Fetroja® – Eosinophilia

SHIONOGI

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Summary

- In the Phase 3 study **APEKS-NP**, eosinophilia was reported as an AE in 3 patients[1]
  - 1 patient (0.7%) in the cefiderocol group experienced eosinophilia, and 2 patients (1.3%) in the meropenem group experienced eosinophilia
- In the Phase 3 study **CREDIBLE-CR**, eosinophilia was reported as an AE in 2 patients[2]
  - 2 patients (2%) in the cefiderocol group experienced eosinophilia, and 1 patient (1%) in the cefiderocol group experienced drug eruption, with maculopapular rash with eosinophilia
- **Diarra et al (2025)** conducted a retrospective, observational, multicenter study evaluating the use of cefiderocol in 45 patients across 22 centers mostly in France between January 2019 and December 2023[3]
  - Cefiderocol treatment was withdrawn in 3 (7%) patients, due to grade 2 hypereosinophilia, grade 4 diarrhea, and acute kidney failure (grade not disclosed)
- **Cipko et al (2021)** described a 81-year-old female patient who experienced peripheral eosinophilia during cefiderocol therapy, in association with AKI and a diagnosis of probable AIN secondary to cefiderocol[4]
  - After cefiderocol treatment (32 days total) was discontinued, peripheral eosinophilia resolved within 1 week, and renal function returned to baseline within 16 days
- **Young et al (2025)** described a case of eosinophilia occurring during cefiderocol desensitization in a pediatric patient[5]
  - The patient experienced desensitization failure, developing elevated eosinophil counts, abnormal LFTs, facial rash, and angioedema, and the patient was diagnosed with DRESS
- Eosinophilia has been identified as an adverse reaction during postapproval use of cefiderocol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure[6]

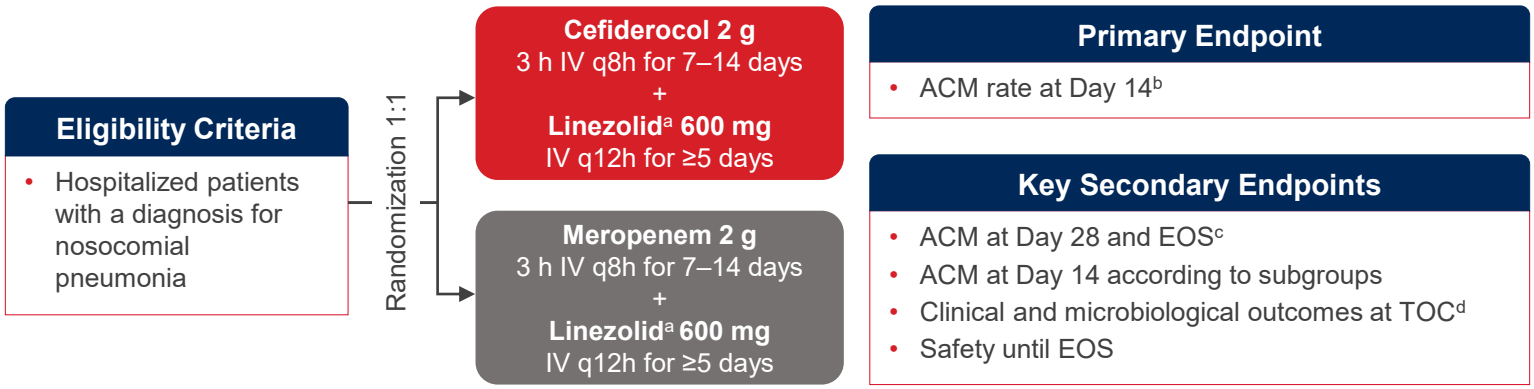
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Clinical Trials

APEKS-NP

APEKS-NP (NCT03032380) was a Phase 3, multicenter, randomized, double-blind, parallel-group, non-inferiority study that assessed the efficacy and safety of cefiderocol in VABP, HABP, or HCABP caused by suspected Gram-negative pathogens.[7]

Figure 1. APEKS-NP Study Design[7]



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

Safety

- A total of 300 patients were randomly assigned to cefiderocol or meropenem, of whom 298 patients (n=148 cefiderocol; n=150 meropenem) received study treatment (ITT and safety populations)[7]
- There were no treatment-related AEs of eosinophilia in either the cefiderocol or meropenem groups[7]
- TEAEs were reported in 130 (88%) patients in the cefiderocol arm and 129 (86%) patients in the meropenem arm[7]
  - Eosinophilia was reported as an AE in 1 patient (0.7%) treated with cefiderocol, which was considered a moderate AE[1]
  - 2 patients (1.3%) in the meropenem group experienced eosinophilia, both of which were considered mild AEs[1]

