

# Outcomes at Test of Cure by baseline pathogen and ceftazidime-taniborbactam or meropenem MIC in the Phase 3 CERTAIN-1 study of patients with complicated urinary tract infection (cUTI)

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## Background

- Taniborbactam is a novel boronate β-lactamase inhibitor that restores ceftazidime activity against most isolates of multidrug-resistant (MDR) and carbapenem-resistant Enterobacterales (CRE) and *Pseudomonas aeruginosa* including isolates producing serine β-lactamases and NDM and VIM metallo-β-lactamases (Hamrick 2020; Hernández-García 2022; Karlowsky 2023)
- Ceftazidime-taniborbactam was superior to meropenem for the primary composite (microbiologic and clinical) endpoint at Test of Cure (Day 19-23) in adults with cUTI in the Phase 3 CERTAIN-1 study (Wagenlehner 2024)
- We assessed composite, microbiologic, and clinical outcomes by ceftazidime-taniborbactam MIC and meropenem MIC in patients with baseline Enterobacterales and *P. aeruginosa*

## Results

Table 1. Susceptibility summary for baseline isolates of Enterobacterales and *P. aeruginosa*

Pathogen Phenotype (n; % of total)	MIC <sub>90</sub> or MIC range (mg/L)						
	Cefepime	Ceftazidime-taniborbactam	Meropenem	Ceftazidime-avibactam	Ceftolozane-tazobactam	Meropenem-vaborbactam	Piperacillin-tazobactam
All Enterobacterales (437; 100%)	512	0.25	0.12	0.5	4	0.06	64
Cefepime resistant (106; 24.3%)	>512	1	2	1	>64	0.5	>128
ESBL (126; 28.8%)	>512	1	1	1	>64	0.25	>128
MDR (167; 38.2%)	>512	1	0.5	1	>64	0.12	>128
Carbapenem resistant (10; 2.3%)	>512	8	64	>64	>64	64	>128
All <i>P. aeruginosa</i> (23; 100%)	32	16	16	32	>64	16	>128
Cefepime resistant (6; 26.1%)	32 - 512	4 - 32	0.25 - >64	8 - 64	2 - >64	0.25 - >64	32 - >128
MDR (7; 30.4%)	16 - 512	4 - 32	0.25 - >64	4 - 64	1 - >64	0.25 - >64	32 - >128
Carbapenem resistant (5; 21.7%)	4 - 512	4 - 16	0.5 - >64	1 - 64	0.5 - >64	0.25 - >64	1 - 128

Abbreviations: ESBL, extended-spectrum β-lactamase; MDR, multidrug-resistant (resistant to at least one agent in at least three classes of antibacterial agents).

Table 2. Composite, microbiologic, and clinical success at Test of Cure (Day 19-23) overall and by MIC in ceftazidime-taniborbactam and meropenem treated patients with baseline Enterobacterales or *P. aeruginosa*

## Results Summary

- Taniborbactam decreased the ceftazidime MIC<sub>90</sub> by 2,048-fold (to 0.25 mg/L) against Enterobacterales overall, by ≥1,024-fold (to 1 mg/L) against ceftazidime resistant, ESBL, and MDR subsets of Enterobacterales, by ≥128-fold (to 8 mg/L) against CRE, and by 2-fold (to 16 mg/L) against *P. aeruginosa* (Table 1)
- Over the range of ceftazidime-taniborbactam MICs of ≤0.008 to 32 mg/L and meropenem MICs of ≤0.03 to 32 mg/mL for baseline pathogens from patients in the extended microITT population, there were no clear MIC thresholds that discriminated between successes and failures at Test of Cure for either study drug (Table 2)

## Conclusions

- Ceftazidime-taniborbactam demonstrated potent in vitro activity against baseline isolates of Enterobacterales and *P. aeruginosa* from patients in the Phase 3 CERTAIN-1 study
- Few patients had baseline isolates with elevated ceftazidime-taniborbactam or meropenem MICs
- There were no clear MIC thresholds that discriminated between successes and failures at Test of Cure for either study drug
- Continued development of ceftazidime-taniborbactam is warranted as a potential treatment for patients with infections due to Enterobacterales and *P. aeruginosa*, including ceftazidime-resistant, ESBL, MDR, and carbapenem-resistant strains

