ORIGINAL ARTICLE

Oral Tebipenem Pivoxil Hydrobromide in Complicated Urinary Tract Infection

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ABSTRACT

BACKGROUND

There is a need for oral antibiotic agents that are effective against multidrug-resistant gram-negative uropathogens. Tebipenem pivoxil hydrobromide is an orally bioavailable carbapenem with activity against uropathogenic Enterobacterales, including extended-spectrum beta-lactamase–producing and fluoroquinolone-resistant strains.

METHODS

In this phase 3, international, double-blind, double-dummy trial, we evaluated the efficacy and safety of orally administered tebipenem pivoxil hydrobromide as compared with intravenous ertapenem in patients with complicated urinary tract infection or acute pyelonephritis. Patients were randomly assigned, in a 1:1 ratio, to receive oral tebipenem pivoxil hydrobromide (at a dose of 600 mg every 8 hours) or intravenous ertapenem (at a dose of 1 g every 24 hours) for 7 to 10 days (or up to 14 days in patients with bacteremia). The primary efficacy end point was overall response (a composite of clinical cure and favorable microbiologic response) at a test-of-cure visit (on day 19, within a ±2-day window) in the microbiologic intention-to-treat population. The noninferiority margin was 12.5%.

RESULTS

A total of 1372 hospitalized adult patients were enrolled; 868 patients (63.3%) were included in the microbiologic intention-to-treat population (50.8% of whom had complicated urinary tract infections and 49.2% of whom had pyelonephritis). An overall response was seen in 264 of 449 patients (58.8%) who received tebipenem pivoxil hydrobromide, as compared with 258 of 419 patients (61.6%) who received ertapenem (weighted difference, −3.3 percentage points; 95% confidence interval [CI], −9.7 to 3.2). Clinical cure at the test-of-cure visit was observed in 93.1% of the patients in the microbiologic intention-to-treat population who received tebipenem pivoxil hydrobromide and 93.6% of patients who received ertapenem (weighted difference, −0.6 percentage point; 95% CI, −4.0 to 2.8); the majority of patients with microbiologic response failures at the test-of-cure visit were asymptomatic patients with recurrent bacteriuria. Secondary and subgroup analyses were supportive of the primary analysis. Adverse events were observed in 25.7% of patients who received tebipenem pivoxil hydrobromide and in 25.6% of patients who received ertapenem; the most common adverse events were mild diarrhea and headache.

CONCLUSIONS

Oral tebipenem pivoxil hydrobromide was noninferior to intravenous ertapenem in the treatment of complicated urinary tract infection and acute pyelonephritis and had a similar safety profile. (Funded by Spero Therapeutics and the Department of Health and Human Services; ADAPT-PO ClinicalTrials.gov number, NCT03788967.)

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A full list of the ADAPT-PO investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Complicated urinary tract infection, including acute pyelonephritis, affects nearly 3 million persons annually in the United States[1] and imparts a substantial clinical and economic burden.[2,3] Increasingly, patients with complicated urinary tract infection or acute pyelonephritis are hospitalized and receive intravenous therapy for antibiotic-resistant uropathogens for which there are limited or no available oral treatment options.[2]

Antimicrobial resistance is escalating worldwide,[3-10] particularly among the common gram-negative pathogens that cause complicated urinary tract infection and acute pyelonephritis.[11,12] Among patients hospitalized for urinary tract infection in the United States, the incidence of extended-spectrum beta-lactamase (ESBL)–producing and fluoroquinolone-resistant Enterobacterales (20% and 33%, respectively) exceeds the thresholds beyond which current treatment guidelines recommend that the empirical use of existing oral agents be avoided.[12,13] Despite these increases, antimicrobial resistance to carbapenems remains low (<2%).[12,14-16] Available oral agents are also limited by safety warnings (e.g., fluoroquinolones) or poor tissue penetration (e.g., nitrofurantoin and fosfomycin) that may predispose patients to treatment failure and selection of bacterial resistance.[17-19] There is a need for effective oral treatment options for patients with complicated urinary tract infection or acute pyelonephritis due to antimicrobial-resistant pathogens.

Tebipenem pivoxil hydrobromide is an orally bioavailable carbapenem prodrug that is rapidly converted to the active moiety, tebipenem, by enterocytes.[20] Tebipenem has broad-spectrum activity against multidrug-resistant gram-negative pathogens, including fluoroquinolone-resistant and ESBL-producing Enterobacterales.[21-27] Tebipenem pivoxil hydrobromide has shown in vivo efficacy in animal models of soft-tissue, pulmonary, and urinary tract infections.[28-30] In this international phase 3 trial (ADAPT-PO), we evaluated oral tebipenem pivoxil hydrobromide as compared with intravenous ertapenem in hospitalized patients with complicated urinary tract infection or acute pyelonephritis.

