Fetroja® - Use In Patients With Altered Iron Homeostasis

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Clinical and Preclinical Studies

Phase 3 Studies

- APEKS-NP, a non-inferiority Phase 3 study compared all-cause mortality (ACM) rates at Day 14 as primary endpoint between cefiderocol and high-dose, extended-infusion meropenem in patients with nosocomial pneumonia. Patients received cefiderocol 2 grams (g) as a 3 hour (h) intravenous (IV) infusion every 8 hours (q8h) or high-dose, extended infusion meropenem (2 g q8h, 3 h infusion) for 7-14 Days[1-5]
  - Low or Normal Iron Levels: ACM rates at Day 14 (12.3% vs 11.6%), Day 28 (20.5% vs 19%) and end of study (EOS) (27% vs 22.3%), as well as clinical cure (63.2% vs 67.2%) and microbiological eradication (43.6% vs 48.1%) rates at test of cure (TOC) were similar between cefiderocol vs meropenem arms in both subgroups of patients with low and normal baseline iron levels[2-5]
  - Blood Transfusion/Iron Supplementation: In patients receiving concomitant blood transfusion and/or iron supplementation, ACM rates were lower at Day 14 (13.5% vs 25.9%), Day 28 (25% vs 37%), and EOS (33.3% vs 40.7%) in cefiderocol vs meropenem arms, and clinical cure (70.3% vs 48.1%) and microbiological eradication (56.3% vs 33.3%) rates were numerically higher in the cefiderocol arm compared with the meropenem arm[2-5]
- CREDIBLE-CR, a randomized, open-label, multicenter, descriptive Phase 3 trial assessed the efficacy and safety of cefiderocol to best available therapy (BAT) in patients with hospital-acquired bacterial pneumonia (HABP), ventilator-associated bacterial pneumonia (VABP), healthcare-associated bacterial pneumonia (HCABP), bloodstream infection (BSI)/sepsis, or complicated urinary tract infection (cUTI) caused by carbapenem-resistant (CR) Gram-negative pathogens, with no hypothesis testing or formal inferential analyses. Cefiderocol 2 g q8h over a 3 h IV infusion or IV BAT was administered for 7-14 Days[6-9]
  - Low or Normal Iron Levels: An analysis was conducted that examined clinical, microbiological, and mortality outcomes in patients with low or normal baseline serum iron levels[7,8]
    - Clinical cure for patients treated with cefiderocol who had low iron levels at TOC was 52.5% compared with normal iron levels (50%), in the carbapenem-resistant microbiological intention-to-treat (CR-Micro-ITT) population[7]
    - Microbiological eradication at TOC for patients treated with cefiderocol who had low iron levels was 27.9% compared with normal iron levels (30%), in the CR-Micro-ITT population[7]
    - ACM rate at Day 28 in patients treated with cefiderocol who had low baseline serum iron was 23.4% compared with patients who had normal iron levels (28.6%), in the safety population[8]
  - Blood Transfusion/Iron Preparation: An analysis was conducted that examined clinical, microbiological, and mortality outcomes in patients that received blood transfusions and/or iron preparations[9]
    - Clinical cure at TOC in patients treated with cefiderocol who received a blood transfusion and/or iron preparation was 41.2% compared to patients who did not receive any supplementation (60.9%), in the CR-Micro-ITT population
    - Microbiological eradication at TOC in patients treated with cefiderocol who received a blood transfusion and/or iron preparation was 20.6% compared to patients who did not receive any supplementation (39.1%), in the CR-Micro-ITT population
    - ACM rate at Day 28 in patients treated with cefiderocol who received a blood transfusion and/or iron preparation was 23.8% compared to patients who did not receive a blood transfusion and/or iron preparation (25.4%), in the safety population

Preclinical Study

- Kidd JM et al (2019) evaluated the efficacy of cefiderocol in an *in vivo* human simulated iron-overloaded murine thigh infection model where 31 clinical strains received treatment for 24 h and 15 clinical strains for 72 h. The treatment group was given cefiderocol or meropenem (2 g q8h) over 3 h[10]
  - Efficacy was defined as a change in $\log_{10}$ colony-forming units (CFU) per thigh at 24 h or 72 h versus 0 h controls
  - Baseline mean bacterial burdens of all isolates at 0 h ranged from 5.5 to 5.9 $\log_{10}$ CFU/thigh and grew by 2.9 to 3.4 $\log_{10}$ CFU/thigh at 24 h without treatment
  - Mean reduction in bacterial burden following cefiderocol treatment in standard and iron-overloaded models at 24 h were -1.46 and -1.55 $\log_{10}$ CFU/thigh (P=0.54), respectively, and -2.48 and -2.53 $\log_{10}$ CFU/thigh (P=0.81) at 72 h. At 24 h, there were no significant differences observed for 24/31 isolates

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Overview/Background

- Cefiderocol is a siderophore-cephalosporin with a novel mechanism for efficiently penetrating the outer cell membrane of Gram-negative pathogens. Cefiderocol binds to ferric iron, is recognized as a siderophore, and is actively transported into bacterial cells through the outer membrane via the bacterial iron transporters which function to incorporate this essential nutrient into the cell for bacterial replication[11]

- The expression of iron transporters along with native bacterial siderophores increases when environmental iron is low. *In vitro* minimum inhibitory concentration (MIC) studies of cefiderocol for Gram-negative bacteria in broth with varying iron concentrations have demonstrated that when iron is removed, the *in vitro* MIC decreases below that observed in standard cation-adjusted Mueller Hinton broth (CAMHB) suggesting increased potency when iron is not available[10]

