Fetroja® – Effect on Iron Homeostasis and Red Blood Cell Parameters

SHIONOGI

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Summary | Clinical Studies | Published Case Report | Prescribing Information | Literature Search | Abbreviations & References

Clinical Studies

- The Phase 2 **APEKS-cUTI** study compared the efficacy and safety of cefiderocol with that of imipenem-cilastatin in patients with cUTIs. Parameters related to iron homeostasis were investigated at baseline and at TOC[1–3]
  - There was no difference in plasma hepcidin or other parameters of iron homeostasis, including transferrin saturation, TIBC, or Hb between the cefiderocol and imipenem-cilastatin groups at TOC[1–3]
  - 1 patient treated with cefiderocol reported a mild AE of iron deficiency anemia which was not considered related to treatment; no other AEs related to iron metabolism were reported[1–3]
- The Phase 3 non-inferiority **APEKS-NP** study compared ACM rates at Day 14 as primary endpoint between cefiderocol and high-dose, extended-infusion meropenem in patients with nosocomial pneumonia. Iron homeostasis-related parameters (ie, hepcidin, iron, transferrin saturation, and TIBC) were measured at baseline and TOC[3–7]
  - There were no notable differences overall between cefiderocol and meropenem arms in the change from baseline to TOC in iron homeostasis parameters[3–7]
  - Anemia was reported in 12 (8.1%) patients in the cefiderocol group and 12 (8%) patients in the meropenem group[4–7]
  - ACM rates at Day 14, Day 28 and EOS, and clinical cure rates at TOC were similar between treatment arms in both subgroups of patients with low and normal baseline iron levels[4–7]
  - In patients receiving concomitant blood transfusion and/or iron supplementation, ACM rates were similar with cefiderocol and meropenem compared with patients not receiving supplementation, and clinical cure and microbiological eradication rates were numerically higher in the cefiderocol arm compared with the meropenem arm[4–7]
- The Phase 3 descriptive **CREDIBLE-CR** study assessed clinical and microbiological outcomes in patients with serious CR Gram-negative bacterial infections treated with cefiderocol or BAT. Part of safety assessments, changes in iron homeostasis parameters in plasma were investigated[8–10]
  - No clinically relevant differences were found between treatment arms in the changes from baseline to TOC in hepcidin, iron levels, transferrin saturation, and TIBC in plasma
- **Saisho Y et al (2018)** attributed decreased iron levels in a Phase 1 study to the uptake of iron by the bone marrow due to hematopoiesis from frequent blood sampling. The investigators did not consider the fluctuation of blood iron levels to be clinically significant or related to cefiderocol[11]

Published Case Report

- **Schellong et al (2024)** reported a patient with NDM-producing *Pseudomonas aeruginosa* osteomyelitis who successfully received cefiderocol for a total of 169 days, including 63 days through OPAT from an elastomeric pump[12]
  - The patient experienced manifest iron deficiency anemia possibly due to the extended treatment duration of cefiderocol

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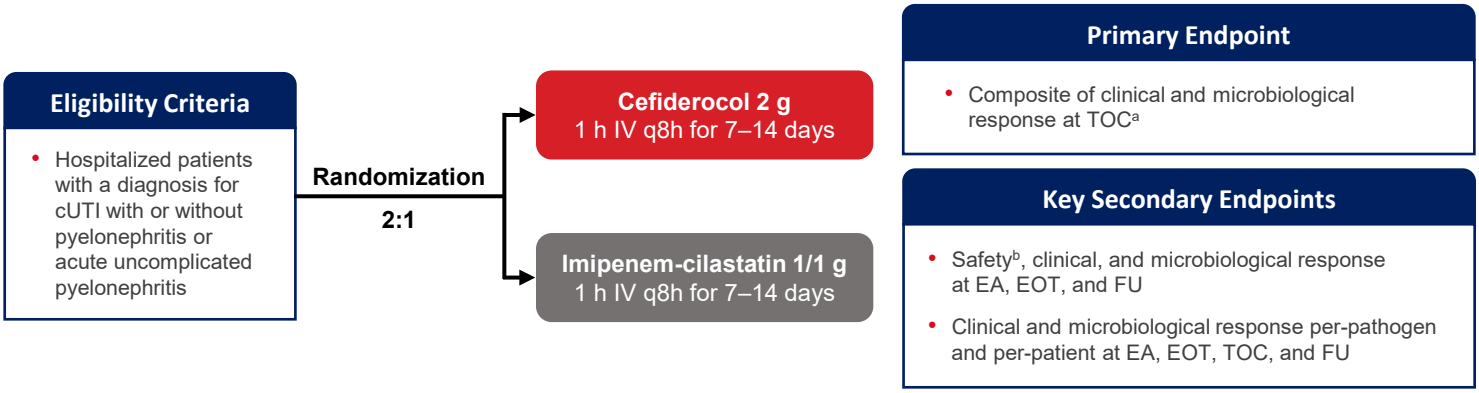
Clinical Studies

APEKS-cUTI

Methods:

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

Figure 1. APEKS-cUTI Study Design[1]



Abbreviations: CFU, colony-forming unit; cUTI, complicated urinary tract infection; EA, early assessment; EOT, end of treatment; FU, follow-up; g, grams; h, hours; IV, intravenous; 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 1 dose of study drug and had qualifying Gram-negative uropathogen (≥1x10^5 CFU/mL).
[b]Safety assessed in all randomly assigned individuals who received at least 1 dose of study drug, according to the treatment they received.

- The safety population consisted of 300 patients in the cefiderocol group and 148 patients in the imipenem-cilastatin group[1]
- Cefiderocol has a catechol moiety that complexes with free iron to facilitate transport into Gram-negative bacteria; therefore, laboratory parameters related to iron metabolism were monitored[1]
- Plasma concentration of hepcidin, iron, transferrin and TIBC were assessed as pre-specified exploratory safety outcomes at baseline and at TOC in patients with acute infection[1]

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Clinical Studies

APEKS-cUTI (Cont.)

