ORIGINAL ARTICLE

Cefepime–Taniborbactam in Complicated Urinary Tract Infection

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ABSTRACT

BACKGROUND

Carbapenem-resistant Enterobacterales species and multidrug-resistant *Pseudomonas aeruginosa* are global health threats. Cefepime–taniborbactam is an investigational β-lactam and β-lactamase inhibitor combination with activity against Enterobacterales species and *P. aeruginosa* expressing serine- and metallo-β-lactamases.

METHODS

In this phase 3, double-blind, randomized trial, we assigned hospitalized adults with complicated urinary tract infection (UTI), including acute pyelonephritis, in a 2:1 ratio to receive intravenous cefepime–taniborbactam (2.5 g) or meropenem (1 g) every 8 hours for 7 days; this duration could be extended up to 14 days in case of bacteremia. The primary outcome was both microbiologic and clinical success (composite success) on trial days 19 to 23 in the microbiologic intention-to-treat (microITT) population (patients who had a qualifying gram-negative pathogen against which both study drugs were active). A prespecified superiority analysis of the primary outcome was performed after confirmation of noninferiority.

RESULTS

Of the 661 patients who underwent randomization, 436 (66.0%) were included in the microITT population. The mean age of the patients was 56.2 years, and 38.1% were 65 years of age or older. In the microITT population, 57.8% of the patients had complicated UTI, 42.2% had acute pyelonephritis, and 13.1% had bacteremia. Composite success occurred in 207 of 293 patients (70.6%) in the cefepime–taniborbactam group and in 83 of 143 patients (58.0%) in the meropenem group. Cefepime–taniborbactam was superior to meropenem regarding the primary outcome (treatment difference, 12.6 percentage points; 95% confidence interval, 3.1 to 22.2; P=0.009). Differences in treatment response were sustained at late follow-up (trial days 28 to 35), when cefepime–taniborbactam had higher composite success and clinical success. Adverse events occurred in 35.5% and 29.0% of patients in the cefepime–taniborbactam group and the meropenem group, respectively, with headache, diarrhea, constipation, hypertension, and nausea the most frequently reported; the frequency of serious adverse events was similar in the two groups.

CONCLUSIONS

Cefepime–taniborbactam was superior to meropenem for the treatment of complicated UTI that included acute pyelonephritis, with a safety profile similar to that of meropenem. (Funded by Venatorx Pharmaceuticals and others; CERTAIN-1 ClinicalTrials.gov number, NCT03840148.)

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Complicated urinary tract infection (UTI), including acute pyelonephritis, is responsible for at least 600,000 annual hospital admissions in the United States,[1] with considerable health care costs.[2,3] Widespread and emerging resistance to β-lactam antibiotics[4-6] complicates management of serious infections, including complicated UTI.

Cefepime, a broad-spectrum, fourth-generation cephalosporin, is used to treat such infections.[7] Resistance to cefepime has increased with the spread of extended-spectrum β-lactamase (ESBL) and carbapenemase enzymes.[7,8] Taniborbactam (formerly VNRX-5133) is a bicyclic boronate β-lactamase inhibitor with potent, selective, direct inhibitory activity against Ambler class A, B, C, and D enzymes, including prevalent serine- and metallo-β-lactamases.[9,10] The cefepime–taniborbactam combination is active in vitro against most isolates of carbapenem-resistant Enterobacterales species, multidrug-resistant *Pseudomonas aeruginosa*, and Enterobacterales species and *P. aeruginosa* organisms that are resistant to both ceftolozane–tazobactam and ceftazidime–avibactam.[11-14] Cefepime–taniborbactam has shown in vivo efficacy against cefepime- and carbapenem-resistant Enterobacterales species and against *P. aeruginosa*.[15-17] Cefepime–taniborbactam has shown an acceptable side-effect profile in healthy volunteers; both cefepime and taniborbactam have well-matched plasma pharmacokinetics with greater than 80% renal elimination.[18-20]

Cefepime–taniborbactam is in development for the treatment of serious gram-negative infections, including complicated UTI. We performed the Cefepime Rescue with Taniborbactam in Complicated UTI (CERTAIN-1) phase 3 trial to evaluate the safety and efficacy of cefepime–taniborbactam as compared with meropenem (a preferred treatment option for infections caused by ESBL-producing gram-negative pathogens) in hospitalized patients with complicated UTI.

METHODS

TRIAL DESIGN AND OVERSIGHT

We conducted this double-blind, double-dummy, randomized, active-controlled trial at 68 sites in 15 countries. The primary objective was to evaluate the efficacy of cefepime–taniborbactam as compared with meropenem in patients with complicated UTI, including acute pyelonephritis.