- The hypoferremic response to infection in mammalian hosts, where iron is sequestered intracellularly to deprive infectious organisms of this essential nutrient, create similar *in vivo* conditions as iron-depleted broth *in vitro* contributing to the efficacy of cefiderocol. However, patients with iron overload may have a diminished hypoferremic response raising concern with the efficacy of cefiderocol in hyperferremic conditions[10]

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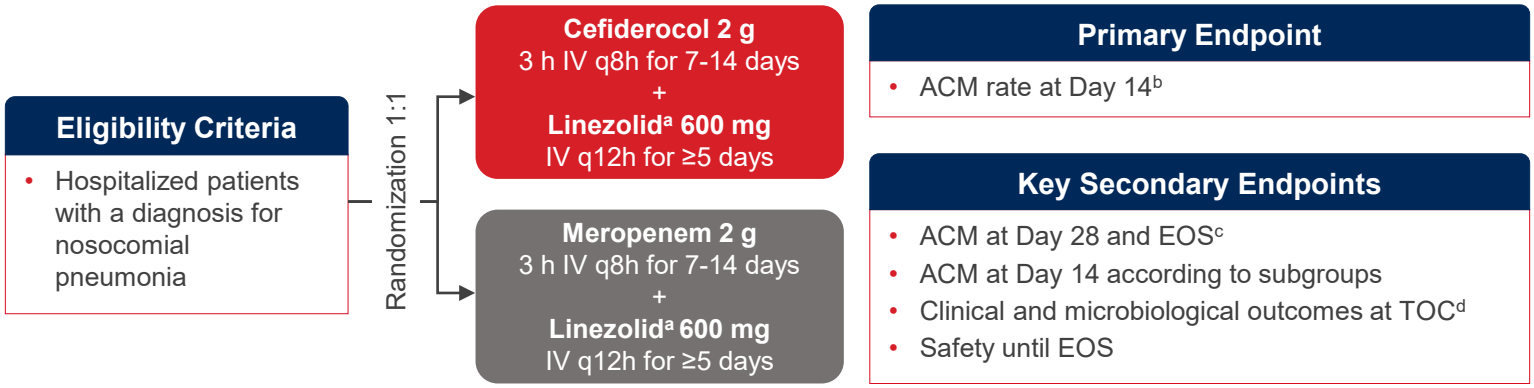
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APEKS-NP

Methods

- APEKS-NP (NCT03032380) was a Phase 3, multicenter, randomized, double-blind, parallel-group, noninferiority study that assessed the efficacy and safety of cefiderocol in VABP, HABP, or HCABP caused by suspected Gram-negative pathogens[2]

Figure 1. APEKS-NP Study Design[2]



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).

- 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 (intention-to-treat [ITT] and safety populations).The primary efficacy analysis was conducted in the modified intention-to-treat (mITT) population (eg, all patients receiving at least 1 dose of study drug, excluding patients with Gram-positive monomicrobial infections)[2]
- Safety was assessed in all randomly assigned individuals who received at least 1 dose of study drug[3]

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APEKS-NP (Cont'd)

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 (defined as male: <11 µmol/L and female: <7 µmol/L) and 50 patients (17.1%) had normal iron levels (defined as male: 11-32 µmol/L and female: 7-31 µmol/L) at randomization. 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[4]
- 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 1**[4]

Table 1. All-Cause Mortality Rates According to Baseline Iron Level Category (mITT Population)[4]

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, 9.0)	3/27 (11.1)	3/23 (13)	−1.9 (−20.1, 16.2)
Day 28	23/112 (20.5)	23/121 (19.0)	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.

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APEKS-NP (Cont'd)

mITT Population

- Clinical cure rates at TOC were similar between treatment arms in both subgroups of patients with low and normal baseline iron levels. There was a numerical difference in favor of cefiderocol in microbiological eradication rates at TOC (treatment difference: 15.4; 95% confidence intervals [CI]: −13.2, 43.9). 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 2**)[4]

Table 2. Clinical and Microbiological Response Rates at Test of Cure According to Baseline Iron Level Category (mITT Population)[4]

	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; N, patients in the mITT population with the corresponding baseline iron category;
N', patients with non-missing baseline pathogens.

[a]Only patients with known baseline iron levels were included in the analysis.

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APEKS-NP (Cont'd)

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 end of treatment (EOT). 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 3**, among patients in the ITT population with known baseline iron levels)[4]

Table 3. Iron Supplementation Received by End of Treatment According to Baseline Iron Level Category (ITT Population)[4]

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)

Abbreviation: 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.

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APEKS-NP (Cont'd)

Role of Blood Transfusion and/or Iron Supplementation (Cont'd)

- 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 4**[5]

Table 4. All-Cause Mortality Rates in Patients With or Without Supplementation (Blood Transfusion, Iron Supplementation, or Both) (mITT Population)[5]

	With Blood Transfusion Only			Without Blood Transfusion		
ACM rate, n/N' (%)[a]	**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 (−5.0, 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**		
ACM rate, n/N' (%)[a]	**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 (−6.0, 10.2)
Day 28	2/16 (12.5)	3/11 (27.3)	−14.8 (−45.7, 16.1)	28/127 (22)	27/135 (20)	2.0 (−7.8, 11.9)
EOS	3/16 (18.8)	3/11 (27.3)	−8.5 (−41.1, 24.0)	35/126 (27.8)	31/135 (23)	4.8 (−5.7, 15.4)
	With Blood Transfusion and/or Iron Supplementation			**Without Any Supplementation**		
ACM rate, n/N' (%)[a]	**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 (12.0)	10/119 (8.4)	3.6 (−4.3, 11.5)
Day 28	9/36 (25)	10/27 (37)	−12.0 (−35.1, 11.0)	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, 16.0)

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; N', patients with non-missing baseline pathogens.