Results:

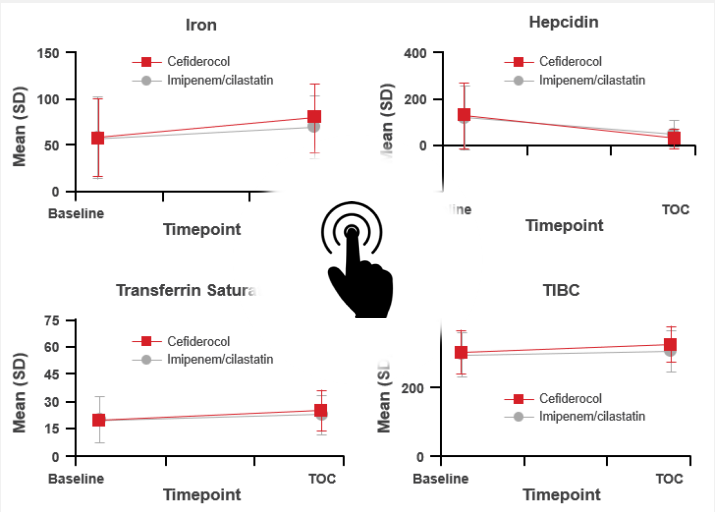
- No difference in plasma hepcidin or other parameters of iron homeostasis, including transferrin saturation, TIBC, or Hb were identified between the cefiderocol and imipenem-cilastatin groups at TOC (**Table 1** and **Figure 2**)[2]

Table 1. Summary of Laboratory Parameters at TOC from APEKS-cUTI[2]

Parameter	Cefiderocol (Mean Value)			Imipenem/Cilastatin (Mean Value)		
	Baseline	Post[a]	Change	Baseline	Post[a]	Change
Hepcidin-25 (ng/mL)	130.8	41.4	–89.4	123.1	53	–70.1
Transferrin saturation (%)	20	25	5	20.3	22.9	2.6
TIBC (µg/dL)	303.3	327.3	24	300.1	308.4	8.3
Hb (g/L)	12.8	13	0.2	12.6	12.7	0.1

Abbreviations: Hb, hemoglobin; TIBC, total iron-binding capacity; TOC, test of cure.
[a]TOC was defined as 7 days (±2 days) after the end of antibiotic treatment.

Figure 2. Change Between Baseline and TOC for Iron, Hepcidin-25, Transferrin Saturation, and TIBC in the APEKS-cUTI Study (Safety Population)[3]



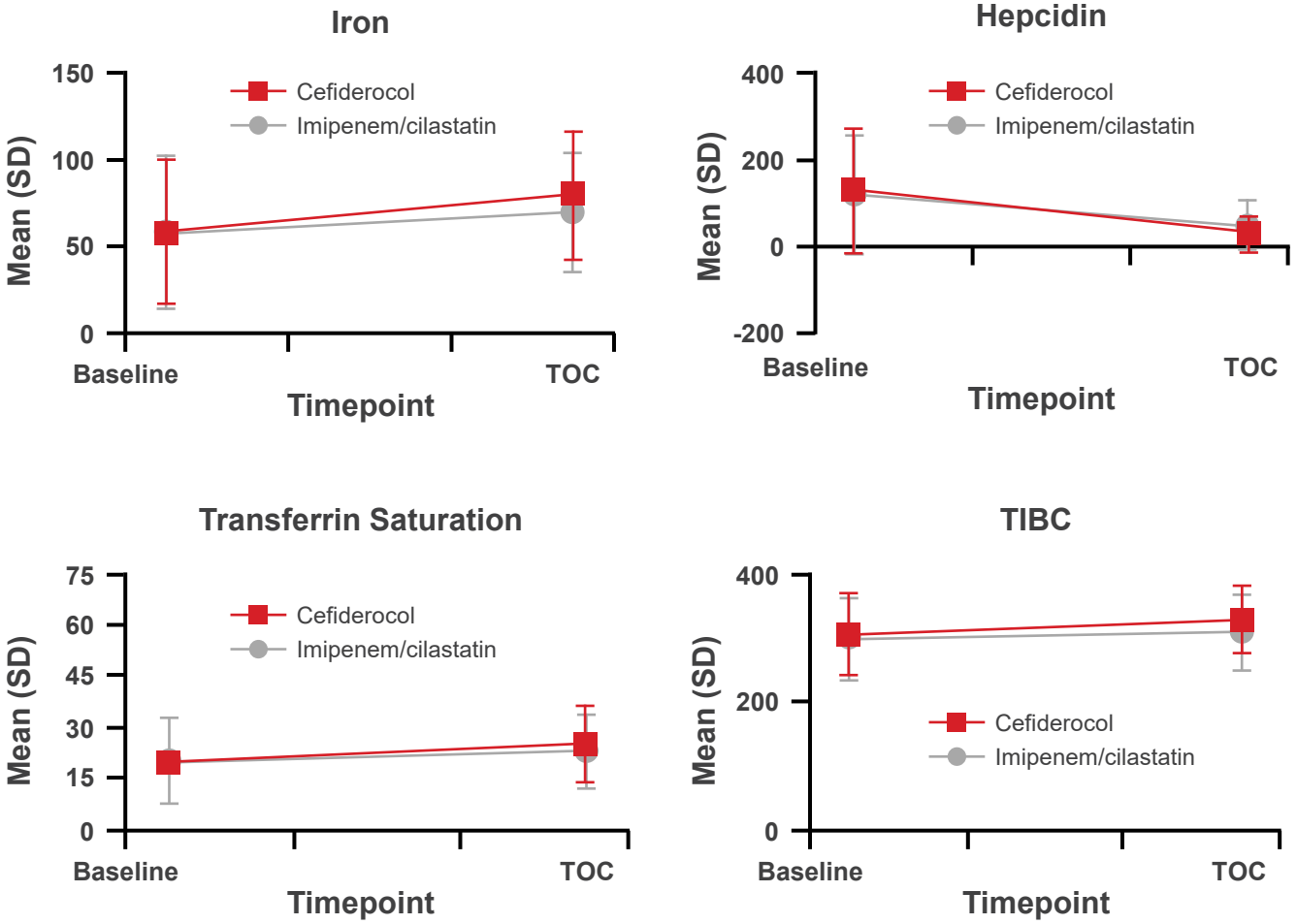
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Clinical Studies

Figure 2. Change Between Baseline and TOC for Iron, Hepcidin-25, Transferrin Saturation, and TIBC in the APEKS-cUTI Study (Safety Population)[3]



Abbreviations: cUTI, complicated urinary tract infection; SD, standard deviation; TIBC, total iron-binding capacity.
Figure adapted from Matsunaga et al. IDWeek. 2020.

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Clinical Studies

APEKS-cUTI (Cont.)

