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Characterization of Shifts in Minimum Inhibitory Concentrations During Treatment with Cefiderocol or Comparators in the Phase 3 CREDIBLE-CR and APEKS-NP Studies

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Introduction

Cefiderocol is a new siderophore cephalosporin with *in vitro* activity against carbapenem-susceptible (CS) and carbapenem-resistant (CR) aerobic Gram-negative bacteria.[1]

The SIDERO multinational surveillance studies[2,3] have shown minimum inhibitory concentrations (MICs) of ≤4 µg/mL for >95% of the clinical isolates, including meropenem-resistant isolates that express metallo-β-lactamases, OXA carbapenemase or *Klebsiella pneumoniae* carbapenemase (KPC) enzymes.

Cefiderocol has been approved in the USA for the treatment of patients with complicated urinary tract infections (cUTI) and hospital-acquired or ventilator-associated bacterial pneumonia (HABP/VABP) caused by Gram-negative bacteria, and in Europe for the treatment of infections due to Gram-negative pathogens with limited treatment options.[4,5]

The efficacy and safety of cefiderocol have been investigated under a streamlined development program.[6] The efficacy and safety of cefiderocol (2g, q8h, 3-hour infusion, 7–14 days) and high-dose, extended-infusion meropenem (2g, q8h, 3-hour infusion, 7–14 days) have been compared in the APEKS-NP study, which was a Phase 3, double-blind, randomized, non-inferiority study in critically ill patients with nosocomial pneumonia (NP).[7] Additionally, the efficacy and safety of cefiderocol have been assessed in the CREDIBLE-CR study, which was a Phase 3, open-label, randomized, descriptive study in critically ill patients with serious Gram-negative infections (NP, bloodstream infection [BSI]/sepsis, and cUTI) caused by CR bacteria.[8,9]

In the current post-hoc analysis, we examined the pathogens that showed ≥4-fold increase in their MIC from baseline in the APEKS-NP and CREDIBLE-CR studies.

Methods

- APEKS-NP (NCT03032380) was a 1:1 randomized, double-blind, multicenter, non-inferiority Phase 3 study in patients with NP, comparing cefiderocol (2g, q8h, 3-hour infusion) with high-dose, extended-infusion meropenem (2g, q8h, 3-hour infusion) both for 7–14 days. No adjunctive Gram-negative therapy was allowed; at least 5 days of linezolid treatment was mandated in both arms to cover Gram-positive bacteria in the cefiderocol arm and methicillin-resistant *Staphylococcus aureus* in both arms. Exclusion criteria included pneumonia caused by a CR pathogen known at the time of randomization.[7]
- CREDIBLE-CR (NCT02714595) was a 2:1 randomized, open-label, multicenter, descriptive (*without prior hypothesis testing*) Phase 3 study in critically ill patients with serious infections (NP, bloodstream infection [BSI]/sepsis, cUTI) caused by CR Gram-negative pathogens. Evidence of CR for eligibility could be provided based on 5 different methods: rapid diagnostic test, treatment failure while on empirical antibiotic therapy and the CR pathogen was collected within 72 hours prior to randomization, presence of *Stenotrophomonas maltophilia*, colonization with CR pathogen at the infection site, or local CR rate >90%. Patients were treated with cefiderocol (2g, q8h, 3-hour infusion) or best available therapy (BAT; up to 3 agents were allowed and their dosing was based on local practice) for 7–14 days. Patients were excluded if they received 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), or required >3 systemic antibiotics for treatment in the BAT arm.[8,9]
- In both studies, appropriate biospecimens were collected for culture and susceptibility testing, which was carried out in the local microbiology laboratory. Pathogens were concurrently frozen and shipped to the central laboratory for confirmation of the species, susceptibility to antibiotics and expression of extended-spectrum beta-lactamase (ESBL) enzymes and/or carbapenemases (IHMA, Schaumburg, IL, USA).
- For each isolate, minimum inhibitory concentrations (MICs) to antibiotics (i.e., amikacin, aztreonam, cefepime, cefiderocol, ceftazidime, ciprofloxacin, colistin, imipenem, meropenem, tigecycline) were evaluated at baseline, during therapy (early assessment [EA], Day 3-4), end of treatment (EOT, last day of treatment), and test of cure (TOC, EOT +7 days) for changes from baseline values according to CLSI guidelines.[10]

Methods (continued)

- For isolates with ≥4-fold increased MIC, whole genome sequencing (WGS) was performed for molecular analysis to identify the clonal origin. The first step of WGS included multi-locus sequencing typing (MSLT) technique and analysis to confirm the identity of isolates between pre- and post-treatment. Only isolates that were the same at baseline and at later time points were included in this analysis. In the second step, isolates that were found to be identical in MSLT, were checked for mutations in genes (**Table 1**) that might be related to cefiderocol resistance. WGS was not performed for isolates in the BAT arm of the CREDIBLE-CR study.[7–9]