Methods

Trial Design and Oversight

We conducted this phase 3, randomized, double-blind, double-dummy, noninferiority trial at 95 sites in Central and Eastern Europe, South Africa, and the United States. The primary objective was to evaluate the efficacy and safety of oral tebipenem pivoxil hydrobromide as compared with intravenous ertapenem in hospitalized adult patients with complicated urinary tract infection or acute pyelonephritis. The trial was conducted according to the Good Clinical Practice guidelines of the International Council for Harmonisation and the principles of the Declaration of Helsinki. The protocol (available with the full text of this article at NEJM.org) and amendments were approved by the institutional review board or ethics committee at each participating site. All the patients provided written informed consent. An independent data and safety monitoring committee provided ongoing monitoring of the safety data.

Spero Therapeutics designed and conducted the trial and prepared the statistical analysis plan. The authors performed the analyses and interpreted the data. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. A medical writer, funded by the sponsor, assisted with the preparation of an earlier version of the manuscript. Confidentiality agreements were in place between the sponsor and the authors.

Eligibility Criteria

Hospitalized male and female patients were eligible if they were at least 18 years of age and had received a diagnosis of complicated urinary tract infection or acute pyelonephritis that met the protocol-specified disease-definition criteria consistent with current regulatory guidance.[31] Key exclusion criteria were confirmed or suspected infection with a carbapenem-resistant pathogen, creatinine clearance of 30 ml per minute or less, receipt of more than one dose of a short-acting antibiotic within 72 hours before randomization, septic shock, severe hepatic impairment, pregnancy, immunocompromise, and hypersensitivity to any beta-lactam antibiotic. Details of the inclusion and exclusion criteria are provided in the Supplementary Appendix, available at NEJM.org.

Randomization and Treatment

Eligible patients were randomly assigned, in a 1:1 ratio, to receive either tebipenem pivoxil hydrobromide at a dose of 600 mg (two 300-mg tablets) administered orally every 8 hours plus a dummy ertapenem infusion every 24 hours or

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ertapenem at a dose of 1 g administered intravenously over a period of 30 minutes every 24 hours plus dummy tebipenem pivoxil hydrobromide tablets administered orally every 8 hours. Both groups received treatment for 7 to 10 days (or up to 14 days in patients with bacteremia) (Fig. S1 in the Supplementary Appendix). Patients with moderate renal insufficiency (baseline creatinine clearance, >30 to ≤50 ml per minute) received 300 mg of tebipenem pivoxil hydrobromide or placebo every 8 hours; no dose adjustment was required for ertapenem. Randomization was automated by means of computer-generated interactive-response technology and was stratified according to diagnosis at baseline (complicated urinary tract infection vs. acute pyelonephritis) and age (<65 years vs. ≥65 years). The sponsor, investigators, and trial personnel responsible for treatment administration and data collection were unaware of the treatment assignments.

ANALYSIS POPULATIONS, END POINTS, AND ASSESSMENTS

The intention-to-treat population included all the patients who underwent randomization. The safety population included all the patients who received at least one dose of a trial drug. The microbiologic intention-to-treat population included all the patients with a confirmed diagnosis of complicated urinary tract infection or acute pyelonephritis and a positive urine culture at baseline (growth of one or two uropathogens at $\geq 10^5$ colony-forming units [CFUs] per milliliter, excluding pathogens not expected to respond to either trial drug, such as nonfermenting gram-negative bacilli [e.g., *Pseudomonas aeruginosa*, carbapenem-resistant Enterobacterales, methicillin-resistant *Staphylococcus aureus*, fungi, or mycobacteria]). The microbiologically evaluable population comprised patients who were included in both the microbiologic intention-to-treat population and the clinically evaluable population.

Consistent with Food and Drug Administration (FDA) guidance,[31] the primary efficacy end point was overall response (a composite of clinical cure and microbiologic response) in the microbiologic intention-to-treat population at the test-of-cure visit (on day 19, within a ±2-day window). Clinical cure was defined as complete resolution or clinically significant alleviation of baseline signs and symptoms of complicated urinary tract infection or acute pyelonephritis and no new symptoms, such that no further antimicrobial therapy was warranted. Microbiologic response was defined as a reduction in the uropathogen level from baseline to less than 10^3 CFU per milliliter in a postbaseline urine culture and a negative repeat blood culture if a culture was positive at baseline.

Key secondary end points were overall response at the test-of-cure visit in the microbiologically evaluable population; overall response at the end-of-treatment visit and the late follow-up visit (day 25, within a ±2-day window) in the microbiologic intention-to-treat and microbiologically evaluable populations; and clinical cure, time to reduction of symptoms, and per-patient and per-pathogen microbiologic responses (based on microbiologic data assessed at a central laboratory) at the end-of-treatment, test-of-cure, and late follow-up visits in the microbiologic intention-to-treat and microbiologically evaluable populations. Postbaseline enteric colonization with carbapenem-resistant Enterobacterales at the test-of-cure visit was an exploratory end point. Safety was assessed on the basis of adverse events, changes in clinical laboratory results (i.e., hematologic screening, clinical chemical testing, and urinalysis), electrocardiograms (ECGs), and vital signs.