## Methods

- MICs were determined by broth microdilution (ISO 20776-1:2019; CLSI M07-Ed11 [2018]; CLSI M100-Ed29 [2019]) for baseline pathogens from patients in the extended microbiologic intent-to-treat (microITT) population (Enterobacterales and/or *P. aeruginosa* at ≥10<sup>5</sup> CFU/mL in urine against which at least 1 study drug had activity [ceftazidime-taniborbactam MIC ≤16 mg/L; meropenem MIC ≤2 mg/L for Enterobacterales or ≤4 mg/L for *P. aeruginosa*])
- Microbiologic success required reduction of all baseline gram-negative pathogen(s) to <10<sup>3</sup> CFU/mL. Patients with a uropathogen at ≥10<sup>3</sup> CFU/mL at Test of Cure that was clonally unrelated to the baseline pathogen of the same species were assessed with a microbiologic response of eradication
- Clinical success required symptomatic resolution or return to pre-morbid baseline of all core signs and symptoms, without additional antibacterial agents for cUTI
- Composite success required microbiologic and clinical success

### Ceftazidime-taniborbactam patients

### Meropenem patients

Ceftazidime-taniborbactam MIC (mg/L)	Composite success n/N (%) <sup>1</sup>							Composite success n/N (%) <sup>1</sup>						
	All Enterobacterales	<i>E. cloacae</i> complex	<i>E. coli</i>	<i>K. pneumoniae</i>	<i>P. mirabilis</i>	<i>S. marcescens</i>	<i>P. aeruginosa</i>	Meropenem MIC (mg/L)	All Enterobacterales	<i>E. cloacae</i> complex	<i>E. coli</i>	<i>K. pneumoniae</i>	<i>P. mirabilis</i>	<i>P. aeruginosa</i>
≤0.008	1/1 (100)	-	-	1/1 (100)	-	-	-	≤0.03	69/112 (61.6)	0/1	60/96 (62.5)	7/13 (53.8)	-	0/1
0.016	13/14 (92.9)	-	10/11 (90.9)	1/1 (100)	-	-	-	0.06	7/13 (53.8)	1/1 (100)	2/3 (66.7)	2/4 (50.0)	1/3 (33.3)	-
0.03	79/97 (81.4)	1/2 (50.0)	66/81 (81.5)	4/4 (100)	2/2 (100)	-	-	0.12	4/9 (44.4)	0/1	-	-	3/7 (42.9)	1/1 (100)
0.06	70/96 (72.9)	2/2 (100)	54/73 (74.0)	8/12 (66.7)	5/6 (83.3)	-	-	0.25	3/3 (100)	-	-	2/2 (100)	-	0/1
0.12	27/36 (75.0)	3/3 (100)	18/25 (72.0)	3/4 (75.0)	-	1/2 (50.0)	-	0.5	-	-	-	-	-	1/1 (100)
0.25	10/20 (50.0)	0/1	6/9 (66.7)	3/9 (33.3)	1/1 (100)	-	-	1	1/2 (50.0)	-	0/1	1/1 (100)	-	0/1
0.5	10/12 (83.3)	2/2 (100)	2/2 (100)	5/7 (71.4)	1/1 (100)	-	-	2	-	-	-	-	-	-
1	5/7 (71.4)	2/3 (66.7)	1/1 (100)	2/3 (66.7)	-	-	-	4	-	-	-	-	-	1/1 (100)
2	2/3 (66.7)	1/1 (100)	-	1/2 (50.0)	-	-	3/6 (50.0)	8	-	-	-	-	-	-
4	2/3 (66.7)	-	-	2/3 (66.7)	-	-	2/5 (40.0)	16	1/1 (100)	-	-	1/1 (100)	-	1/1 (100)
8	0/1	-	-	0/1	-	-	2/3 (66.7)	32	1/1 (100)	-	-	1/1 (100)	-	-
16	1/1 (100)	-	-	-	-	1/1 (100)	-	64	-	-	-	-	-	-
32	-	-	-	-	-	-	1/2 (50.0)	>64	-	-	-	-	-	-
Overall n/N (%)	220/289 (76.1)	11/14 (78.6)	157/202 (77.7)	30/47 (63.8)	9/10 (90.0)	2/3 (66.7)	8/16 (50.0)	Overall n/N (%)	86/140 (61.4)	1/3 (33.3)	62/100 (62.0)	14/22 (63.6)	4/10 (40.0)	4/7 (57.1)

