Fetroja® - Development of Non-Susceptibility in the Clinical Development Program

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

- In the **APEKS-cUTI** study in the cefiderocol arm, a total of six isolates had a ≥4-fold increase in cefiderocol minimum inhibitory concentration (MIC) from baseline. None of the pathogens had a cefiderocol MIC >1 µg/mL or developed resistance to cefiderocol. Additionally, three isolates in the imipenem-cilastatin arm developed a ≥4-fold increase in imipenem MIC from baseline, of which one isolate met the criteria of resistance[1-4]

- In the **APEKS-NP** study in the cefiderocol arm, a total of five isolates had a ≥4-fold increase in MIC from baseline. Of these five isolates, one isolate had intermediate susceptibility at end of treatment (EOT) based on Clinical Laboratory Standards Institute (CLSI) and FDA susceptibility breakpoints and the other isolates were susceptible to cefiderocol with MICs ≤4 µg/mL. In the meropenem arm, a ≥4-fold increase in meropenem MIC occurred in five isolates and the extent of MIC increase ranged from 4- to 512-fold[5-7]

- In the **CREDIBLE-CR** study, which enrolled patients with serious carbapenem-resistant (CR) Gram-negative infections, a total of nine isolates demonstrated a ≥4-fold increase in MIC from baseline in the cefiderocol arm. Of these nine isolates, there was one *Acinetobacter baumannii* that was resistant to cefiderocol and one with intermediate susceptibility, in addition to one cefiderocol-resistant *Pseudomonas aeruginosa* according to CLSI breakpoints. One *A. baumannii* isolate was resistant following treatment based on FDA and European Committee on Antimicrobial Susceptibility Testing (EUCAST) susceptibility breakpoints. In the best-available therapy (BAT) arm, there were eight isolates with a ≥4-fold increase in baseline MIC to the active agents, all of which met the criteria for resistance[7-9]

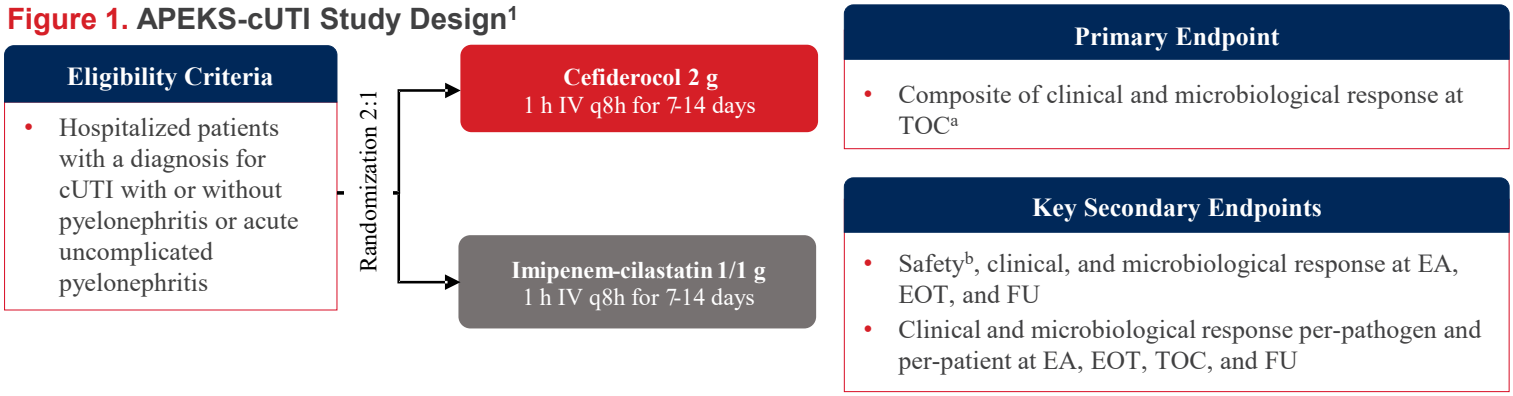
Fetroja® - Development of Non-Susceptibility in the Clinical Development Program

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.**

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 complicated urinary tract infections (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. Adverse events were monitored daily during treatment administration in the hospital.

- Cefiderocol and imipenem MICs for Gram-negative bacteria isolated at randomization and at later time points were investigated by the central laboratory according to Clinical Laboratory Standards Institute (CLSI) guidelines[1,2]

Fetroja® - Development of Non-Susceptibility in the Clinical Development Program

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.**

Results

- The modified intent-to-treat (mITT) population consisted of 371 patients (252 patients in the cefiderocol group and 119 patients in the imipenem-cilastatin group)[1,2]
- A total of six patients had a ≥4-fold increase in cefiderocol MIC from baseline (Table 1). No patient had an MIC that was higher than 1 µg/mL.[2] One patient with *P. aeruginosa* cleared the infection at test of cure (TOC [defined as EOT + 7±2 days]) but had a new *P. aeruginosa* isolate (genetically different based on electrophoresis) with an MIC of 8 µg/mL at follow-up (FU) [2,3,4]
  - None of the pathogens isolated at baseline developed resistance to cefiderocol
- Additionally, three patients in the imipenem-cilastatin group experienced a ≥4-fold increase in MIC from baseline, of which one isolate met the criteria of resistance[2,3,4]