STATISTICAL ANALYSIS

We calculated that enrollment of approximately 1200 patients up to a maximum of 1450 (contingent on the number of evaluable patients to be included in the primary analysis population) would provide the trial with at least 90% power for the assessment of the primary end point within a noninferiority margin of 10% at a one-sided significance level of 0.025. As specified in the protocol, a data review committee performed a blinded reassessment of the sample size after response data were available from 70% of the patients at the test-of-cure visit to confirm the initial sample-size estimate as adequate or to recommend an increase in sample size to ensure adequate power for measurement of the primary end point. The data review committee recommended enrollment up to the protocol-allowed maximum of 1450 patients. However, the sponsor, in consultation with the FDA, revised the noninferiority margin to 12.5% before the database lock, owing to the coronavirus disease 2019 pandemic and the resulting operational challenges

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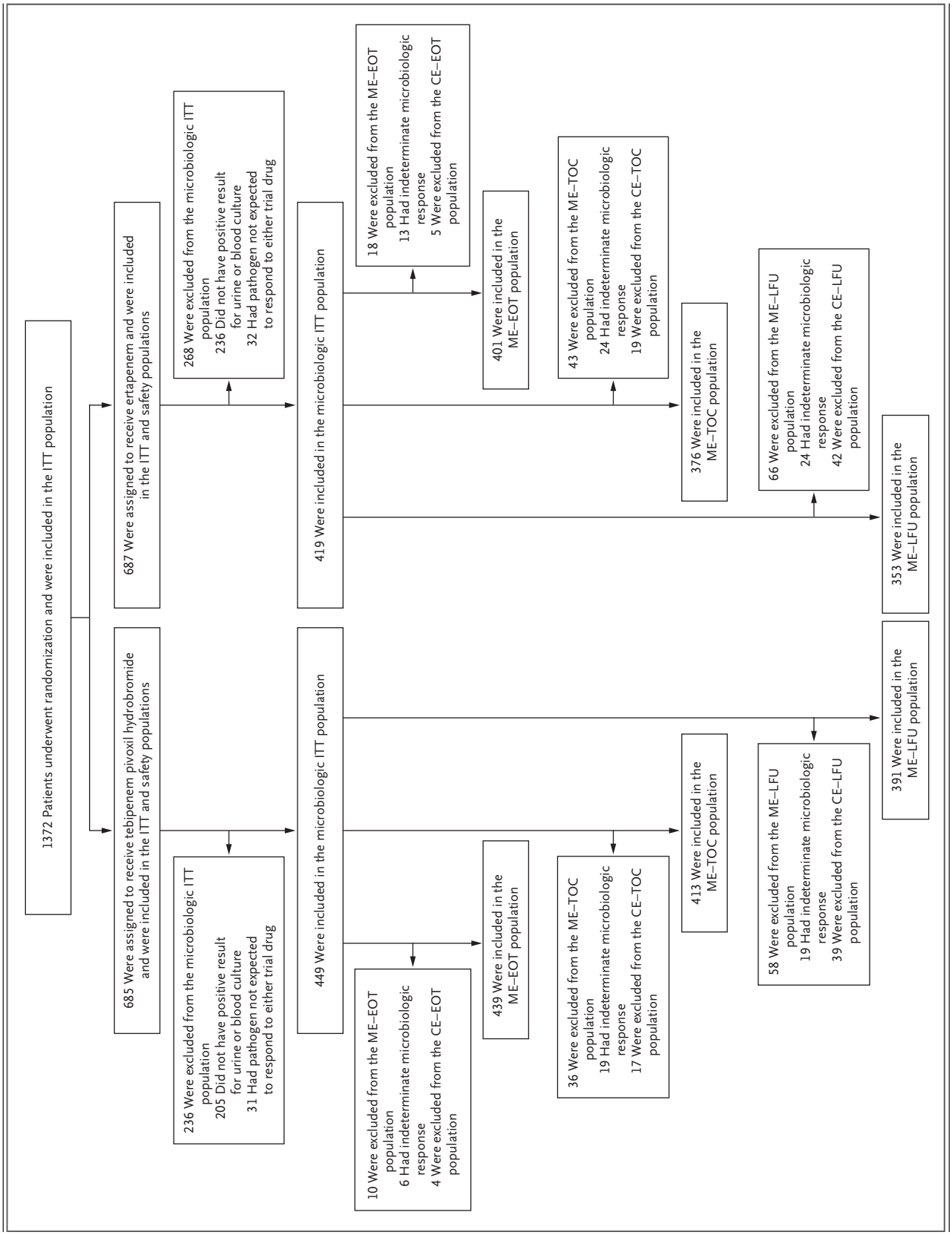

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Figure 1 (facing page). Randomization and Populations Used for Analysis.