[a]All patients in the overall mITT population are included regardless of their baseline iron level status.

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APEKS-NP (Cont'd)

Role of Blood Transfusion and/or Iron Supplementation (Cont'd)

- 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 5**[5]

Table 5. Clinical and Microbiological Response Rates at Test of Cure in Patients With or Without Supplementation (Blood Transfusion, Iron Supplementation, or Both) (mITT Population)[5]

	With Blood Transfusion Only			Without Blood Transfusion		
Clinical response rate, n/N (%)	**Cefiderocol (N=26)**	**Meropenem (N=17)**	**Difference (95% CI)**	**Cefiderocol (N=119)**	**Meropenem (N=130)**	**Difference (95% CI)**
Clinical cure	17 (65.4)	6 (35.3)	30.1 (0.9, 59.3)	77 (64.7)	92 (70.8)	−6.1 (−17.7, 5.5)
Clinical failure	5 (19.2)	7 (41.2)		22 (18.5)	24 (18.5)	
Indeterminate	4 (15.4)	4 (23.5)		20 (16.8)	14 (10.8)	
Microbiological eradication rate, n/N' (%)	**Cefiderocol (N=24)**	**Meropenem (N=17)**	**Difference (95% CI)**	**Cefiderocol (N=100)**	**Meropenem (N=110)**	**Difference (95% CI)**
Eradication	11 (45.8)	4 (23.5)	22.3 (−6.1, 50.7)	48 (48.0)	57 (51.8)	−3.8 (−17.3, 9.7)
Persistence	6 (25.0)	5 (29.4)		20 (20.0)	22 (20.0)	
Indeterminate	7 (29.2)	8 (47.1)		32 (32.0)	31 (28.2)	
	With Iron Supplementation Only			**Without Iron Supplementation**		
Clinical response rate, n/N (%)	**Cefiderocol (N=16)**	**Meropenem (N=11)**	**Difference (95% CI)**	**Cefiderocol (N=129)**	**Meropenem (N=136)**	**Difference (95% CI)**
Clinical cure	13 (81.3)	8 (72.7)	8.5 (−24.0, 41.1)	81 (62.8)	90 (66.2)	−3.4 (−14.9, 8.1)
Clinical failure	3 (18.8)	3 (27.3)		24 (18.6)	28 (20.6)	
Indeterminate	0 (0)	0 (0)		24 (18.6)	18 (13.2)	
Microbiological eradication rate, n/N' (%)	**Cefiderocol (N=12)**	**Meropenem (N=8)**	**Difference (95% CI)**	**Cefiderocol (N=112)**	**Meropenem (N=119)**	**Difference (95% CI)**
Eradication	9 (75)	4 (50)	25.0	50 (44.6)	57 (47.9)	−3.3 (−16.1, 9.6)
Persistence	0 (0)	2 (25)		26 (23.2)	25 (21)	
Indeterminate	3 (25)	2 (25)		36 (32.1)	37 (31.1)	
	With Blood Transfusion and/or Iron Supplementation			**Without Any Supplementation**		
Clinical response rate, n/N (%)	**Cefiderocol (N=37)**	**Meropenem (N=27)**	**Difference (95% CI)**	**Cefiderocol (N=108)**	**Meropenem (N=120)**	**Difference (95% CI)**
Clinical cure	26 (70.3)	13 (48.1)	22.1 (−1.8, 46.0)	68 (63)	85 (70.8)	−7.9 (−20.1, 4.3)
Clinical failure	7 (18.9)	10 (37)		20 (18.5)	21 (17.5)	
Indeterminate	4 (10.8)	4 (14.8)		20 (18.5)	14 (11.7)	
Microbiological eradication rate, n/N' (%)	**Cefiderocol (N=32)**	**Meropenem (N=24)**	**Difference (95% CI)**	**Cefiderocol (N=92)**	**Meropenem (N=103)**	**Difference (95% CI)**
Eradication	18 (56.3)	8 (33.3)	22.9 (−2.6, 48.4)	41 (44.6)	53 (51.5)	−6.9 (−20.9, 7.1)
Persistence	6 (18.8)	7 (29.2)		20 (21.7)	20 (19.4)	
Indeterminate	8 (25)	9 (37.5)		31 (33.7)	30 (29.1)	

All patients in the overall mITT population are included regardless of their baseline iron level status.

Abbreviations: CI, confidence interval; mITT, modified intention-to-treat; N, patients in the mITT population receiving the corresponding iron supplementation; N', patients with non-missing baseline pathogens.