The trial was designed and conducted by Venatorx Pharmaceuticals in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation and the ethical principles of the Declaration of Helsinki. The protocol and its amendments (available with the full text of this article at NEJM.org) were approved by an independent ethics committee at each participating site. An independent data and safety monitoring committee monitored the collection of patient safety data. All the patients provided written informed consent.

Representatives of Venatorx Pharmaceuticals gathered the data. The authors performed the analyses, interpreted the data, and vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. The authors participated in the writing of the first draft of the manuscript and in making the decision to submit the manuscript for publication. A data confidentiality agreement was in place between the sponsor and the investigators. Medical writers who were funded by the sponsor assisted with manuscript preparation.

ELIGIBILITY CRITERIA

Adult patients (≥18 years of age) with a diagnosis of either complicated UTI or acute pyelonephritis were eligible if they met the disease-specific criteria outlined in current regulatory guidelines.[21,22] Patients with complicated UTI had pyuria, at least one systemic sign and at least one local sign or symptom, and at least one complicating factor (urinary tract functional or anatomic abnormality) (Table S1 in the Supplementary Appendix, available at NEJM.org). Patients with acute pyelonephritis had pyuria, at least one systemic sign or symptom, and flank pain or costovertebral angle tenderness.

Patients were excluded if they had received antibacterial drug therapy for complicated UTI for more than 24 hours before randomization, had an infection with a meropenem-resistant pathogen, or warranted nontrial systemic antibacterial therapy. Also excluded were patients with an estimated glomerular filtration rate of less than 30 ml per minute per 1.73 m^2 of body-surface area or who had prostatitis, perinephric or renal abscess, severe hepatic impairment, or hypersensitivity to any β-lactam antibiotic or who had undergone renal transplantation. Randomization was performed before the availability of baseline culture results.

RANDOMIZATION AND TREATMENT

Patients were randomly assigned in a 2:1 ratio to receive cefepime–taniborbactam (at a dose of 2.5 g; 2 g of cefepime and 0.5 g of taniborbactam) intravenously over a 2-hour period every 8 hours plus meropenem placebo or meropenem (at a dose of 1 g) intravenously over a 30-minute period every 8 hours plus cefepime–taniborbactam placebo for 7 days; the duration of administration could be extended up to 14 days for patients with bacteremia (Fig. S1). Dose adjustments for patients with renal impairment are described in the protocol. Oral step-down therapy was not permitted.

An interactive-response system was used for randomization with a central computer-generated sequence and a block size of 6. Randomization was stratified according to infection type (complicated UTI or acute pyelonephritis only) and region (North America and Western Europe, Eastern Europe, or rest of the world). Trial drugs were prepared in an unblinded manner at each trial site by pharmacy staff members who were not permitted to perform any other trial procedures. The trial sponsor, investigators, site staff members who were participating in patient care or clinical evaluations, and patients were not aware of treatment assignments.

TRIAL POPULATIONS

The intention-to-treat (ITT) population included all the patients who had undergone randomization. The safety population included all the patients who had received at least one dose of a trial drug. The microbiologic ITT (microITT) population included patients who had a positive baseline urine culture with at least 10^5 colony-forming units (CFU) per milliliter of a qualifying gram-negative pathogen against which both cefepime–taniborbactam and meropenem had antibacterial activity, with no more than 2 microorganisms identified regardless of colony count (Table S2). For Enterobacterales species, the minimal inhibitory concentration (MIC) was 16 μg per milliliter or less for cefepime–taniborbactam and 2 μg per milliliter or less for meropenem; for *P. aeruginosa*, the respective MIC was 16 μg per milliliter or less and 4 μg per milliliter or less. Patients with monomicrobial gram-positive infection were not included in the microITT population. The extended microITT population included all the patients in the microITT population plus patients who had a positive baseline urine culture of a gram-negative pathogen against which at least one trial drug had antibacterial activity. Genotypic relatedness of serial isolates was assessed in cases of microbiologic failure.

OUTCOMES

The primary efficacy outcome was a composite of both microbiologic and clinical success in the microITT population at test of cure on trial days 19 to 23. This objective was consistent with the guidance of the Food and Drug Administration regarding the development of drugs for the treatment of complicated urinary tract infection.[21]

The microITT population has been commonly used as the primary analysis population in antibiotic noninferiority trials so that the microbiologic component of the primary outcome can be assessed. The resulting exclusion of some patients from the microITT population has been based on test results of samples collected before randomization but with results that were not available until after randomization, so assignment to the microITT population has also been at random.

In our trial, microbiologic success was defined as a reduction of all gram-negative bacterial pathogens found at baseline to less than 10^3 CFU per milliliter. Clinical success was defined as symptomatic resolution or return to preinfection baseline of all core signs and symptoms, with no use of additional antibacterial agents for complicated UTI (Table S3).

