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Safety Profile of the Novel Siderophore Cephalosporin Cefiderocol in Randomized Phase 2 and Phase 3 Clinical Studies of Serious Gram-Negative Infections

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Introduction

Cefiderocol is a new siderophore cephalosporin with potent, broad-spectrum activity against Gram-negative bacteria[1], both carbapenem-susceptible and carbapenem-resistant (CR) strains.[2,3] As a siderophore, it is an iron chelator with high affinity to ferrous iron and it facilitates iron transport into bacteria via iron-binding proteins.[3,4] It does not bind significantly to other cations.[3]

Cefiderocol has been approved for the treatment of complicated urinary tract infections (cUTIs) and nosocomial pneumonia (NP; hospital-acquired and ventilator-associated bacterial pneumonia) in the USA,[5] and in Europe for the treatment of infections caused by aerobic Gram-negative bacteria in adults with limited treatment options.[6]

The efficacy and safety of cefiderocol for serious Gram-negative infections has been investigated in three prospective, randomized trials – APEKS-cUTI[7], APEKS-NP[8], and CREDIBLE-CR[9] – and the current analysis presents the safety profile across these trials.

Methods

- APEKS-cUTI (NCT02321800) was a 2:1 randomized, double-blind, multicenter, non-inferiority Phase 2 study conducted in 67 hospitals across 15 countries in patients with cUTI or acute uncomplicated pyelonephritis, and compared cefiderocol (2 g, q8h, 1-hour infusion) with imipenem-cilastatin (1 g/1 g, three-times daily, 1-hour infusion). No adjunctive Gram-negative therapy was allowed.[7]
- APEKS-NP (NCT03032380) was a 1:1 randomized, double-blind, multicenter, non-inferiority Phase 3 study in patients with NP, comparing cefiderocol (2 g, q8h, 3-hour infusion) with meropenem (2 g, q8h, 3-hour infusion). No adjunctive Gram-negative therapy was allowed; linezolid was mandated in both arms to cover Gram-positive bacteria in the cefiderocol arm and methicillin-resistant *Staphylococcus aureus* in both arms for at least 5 days. Exclusion criteria included pneumonia caused by a CR pathogen known at randomization, and an Acute Physiology And Chronic Health Evaluation II (APACHE II) score >35.[8]
- CREDIBLE-CR (NCT02714595) was a 2:1 randomized, open-label, multicenter, descriptive (*without prior hypothesis testing*) Phase 3 study conducted in 95 sites across 16 countries in patients with serious infection (cUTI, NP, bloodstream infections and sepsis [BSI/sepsis]) caused by CR Gram-negative pathogens. Patients were treated with cefiderocol (2 g, q8h, 3-hour infusion [± one Gram-negative adjunctive treatment, not for cUTI]) or best available therapy (BAT; dosing based on local label). The study had only limited exclusion criteria: receipt of potentially effective antibiotics for the current CR infection within 72 hours prior to randomization (with a continuous duration of >24 hours for cUTI or >36 hours for other infections), the need for >3 systemic antibiotics as BAT, APACHE II score >30, and/or refractory septic shock.[9]
- For all three studies, safety was assessed in all randomly assigned individuals who received at least one dose of study drug, according to the treatment received.
- Assessments included daily recording of treatment-emergent adverse events (TEAEs), classified according to Medical Dictionary for Regulatory Activities (v18.1 or later), and clinical laboratory investigations. The relationship to treatment, severity, and seriousness of TEAEs were determined by the investigator. TEAEs of interest included *Clostridioides difficile*-related events, iron homeostasis parameters (given the mode of action of cefiderocol) and β-lactam class effects, including liver-related adverse events (AEs), and seizures/epilepsy.

