Poster 1860

ESCMID Global 2026
17–21 April 2026
Munich, Germany

Efficacy and safety of cefiderocol or colistin in a randomised, open-label Phase 3 study in Chinese participants with carbapenem-resistant Gram-negative bacterial infections

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INTRODUCTION

- In China and globally, carbapenem-resistant Gram-negative bacterial infections (CR-GNBIs) are associated with increased risk of mortality, thus, new antibiotics are needed [1–4].
- Cefiderocol, a siderophore cephalosporin, has potent *in vitro* activity against aerobic Gram-negative bacteria, including Enterobacterales and non-fermenting species [5]. Cefiderocol has maintained *in vitro* activity against carbapenem-resistant strains, including both carbapenemase-positive and carbapenemase-negative strains [5].
- The efficacy and safety of cefiderocol or best-available therapy (BAT) were investigated previously in patients with serious CR-GNBIs in the pathogen-focused, international, randomised Phase 3 CREDIBLE-CR study [6], which study did not enrol patients in China. Therefore, a new Phase 3 randomised study was conducted in Chinese patients to address the burden of serious Gram-negative bacterial infections in China.

OBJECTIVES

- The objective of this randomised Phase 3 study was to investigate the efficacy and safety of cefiderocol + meropenem or colistin + meropenem in adult hospitalised patients with CR-GNBIs (excluding all *Stenotrophomonas maltophilia* infections), who were treated with intravenous antibiotics for approximately 7–14 days.

PARTICIPANTS AND METHODS

- Study design: a multicentre, randomised (2:1), open-label Phase 3 study (registration: ChiCTR2400094663). Informed consent was acquired from all patients.
- Participants: adult hospitalised patients with CR-GNBIs requiring intravenous antibiotic treatment for approximately 7–14 days.
- Participants were planned to be enrolled with complicated urinary tract infection (cUTI), hospital-acquired or ventilator-associated bacterial pneumonia (HABP/VABP), healthcare-associated pneumonia (HCAP), complicated intra-abdominal infections (cIAIs), bloodstream infection (BSI) or sepsis.
- Patients excluded with only *S. maltophilia* infections or if *S. maltophilia* was the main pathogen, central nervous system infections, invasive fungal infections, cystic fibrosis, moderate/severe bronchiectasis, shock at randomisation, creatinine clearance <30 ml/min, and patients with GNBIs requiring >2 systemic antibiotics, or >21 days duration of treatment.
- Treatment arms: **cefiderocol** (2 g every 8 hours [q8h]) + meropenem (1 g or 0.5 g, q8h), and **colistin** (maintenance dose 9 million IU/day) + meropenem (1 g or 0.5 g, q8h).
  - Doses of cefiderocol, colistin and meropenem were adjusted by renal function.

OUTCOMES AND STATISTICS

- Primary outcomes included (CR-microbiological intention-to-treat [CR-MITT] population):
  - 1) clinical response at test-of-cure (TOC)
  - 2) microbiological eradication at TOC
  - 3) ACM at Day 14
  - 4) ACM at Day 28
  - 5) composite outcome of clinical response and microbiological eradication at TOC in patients with cUTI.
- The TOC visit occurred 7 ± 3 days after the end-of-treatment (last day of treatment) visit.
- Clinical response rate by baseline pathogen was a secondary outcome.
- The safety profile of cefiderocol + meropenem or colistin + meropenem (Safety population) was also a secondary outcome.
- Statistical analyses were descriptive in nature; no formal sample size calculation or hypothesis testing was performed.

RESULTS

Baseline demographics and clinical characteristics

- After randomisation, 47 participants received cefiderocol + meropenem and 25 participants received colistin + meropenem in the ITT population. Of these 72 eligible participants, 67 had CR-GNBIs (cefiderocol: 45; colistin: 22) in the CR-MITT population (**Table 1**).
- Demographics and baseline characteristics of participants are shown in **Table 1**.
- The mean (SD) duration of treatment was 12.4 (4.05) days and 9.6 (4.94) days in the cefiderocol and colistin arms, respectively (ITT population).