Table 1. Patients with ≥4-fold Increase in MIC to Cefiderocol and Imipenem in the APEKS-cUTI Study (mITT Population)[3,4]

Gram-negative Uropathogen	MIC (µg/mL)		MIC Increase
	Baseline	Post	
Cefiderocol			
Escherichia coli	0.03	0.25 (FU)	8
Enterobacter cloacae complex	0.12	0.5 (TOC)	4
		0.25 (FU)	2
Escherichia coli	0.25	0.5 (TOC)	2
		1 (FU)	4
Escherichia coli	0.03	0.12 (TOC)	4
		0.06 (FU)	2
Proteus mirabilis	0.06	0.5 (TOC)	8
		0.03 (FU)	0.5
Enterobacter aerogenes	0.015	0.12 (FU)	8
Imipenem			
P. aeruginosa	1	>8 (TOC)	8
		>8 (FU)	8
E. coli	0.12	0.5 (FU)	4
E. coli	0.12	0.5 (FU)	4

Abbreviations: FU, follow-up; MIC, minimum inhibitory concentration; mITT, modified intent-to-treat; TOC, test of cure.

Fetroja® - Development of Non-Susceptibility in the Clinical Development Program

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. Patients with ≥4-fold Increase in MIC to Cefiderocol and Imipenem in the APEKS-cUTI Study (mITT Population)[3,4]

Gram-negative Uropathogen	MIC (µg/mL)		MIC Increase
	Baseline	Post	
Cefiderocol			
Escherichia coli	0.03	0.25 (FU)	8
Enterobacter cloacae complex	0.12	0.5 (TOC)	4
		0.25 (FU)	2
Escherichia coli	0.25	0.5 (TOC)	2
		1 (FU)	4
Escherichia coli	0.03	0.12 (TOC)	4
		0.06 (FU)	2
Proteus mirabilis	0.06	0.5 (TOC)	8
		0.03 (FU)	0.5
Enterobacter aerogenes	0.015	0.12 (FU)	8
Imipenem			
P. aeruginosa	1	>8 (TOC)	8
		>8 (FU)	8
E. coli	0.12	0.5 (FU)	4
E. coli	0.12	0.5 (FU)	4

Abbreviations: FU, follow-up; MIC, minimum inhibitory concentration; mITT, modified intent-to-treat; TOC, test of cure.

Fetroja® - Development of Non-Susceptibility in the Clinical Development Program

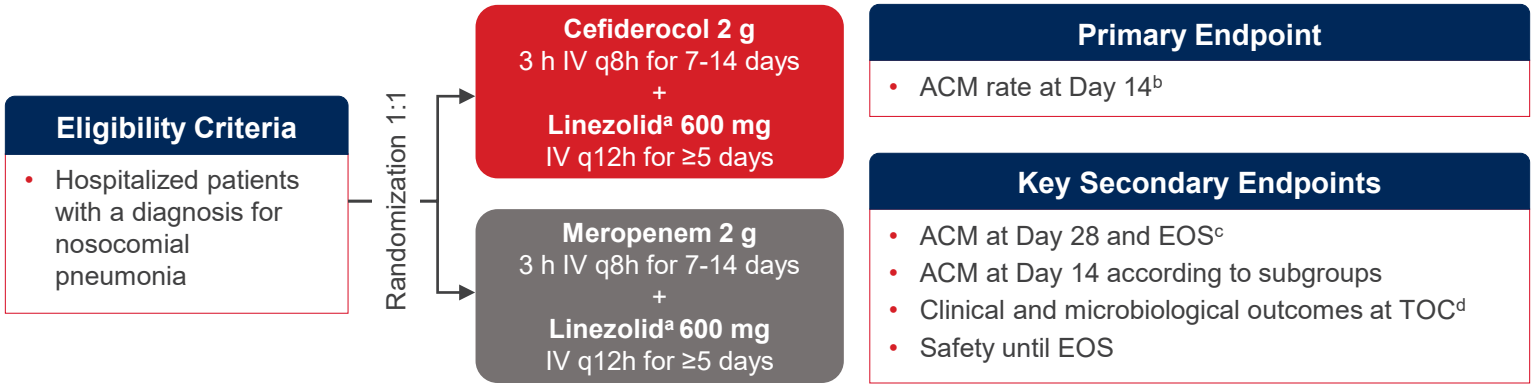
SHIONOGI

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.**

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 hospital-acquired bacterial pneumonia (HABP), ventilator-associated bacterial pneumonia (VABP), or healthcare-associated bacterial pneumonia (HCABP) caused by suspected Gram-negative pathogens[5]

Figure 2. APEKS-NP Study Design[5]



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).