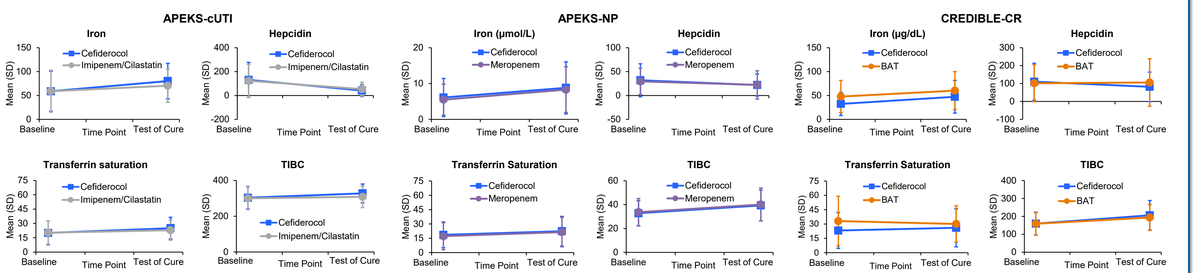
Table 1. Baseline characteristics and treatment duration (safety populations)

	APEKS-cUTI		APEKS-NP		CREDIBLE-CR	
	Cefiderocol	Imipenem-cilastatin	Cefiderocol	Meropenem	Cefiderocol	BAT
	N=300	N=148	N=148	N=150	N=101	N=49
Age						
Mean (SD), years	61.1 (16.5)	61.3 (17.8)	64.7 (14.5)	65.6 (15.1)	63.1 (19.0)	63.0 (16.7)
≥65 years, n (%)	158 (52.7)	78 (52.7)	83 (56.1)	92 (61.3)	64 (63.4)	22 (44.9)
Male, n (%)	137 (45.7)	66 (44.6)	101 (68.2)	104 (69.3)	66 (65.3)	35 (71.4)
Region						
North America	NA	NA	6 (4.1)	6 (4.0)	6 (5.9)	3 (6.1)
South America			0	0	9 (8.9)	4 (8.2)
Europe			99 (66.9)	100 (66.7)	57 (56.4)	28 (57.1)
Asia			43 (29.1)	44 (29.3)	29 (28.7)	14 (28.6)
ICU, n (%)	NA	NA	103 (69.6)	99 (66.0)	57 (56.4)	21 (42.9)
APACHE II score, mean (SD)	NA	NA	16.1 (6.1)	16.3 (6.9)	15.3 (6.5)	15.4 (6.2)
Severity of diseases						
Mild	33 (11.0)	11 (7.4)	4 (2.7)	7 (4.7)	5 (5.0)	4 (8.2)
Moderate	208 (69.3)	112 (75.7)	73 (49.3)	93 (62.0)	41 (40.6)	22 (44.9)
Severe	59 (19.7)	25 (16.9)	71 (48.0)	50 (33.3)	55 (54.5)	23 (46.9)
Ventilated	NA	NA	91 (62%)	87 (58%)	50 (50%)	26 (53%)
Creatinine clearance						
Mean (SD), mL/min	81.8 (31.6)*	77.6 (32.7)	77.8 (55.1)	82.1 (56.2)	85.8 (79.3)	88.9 (64.2)
Moderate/severe†, n (%)	57 (19.0)	35 (23.7)	49 (33.1)	52 (34.7)	43 (42.6)	15 (30.6)
Treatment duration, median (range), days	9 (1–15)	9 (2–15)	10 (2–22)	8.5 (1–22)	NP+B/S: 11 (2–22) cUTI: 10.5 (2–29)	NP+B/S: 13 (2–22) cUTI: 6.5 (2–14)
Concomitant antimicrobial agents	56 (18.7)	30 (20.3)	76 (51.4)	73 (48.7)	57 (56.4)	29 (59.2)

*N=298. †Moderate 30–50 mL/min; severe <30 mL/min; B/S, bloodstream infections and sepsis; NA, not available; SD, standard deviation.

Results

Figure 1. Change between baseline and test of cure in iron, hepcidin 25, transferrin saturation, and total iron-binding capacity in APEKS-cUTI, APEKS-NP, and CREDIBLE-CR (safety populations)



BAT, best available therapy; TIBC, total iron-binding capacity.

Patients

- A total of 549 patients received cefiderocol across the three studies. The baseline characteristics of patients in the safety populations of the three studies are shown in Table 1. Within studies, characteristics were generally well balanced between arms, except that in CREDIBLE-CR, patients in the BAT arm were generally younger (≥65 years, 44.9% vs 63.4%) and there were more males (71.4% vs 65.3%) compared with the cefiderocol arm.
- The CREDIBLE-CR study enrolled more patients with severe disease in both treatment arms than the other two studies. There was also a numerical difference in severity of disease between the cefiderocol and meropenem arms in the APEKS-NP study (**Table 1**).
- The median duration of treatment with cefiderocol was similar across studies (**Table 1**).

