Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

SHIONOGI

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.**

Summary

- **APEKS-cUTI**, a Phase 2, multicenter, double-blind, parallel-group non-inferiority trial evaluated the efficacy and safety of cefiderocol in patients hospitalized with complicated urinary tract infection (cUTI) with or without pyelonephritis or acute uncomplicated pyelonephritis (AUP), who were randomized to receive 1 hour (h) intravenous (IV) infusions of cefiderocol 2 grams (g) or imipenem-cilastatin 1 g every 8 h (q8h) for 7-14 days[1]
  - One death ([1/300]; <1%) was reported in the cefiderocol arm and was considered unrelated to the study drug by the investigator[1,2]
- **APEKS-NP**, a Phase 3, multicenter, randomized, double-blind, non-inferiority trial, assessed the efficacy and safety of cefiderocol in patients with hospital-acquired bacterial pneumonia (HABP), ventilator-associated bacterial pneumonia (VABP) or healthcare-associated bacterial pneumonia (HCABP) caused by suspected Gram-negative pathogens, who were randomized to receive 3 h IV infusions of either cefiderocol 2 g or meropenem 2 g q8h for 7-14 days, in addition to adjunctive linezolid (600 mg q12h for at least 5 days)[3-5]
  - The primary endpoint of Day 14 all-cause mortality (ACM) occurred in 18 (12.4%) patients in the cefiderocol arm and 17 (11.6%) patients in the meropenem arm, treatment difference: 0.8 (95% CI: -6.6; 8.2). The secondary endpoints of ACM at Day 28 and end of study (EOS) were also similar between the cefiderocol and meropenem treatment arms[3,4]
- **CREDIBLE-CR**, a randomized, open-label, multicenter, descriptive Phase 3 trial assessed the efficacy and safety of cefiderocol to best available therapy (BAT) in patients with HABP, VABP, HCABP, bloodstream infection (BSI), sepsis, or cUTI caused by carbapenem-resistant (CR) Gram-negative pathogens, with no hypothesis testing or formal inferential analyses. Cefiderocol 2 g q8h over a 3 h IV infusion or IV BAT was administered for 7-14 days[6]
  - The ACM rate was 34% in the cefiderocol group and 18% in the BAT group through the end of the study[6]
  - An evaluation of the study deaths by an external, independent, masked adjudication committee found that approximately 50% of deaths were attributable to causes other than the underlying Gram-negative infection in both treatment groups. In addition, none of the deaths in the cefiderocol group were considered drug-related (eg, drug toxicity)[6]
  - Logistic regression analysis for Day 28 ACM did not identify a baseline parameter that explained the mortality difference[6]
  - *Acinetobacter* species (spp.) infections may have impacted the ACM difference. The ACM was higher in the cefiderocol group than the BAT group for patients with polymicrobial *Pseudomonas aeruginosa* and *Acinetobacter* infections but was identical in patients with only *P. aeruginosa* infections[6]
  - Of the patients with *Acinetobacter* spp. infections, the incidence of moderate-severe renal impairment, ongoing shock, or shock within 31 days prior to randomization, or intensive care unit (ICU) at randomization was higher at baseline in the cefiderocol group than the BAT group[6]
  - The list of individual patient profile deaths from both treatment groups from the CREDIBLE-CR study is provided in the **Appendix (Table 5)**[6,7]

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

SHIONOGI

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.**

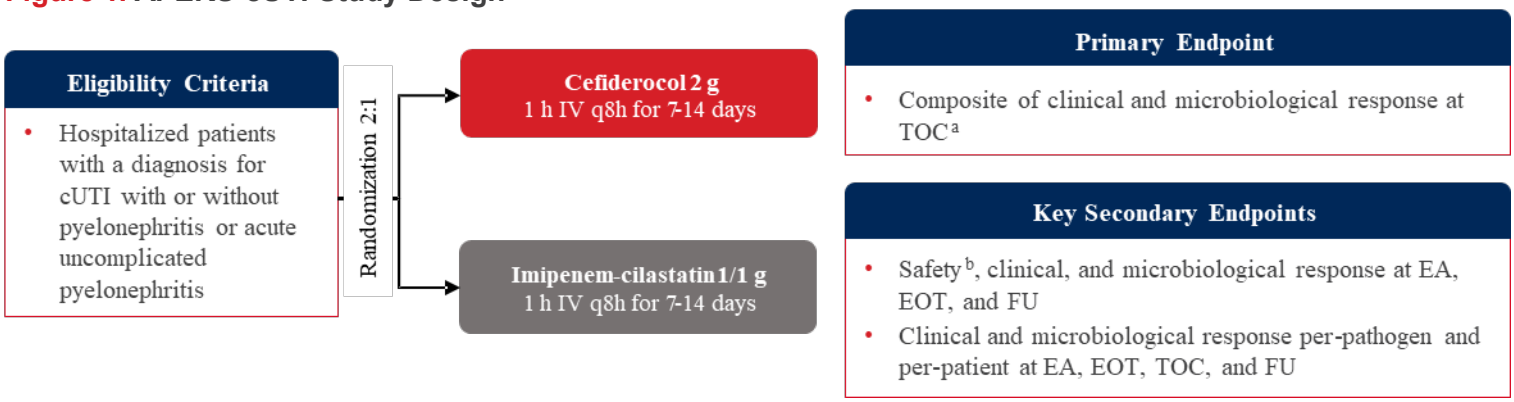
Phase 2 Pivotal Study

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]



[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. Adverse events were monitored daily during treatment administration in the hospital.

- A total of 452 patients were randomly assigned to cefiderocol (n=303) or imipenem-cilastatin (n=149), of whom 448 patients (n=300 cefiderocol; n=148 imipenem-cilastatin) received treatment[1]

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

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.**

Phase 2 Pivotal Study

APEKS-cUTI

Results

- One death (0.33% [1/33]) was reported in the cefiderocol arm due to cardiac arrest which was considered unrelated to the study drug by the investigator[1]
  - The patient was a 76-year-old man who had a normal electrocardiogram during enrollment, but had a complicated medical history, including benign prostatic hyperplasia, cerebral infarction, dementia, diabetes mellitus, epilepsy, extrapyramidal disorder, and heart disease[1]
  - The patient had cUTI without pyelonephritis and was treated with cefiderocol for seven days[1,2]

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

SHIONOGI

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.**

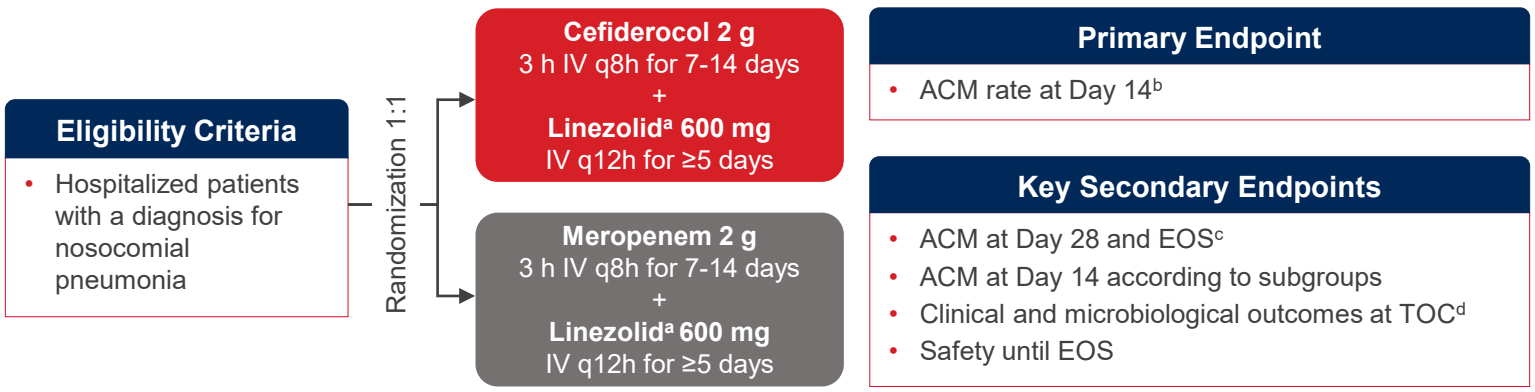
Phase 3 Clinical Studies

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 VABP, HABP, or HCABP caused by suspected Gram-negative pathogens[3]

Figure 2. APEKS-NP Study Design[3]



[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).

- 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). Three 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]

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

SHIONOGI

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.**

Phase 3 Clinical Studies

APEKS-NP

Results

- 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)[3,4]
- The between-group comparison of Day 14 ACM was unaffected by pneumonia diagnosis, APACHE II score, ICU admission, baseline mechanical ventilation, or by pathogen type[3,4]
- The secondary endpoints of ACM at Day 28 (21.0% and 20.5%, respectively) and EOS (26.8% and 23.3%) were also similar in the cefiderocol and meropenem treatment arms, respectively[3,4]
- The primary and secondary endpoints and Day 14 ACM by subgroups are shown in **Table 1** and **Table 2**, respectively. Day 28 and EOS ACM by subgroups can be found in the **Appendix (Tables 1 and 2)**[3,4]

Table 1. Primary and Secondary Endpoints in APEKS-NP (mITT Population)[3,4]

ACM rate	Cefiderocol (n=145)	Meropenem (n=147)	Treatment difference (95% CI)
Primary endpoint			
Day 14	12.4% (18/145)	11.6% (17/146)	0.8 (-6.6; 8.2)
Secondary endpoints			
Day 28	21.0% (30/143)	20.5% (30/146)	0.4 (-8.9; 9.8)
End of study	26.8% (38/142)	23.3% (34/146)	3.6 (-6.3; 13.4)

Data expressed as %.
Abbreviations: ACM, all-cause mortality; CI, confidence interval; mITT, modified intent-to-treat.

Table 2. Day 14 All-Cause Mortality by Subgroup in APEKS-NP (mITT Population)[3,5]

Subgroup	Cefiderocol (N=145) n/N (%)	Meropenem (N=147) n/N (%)	Treatment Comparison: Difference (%)	Treatment Comparison: 95% CI
Overall	18/145 (12)	17/146 (12)	0.8	(-6.7, 8.2)
Clinical Diagnosis				
HABP	6/59 (10)	9/60 (15)	-4.8	(-16.7, 7.0)
VABP	9/59 (15)	8/63 (13)	2.6	(-9.8, 14.9)
HCABP	3/27 (11)	0/23 (0)	11.1	(-3.7, 23.5)
APACHE II score				
≤ 15	6/74 (8)	5/76 (7)	1.5	(-8.8, 9.9)
16 – 19	5/31 (16)	3/25 (12)	4.1	(-14.0, 22.3)
≥ 20	7/40 (18)	9/45 (20)	-2.5	(-18.1, 14.1)
ICU at Randomization				
Yes	15/102 (15)	16/96 (17)	-2.0	(-12.1, 8.2)
No	3/43 (7)	1/50 (2)	5.0	(-3.6, 13.5)
Ventilation at Randomization				
Yes	14/89 (16)	12/85 (14)	1.6	(-9.0, 12.2)
No	4/56 (7)	5/61 (8)	-1.1	(-10.7, 8.6)
Top 5 baseline pathogens				
Klebsiella pneumoniae	5/45 (11)	5/44 (11)	-0.9	(-13.7, 11.8)
Pseudomonas aeruginosa	2/24 (8)	3/23 (13)	-4.7	(-22.4, 12.9)
Acinetobacter baumannii	5/23 (22)	4/24 (17)	5.1	(-12.4, 22.6)
Escherichia coli	4/19 (21)	3/22 (14)	7.4	(-10.3, 30.7)
Enterobacter cloacae	0/7 (0)	1/8 (13)	-12.5	(-35.1, 10.4)

Percentages for overall were calculated as the number of patients who died by any causes at or before Day 14 divided by the total number of patients in the analysis populations with known survival status at Day 14. N' is the number of patients within the category with known survival status. The treatment difference (cefiderocol minus meropenem) is the estimate of the difference in the all-cause mortality rate at Day 14 between the two treatment arms. The 95% CI (two-sided) is calculated using a normal approximation to the difference between two binomial proportions (Wald method). The widths of the CIs were not adjusted for multiplicity and therefore cannot be used to infer treatment effects.
Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; HABP, hospital-acquired bacterial pneumonia; HCABP, healthcare-associated bacterial pneumonia; ICU, intensive care unit; mITT, modified intent-to-treat; VABP, ventilator-associated bacterial pneumonia.