Table 1. Baseline demographics, clinical characteristics, and CR Gram-negative bacteria in the CR-MITT population

	Cefiderocol + meropenem (N = 45)	Colistin + meropenem (N = 22)
Age (years), mean ± SD	64 ± 13.8	64 ± 14.8
≥65 years old, n (%)	24 (53.3)	12 (54.5)
Sex (male), n (%)	32 (71.1)	15 (68.2)
APACHE II score ≥16, n (%)	21 (46.7)	10 (45.5)
Clinical diagnosis at baseline, n (%)		
HABP/VABP/HCAP	28 (62.2)	15 (68.2)
BSI	8 (17.8)	4 (18.2)
cUTI	9 (20.0)	3 (13.6)
Renal grading group by CrCl, n (%)		
≥120 mL/min (ARC)	12 (26.7)	4 (18.2)
≥90 to <120 mL/min (normal)	12 (26.7)	5 (22.7)
≥60 to <90 mL/min (mild)	9 (20.0)	7 (31.8)
≥30 to <60 mL/min (moderate)	12 (26.7)	6 (27.3)
Ventilation at randomisation, n (%) [pneumonia only]	21/28 (75.0)	12/15 (80.0)
Prior systemic antibiotic use, n (%)	42 (93)	20 (90.9)
Any other infections	21 (46.7)	9 (40.9)
Baseline CR Gram-negative pathogens, n (%)[a]		
Overall	N=45	N=22
Klebsiella pneumoniae	20 (44.4)	8 (36.4)
Acinetobacter baumannii	17 (37.8)	10 (45.5)
Pseudomonas aeruginosa	8 (17.8)	1 (4.5)
Escherichia coli	3 (6.7)	2 (9.1)
HABP/VABP/HCAP	N'=28	N'=15
Acinetobacter baumannii	16 (57.1)	10 (66.7)
Klebsiella pneumoniae	9 (32.1)	4 (26.7)
Pseudomonas aeruginosa	7 (25.0)	1 (6.7)
BSI	N'=8	N'=4
Klebsiella pneumoniae	6 (75.0)	2 (50.0)
Escherichia coli	1 (12.5)	1 (25.0)
cUTI	N'=9	N'=3
Klebsiella pneumoniae	5 (55.6)	2 (66.7)
Escherichia coli	2 (22.2)	1 (33.3)

Abbreviations: APACHE II, Acute Physiologic Assessment And Chronic Health Evaluation II score; ARC, augmented renal clearance; BSI, bloodstream infection; CR, carbapenem-resistant; CrCl, creatinine clearance; CR-MITT, carbapenem-resistant microbiological intent-to-treat; cUTI, complicated urinary tract infection; HABP, hospital-acquired bacterial pneumonia; HCAP, healthcare-associated pneumonia; SD, standard deviation; VABP, ventilator-associated bacterial pneumonia. [a] Only pathogens in >1 patients are shown. N = total number of participants; N' = total number of participants with specific infections.

Clinical and microbiological outcomes at TOC

- Overall clinical response and microbiological eradication rates were 53.3% (24/45) and 31.1% (14/45) with cefiderocol and 22.7% (5/22) and 22.7% (5/22) with colistin, respectively (**Figure 1**).
- In participants with pneumonia, clinical response rates in the cefiderocol and colistin arms were 53.6% (15/28) and 33.3% (5/15), respectively, and microbiological eradication rates were 25.0% (7/28) and 26.7% (4/15), respectively (**Figure 1**).
- The clinical response and microbiological eradication rates in participants with bloodstream infection were 50.0% (4/8) and 50.0% (4/8) in the cefiderocol arm and 0% (0/4) and 25% (1/4) in the colistin arm, respectively (**Figure 1**).
- Among participants with cUTI, clinical response and microbiological eradication rates were 55.6% (5/9) and 33.3% (3/9) in the cefiderocol arm and 0% (0/3) and 0% (0/3) in the colistin arm, respectively (**Figure 1**). The composite response rates in these patients were 33.3% (3/9) and 0% (0/3) in the cefiderocol and colistin arms, respectively (**Figure 1**).
- Numerical differences between cefiderocol and colistin treatments were seen in clinical response rates at TOC among patients with infections caused by CR *K. pneumoniae*, CR *A. baumannii* and CR *P. aeruginosa* (**Table 2**).

All-cause mortality

- Overall ACM at day 28 was 13.3% (6/45) with cefiderocol and 18.2% (4/22) with colistin (**Figure 2**). None of the patients with cUTI died in either treatment arm.

Figure 1. Clinical and microbiological outcomes and composite response rates in patients with cUTI at TOC in the CR-MITT population