Table 2. Overall safety parameters (safety populations)

	APEKS-cUTI		APEKS-NP		CREDIBLE-CR	
	Cefiderocol	Imipenem-cilastatin	Cefiderocol	Meropenem	Cefiderocol	BAT
	N=300	N=148	N=148	N=150	N=101	N=49
TEAEs, n (%)						
Any	122 (40.7)	76 (51.4)	130 (87.8)	129 (86.0)	92 (91.1)	47 (95.9)
Mild	77 (25.7)	36 (24.3)	33 (22.3)	37 (24.7)	23 (22.8)	9 (18.4)
Moderate	39 (13.0)	35 (23.6)	41 (27.7)	47 (31.3)	26 (25.7)	16 (32.7)
Severe	6 (2.0)*	5 (3.4)*	56 (37.8)*	45 (30.0)*	43 (42.6)	22 (44.9)
TEAEs leading to discontinuation	5 (1.7)	3 (2.0)	12 (8.1)	14 (9.3)	10 (9.9)	3 (6.1)
TEAEs leading to death	1 (0.3)	0	39 (26.4)	35 (23.3)	34 (33.7)	9 (18.4)
Drug-related TEAEs, n (%)						
Any	27 (9.0)	17 (11.5)	14 (9.5)	17 (11.3)	15 (14.9)	11 (22.4)
Drug-related TEAEs leading to treatment discontinuation	3 (1.0)	0	2 (1.4)	2 (1.3)	3 (3.0)	2 (4.1)
SAEs						
Any	14 (4.7)	12 (8.1)	54 (36.5)	45 (30.0)	50 (49.5)	23 (46.9)
Drug-related	1 (0.3)	1 (0.7)	3 (2.0)	5 (3.3)	1 (1.0)	5 (10.2)
Infections and infestations	1 (0.3)	1 (0.7)	1 (0.7)	2 (1.3)	0	1 (2.0)
Blood and lymphatic system disorders	0	0	0	1 (0.7)	0	0
General disorders and administration site conditions	0	0	0	1 (0.7)	0	0
Investigations	0	0	2 (1.4)	2 (1.3)	1 (1.0)	0
Respiratory, thoracic and mediastinal disorders	0	0	1 (0.7)	0	0	1 (2.0)
Immune system disorders	0	0	0	0	0	1 (2.0)
Metabolism and nutrition disorders	0	0	0	0	0	1 (2.0)
Nervous system disorders	0	0	0	0	0	1 (2.0)
Renal and urinary disorders	0	0	0	0	0	2 (4.1)

Data are patients. *Adverse events with missing severity were counted as severe.

Safety overview

- Within studies, the rates of TEAEs and serious adverse events (SAEs) were similar between cefiderocol and comparators, except in APEKS-cUTI, where rates were numerically lower with cefiderocol (**Table 2**). Severity rates in APEKS-NP and CREDIBLE-CR were similar between treatment arms. SAEs leading to death occurred at a higher rate in the cefiderocol arm than in the BAT arm in the CREDIBLE-CR study, frequently within 'Infections and infestations' System Organ Class (cefiderocol: 29%; BAT: 22%).
- Rates of drug-related TEAEs and drug-related SAEs were comparable between treatment arms in APEKS-cUTI and APEKS-NP (**Table 2**). In CREDIBLE-CR, rates were higher with BAT both for drug-related TEAEs (22.4% vs 14.9%) and drug-related SAEs (10.2% vs 1.0%). Drug-related TEAEs were frequently due to colistin in the BAT arm.
- Within studies, the rates of discontinuation due to TEAEs and drug-related TEAEs were similar between treatment arms (**Table 2**).
- Patients discontinued the study due to cefiderocol-related TEAEs as follows: APEKS-cUTI: diarrhea (n=1), drug hypersensitivity (n=1) and increased hepatic enzymes (n=1); APEKS-NP: alanine aminotransferase [ALT] increased (n=1), and ALT increased, aspartate aminotransferase increased, and hepatic failure (n=1); and CREDIBLE-CR: pyrexia (n=1), transaminases increased (n=1) and drug eruption (n=1).
- In APEKS-cUTI and APEKS-NP, the rate of TEAEs leading to death was similar between the treatment arms. In CREDIBLE-CR, the rate of TEAEs leading to death was higher in the cefiderocol arm (33.7%) compared with the BAT arm (18.4%). This imbalance may be a result of the greater proportion of patients in the cefiderocol arm, compared with the BAT arm, who had *Acinetobacter* spp. infections and had shock or being at ICU at randomization admission.[9] No drug-related toxicity was identified with cefiderocol.[9]