The intention-to-treat (ITT) population included all patients who underwent randomization. The safety population included all patients who underwent randomization and received at least one dose of trial drug. The microbiologic ITT population included all patients who received a confirmed diagnosis of complicated urinary tract infection or acute pyelonephritis and a positive urine culture at baseline (growth of one or two uropathogens at $\geq 10^5$ colony-forming units per milliliter, excluding pathogens not expected to respond to either trial drug, such as nonfermenting gram-negative bacilli [e.g., *Pseudomonas aeruginosa*, carbapenem-resistant Enterobacterales, methicillin-resistant *Staphylococcus aureus*, fungi, or mycobacteria]). The microbiologically evaluable (ME) population was separately defined for each visit and comprised patients who were included in both the microbiologic ITT population and the clinically evaluable (CE) population (Fig. S2). Mutually exclusive reasons other than "not included in microbiologic ITT" are shown for the ME populations. A patient may have been excluded from an analysis population for more than one reason. EOT denotes end of treatment, LFU late follow-up, and TOC test of cure.

to recruitment and potential effect on trial data integrity, data availability, and patient and staff safety.

The primary analysis was the comparison of the overall response at the test-of-cure visit in the microbiologic intention-to-treat population. The 95% confidence interval for the weighted difference between treatment groups was calculated with the use of the Cochran–Mantel–Haenszel weighted Miettinen and Nurminen method (stratified according to age at the time of informed consent and baseline diagnosis). Although not powered to assess noninferiority, analyses of secondary end points for clinical response and microbiologic response were made with the use of the same method that was used for the primary end point. We performed secondary and exploratory analyses to assess consistency with the conclusions regarding the primary end point. Missing data were classified as indeterminate responses and counted as treatment failures in the analyses in the microbiologic intention-to-treat population.

RESULTS

TRIAL POPULATION

From June 2019 through May 2020, a total of 1372 patients underwent randomization (the intention-to-treat population) and received at least one dose of trial drug (safety population), and 868 patients (63.3%) were included in the microbiologic intention-to-treat population (Fig. 1 and Fig. S2). Adherence to the assigned regimen (defined as receipt of 100% of the planned trial doses) was 99.6% in the tebipenem pivoxil hydrobromide group and 99.1% in the ertapenem group. At baseline, the demographic and clinical characteristics of the patients were well-balanced between the treatment groups (Table 1 and Table S1). The mean age of the patients was 58.1 years; 46.1% of the patients were 65 years of age or older. In the microbiologic intention-to-treat population, 50.8% of the patients had complicated urinary tract infection and 49.2% had acute pyelonephritis at the time of enrollment. A total of 11.5% of the patients had bacteremia at baseline and 19.7% met the criteria for modified systemic inflammatory response syndrome (SIRS); both conditions indicate more severe disease.

More than 90% of the baseline pathogens were Enterobacterales, primarily *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, and *Proteus mirabilis* (Table S2). In the microbiologic intention-to-treat population, 24.3% of the patients were infected with pathogens that met phenotypic criteria for ESBL-producing uropathogens, 39% with fluoroquinolone-nonsusceptible uropathogens, and 43% with uropathogens resistant to trimethoprim–sulfamethoxazole (Table 1 and Tables S1 and S4). Genotype testing confirmed the presence of one or more beta-lactamases in all the ESBL-positive phenotype isolates. The minimum inhibitory concentrations (MICs) of tebipenem and ertapenem for uropathogens at baseline are provided in Table S3. The mean (±SD) duration of therapy was 8.7±1.8 days for tebipenem pivoxil hydrobromide and 8.5±1.9 days for ertapenem. All the patients (100%) received at least 80% of the intended doses of the oral trial drug, and 99.6% of the patients received at least 80% of the intended doses of intravenous trial drug.

EFFICACY

Oral tebipenem pivoxil hydrobromide was noninferior to intravenous ertapenem with respect to the primary end point of overall response at the test-of-cure visit (58.8% and 61.6% of the patients, respectively; weighted difference, –3.3 percentage points; 95% confidence interval [CI],

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

Characteristic	Tebipenem Pivoxil Hydrobromide (N=449)	Ertapenem (N=419)	Overall (N=868)
Age — yr	57.6±18.7	58.7±17.9	58.1±18.3
Age category — no. (%)			
≥18 to <65 yr	246 (54.8)	222 (53.0)	468 (53.9)
≥65 to <75 yr	122 (27.2)	132 (31.5)	254 (29.3)
≥75 yr	81 (18.0)	65 (15.5)	146 (16.8)
Female sex — no. (%)	252 (56.1)	253 (60.4)	505 (58.2)
Race or ethnic group — no. (%)†			
White	446 (99.3)	417 (99.5)	863 (99.4)
Black	3 (0.7)	1 (0.2)	4 (0.5)
Asian	0	1 (0.2)	1 (0.1)
Hispanic	7 (1.6)	2 (0.5)	9 (1.0)
Body-mass index‡	27.3±5.6	27.4±5.1	27.3±5.3
Geographic region — no. (%)			
Central and Eastern Europe	443 (98.7)	413 (98.6)	856 (98.6)
South Africa	3 (0.7)	2 (0.5)	5 (0.6)
United States	3 (0.7)	4 (1.0)	7 (0.8)
Infection type — no. (%)§			
Complicated urinary tract infection	223 (49.7)	218 (52.0)	441 (50.8)
Acute pyelonephritis	226 (50.3)	201 (48.0)	427 (49.2)
Estimated creatinine clearance — ml/min	89.1±36.8	85.8±30.9	87.5±34.1
Bacteremia — no. (%)	47 (10.5)	53 (12.6)	100 (11.5)
Modified SIRS criteria — no. (%)¶	98 (21.8)	73 (17.4)	171 (19.7)
Systemic antibiotic use within 30 days before randomization — no. (%)	19 (4.2)	22 (5.3)	41 (4.7)
Receipt of a single dose of short-acting systemic antibiotics within 72 hr before randomization	6 (1.3)	15 (3.6)	21 (2.4)
Infection with resistant Enterobacterales pathogen — no. of patients with resistant pathogen/total no. with Enterobacterales pathogen (%)¶‖			
ESBL-positive	105/396 (26.5)	85/386 (22.0)	190/782 (24.3)
Fluoroquinolone-nonsusceptible	159/396 (40.2)	146/386 (37.8)	305/782 (39.0)
TMP-SMX–resistant	168/396 (42.4)	168/386 (43.5)	336/782 (43.0)