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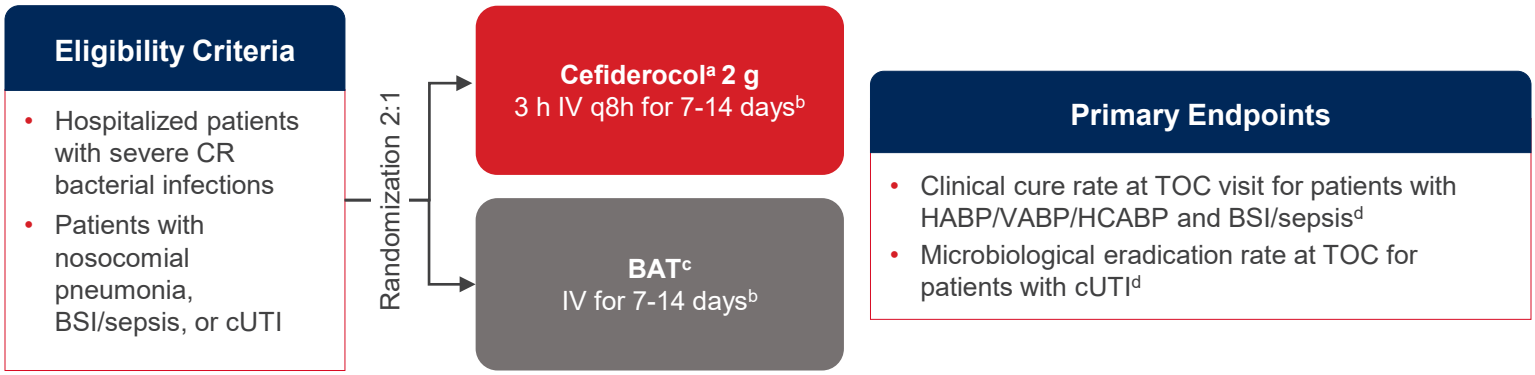
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CREDIBLE-CR

Methods

- CREDIBLE-CR (NCT02714595) was a Phase 3, prospective, open-label, multicenter, randomized, parallel-group, descriptive study that assessed the efficacy and safety of cefiderocol and BAT in hospitalized patients with severe CR bacterial infections[6]
- CREDIBLE-CR was a descriptive study with no hypothesis testing or formal inferential analyses[6]

Figure 2. CREDIBLE-CR Study Design[6]



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.

- A total of 152 patients were randomly assigned to cefiderocol or BAT, of whom 150 patients (n=101 cefiderocol; n=49 BAT) received at least one dose of study treatment (ITT and safety population)
- A total of 118 patients were included in the CR-Micro-ITT population, which included patients randomized to cefiderocol (n=80) and BAT (n=38) whose baseline Gram-negative pathogen was CR as confirmed by central laboratory testing[6]

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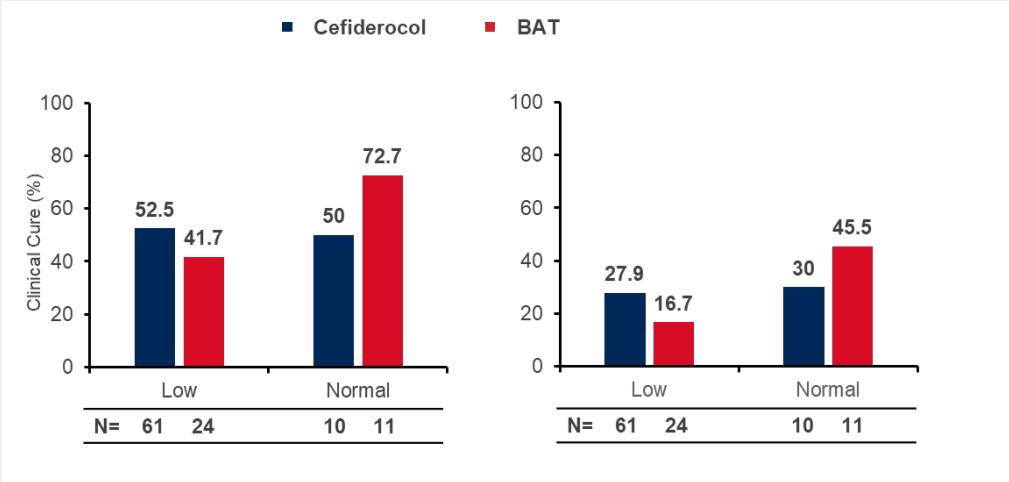
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CREDIBLE-CR (Cont'd)

Patients with Low/Normal Iron

- An analysis was conducted in the Phase 3 CREDIBLE-CR clinical study that examined clinical, microbiological, and mortality outcomes in patients with low or normal baseline serum iron levels (normal iron level ranges defined as 59-178 µg/mL in males and 37-173 µg/mL in females)[7,8]
- When examining clinical cure and microbiological eradication rates in the CR-Micro-ITT population, descriptions of the baseline iron status (low or normal) were available for 71 patients in the cefiderocol group (low iron [n=61]; normal iron [n=10]) and 35 patients in the BAT group (low iron [n=24]; normal iron [n=11]). The clinical cure rates and microbiological eradication rates for these 106 patients are shown in **Figure 3**[7]

Figure 3. Clinical and Microbiological TOC Outcome by Baseline Iron Levels at TOC in the Carbapenem-resistant Microbiological ITT Population[7]