Ceftazidime-taniborbactam MIC (mg/L)	Microbiologic success n/N (%) <sup>1,2</sup>							Microbiologic success n/N (%) <sup>1,2</sup>						
	All Enterobacterales	<i>E. cloacae</i> complex	<i>E. coli</i>	<i>K. pneumoniae</i>	<i>P. mirabilis</i>	<i>S. marcescens</i>	<i>P. aeruginosa</i>	Meropenem MIC (mg/L)	All Enterobacterales	<i>E. cloacae</i> complex	<i>E. coli</i>	<i>K. pneumoniae</i>	<i>P. mirabilis</i>	<i>P. aeruginosa</i>
≤0.008	1/1 (100)	-	-	1/1 (100)	-	-	-	≤0.03	80/112 (71.4)	0/1	69/96 (71.9)	9/13 (69.2)	-	0/1
0.016	13/14 (92.9)	-	10/11 (90.9)	1/1 (100)	-	-	-	0.06	7/13 (53.8)	1/1 (100)	2/3 (66.7)	2/4 (50.0)	1/3 (33.3)	-
0.03	86/97 (88.7)	1/2 (50.0)	72/81 (88.9)	4/4 (100)	2/2 (100)	-	-	0.12	4/9 (44.4)	0/1	-	-	3/7 (42.9)	1/1 (100)
0.06	82/96 (85.4)	2/2 (100)	62/73 (84.9)	11/12 (91.7)	6/6 (100)	-	-	0.25	3/3 (100)	-	-	2/2 (100)	-	1/1 (100)
0.12	30/36 (83.3)	3/3 (100)	20/25 (80.0)	3/4 (75.0)	-	2/2 (100)	-	0.5	-	-	-	-	-	1/1 (100)
0.25	10/20 (50.0)	0/1	6/9 (66.7)	3/9 (33.3)	1/1 (100)	-	-	1	1/2 (50.0)	-	0/1	1/1 (100)	-	0/1
0.5	10/12 (83.3)	2/2 (100)	2/2 (100)	5/7 (71.4)	1/1 (100)	-	-	2	-	-	-	-	-	-
1	5/7 (71.4)	2/3 (66.7)	1/1 (100)	2/3 (66.7)	-	-	-	4	-	-	-	-	-	1/1 (100)
2	2/3 (66.7)	1/1 (100)	-	1/2 (50.0)	-	-	3/6 (50.0)	8	-	-	-	-	-	-
4	2/3 (66.7)	-	-	2/3 (66.7)	-	-	2/5 (40.0)	16	1/1 (100)	-	-	1/1 (100)	-	1/1 (100)
8	0/1	-	-	0/1	-	-	2/3 (66.7)	32	1/1 (100)	-	-	1/1 (100)	-	-
16	1/1 (100)	-	-	-	-	1/1 (100)	-	64	-	-	-	-	-	-
32	-	-	-	-	-	-	1/2 (50.0)	>64	-	-	-	-	-	-
Overall n/N (%)	242/289 (83.7)	11/14 (78.6)	173/202 (85.6)	33/47 (70.2)	10/10 (100)	3/3 (100)	8/16 (50.0)	Overall n/N (%)	97/140 (69.3)	1/3 (33.3)	71/100 (71.0)	16/22 (72.7)	4/10 (40.0)	5/7 (71.4)