- The microbiological samples collected at randomization and at subsequent time points (i.e., early assessment [EA], EOT, TOC, and FU) were sent to the central laboratory for species confirmation, antibiotic susceptibility testing and expression of various β-lactamases or carbapenemases[5-7]
- Susceptibility testing was performed based on CLSI guidelines, and cefiderocol MIC values were determined using iron-depleted cation-adjusted Mueller-Hinton broth (ID-CAMHB). Gram-negative isolates with increased cefiderocol MIC were re-tested in duplicate and median MICs were calculated[5-7]
- Whole-genome sequencing (WGS) was utilized to identify mutations in selected genes related to iron transport, β-lactamases, and carbapenemases for isolates in the cefiderocol arm[6,7]

Fetroja® - Development of Non-Susceptibility in the Clinical Development Program

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.**

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 (intent-to-treat [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)[5]
- In the cefiderocol arm, a total of five isolates had a ≥4-fold increase in MIC from baseline (Table 2). Of these isolates, 4/5 were susceptible to cefiderocol as demonstrated by an MIC ≤4 µg/mL at the end of treatment[7]
  - One *Enterobacter cloacae* isolate had a 4-fold MIC increase from baseline (2 µg/mL to 8 µg/mL, respectively) and was considered to have intermediate susceptibility according to CLSI and FDA susceptibility breakpoints. This isolate had a mutation identified in the ACT-17 gene, which resulted in an amino acid substitution (i.e., A313P)[7]
- In the meropenem arm, a ≥4-fold increase in meropenem MIC occurred in five isolates (Table 3) with an MIC increase of 4- to 512-fold[6]
- None of the patients in either treatment arm with a ≥4-fold increase in MIC from baseline died by Day 14[6,7]

Table 2. Pre and Post MIC Changes, Resistance Criteria, Identified β-Lactamases, and Post-Treatment Whole-Genome Sequencing-Identified Mutations in Multilocus Sequence Typing-Confirmed Isogenic Isolates with a ≥4-Fold Post-Treatment Increase in MIC in the Cefiderocol Arm from APEKS-NP (mITT Population)[7]

Species and Site of Infection	Time Point for MIC Value	Original (pre-) MIC	Fold of Change in MIC	Cefiderocol MIC Retests				Resistance According to Established Criteria Based on Median MIC			β-lactamase Identified at Baseline and Post-treatment (WGS)	Post-treatment Mutation Identified (WGS)
				MIC#1 (µg/mL)	MIC#2 (µg/mL)	Median (µg/mL)	Fold of Median Change in MIC	CLSI 2024 M100	FDA SIR 10/5/2/1 ENT & 4/2/1 STA	EUCAST SIR 2024 ENT; 2-2-2 STA		
K. aerogenes	Baseline	0.03		0.06	0.12	0.06		S	S	S	AmpC^	
	EA	0.5	8+	0.25	0.25	0.25	4+	S	S	S	AmpC^	Not identified
K. pneumoniae	Baseline	0.06		≤0.03	0.03	0.03		S	S	S	SHV-1	
	EA	0.25	4+	0.25	0.5	0.25	8+	S	S	S	SHV-1	Not identified
K. pneumoniae	Baseline	0.25		0.25	0.5	0.25		S	S	S	CTX-M-15; OXA-1-like; TEM-1; SHV-11	
	TOC	1	4+	1	1	1	4+	S	S	S	CTX-M-15; OXA-1-like; SHV-11	Not identified
E. cloacae[a]	Baseline	1		2	4	2		S	S	S	ACT-17^	
	EOT	4	4+	8	8	8	4+	I	I	R	ACT-17-like^	ACT-17-like (A313P)
S. marcescens[a]	Baseline	0.06		0.12	0.25	0.12		S	S	S	SRT-2-like^	
	EA	0.25	4+	0.5	1	0.5	4+	S	S	S	SRT-2-like^	Not identified

Abbreviations: CLSI, Clinical and Laboratory Standards Institute; EA, early assessment; ENT, Enterobacterales; EOT, end of treatment; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FDA, U.S. Food and Drug Administration; I, intermediate; MIC, minimum inhibitory concentration; mITT, modified intent-to-treat; NF, non-fermenters; PA, *Pseudomonas aeruginosa*; R, resistant; S, susceptible; TOC, test of cure; WGS, whole-genome sequencing.
#100% match to OMV/MIR/ACT/EC family class C β-lactamase; variant name is unidentified.
^The *E. cloacae* and *S. marcescens* isolates were found in the same patient in the same biospecimen. The ACT-17 enzyme belongs to Class C AmpC enzymes.
‡This enzyme belongs to Class C AmpC enzymes in *Enterobacter* spp.
‡‡This enzyme belongs to Class C AmpC enzymes in *Serratia* spp.

Table 3. Pre and Post MICs and the Mechanisms of Resistance in Pathogens with ≥4-fold MIC Increases in the Meropenem Arm from APEKS-NP (mITT Population)[6]

Isolate	MIC (µg/mL)		Fold Change in MIC	Day of Isolation	Mutation Identified in Post-Treatment Isolates
	Pre-Treatmenta	Post-Treatment			
K. pneumoniae	2	8	4	EA visit	Not identified
P. aeruginosa	0.12	64	512	EA visit	Not identified
P. aeruginosa	0.25	4	16	TOC visit	Opr-D truncation
P. aeruginosa	0.25	4	16	TOC visit	Opr-D truncation
C. freundii	≤0.03	0.12	4	EA visit	Not identified

Abbreviations: EA, early assessment; MIC, minimum inhibitory concentration; mITT, modified intent-to-treat; TOC, test of cure.
aLatest isolate before study drug initiation.