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

SHIONOGI

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.**

Table 1. Primary and Secondary Endpoints in APEKS-NP (mITT Population)[3,4]

ACM rate	Cefiderocol (n=145)	Meropenem (n=147)	Treatment difference (95% CI)
Primary endpoint			
Day 14	12.4% (18/145)	11.6% (17/146)	0.8 (-6.6; 8.2)
Secondary endpoints			
Day 28	21.0% (30/143)	20.5% (30/146)	0.4 (-8.9; 9.8)
End of study	26.8% (38/142)	23.3% (34/146)	3.6 (-6.3; 13.4)

Data expressed as %.
Abbreviations: ACM, all-cause mortality; CI, confidence interval; mITT, modified intent-to-treat.

Table 2. Day 14 All-Cause Mortality by Subgroup in APEKS-NP (mITT Population)[3,5]

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

SHIONOGI

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.**

Table 2. Day 14 All-Cause Mortality by Subgroup in APEKS-NP (mITT Population)[3,5]

Subgroup	Cefiderocol (N=145) n/N' (%)	Meropenem (N=147) n/N' (%)	Treatment Comparison	
			Difference (%)	95% CI
Overall	18/145 (12)	17/146 (12)	0.8	(-6.7, 8.2)
Clinical Diagnosis				
HABP	6/59 (10)	9/60 (15)	-4.8	(-16.7, 7.0)
VABP	9/59 (15)	8/63 (13)	2.6	(-9.8, 14.9)
HCABP	3/27 (11)	0/23 (0)	11.1	(-0.7, 23.0)
APACHE II score				
≤ 15	6/74 (8)	5/76 (7)	1.5	(-6.8, 9.9)
16 – 19	5/31 (16)	3/25 (12)	4.1	(-14.0, 22.3)
≥ 20	7/40 (18)	9/45 (20)	-2.5	(-19.1, 14.1)
ICU at Randomization				
Yes	15/102 (15)	16/96 (17)	-2.0	(-12.1, 8.2)
No	3/43 (7)	1/50 (2)	5.0	(-3.6, 13.5)
Ventilation at Randomization				
Yes	14/89 (16)	12/85 (14)	1.6	(-9.0, 12.2)
No	4/56 (7)	5/61 (8)	-1.1	(-10.7, 8.6)
Top 5 baseline pathogens				
Klebsiella pneumoniae	5/48 (10)	5/44 (11)	-0.9	(-13.7, 11.8)
Pseudomonas aeruginosa	2/24 (8)	3/23 (13)	-4.7	(-22.4, 12.9)
Acinetobacter baumannii	5/23 (22)	4/24 (17)	5.1	(-17.4, 27.6)
Escherichia coli	4/19 (21)	3/22 (14)	7.4	(-15.9, 30.7)
Enterobacter cloacae	0/7 (0)	1/8 (13)	-12.5	(-35.5, 10.4)

Percentages for overall were calculated as the number of patients who died by any causes at or before Day 14 divided by the total number of patients in the analysis populations with known survival status at Day 14. N' is the number of patients within the category with known survival status. The treatment difference (cefiderocol minus meropenem) is the estimate of the difference in the all-cause mortality rate at Day 14 between the two treatment arms. The 95% CI (two-sided) is calculated using a normal approximation to the difference between two binomial proportions (Wald method). The widths of the CIs were not adjusted for multiplicity and therefore cannot be used to infer treatment effects.

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; HABP, hospital-acquired bacterial pneumonia; HCABP, healthcare-associated bacterial pneumonia; ICU, intensive care unit; mITT, modified intent-to-treat; VABP, ventilator-associated bacterial pneumonia.

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

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.**

Phase 3 Clinical Studies

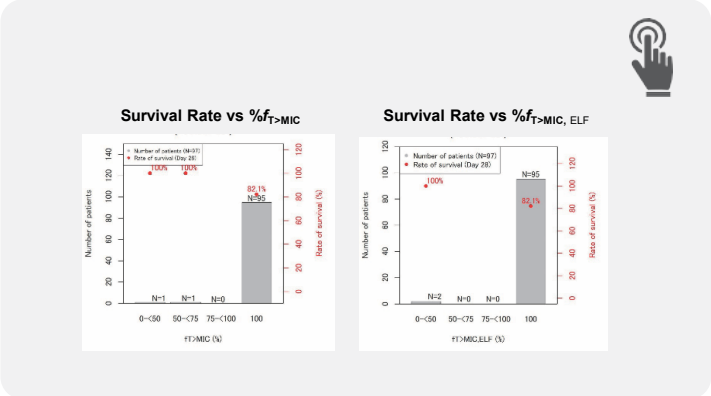
APEKS-NP

***Results* (Cont'd)**

Pharmacokinetic/Pharmacodynamic Analyses

- A pharmacokinetic (PK)/pharmacodynamic (PD) analysis for APEKS-NP was conducted based on an intrapulmonary PK model that was developed using cefiderocol data from healthy volunteers and patients with pneumonia.[8]
- The relationship of the percentage of time for which free drug concentration exceeded the minimum inhibitory concentration over the dosing interval (%$f_{T>MIC}$) as well as %$f_{T>MIC}$ in epithelial lining fluid (%$f_{T>MIC, ELF}$) with the outcomes, including Day 28 survival rate was evaluated.[8,9]
- In APEKS-NP, there was no PK/PD relationship identified for survival rate at Day 28. The %$f_{T>MIC}$ was 100% in 95/97 (98%) patients and %$f_{T>MIC, ELF}$ was 100% in 95/97 (98%) patients (Figure 3).[10]

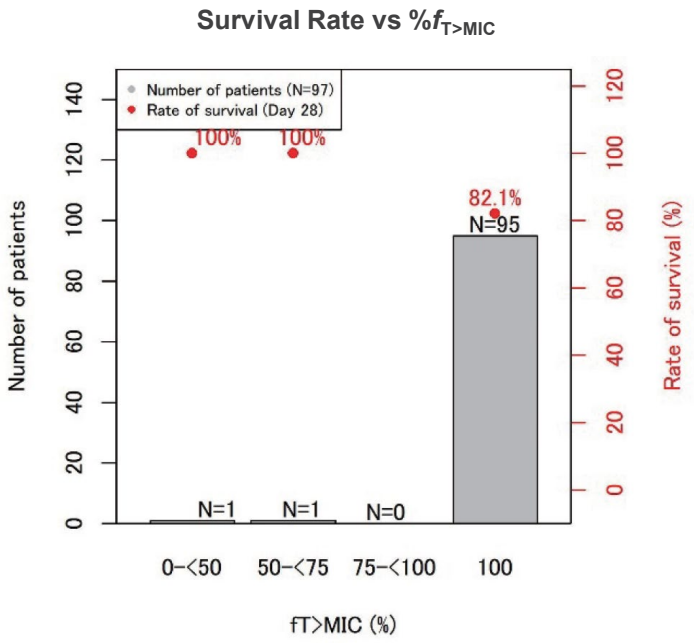
Figure 3. Relationship of %f_T>MIC and %f_T>$_{MIC, ELF}$ with Survival Rate[10]

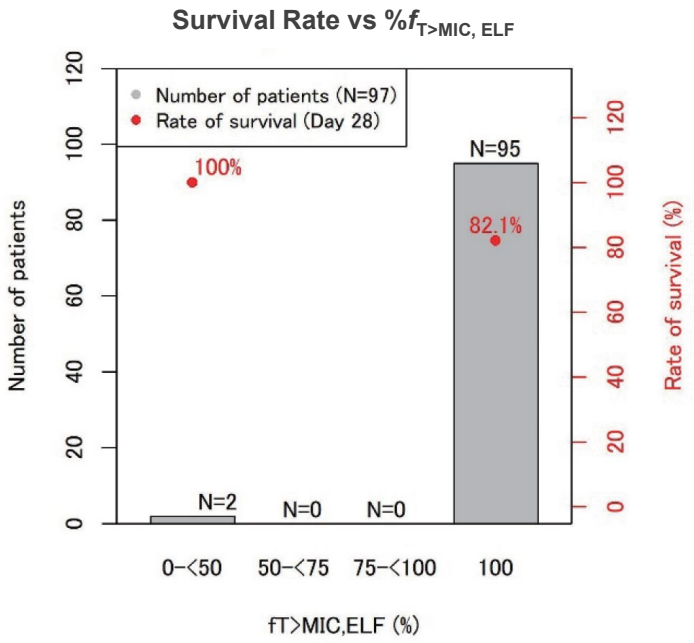


Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

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.**

Figure 3. Relationship of $\%f_{T>MIC}$ and $\%f_{T>MIC,\ ELF}$ with Survival Rate[10]





Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

SHIONOGI

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.**

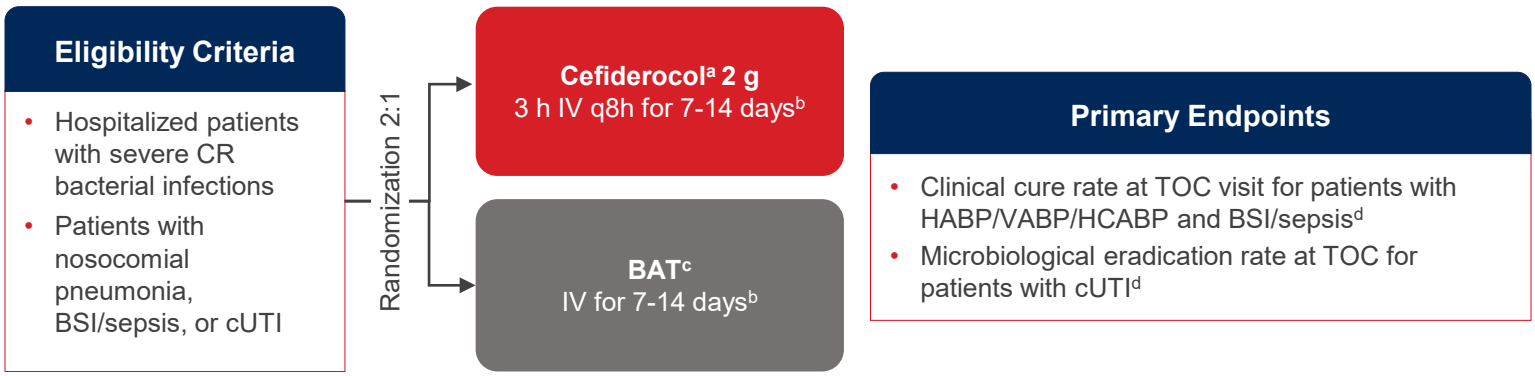
Phase 3 Clinical Studies

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[6]
- CREDIBLE-CR was a descriptive study with no hypothesis testing or formal inferential analyses[6]

Figure 4. CREDIBLE-CR Study Design[6]



[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 three systemic antibiotics.
[d]Defined as all patients with a confirmed CR Gram-negative pathogen who received at least one 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)[6]

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

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.**

Phase 3 Clinical Studies

CREDIBLE-CR

Characteristics

In the ITT population in the cefiderocol and BAT groups, the proportion of patients had the following infections[6]:

- HABP/VABP/HCABP: 45 (45%) and 22 (45%)
- BSI/sepsis: 30 (30%) and 17 (35%)
- cUTI: 26 (26%) and 10 (20%)

- A numerically higher proportion of patients in the cefiderocol group compared with BAT group were aged ≥65 years (63% vs 45%)
- Moderate renal impairment (CrCl 30 mL/min-50 mL/min) was seen in 23% vs 16% of patients in the cefiderocol and BAT groups, respectively. Severe renal impairment (CrCl <30 mL/min) was seen in 20% vs 14% of patients in the cefiderocol and BAT groups, respectively
- The percentage of patients who were in the ICU at randomization (56% vs 43%) was numerically higher in the cefiderocol group compared with the BAT group[6]
- The overall summary of treatment-emergent adverse events (TEAEs) of cefiderocol and BAT groups is shown in **Table 3**[6]

Table 3. Safety Summary in CREDIBLE-CR Study (Safety Population)[6]

	Cefiderocol (n=101)	BAT (n=49)
Patients with TEAEs	92 (91%)	47 (96%)
Patients with treatment-related AEs	15 (15%)	11 (22%)
Patients discontinuing due to TEAEs	10 (10%)	3 (6%)
Patients discontinuing due to treatment-related AEs	3 (3%)	2 (4%)
Patients with treatment-emergent SAEs	50 (50%)	23 (47%)
Patients with treatment-related SAEs	1 (1%)	5 (10%)
TEAEs leading to death*	34 (34%)	9 (18%)

Data expressed as n (%).
Adverse events that started after the first dose of the study drug and up to end of study visit were defined as treatment emergent. A patient could have two or more AE terms in this but would be counted only once within a System Organ Class category. One patient who received cefiderocol after completion of BAT is included in BAT arm in this table.
AE=adverse event; BAT, best-available therapy; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
*Patients could have experienced ≥1 SAE that led to death.