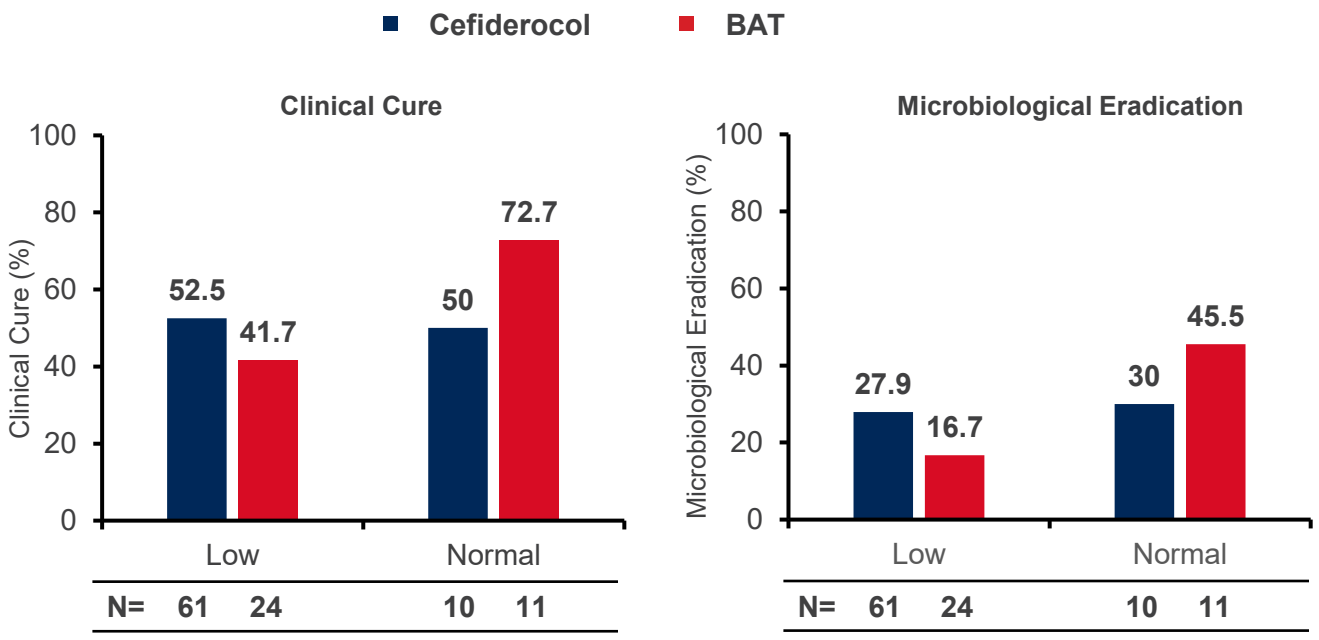
Abbreviations: BAT, best available therapy; ITT, intent-to-treat; TOC, test of cure.

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CREDIBLE-CR (Cont'd)

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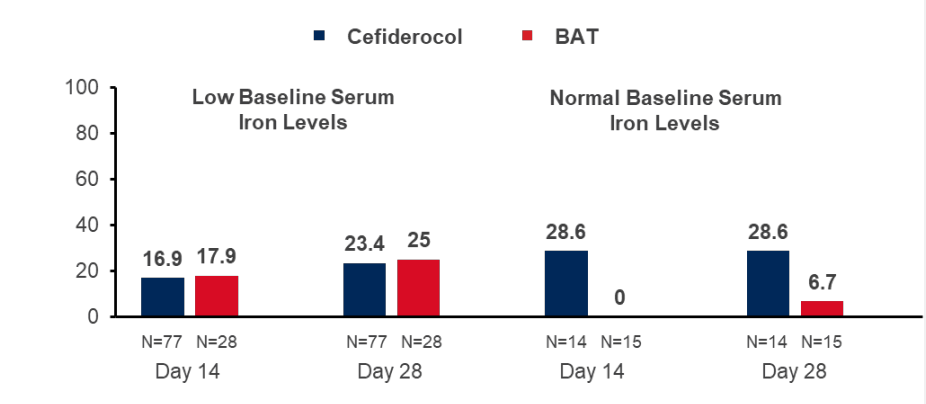
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Mortality

- When examining the ACM in the safety population, descriptions of the baseline iron status (low or normal serum iron levels) were available for 91 patients in the cefiderocol group (low iron [n=77]; normal iron [n=14]) and 43 patients in the BAT group (low iron [n=28]; normal iron [n=15])[8]
- The Day 14 and Day 28 ACM rates in patients treated with cefiderocol who had low baseline serum iron levels were 16.9% and 23.4%, respectively compared with ACM rates in patients who had normal baseline serum iron levels at Day 14 and Day 28 (28.6% ACM rate at both timepoints) (see **Figure 4** below)[8]

Figure 4. Day 14 and Day 28 ACM Rates in Patients According to Baseline Serum Iron Levels (ITT/Safety Population)[8]



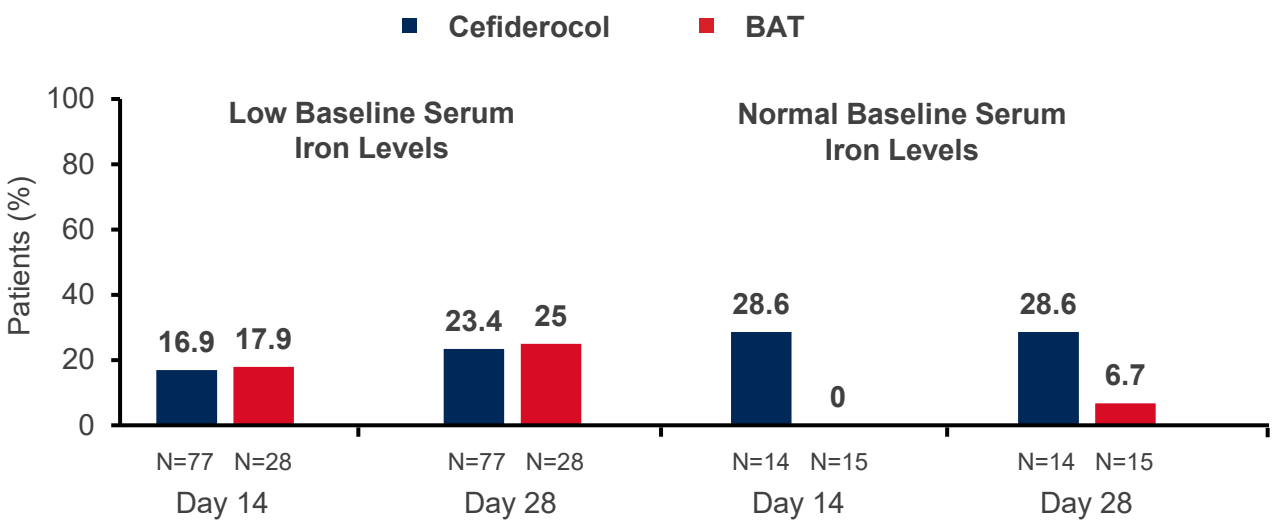
Abbreviations: ACM, all-cause mortality; BAT, best available therapy; ITT, intention-to-treat.