- 1 patient treated with cefiderocol reported a mild AE of iron deficiency anemia which was not considered related to treatment; no other AEs related to iron metabolism were reported. The incidence of TEAEs related to anemia from **APEKS-cUTI** are listed in **Table 2**[2]

Table 2. Incidence (%) of TEAEs (Safety Population) by Preferred Terms[2]

AEs	Cefiderocol (n=300) n (%)	Imipenem (n=148) n (%)
AEs related to anemia		
Anemia	1 (0.3)	1 (0.7)
Iron deficiency anemia	1 (0.3)	0
Hemorrhagic anemia	1 (0.3)	0

Abbreviations: AEs, adverse events; TEAEs, treatment-emergent adverse events.

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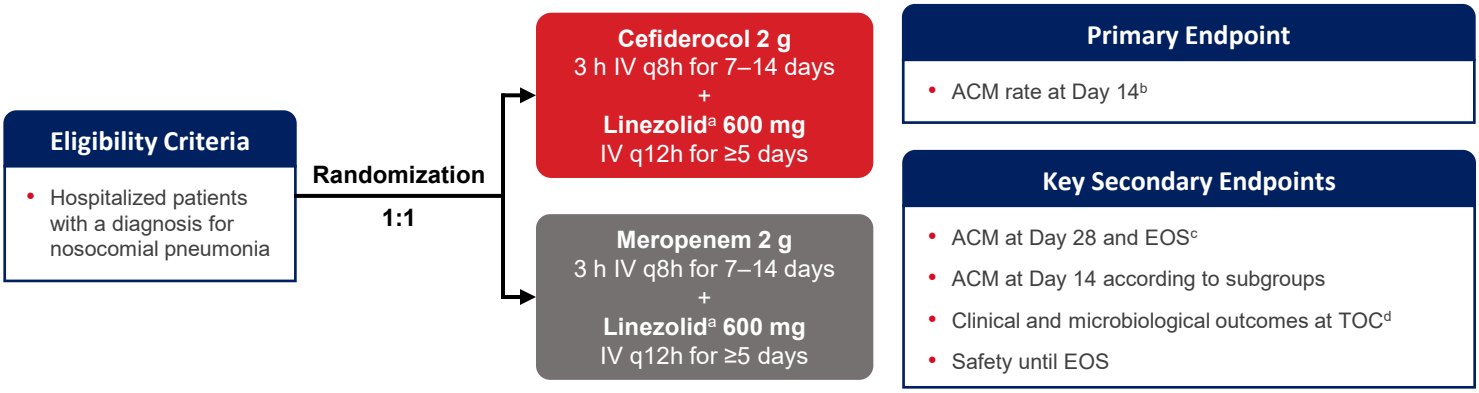
Clinical Studies

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 HABP, HCABP, or VABP caused by suspected Gram-negative pathogens[4]

Figure 3. APEKS-NP Study Design[4]



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, every 8 hours; q12h, every 12 hours; 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 LRTI.
[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 arm; N=150 meropenem arm) received study treatment (ITT and safety populations)[4]
- The primary efficacy analysis was conducted in the mITT population (ie, all patients receiving at least 1 dose of study drug, excluding patients with Gram-positive monomicrobial infections)[4]
- Safety was assessed in all randomly assigned individuals who received at least 1 dose of study drug[5]

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Clinical Studies

APEKS-NP (Cont.)

Results:

- There were no notable differences observed between treatment arms in the change from baseline to TOC with regard to iron parameters as shown in **Table 3**[5]

Table 3. Summary of Laboratory Parameters at TOC from APEKS-NP[5]

Parameter	Cefiderocol (Mean Value)			Meropenem (Mean Value)		
	Baseline	Post[a]	Change	Baseline	Post[a]	Change
Hepcidin (nmol/L)	31.308	21.854	–9.453	28.980	22.172	–6.809
Transferrin saturation (%)	17.6	22.4	4.8	17.5	21.5	4
TIBC (µmol/L)	33.3	39.3	6	35	40.1	5
Hb (g/L)	109.95	106.59	–3.35	113.90	110.92	–2.98

Abbreviations: Hb, hemoglobin; TIBC, total iron-binding capacity; TOC, test of cure.
[a]TOC was defined as 7 days (±2 days) after the end of antibiotic treatment.

- Anemia was reported in 12 (8.1%) patients in the cefiderocol group and 12 (8%) patients in the meropenem group. The incidence of TEAEs related to anemia from **APEKS-NP** are listed in **Table 4**[6]

Table 4. Incidence (%) of AEs (Safety Population) by Preferred Terms[6]

AEs	Cefiderocol (n=148) n (%)	Meropenem (n=150) n (%)
Blood and lymphatic system disorders		
Anemia	12 (8.1)	12 (8)
Anemia of chronic disease	2 (1.4)	0
Hemorrhagic anemia	0	2 (1.3)
Iron deficiency anemia	3 (2)	0
Nephrogenic anemia	0	1 (0.7)
Normochromic normocytic anemia	1 (0.7)	0
Investigations		
Hb decreased	1 (0.7)	0
Red blood cell decreased	1 (0.7)	0

Abbreviations: AEs, adverse events; Hb, hemoglobin.
Table adapted from Skaar et al. *Eur J Clin Microbiol Infect Dis*. 2022.

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Clinical Studies

APEKS-NP (Cont.)

Role of Baseline Iron Levels

- In the ITT population, baseline serum iron concentrations were available for 292 patients. Most patients (n=242, 82.9%) had low iron levels and 50 patients (17.1%) had normal iron levels at randomization[6]
- In the mITT population with baseline serum iron concentrations available (n=286), the distribution of patients with low and normal iron levels was similar between treatment arms: 114 patients receiving cefiderocol and 122 receiving meropenem had low iron levels, and 27 and 23 patients, respectively, had normal iron levels[6]
- ACM rates at Day 14, Day 28 and EOS were similar between treatment arms in both subgroups of patients with low and normal baseline iron levels, as shown in **Table 5**[6]

Table 5. ACM Rates According to Baseline Iron Level Category (mITT Population)[6]

ACM Rate, n/N' (%)[a]	Low Iron Level			Normal Iron Level		
	Cefiderocol	Meropenem	Difference (95% CI)	Cefiderocol	Meropenem	Difference (95% CI)
Day 14	14/114 (12.3)	14/121 (11.6)	0.7 (−7.6, 9)	3/27 (11.1)	3/23 (13)	−1.9 (−20.1, 16.2)
Day 28	23/112 (20.5)	23/121 (19)	1.5 (−8.7, 11.8)	6/27 (22.2)	5/23 (21.7)	0.5 (−22.5, 23.5)
EOS	30/111 (27)	27/121 (22.3)	4.7 (−6.4, 15.8)	6/27 (22.2)	5/23 (21.7)	0.5 (−22.5, 23.5)

Abbreviations: ACM, all-cause mortality; CI, confidence interval; EOS, end of study; mITT, modified intention-to-treat.
[a]The percentage was calculated using number of patients (N) with known vital status within each category as the denominator. Only patients with known baseline iron levels were included in the analysis.
Table adapted from Skaar et al. *Eur J Clin Microbiol Infect Dis*. 2022.