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

SHIONOGI

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.**

Table 3. Safety Summary in CREDIBLE-CR Study (Safety Population)[6]

	Cefiderocol (n=101)	BAT (n=49)
Patients with TEAEs	92 (91%)	47 (96%)
Patients with treatment-related AEs	15 (15%)	11 (22%)
Patients discontinuing due to TEAEs	10 (10%)	3 (6%)
Patients discontinuing due to treatment-related AEs	3 (3%)	2 (4%)
Patients with treatment-emergent SAEs	50 (50%)	23 (47%)
Patients with treatment-related SAEs	1 (1%)	5 (10%)
TEAEs leading to death[a]	34 (34%)	9 (18%)

Data expressed as n (%).
Adverse events that started after the first dose of the study drug and up to end of study visit were defined as treatment emergent. A patient could have two or more adverse events but would be counted only once within a System Organ Class category. One patient who received cefiderocol after completion of BAT is included in BAT arm in this table.
Abbreviations: BAT, best-available therapy; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
[a]Patients could have experienced ≥1 SAE that led to death.

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

SHIONOGI

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.**

Phase 3 Clinical Studies

CREDIBLE-CR

Mortality

- ACM through EOS was higher in the cefiderocol group compared to BAT (34 [34%] vs 9 [18%], respectively) (**Table 4**). None of the deaths were considered to be related to cefiderocol (eg. drug toxicity)[6]
- A total of seven additional deaths (two patients in the cefiderocol arm and five patients in the BAT arm) were spontaneously reported after the EOS timepoint. ACM including the deaths after EOS occurred in 36 (35.6%) patients in the cefiderocol arm and 14 (28.6%) patients in the BAT arm.[6]

Table 4. All-Cause Mortality in the CREDIBLE-CR Study (Safety Population)[6]

	Cefiderocol (N=101) n (%)	BAT (N=49) n (%)
14-day mortality	19 (19)	6 (12)
28-day mortality	25 (25)	9 (18)
End of study[a]	34 (34)	9 (18)

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).
Percentage was calculated using N as the denominator where n is the number of patients who had the specified clinical diagnosis and known vital status at each time point.
Abbreviations: BAT, best-available therapy.
[a]The additional deaths reported spontaneously after study ended (two patients in the cefiderocol group and five patients in the BAT group) were not included in this table.

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

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.**

Phase 3 Clinical Studies

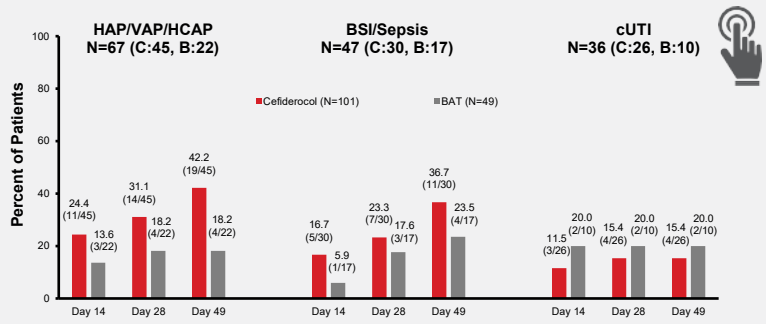
CREDIBLE-CR

Mortality **(Cont'd)**

When comparing the individual clinical diagnoses at three time points throughout the study, mortality was higher in patients treated with cefiderocol compared to BAT for HABP/VABP/HCABP and BSI/sepsis, while mortality was lower for cUTI (Figure 5).[6]

A post-hoc analyses of the mortality difference as requested for regulatory review (including mortality at Day 49 [21 days of treatment plus 28 days of follow-up]) is described in Table 5.[6]

Figure 5. All-Cause Mortality by Infection Site in the CREDIBLE-CR Study (Safety Population)[6,11]



Abbreviations: BAT, best-available therapy; BSI, bloodstream infection; cUTI, complicated urinary tract infection; EOS, end of study; HABP, hospital-acquired bacterial pneumonia; HCABP, healthcare-associated bacterial pneumonia; VABP, ventilator-associated bacterial pneumonia.

Table 5. All-Cause Mortality (Safety Population) with Treatment Difference and 95% CI in Post-Hoc Analyses[7]

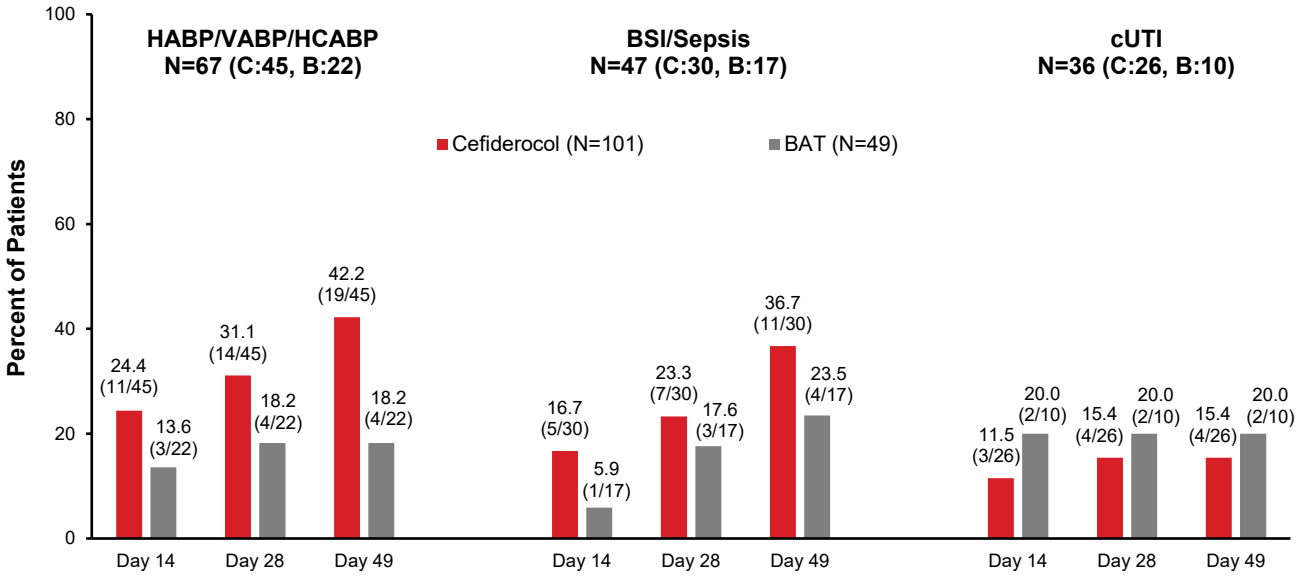
	Cefiderocol (n=101)	BAT (n=49)	Treatment Difference	95% CI
Day 28[a,b]	25 (25%)	9 (18%)	6.4%	-8.6 to 19.2
EOS[b]	34 (34%)	9 (18%)	15.3%	-0.2 to 28.6
Day 49[a]	34 (34%)	10 (20%)	13.3%	-2.5 to 26.9

Abbreviations: BAT, best available treatment; CI, confidence interval; EOS, end of study (end of treatment +28 (±3 days); FDA, US Food and Drug Administration; EMA, European Medicines Agency.
[a]FDA-requested post-hoc statistical testing.
[b]EMA-requested post-hoc statistical testing.

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

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.**

Figure 5. All-Cause Mortality by Infection Site in the CREDIBLE-CR Study (Safety Population)[6,11]



Abbreviations: B, best-available therapy; BSI, bloodstream infection; C, cefiderocol; cUTI, complicated urinary tract infection; EOS, end of study; HABP, hospital-acquired bacterial pneumonia; HCABP, healthcare-associated bacterial pneumonia; VABP, ventilator-associated bacterial pneumonia.

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

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.**

Table 5. All-Cause Mortality (Safety Population) with Treatment Difference and 95% CI in Post-Hoc Analyses[7]

	Cefiderocol (n=101)	BAT (n=49)	Treatment Difference	95% CI
Day 28[a,b]	25 (25%)	9 (18%)	6.4%	-8.6 to 19.2
EOS[b]	34 (34%)	9 (18%)	15.3%	-0.2 to 28.6
Day 49[a]	34 (34%)	10 (20%)	13.3%	-2.5 to 26.9

Abbreviations: BAT, best available treatment; CI, confidence interval; EOS, end of study (end of treatment +28 (±3 days); FDA, US Food and Drug Administration; EMA, European Medicines Agency.
[a]FDA-requested post-hoc statistical testing.
[b]EMA-requested post-hoc statistical testing.

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

SHIONOGI

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.**

Phase 3 Clinical Studies

CREDIBLE-CR
***Mortality* (Cont'd)**

- A post-hoc logistic regression analysis for Day 28 ACM did not identify a baseline parameter that explained the mortality difference **Appendix (Table 3)**[6,7]
- The baseline characteristics of the mortality cases at Day 49 in the cefiderocol and BAT arms are shown in the **Appendix (Table 4)**[11]
- *Acinetobacter* spp. infections may have impacted the ACM difference. The ACM was higher in the cefiderocol group than the BAT group for patients with polymicrobial *Pseudomonas aeruginosa* and *Acinetobacter* spp. infections but was identical in patients with only *P. aeruginosa* infections (**Table 6**)[6]
- Of the patients with *Acinetobacter* spp. infections, the incidence of CrCl <50 mL/min (33% and 18%), ongoing shock (19% and 6%), shock within 31 days prior to randomization (26% and 6%), or ICU at randomization (81% and 47%) was higher at baseline in the cefiderocol group than the BAT group, respectively[6]

Table 6. All-Cause Mortality Rates Through End of Study by Pathogen (Safety Population)[6]

Pathogen(s)	Cefiderocol (N=101) n/N (%)	BAT (N=49) n/N (%)
Acinetobacter spp.[a]	21/42 (50)	3/17 (18)
A. baumannii	19/39 (49)	3/17 (18)
Klebsiella pneumoniae	8/34 (24)	4/16 (25)
without *Acinetobacter* spp.	6/28 (21)	4/15 (27)
Pseudomonas aeruginosa	6/17 (35)	2/12 (17)
without *Acinetobacter* spp.	2/11 (18)	2/11 (18)
E. coli	1/6 (17)	0/3 (0)
without *Acinetobacter* spp.	0/3 (0)	0/1 (0)
S. maltophilia	4/5 (80)	NA
without *Acinetobacter* spp.	2/3 (67)	NA

Data are n/N. n=number of cases. N=total number of patients within the category.
Abbreviations: BAT, best available therapy; NA; not available; spp., species.
[a]Includes *Acinetobacter baumannii* (cefiderocol 39; BAT 17), *A. nosocomialis* (cefiderocol 2; BAT 0), and *A. radioresistens* (cefiderocol 1; BAT 0).