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Figure 4. Day 14 and Day 28 ACM Rates in Patients According to Baseline Serum Iron Levels (ITT/Safety Population)[8]



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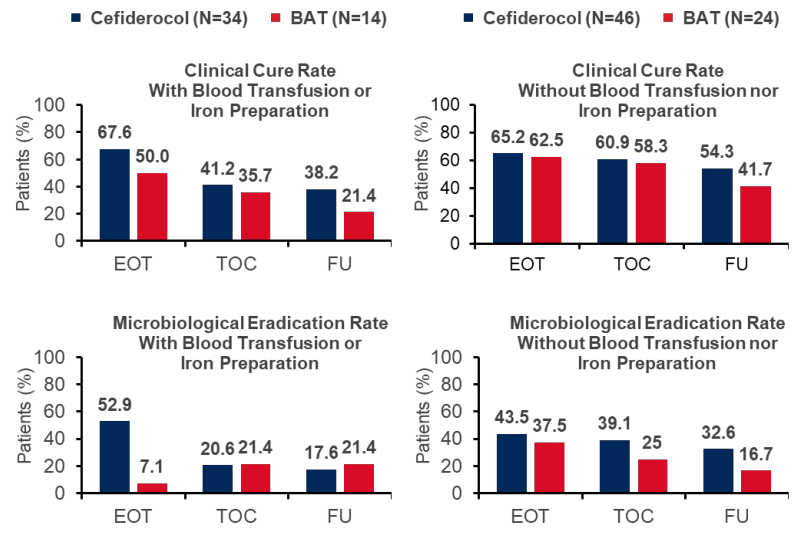
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Patients Receiving Blood Transfusions and/or Iron Preparations

- An analysis was conducted in the Phase 3 CREDIBLE-CR clinical study that examined clinical, microbiological, and mortality outcomes in patients who received blood transfusions and/or received iron preparations[7,9]
- When examining clinical cure and microbiological eradication rates at TOC in the CR-Micro-ITT population, descriptions of patients receiving a blood transfusion and/or iron preparation were available for 34 patients in the cefiderocol group and 14 patients in the BAT group. The clinical cure and microbiological eradication rates for patients with and without a blood transfusion and/or iron preparation at different timepoints are shown below in **Figure 5**[9]

Figure 5. Outcomes in Patients With or Without Blood Transfusion and/or Iron Preparation by Time Point in the CR-Micro-ITT Population[9]



Abbreviations: BAT, best available therapy; CR-Micro-ITT, carbapenem-resistant microbiological intention-to-treat; EOT, end of treatment; FU, follow-up; TOC, test of cure.

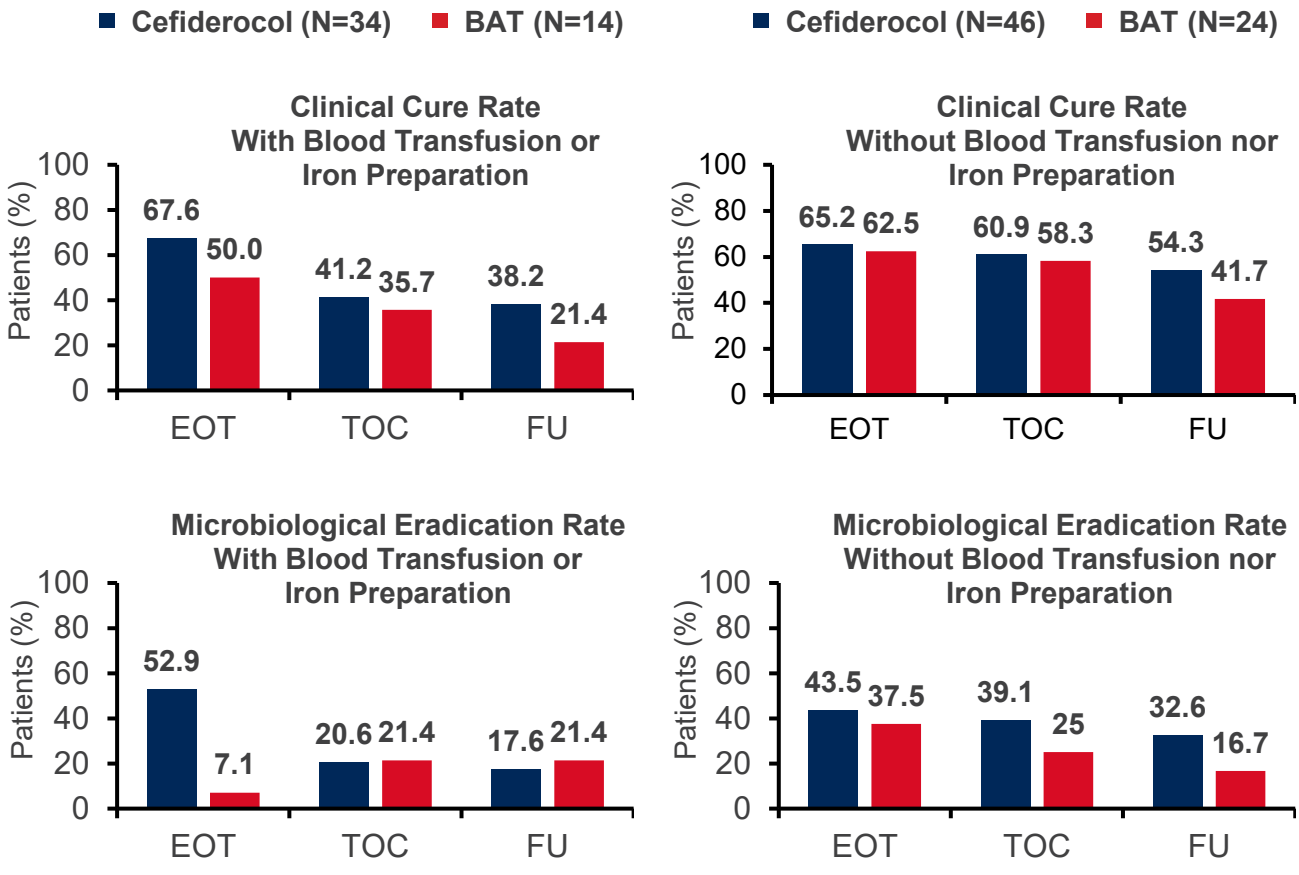
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Figure 5. Outcomes in Patients With or Without Blood Transfusion and/or Iron Preparation by Time Point in the CR-Micro-ITT Population[9]