Ceftazidime-taniborbactam MIC (mg/L)	Clinical success n/N (%) <sup>1</sup>							Clinical success n/N (%) <sup>1</sup>						
	All Enterobacterales	<i>E. cloacae</i> complex	<i>E. coli</i>	<i>K. pneumoniae</i>	<i>P. mirabilis</i>	<i>S. marcescens</i>	<i>P. aeruginosa</i>	Meropenem MIC (mg/L)	All Enterobacterales	<i>E. cloacae</i> complex	<i>E. coli</i>	<i>K. pneumoniae</i>	<i>P. mirabilis</i>	<i>P. aeruginosa</i>
≤0.008	1/1 (100)	-	-	1/1 (100)	-	-	-	≤0.03	89/112 (79.5)	1/1 (100)	77/96 (80.2)	9/13 (69.2)	-	1/1 (100)
0.016	13/14 (92.9)	-	10/11 (90.9)	1/1 (100)	-	-	-	0.06	11/13 (84.6)	1/1 (100)	3/3 (100)	2/4 (50.0)	3/3 (100)	-
0.03	88/97 (90.7)	2/2 (100)	74/81 (91.4)	4/4 (100)	2/2 (100)	-	-	0.12	8/9 (88.9)	1/1 (100)	-	-	6/7 (85.7)	1/1 (100)
0.06	78/96 (81.3)	2/2 (100)	60/73 (82.2)	8/12 (66.7)	5/6 (83.3)	-	-	0.25	3/3 (100)	-	-	2/2 (100)	-	0/1
0.12	30/36 (83.3)	3/3 (100)	21/25 (84.0)	3/4 (75.0)	-	1/2 (50.0)	-	0.5	-	-	-	-	-	1/1 (100)
0.25	17/20 (85.0)	1/1 (100)	9/9 (100)	6/9 (66.7)	1/1 (100)	-	-	1	1/2 (50.0)	-	0/1	1/1 (100)	-	1/1 (100)
0.5	11/12 (91.7)	2/2 (100)	2/2 (100)	6/7 (85.7)	1/1 (100)	-	-	2	-	-	-	-	-	-
1	6/7 (85.7)	3/3 (100)	1/1 (100)	2/3 (66.7)	-	-	-	4	-	-	-	-	-	1/1 (100)
2	2/3 (66.7)	1/1 (100)	-	1/2 (50.0)	-	-	5/6 (83.3)	8	-	-	-	-	-	-
4	3/3 (100)	-	-	3/3 (100)	-	-	4/5 (80.0)	16	1/1 (100)	-	-	1/1 (100)	-	1/1 (100)
8	1/1 (100)	-	-	1/1 (100)	-	-	2/3 (66.7)	32	1/1 (100)	-	-	1/1 (100)	-	-
16	1/1 (100)	-	-	-	-	1/1 (100)	-	64	-	-	-	-	-	-
32	-	-	-	-	-	-	2/2 (100)	>64	-	-	-	-	-	-
Overall n/N (%)	249/289 (86.2)	14/14 (100)	177/202 (87.6)	36/47 (76.6)	9/10 (90.0)	2/3 (66.7)	13/16 (81.3)	Overall n/N (%)	113/140 (80.7)	3/3 (100)	80/100 (80.0)	16/22 (72.7)	9/10 (90.0)	6/7 (85.7)

<sup>1</sup>n/N = Number of patients with pathogen and ceftazidime-taniborbactam or meropenem MIC who are a microbiologic and/or symptomatic clinical success / Number of patients with pathogen and ceftazidime-taniborbactam or meropenem MIC. Patients may have had more than 1 pathogen at baseline.  
<sup>2</sup>For this analysis, patients with a uropathogen at ≥10<sup>3</sup> CFU/mL at TOC that was clonally unrelated to the baseline pathogen of the same species were assessed with a microbiologic response of eradication.

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