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Clinical Studies

APEKS-NP (Cont.)

- Clinical cure rates at TOC were similar between treatment arms in both subgroups of patients with low and normal baseline iron levels, as shown in **Table 6**[6]
- There was a numerical difference in favor of cefiderocol in microbiological eradication rates at TOC (treatment difference: 15.4; 95% CI: −13.2 to 43.9 [**Table 6**])[6]
- Rates of clinical cure and microbiological eradication were generally numerically greater in patients with normal baseline iron levels, compared with those with low baseline iron levels (**Table 6**)[6]

Table 6. Clinical and Microbiological Response Rates at TOC According to Baseline Iron Level Category (mITT Population)[6]

	Low Iron Level[a]			Normal Iron Level[a]		
	Cefiderocol	Meropenem	Difference (95% CI)	Cefiderocol	Meropenem	Difference (95% CI)
Clinical response rate, n/N (%)						
Clinical cure	72/114 (63.2)	82/122 (67.2)	−4.1 (−16.2, 8.1)	19/27 (70.4)	16/23 (69.6)	0.8 (−24.7, 26.3)
Clinical failure	24/114 (21.1)	25/122 (20.5)		3/27 (11.1)	5/23 (21.7)	
Indeterminate	18/114 (15.8)	15/122 (12.3)		5/27 (18.5)	2/23 (8.7)	
Microbiological eradication rate, n/N' (%)						
Eradication	41/94 (43.6)	51/106 (48.1)	−4.5 (−18.3, 9.3)	17/26 (65.4)	10/20 (50)	15.4 (−13.2, 43.9)
Persistence	20/94 (21.3)	22/106 (20.8)		3/26 (11.5)	5/20 (25)	
Indeterminate	33/94 (35.1)	33/106 (31.1)		6/26 (23.1)	5/20 (25)	

Abbreviations: CI, confidence interval; mITT, modified intention-to-treat.
[a]Only patients with known baseline iron levels were included in the analysis.
N, patients in the mITT population with the corresponding baseline iron category.
N′, patients with non-missing baseline pathogens.
Table adapted from Skaar et al. *Eur J Clin Microbiol Infect Dis*. 2022.

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Clinical Studies

APEKS-NP (Cont.)

Role of Blood Transfusion and/or Iron Supplementation

- Within the mITT population, 37 patients in the cefiderocol arm and 27 in the meropenem arm received concomitant blood transfusion (26 in the cefiderocol arm and 17 in the meropenem arm) and/or iron supplementation (16 in the cefiderocol arm and 11 in the meropenem arm) by EOT[6]
- The majority of patients receiving blood transfusion or iron supplementation had low baseline iron levels: 83.8% receiving cefiderocol and 77.8% receiving meropenem (as shown in **Table 7**, among patients in the ITT population with known baseline iron levels)[6]

Table 7. Iron Supplementation Received by EOT According to Baseline Iron Level Category (ITT Population)[6]

Supplementation, n (%)	Low Iron Level		Normal Iron Level	
	Cefiderocol (n=117)	Meropenem (n=125)	Cefiderocol (n=27)	Meropenem (n=23)
Blood transfusion[a]	21 (17.9)	14 (11.2)	3 (11.1)	3 (13)
Iron supplementation	15 (12.8)	8 (6.4)	1 (3.8)	3 (13)
Blood transfusion and/ or iron supplementation[a]	31 (26.5)	21 (16.8)	4 (14.9)	6 (26.1)

Abbreviations: EOT, end of treatment; ITT, intention-to-treat.
[a]Number of patients with known baseline iron levels among those who received blood transfusion; for 2 patients, baseline iron level data were not available.
Table adapted from Skaar et al. *Eur J Clin Microbiol Infect Dis*. 2022.

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Clinical Studies

APEKS-NP (Cont.)

- ACM rates were similar with cefiderocol and meropenem, or lower with cefiderocol, in patients receiving concomitant blood and/or iron supplementation compared with patients not receiving any supplementation, as shown in **Table 8**[7]

Table 8. ACM Rates in Patients With or Without Supplementation (Blood Transfusion, Iron Supplementation, or Both) (mITT Population)[7]

ACM Rate, n/N' (%)[a]	With Blood Transfusion Only			Without Blood Transfusion		
	Cefiderocol	Meropenem	Difference (95% CI)	Cefiderocol	Meropenem	Difference (95% CI)
Day 14	5/26 (19.2)	6/17 (35.3)	−16.1 (−43.4, 11.2)	13/119 (10.9)	11/129 (8.5)	2.4 (−5, 9.8)
Day 28	8/25 (32)	7/17 (41.2)	−9.2 (−38.9, 20.5)	22/118 (18.6)	23/129 (17.8)	0.8 (−8.8, 10.5)
EOS	10/25 (40)	8/17 (47.1)	−7.1 (−37.6, 23.5)	28/117 (23.9)	26/129 (20.2)	3.8 (−6.6, 14.2)
	With Iron Supplementation Only			Without Iron Supplementation		
	Cefiderocol	Meropenem	Difference (95% CI)	Cefiderocol	Meropenem	Difference (95% CI)
Day 14	0/16 (0)	1/11 (9.1)	−9.1 (−26.1, 7.9)	18/129 (14)	16/135 (11.9)	2.1 (−6, 10.2)
Day 28	2/16 (12.5)	3/11 (27.3)	−14.8 (−45.7, 16.1)	28/127 (22)	27/135 (20)	2 (−7.8, 11.9)
EOS	3/16 (18.8)	3/11 (27.3)	−8.5 (−41.1, 24)	35/126 (27.8)	31/135 (23)	4.8 (−5.7, 15.4)
	With Blood Transfusion and/or Iron Supplementation			Without Any Supplementation		
	Cefiderocol	Meropenem	Difference (95% CI)	Cefiderocol	Meropenem	Difference (95% CI)
Day 14	5/37 (13.5)	7/27 (25.9)	−12.4 (−32.3, 7.5)	13/108 (12)	10/119 (8.4)	3.6 (−4.3, 11.5)
Day 28	9/36 (25)	10/27 (37)	−12 (−35.1, 11)	21/107 (19.6)	20/119 (16.8)	2.8 (−7.3, 12.9)
EOS	12/36 (33.3)	11/27 (40.7)	−7.4 (−31.5, 16.7)	26/106 (24.5)	23/119 (19.3)	5.2 (−5.6, 16)

Abbreviations: ACM, all-cause mortality; CI, confidence interval; EOS, end of study; mITT, modified intention-to-treat; N, patients with known vital status in the mITT population receiving the corresponding iron supplementation.
All patients in the overall mITT population are included regardless of their baseline iron level status.
Table adapted from Skaar et al. *Eur J Clin Microbiol Infect Dis*. 2022 (Supplementary Materials).