Abbreviations: BAT, best available therapy; CR-Micro-ITT, carbapenem-resistant microbiological intention-to-treat; EOT, end of treatment; FU, follow-up; TOC, test of cure.

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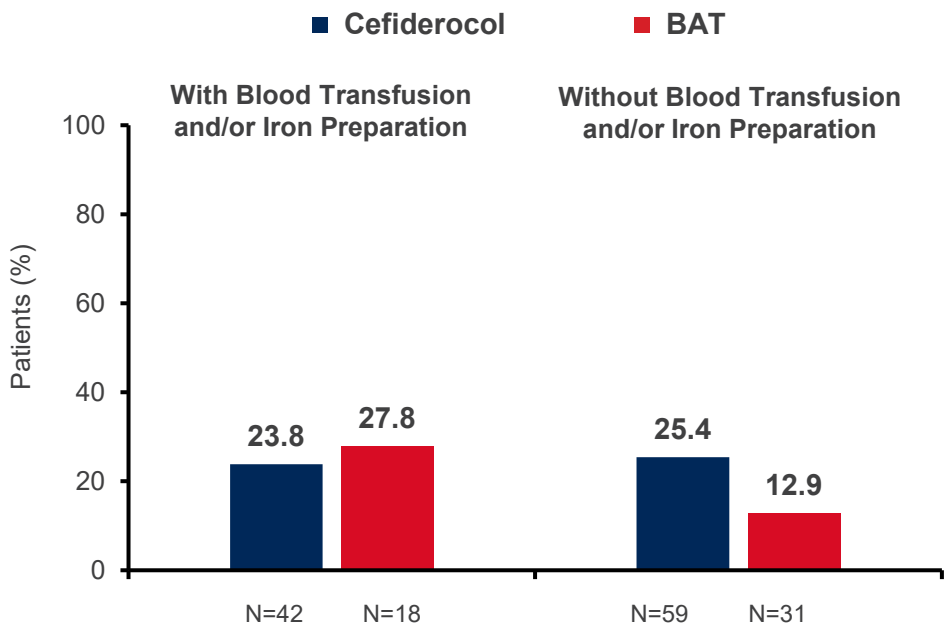
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Patients Receiving Blood Transfusions and/or Iron Preparations

- When examining the ACM in the safety population, descriptions of patients receiving a blood transfusion and/or iron preparation were available for 42 patients in the cefiderocol group (blood transfusion [n=34]; iron preparation [n=10]); blood transfusion and iron preparation [n=2]) and 18 patients in the BAT group (blood transfusion [n=16]; iron preparation [n=5]); blood transfusion and iron preparation [n=3])[9]
- The Day 28 ACM rate in the cefiderocol group in patients with and without a blood transfusion and/or iron preparation was 23.8% and 25.4%, respectively (see **Figure 6** below).[9]

Figure 6. Day 28 ACM Rates in Patients With or Without Blood Transfusion and/or Iron Preparation (ITT/Safety Population)[9]



Abbreviations: ACM, all-cause mortality; BAT, best available therapy; ITT, intention-to-treat.