Key secondary outcomes were composite success in the extended microITT population and composite success, microbiologic success, and clinical success in the microITT population at the end of treatment (i.e., ≤24 hours after the last dose of a trial drug) and at late follow-up (trial days 28 to 35). Prespecified subgroup analyses included composite, microbiologic, and clinical success at test of cure according to pathogen and resistance category (cefepime-resistant, ESBL-producing, and multidrug-resistant) and microbiologic success on the basis of the MIC at test of cure in the microITT population. Seventeen additional prespecified subgroup analyses were performed at test of cure in the microITT population; of these analyses, 8 are described in this report. Safety analyses included assessments of adverse events, vital signs, and clinical laboratory results.

STATISTICAL ANALYSIS

We determined that the enrollment of at least 396 patients in the microITT population would provide the trial with more than 90% power for the assessment of the primary outcome, assuming that 75% of the patients in the two treatment groups had composite success. The noninferiority margin for the cefepime–taniborbactam group as compared with the meropenem group was –15 percentage points at a two-sided alpha level of 0.05. On the assumption that 68% of the patients who had undergone randomization would be included in the microITT population, we determined that an overall enrollment of at least 582 patients was required.

Clinical success was programmatically deter-

Table 1. Characteristics of the Patients at Baseline (Microbiologic Intention-to-Treat Population).*

Characteristic	Cefepime–Taniborbactam (N=293)	Meropenem (N=143)
Age		
Mean	56.5±17.6	55.8±17.9
Distribution — no. (%)		
<65 yr	180 (61.4)	90 (62.9)
65 to 75 yr	72 (24.6)	35 (24.5)
>75 yr	41 (14.0)	18 (12.6)
Female sex — no. (%)	161 (54.9)	69 (48.3)
Race or ethnic group — no. (%)†		
American Indian or Alaska Native	3 (1.0)	0
Asian	26 (8.9)	6 (4.2)
Black	1 (0.3)	0
White	257 (87.7)	131 (91.6)
Other	6 (2.0)	6 (4.2)
Hispanic or Latino ethnic group — no. (%)†		
Yes	29 (9.9)	12 (8.4)
No	263 (89.8)	130 (90.9)
Missing data	1 (0.3)	1 (0.7)
Geographic region — no. (%)		
North America or western Europe	14 (4.8)	8 (5.6)
Eastern Europe	236 (80.5)	121 (84.6)
Rest of world	43 (14.7)	14 (9.8)
Body-mass index — no. (%)‡		
<18.5	10 (3.4)	3 (2.1)
18.5 to 24.9	89 (30.4)	45 (31.5)
25 to 29.9	113 (38.6)	54 (37.8)
≥30	81 (27.6)	39 (27.3)
Missing data	0	2 (1.4)
Status for eGFR — no. (%)§		
Normal: ≥90 ml/min/1.73 m^2	66 (22.5)	29 (20.3)
Mild impairment: 60 to <90 ml/min/1.73 m^2	138 (47.1)	75 (52.4)
Moderate impairment: 30 to <60 ml/min/1.73 m^2	84 (28.7)	38 (26.6)
Severe impairment: <30 ml/min/1.73 m^2	5 (1.7)	1 (0.7)
Infection type — no. (%)		
Complicated UTI	167 (57.0)	85 (59.4)
Acute pyelonephritis	126 (43.0)	58 (40.6)
Bacteremia — no. (%)	38 (13.0)	19 (13.3)
SIRS criteria — no. (%)¶	70 (23.9)	36 (25.2)
Diabetes — no. (%)	49 (16.7)	24 (16.8)

Table 1. (Continued.)

Characteristic	Cefepime–Taniborbactam (N=293)	Meropenem (N=143)
Gram-negative pathogen — no. (%)	293 (100)	143 (100)
Enterobacterales species		
Any	281 (95.9)	137 (95.8)
Cefepime-resistant	66 (22.5)	30 (21.0)
ESBL-producing‖	76 (25.9)	40 (28.0)
Multidrug-resistant**	100 (34.1)	55 (38.5)

* Plus–minus values are means ±SD. The microbiologic intention-to-treat (microITT) population consisted of patients who had a positive baseline urine culture with at least 10^5 colony-forming units per milliliter of a qualifying gram-negative pathogen against which both trial drugs had antibacterial activity. Percentages may not total 100 because of rounding. UTI denotes urinary tract infection.
† Race and ethnic group were reported by the patients.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The estimated glomerular filtration rate (eGFR) was calculated with the use of the Modification of Diet in Renal Disease formula according to serum creatinine levels measured by the central laboratory.
¶ The criteria for the systemic inflammatory response syndrome (SIRS) include 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 (>12×10^9 cells per liter), or leukopenia (<4×10^9 cells per liter).
‖ The extended-spectrum β-lactamase (ESBL) phenotype was defined as pathogens that had a minimal inhibitory concentration for ceftazidime, aztreonam, or cefepime of 2 μg per milliliter or more.
** Multidrug-resistant pathogens were defined as being nonsusceptible to at least one agent in three or more categories of antibacterial agents.

