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# Phase 3, randomized, multicentre study of ceftazidime-avibactam versus meropenem in adults with nosocomial pneumonia including ventilator-associated pneumonia (REPROVE)

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**Background:** The randomised, double-blind, multicentre, Phase 3 REPROVE study (NCT01808092) compared the efficacy, safety and tolerability of ceftazidime-avibactam versus meropenem in the treatment of adults with nosocomial pneumonia (NP), including ventilator-associated pneumonia (VAP).

**Material/methods:** Adults (18–90 years) with NP, including VAP, were randomised 1:1 to receive ceftazidime-avibactam 2000-500 mg 2-h intravenous (IV) infusions every 8 h (q8h) or meropenem

1000 mg 30-min IV infusions q8h for 7–14 days (doses adjusted for renal function). The primary endpoint was assessment of non-inferiority of ceftazidime-avibactam compared with meropenem in clinical cure at test-of-cure visit, 21–25 days from randomisation, in the clinically modified intent-to-treat (cMITT) population (minimal disease criteria excluding patients with only non-target pathogens) and the clinically evaluable (CE) subset of the cMITT, based on a 12.5% non-inferiority margin. Secondary endpoints included clinical cure at TOC by ceftazidime susceptibility of baseline isolates (mMITT and CE populations), per-pathogen favourable microbiological response at TOC (mMITT and eME populations) and all-cause mortality at Day 28 (cMITT and CE populations).

**Results:** Between April 2013 and December 2015, 879 patients were randomised in 23 countries; excluding 62 patients with moderate/severe renal impairment (CrCL 16–50 mL/min) recruited prior to a protocol amendment to the dose regimen for patients with moderate/severe renal impairment; 405 and 403 patients received ceftazidime-avibactam and meropenem respectively (9 patients received no study treatment). Baseline characteristics were well-matched between treatment arms; 107/808 (13.2%) patients had an APACHE score ≥20 and 280/808 (34.7%) had VAP. Predominant Gram-negative pathogens isolated at baseline in the microbiological MITT (mMITT) population were *Klebsiella pneumoniae* (36.6%) and *Pseudomonas aeruginosa* (29.6%): 100/355 (28.2%) patients had ≥1 ceftazidime non-susceptible isolate. Key efficacy results are shown in the Table. Ceftazidime-avibactam was non-inferior to meropenem for the primary endpoint of clinical cure at test-of-cure in the cMITT ($p=0.007$) and CE ($p<0.001$) populations. Subgroup analyses in non-VAP and VAP patients were consistent with the primary analysis. Efficacy of ceftazidime-avibactam against ceftazidime-non-susceptible pathogens was similar to that against ceftazidime-susceptible pathogens and was also comparable to meropenem. The adverse event rate with ceftazidime-avibactam was 74.6% versus 74.2% with meropenem; serious adverse event rates were 18.5% and 13.4%, respectively. The most frequent adverse event in both treatment arms was diarrhoea.

**Conclusions:** Ceftazidime-avibactam was effective in the treatment of NP, including VAP, as demonstrated by non-inferiority to meropenem in both co-primary cMITT and CE populations. Safety and tolerability observations were consistent with the known profile of ceftazidime-avibactam.

**Table. Key efficacy outcomes**

| | Patients, n/N (%) | | |
|---|---|---|---|
| | Ceftazidime-avibactam | Meropenem | Difference, % (95% CI) |
| **Primary efficacy endpoint[a]** | | | |
| **Clinical cure at TOC** | | | |
| cMITT population | 245/356 (68.8) | 270/370 (73.0) | –4.2 (–10.76, 2.46) |
| CE population | 199/257 (77.4) | 211/270 (78.1) | –0.7 (–7.86, 6.39) |
| **Subgroup analysis of clinical cure at TOC** | | | |
| cMITT population | | | |
| VAP | 83/118 (70.3) | 95/128 (74.2) | –3.9 (–15.11, 7.31) |
| Non-VAP | 162/238 (68.1) | 175/242 (72.3) | –4.2 (–12.41, 3.95) |
| CE population | | | |
| VAP | 62/80 (77.5) | 63/83 (75.9) | 1.6 (–11.55, 14.63) |
| Non-VAP | 137/177 (77.4) | 148/187 (79.1) | –1.7 (–10.30, 6.75) |
| **Secondary efficacy endpoints** | | | |
| **Clinical cure at TOC by ceftazidime susceptibility of baseline isolates[b]** | | | |
| mMITT population | | | |
| Ceftazidime-non-susceptible | 35/45 (77.8) | 40/54 (74.1) | 3.7 (–13.73, 20.38) |
| Ceftazidime-susceptible | 80/119 (67.2) | 96/126 (76.2) | –9.0 (–20.17, 2.33) |
| CE population | | | |
| Ceftazidime-non-susceptible | 29/36 (80.6) | 32/41 (78.0) | 2.5 (–16.42, 20.74) |
| Ceftazidime-susceptible | 63/84 (75.0) | 69/88 (78.4) | –3.4 (–16.18, 9.30) |
| **Per-pathogen favourable microbiological response at TOC** | | | |
| mMITT population | | | |
| *K. pneumoniae* | 37/59 (62.7) | 53/71 (74.6) | –11.9 (–27.76, 4.03) |
| *P. aeruginosa* | 22/58 (37.9) | 18/47 (38.3) | –0.4 (–19.01, 17.98) |
| eME population | | | |
| *K. pneumoniae* | 29/37 (78.4) | 39/49 (79.6) | –1.2 (–19.60, 15.96) |
| *P. aeruginosa* | 18/42 (42.9) | 14/35 (40.0) | 2.9 (–19.13, 24.32) |
| **All-cause mortality at Day 28** | | | |
| cMITT population | 30/356 (8.4) | 27/370 (7.3) | 1.1 (–2.84, 5.18) |
| CE population | 12/257 (4.7) | 9/270 (3.3) | 1.3 (–2.14, 5.04) |

[a]No formal statistical analysis was performed on subgroups or secondary endpoints.

[b]Ceftazidime-non-susceptible includes both the CLSI-breakpoint-defined ceftazidime resistant and intermediate categories (i.e. MIC ≥8 mg/L for *Enterobacteriaceae* and ≥16 mg/L for *P. aeruginosa* or disk diffusion diameters ≤20 mm for *Enterobacteriaceae* and ≤17 mm for *P. aeruginosa* from local laboratory).

CE, clinically evaluable; eME, extended microbiologically evaluable; TOC, test-of-cure.

CIs for the treatment differences were computed using the method of Miettinen and Nurminen (1985).