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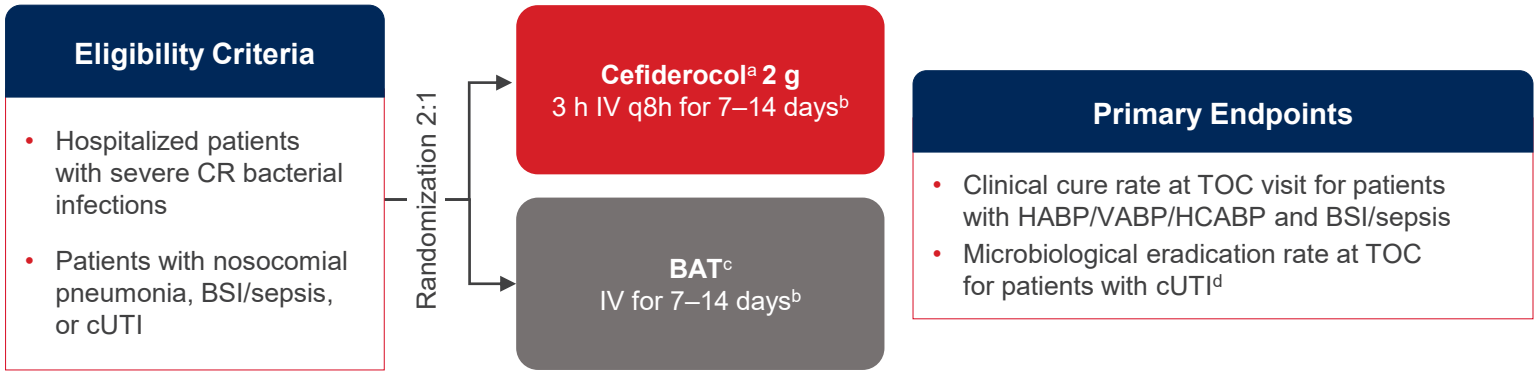
Clinical Trials

CREDIBLE-CR

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 2. CREDIBLE-CR Study Design[3]



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

Safety

- 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]
- TEAEs were reported in 92 (91%) patients in the cefiderocol arm and 47 (96%) patients in the BAT arm[8,9]
  - Eosinophilia was reported as an AE in 2 patients (2%) treated with cefiderocol, both of which were considered mild and unrelated to study treatment[2]
  - Drug eruption was reported as an AE in 1 patient (1%) in the cefiderocol group, who experienced a maculopapular rash with eosinophilia and was considered moderate and related to study treatment[2]
  - There were no eosinophilia AEs reported in the BAT group[2]

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Retrospective Study

Diarra et al (2025) published the results of a retrospective, observational, multicenter study designed to evaluate the use of cefiderocol across 22 centers mostly in France between January 2019 and December 2023.[3]

- A total of 45 patients were included in the analysis, 73% were male, median (IQR) age was 62 (29) years and the median (IQR) CCI was 3 (5)
- Most patients received 6 g of cefiderocol per day, and the median duration of cefiderocol treatment was 34 days
  - Cefiderocol was used in combination with another antibiotic in 40 cases (89%)

Safety[3]

- AEs were graded on a 1–5 scale: grade 1 (mild), grade 2 (moderate), grade 3 (severe), grade 4 (life-threatening or disabling), and grade 5 (resulting in death)
- Cefiderocol treatment was withdrawn in 3 (7%) patients, due to grade 2 hypereosinophilia, grade 4 diarrhea, and acute kidney failure (grade not disclosed)

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Case Report

Cipko et al (2021) described a case of peripheral eosinophilia occurring during cefiderocol salvage therapy for a retained spinal hardware infection involving *Pseudomonas aeruginosa* and extensively drug-resistant *Acinetobacter baumannii*. The 81-year-old woman initially underwent a spinal surgery to treat neuropathic back pain.[4]

- Postoperatively, the patient developed a wound infection with purulence and dehiscence. Wound specimens revealed pan-susceptible *P. aeruginosa* and XDR *A. baumannii*
  - Further molecular characterization showed that the *A. baumannii* isolate produced OXA-23 and the cefiderocol MIC was 0.5 µg/mL
- The hardware was not removable due to spinal instability. Multiple prior antibiotic regimens including ceftriaxone, piperacillin–tazobactam, and colistin+tigecycline resulted in persistent isolation of organisms and side effects
- On Day 50, cefiderocol monotherapy was initiated at 1.5 g q8h and later dose-adjusted to 2 g q8h according to renal function
- After 24 days of cefiderocol, the patient developed AKI (creatinine increase from 84 to 173 µmol/L) associated with peripheral eosinophilia (0.60×10^{-9}/L; normal, $0.04–0.44\times10^{-9}$/L) and accelerated hypertension
- There were no concomitant nephrotoxic medications, and a nephrology assessment concluded probable AIN secondary to cefiderocol (Naranjo probability=6)
- Cefiderocol was stopped after 32 days of therapy:
  - Peripheral eosinophilia resolved within 1 week
  - Creatinine levels returned to baseline 16 days following discontinuation of cefiderocol

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Desensitization Program Study