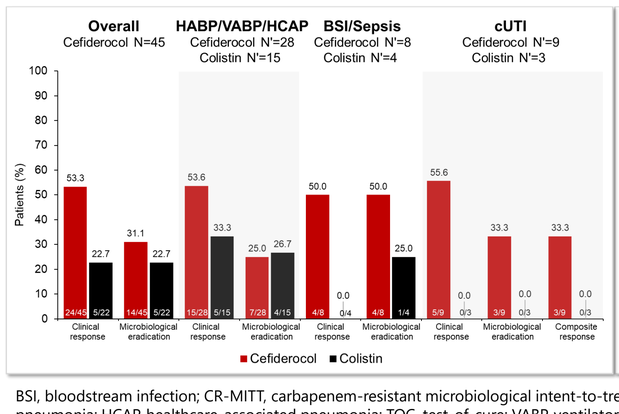
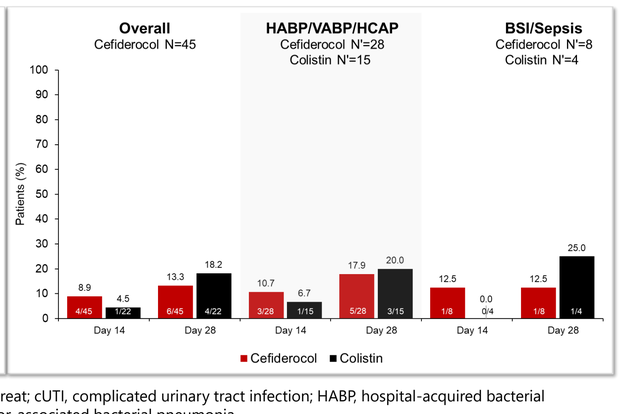


Figure 2. All-cause mortality at days 14 and 28 in the CR-MITT population



BSI, bloodstream infection; CR-MITT, carbapenem-resistant microbiological intent-to-treat; cUTI, complicated urinary tract infection; HABP, hospital-acquired bacterial pneumonia; HCAP, healthcare-associated pneumonia; TOC, test-of-cure; VABP, ventilator-associated bacterial pneumonia.

Table 2. Clinical response rates by pathogen in Chinese participants with CR-GNBIs in the CR-MITT population

	Cefiderocol + meropenem (N = 45)	Colistin + meropenem (N = 22)
Clinical response rate at TOC by CR-GNBI,[a] n/N' (%) [95% CI][b]		
Klebsiella pneumoniae	8/20 (40.0) [19.1–64.0]	1/8 (12.5) [0.3–52.7]
Acinetobacter baumannii	11/17 (64.7) [38.3–85.8]	4/10 (40.0) [12.2–73.8]
Pseudomonas aeruginosa	5/8 (62.5) [24.5–91.5]	0/1 (0) [0–97.5]

CI, confidence interval; CR-GNBI, carbapenem-resistant Gram-negative bacterial infection; CR-MITT, carbapenem-resistant microbiological intention-to-treat; TOC, test of cure.
[a] Only the top three pathogens are shown. N' = total number of participants with specific infections; n = number of participants with outcome.
[b]CLopper-Pearson test was used to calculate 95% CIs.

Safety

- In the safety population, 93.6% of cefiderocol-treated participants and 100% of colistin-treated participants experienced treatment-emergent adverse events (TEAEs, **Table 3**).
- A total 234 and 135 TEAEs emerged in the cefiderocol and colistin arms, respectively.
- The incidence of drug-related adverse events was numerically lower with cefiderocol than with colistin: 17 participants (36.2%) experienced 38 events with cefiderocol, and 18 participants (72.0%) experienced 41 events with colistin (**Table 3**).
- Drug-related serious adverse events occurred in 4.3% and 12.0% of patients in the cefiderocol and colistin arms, respectively (**Table 3**).
- Overall, eight patients (17.0%) in the cefiderocol arm and six patients (24.0%) in the colistin arm experienced adverse events leading to death; none of the deaths were related to study drug (**Table 3**).

Table 3. Adverse events with cefiderocol + meropenem or colistin + meropenem treatment in the Safety population

Adverse events	Cefiderocol + meropenem (N=47)	Colistin + meropenem (N=25)
Any TEAEs, n (%)	44 (93.6)	25 (100.0)
Drug-related TEAEs,[a] n (%)	17 (36.2)	18 (72.0)
SAEs, n (%)	13 (27.7)	10 (40.0)
Drug-related SAEs, n (%)	2 (4.3)	3 (12.0)
SAEs with outcome of death, n (%)	8 (17.0)	6 (24.0)
Drug-related TEAEs with outcome of death, n (%)	0 (0)	0 (0)
TEAEs leading to any drug discontinuation, n (%)	2 (4.3)	8 (32.0)
Drug-related TEAEs leading to any drug discontinuation, n (%)	1 (2.1)	7 (28.0)

AE, adverse event; SAE, serious adverse event. [a]Drug-related AE: related to cefiderocol, colistin or meropenem.

CONCLUSIONS

Cefiderocol was an efficacious and well tolerated treatment for Chinese adult patients with CR Gram-negative bacterial infections, and cefiderocol treatment was associated with less frequent drug-related adverse events.

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Acknowledgements

Editorial support was provided by Highfield, Oxford, United Kingdom; this support was funded by Shionogi & Co., Ltd., Osaka, Japan. The study was funded by Shionogi China Co., Ltd., Shanghai, China.

Conflict of interest

LZ, XZ, FG, HM, TS, and TB are employees of the Shionogi Group. HH and YZ have no conflict of interest.

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