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Susceptibility Profiles of Baseline Gram-negative Pathogens from CERTAIN-1, a Phase 3 Study comparing Cefepime-taniborbactam to Meropenem in Adults with Complicated Urinary Tract Infection (cUTI)

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Abstract:

Background: Taniborbactam is an investigational β-lactamase inhibitor that restores cefepime (FEP) activity against FEP-, carbapenem-, and multidrug-resistant (MDR) Enterobacterales and *Pseudomonas aeruginosa* producing serine- and metallo-β-lactamases. Cefepime-taniborbactam (FTB) was superior to meropenem (MEM) for the primary composite (microbiologic and clinical) endpoint at test of cure in adults with cUTI in the CERTAIN-1 study (NCT03840148). We compared susceptibility to FEP, FTB, and MEM among Enterobacterales and *P. aeruginosa* recovered at baseline. **Methods:** MICs were determined by broth microdilution (CLSI M07) for baseline pathogens from patients in the extended microbiologic intent-to-treat population (Enterobacterales and/or *P. aeruginosa* at ≥10^5 CFU/mL in urine against which ≥1 study drug had activity [FTB MIC ≤16 µg/mL; MEM MIC ≤2 µg/mL (Enterobacterales) or ≤4 µg/mL (*P. aeruginosa*)]). Phenotypic subsets included ESBL, and FEP-, multidrug-, and carbapenem resistance (CLSI M100). **Results:** Taniborbactam decreased the FEP MIC_{90} by ≥1,024-fold (to 1 µg/mL) against FEP-resistant, ESBL, and MDR subsets of Enterobacterales and by ≥128-fold (to 8 µg/mL) against carbapenem-resistant Enterobacterales (Table). FTB at ≤16 µg/mL inhibited 66.7%, 71.4% and 100% of FEP-, multidrug-, and carbapenem-resistant *P. aeruginosa*, respectively. Higher percentages of Enterobacterales and *P. aeruginosa* isolates, regardless of resistance phenotype, were inhibited by FTB compared to MEM.

Table. Cefepime (FEP), Cefepime-taniborbactam (FTB), and Meropenem (MEM) Susceptibility Summary for Baseline Isolates of Enterobacterales and *P. aeruginosa* from Patients in the Extended Microbiological Intent-to-Treat (extended MicroITT) Population

	MIC_{90} or MIC range (µg/mL)			%Susceptible		
Pathogen/phenotype (n)	**FEP**	**FTB**	**MEM**	**FEP**	**FTB***	**MEM**
Enterobacterales overall (437)	512	0.25	0.12	73.5	99.8	96.8
Cefepime-resistant (106)	>512	1	2	0	99.1	88.7
ESBL (126)	>512	1	1	8.7	99.2	90.5
MDR (167)	>512	1	0.5	34.7	99.4	91.6
Carbapenem-resistant (10)	>512	8	64	10.0	100	0
P. aeruginosa overall (23)	32	16	16	69.6	91.3	82.6
Cefepime-resistant (6)	32-512	4-32	0.25->64	0	66.7	50.0
MDR (7)	16-512	4-32	0.25->64	0	71.4	57.1
Carbapenem-resistant (5)	4-512	4-16	0.5->64	40.0	100	20.0

Abbreviations: ESBL, extended spectrum β-lactamase (aztreonam, ceftazidime and/or cefepime MIC ≥2 µg/mL); FEP, cefepime; FTB, cefepime-taniborbactam; MDR, multidrug-resistant (resistant to ≥1 agent in ≥3 classes); MEM, meropenem.*In the absence of breakpoints, %Susceptible for cefepime-taniborbactam reflects % of isolates inhibited at ≤16 µg/mL.

Conclusions: Taniborbactam potentiated FEP activity against resistant isolates of Enterobacterales and *P. aeruginosa* from patients in the CERTAIN-1 cUTI study. These results are consistent with the ability of taniborbactam to restore FEP activity against most isolates of FEP-, multidrug-, and carbapenem-resistant gram-negative pathogens producing serine- and metallo-β-lactamases in nonclinical studies.

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