Fetroja® - Development of Non-Susceptibility in the Clinical Development Program

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. Pre and Post MIC Changes, Resistance Criteria, Identified β-Lactamases, and Post-Treatment Whole-Genome Sequencing-Identified Mutations in Multilocus Sequence Typing-Confirmed Isogenic Isolates with a ≥4-Fold Post-Treatment Increase in MIC in the Cefiderocol Arm from APEKS-NP (mITT Population)[7]

Species and Site of Infection	Time Point for MIC Increase	Original MIC (µg/mL)	Fold of Baseline MIC	Cefiderocol MIC Retests				Resistance According to Established Criteria Based on Median MIC			β-lactamase Identified at Baseline and Post-treatment (WGS)	Post-treatment Mutation Identified (WGS)
				MIC#2 (µg/mL)	MIC#3 (µg/mL)	Median MIC (µg/mL)	Fold of Median Baseline MIC	CLSI S/I/R ≤4/8/≥16	FDA S/I/R ≤4/8/≥16 ENT & ≤1/2/≥4 NF	EUCAST S/R ≤2/>2 (ENT, PA)		
K. aerogenes	Baseline	0.06		0.06	0.12	0.06		S	S	S	AmpC[a]	
	EA	0.5	8×	0.25	0.25	0.25	4×	S	S	S	AmpC[a]	Not identified
K. pneumoniae	Baseline	0.06		≤0.03	0.03	0.03		S	S	S	SHV-1	
	EA	0.25	4×	0.25	0.5	0.25	8×	S	S	S	SHV-1	Not identified
K. pneumoniae	Baseline	0.25		0.25	0.5	0.25		S	S	S	CTX-M-15; OXA-1-like; TEM-1; SHV-11	
	TOC	1	4×	1	1	1	4×	S	S	S	CTX-M-15; OXA-1-like; SHV-11	Not identified
E. cloacae[b]	Baseline	1		2	4	2		S	S	S	ACT-17[c]	
	EOT	4	4×	8	8	8	4×	I	I	R	ACT-17-like[c]	ACT-17-like (A313P)
S. marcescens[b]	Baseline	0.06		0.12	0.25	0.12		S	S	S	SRT-2-like[d]	
	EA	0.25	4×	0.5	1	0.5	4×	S	S	S	SRT-2-like[d]	Not identified

Abbreviations: CLSI, Clinical and Laboratory Standards Institute; EA, early assessment; ENT, Enterobacterales; EOT, end of treatment; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FDA, U.S. Food and Drug Administration; I, intermediate; MIC, minimum inhibitory concentration; mITT, modified intent-to-treat; NF, non-fermenters; PA, *Pseudomonas aeruginosa*; R, resistant; S, susceptible; TOC, test of cure; WGS, whole-genome sequencing.

[a]100% match to CMY/MIR/ACT/EC family class C β-lactamase; variant name is unidentified.

[b]The *E. cloacae* and *S. marcescens* isolates were found in the same patient in the same biospecimen. The ACT-17 enzyme belongs to Class C AmpC enzymes.

[c]This enzyme belongs to Class C AmpC enzymes in *Enterobacter* spp.

[d]This enzyme belongs to Class C AmpC enzymes in *Serratia* spp.

Fetroja® - Development of Non-Susceptibility in the Clinical Development Program

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. Pre and Post MICs and the Mechanisms of Resistance in Pathogens with ≥4-fold MIC Increases in the Meropenem Arm from APEKS-NP (mITT Population)[6]

Isolate	MIC (µg/mL)		Fold Change in MIC	Day of Isolation	Mutation Identified in Post-Treatment Isolates
	Pre-Treatment[a]	Post-Treatment			
K. pneumoniae	2	8	4	EA visit	Not identified
P. aeruginosa	0.12	64	512	EA visit	Not identified
P. aeruginosa	0.25	4	16	TOC visit	Opr-D truncation
P. aeruginosa	0.25	4	16	TOC visit	Opr-D truncation
C. freundii	≤0.03	0.12	4	EA visit	Not identified

Abbreviations: EA, early assessment; MIC, minimum inhibitory concentration; mITT, modified intent-to-treat; TOC, test of cure.
[a]Latest isolate before study drug initiation.