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

SHIONOGI

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.**

Table 6. All-Cause Mortality Rates Through End of Study by Pathogen (Safety Population)[6]

Pathogen(s)	Cefiderocol (N=101) n/N (%)	BAT (N=49) n/N (%)
Acinetobacter spp.[a]	21/42 (50)	3/17 (18)
A. baumannii	19/39 (49)	3/17 (18)
Klebsiella pneumoniae	8/34 (24)	4/16 (25)
without *Acinetobacter* spp.	6/28 (21)	4/15 (27)
Pseudomonas aeruginosa	6/17 (35)	2/12 (17)
without *Acinetobacter* spp.	2/11 (18)	2/11 (18)
E. coli	1/6 (17)	0/3 (0)
without *Acinetobacter* spp.	0/3 (0)	0/1 (0)
S. maltophilia	4/5 (80)	NA
without *Acinetobacter* spp.	2/3 (67)	NA

Data are n/N. n=number of cases. N=total number of patients within the category.
Abbreviations: BAT, best available therapy; NA; not available; spp., species.
[a]Includes *Acinetobacter baumannii* (cefiderocol 39; BAT 17), *A. nosocomialis* (cefiderocol 2; BAT 0), and *A. radioresistens* (cefiderocol 1; BAT 0).

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

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.**

Phase 3 Clinical Trials

CREDIBLE-CR
***Mortality* (Cont'd)**

External Adjudication Committee

- An external, independent, blinded adjudication committee determined attributable mortality in the CREDIBLE-CR study. The members of the adjudication committee were blinded to the treatment and results of the trial[6]
- Each member independently assessed whether the cause of death was unrelated to the original Gram-negative infection, marked under Category 1, or if the death was directly related to the original Gram-negative infection, recorded under Category 2[6]
- All deaths listed under Category 1 were further characterized as being due to an underlying comorbidity, a different infection, a drug-related adverse event, or an iatrogenic cause. Deaths in Category 2 were further assessed for study regimen treatment failure.[6,11]
- The categorization of the deaths is shown in **Table 7**. None of the deaths were categorized as a drug-related adverse event[6]
- Approximately 50% of deaths were attributable causes other than the original Gram-negative infection in both treatment groups (cefiderocol: 16/34 and BAT: 4/9, respectively).[6] The difference in mortality between the cefiderocol group and the BAT group was similar for deaths in Category 1 and in Category 2[11]

Table 7. Categorization of Deaths by the Adjudication Committee (Safety Population)[10]

Category and Subcategory	Cefiderocol N=101 n (%)	BAT N=49 n (%)
Overall mortality	34 (33.7)	9 (18.4)
1. Death not directly related to the Gram-negative infection for which the patient was randomized into the CREDIBLE-CR study	16 (15.8)	4 (8.2)
1A. Likely due to the patient's underlying comorbidity	10 (9.9)	2 (4.1)
1B. Related to infection other than original Gram-negative infection	4 (4.0)	2 (4.1)
1C. Due to drug-related AE	0	0
1D. Due to iatrogenic cause	0	0
Cases that did not have a unanimous subcategory vote in category 1	2 (2.0)	0
2. Death directly related to the Gram-negative infection for which the patient was randomized into the CREDIBLE-CR study	18 (17.8)	5 (10.2)
Yes. Infection-related death represents a failure of antibiotic treatment	16 (15.8)	4 (8.2)
No. Infection-related death does not represent a failure of antibiotic treatment	1 (1.0)	1 (2.0)
Cases that did not have a unanimous subcategory vote in category 2	1 (1.0)	0

Abbreviations: AE, adverse event; BAT, best-available therapy.

The list of individual patient profile deaths from both treatment groups from the CREDIBLE-CR study is provided in the **Appendix (Table 5)**[7]

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

SHIONOGI

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.**

Table 7. Categorization of Deaths by the Adjudication Committee (Safety Population)[11]

Category and Subcategory	Cefiderocol N=101 n (%)	BAT N=49 n (%)
Overall mortality	34 (33.7)	9 (18.4)
1. Death not directly related to the Gram-negative infection for which the patient was randomized into the CREDIBLE-CR study	16 (15.8)	4 (8.2)
1A. Likely due to the patient's underlying comorbidity	10 (9.9)	2 (4.1)
1B. Related to infection other than original Gram-negative infection	4 (4.0)	2 (4.1)
1C. Due to drug-related AE	0	0
1D. Due to iatrogenic cause	0	0
Cases that did not have a unanimous subcategory vote in category 1	2 (2.0)	0
2. Death directly related to the Gram-negative infection for which the patient was randomized into the CREDIBLE-CR study	18 (17.8)	5 (10.2)
Yes. Infection-related death represents a failure of antibiotic treatment	16 (15.8)	4 (8.2)
No. Infection-related death does not represent a failure of antibiotic treatment	1 (1.0)	1 (2.0)
Cases that did not have a unanimous subcategory vote in category 2	1 (1.0)	0

Abbreviations: AE, adverse event; BAT, best-available therapy.

The list of individual patient profile deaths from both treatment groups from the CREDIBLE-CR study is provided in the Appendix (Table 5).[7]

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

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.**

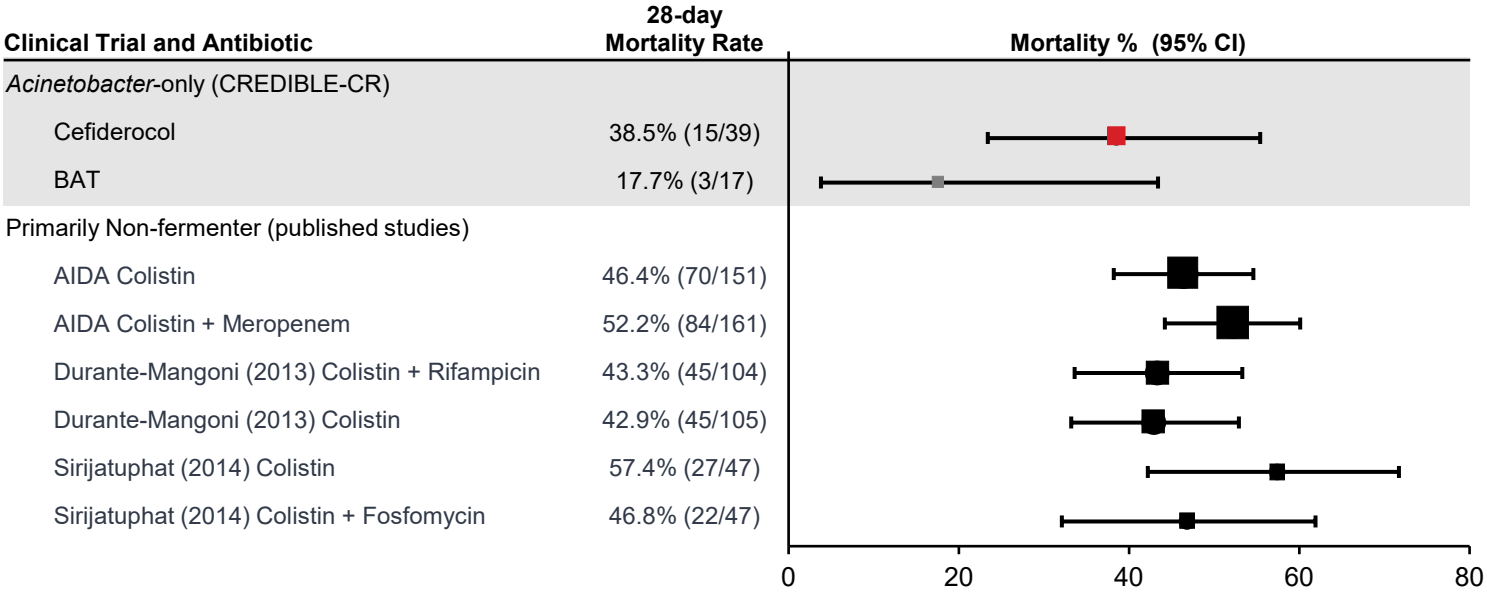
Phase 3 Clinical Studies

CREDIBLE-CR

Meta-analysis

- **Lodise et al (2022)** demonstrated that, in patients with *Acinetobacter* spp., ACM rates in CREDIBLE-CR were comparable to rates in other pathogen-focused studies (see **Figure 6)**

Figure 6. Day 28 All-Cause Mortality Rates in Carbapenem-Resistant *Acinetobacter*-Focused Studies[12]



Abbreviations: BAT, best available therapy; CI, confidence interval; CR-micro-ITT population, carbapenem-resistant microbiological intent-to treat population; CR GN, carbapenem-resistant Gram-negative.

*Primary analysis population was the CR-micro-ITT population (confirmed CR GN pathogen and ≥1 dose of study drug).

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

SHIONOGI

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.**

Phase 3 Clinical Trials

CREDIBLE-CR

Pharmacokinetic/Pharmacodynamic Analyses

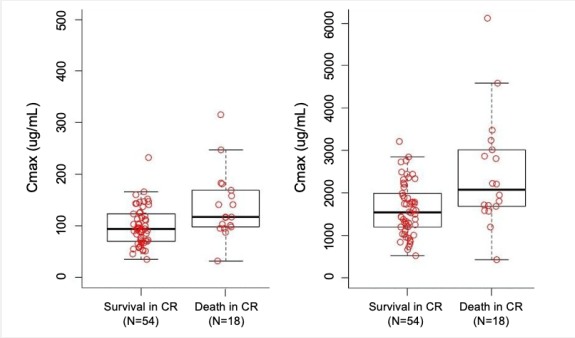
- A population PK model was developed using plasma concentration data of cefiderocol from various studies, including the Phase 2 (APEKS-cUTI) and Phase 3 (APEKS-NP, CREDIBLE-CR) clinical trials. Post-hoc estimates of maximum plasma concentration (C_{max}) and daily area under the curve (AUC) for patients in the CREDIBLE-CR study were calculated using the final population PK model[9,13]
- In CREDIBLE-CR, the geometric mean for cefiderocol C_{max} and daily AUC in death cases was 1.4-fold higher than survival cases (Table 8 and Figure 7)[13]

Table 8. Post-Hoc Estimates of Cefiderocol Exposure for Death Cases and Survival Cases in CREDIBLE-CR[12]

Vital Status	N	C_{max} (µg/mL)[a]	Daily AUC (µg·hr/mL)[a]
Survival	54	92.5 (39.4)	1495 (42.5)
Death	18	125 (52.2)	2130 (63.3)

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration.
[a]Geometric mean (CV%) of parameters estimated using the final model.

Figure 7. Box Plots of Post-Hoc Estimates for Cefiderocol Exposure in Death Cases and Survival Cases in CREDIBLE-CR[12]



Abbreviation: CR, Credible-CR study.