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Pre-Clinical Studies

Iron Overload

- Cefiderocol has demonstrated greater *in vitro* activity against Gram-negative bacteria in iron depleted media. In order to study the effect in iron overloaded conditions, **Kidd JM et al (2019)** compared the efficacy of cefiderocol against Gram-negative infections between iron overloaded and standard murine thigh infection models[10]
- The iron-overloaded murine thigh infection model was previously established and showed that the PK of cefiderocol was not altered by 14 Days of treatment with iron dextran[12]

Methods

- Female CD-1 mice randomized to the iron overloaded model were given iron dextran 100 mg/kg/d for 14 Days or no injections in the standard model. All study mice were rendered neutropenic and both thighs were inoculated with bacterial suspensions of 10^7 CFU/mL[10]
- 31 clinical strains with previously determined cefiderocol MIC ranges for *Acinetobacter baumannii* (0.25-64 mg/L), *Pseudomonas aeruginosa* (0.5-8 mg/L), and Enterobacterales (0.25-16 mg/L) were used[10]
- 2 hours post inoculation, treatment mice were dosed with meropenem or cefiderocol regimens simulating human plasma PK of clinical doses at 2 g q8h over 3 h[10]
- For the 31 strains, treatment lasted 24 h. Control mice were sacrificed (0 h) or dosed with saline placebo following the same treatment schedule (24 h)[10]
- Meropenem was included as a positive control to determine if iron overload impacted pathogen fitness[10]

- To see if adaptive resistance was observed in the presence of iron overload, an extended treatment period was evaluated for select isolates (15 strains) in a separate experiment, following the same procedures performed both in standard and iron-overloaded mice; cefiderocol treatment was given over 72 h. Efficacy was defined as a change in $\log_{10}$ CFU/thigh at 24 h or 72 h versus 0 h controls[10]

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Iron Overload

Results

- Baseline mean bacterial burdens of all isolates at 0 h ranged from 5.5 to 5.9 $\log_{10}$ CFU/thigh and grew by 2.9 to 3.4 $\log_{10}$ CFU/thigh at 24 h without treatment[10]
- For meropenem, mean reductions in bacterial burden in standard and iron-overloaded models at 24 h were -0.81 and -1.19 $\log_{10}$ CFU/thigh (*P*=0.25). For cefiderocol, mean reductions in bacterial burden in standard and iron-overloaded models at 24 h were -1.46 and -1.55 $\log_{10}$ CFU/thigh (*P*=0.54), respectively and -2.48 and -2.53 $\log_{10}$ CFU/thigh (*P*=0.81) at 72 h (**Table 6**)[10]
- No significant differences in cefiderocol efficacy were noted between standard and iron-overloaded models at 24 h in 24 of 31 individual isolates. No trends were observed favoring the efficacy of cefiderocol in either model[10]

- The overall efficacy of cefiderocol was not significantly different between models at 24, 48, and 72 h despite the increase in strain growth in the iron overload model at 48 and 72 h (**Table 6**). There was no evidence of adaptive resistance in isolates in either model since there was no decrease in efficacy from 24 to 72 h[10]

Table 6. Mean Efficacy between Standard and Iron Overloaded Models Averaged across All Strains[10]

	Standard Model $\log_{10}$ CFU/thigh	Iron Overloaded Model $\log_{10}$ CFU/thigh	*P*-value
Meropenem 24 h Efficacy (12 strains)			
Baseline	5.77 ± 0.45	5.92 ± 0.47	0.064
Saline (Δ)	+2.94 ± 0.99	+2.90 ± 0.77	0.833
Meropenem HSR (Δ)	-0.81 ± 1.94	-1.19 ± 2.04	0.247
Cefiderocol 24 h Efficacy (31 strains)			
Baseline	5.75 ± 0.47	5.81 ± 0.51	0.227
Saline (Δ)	+3.17 ± 1.07	+3.43 ± 0.77	0.008
Cefiderocol HSR (Δ)	-1.46 ± 1.40	-1.55 ± 1.48	0.536
Cefiderocol 72 h Efficacy (15 strains)			
Baseline	5.52 ± 0.44	5.54 ± 0.38	0.697
Saline 24 h (Δ)	+3.54 ± 0.77	+3.53 ± 0.71	0.905
Cefiderocol HSR 24 h (Δ)	-1.77 ± 1.12	-1.95 ± 0.77	0.187
Saline 48 h (Δ)	+3.13 ± 1.15	+3.88 ± 0.47	<0.001
Cefiderocol HSR 48 h (Δ)	-2.05 ± 1.82	-2.35 ±1.12	0.179
Saline 72 h (Δ)	+2.02 ± 1.83	+3.73 ± 0.16	0.037
Cefiderocol HSR 72 h (Δ)	-2.48 ± 1.48	-2.53 ± 1.42	0.807

Burdens in saline-dosed controls and treatment groups are presented as changed (Δ) from baseline.
Abbreviations: h, hour; HSR, human simulated regimen.

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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

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Abbreviations

ACM	all-cause mortality	g	gram
AE	adverse event	h	hour
AUP	acute uncomplicated pyelonephritis	HABP	hospital-acquired bacterial pneumonia
BAT	best available therapy	HCABP	healthcare-associated bacterial pneumonia
BSI	bloodstream infection	ID-CAMHB	iron-depleted cation-adjusted Mueller-Hinton broth
CAMHB	Cation-adjusted Mueller-Hinton broth	ITT	intent-to-treat
CFU	colony-forming units	IV	intravenous
CI	confidence interval	MIC	minimum inhibitory concentration
CR	carbapenem-resistant	Micro-ITT	microbiological intent-to-treat population
CR-Micro-ITT	carbapenem-resistant microbiological intent-to-treat population	mITT	modified intent-to-treat
cUTI	complicated urinary tract infection	PK	pharmacokinetics
EOS	end of study	q8h	every 8 hours
FDA	Food and Drug Administration	q12h	every 12 hours
FU	follow up	TOC	test of cure
VAP	ventilator-associated pneumonia		

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Literature Search

As of October 2026, a computerized search of the published medical literature using internal and external databases (ie, Medline® and Embase®) has failed to identify additional relevant references regarding altered iron homeostasis and cefiderocol. Please keep in mind that medical literature databases, while considered a major source of biomedical information, are selective in their sources, and the information derived from it should not be considered all-inclusive.

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ENCLOSURE

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