Fetroja® - Development of Non-Susceptibility in the Clinical Development Program

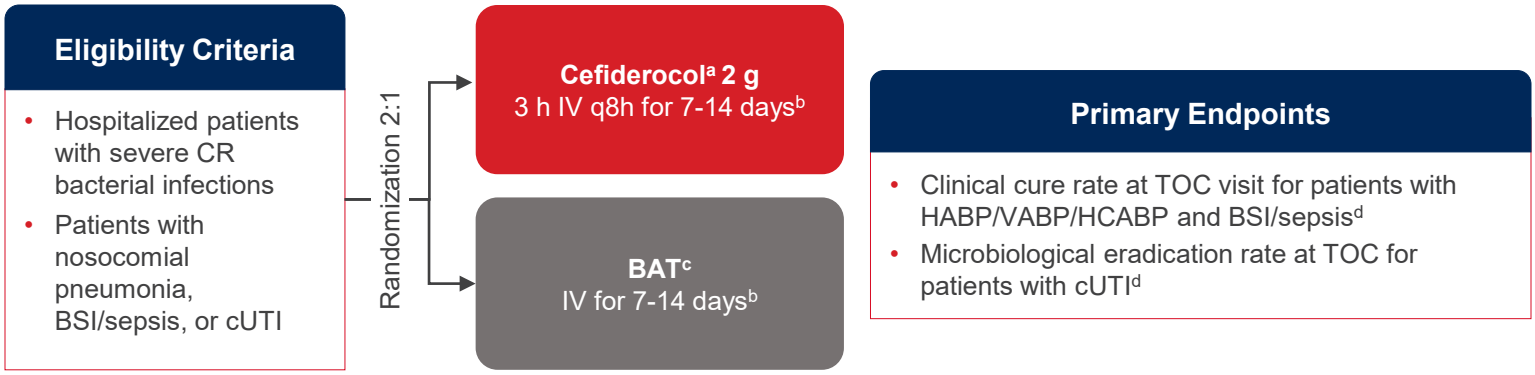
SHIONOGI

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.**

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[8]
- CREDIBLE-CR was a descriptive study with no hypothesis testing or formal inferential analyses[8]

Figure 3. CREDIBLE-CR Study Design[8]



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 three systemic antibiotics.

[d]Defined as all patients with a confirmed CR Gram-negative pathogen who received at least one dose of study drug.

- The microbiological samples collected at randomization and at EA, EOT, TOC, and FU were sent to the central laboratory for species confirmation, antibiotic susceptibility testing and expression of various β-lactamases or carbapenemases[7-9]
- CLSI guidelines were utilized for antibiotic susceptibility testing. For cefiderocol MIC determination, ID-CAMHB was used. Gram-negative isolates with increased cefiderocol MIC were re-tested in duplicates and median MICs were calculated[7-9]
- Whole-genome sequencing was utilized to identify mutations in selected genes related to iron transport, β-lactamases, and carbapenemases[7,9]

Fetroja® - Development of Non-Susceptibility in the Clinical Development Program

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.**

Results

- 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)[8]
- In the cefiderocol arm, a total of nine isolates demonstrated a ≥4-fold increase in MIC from baseline (Table 4). Of these nine isolates, there were three that had a MIC that exceeded 4 µg/mL (2 *A. baumannii*, 1 *P. aeruginosa*)[7]
- Three isolates with confirmed repeat MIC increase had mutations based on WGS[7]
  - One *A. baumannii* isolate had an amino acid substitution (H370Y) in penicillin binding protein 3 (PB3) and a 4-fold MIC increase was observed (1 µg/mL to 4 µg/mL, respectively)
  - One *A. baumannii* isolate with a 64-fold MIC increase from baseline (1 µg/mL to 64 µg/mL, respectively) developed two mutations in an acquired OXA-23 gene (encoding amino acid substitutions N85I and P225S)
  - One *P. aeruginosa* isolate with a 16-fold MIC increase (0.12 µg/mL to 2 µg/mL, respectively) had a deletion in PDC-30 enzyme (4 amino acid deletion "TPMA" position 316-319)
- In the BAT group, there were eight isolates with a ≥4-fold increase in baseline MIC to the active agents, all of which met the criteria for resistance (Table 5). The potential mutations in these isolates were not studied[7,9]

Table 4. Pre and Post MIC Changes, Resistance Criteria, Identified β-Lactamases, and Post-Treatment Whole-Genome Sequencing-Identified Mutations in Multilocus Sequence Typing-Confirmed Isogenic Isolates with a ≥4-Fold Post-Treatment Increase in MIC in the Cefiderocol Arm from CREDIBLE-CR (Micro ITT Population)[7]