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Clinical Studies

APEKS-NP (Cont.)

- Among patients receiving blood transfusion and/or iron supplementation, clinical cure and microbiological eradication rates were higher in the cefiderocol arm compared with the meropenem arm, as shown in **Table 9**[7]

Table 9. Clinical and Microbiological Response Rates at TOC in Patients With or Without Supplementation (Blood Transfusion, Iron Supplementation, or Any) (mITT Population)[7]

	With Blood Transfusion Only			Without Blood Transfusion		
	Cefiderocol	**Meropenem**	**Difference (95% CI)**	**Cefiderocol**	**Meropenem**	**Difference (95% CI)**
Clinical response rate, n/N (%)						
Clinical cure	17/26 (65.4)	6/17 (35.3)	30.1 (0.9, 59.3)	77/119 (64.7)	92/130 (70.8)	−6.1 (−17.7, 5.5)
Clinical failure	5/26 (19.2)	7/17 (41.2)		22/119 (18.5)	24/130 (18.5)	
Indeterminate	4/26 (15.4)	4/17 (23.5)		20/119 (16.8)	14/130 (10.8)	
Microbiological eradication rate, n/N' (%)						
Eradication	11/24 (45.8)	4/17 (23.5)	22.3 (−6.1, 50.7)	48/100 (48)	57/110 (51.8)	−3.8 (−17.3, 9.7)
Persistence	6/24 (25)	5/17 (29.4)		20/100 (20)	22/110 (20)	
Indeterminate	7/24 (29.2)	8/17 (47.1)		32/100 (32)	31/110 (28.2)	
	With Iron Supplementation Only			**Without Iron Supplementation**		
	Cefiderocol	**Meropenem**	**Difference (95% CI)**	**Cefiderocol**	**Meropenem**	**Difference (95% CI)**
Clinical response rate, n/N (%)						
Clinical cure	13/16 (81.3)	8/11 (72.7)	8.5 (−24, 41.1)	81/129 (62.8)	90/136 (66.2)	−3.4 (−14.9, 8.1)
Clinical failure	3/16 (18.8)	3/11 (27.3)		24/129 (18.6)	28/136 (20.6)	
Indeterminate	0/16 (0)	0/11 (0)		24/129 (18.6)	18/136 (13.2)	
Microbiological eradication rate, n/N' (%)						
Eradication	9/12 (75)	4/8 (50)	25	50/112 (44.6)	57/119 (47.9)	−3.3 (−16.1, 9.6)
Persistence	0/12 (0)	2/8 (25)		26/112 (23.2)	25/119 (21)	
Indeterminate	3/12 (25)	2/8 (25)		36/112 (32.1)	37/119 (31.1)	
	With Blood Transfusion and/or Iron Supplementation			**Without Any Supplementation**		
	Cefiderocol	**Meropenem**	**Difference (95% CI)**	**Cefiderocol**	**Meropenem**	**Difference (95% CI)**
Clinical response rate, n/N (%)						
Clinical cure	26/37 (70.3)	13/27 (48.1)	22.1 (−1.8, 46)	68/108 (63)	85/120 (70.8)	−7.9 (−20.1, 4.3)
Clinical failure	7/37 (18.9)	10/27 (37)		20/108 (18.5)	21/120 (17.5)	
Indeterminate	4/37 (10.8)	4/27 (14.8)		20/108 (18.5)	14/120 (11.7)	
Microbiological eradication rate, n/N' (%)						
Eradication	18/32 (56.3)	8/24 (33.3)	22.9 (−2.6, 48.4)	41/92 (44.6)	53/103 (51.5)	−6.9 (−20.9, 7.1)
Persistence	6/32 (18.8)	7/24 (29.2)		20/92 (21.7)	20/103 (19.4)	
Indeterminate	8/32 (25)	9/24 (37.5)		31/92 (33.7)	30/103 (29.1)	

Abbreviations: CI, confidence interval; mITT, modified intention-to-treat.
All patients in the overall mITT population are included regardless of their baseline iron level status. N, patients in the mITT population receiving the corresponding iron supplementation; N', patients with non-missing baseline pathogens.
Table adapted from Skaar et al. *Eur J Clin Microbiol Infect Dis*. 2022 (Supplementary Materials).

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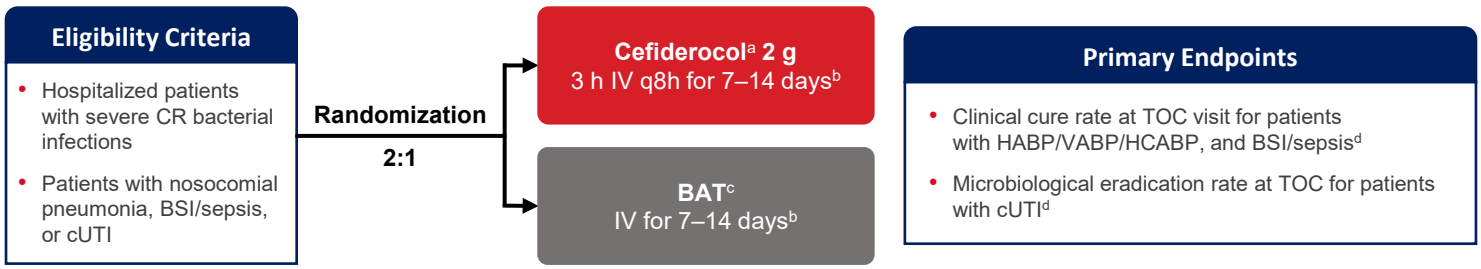
Clinical Studies

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

Figure 4. CREDIBLE-CR Study Design[8]



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, 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 at least 1 dose of study drug.

- BAT was selected prior to randomization by the investigator and could include up to 3 systemic antibiotics[8]
- Cefiderocol treatment could be complemented with 1 adjunctive antibiotic therapy, excluding polymyxins, cephalosporins, and carbapenems, including combinations with a β-lactamase inhibitor[8]

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Clinical Studies

CREDIBLE-CR (Cont.)