Drug-related TEAEs

- The most common drug-related TEAEs in patients receiving cefiderocol in CREDIBLE-CR and APEKS-NP were 'Investigations' (7.9% and 2.7%, respectively) (**Table 3**). In all three studies, investigations were mainly related to liver function tests.
- The next most frequent cefiderocol-related TEAEs (and the most frequent in APEKS-cUTI) were gastrointestinal disorders (**Table 3**), mainly diarrhea (4/9 in APEKS-cUTI, 3/3 in APEKS-NP, and 2/4 in CREDIBLE-CR).
- Drug-related 'Infections and infestations' with cefiderocol were observed in four patients in APEKS-cUTI (candiduria 2/4, *C. difficile* colitis 1/4 and oral candidiasis 1/4), three patients in APEKS-NP (*C. difficile* infection 1/3, oral candidiasis 1/3, and sepsis 1/3) and in two patients in CREDIBLE-CR (*C. difficile* colitis 1/2 and pseudomembranous colitis 1/2) (**Table 3**). The rates were approximately 4% in all three comparator arms.

Table 3. Drug-related TEAEs overall and by System Organ Class

	APEKS-cUTI		APEKS-NP		CREDIBLE-CR	
	Cefiderocol	Imipenem-cilastatin	Cefiderocol	Meropenem	Cefiderocol	BAT
	N=300	N=148	N=148	N=150	N=101	N=49
Overall	27 (9.0)	17 (11.5)	14 (9.5)	17 (11.3)	15 (14.9)	11 (22.4)
System Organ Class						
Investigations	5 (1.7)	2 (1.4)	4 (2.7)	4 (2.7)	8 (7.9)	2 (4.1)
Gastrointestinal disorders	9 (3.0)	5 (3.4)	3 (2.0)	5 (3.3)	4 (4.0)	1 (2.0)
Infections and infestations	4 (1.3)	6 (4.1)	3 (2.0)	6 (4.0)	2 (2.0)	2 (4.1)
Nervous system disorders	1 (0.3)	4 (2.7)	3 (2.0)	0	1 (1.0)	1 (2.0)
General disorders and administration site conditions	5 (1.7)	0	0	2 (1.3)	2 (2.0)	0
Skin and subcutaneous tissue disorders	3 (1.0)	0	2 (1.4)	1 (0.7)	2 (2.0)	0
Respiratory, thoracic and mediastinal disease	0	0	2 (1.4)	0	1 (1.0)	1 (2.0)
Metabolism and nutrition disorders	0	0	0	0	1 (1.0)	1 (2.0)
Vascular disorders	0	0	0	0	1 (1.0)	0
Hepatobiliary disorders	0	1 (0.7)	1 (0.7)	1 (0.7)	0	0
Psychiatric disorders	0	0	1 (0.7)	0	0	0
Ear and labyrinth disorders	0	0	1 (0.7)	0	0	0
Immune system disorders	1 (0.3)	0	0	0	0	1 (2.0)
Musculoskeletal and connective tissue disorders	1 (0.3)	0	0	0	0	0
Renal and urinary disorders	0	0	0	0	0	5 (10.2)
Blood and lymphatic system disorders	0	0	0	2 (1.3)	0	0
Cardiac disorders	0	1 (0.7)	0	0	0	0
Reproductive system and breast disorders	0	0	0	1 (0.7)	0	0

Data are patients and are displayed in order of decreasing frequency (%) for cefiderocol in any study.
Although a patient may have had two or more TEAEs, the patient was counted only once within a System Organ Class category.

