, or complicated urinary tract infection. *Antimicrob Agents Chemother*. 2021;65(3):e01437-20. doi:10.1128/aac.01437-20

ENCLOSURE

Fetroja® (cefiderocol) for injection, for intravenous use [Prescribing Information]. Shionogi Inc.