Results:

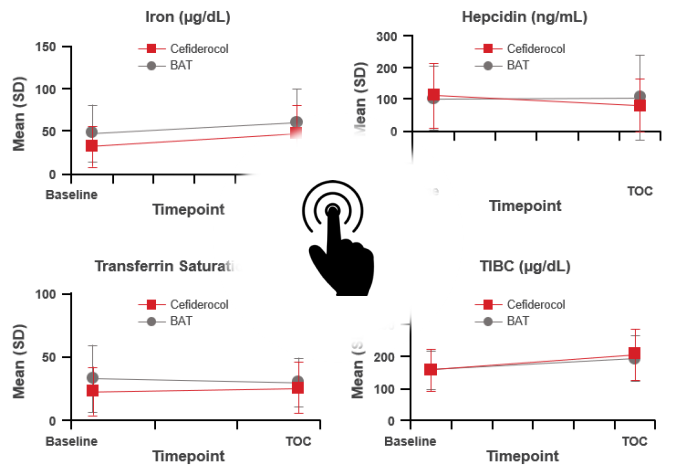
- A total of 152 patients were randomly assigned to cefiderocol or BAT, of whom 150 patients (n=101 cefiderocol; n=49 BAT) received treatment (ITT and safety population)[8]
- Overall, there were no significant differences observed between treatment groups in the change from baseline to TOC with regard to iron parameters as shown in **Table 10** and **Figure 5**[9,10]

Table 10. Summary of Laboratory Parameters at TOC from CREDIBLE-CR[9]

Parameter	Cefiderocol (Mean Value)			BAT (Mean Value)		
	Baseline	Post[a]	Change	Baseline	Post[a]	Change
Hepcidin (ng/mL)	115.071	81.645	–33.426	98.083	105.853	7.770
Transferrin saturation (%)	20.7	26	5.3	29.4	30.1	0.7
TIBC (µg/dL)	163.2	205.6	42.5	173.3	193.5	20.2
Hb (g/dL)	9.579	9.900	0.321	9.234	9.503	0.269

Abbreviations: BAT, best available therapy; Hb, hemoglobin; TIBC, total iron-binding capacity; TOC, test of cure.
[a]TOC was defined as 7 days (±2 days) after the end of antibiotic treatment.

Figure 5. Change Between Baseline and TOC for Iron, Hepcidin-25, Transferrin Saturation, and TIBC in CREDIBLE-CR (Safety Population)[10]



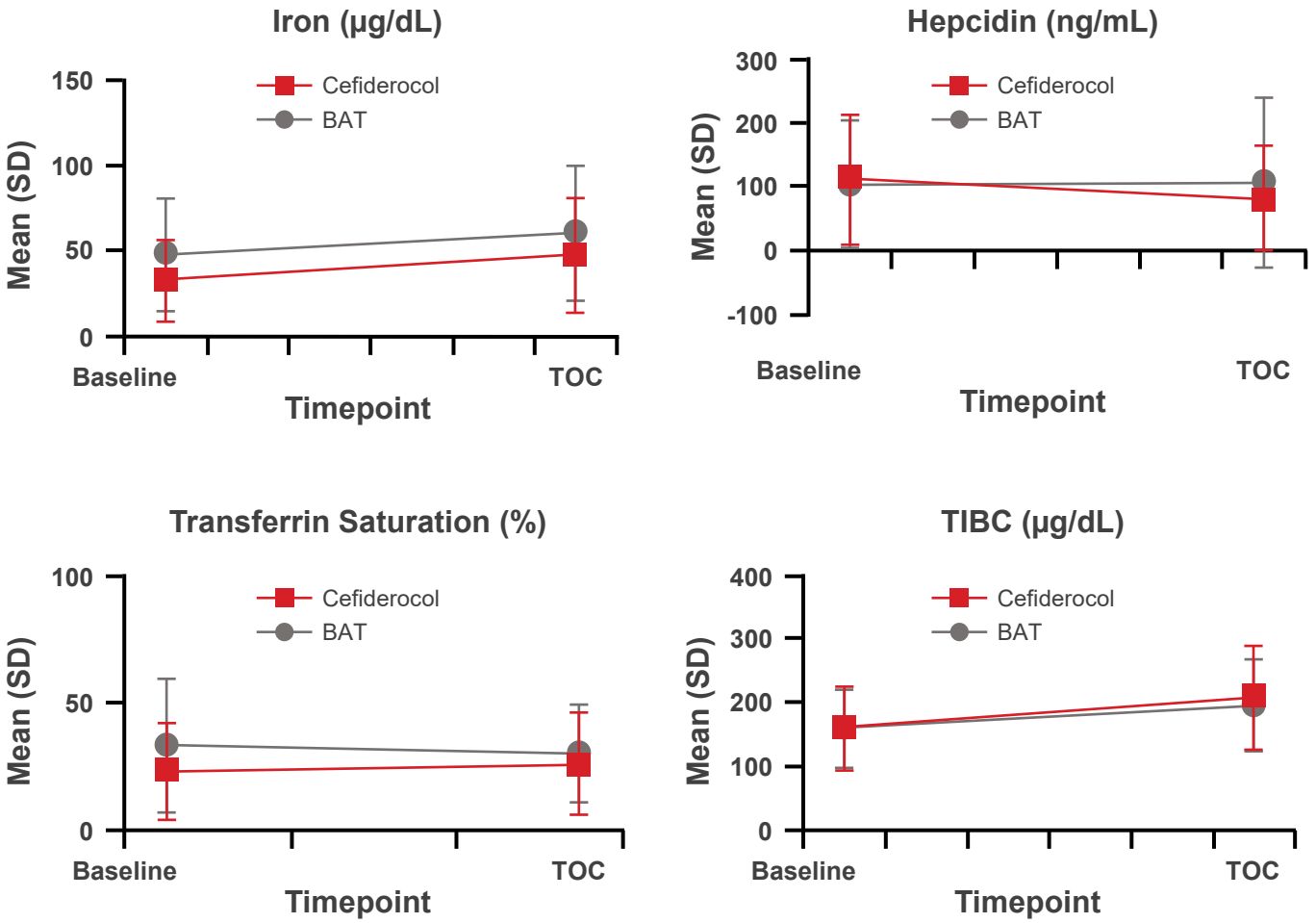
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Clinical Studies

Figure 5. Change Between Baseline and TOC for Iron, Hepcidin-25, Transferrin Saturation, and TIBC in CREDIBLE-CR (Safety Population)[10]



Abbreviations: BAT, best available therapy; SD, standard deviation; TIBC, total iron-binding capacity.
Figure adapted from Longshaw et al. ISICEM. 2021.