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

SHIONOGI

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.**

Table 8. Post-Hoc Estimates of Cefiderocol Exposure for Death Cases and Survival Cases in CREDIBLE-CR[13]

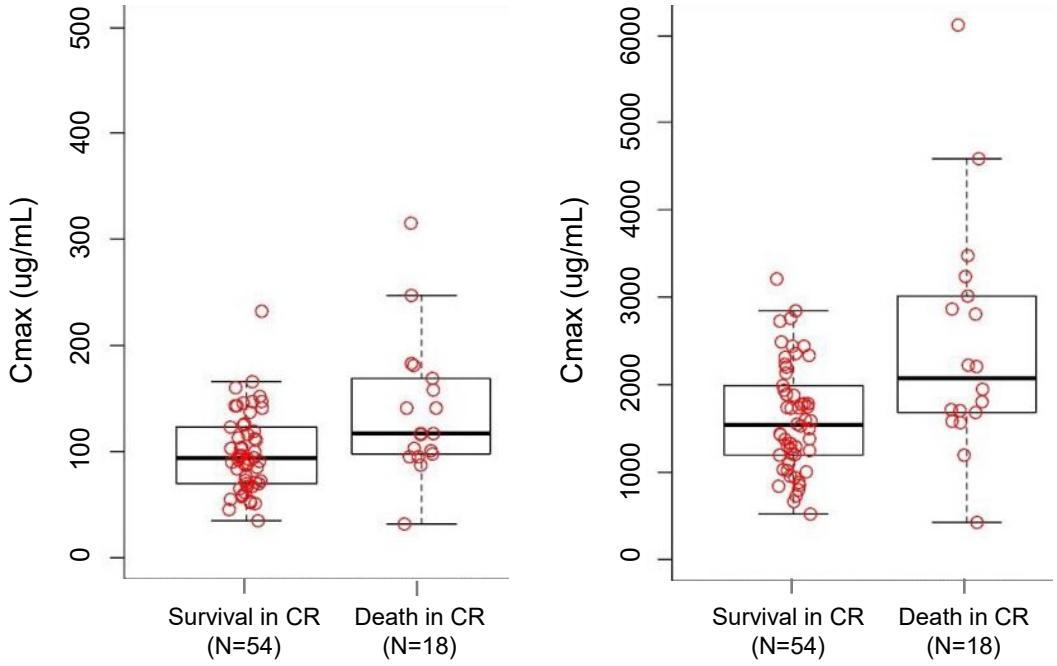
Vital Status	N	C_{max} (µg/mL)[a]	Daily AUC (µg·hr/mL)[a]
Survival	54	92.5 (39.4)	1495 (42.5)
Death	18	125 (52.2)	2130 (63.3)

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration.
[a]Geometric mean (CV%) of parameters estimated using the final model.

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

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.**

Figure 7. Box Plots of Post-Hoc Estimates for Cefiderocol Exposure in Death Cases and Survival Cases in CREDIBLE-CR[13]



Abbreviations: CR, Credible-CR study.

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

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.**

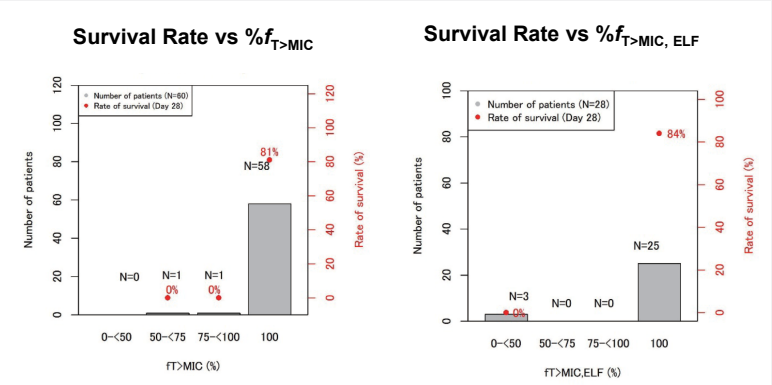
Phase 3 Clinical Trials

CREDIBLE-CR

***Pharmacokinetic/Pharmacodynamic Analyses* (Cont'd)**

- In addition, a population PK analysis evaluated the relationship of $\%f_{T>MIC}$ as well as $\%f_{T>MIC,\ ELF}$ with outcomes, including survival rate (at Day 28) in CREDIBLE-CR (see **Figure 8**)[10]
- In CREDIBLE-CR, there was no PK/PD relationship identified for vitality status.[8,9] In the cefiderocol group, the $\%f_{T>MIC}$ was 100% in 97% (58/60) of the patients. The $\%f_{T>MIC,\ ELF}$ was 100% in 89% (25/28) of the patients[8,9]

Figure 8. Relationship of $\%f_{T>MIC}$ (All Infection Sites) and $\%f_{T>MIC,\ ELF}$ (HABP, VABP, HCABP) with Survival Rate[10]

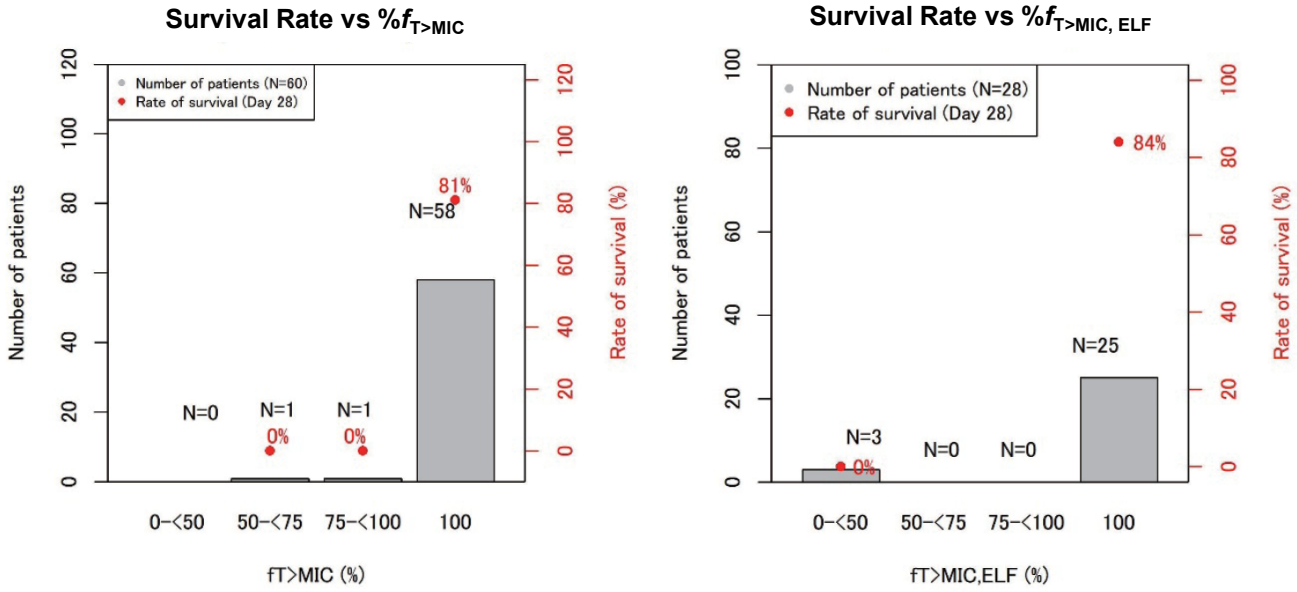


Abbreviations: ELF, epithelial lining fluid; $\%f_{T>MIC}$, percentage of time for which free drug concentration exceeded the minimum inhibitory concentration over the dosing interval $\%f_{T>MIC,\ ELF}$, percentage of time for which free drug concentration in ELF exceeded the minimum inhibitory concentration over the dosing interval; HABP, hospital-acquired bacterial pneumonia; HCABP, healthcare-associated bacterial pneumonia; VAPB, ventilator-associated bacterial pneumonia .

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

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.**

Figure 8. Relationship of $\%f_{T>MIC}$ (All Infection Sites) and $\%f_{T>MIC, ELF}$ (HABP, VABP, HCABP) with Survival Rate[10]



Abbreviations: ELF, epithelial lining fluid; $\%f_{T>MIC}$, percentage of time for which free drug concentration exceeded the minimum inhibitory concentration over the dosing interval $\%f_{T>MIC, ELF}$, percentage of time for which free drug concentration in ELF exceeded the minimum inhibitory concentration over the dosing interval; HABP, hospital-acquired bacterial pneumonia; HCABP, healthcare-associated bacterial pneumonia; VABP, ventilator-associated bacterial pneumonia .

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

SHIONOGI

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.**

Relevant Prescribing Information

Fetroja® is indicated in patients 18 years of age or older for the treatment of:[13]

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

Fetroja is contraindicated in patients with a known history of severe hypersensitivity to cefiderocol or other beta-lactam antibacterial drugs, or any other component of Fetroja.[13]

As described in **Warnings and Precautions section 5.1** of the **Fetroja Full Prescribing Information**[13]**:**

> An increase in all-cause mortality was observed in patients treated with Fetroja as compared to best available therapy (BAT) in a multinational, randomized, open-label trial in critically ill patients with carbapenem-resistant Gram-negative bacterial infections (NCT02714595). Patients with nosocomial pneumonia, bloodstream infections, sepsis, or cUTI were included in the trial. BAT regimens varied according to local practices and consisted of 1 to 3 antibacterial drugs with activity against Gram-negative bacteria. Most of the BAT regimens contained colistin.
>
> The increase in all-cause mortality occurred in patients treated for nosocomial pneumonia, bloodstream infections, or sepsis. The 28-Day all-cause mortality was higher in patients treated with Fetroja than in patients treated with BAT [25/101 (24.8%) vs. 9/49 (18.4%), treatment difference 6.4%, 95% CI (-8.6, 19.2)]. All-cause mortality remained higher in patients treated with Fetroja than in patients treated with BAT through Day 49 [34/101 (33.7%) vs. 10/49 (20.4%), treatment difference 13.3%, 95% CI (-2.5, 26.9)]. Generally, deaths were in patients with infections caused by Gram-negative organisms, including non-fermenters such as *Acinetobacter baumannii* complex, *Stenotrophomonas maltophilia*, and *Pseudomonas aeruginosa*, and were the result of worsening or complications of infection, or underlying comorbidities. The cause of the increase in mortality has not been established.
>
> Closely monitor the clinical response to therapy in patients with cUTI and HABP/VABP.

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

SHIONOGI

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.**

Abbreviations

ACM	all-cause mortality	EOT	end of treatment
AE	adverse event	F	female
AKI	acute kidney injury	FDA	Food and Drug Administration
APACHE II	Acute Physiology and Chronic Health Evaluation II	g	gram
ARC	augmented renal clearance	GI	gastrointestinal
ARDS	acute respiratory distress syndrome	h	hour
AUC	area under the concentration-time curve	HABP	hospital-acquired bacterial pneumonia
AUP	acute uncomplicated pyelonephritis	HCABP	healthcare-associated bacterial pneumonia
BAT	best available therapy	ICU	intensive care unit
BSI	bloodstream infection	ID	identification number
CCI	Charlston Comorbidity Index	IV	Intravenous
CFU	colony-forming units	m	male
CI	confidence interval	MDR	multidrug-resistant
C_{max}	maximum plasma concentration	MIC	minimum inhibitory concentration
COPD	chronic obstructive pulmonary disease	Micro-ITT	microbiological intent-to-treat
CP	Child-Pugh	mITT	modified intent-to-treat
CPIS	Clinical Pulmonary Infection Score	NA	not available
CR	carbapenem-resistant	NYHA	New York Heart Association
CrCL	creatinine clearance	OR	odds ratio
CR GN	carbapenem-resistant Gram-negative	PD	pharmacodynamic
CRRT	continuous renal replacement therapy	PK	pharmacokinetics
CR-micro-ITT	carbapenem-resistant microbiological intent-to-treat	RRT	renal replacement therapy
CT	computed tomography	SAE	serious adverse event
cUTI	complicated urinary tract infection	SOFA	Sequential Organ Failure Assessment
DNR	do not resuscitate	spp	species
Dx	diagnosis	TEAE	test of cure
EA	early assessment	TOC	test of cure
EF	ejection fraction	Tx	treatment
ELF	epithelial lining fluid	UTI	urinary tract infection
EMA	European Medecines Agency	VABP	ventilator-associated bacterial pneumonia
EOS	end of study	VAP	ventilator-associated pneumonia