mined on the basis of the results on standardized assessment questionnaires of patients' symptoms administered by staff members at the investigative site. Missing data were counted as treatment failures for analyses in the microITT, extended microITT, and ITT populations. The percentage of patients with composite success was calculated as the number of successes divided by total number of patients in each treatment group. The difference in success between treatments (cefepime–taniborbactam minus meropenem) was calculated with the 95% confidence interval of between-group differences according to the Miettinen and Nurminen method.[23] If the lower boundary of the 95% confidence interval for the between-group difference in success was at least –15 percentage points, noninferiority was declared. A prespecified superiority assessment was to be conducted if noninferiority had been determined. If the lower boundary of the 95% confidence interval was 0 or more, superiority was determined. A two-sided P value was calculated to understand the strength of evidence associated with the superiority conclusion. Confidence intervals for secondary outcomes and subgroups were not adjusted for multiplicity and were used only to assess the consistency of treatment effect.

RESULTS

TRIAL POPULATION

Of 661 patients who were enrolled from August 2019 through December 2021, a total of 436 (66.0%) were included in the microITT population and 657 (99.4%) were included in the safety population (Fig. S2). The most frequent reason for exclusion from the microITT population was the absence of a qualifying baseline gram-negative pathogen. The clinical and demographic characteristics of the patients were well-balanced between the treatment groups at baseline. Table 1 provides details regarding the microITT population, and Table S4 provides details regarding the ITT population.

The mean age of the patients was 56.2 years; 38.1% of the patients were 65 years of age or older. In the microITT population, 57.8% of the patients had complicated UTI and 42.2% had acute pyelonephritis. Only 6.9% of the patients received antibiotics within 72 hours before randomization. Bacteremia was present in 13.1% of the patients at baseline, and 24.3% met the criteria for systemic inflammatory response syndrome (SIRS).[24]

The majority of baseline pathogens in the microITT population were Enterobacterales species

(95.9%), primarily *Escherichia coli* (69.0%), *Klebsiella pneumoniae* (13.8%), *Proteus mirabilis* (4.6%), and *Enterobacter cloacae* complex (3.9%); 4.1% of baseline isolates were *P. aeruginosa* (Table S5). Baseline pathogens that were resistant to cefepime (as defined by the Clinical and Laboratory Standards Institute)[25], phenotypic ESBL-producing pathogens, and multidrug-resistant pathogens[26] were detected in 22.0%, 26.6%, and 35.6%, respectively, of the microITT population (Table 1).

Most patients completed both the trial treatment (93.9% in the cefepime–taniborbactam group and 96.4% in the meropenem group) and the trial (96.6% and 97.3%, respectively). The median treatment duration was the same in the two groups: 7 days (range, 1 to 15) in the cefepime–taniborbactam group and 7 days (range, 2 to 15) in the meropenem group; the median duration was similar in the two groups among the patients with bacteremia (12 days and 14 days, respectively).

EFFICACY OUTCOMES

A composite response of both microbiologic and clinical success at test of cure on trial days 19 to 23 in the microITT population (the primary outcome) occurred in 207 of 293 patients (70.6%) in the cefepime–taniborbactam group and in 83 of 143 patients (58.0%) in the meropenem group. A prespecified superiority assessment after a determination of noninferiority for the primary efficacy outcome showed the superiority of cefepime–taniborbactam over meropenem, with a treatment difference of 12.6 percentage points (95% confidence interval [CI], 3.1 to 22.2; P=0.009) (Table 2 and Fig. 1). Differences in treatment response were sustained at late follow-up, at which time cefepime–taniborbactam had both higher composite success and higher clinical success than meropenem. In the extended microITT population, cefepime–taniborbactam also had higher composite success than meropenem (Table 2).