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Clinical Studies

CREDIBLE-CR (Cont.)

- The incidence of TEAEs related to anemia in **CREDIBLE-CR** are shown in **Table 11**[10]

Table 11. Incidence (%) of AEs (Safety Population) by Preferred Terms[10]

AEs	Cefiderocol (n=101) n (%)	BAT (n=49) n (%)
AEs related to anemia		
Anemia	8 (7.9)	2 (4.1)
Anemia of chronic disease	1 (1)	1 (2)
Normochromic normocytic anemia	1 (1)	0

Abbreviations: AEs, adverse events; BAT, best available therapy.
Table adapted from Longshaw et al. ISICEM. 2021.

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Clinical Studies

Phase 1 Study

Methods:

- The PK, safety, and tolerability of cefiderocol were evaluated in a Phase 1, single-center, randomized, double-blind, placebo-controlled study in healthy Japanese and Caucasian adults. The effects of cefiderocol on blood iron and TIBC were evaluated[11]
- The study consisted of 2 parts: a single ascending-dose study (n=40) and a multiple ascending-dose study (n=30). The multiple-dose study was planned to include up to 2 doses of cefiderocol, 1000 mg and 2000 mg, in 2 groups. 54 subjects received cefiderocol and 16 received placebo[11]

Results:

- In the single-dose study, the mean value of blood iron was slightly below the LLN of the reference range in the 500 mg group on Day 5 (71.2 µg/dL) as well as on Day 8 (68.3 µg/dL). Values were also below the LLN in the 1000 mg group on Day 8 (76.8 µg/dL). No mean value below the LLN was detected in the 2000 mg group or in the placebo group[11]
- In the multiple-dose study, the mean value of blood iron was slightly below the LLN on Days 5, 11, and 17 in the first 1000 mg group, and on Days 5, 11, 13, 14, and 17 in the second 1000 mg group (Table 12). The fluctuation in blood iron levels among the groups was not believed to be clinically significant or related to the study drug. No mean value below the LLN was detected in the 2000 mg group or in the placebo group. TIBC in the cefiderocol groups did not show a significant change when compared to placebo group[11]

Table 12. Iron Levels in the Multiple-Dose Study[11]

Timepoint	Statistic	Iron Level[a] (µg/dL)			
		Cefiderocol			
		1000 mg 1st (n=8)	1000 mg 2nd (n=8)[b]	2000 mg (n=8)	Placebo (n=6)
Day 1 (baseline)	Mean (Change from baseline) SD Range	91.6 (0) 17.2 59–115	96.5 (0) 23.3 50–129	132.3 (0) 49.9 60–230	118.7 (0) 32.2 102–183
Day 2	Mean (Change from baseline) SD Range	82.5 (–9.1) 22.1 [illegible]	113.1 (+16.6) 17.1 80–135	123.6 (–8.6) 35.6 81–196	125.5 (+6.8) 21.9 100–164
Day 3	Mean (Change from baseline) SD Range	[illegible] [illegible] [illegible]	[illegible] [illegible] [illegible]	111.6 (–20.6) 35.5 60–182	115.8 (–2.8) 29.8 84–161
Day 5	Mean (Change from baseline) SD Range	[illegible] [illegible] [illegible]	[illegible] [illegible] [illegible]	109.1 (–23.1) 24.8 86–166	98.8 (–19.8) 16.0 77–113
Day 8	Mean (Change from baseline) SD Range	[illegible] [illegible] [illegible]	[illegible] [illegible] [illegible]	[illegible]3.4 (–28.9) 21.2 74–143	121.0 (+2.3) 23.5 95–156
Day 10	Mean (Change from baseline) SD Range	[illegible] [illegible] [illegible]	[illegible] [illegible] [illegible]	[illegible]3 (–43.0) 33.4 92–154	116.3 (–2.3) 27.3 78–152
Day 11	Mean (Change from baseline) SD Range	[illegible] [illegible] [illegible]	[illegible] [illegible] [illegible]	[illegible].8 (–36.5) 36.1 46–141	121.5 (+2.8) 21.7 82–138
Day 12	Mean (Change from baseline) SD Range	[illegible] [illegible] [illegible]	[illegible] [illegible] [illegible]	109.1 (–23.1) 40.2 51–168	121.0 (+2.3) 22.2 91–156
Day 13	Mean (Change from baseline) SD Range	[illegible] [illegible] [illegible]	[illegible] [illegible] [illegible]	90.4 (–41.9) 13.4 75–116	82.0 (–36.7) 48.1 39–167
Day 14	Mean (Change from baseline) SD Range	95.6 (+4.0) 32.9 56–154	64.6 (–34.0) 26.0 29–109	85.4 (–46.9) 27.8 57–136	85.8 (–32.8) 33.5 51–137
Day 17	Mean (Change from baseline) SD Range	60.6 (–31.0) 33.3 33–139	64.3 (–34.3) 17.5 37–82	100.9 (–31.4) 33.9 59–168	87.2 (–31.5) 32.8 49–128

- The investigators attributed the decreased iron levels to the uptake of iron by the bone marrow due to hematopoiesis from frequent blood sampling. The investigators did not consider the fluctuation of blood iron levels to be clinically significant or related to cefiderocol[11]

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Clinical Studies

Table 12. Iron Levels in the Multiple-Dose Study[11]