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

SHIONOGI

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.**

References

1. Portsmouth S, van Veenuyzen 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. Data on File 1. Shionogi Inc.
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 study. *Lancet Infect Dis*. 2021;21(2):213-225. doi:10.1016/S1473-3099(20)30731-3
4. Data on File 3. Shionogi Inc.
5. 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 study. *Lancet Infect Dis*. 2021; Suppl 1. 21(2):213-225. doi:10.1016/S1473-3099(20)30731-3
6. 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, multicenter, pathogen-focused, descriptive, phase 3 trial. *Lancet Infect Dis*. 2021;21(2): 226-240. doi:10.1016/S1473-3099(20)30796-9
7. 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, multicenter, pathogen-focused, descriptive, phase 3 trial. *Lancet Infect Dis*. 2021. Suppl 1. 21(2): 226-240. doi:10.1016/S1473-3099(20)30796-9

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

SHIONOGI

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.**

References (Cont'd)

8. Kawaguchi N, Katsube T, Echols R, Wajima T, Nicolau DP. Intrapulmonary pharmacokinetic modeling and simulation of cefidercol, a parenteral siderophore cephalosporin, in patients with pneumonia and healthy subjects. *J Clin Pharmacol*. 2022;62(5):670-680. doi:10.1002/jcph.1986
9. Kawaguchi N, Katsube T, Echols R, Wajima T. 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
10. Katsube T, Kawaguchi N, Matsunaga Y, et al. Pharmacokinetic/pharmacodynamic analyses of cefiderocol in critically ill patients. Poster presented at: ID Week 2020. October 21-25, 2020. Virtual Conference, Online.
11. Data on File 4. Shionogi Inc.
12. Lodise TP, Bassetti M, Ferrer R, Naas T, Niki Y, Paterson DL. All-cause mortality rates in adults with carbapenem-resistant Gram-negative bacterial infections: a comprehensive review of pathogen-focused, prospective, randomized, interventional clinical studies. *Expert Rev Anti Infect Ther*. 2022;20(5):707-719. doi:10.1080/14787210.2022.2020099
13. Data on File 29. Shionogi Inc.
14. Fetroja® (cefiderocol) for injection, for intravenous use [Prescribing Information]. Shionogi Inc.

ENCLOSURE

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

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

SHIONOGI

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.**

Appendix

Appendix Table 1. Day 28 All-Cause Mortality by Subgroup in APEKS-NP (mITT Population)[5]

			Treatment Comparison	
Subgroup	**Cefiderocol (N=145) n/N' (%)**	**Meropenem (N=147) n/N' (%)**	**Difference (%)**	**95% CI**
Overall	30/143 (21)	30/146 (21)	0.4	(-8.9, 9.8)
Clinical Diagnosis				
HABP	13/59 (22)	15/60 (25)	-3.0	(-18.2, 12.3)
VABP	13/57 (23)	14/63 (22)	0.6	(-14.4, 15.6)
HCABP	4/27 (15)	1/23 (4)	10.5	(-5.3, 26.2)
APACHE II score				
≤15	14/74 (19)	10/76 (13)	5.8	(-6.0, 17.5)
16 – 19	7/31 (23)	7/25 (28)	-5.4	(-28.4, 17.5)
≥20	9/38 (24)	13/45 (29)	-5.2	(-24.1, 13.7)
ICU at Randomization				
Yes	26/100 (26)	26/96 (27)	-1.1	(-13.4, 11.3)
No	4/43 (9)	4/50 (8)	1.3	(-10.2, 12.8)
Ventilation Status at Randomization				
Yes	24/87 (28)	22/85 (26)	1.7	(-11.5, 14.9)
No	6/56 (11)	8/61 (13)	-2.4	(-14.1, 9.3)
Top 5 baseline pathogens[a]				
Klebsiella pneumoniae	11/48 (23)	12/44 (27)	-4.4	(-22.1, 13.4)
Pseudomonas aeruginosa	2/24 (8)	6/23 (26)	-17.8	(-38.8, 3.3)
Acinetobacter baumannii	7/22 (32)	6/24 (25)	6.8	(-19.2, 32.9)
Escherichia coli	6/19 (32)	4/22 (18)	13.4	(-13.0, 39.8)
Enterobacter cloacae	0/7 (0)	2/8 (25)	-25.0	NA

N' is the number of patients within the category with known survival status. The treatment difference (cefiderocol minus meropenem) is the estimate of the difference in the all-cause mortality rate at Day 28 between the two treatment arms. The 95% CI (two-sided) is calculated using a normal approximation to the difference between two binomial proportions (Wald method).

The widths of the CIs were not adjusted for multiplicity and therefore cannot be used to infer treatment effects. For subgroups with a frequency less than 10 in any treatment arm, the 95% CIs are not presented.

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; HABP, hospital-acquired bacterial pneumonia; HCABP, healthcare-associated bacterial pneumonia; ICU, intensive care unit; mITT, modified intent-to-treat; VABP, ventilator-associated bacterial pneumonia.

[a]Post-hoc subgroup category

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

SHIONOGI

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.**

Appendix (Cont'd)

Appendix Table 2. End of study All-Cause Mortality by Subgroup in APEKS-NP (mITT Population)[4]

			Treatment Comparison[a]	
Subgroup	**Cefiderocol (N=145) n/N' (%)**	**Meropenem (N=147) n/N' (%)**	**Difference (%)**	**95% CI[b]**
Overall	38/142 (26.8)	34/146 (23.3)	3.5	(-6.5, 13.5)
Clinical Diagnosis				
HABP	18/58 (31.0)	15/60 (25.0)	6.0	(-10.1, 22.2)
VABP	15/57 (26.3)	17/63 (27.0)	-0.7	(-16.5, 15.2)
HCABP	5/27 (18.5)	2/23 (8.7)	9.8	(-8.8, 28.5)
APACHE II score				
≤15	16/73 (21.9)	13/76 (17.1)	4.8	(-7.9, 17.5)
16 – 19	10/31 (32.3)	7/25 (28.0)	4.3	(-19.8, 28.4)
≥20	12/38 (31.6)	14/45 (31.1)	0.5	(-19.6, 20.5)
ICU admission				
Yes	33/100 (33.0)	29/96 (30.2)	2.8	(-10.2, 15.8)
No	5/42 (11.9)	5/50 (10.0)	1.9	(-10.9, 14.8)
Ventilation Status at Randomization				
Yes	29/87 (33.3)	25/85 (29.4)	3.9	(-9.9, 17.8)
No	9/55 (16.4)	9/61 (14.8)	1.6	(-11.6, 14.8)
Top 5 baseline pathogens[c,d]				
Klebsiella pneumoniae	15/48 (31.3)	14/44 (31.8)	-0.6	(-19.6, 18.4)
Pseudomonas aeruginosa	4/24 (16.7)	6/23 (26.1)	-9.4	(-32.8, 13.9)
Acinetobacter baumannii	8/22 (36.4)	7/24 (29.2)	7.2	(-19.9, 34.3)
Escherichia coli	6/19 (31.6)	4/22 (18.2)	13.4	(-13.0, 39.8)
Enterobacter cloacae	0/7 (0.0)	2/8 (25.0)	-25.0	

Percentages for overall are calculated as the number of subjects who died by any causes at or before EOS divided by the total number of subjects in the analysis populations with known survival status at EOS. Percentages in the subgroups are calculated as the number of subjects who died by any causes at or before EOS since first infusion of study drug for the given subgroup divided by N', i.e. the analysis populations in that subgroup with known survival status at EOS.

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; EOS, end-of-study; HABP, hospital-acquired bacterial pneumonia; HCABP, healthcare-associated bacterial pneumonia; ICU, intensive care unit; mITT, modified intent-to-treat; VABP, ventilator-associated bacterial pneumonia.

[a]Treatment difference (cefiderocol minus meropenem) is the estimate of the difference in the all-cause mortality rate at EOS between the 2 treatment arms.

[b]The 95% CI (2-sided) was calculated using a normal approximation to the difference between 2 binomial proportions (Wald method). For subgroups with number of subjects < 10 in any treatment arm, the 95% CIs are not presented.

[c]Top 5 baseline pathogens based on frequency across both treatment groups in the analysis population.

[d]Post hoc subgroup category.

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

SHIONOGI

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.**

Appendix (Cont'd)

Appendix Table 3. Logistic Regression Model for Day 28 All-Cause Mortality in CREDIBLE-CR (Safety Population)[7]

Covariate	Adjusted Odds Ratio for Treatment (95% CI)	Unadjusted Odds Ratio for Treatment (95% CI)	Percent Change of Log OR
Age (continuous)	1.46 [0.61, 3.44]	1.46 [0.62, 3.43]	-1.20%
Age, years (≥65 or <65)	1.30 [0.54, 3.10]	1.46 [0.62, 3.43]	-31.40%
Age, years (≥75 or <75)	1.47 [0.62, 3.46]	1.46 [0.62, 3.43]	1.10%
Sex	1.45 [0.62, 3.41]	1.46 [0.62, 3.43]	-2.10%
Clinical diagnosis	1.49 [0.63, 3.52]	1.46 [0.62, 3.43]	5.40%
APACHE (continuous)	1.49 [0.62, 3.57]	1.46 [0.62, 3.43]	4.70%
APACHE (≥16, ≤15)	1.46 [0.62, 3.44]	1.46 [0.62, 3.43]	-0.10%
SOFA (continuous)	1.53 [0.62, 3.74]	1.48 [0.63, 3.48]	7.50%
SOFA (≥10, ≤9)	1.43 [0.60, 3.40]	1.48 [0.63, 3.48]	-8.70%
Region	1.51 [0.63, 3.61]	1.46 [0.62, 3.43]	7.80%
Race	1.50 [0.63, 3.57]	1.46 [0.62, 3.43]	7.60%
Weight (continuous)	1.45 [0.62, 3.43]	1.46 [0.62, 3.43]	-1.40%
Weight (<40, ≥40)	1.48 [0.63, 3.48]	1.46 [0.62, 3.43]	3.20%
Length of hospitalization before randomization	1.46 [0.62, 3.42]	1.46 [0.62, 3.43]	-1.20%
Length of infection before randomization	1.45 [0.61, 3.41]	1.46 [0.62, 3.43]	-2.50%
Severity	1.38 [0.58, 3.27]	1.46 [0.62, 3.43]	-15.50%
CCI (continuous)	1.47 [0.60, 3.60]	1.46 [0.62, 3.43]	2.10%
CCI (≥6, ≤5)	1.55 [0.64, 3.75]	1.46 [0.62, 3.43]	16.10%
CrCL (Continuous)	1.45 [0.62, 3.41]	1.46 [0.62, 3.43]	-2.10%
CrCL (<50, or ≥50)	1.39 [0.59, 3.29]	1.46 [0.62, 3.43]	-12.80%
RRT	1.35 [0.57, 3.20]	1.46 [0.62, 3.43]	-21.80%
Renal Disease	1.50 [0.63, 3.55]	1.46 [0.62, 3.43]	6.00%
Cerebrovascular disease	1.44 [0.61, 3.39]	1.46 [0.62, 3.43]	-3.60%
Moderate or severe liver disease	1.42 [0.60, 3.38]	1.46 [0.62, 3.43]	-7.80%
Myocardial infarction	1.35 [0.57, 3.19]	1.46 [0.62, 3.43]	-20.50%
Cancer	1.49 [0.63, 3.51]	1.46 [0.62, 3.43]	5.10%
Metastatic solid tumor	1.42 [0.60, 3.36]	1.46 [0.62, 3.43]	-7.00%
Surgery	1.45 [0.62, 3.43]	1.46 [0.62, 3.43]	-1.70%
Surgery or Trauma	1.55 [0.65, 3.69]	1.46 [0.62, 3.43]	15.80%
Cardiac arrest	1.45 [0.62, 3.42]	1.46 [0.62, 3.43]	-1.70%
Dementia and Parkinson's disease	1.49 [0.63, 3.51]	1.46 [0.62, 3.43]	4.60%
COPD	1.44 [0.60, 3.46]	1.46 [0.62, 3.43]	-3.80%
Diabetes	1.46 [0.62, 3.43]	1.46 [0.62, 3.43]	0.00%
Diabetes and chronic complications	1.39 [0.59, 3.28]	1.46 [0.62, 3.43]	-13.50%
Congestive heart failure	1.51 [0.64, 3.58]	1.46 [0.62, 3.43]	8.80%
Trauma	1.63 [0.69, 3.85]	1.46 [0.62, 3.43]	28.20%
Ventilation	1.57 [0.65, 3.78]	1.46 [0.62, 3.43]	18.20%
Immunocompromised	1.54 [0.65, 3.64]	1.46 [0.62, 3.43]	13.60%
Past vasopressor use	1.52 [0.63, 3.65]	1.46 [0.62, 3.43]	10.10%
ARDS	1.45 [0.61, 3.40]	1.46 [0.62, 3.43]	-2.80%
ICU at randomization	1.35 [0.57, 3.20]	1.46 [0.62, 3.43]	-21.30%
Shock	1.35 [0.56, 3.23]	1.46 [0.62, 3.43]	-21.50%

Cardiac arrest, shock, myocardial infarction, cerebrovascular disease, surgery, trauma, surgery, or trauma are included if it happened within 31 days before randomization.