Species and Site of Infection	Time Point for MIC Increase	Original MIC (µg/mL)	Fold of Baseline MIC	Cefiderocol MIC Retests				Resistance According to Established Criteria Based on Median MIC			β-lactamase Identified at Baseline and Post-treatment (WGS)	Post-treatment Mutation Identified (WGS)
				MIC#2 (µg/mL)	MIC#3 (µg/mL)	Median MIC (µg/mL)	Fold of Median Baseline MIC	CLSI S/I/R 54/8/18	FDA S/I/R 54/8/18 ENT & s1/2/3/4 NF	EUCAST S/R ≤2/>2 (ENT, PA)		
A. baumannii	Baseline	0.25		1	1	1		S	S	S	ADC-25-like[a], OXA-23; OXA-66[b], TEM-1D	
	Day 14	4	16×	2	4	4	4×	S	R	R	ADC-25-like[a], OXA-23; OXA-69[b], TEM-1D	PBP3 (H370Y)
A. baumannii	Baseline	1		1	2	1		S	S	S	ADC-25-like[a], OXA-23; OXA-69[b]	
	EOT	8	8×	64	64	64	64×	R	R	R	ADC-25-like[a], OXA-23-like; OXA-69[b]	OXA-23 (N85I and P225S)
A. baumannii[c]	Baseline	1		0.25	1	1		S	S	S	ADC-25-like[a], OXA-23; OXA-71[d]	
	Unscheduled (Day 10)	8	8×	8	8	8	8×	I	R	R	ADC-25-like[a], OXA-23; OXA-71[d]	Not identified
K. pneumoniae	Baseline	0.06		≤0.03	0.06	0.06		S	S	S	SHV-61-like[e]	
	Unscheduled (Day 8)	0.5	8×	1	1	1	16×	S	S	S	SHV-61-like[e] partial CDS; TEM-1B	Not identified
K. pneumoniae[f]	Baseline	0.25		0.12	0.25	0.25		S	S	S	KPC-2; SHV-1	
	Day 14	2	8×	4	2	2	8×	S	S	S	KPC-2; SHV-1	Not identified
P. aeruginosa	Baseline	0.12		0.12	0.12	0.12		S	S	S	OXA-847[g], PDC-11; VIM-2	
	EA	16	128×	16	16	16	128×	R	R	R	OXA-847[g], PDC-11; VIM-2	Not identified
P. aeruginosa	Baseline	0.25		0.12	0.12	0.12		S	S	S	OXA-488[f], PDC-30	
	EOT	2	8×	2	2	2	16×	S	I	S	OXA-488[f], PDC-30-like	PDC30 (4 AA deletion "TPMA" position 316-319)
P. aeruginosa	Baseline	0.5		1	0.25	0.5		S	S	S	Oxa-50-like[h], PDC-11	
	EOT	2	4×	4	2	2	4×	S	I	S	Oxa-50-like[h], PDC-11	Not identified
S. maltophilia[i]	Baseline	0.06		0.06	0.12	0.06		NA	NA	NA	L1, L2[k]	
	EOT	0.25	4×	0.12	0.25	0.25	4×	NA	NA	NA	L1, L2[k]	Not identified

Abbreviations: CDS, coding sequences; CLSI, Clinical and Laboratory Standards Institute; EA, Early Assessment; ENT, Enterobacterales; EOT, end of treatment; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FDA, U.S. Food and Drug Administration; I, intermediate; MIC, minimum inhibitory concentration; Micro ITT, microbiological intent-to-treat; NF, non-fermenters; NT, not tested; PA, *Pseudomonas aeruginosa*; R, resistant; S, susceptible; TOC, test of cure; WGS, whole-genome sequencing.

[a]Treatment with combination of cefiderocol/ampicillin-sulbactam. [b]Treatment with combination of cefiderocol+tigecycline. [c]Treatment with combination of cefiderocol+levofloxacin. [d]In *A. baumannii*, OXA-66, OXA-69, OXA-71, and ADC-25 are naturally occurring and weakly expressed. [e]In *K. pneumoniae*, SHV-61 is naturally occurring. [f]In *P. aeruginosa*, OXA-847 and OXA-488 are naturally occurring and weakly expressed, and do not interfere with common resistance patterns. They belong to OXA-50-like group of β-lactamases. [g]OXA-50-like groups of β-lactamases are naturally occurring enzymes and weakly expressed. [h]L1 and L2 are naturally occurring β-lactamases; L1: a metallo-β-lactamase and L2: an extended-spectrum β-lactamase, respectively. L1 was not available in the ResFinder database but was detected by manual analysis of the assembled sequence.

Table 5. Pre and Post MICs and the Mechanisms of Resistance in Pathogens with ≥4-Fold MIC Increases in the Best-Available Therapy[a] Arm from CREDIBLE-CR (Micro ITT Population)[8,9]

Isolate	MIC (µg/mL)		Fold Change in MIC	Day of Isolation	Mutation Identified in Post-Treatment Isolates
	Pre-Treatment[b]	Post-Treatment			
Ceftazidime/avibactam					
K. pneumoniae	0.25	16	64	20	Not evaluated
Tigecycline					
K. pneumoniae[c]	1	>4	>4	13	Not evaluated
A. baumannii[d]	2	>4	>4	11	Not evaluated
Colistin					
K. pneumoniae	≤0.5	>8	>16	13	Not evaluated
K. pneumoniae[c]	≤0.5	8	>16	13	Not evaluated
A. baumannii[d]	≤0.5	>8	>16	4	Not evaluated
A. baumannii[e]	1	>8	>8	14	Not evaluated
E. coli[e]	2	8	>4	14	Not evaluated

Abbreviations: BAT, best-available therapy; CR, carbapenem-resistant; ITT, intent-to-treat; MIC, minimum inhibitory concentration; Micro ITT, microbiological intent-to-treat.