Young et al (2025) described a case of eosinophilia occurring during cefiderocol desensitization in a pediatric patient undergoing aHSCT. RUSH and ULTRA-RUSH desensitization programs were used to allow administration of medications under strict medical supervision.[5]

Methods[5]

- Anaphylaxis protocols with pre-prescribed medications were available during administration
- During IV antibiotic desensitization, 3 stock solutions of increasing concentrations were prepared

Results[5]

- 1 patient failed desensitization to cefiderocol, developing elevated eosinophil counts, abnormal LFTs, facial rash, and angioedema
- The patient was diagnosed with DRESS

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Post-Marketing AEs

As of March 2026, a search of our post-marketing safety surveillance database and the FDA Adverse Event Reporting System (FAERS) revealed that there has been spontaneous reporting of eosinophilia since the market introduction of cefiderocol. Because these adverse reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency. Furthermore, a causal relationship between the product and the AE you are inquiring about cannot be established.[10,11]

Healthcare professionals are encouraged to report suspected AEs associated with cefiderocol, including eosinophilia, to Shionogi Medical Information at (800) 849-9707 or via email at medinfo@shionogi.com, and to the FDA through the MedWatch Adverse Event Reporting Program (www.fda.gov/medwatch).

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Relevant Prescribing Information

Fetroja® is indicated in patients 18 years of age or older for the treatment of:[6]

- 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:[6]

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

Section 6.2 Postmarketing Experience of the **Fetroja Full Prescribing Information** states the following:[6]

- The following adverse reactions have been identified during postapproval use of Fetroja. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure
- Blood and lymphatic system disorders: neutropenia, eosinophilia

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Literature Search

As of March 2026, a computerized search of the published medical literature using internal and external databases (i.e., Medline® and Embase®) has identified an additional relevant reference regarding cefiderocol and eosinophilia. For your review, this reference is listed in the bibliography below:

- Wicky P-H, Poiraud J, Alves M, et al. Cefiderocol treatment for severe infections due to difficult-to-treat-resistant non-fermentative Gram-negative bacilli in ICU patients: a case series and narrative literature review. *Antibiotics (Basel)*. 2023;12(6):991. [Web Link]

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

Abbreviations

ACM	all-cause mortality	HABP	hospital-acquired bacterial pneumonia
AE	adverse event	HCABP	healthcare-associated bacterial pneumonia
aHSCT	allogeneic hematopoietic stem cell transplantation	ITT	intention-to-treat
AIN	acute interstitial nephritis	IV	intravenous
AKI	acute kidney injury	IQR	interquartile range
BAT	best available therapy	LFT	liver function test
BSI	bloodstream infection	LRTI	lower respiratory tract infection
CCI	Charlson Comorbidity Index	MIC	minimum inhibitory concentration
CR	carbapenem-resistant	mITT	modified intention-to-treat
cUTI	complicated urinary tract infection	OXA	oxacillinase
DRESS	drug reaction with eosinophilia and systemic symptoms	q8h	once every 8 hours
EOS	end of study	q12h	once every 12 hours
EOT	end of treatment	TEAE	treatment-emergent adverse event
FAERS	FDA Adverse Event Reporting System	TOC	test of cure
FDA	US Food and Drug Administration	VABP	ventilator-associated bacterial pneumonia
g	grams	XDR	extensively drug-resistant
h	hours		

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References

1. Data on File 3. Shionogi Inc.
2. Data on File 4. Shionogi Inc.
3. Diarra A, Degrendel M, Eberl I, et al. Real-life cefiderocol use in bone and joint infection: a French national cohort. *Antibiotics (Basel)*. 2025;14(4):388. [Web Link]
4. Cipko K, Gordon AK, Adhikari S, Konecny P. Cefiderocol treatment of *Pseudomonas aeruginosa* and extensively drug-resistant *Acinetobacter baumannii* retained spinal hardware infection causing reversible acute interstitial nephritis. *Int J Infect Dis*. 2021;109:108-111. [Web Link]
5. Young H, Michaelis LJ, Meyer R. Desensitisation programmes — pharmacy involvement in children presenting with allergies having an allogenic hematopoietic stem cell transplant. Poster presented at: EBMT; March 30-April 02, 2025; Florence, Italy.
6. Fetroja® (cefiderocol) for injection, for intravenous use [Prescribing Information]. Shionogi Inc.
7. 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. [Web Link]
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. [Web Link]
9. Matsunaga Y, Sonoyama T, Casanova L, et al. Safety profile of the novel siderophore cephalosporin cefiderocol in randomized phase 2 and phase 3 clinical studies of serious Gram-negative infections. Poster presented at: IDWeek; October 21-25, 2020; Virtual Conference, Online.
10. Data on File 117. Shionogi Inc.
11. FDA Adverse Events Reporting System (FAERS) Public Dashboard. Cefiderocol, Cefiderocol Sulfate Tosylate. Last accessed August 2026. [Web Link]

Enclosure

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