* The microbiologic intention-to-treat population included all patients with a confirmed diagnosis of complicated urinary tract infection or acute pyelonephritis and a positive urine culture at baseline (growth of one or two uropathogens at $\geq 10^5$ colony-forming units per milliliter, excluding pathogens not expected to respond to either trial drug, such as non-fermenting gram-negative bacilli [e.g., *Pseudomonas aeruginosa*, carbapenem-resistant Enterobacterales, methicillin-resistant *Staphylococcus aureus*, fungi, or mycobacteria]). Plus–minus values are means ±SD. ESBL denotes extended-spectrum beta-lactamase, and TMP-SMX trimethoprim–sulfamethoxazole.

† Race and ethnic group were reported by the patient.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Patients who met the protocol criteria for complicated urinary tract infection (inclusion criterion 4a as defined by Food and Drug Administration guidance) and also had flank pain or costovertebral tenderness were categorized as having complicated urinary tract infection rather than acute pyelonephritis. Patients with acute pyelonephritis included patients with no identifiable risk factors for complicated disease and those with characteristics that may be considered as meeting the definition of complicated urinary tract infection in routine clinical practice, including but not limited to male sex and metabolic abnormalities (e.g., diabetes or glucose intolerance).

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Table 1. (Continued.)

¶ Modified criteria for the systemic inflammatory response syndrome (SIRS) include at least two of the following symptoms at baseline: a body temperature lower than 36°C or higher than 38°C, a heart rate of more than 90 beats per minute, a respiratory rate of more than 20 breaths per minute, and a white-cell count less than 4×10^9 cells per liter or more than 12×10^9 cells per liter.

‖ Infection with resistant Enterobacterales pathogen includes pathogens isolated from urine or blood source or both. Resistant phenotypes were defined as ESBL-positive, a minimum inhibitory concentration (MIC) of ceftazidime of 2 μg per milliliter or more (or a MIC of ceftriaxone of ≥2 μg per milliliter if data on ceftazidime susceptibility were not available); fluoroquinolone-nonsusceptible, a MIC of levofloxacin of 1 μg per milliliter or more; and TMP-SMX–resistant, a MIC of TMP-SMX of 4 μg per milliliter (TMP) and 76 μg per milliliter (SMX). Patients could be included in more than one resistant-phenotype category.

Table 2. Primary and Secondary Efficacy End Points (Microbiologic Intention-to-Treat Population).

End Point	Tebipenem Pivoxil Hydrobromide (N=449)	Ertapenem (N=419)	Treatment Difference (95% CI)*
	number (percent)		*percentage points*
Primary end point			
Overall response at test-of-cure visit†	264 (58.8)	258 (61.6)	–3.3 (–9.7 to 3.2)
Secondary end points			
Overall response at end-of-treatment visit†	437 (97.3)	396 (94.5)	2.8 (0.1 to 5.7)
Clinical response‡			
Clinical improvement at day 5	336 (74.8)	321 (76.6)	–1.9 (–7.6 to 3.8)
Clinical cure at end-of-treatment visit	446 (99.3)	410 (97.9)	1.4 (–0.1 to 3.4)
Clinical cure at test-of-cure visit	418 (93.1)	392 (93.6)	–0.6 (–4.0 to 2.8)
Sustained clinical cure at late follow-up	398 (88.6)	377 (90.0)	–1.5 (–5.7 to 2.6)
Microbiologic response§			
Response at day 5	427 (95.1)	397 (94.7)	0.3 (–2.7 to 3.4)
Response at end-of-treatment visit	439 (97.8)	403 (96.2)	1.5 (–0.8 to 4.1)
Response at test-of-cure visit	267 (59.5)	266 (63.5)	–4.5 (–10.8 to 1.9)
Sustained response at late follow-up	257 (57.2)	244 (58.2)	–1.5 (–7.9 to 5.0)

* Confidence intervals were calculated with the use of the method of Miettinen and Nurminen and the Cochran–Mantel–Haenszel test, with differences between the two trial groups summarized as weighted differences (stratified according to age at informed consent and diagnosis at baseline). Confidence intervals for secondary end points were not adjusted for multiplicity and were used to demonstrate consistency of the treatment effect with the primary end point; they cannot be used to infer effects.

