CERTAIN-1 Subgroup Analysis: A Phase 3 Study of Cefepime-Taniborbactam Efficacy and Safety in the Treatment of Complicated Urinary Tract Infections (cUTI)

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Background

- Due to increasing antimicrobial resistance, the CDC and WHO have identified public health threat pathogens including extended-spectrum β-lactamase (ESBL)-producing Enterobacterales, carbapenem-resistant Enterobacterales (CRE), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), and multidrug-resistant (MDR) *P. aeruginosa* (WHO 2017; CDC 2021). Although not yet cited by public health authorities as problematic pathogens, metallo-carbapenemase-producing CRE and CRPA are emerging (Tenover 2022; Estabrook 2023), with few treatment options available.
- Cefepime-taniborbactam is an investigational β-lactam/β-lactamase inhibitor combination that is active against CRE and CRPA-expressing serine and metallo-β-lactamases (Hamrick 2020; Liu 2020; Karlowsky 2022).
- In the Phase 3 CERTAIN-1 (Cefepime Rescue with Taniborbactam in cUTI) study (ClinicalTrials.gov identifier NCT03840148), cefepime-taniborbactam was superior to meropenem for the primary composite (clinical and microbiologic) endpoint at Test of Cure (TOC). Subgroup analyses were performed in the CERTAIN-1 study to determine the consistency of response, including for subgroups of patients with infections that were potentially more challenging to treat (e.g., bacteremia).

Methods

- CERTAIN-1 was a randomized, double-blind/double-dummy, study comparing cefepime-taniborbactam (2.5g q8h) to meropenem (1g q8h) in adults hospitalized with cUTI or acute pyelonephritis.
- The primary endpoint was the composite (microbiologic and clinical) success at the TOC visit in the microbiological intent-to-treat (microITT) population, defined as entry urine culture with Gram-negative pathogen(s) at $\geq 10^5$ CFU/mL against which both cefepime-taniborbactam and meropenem have antibacterial activity; no more than 2 microorganisms identified in the entry urine culture
- Patients were programmatically categorized as success or failure, with any indeterminate responses (e.g., those with missing data) considered failures for the primary analysis.
- Non-inferiority margin set at 15%; prespecified superiority test for the primary endpoint was performed following confirmation of non-inferiority
- The difference in composite success rates between treatments (cefepime-taniborbactam vs meropenem) was determined with a 95% confidence interval (CI) calculated using the method of Miettinen and Nurminen without controlling for the stratification factors of infection type and region. A pre-specified test for superiority was conducted if non-inferiority was demonstrated (NI margin 15%) and superiority concluded if the lower limit of the 95% CI for the difference in the composite success rates between treatments was ≥0.
- Subgroup analyses of the primary efficacy endpoint in the microITT analysis population were pre-specified and performed for patient demographic and disease-related baseline characteristics. For these analyses the treatment difference for composite success and the corresponding 95% CI were calculated.

Results

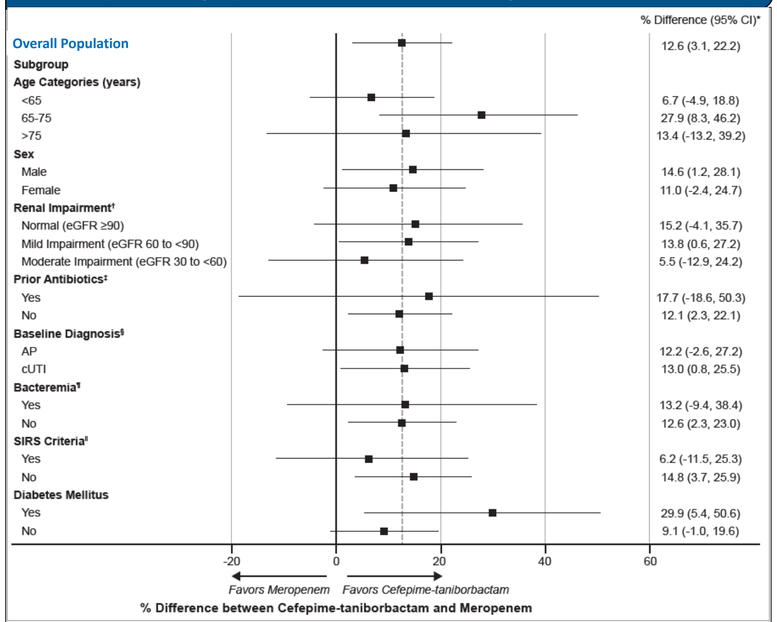
- A total of 661 patients were randomized to cefepime-taniborbactam (N=441) or meropenem (N=220), and 436 patients (66.0%) were included in the microITT population (293 cefepime-taniborbactam, 143 meropenem).
- Demographic and disease-related baseline characteristics were well balanced between the treatment groups. Notably, 38.1% of patients were ≥ 65 years of age, 78.2% of patients had some degree of renal impairment, and 13.1% had baseline bacteremia (Table).
- Composite success rates were 70.6% and 58.0% for cefepime-taniborbactam and meropenem groups, respectively for the primary endpoint at the TOC visit, and cefepime-taniborbactam was superior to meropenem (treatment difference [cefepime-taniborbactam minus meropenem], 12.6%; 95% CI, 3.1 to 22.2; p=0.0088).
- For the subgroup analyses, composite success rates were consistent with the primary analysis with numerically higher success rates in patients treated with cefepime-taniborbactam than meropenem across subgroups (Table, Figure).
- Patients with potentially more serious infections (e.g., secondary bacteremia and sepsis), patients meeting SIRS criteria, and patients in at-risk subgroups (e.g., age ≥ 65, diabetes mellitus) showed consistently high success rates when treated with cefepime-taniborbactam.