[a]BAT agents were selected based on local standard of care for CR infections, and MICs were confirmed by the central laboratory.

[b]Latest isolate before study drug initiation.

[c]The patient had *K. pneumoniae* infection and was treated with tigecycline and colistin; MIC increased to both agents.

[d]The patient had *A. baumannii* infection and was treated with tigecycline and colistin; MIC increased to both agents.

[e]Polymicrobial infection treated with colistin; increase in MIC for both pathogens.

Fetroja® - Development of Non-Susceptibility in the Clinical Development Program

SHIONOGI

Table 4. Pre and Post MIC Changes, Resistance Criteria, Identified β-Lactamases, and Post-Treatment Whole-Genome Sequencing-Identified Mutations in Multilocus Sequence Typing Confirmed Isogenic Isolates with a ≥4-Fold Post-Treatment Increase in MIC in the Cefiderocol Arm from CREDIBLE-CR (Micro ITT Population)[7]

Species and Site of Infection	Time Point for MIC Increase	Original MIC (µg/mL)	Fold of Baseline MIC	Cefiderocol MIC Retests				Resistance According to Established Criteria Based on Median MIC			β-lactamase Identified at Baseline and Post-treatment (WGS)	Post-treatment Mutation Identified (WGS)
				MIC#2 (µg/mL)	MIC#3 (µg/mL)	Median MIC (µg/mL)	Fold of Median Baseline MIC	CLSI S/I/R ≤4/8/≥16	FDA S/I/R ≤4/8/≥16 ENT & ≤1/2/≥4 NF	EUCAST S/R ≤2/>2 (ENT, PA)		
A. baumannii	Baseline	0.25		1	1	1		S	S	S	ADC-25-like[d]; OXA-23; OXA-66[d]; TEM-1D	
	Day 14	4	16×	2	4	4	4×	S	R	R	ADC-25-like[d]; OXA-23; OXA-66[d]; TEM-1D	PBP3 (H370Y)
A. baumannii	Baseline	1		1	2	1		S	S	S	ADC-25-like[d]; OXA-23; OXA-69[d]	
	EOT	8	8×	64	64	64	64×	R	R	R	ADC-25-like[d]; OXA-23-like; OXA-69[d]	OXA-23 (N85I and P225S)
A. baumannii[a]	Baseline	1		0.25	1	1		S	S	S	ADC-25-like[d]; OXA-23; OXA-71[d]	
	Unscheduled (Day 10)	8	8×	8	8	8	8×	I	R	R	ADC-25-like[d]; OXA-23; OXA-71[d]	Not identified
K. pneumoniae	Baseline	0.06		≤0.03	0.06	0.06		S	S	S	SHV-61-like[e]	
	Unscheduled (Day 8)	0.5	8×	1	1	1	16×	S	S	S	SHV-61-like[e] partial CDS; TEM-18	Not identified
K. pneumoniae[b]	Baseline	0.25		0.12	0.25	0.25		S	S	S	KPC-2; SHV-1	
	Day 14	2	8×	4	2	2	8×	S	S	S	KPC-2; SHV-1	Not identified
P. aeruginosa	Baseline	0.12		0.12	0.12	0.12		S	S	S	OXA-847[f]; PDC-11; VIM-2	
	EA	16	128×	16	16	16	128×	R	R	R	OXA-847[f]; PDC-11; VIM-2	Not identified
P. aeruginosa	Baseline	0.25		0.12	0.12	0.12		S	S	S	OXA-488[f]; PDC-30	
	EOT	2	8×	2	2	2	16×	S	I	S	OXA-488[f]; PDC-30-like	PDC30 (4 AA deletion "TPMA" position 316-319)
P. aeruginosa	Baseline	0.5		1	0.25	0.5		S	S	S	Oxa-50-like[g]; PDC-11	
	EOT	2	4×	4	2	2	4×	S	I	S	Oxa-50-like[g]; PDC-11	Not identified
S. maltophilia[c]	Baseline	0.06		0.06	0.12	0.06		NA	NA	NA	L1, L2[h]	
	EOT	0.25	4×	0.12	0.25	0.25	4×	NA	NA	NA	L1, L2[h]	Not identified

Abbreviations: CDS, coding sequences; CLSI, Clinical and Laboratory Standards Institute; EA, Early Assessment; ENT, Enterobacterales; EOT, end of treatment; EUCAST, European Committee on Antimicrobial Susceptibility Testing; FDA, U.S. Food and Drug Administration; I, intermediate; MIC, minimum inhibitory concentration; Micro ITT, microbiological intent-to-treat; NA, not available; NF, non-fermenters; PA, *Pseudomonas aeruginosa*; R, resistant; S, susceptible; TOC, test of cure; WGS, whole-genome sequencing.