† Overall response was defined as a composite of clinical cure and microbiologic response (see below) at the test-of-cure visit (on day 19, within a ±2-day window).

‡ Clinical improvement at day 5 was defined as improvement by at least one grade in at least one baseline sign or symptom of complicated urinary tract infection or acute pyelonephritis and no worsening of any baseline signs or symptoms and no new signs or symptoms of either infection that resulted in the initiation of a nontrial antibacterial therapy. Clinical cure was defined as a complete resolution or reduction of signs and symptoms of complicated urinary tract infection or acute pyelonephritis that were present at baseline and no new symptoms such that no further antimicrobial therapy was warranted. Late follow-up occurred at 25 days, within a ±2-day window.

§ Microbiologic response was defined as a reduction in the baseline uropathogen to less than 10^3 colony-forming units per milliliter and a negative repeated blood culture if the blood culture was positive for a uropathogen at baseline.

–9.7 to 3.2) (Table 2). Overall response at the end-of-treatment visit was 97.3% in the tebipenem pivoxil hydrobromide group and 94.5% in the ertapenem group. Across all the subgroups, prespecified analysis of overall response at the test-of-cure visit according to baseline characteristics was consistent with the results of the primary analysis (Fig. 2). The 95% confidence intervals

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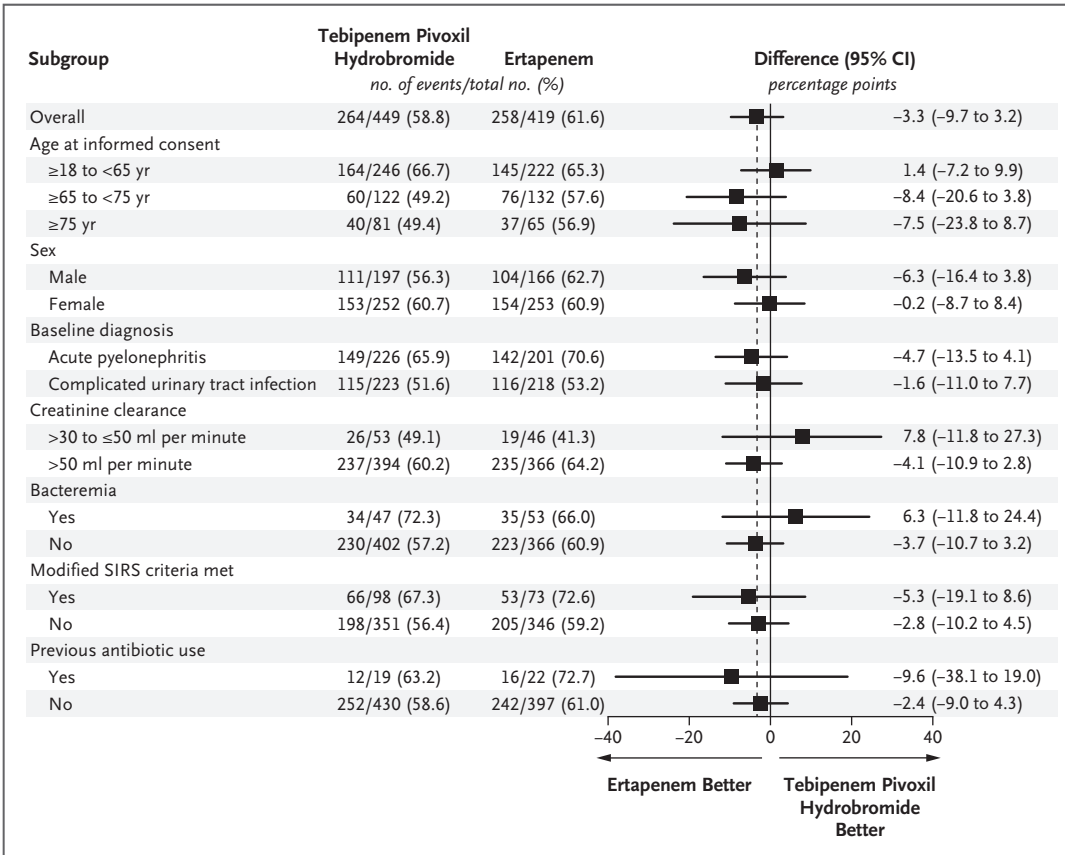

Figure 2. Overall Response at Test-of-Cure Visit According to Characteristics of the Patients at Baseline.