Results (continued)

Adverse events of interest

- The incidence of *C. difficile*-related events with cefiderocol was low (**Table 4**) across the three studies (eight patients); events were either mild or moderate and only one event in a patient in APEKS-cUTI was an SAE (mild colitis, considered to be related to treatment).
- Four patients receiving cefiderocol had seizures, one of whom had a history of epilepsy (**Table 4**). In CREDIBLE-CR, one patient had three seizures. None of the seizures were considered to be related to cefiderocol.
- Rash/hypersensitivity reactions were reported at a similar or lower incidence compared with comparator treatments. No serious AEs related to rash/hypersensitivity were reported in any of the studies. Only one case of rash related to cefiderocol was reported in both APEKS-NP and CREDIBLE-CR studies, all other events were not related to cefiderocol.
- The occurrence of liver-related AEs was similar between treatment arms in APEKS-cUTI and APEKS-NP (**Table 4**). In CREDIBLE-CR, the incidence of liver-related AEs was higher in the cefiderocol arm than in the BAT arm (29.7% vs 14.3%). Review of all patients with elevated liver enzymes revealed that in the majority of cases, the patients' underlying medical history (e.g. hepatitis) or concomitant medications suggested alternate etiologies. None of these cases met the criteria for Hy's law, or drug-induced liver injury.
- Within all three studies, there were no notable differences between treatment arms in the change from baseline to test of cure in transferrin saturation, hepcidin 25, total iron-binding capacity and iron levels (**Figure 1**).

Table 4. *C. difficile* events, seizures and liver events by patient in the safety populations

	APEKS-cUTI		APEKS-NP		CREDIBLE-CR	
	Cefiderocol	Imipenem-cilastatin	Cefiderocol	Meropenem	Cefiderocol	BAT
	N=300	N=148	N=148	N=150	N=101	N=49
C. difficile events	Mild colitis, SAE (n=1)	Mild infection (n=1) Moderate colitis (n=2) Moderate colitis and severe colitis, SAE (n=1) Moderate colitis, SAE (n=1)	Mild infection (n=1) Moderate infection (n=3)	Mild infection (n=2) Moderate colitis (n=1) Severe infection (n=1)	Mild pseudo-membranous colitis (n=1) Moderate infection (n=1) Moderate colitis (n=1)	Moderate pseudo-membranous colitis (n=1)
Seizures	Non-serious, epileptic seizure TEAE with a history of epilepsy (n=1)	0	Mild seizure (n=2) Severe status epilepticus, SAE (n=1)	Moderate seizure (n=2)	Mild seizures (n=1)	Severe status epilepticus, SAE (n=1)
Liver events	Total: 2 (0.7%) Severe elevation of liver enzymes (n=1) Moderate elevation of liver enzymes (n=1)	Total: 1 (0.7%) Moderate abnormal hepatic function (n=1)	ALT increased (n=9) AST increased (n=10) Hepatic enzyme increased (n=4) Hypoalbuminaemia (n=5) GGT increased (n=5) Transaminases increased (n=4)	ALT increased (n=6) AST increased (n=6) Hepatic enzyme increased (n=10) Hypoalbuminaemia (n=8) GGT increased (n=2) Transaminases increased (n=4)	Total: 30 (29.7%) ALT increased (n=7) AST increased (n=8) Liver function test abnormal (n=8)	Total: 7 (14.3%) AST increased (n=1) Liver function test abnormal (n=4)

n=patients. AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase.

Conclusions

Cefiderocol 2 g, q8h treatment (or at doses adjusted for renal function) in a total of 549 patients demonstrated a comparable safety profile to comparators, including high-dose imipenem and high-dose meropenem, and was generally well tolerated in critically ill patients, including patients who required mechanical ventilation and ICU admission.

The incidence of drug-related TEAEs was generally similar to that in the comparator arms. In CREDIBLE-CR, the incidence of 'Infections and infestations' was higher in the cefiderocol arm than in the BAT arm, and although many of these AEs were SAEs leading to death, none were judged by the investigator to be related to cefiderocol.

The incidences of β-lactam class effects of seizure and liver events were similar between treatment arms in APEKS-cUTI and APEKS-NP. In CREDIBLE-CR, there were more liver-related AEs in the cefiderocol arm compared with the BAT arm but there was no drug-induced liver injury and none of the cases met the clinical and biochemical criteria for Hy's law. In the majority of cases, the patients' underlying medical history or concomitant medications suggested alternate etiologies.

Cefiderocol was not associated with an excess of iron homeostasis-related adverse events compared with the other non-siderophore antibiotics used.

No unexpected safety concerns were identified across studies. In the CREDIBLE-CR study, TEAEs (or SAEs) leading to death occurred more frequently in the cefiderocol arm than BAT arm, which were not adverse drug reactions. Further explanation is provided by Bassetti et al.[9,10]

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