[a]Treatment with combination of cefiderocol+ampicillin-sulbactam. [b]Treatment with combination of cefiderocol+tigecycline. [c]Treatment with combination of cefiderocol+levofloxacin. [d]In *A. baumannii*, OXA-66, OXA-69, OXA-71, and ADC-25 are naturally occurring and weakly expressed. [e]In *K. pneumoniae*, SHV-61 is naturally occurring. [f]In *P. aeruginosa*, OXA-847 and OXA-488 are naturally occurring and weakly expressed, and do not interfere with common resistance patterns. They belong to OXA-50-like group of β-lactamases. [g]OXA-50–like groups of β-lactamases are naturally occurring enzymes and weakly expressed. [h]L1 and L2 are naturally occurring β-lactamases; L1: a metallo-β-lactamase and L2: an extended-spectrum β-lactamase, respectively. L1 was not available in the ResFinder database but was detected by manual analysis of the assembled sequence.

Fetroja® - Development of Non-Susceptibility in the Clinical Development Program

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 5. Pre and Post MICs and the Mechanisms of Resistance in Pathogens with ≥4-Fold MIC Increases in the Best-Available Therapy[a] Arm from CREDIBLE-CR (Micro ITT Population)[8,9]

Isolate	MIC (µg/mL)		Fold Change in MIC	Day of Isolation	Mutation Identified in Post-Treatment Isolates
	Pre-Treatment[b]	Post-Treatment			
Ceftazidime/avibactam					
K. pneumoniae	0.25	16	64	20	Not evaluated
Tigecycline					
K. pneumoniae[c]	1	>4	>4	13	Not evaluated
A. baumannii[d]	2	>4	>4	11	Not evaluated
Colistin					
K. pneumoniae	≤0.5	>8	>16	13	Not evaluated
K. pneumoniae[c]	≤0.5	8	>16	13	Not evaluated
A. baumannii[d]	≤0.5	>8	>16	4	Not evaluated
A. baumannii[e]	1	>8	>8	14	Not evaluated
E. coli[e]	2	8	>4	14	Not evaluated

Abbreviations: BAT, best-available therapy; CR, carbapenem-resistant; MIC, minimum inhibitory concentration; Micro ITT, microbiological intent-to-treat.
[a]BAT agents were selected based on local standard of care for CR infections, and MICs were confirmed by the central laboratory.
[b]Latest isolate before study drug initiation.
[c]The patient had *K. pneumoniae* infection and was treated with tigecycline and colistin; MIC increased to both agents.
[d]The patient had *A. baumannii* infection and was treated with tigecycline and colistin; MIC increased to both agents.
[e]Polymicrobial infection treated with colistin; increase in MIC for both pathogens.

Fetroja® - Development of Non-Susceptibility in the Clinical Development Program

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[10]:

- 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,* and *Serratia marcescens*:
  - *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.[10]

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

Fetroja® - Development of Non-Susceptibility in the Clinical Development Program

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

BAT	best available therapy	I	intermediate
BSI	bloodstream infection	ITT	intent-to-treat
CDS	coding sequences	ID-CAMHB	iron-depleted cation-adjusted Mueller-Hinton broth
CLSI	Clinical and Laboratory Standards Institute	IV	intravenous
CR	carbapenem-resistant	MIC	minimum inhibitory concentration
cUTI	complicated urinary tract infection	mITT	modified intent-to-treat
EA	early assessment	NA	not applicable
EOT	end of treatment	NF	non-fermenters
ENT	Enterobacterales	PA	*Pseudomonas aeruginosa*
EUCAST	European Committee on Antimicrobial Susceptibility Testing	R	resistant
FDA	Food and Drug Administration	S	susceptible
FU	follow-up	TOC	test of cure
g	gram	VABP	ventilator-associated bacterial pneumonia
h	hour	WGS	whole-genome sequencing

Fetroja® - Development of Non-Susceptibility in the Clinical Development Program

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 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. Shionogi Inc. Cefiderocol Briefing Document. U.S. Food and Drug Administration. https://www.fda.gov/advisory-committees/advisory-committee-calendar/october-16-2019-antimicrobial-drugs-advisory-committee-meeting-announcement-10162019-10162019. Published October 11, 2019. Accessed June 13, 2022
3. Shionogi Inc. Shionogi presentation for the October 16, 2019 meeting of the Antimicrobial Drugs Advisory Committee. U.S. Food and Drug Administration. https://www.fda.gov/advisory-committees/advisory-committee-calendar/october-16-2019-antimicrobial-drugs-advisory-committee-meeting-announcement-10162019-10162019. Published October 11, 2019. Accessed June 13, 2022
4. Data on File 23. 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 trial. *Lancet Infect Dis*. 2021;21(2):213-225. doi:10.1016/S1473-3099(20)30731-3
6. 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. Suppl 1. doi:10.1016/S1473-3099(20)30731-3
7. Nordmann P, Shields RK, Doi Y, et al. Mechanisms of reduced susceptibility to cefiderocol among isolates from the CREDIBLE-CR and APEKS-NP clinical trials. *Microb Drug Resist*. 2022; 28(4):398-407. doi:10.1089/mdr.2021.0180
8. 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
9. 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. Suppl 1. doi:10.1016/S1473-3099(20)30796-9
10. Fetroja® (cefiderocol) for injection, for intravenous use [Prescribing Information]. Shionogi Inc.

ENCLOSURE

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