The microbiologic intention-to-treat population included all patients with a confirmed diagnosis of complicated urinary tract infection or acute pyelonephritis and a positive urine culture at baseline (growth of one or two uropathogens at $\geq 10^5$ colony-forming units per milliliter, excluding pathogens not expected to respond to either trial drug, such as nonfermenting gram-negative bacilli [e.g., *Pseudomonas aeruginosa*, carbapenem-resistant Enterobacterales, methicillin-resistant *Staphylococcus aureus*, fungi, or mycobacteria]). Modified criteria for the systemic inflammatory response syndrome (SIRS) include at least two of the following symptoms at baseline: body temperature lower than 36°C or higher than 38°C, heart rate more than 90 beats per minute, respiratory rate more than 20 breaths per minute, and white-cell count less than 4×10^9 cells per liter or more than 12×10^9 cells per liter. The dashed line represents the primary analysis result in the overall population.

for the treatment difference crossed zero in all cases and overlapped with the overall treatment effect, including differences in disease type, creatinine-clearance category, and disease severity. Among patients with bacteremia at baseline, overall responses were 93.6% with tebipenem pivoxil hydrobromide and 96.2% with ertapenem at the end-of-treatment visit and 72.3% and 66.0%, respectively, at the test-of-cure visit (Fig. 2).

Across all visits, clinical cure was observed in more than 97% of the patients at the end-of-treatment visit, more than 93% at the test-of-cure visit, and more than 88% at late follow-up assessments in each treatment group (Table 2). Clinical cure was observed at the test-of-cure visit in 93.1% of the patients in the tebipenem pivoxil hydrobromide group and in 93.6% of the patients in the ertapenem group (weighted difference, –0.6 percentage point; 95% CI, –4.0 to 2.8). Clinical failures that resulted in the use of nontrial antimicrobial therapy at each visit are described in Table S5, and clinical responses according to disease type (complicated urinary tract infection or acute pyelonephritis) are described in Table S6. Kaplan–Meier analysis of the time to resolution or reduction of signs and

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symptoms from baseline showed no clinically relevant differences between the treatment groups (Fig. S3).

Favorable per-patient microbiologic responses at day 5 were seen in 95.1% of the patients in the tebipenem pivoxil hydrobromide group and in 94.7% of those in the ertapenem group, and at the end-of-treatment visit in 97.8% and 96.2%, respectively; responses were lower in each of the treatment groups at the test-of-cure visit (59.5% in the tebipenem pivoxil hydrobromide group and 63.5% in the ertapenem group) and were generally stable and similar in the two treatment groups at late follow-up assessments (57.2% and 58.2%, respectively) (Table 2). Given the percentages of patients with clinical cure at each visit, overall response at the test-of-cure visit was driven primarily by microbiologic outcomes.

Per-pathogen responses at the end-of-treatment visit were 96.3% or more in both treatment groups across all pathogens and were similar among the Enterobacterales pathogens (≥97%) and resistant subsets (≥90%, including phenotypes that are ESBL-positive, fluoroquinolone-nonsusceptible, and resistant to trimethoprim–sulfamethoxazole) in either treatment group. At the test-of-cure visit, per-pathogen clinical responses remained stable, whereas per-pathogen microbiologic responses declined proportionally from the end-of-treatment visit in the two groups (62.1% with tebipenem pivoxil hydrobromide and 65.1% with ertapenem). Details of the clinical and microbiologic responses are provided in Table S7.

Similar microbiologic responses in both treatment groups were observed among the Enterobacterales pathogens at the test-of-cure visit, and test-of-cure responses for *E. coli* — the most common uropathogen isolated — also were similar in both treatment groups (62.7% with tebipenem pivoxil hydrobromide and 65.2% with ertapenem). Per-pathogen responses were numerically lower in the tebipenem pivoxil hydrobromide group than in the ertapenem group in each resistant-phenotype category; however, owing to co-resistance, there was substantial overlap between these populations. Furthermore, there was no correlation between the observed microbiologic response and the MIC of the trial drug in either group (Table S8). Microbiologic responses with respect to gram-positive pathogens, including *Enterococcus faecalis*, were higher overall in the tebipenem pivoxil hydrobromide group than in the ertapenem group (75.0% vs. 58.5%). Enterobacterales pathogens with postbaseline increases in MIC by a factor of four or more were uncommon (2.2% in both groups) (Fig. S4). Since clinical cure was observed in most patients at the test-of-cure visit, most microbiologic persistence represented asymptomatic bacteriuria in patients who received no further antimicrobial treatment.

SAFETY

The overall incidence of adverse events was approximately 26% in both treatment groups. Diarrhea, headache, and nausea were the only adverse events reported in more than 1% of the patients in either treatment group. Most adverse events were mild or moderate in severity and non–treatment-limiting (Tables 3 and S10). Adverse events leading to premature discontinuation of the trial drug occurred in 1 patient (0.1%) in the tebipenem pivoxil hydrobromide group and in 8 patients (1.2%) in the ertapenem group. Nine patients (1.3%) in the tebipenem pivoxil hydrobromide group and 12 patients (1.7%) in the ertapenem group had at least one serious adverse event (Table S11). No serious adverse events in the tebipenem pivoxil hydrobromide group were assessed by the investigator as being related to the trial drug; two adverse events in the ertapenem group, both of which were *Clostridioides difficile*–associated events, were assessed as being related to the trial drug. Three *C. difficile*–associated adverse events occurred in the ertapenem group, and none occurred in the tebipenem pivoxil hydrobromide group.