Table: Composite Success (Microbiological and Clinical Success) at Test of Cure by Subgroup in the Phase 3 CERTAIN1 Study (microITT Analysis Population)

Subgroup	Cefepime-taniborbactam (N = 293) n/N1 (%)	Meropenem (N = 143) n/N1 (%)	Treatment Difference Cefepime-taniborbactam vs Meropenem Response Rate Difference % (95% CI) *
Overall	**207/293 (70.6%)**	**83/143 (58.0%)**	**12.6 (3.1, 22.2)**
Age (years)			
<65	128/180 (71.1%)	58/90 (64.4%)	6.7 (-4.9, 18.8)
65 - 75	53/72 (73.6%)	16/35 (45.7%)	27.9 (8.3, 46.2)
>75	26/41 (63.4%)	9/18 (50.0%)	13.4 (-13.2, 39.2)
Sex			
Male	96/132 (72.7%)	43/74 (58.1%)	14.6 (1.2, 28.1)
Female	111/161 (68.9%)	40/69 (58.0%)	11.0 (-2.4, 24.7)
Race			
American Indian or Alaska Native	3/3 (100%)	0	
Asian	21/26 (80.8%)	2/6 (33.3%)	47.4 (5.8, 76.0)
Black or African American	0/1	0	13.5 (-2.0, 29.1)
White	179/257 (69.6%)	77/131 (58.8%)	10.9 (0.9, 21.0)
Other	4/6 (66.7%)	4/6 (66.7%)	0.0 (-49.9, 49.9)
Ethnicity			
Hispanic or Latino	19/29 (65.5%)	6/12 (50.0%)	15.5 (-16.3, 45.9)
Not Hispanic or Latino	187/263 (71.1%)	76/130 (58.5%)	12.6 (2.7, 22.8)
BMI (kg/m2)			
Underweight <18.5	6/10 (60.0%)	2/3 (66.7%)	
Normal weight 18.5 to 24.9	65/89 (73.0%)	30/45 (66.7%)	6.4 (-9.5, 23.4)
Overweight 25 to 29.9	78/113 (69.0%)	30/54 (55.6%)	13.5 (-2.0, 29.1)
Obese ≥30	58/81 (71.6%)	21/39 (53.8%)	17.8 (-0.4, 35.8)
Renal Impairment (mL/min/1.73m2)†			
Normal (eGFR ≥90)	51/66 (77.3%)	18/29 (62.1%)	15.2 (-4.1, 35.7)
Mild Impairment (eGFR 60 to < 90)	100/138 (72.5%)	44/75 (58.7%)	13.8 (0.6, 27.2)
Moderate Impairment (eGFR 30 to < 60)	51/84 (60.7%)	21/38 (55.3%)	5.5 (-12.9, 24.2)
Severe (eGFR < 30)	5/5 (100%)	0/1 (0.0%)	
Region			
North America and Western Europe	8/14 (57.1%)	3/8 (37.5%)	19.6 (-23.4, 55.6)
Eastern Europe	167/236 (70.8%)	73/121 (60.3%)	10.4 (0.1, 21.0)
Rest of World	32/43 (74.4%)	7/14 (50.0%)	24.4 (-3.5, 51.2)
Prior Antibiotic Within 72 Hr of Randomization			
Yes	12/19 (63.2%)	5/11 (45.5%)	17.7 (-18.6, 50.3)
No	195/274 (71.2%)	78/132 (59.1%)	12.1 (2.3, 22.1)
Baseline Diagnosis			
Acute Pyelonephritis Only	87/126 (69.0%)	33/58 (56.9%)	12.2 (-2.6, 27.2)
cUTI	120/167 (71.9%)	50/85 (58.8%)	13.0 (0.8, 25.5)
Complicating Factor present			
Yes	121/168 (72.0%)	51/86 (59.3%)	12.7 (0.5, 25.2)
No	86/125 (68.8%)	32/57 (56.1%)	12.7 (-2.3, 27.8)
Type of Complicating Factor present			
Chronic Urinary Retention	59/80 (73.8%)	22/39 (56.4%)	17.3 (-0.6, 35.4)
Indwelling Catheter	12/22 (54.5%)	6/11 (54.5%)	0.0 (-33.4, 34.4)
Neurogenic Bladder with Presence or History of Urine Residual Volume of >100 mL	22/29 (75.9%)	7/13 (53.8%)	22.0 (-7.9, 51.1)
Obstructive Uropathy	59/80 (73.8%)	26/46 (56.5%)	17.2 (0.2, 34.2)
Other	5/9 (55.6%)	2/5 (40.0%)	15.6 (-36.6, 59.6)
SIRS (i.e., sepsis) criteria			
Yes	51/70 (72.9%)	24/36 (66.7%)	6.2 (-11.5, 25.3)
No	156/223 (70.0%)	59/107 (55.1%)	14.8 (3.7, 25.9)
Prior UTI			
Yes	25/42 (59.5%)	8/19 (42.1%)	17.4 (-9.5, 41.9)
UTI within the past year	9/13 (69.2%)	0/4	69.2 (11.9, 87.7)
No UTI within the past year	16/29 (55.2%)	8/15 (53.3%)	1.8 (-27.6, 31.7)
No	182/251 (72.5%)	75/124 (60.5%)	12.0 (2.0, 22.3)
Diabetes			
Yes	31/49 (63.3%)	8/24 (33.3%)	29.9 (5.4, 50.6)
No	176/244 (72.1%)	75/119 (63.0%)	9.1 (-1.0, 19.6)
Bacteremia			
Yes	31/38 (81.6%)	13/19 (68.4%)	13.2 (-9.4, 38.4)
No	176/255 (69.0%)	70/124 (56.5%)	12.6 (2.3, 23.0)
Monomicrobic vs Polymicrobic Infection			
Monomicrobic Infection	206/287 (71.8%)	82/138 (59.4%)	12.4 (2.8, 22.1)
2 gram(-) pathogens	1/4 (25.0%)	1/4 (25.0%)	0.0 (-57.8, 57.8)
1 gram(-) and 1 gram(+) pathogen	0/2	0/1	