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; CCI, Charlson Comorbidity Index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CrCL, creatinine clearance; ICU, intensive care unit; OR, odds ratio; RRT, renal replacement therapy; SOFA, Sequential Organ Failure Assessment.

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

SHIONOGI

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.**

Appendix (Cont'd)

Appendix Table 4. Day 49 All-Cause Mortality Cases and Baseline Characteristics in the Safety Population[11]

	Cefiderocol (N=101) n/N' (%)	BAT (N=49) n/N' (%)
Overall	34/101 (33.7%)	10/49 (20.4)
Sex		
Male	23/66 (34.8)	8/35 (22.9)
Female	11/35 (31.4)	2/14 (14.3)
Age, years		
<65	10/37 (27.0)	3/27 (11.1)
≥65	24/64 (37.5)	7/22 (31.8)
Race		
White	18/63 (28.6)	7/32 (21.9)
Asian	14/29 (48.3)	3/14 (21.4)
Other	2/9 (22.2)	0/3 (0)
Baseline CR pathogen group		
Enterobacteriaceae	7/29 (24.1)	3/11 (27.3)
Nonfermenters	22/49 (44.9)	6/25 (24)
Mixed	1/2 (50)	0/2 (0)
Total APACHE II score group		
≤15	13/55 (23.6)	5/27 (18.5)
≥16	21/46 (45.7)	5/22 (22.7)
Ventilation at Baseline		
Yes	24/50 (48)	8/26 (30.8)
No	10/51 (19.6)	2/23 (8.7)
Intensive care unit at Baseline		
Yes	22/57 (38.6)	6/21 (28.6)
No	12/44 (27.3)	4/28 (14.3)
Iron at Baseline		
Low	26/77 (33.8)	7/28 (25.0)
Normal	5/14 (35.7)	1/15 (6.7)
Total CCI at Baseline		
≤5	10/52 (19.2)	2/24 (8.3)
≥6	24/49 (49.0)	8/25 (32.0)
Severity		
Mild	1/5 (20.0)	0/4 (0.0)
Moderate	14/41 (34.1)	3/22 (13.6)
Severe	19/55 (34.5)	7/23 (30.4)
SOFA		
≤6	16/67 (23.9)	2/32 (6.3)
≥7	18/33 (54.5)	8/17 (47.1)
CPIS		
≤5	13/30 (43.3)	4/16 (25.0)
≥6	5/14 (35.7)	0/5 (0.0)
Creatinine clearance renal grading group		
≥120 mL/min (ARC)	3/20 (15.0)	2/12 (16.7)
>80 mL to <120 mL/min (normal)	4/18 (22.2)	1/10 (10.0)
>50 mL to 80 mL/min (mild)	9/20 (45.0)	3/12 (25.0)
30 mL/min to 50 mL/min (moderate)	10/23 (43.5)	2/8 (25.0)
<30 mL/min (severe)	8/20 (40.0)	2/7 (28.6)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ARC, augmented renal clearance: CCI, Charlson Comorbidity Index; CPIS, Clinical Pulmonary Infection Score: CR, carbapenem-resistant; SOFA, Sequential Organ Failure Assessment.

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

SHIONOGI

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.**

Appendix (Cont'd)

Appendix Table 5. Detailed Listing of Deaths up to End of Study in CREDIBLE-CR (Safety Population)[7]

Adjudication Committee Category[a]	Age/ Sex	Dx	Comorbid Conditions	Pathogen/MIC (µg/mL)	ICU/ Shock (Y/N)	Clinical Outcome EOT/TOC	Microbiological Outcome EOT/TOC	MIC Increase (Y/N)	Cause of Death	Study Day of Death/ Time to Death Since Last Dose (Days)	Sepsis as cause of Death (Y/N)
Cefiderocol Group											
2	64/ F	BSI	Chronic respiratory failure, bronchopulmonary aspergillosis, allergic tracheobronchitis	*A. baumannii*/ 0.12	Y/N	Clinical failure/ Clinical failure	Indeterminate/ Indeterminate	N	Septic shock	11/2	Y
2	29/ F	BSI	Metastatic rectal cancer (liver, lungs, brain, arm), malnutrition, acute kidney injury, dyspnea	*A. baumannii*/ 0.06	Y/N	Clinical failure/ Clinical failure	Indeterminate/ Indeterminate	N	Septic shock (and cardiac arrest SAE)	6/0	Y
2	64/ M	VAP	Peripheral vascular disease (graft surgery), cardiac arrest, acute renal failure	*A. baumannii*/ 0.25	Y/N	Indeterminate/ Indeterminate	Indeterminate/ Indeterminate	N	Septic shock	4/0	Y
2	69/ M	VAP	Pulmonary hemorrhage (iatrogenic), hemothorax, septic shock	*A. baumannii*/ 1.0	Y/Y	Clinical failure/ Clinical failure	Indeterminate/ Indeterminate	Y	Non-resolved sepsis	9/0	Y
2	45/ M	VAP	Severe burns on face and body (petrol bomb), smoke inhalation, acute respiratory failure, acute renal failure	*A. baumannii*/ 0.25	Y/N	Clinical failure/ Clinical failure	Persistence/ Persistence	Y	Septic shock	39/20	Y

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

SHIONOGI

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.**

Appendix (Cont'd)

Appendix Table 5. Detailed Listing of Deaths up to End of Study in CREDIBLE-CR (Safety Population)[7]

Adjudication Committee Category[a]	Age/ Sex	Dx	Comorbid Conditions	Pathogen/MIC (µg/mL)	ICU/ Shock (Y/N)	Clinical Outcome EOT/TOC	Microbiological Outcome EOT/TOC	MIC Increase (Y/N)	Cause of Death	Study Day of Death/ Time to Death Since Last Dose (Days)	Sepsis as cause of Death (Y/N)
Cefiderocol Group											
2	78/ M	HAP	Aortic aneurysm rupture, abnormal liver function, acute renal failure	*A. baumannii, E. coli, K. pneumoniae*/ 0.5, 0.6, and 0.25	Y/N	Clinical cure/ Clinical failure	Persistence/ Persistence	Y	Septic shock – multiple organ failure	31/17	Y
1-A	66/ F	VAP	Ocular lymphoma, liver cirrhosis, bronchiectasis, respiratory failure, AKI	*A. baumannii, P. aeruginosa*/ 2.0 and 0.12	Y/Y	Clinical cure/ Clinical failure	Persistence/ Persistence	Y	Septic shock	45/30	Y
2	65/ M	VAP	Lung adenocarcinoma, esophagus perforation, mediastinitis, septic shock	*A. baumannii, P. aeruginosa*/ 0.5 and 1.0	N/N	Clinical failure/ Clinical failure	Persistence/ Indeterminate	Y	Sepsis	13/2	Y
1-B	78/ M	VAP	Progressive dyspnea, non-small cell lung cancer, brain/liver metastases, COPD	*A. baumannii, S. maltophilia*/ 1.0 and 0.25	Y/Y	Clinical failure/ Clinical failure	Persistence/ Indeterminate	N	Hypoxic respiratory failure, septic shock	19/9	Y
2	47/ M	VAP	Hepatic cirrhosis, spontaneous bacterial peritonitis, upper GI hemorrhage, bacteremia, fungaemia, septic shock, hepatic encephalopathy, metabolic acidosis	*A. nosocomialis, P. aeruginosa, S. maltophilia, Chryseobacterium indologenes*/ 64.0, 0.5, 0.12, and 0.06	Y/Y	Clinical failure/ Indeterminate	Persistence/ Indeterminate	Y	Worsening liver failure, worsening septic shock (DNR palliative extubation)	8/0	Y

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

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.**

Appendix (Cont'd)

Appendix Table 5. Detailed Listing of Deaths up to End of Study in CREDIBLE-CR (Safety Population)[7]

Adjudication Committee Category[a]	Age/ Sex	Dx	Comorbid Conditions	Pathogen/MIC (µg/mL)	ICU/ Shock (Y/N)	Clinical Outcome EOT/TOC	Microbiological Outcome EOT/TOC	MIC Increase (Y/N)	Cause of Death	Study Day of Death/ Time to Death Since Last Dose (Days)	Sepsis as cause of Death (Y/N)
Cefiderocol Group											
1-B	47/ F	BSI	Cholangiocarcinom, gall bladder cancer, bacteremia, disseminated intravascular coagulation	*K. pneumoniae*/ 1.0	N/N	Indeterminate/ Indeterminate	Indeterminate/ Indeterminate	N	Septic shock	9/0	Y
1	77/ M	BSI	Hemorrhage intracranial, HAP, septic shock	*K. pneumoniae*/ 1.0	N/Y	Clinical cure/ Clinical cure	Eradication/ Eradication	N	Sepsis	36/28	Y
2	78/ F	cUTI	Myocardial infarction, cholecystitis, ARDS, anoxic brain damage	*P. aeruginosa*/ 1.0	N/N	Indeterminate/ Indeterminate	Indeterminate/ Indeterminate	N	Septic shock	2/0	Y
1-A	24/ F	BSI	Trauma with head, lung, and abdominal injuries; traumatic skull fracture; acute respiratory failure; traumatic liver injury; cerebral hemorrhage; bacteremia	*A. baumannii*/ 0.12	Y/N	Clinical failure/ Clinical failure	Indeterminate/ Indeterminate	N	Multiple trauma and skull fracture (declared brain dead, life support withdrawn)	6/4	N
1-A	84/ M	BSI	Congestive heart failure (NYHA: 4; EF: 15-20%), suspected malignant mesothelioma per CT, COPD, pneumonia, acute on chronic renal failure	*A. baumannii*/ NA	N/Y	Clinical cure/ Clinical cure	Eradication/ Eradication	NA	Congestive heart failure exacerbation	35/14	N

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

SHIONOGI

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.**

Appendix (Cont'd)

Appendix Table 5. Detailed Listing of Deaths up to End of Study in CREDIBLE-CR (Safety Population)[7]