Table 1. Genes related to cefiderocol transport and mechanism of action

Species	Enterobacterales	*P. aeruginosa*	*A. baumannii*	*S. maltophilia*
β-lactamases	All	All	All	All
Iron transporter	fiu, cir	piuA, piuC, pirA	piuC, bauA, pfeA, feoB, feoA	piuA, piuC, pirA
Iron transport-related	exbB, exbD, tonB	exbB, exbD, tonB	exbB, exbD, tonB	exbB, exbD, tonB
Others	ftsI (PBP 3) BaeS/R, OmpR/EnvZ (two-component regulation) pcnB (polynucleotide adenyl-transferase)	ftsI (PBP 3) pvdS (pyoverdine synthesis regulator)	ftsI (PBP 3)	ftsI (PBP 2)
Porin (only for APEKS-NP)	ompC, ompF	oprD	oprD, carO	N/A

Results

- In the APEKS-NP study, a baseline Gram-negative pathogen was confirmed in 124 patients (a total of 159 isolates) in the cefiderocol arm and in 127 patients (a total of 164 isolates) in the meropenem arm among 298 randomized patients. The most frequent species was *Klebsiella pneumoniae* (cefiderocol: 48 [33%]; meropenem: 44 [30%]), followed by *Pseudomonas aeruginosa* (cefiderocol: 24 [17%]; meropenem: 24 [16%]) and *Acinetobacter baumannii* (cefiderocol: 23 [16%]; meropenem: 24 [16%]) in the modified intention-to-treat (mITT) population.
- Baseline MIC values for the most frequent pathogens are shown in **Table 2**.

Table 2. Baseline MICs for most frequent pathogens in cefiderocol and meropenem arms in the mITT in APEKS-NP study[7]

Species [number tested]	Cefiderocol MIC_{90} (range), µg/mL	Meropenem MIC_{90} (range), µg/mL
Klebsiella pneumoniae [n1=47; n2=37]	2 (≤0.03–4)	1 (≤0.03–64)
Escherichia coli [n1=19; n2=21]	1 (≤0.03–1)	≤0.03 (≤0.03–≤0·03)
Enterobacter cloacae [n1=7; n2=8]	– (0.06–2)	– (≤0.03–0·12)
Pseudomonas aeruginosa [n1=24; n2=23]	0·5 (≤0.03–1)	32 (0.06–>64)
Acinetobacter baumannii [n1=22; n2=24]	2 (≤0.03–>64)	>64 (0.12–>64)

MIC_{90} was calculated for species with ≥10 isolates at baseline. n1 is the n number of tested isolates in the cefiderocol arm, n2 is the n number of tested isolates for the meropenem arm.

- In the APEKS-NP study, ≥4-fold cefiderocol MIC increase was found in 7 isolates from 6 patients and ≥4-fold meropenem MIC increased in 5 isolates from 5 patients (**Table 3**). For most isolates, cefiderocol MIC increased by 4–8-fold but remained ≤4 µg/mL. In the meropenem arm, the magnitude of MIC increase was up to 4–512-fold.
- Mutations were identified in 3 isolates: mutation in ACT-17 gene, a Class C beta-lactamase enzyme, in *Enterobacter cloacae*, and OprD truncation in 2 *P. aeruginosa* isolates.

Results

Table 3. MIC changes in APEKS-NP in the modified intention-to-treat population[7]

Isolate	MIC (µg/mL) Pre-treatment*	MIC (µg/mL) Post-treatment	Fold change of MIC	Day of isolation	Mutation identified in post-treatment isolates
Cefiderocol arm					
E. aerogenes	0.06	0.5	8	EA visit	Not identified
	0.06	0.5	8	EA visit	Not identified
K. pneumoniae	≤0.03	0.12	≥4	EOT visit	Not identified
	0.06	0.25	4	EA visit	Not identified
	0.25	1	4	TOC visit	Not identified
E. cloacae	1	4	4	EOT visit	ACT-17 mutation (A313P)
S. marcescens	0.06	0.25	4	EA visit	None
Meropenem arm					
K. pneumoniae	2	8	4	EA visit	Not identified
P. aeruginosa	0.12	64	512	EA visit	Not identified
	0.25	4	16	TOC visit	Opr-D truncation
	0.25	4	16	TOC visit	Opr-D truncation
C. freundii	≤0.03	0.12	4	EA visit	Not identified

*Latest isolate before study drug initiation; EA: early assessment; EOT: end of therapy; TOC: test of cure.