Timepoint	Statistic	Iron Level[a] (µg/dL)			
		Cefiderocol			
		1000 mg 1st (n=8)	1000 mg 2nd (n=8)[b]	2000 mg (n=8)	Placebo (n=6)
Day 1 (baseline)	Mean (Change from baseline) SD Range	91.6 (0) 17.2 59–115	96.5 (0) 23.3 50–129	132.3 (0) 49.9 60–230	118.7 (0) 32.2 102–183
Day 2	Mean (Change from baseline) SD Range	82.5 (–9.1) 22.3 52–116	113.1 (+16.6) 17.1 80–135	123.6 (–8.6) 35.6 81–196	125.5 (+6.8) 21.9 100–164
Day 3	Mean (Change from baseline) SD Range	95.5 (+3.9) 17.8 72–119	92.1 (–4.4) 15.7 69–114	111.6 (–20.6) 35.5 60–182	115.8 (–2.8) 29.8 84–161
Day 5	Mean (Change from baseline) SD Range	74.5 (–17.1) 13.1 55–94	72 (–24.5) 18.4 53–104	109.1 (–23.1) 24.8 86–166	98.8 (–19.8) 16 77–113
Day 8	Mean (Change from baseline) SD Range	96.9 (+5.3) 19.1 64–130	97.9 (+1.4) 12.6 81–110	103.4 (–28.9) 21.2 74–143	121 (+2.3) 23.5 95–156
Day 10	Mean (Change from baseline) SD Range	80.5 (–11.1) 25.7 23–104	89.3 (–9.3) 18 65–105	89.3 (–43) 33.4 52–154	116.3 (–2.3) 27.3 78–152
Day 11	Mean (Change from baseline) SD Range	65 (–26.6) 26.6 14–87	66.9 (–31.7) 36.9 35–116	95.8 (–36.5) 36.1 46–141	121.5 (+2.8) 21.7 82–138
Day 12	Mean (Change from baseline) SD Range	86.6 (–5) 30.6 18–111	83.4 (–15.1) 22.9 55–111	109.1 (–23.1) 40.2 51–168	121 (+2.3) 22.2 91–156
Day 13	Mean (Change from baseline) SD Range	87.1 (–4.5) 41.6 50–178	71.1 (–27.4) 25.7 36–107	90.4 (–41.9) 13.4 75–116	82 (–36.7) 48.1 39–167
Day 14	Mean (Change from baseline) SD Range	95.6 (+4) 32.9 56–154	64.6 (–34) 26 29–109	85.4 (–46.9) 27.8 57–136	85.8 (–32.8) 33.5 51–137
Day 17	Mean (Change from baseline) SD Range	60.6 (–31) 33.3 33–139	64.3 (–34.3) 17.5 37–82	100.9 (–31.4) 33.9 59–168	87.2 (–31.5) 32.8 49–128

Abbreviation: SD, standard deviation.
[a]Reference range: 80–199 g/dL for males, and 70–179 g/dL for females.
[b]n=7 for days 10, 11, 12, 14, and 17.
Table adapted from Saisho et al. *Antimicrob Agents Chemother*. 2018.

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Published Case Report

Schellong et al (2024) described a male patient who presented to a hospital in Germany with osteomyelitis due to NDM-producing *P. aeruginosa* that received cefiderocol for a total of 169 days, including 63 days through OPAT.[12]

- During a prior hospitalization, NDM-producing *P. aeruginosa* and *Enterococcus faecalis* was isolated from multiple bone cultures and was treated with ampicillin/sulbactam 3 g q8h for 28 days, and was subsequently treated with cefiderocol 2–3 g q6h for 14 days
- During the patient's current hospitalization, multiple cultures from the tibial medullary cavity revealed NDM-producing *P. aeruginosa* with a cefiderocol MIC of 0.5 mg/L as tested by the Etest method on Mueller-Hinton agar
- Cefiderocol 2 g q8h was started and after 23 days of therapy, the patient was discharged and switched to outpatient cefiderocol treatment via a PICC line for 63 days
- The OPAT service utilized an elastomeric pump (EASYPUMP II ST 400-4-S, B. Braun, Melsungen, Germany) to provide cefiderocol over the 3 h infusion duration
  - There were no reported complications during OPAT
- Planned readmission occurred after OPAT, where the patient underwent autogenous cancellous bone grafting with 4 g of cefiderocol followed by IV cefiderocol 3 g q8h for 83 days
  - Investigators utilized therapeutic drug monitoring to guide dosing
- *P. aeruginosa* was not seen on subsequent cultures
- Manifest iron deficiency anemia was observed 10 days after cefiderocol cessation which could possibly be related to the extended therapy duration
  - The Hb was 5.1 mmol/L (normal range, 8.7–10.9 mmol/L), serum iron was 1.5 µmol/L (normal range, 6.3–30.1 µmol/L), transferrin saturation was 2% (normal range, 16–45%), and ferritin was 11.4 µg/L (normal range, 30–400 µg/L)

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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:[13]

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

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

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Literature Search

As of Febuary 2026, a computerized search of the published medical literature using internal and external databases (ie, Medline® and Embase®) has identified additional relevant references regarding cefiderocol and the impact of iron levels. For your review, these references are listed in the bibliography as follows:

- Kidd JM, Abdelraouf K, Nicolau DP. Development of neutropenic murine models of iron overload and depletion to study the efficacy of siderophore-antibiotic conjugates. *Antimicrob Agents Chemother*. 2019;64(1):e01961-19. [Web Link]
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- Longshaw C, Weiss G, Skaar EP, et al. Effects of iron supplementation on the efficacy of cefiderocol in patients with carbapenem-resistant infections in the pathogen-focused CREDIBLE-CR study. Poster presented at the 40th ISICEM; August 31-September 03, 2021; Brussels, Belgium.

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.

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Abbreviations

ACM	all-cause mortality	ITT	intention-to-treat
AE	adverse event	IV	intravenous
BAT	best available therapy	LLN	lower limit of normal
BSI	bloodstream infection	LRTI	lower respiratory tract infection
CFU	colony-forming unit	MIC	minimum inhibitory concentration
CI	confidence interval	mITT	modified intention-to-treat
CR	carbapenem-resistant	NDM	New Delhi metallo-β-lactamase
cUTI	complicated urinary tract infection	OPAT	outpatient parenteral antimicrobial therapy
EA	early assessment	PICC	peripherally inserted central catheter
EOS	end of study	PK	pharmacokinetics
EOT	end of treatment	q6h	every 6 hours
FDA	US Food and Drug Administration	q8h	every 8 hours
FU	follow-up	q12h	every 12 hours
g	grams	TEAE	treatment-emergent adverse event
h	hours	TIBC	total iron-binding capacity
Hb	hemoglobin	TOC	test of cure
HABP	hospital-acquired bacterial pneumonia	VABP	ventilator-associated bacterial pneumonia
HCABP	healthcare-associated bacterial pneumonia		

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6. Skaar EP, Echols R, Matsunaga Y, Menon A, Portsmouth S. Iron serum levels and iron homeostasis parameters in patients with nosocomial pneumonia treated with cefiderocol: *post hoc* analysis of the APEKS-NP study. *Eur J Clin Microbiol Infect Dis*. 2022;41(3):467-476. [Web Link]
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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]
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12. Schellong P, Wennek-Klose J, Spiegel C, Rödel J, Hagel S. Successful outpatient parenteral antibiotic therapy with cefiderocol for osteomyelitis caused by multi-drug resistant Gram-negative bacteria: a case report. *JAC Antimicrob Resist*. 2024;6(1):dlae015. [Web Link]
13. Fetroja® (cefiderocol) for injection, for intravenous use [Prescribing Information]. Shionogi Inc.

Enclosure

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