Measures of composite success at test of cure in subgroups according to age, infection type, disease severity (bacteremia and SIRS), and renal impairment were consistent with the primary efficacy result (Fig. 1). Follow-up blood cultures were negative in all patients with baseline bacteremia, and composite success at test of cure for patients with bacteremia was 81.6% in the cefepime–taniborbactam group and 68.4% in the meropenem group. Frequencies of composite success at test of cure according to baseline pathogen and phenotypic resistance category were consistent with the primary efficacy result (Table 3). Frequencies of clinical success according to baseline pathogen and resistance category were high and similar in the two treatment groups. At test of cure, the frequency of per-patient microbiologic success was numerically higher in the cefepime–taniborbactam group for each baseline pathogen and resistance category, except in patients with *K. pneumoniae* and *P. aeruginosa*, in whom the frequency of microbiologic success was similar in the two groups (Table 3). Treatment success according to pathogen and resistance category remained high at late follow-up in the microITT population (Table S6). In the extended microITT population, cefepime–taniborbactam had composite success at test of cure in 8 of 10 patients with meropenem-resistant pathogens, including with *K. pneumoniae* (in 6 of 7 patients), *P. aeruginosa* (in 1 of 2 patients), and *Serratia marcescens* (in 1 of 1 patient). During the trial, resistance to cefepime–taniborbactam or meropenem did not develop in any of the pathogens identified at baseline. Additional secondary efficacy analyses are provided in Table S7. A post hoc analysis of clinical success according to visit for the ITT population is provided in Table S8.

SAFETY

Adverse events occurred during treatment in 35.5% of the patients in the cefepime–taniborbactam group and in 29.0% of those in the meropenem group (Table 4 and Table S9). Most adverse events in both groups were mild or moderate in severity and did not result in the discontinuation of treatment. Premature discontinuation of a trial drug occurred in 3.0% of the patients in the cefepime–taniborbactam group and in 0.9% of those in the meropenem group. Reasons for treatment discontinuation in the cefepime–taniborbactam group were heterogeneous, with no event occurring more than once (Table S10).

The most frequently reported adverse events in the cefepime–taniborbactam group were headache, gastrointestinal events (including diarrhea, constipation, and nausea), and hypertension (Table 4). *Clostridium difficile* infection was reported in 3 patients in the cefepime–taniborbactam group and in no patients in the meropenem group. No clinically significant between-group differences in adverse trends were reported with

Table 2. Primary and Secondary Efficacy Outcomes.*

Outcome, Population, and Time of Assessment	Cefepime–Taniborbactam	Meropenem	Treatment Difference (95% CI)
	no./total no. of patients (%)		*percentage points*
Microbiologic intention-to-treat population			
Primary outcome†			
Composite success at test of cure	207/293 (70.6)	83/143 (58.0)	12.6 (3.1 to 22.2)‡
Microbiologic§	229/293 (78.2)	95/143 (66.4)	11.7 (2.9 to 21.0)
Clinical¶	251/293 (85.7)	116/143 (81.1)	4.5 (–2.6 to 12.6)
Secondary outcome‖			
Composite success at end of treatment	261/293 (89.1)	123/143 (86.0)	3.1 (–3.2 to 10.4)
Microbiologic§	284/293 (96.9)	139/143 (97.2)	–0.3 (–3.5 to 4.1)
Clinical¶	265/293 (90.4)	127/143 (88.8)	1.6 (–4.1 to 8.5)
Composite success at late follow-up	187/293 (63.8)	74/143 (51.7)	12.1 (2.2 to 21.9)
Microbiologic§	207/293 (70.6)	90/143 (62.9)	7.7 (–1.6 to 17.3)
Clinical¶	238/293 (81.2)	102/143 (71.3)	9.9 (1.5 to 18.8)
Extended microbiologic intention-to-treat population			
Secondary outcome			
Composite success at test of cure	216/305 (70.8)	86/147 (58.5)	12.3 (3.0 to 21.8)
Microbiologic§	238/305 (78.0)	98/147 (66.7)	11.4 (2.7 to 20.5)
Clinical¶	262/305 (85.9)	119/147 (81.0)	4.9 (–2.1 to 12.9)

* Outcomes are reported in both the microbiologic and extended microbiologic intention-to-treat populations.
† The primary efficacy outcome was both microbiologic and clinical success (composite success) in the microbiologic intention-to-treat population at the test-of-cure visit (trial days 19 to 23 after initiation of intravenous therapy with the assigned trial drug). Individual component responses (microbiologic success and clinical success) were prespecified as secondary outcomes.
‡ P=0.009.
§ Microbiologic success was defined as the reduction of all gram-negative bacterial pathogens found at baseline from 10^5 colony-forming units per milliliter or more to less than 10^3 colony-forming units per milliliter in urine culture obtained at the post-treatment visit.
¶ Clinical success was defined as symptomatic resolution or a return to preinfection baseline of all core signs and symptoms, with no use of additional antibacterial drugs for complicated urinary tract infection. A post hoc analysis of clinical success at each post-treatment visit in the intention-to-treat population is provided in Table S8.
‖ Secondary outcomes that were assessed in the microbiologic intention-to-treat analysis population included the composite outcome and its components (microbiologic success and clinical success) at the end-of-treatment visit (≤24 hours after the last dose of a trial drug) and late follow-up visit (trial days 28 to 35 after the initiation of intravenous therapy with the assigned trial drug).

respect to laboratory test results (including those that were potentially clinically significant) or vital signs. Increases in levels of alanine aminotransferase and aspartate aminotransferase were reported in less than 1% of the patients in the cefepime–taniborbactam group. No cases fulfilling Hy's Law criteria were observed in patients with abnormal liver-function tests in either treatment group.