- In the CREDIBLE-CR study, at least one CR Gram-negative pathogen was confirmed in 80 patients in the cefiderocol arm (a total of 87 CR isolates) and in 38 patients (a total of 40 CR isolates) in the BAT arm among 150 randomized patients. *A. baumannii* (cefiderocol: 37 [46%]; BAT: 17 [45%]), *K. pneumoniae* (cefiderocol: 27 [34%]; BAT: 12 [32%]), and *P. aeruginosa* (cefiderocol: 12 [15%]; BAT: 10 [26%]) were the most frequent CR pathogens.
- Baseline cefiderocol MIC values are shown in **Table 4**. Overall, only 4 CR pathogens had cefiderocol MICs >4 µg/mL (i.e., investigational Clinical and Laboratory Standards Institute [CLSI] susceptibility breakpoint), and 6 CR pathogens had MIC=4 µg/mL (above the European Committee on Antimicrobial Susceptibility Testing [EUCAST] susceptibility breakpoint of 2 µg/mL). Due to feasibility limitations and high variability of BAT agents, MICs in the BAT arm are not shown.

Table 4. Baseline MIC for most frequent pathogens in the cefiderocol arm in the CR-Micro-ITT population in the CREDIBLE-CR study[8,9]

Species [number tested]	Cefiderocol MIC_{90} (range), µg/mL (N=80)
A. baumannii [n=36]	1 (0.06–16)
K. pneumoniae [n=27]	4 (0.06–4)
P. aeruginosa [n=12]	2 (0.12–4)
S. maltophilia [n=5]	– (≤0.03–0.25)
A. nosocomialis [n=2]	– (0.5–>64)
E. cloacae [n=2]	– (1–16)
E. coli [n=2]	– (≤0.03–16)

MIC_{90} was calculated for species with ≥10 isolates at baseline.

- In the CREDIBLE-CR study, ≥4-fold cefiderocol MIC increase was detected in 12 isolates from 12 patients. ≥4-fold MIC increase to the active agent was found in the BAT arm in 6 isolates from 5 patients (**Table 5**). One *K. pneumoniae* isolate and 1 *A. baumannii* isolate had MIC increased to both agents given as treatment (**Table 5**).
- In the cefiderocol arm, 75% of post-treatment isolates had MIC ≤2 µg/mL, and 2 isolates had MIC=8 µg/mL and 1 isolate had MIC=16 µg/mL. All isolates in the BAT arm were assessed resistant to the respective agent based on established breakpoints.
- From sequencing analysis, mutations in genes related to iron-transport were not identified. Mutations in cefiderocol target gene PBP-3 was identified in 1 *A. baumannii* isolate and in Class-C enzymes (PDC-30) in 1 *P. aeruginosa* isolate (**Table 5**).

Results (continued)

Table 5. MIC changes in CREDIBLE-CR study in the CR-Micro-ITT population[8]

Isolate	MIC (µg/mL) Pre-treatment*	MIC (µg/mL) Post-treatment	Fold change of MIC	Day of isolation	Mutation identified in post-treatment isolates
Cefiderocol arm					
A. baumannii	0.06	1	16	3	Not identified
	0.25	1	4	3	Not identified
	0.25	2	8	14	Not identified
	1	8	8	15	PBP-3 mutation (H370Y)
	1	8	8	10	Not identified
K. pneumoniae	0.06	0.5	8	8	Not identified
	0.12	0.5	4	17	Not identified
	0.25	2	8	14	Not identified
P. aeruginosa	025	2	8	22	PDC-30 mutation (4 AA deletion "TPMA" position 316-319)
	0.12	16	128	3	Not identified
	0.5	2	4	16	Not identified
S. maltophilia	0.06	0.25	4	14	Not identified
BAT arm**					
Ceftazidime/avibactam					
K. pneumoniae	0.25	16	64	20	Not tested
Tigecycline					
K. pneumoniae§	1	>4	>4	13	Not tested
A. baumannii†	2	>4	>4	11	Not tested
Colistin					
K. pneumoniae	≤0.5	>8	>16	13	Not tested
K. pneumoniae§	≤0.5	8	>16	13	Not tested
A. baumannii†	≤0.5	>8	>16	4	Not tested
A. baumannii‡	1	>8	>8	14	Not tested
E. coli‡	2	8	>4	14	Not tested

*Latest isolate before study drug initiation; **BAT agents were selected based on local standard of care for CR infections, and MICs were confirmed by the central laboratory. §Infection was treated with tigecycline and colistin; MIC increased to both agents. †Infection was treated with tigecycline and colistin; MIC increased to both agents. ‡Polymicrobial infection treated with colistin; both pathogens increased the MIC.

Conclusions

Resistance acquisition with cefiderocol treatment was infrequent.

Among isolates with ≥4-fold MIC increase during cefiderocol treatment, actual cefiderocol MIC values remained ≤4 µg/mL for 16 of 19 (84%) isolates and would not be considered resistant. Frequency of ≥4-fold MIC increase in BAT and meropenem arms was similar to that of cefiderocol, but the magnitude was greater.

Acquisition of contributory resistance mechanisms has not been identified except for the mutation in PBP 3 and some β-lactamases.

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