Adjudication Committee Category[a]	Age/ Sex	Dx	Comorbid Conditions	Pathogen/MIC (µg/mL)	ICU/ Shock (Y/N)	Clinical Outcome EOT/TOC	Microbiological Outcome EOT/TOC	MIC Increase (Y/N)	Cause of Death	Study Day of Death/ Time to Death Since Last Dose (Days)	Sepsis as cause of Death (Y/N)
Cefiderocol Group											
1-B	70/ F	BSI	Hyperlipidemia, diabetes mellitus, renal failure, toxic epidermal necrolysis, sepsis	*A. baumannii*/ 0.25	Y/N	Clinical cure/ Clinical failure	Eradication/ Indeterminate	N	Cardiac arrest	19/5	N
1-A	86/ F	HAP	Chronic kidney disease, urosepsis, asystole, HAP, continuous renal replacement therapy	*A. baumannii*/ 0.06	Y/N	Indeterminate/ Indeterminate	Indeterminate/ Indeterminate	N	AKI aggravation (CRRT stopped due to financial reasons)	5/0	N
2	65/ M	HAP	Leukocytoclastic vasculitis, necrotic skin ulcers, septic shock, respiratory failure, renal failure	*A. baumannii*/ ≤0.03	Y/Y	Clinical failure/ Clinical failure	Persistence/ Indeterminate	NA	Deterioration of *Acinetobacter* pneumonia	14/0	N
2	71/ M	HAP	Parkinsonism, pseudomembranous ileus, septic shock, pulmonary edema	*A. baumannii*/ 0.25	Y/Y	Clinical failure/ Clinical failure	Indeterminate/ Indeterminate	N	Pneumonia	3/0	N
2	73/ M	HAP	Diabetes mellitus, pneumoconiosis, acute intestinal infarction	*A. baumannii*/ 0.12	Y/N	Clinical cure/ Clinical failure	Eradication/ Persistence	N	Pneumonia	37/23	N
1-A	82/ M	Sepsis	Gangrenous cholecystitis, pneumonia, septic shock, AKI	*A. baumannii*/ 2.0	N/N	Clinical cure/ Clinical cure	Eradication/ Persistence	Y	Obstructive airways disorder	27/18	N

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

SHIONOGI

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.**

Appendix (Cont'd)

Appendix Table 5. Detailed Listing of Deaths up to End of Study in CREDIBLE-CR (Safety Population)[7]

Adjudication Committee Category[a]	Age/ Sex	Dx	Comorbid Conditions	Pathogen/MIC (µg/mL)	ICU/ Shock (Y/N)	Clinical Outcome EOT/TOC	Microbiological Outcome EOT/TOC	MIC Increase (Y/N)	Cause of Death	Study Day of Death/ Time to Death Since Last Dose (Days)	Sepsis as cause of Death (Y/N)
Cefiderocol Group											
2	54/ M	VAP	Lung carcinoma (stage IIIB), pneumothorax, deep upper limb vein thrombosis, brain metastases, bilateral pneumonia, septic shock	*A. baumannii*/ 16.0	Y/Y	Clinical failure/ Clinical failure	Persistence/ Indeterminate	N	Pneumonia, bacteremia	18/4	N
2	80/ F	HAP	Upper GI bleeding, urinary tract infection, HAP	*A. baumannii*, *P. aeruginosa*, *K. pneumoniae*/ 1.0, 0.25, and 0.25	N/N	Indeterminate/ Clinical failure	Persistence/ Indeterminate	Y	Pneumonia aggravated (mechanical ventilation refused by family)	13/1	N
2	71/ F	VAP	Lung adenocarcinoma (stage IV, lobectomy), ARDS, septic shock	*A. nosocomialis*/ 0.5	Y/Y	Clinical failure/ Clinical failure	Indeterminate/ Indeterminate	N	Multiple organ failure, aggravation of VAP	3/0	N
2	68/ M	HAP	Adenocarcinoma of the esophagus metastatic, pulmonary emphysema, hypertrophic cardiomyopathy, chronic kidney disease	*E. cloacae*/ 16.0	Y/N	Clinical failure/ Clinical failure	Indeterminate/ Indeterminate	N	Deterioration of respiratory function (limitation of care decided by family and medical staff)	12/6	N
1-A	46/ M	HAP	Type 2 diabetes mellitus, hepatic failure, nosocomial pneumonia, septic shock	*K. oxytoca*, *K. pneumoniae*/ 0.06 and 0.25	Y/Y	Clinical failure/ Clinical cure	Persistence/ Indeterminate	N	Refractory hepatic failure	35/26	N

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

SHIONOGI

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.**

Appendix (Cont'd)

Appendix Table 5. Detailed Listing of Deaths up to End of Study in CREDIBLE-CR (Safety Population)[7]

Adjudication Committee Category[a]	Age/ Sex	Dx	Comorbid Conditions	Pathogen/MIC (µg/mL)	ICU/ Shock (Y/N)	Clinical Outcome EOT/TOC	Microbiological Outcome EOT/TOC	MIC Increase (Y/N)	Cause of Death	Study Day of Death/ Time to Death Since Last Dose (Days)	Sepsis as cause of Death (Y/N)
Cefiderocol Group											
1-A	79/ M	BSI	Radical cystectomy for bladder, intestinal perforation, sepsis	*K. pneumoniae*/ 2.0	N/N	Clinical failure/ Clinical failure	Indeterminate/ Indeterminate	N	Cardiac arrest	3/0	N
1-B	70/ M	BSI	Transitional cell carcinoma of bladder, urosepsis, AKI, mechanical ventilation	*K. pneumoniae*/ 2.0	Y/Y	Clinical failure/ Clinical failure	Eradication/ Indeterminate	N	Bacteremia, bladder cancer	48/26	N
2	92/ M	cUTI	COPD, ischemic cardiomyopathy, transient ischemic attack	*K. pneumoniae*/ 1.0	N/N	Indeterminate/ Indeterminate	Indeterminate/ Indeterminate	N	Refractory shock of undetermined origin (family asked for no intensive care admission)	4/0	N
1-A	83/ M	cUTI	Diabetes mellitus, chronic renal failure, arterial hypertension	None/NA	N/N	Indeterminate/ Indeterminate	NA	NA	Progression of renal failure (study participation revoked, and minimal intervention requested)	7/2	N
1	77/ M	cUTI	Diabetes mellitus, cerebrovascular accident, neurogenic bladder	None/NA	N/N	Clinical cure/ Indeterminate	NA	NA	Pneumonia aspiration	25/13	N
1-A	54/ M	Sepsis	Epilepsy, spinal cord injury, paraplegia, craniocerebral injury	*P. aeruginosa*/ 0.5	N/N	Clinical cure/ Clinical cure	Indeterminate/ Indeterminate	N	Cardio-respiratory arrest that led to sudden death	43/21	N

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

SHIONOGI

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.**

Appendix (Cont'd)

Appendix Table 5. Detailed Listing of Deaths up to End of Study in CREDIBLE-CR (Safety Population)[7]

Adjudication Committee Category	Age/ Sex	Dx	Comorbid Conditions	Pathogen/MIC (µg/mL)	ICU/ Shock (Y/N)	Clinical Outcome EOT/TOC	Microbiological Outcome EOT/TOC	MIC Increase (Y/N)	Cause of Death	Study Day of Death/ Time to Death Since Last Dose (Days)	Sepsis as cause of Death (Y/N)
Cefiderocol Group											
1-A	70/ M	VAP	Diabetes mellitus, ischemic cardiomyopathy, COPD, cardiac failure, respiratory failure	*S. maltophilia*/ <0.03	Y/Y	Clinical cure/ Indeterminate	Eradication/ Indeterminate	N	Cardiogenic shock secondary to myocardial infarct	13/2	N
2	84/ F	VAP	Lacunar infarction, pneumonia, infected bed sore, AKI	*S. maltophilia*/ 0.06	Y/N	Clinical failure/ Clinical failure	Persistence/ Indeterminate	Y	Cardiac Arrest	15/1	N
BAT Group											
1-B	77/ M	BSI	Hemorrhagic shock from hemothorax, pneumonia, respiratory failure, acute renal failure, bacteremia	*A. baumannii*/ colistin: >8.0; ampicillin-sulbactam: NA	Y/N	Clinical failure/ Clinical failure	Indeterminate/ Indeterminate	N	Multiple organ dysfunction syndrome due to septic shock caused by *P. aeruginosa* BSI	10/8	Y
2	73/ F	BSI	Altered state of consciousness, AKI, acute liver failure, septic shock	*K. pneumoniae*/ colistin: ≤0.5; fosfomycin: NA	Y/Y	Clinical failure/ Clinical failure	Indeterminate/ Persistence	Y	Refractory septic shock	17/7	Y
2	62/ M	cUTI	Liver cirrhosis, ureterolithiasis, hydronephrosis, septic shock	*P. aeruginosa*/ colistin: 1.0	Y/Y	Clinical failure/ Clinical failure	Indeterminate/ Indeterminate	N	Septic shock aggravated, central vein catheter-related BSI	6/0	Y
2	84/ F	VAP	Hemodialysis, pneumonia, acute respiratory failure, decubitus ulcers	*K. pneumoniae*/ colistin: ≤0.5; tigecycline: 1.0	Y/N	Clinical failure/ Clinical failure	Persistence/ Persistence	Y	Septicemia with chronic renal failure, cardiopulmonary arrest that developed during sepsis	24/12	Y

Fetroja® - Mortality in Phase 2 and Phase 3 Clinical Studies

SHIONOGI

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.**

Appendix (Cont'd)

Appendix Table 5. Detailed Listing of Deaths up to End of Study in CREDIBLE-CR (Safety Population)[7]

Adjudication Committee Category	Age/ Sex	Dx	Comorbid Conditions	Pathogen/MIC (µg/mL)	ICU/ Shock (Y/N)	Clinical Outcome EOT/TOC	Microbiological Outcome EOT/TOC	MIC Increase (Y/N)	Cause of Death	Study Day of Death/ Time to Death Since Last Dose (Days)	Sepsis as cause of Death (Y/N)
BAT Group											
1-A	74/ M	VAP	Adenocarcinoma of lung, left upper lobectomy, septic shock, VAP *Enterobacter cloacae*	*A. baumannii*, *E. asburiae*/ CIP: >4.0 and 1.0; SXT: 1.0 and 0.5, respectively	N/Y	Clinical cure/ Indeterminate	Persistence/ Indeterminate	N	Bradycardia	14/5	N
2	42/ M	VAP	End stage renal disease, pancreato-duodenectomy, cardiac arrest	*A. baumannii*/ colistin: 2.0; cefepime: >16.0	N/N	Clinical failure/ Indeterminate	Persistence/ Indeterminate	N	Acute respiratory failure cardiac arrest (DNR)	13/1	N
1-A	85/ M	cUTI	Benign prostate hyperplasia, bilateral nephrostomy, blood creatinine increased	*K. pneumoniae*/ colistin: 1.0; fosfomycin: NA	N/N	Indeterminate/ Indeterminate	Indeterminate/ Indeterminate	N	Metabolic acidosis due to primary disease, acute renal failure (per PI)	6/0	N
1-B	57/ M	HAP	Liver cirrhosis (CP class C), pseudomembranous colitis	*K. pneumoniae*/ colistin: ≤0.5; imipenem/cilastatin: 2.0	Y/N	Indeterminate/ Indeterminate	Indeterminate/ Indeterminate	N	Multiple organ failure	11/0	N
2	69/ M	BSI	Colon cancer, colectomy and ileostomy, fecal peritonitis, subphrenic abscess, septic shock, renal failure	P. aeruginosa/ Ceftazidime/ avibactam: 8.0; CIP: 0.5	Y/N	Clinical failure/ Clinical failure	Indeterminate/ Indeterminate	N	General physical health deterioration	24/9	N

Abbreviations: AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; BAT, best available therapy; BSI, bloodstream infection; CIP, ciprofloxacin; COPD, chronic obstructive pulmonary disease; CP, Child-Pugh; CRRT, continuous renal replacement therapy; CT, computed tomography; cUTI, complicated urinary tract infection; DNR, do not resuscitate; Dx, diagnosis; EF, ejection fraction; EOT, end of treatment; F, female; GI, gastrointestinal; HAP, hospital-acquired pneumonia; HCAP, healthcare-associated pneumonia; ID, identification number;
M, male; MIC, minimum inhibitory concentration; N, no; NA, not applicable; NYHA, New York Heart Association; TOC, test of cure; Tx, treatment; UTI, urinary tract infection; VAP, ventilator-associated pneumonia; Y, yes.
adjudication committee categories: Category 1: death not directly related to the underlying Gram-negative infection; 1-A, due to an underlying disease; 1-B, due to a different infection; 1-C, due to a drug-related adverse event; 1-D, due to an iatrogenic cause. Category 2: death directly related to the Gram-negative infection/lack of effectiveness.