Serious adverse events occurred in a similar percentage of patients in each treatment group (2.0% in the cefepime–taniborbactam group and 1.8% in the meropenem group). The most frequently reported serious adverse events were coronavirus disease 2019, which was reported in 2 patients (0.5%) in the cefepime–taniborbactam group, and pyelonephritis, which was reported in 2 patients (0.9%) in the meropenem group (Table S11). In the cefepime–taniborbactam group, two serious adverse events (angioedema and gastrointestinal candidiasis) were considered by the investigator to be related to the trial drug. One patient with diabetes who received cefepime–taniborbactam died on trial day 27 at 20 days after treatment cessation and following two additional hospitalizations for hypoglycemia. The death was assessed by the investigator as unrelated to the trial drug.

DISCUSSION

In the CERTAIN-1 trial, we found that cefepime–taniborbactam was superior to meropenem therapy regarding composite (both microbiologic and

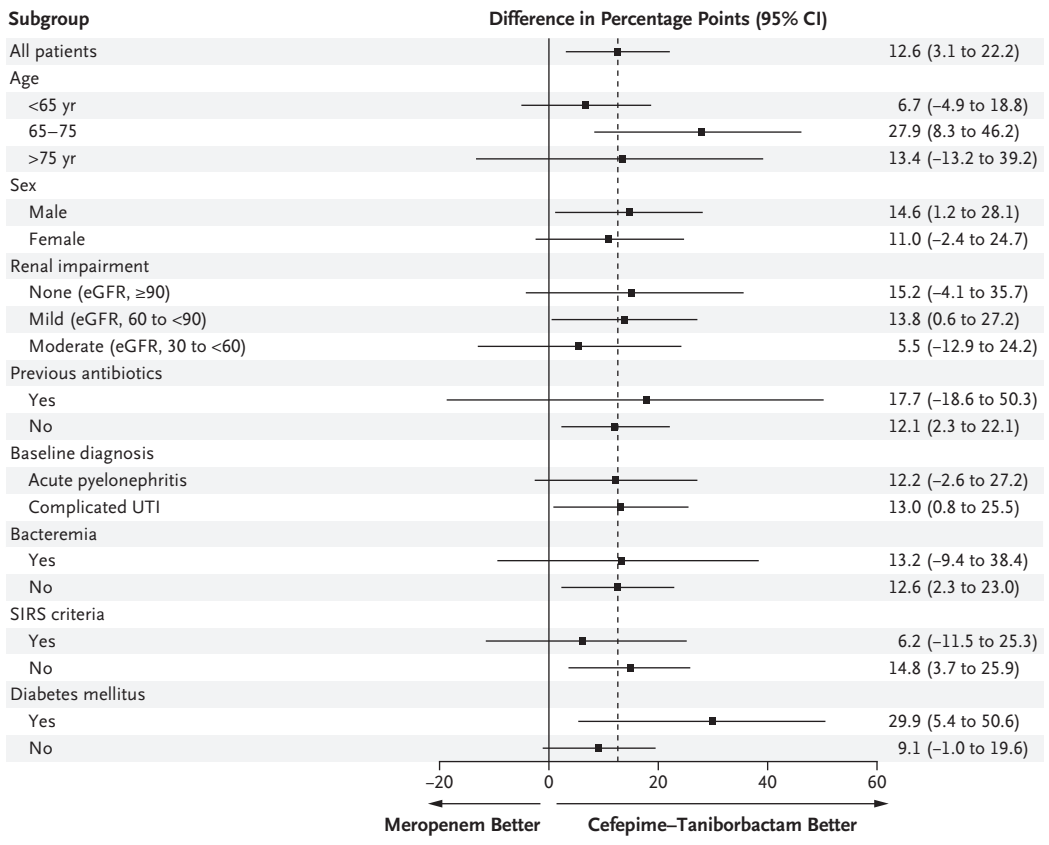

Figure 1. Composite Success Overall and According to Subgroup (Microbiologic Intention-to-Treat Population).