CI = Confidence interval; n / N1 = Number of patients in the subgroup who are an overall success / Number of patients in the subgroup in each treatment group.
Two meropenem patients had missing BMI calculations and were not included in the analysis. Point estimates of the rate difference and its CI are not provided for subgroups with less than 5 patients in one or both treatment groups. *95% confidence intervals of between treatment differences are based on Miettinen and Nurminen method.
†Renal status is based on eGFR calculated using the MDRD formula.

Figure: Forest Plot of Composite Success (Microbiological and Clinical Success) at Test of Cure for Important Subgroups in the Phase 3 CERTAIN-1 Study (microITT Analysis Population)



AP = acute pyelonephritis; CI = Confidence Interval; cUTI = complicated urinary tract infection; eGFR = estimated glomerular filtration rate; SIRS = systemic inflammatory response syndrome.
The black vertical solid line represents a difference of zero. The dotted line represents the point estimate observed in the overall population. Subgroups with n ≤5 patients are not presented. *95% confidence intervals (CI) of between-treatment response rate differences are based on Miettinen and Nurminen method.
†Baseline renal status and estimated glomerular filtration rate (eGFR) is calculated using the Modification of Diet in Renal Disease (MDRD) formula using serum creatinine measured by the central laboratory. Units are in mL/min/1.73m^2. ‡Systemic antibiotics administered within 72 hours prior to randomization. §Criteria for each infection type defined in the protocol. ¶Bacteremia is defined as a patient with non-contaminant bacteria identified in blood culture at baseline. #Systemic inflammatory response syndrome (SIRS) criteria is defined as at least two of the following at baseline: fever >38°C or hypothermia <36°C, tachycardia >90 beats per minute, tachypnea >20 breaths per minute, leukocytosis >12x10^9 cells per liter or leucopoenia <4x10^9 cells per liter.

Conclusions

- Cefepime-taniborbactam was superior to meropenem for composite success at TOC in the overall microITT population.
- Composite success rates were numerically higher in all subgroups, consistent with the primary efficacy outcome.
- No single subgroup or subgroups drove the superiority finding.
- The same trend toward higher numerical outcomes was observed across subgroups indicative of more severe disease and patient subsets at greater risk of poor outcomes.

References:
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