Shown is a forest plot of the percentage-point difference in a composite of both microbiologic and clinical success (the primary outcome) between cefepime–taniborbactam and meropenem treatment among patients with complicated urinary tract infection (UTI) in the microbiologic intention-to-treat (microITT) population. This population consisted of patients who had a positive baseline urine culture with at least 10^5 colony-forming units per milliliter of a qualifying gram-negative pathogen against which both trial drugs had antibacterial activity. The solid vertical line represents a value of zero, and the dashed vertical line represents the point estimate observed in the overall population. Subgroups with no more than 5 patients are not presented. The estimated glomerular filtration rate (eGFR) was calculated with the use of the Modification of Diet in Renal Disease formula on the basis of serum creatinine measured by the central laboratory. Units are shown in milliliters per minute per 1.73 m^2 of body-surface area. The administration of previous antibiotics was determined within 72 hours before randomization. The criteria for the systemic inflammatory response syndrome (SIRS) include 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 (>12×10^9 cells per liter), or leukopenia (<4×10^9 cells per liter).

clinical) success at test of cure among hospitalized adults with complicated urinary tract infection. The between-group differences in treatment response were sustained at late follow-up, at which time the cefepime–taniborbactam group had higher frequencies of composite and clinical success than the meropenem group. Results consistent with the primary findings were observed across subgroups of patients, including those with potentially more severe disease (bacteremia or SIRS) and across baseline pathogens and antimicrobial-resistance categories. Cefepime–taniborbactam also had composite success in 8 of 10 patients in the extended microITT population who had meropenem-resistant Enterobacterales species or *P. aeruginosa*.

The higher frequencies of success (both composite and clinical) with cefepime–taniborbactam at late follow-up on trial days 28 to 35 are noteworthy because patients in the microITT popula-

Table 3. Composite, Microbiologic, and Clinical Success at Test of Cure, According to Pathogen (Microbiologic Intention-to-Treat Population).*

Baseline Pathogen and Outcome	Cefepime–Taniborbactam	Meropenem
	no./total no. of patients (%)	
Composite success		
Enterobacterales species or category	202/281 (72)	80/137 (58)
Enterobacter cloacae complex	11/14 (79)	1/3 (33)
Escherichia coli	147/202 (73)	58/99 (59)
Klebsiella pneumoniae	24/40 (60)	12/20 (60)
Proteus mirabilis	8/10 (80)	4/10 (40)
Cefepime-resistant	47/66 (71)	16/30 (53)
ESBL-producing	54/76 (71)	22/40 (55)
Multidrug-resistant	68/100 (68)	33/55 (60)
Pseudomonas aeruginosa	5/12 (42)†	3/6 (50)
Microbiologic success		
Enterobacterales species or category	224/281 (80)	91/137 (66)
E. cloacae complex	11/14 (79)	1/3 (33)
E. coli	163/202 (81)	67/99 (68)
K. pneumoniae	27/40 (68)	14/20 (70)
P. mirabilis	9/10 (90)	4/10 (40)
Cefepime-resistant	50/66 (76)	18/30 (60)
ESBL-producing	57/76 (75)	25/40 (62)
Multidrug-resistant	71/100 (71)	38/55 (69)
P. aeruginosa	5/12 (42)†	4/6 (67)
Clinical success		
Enterobacterales species or category	241/281 (86)	111/137 (81)
E. cloacae complex	14/14 (100)	3/3 (100)
E. coli	177/202 (88)	80/99 (81)
K. pneumoniae	29/40 (72)	14/20 (70)
P. mirabilis	9/10 (90)	9/10 (90)
Cefepime-resistant	54/66 (82)	25/30 (83)
ESBL-producing	64/76 (84)	32/40 (80)
Multidrug-resistant	87/100 (87)	46/55 (84)
P. aeruginosa	10/12 (83)	5/6 (83)

* Listed are pathogens that were present at baseline in at least 10 patients in the cefepime–taniborbactam group. Patients may have had more than one pathogen at baseline. Percentages have been rounded because some denominators in the table were less than 100.

† Genotyping determined that one patient in the cefepime–taniborbactam group with *P. aeruginosa* infection had an isolate at test of cure that was unrelated to the baseline isolate. Thus, when genotyping results were considered, this patient was considered to have both composite success and microbiologic success.

tion had pathogens that were susceptible to both cefepime–taniborbactam and meropenem. The trial results show the treatment effect of cefepime–taniborbactam according to both the regulatory outcome (composite success) and clinical success as used in clinical practice. In several clinical trials, including those involving patients with complicated UTI, investigators have questioned the routine use of piperacillin–tazobactam for the treatment of ESBL-producing Enterobacterales species.[27-29] Whether a combination of β-lactam and β-lactamase inhibitors such as cefepime–taniborbactam is preferred over a carbapenem for the treatment of complicated UTI caused by ESBL-

Table 4. Summary of Adverse Events (Safety Population).*

Event	Cefepime–Taniborbactam (N=440)	Meropenem (N=217)
Any adverse event — no. of patients (%)	156 (35.5)	63 (29.0)
No. of adverse events	341	114
Mild — no./total no. (%)	226/341 (66.3)	82/114 (71.9)
Moderate — no./total no. (%)	100/341 (29.3)	25/114 (21.9)
Severe — no./total no. (%)	15/341 (4.4)	7/114 (6.1)
Adverse event related to a trial drug — no. of patients (%)†	59 (13.4)	19 (8.8)
Adverse event reported in ≥1% of patients in either treatment group — no. of patients (%)‡		
Headache	27 (6.1)	8 (3.7)
Diarrhea	18 (4.1)	5 (2.3)
Constipation	14 (3.2)	3 (1.4)
Hypertension	10 (2.3)	2 (0.9)
Nausea	9 (2.0)	2 (0.9)
Abdominal distention	7 (1.6)	3 (1.4)
Anemia	7 (1.6)	3 (1.4)
Dizziness	7 (1.6)	1 (0.5)
Hypokalemia	7 (1.6)	1 (0.5)
Phlebitis	6 (1.4)	1 (0.5)
Vomiting	6 (1.4)	1 (0.5)
Cough	5 (1.1)	2 (0.9)
Pyrexia	5 (1.1)	3 (1.4)
Increased alanine aminotransferase	4 (0.9)	5 (2.3)
Vulvovaginal candidiasis	3 (0.7)	3 (1.4)
Discontinuation of trial drug — no. (%)§	13 (3.0)	2 (0.9)
Serious adverse event — no. of patients (%)¶		
Any	9 (2.0)	4 (1.8)
Related to a trial drug†	2 (0.5)	0

* The safety population included all the patients who had received any dose of a trial drug. Adverse events that were reported during treatment are listed in the order of descending frequency in the cefepime–taniborbactam group. Events were coded according to the terms used in the *Medical Dictionary for Regulatory Activities* (version 24.0).
† The relationship of the adverse event to a trial drug was assessed by the investigator.
‡ The incidence and type of adverse events listed according to system organ class, preferred term, and severity are detailed in Table S10.
§ The incidence and type of adverse events leading to discontinuation of a trial drug are detailed in Table S11.
¶ The incidence and type of serious adverse events are detailed in Table S12.

producing Enterobacterales species will need to be assessed in future research.[30]

Cefepime–taniborbactam, which contains the highest recommended dose of cefepime (2 g every 8 hours), had a similar risk of adverse events and serious adverse events as meropenem. Although gastrointestinal events were the most common adverse events in the two groups, the incidence of any specific event was less than 5%. The number of patients who discontinued cefepime–taniborbactam because of adverse events was higher than that observed for meropenem (3.0% vs. 0.9%); events leading to discontinuation were heterogeneous. Overall, the safety profile of cefepime–taniborbactam was similar to that of meropenem[31] and to the historical profile of cefepime.[32]

Baseline characteristics and microbiologic features were well balanced between treatment

groups overall and in the primary analysis population. Therefore, the superiority of cefepime–taniborbactam was not explained by differences in these factors across treatment groups. The exclusion of oral step-down antibiotics in this trial allowed for an evaluation of the effect of trial treatments without the possible confounding effect of additional antibacterial therapy. The treatment duration was fixed at 7 days in patients without bacteremia, a period that was consistent with current recommendations for shorter therapy.[33] However, the lack of oral step-down antibiotics, the fixed duration of intravenous therapy, and the requirement for inpatient participation may not reflect clinical practice in all regions of the world. Most trial patients (81.9% of the microITT population) were located in eastern Europe. However, even though regional differences may exist in susceptibility patterns, geographic location did not alter either the pathophysiological features of complicated UTI or the expected response to antibiotics, because inclusion in the primary analysis population required that both trial drugs were active against the baseline pathogens. The representativeness of the patients in the trial, including those with multidrug-resistant pathogens, is provided in Tables S12 and S13 and supports the generalizability of the results. Finally, the use of the composite primary outcome of clinical success plus a more stringent definition of microbiologic eradication ($<10^3$ CFU per milliliter on urine culture[21,22]) on the basis of updated regulatory guidance was stricter than the outcome used in registration trials of more recently approved treatments for complicated UTI.[34-38] However, the composite outcome classifies patients with asymptomatic bacteriuria as having composite failure, which is inconsistent with clinical practice and necessitates complementary analysis of clinical success alone in the interpretation of results.

In patients with complicated UTI (including acute pyelonephritis), cefepime–taniborbactam was superior to meropenem regarding composite success at test of cure. The frequencies of both composite success and clinical success were higher in the cefepime–taniborbactam group than in the meropenem group at late follow-up. Cefepime–taniborbactam and meropenem had similar safety profiles. Thus, cefepime–taniborbactam was shown to be a potential treatment option for patients with complicated UTI and acute pyelonephritis caused by Enterobacterales species and *P. aeruginosa*, including antimicrobial-resistant strains.

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