Adverse events associated with abnormal liver-function tests were uncommon (≤1% in each treatment group), and no patient met Hy's law criteria for drug-induced liver injury. No unexpected changes in clinical laboratory or ECG findings were observed. The percentage of patients with postbaseline enteric colonization (negative results at baseline but positive results at the test-of-cure visit) with carbapenem-resistant Enterobacterales pathogens was 1.9% with tebipenem pivoxil hydrobromide as compared with 3.1% with ertapenem in the microbiologic intention-to-treat population, and no cases were associated with postbaseline invasive disease.

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Table 3. Incidence of Adverse Events Occurring during Treatment (Safety Population).*

Event	Tebipenem Pivoxil Hydrobromide (N=685)	Ertapenem (N=687)
	number (percent)	
Any adverse event	176 (25.7)	176 (25.6)
Any severe adverse event	10 (1.5)	9 (1.3)
Drug-related adverse event†	64 (9.3)	42 (6.1)
Serious adverse event	9 (1.3)	12 (1.7)
Adverse event leading to drug discontinuation	1 (0.1)	8 (1.2)
Adverse events occurring in >1% of patients, according to preferred term		
Alanine aminotransferase level increase	7 (1.0)	7 (1.0)
Aspartate aminotransferase level increase	7 (1.0)	5 (0.7)
Diarrhea‡	39 (5.7)	30 (4.4)
Edema peripheral	3 (0.4)	7 (1.0)
Headache	26 (3.8)	26 (3.8)
Hypertension	3 (0.4)	7 (1.0)
Nausea	10 (1.5)	6 (0.9)
Vulvovaginal candidiasis	5 (0.7)	7 (1.0)

* The safety population included all the patients who received at least one dose of a trial drug. Adverse events that occurred during treatment include adverse events with an onset date and time on or after the date and time of the first dose of trial medication up to the last follow-up visit. Patients with multiple adverse events were counted once for each adverse event category and preferred term.
† Relatedness to the trial drug was assessed by the investigator.
‡ Three *Clostridioides difficile*–associated adverse events of diarrhea were reported during the trial; all occurred in the ertapenem group.

DISCUSSION

In this trial, tebipenem pivoxil hydrobromide was noninferior to intravenous ertapenem for the treatment of patients with complicated urinary tract infection or acute pyelonephritis. Results were consistent across trial populations and subpopulations, infection types, and causative uropathogens. Clinical cure was observed in 90% or more of the patients in both treatment groups at the end-of-treatment and test-of-cure visits and was sustained in follow-up. Favorable microbiologic response of the causative uropathogen was seen in at least 96% of the patients in both treatment groups by the end of treatment, and responses decreased proportionally in both treatment groups at later visits. This posttreatment discordance between clinical and microbiologic responses may be the result of protected foci of bacteria in patients with complicated urinary tract infection who have underlying functional or anatomical abnormalities, including urinary tract instrumentation, that may lead to asymptomatic regrowth of pathogens after the discontinuation of antimicrobial therapy. There was no relationship between response and the MIC for the baseline pathogen, including pathogens with resistant phenotypes, and no increase in the MIC of the trial drug for 97.8% of persistent Enterobacterales pathogens. The sustained clinical cure observed at test-of-cure and late-follow-up visits suggests that the majority of post-therapy microbiologic persistence represented asymptomatic bacteriuria,[32] which generally does not necessitate antibacterial therapy. This observation is consistent with findings from published trials involving complicated urinary tract infection or acute pyelonephritis, and the microbiologic responses in this trial were within the ranges previously reported.[33-37]

The characteristics of the patients at baseline were noteworthy for the high proportion of patients with complicated disease (as specified in the inclusion criteria for complicated urinary tract infection) and the high proportion of those with infection with resistant pathogens. Oral tebipenem pivoxil hydrobromide was as effective as intravenous ertapenem across all the subgroups, including in patients with more severe disease (i.e., bacteremia and SIRS). The incorporation of a full course of oral tebipenem pivoxil hydrobromide as compared with intravenous ertapenem in the trial design allowed for several distinct analyses. Analysis of clinical and microbiologic responses among the patients with baseline bacteremia (11.5%) revealed that oral tebipenem pivoxil hydrobromide — without initial intravenous therapy — was associated with overall responses that were similar to those observed with ertapenem. In addition, a full course of oral tebipenem pivoxil hydrobromide did not lead to a greater risk of post-treatment enteric colonization with carbapenem-resistant Enterobacterales pathogens than ertapenem. No increased risk of *C. difficile* infection associated with treatment with an oral carbapenem was observed in this trial. A trial assessing the effect of tebipenem pivoxil

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hydrobromide on the gut microbiota is underway (ClinicalTrials.gov number, NCT04376554). The safety profile of tebipenem pivoxil hydrobromide was consistent with a carbapenem antibiotic; the incidence of adverse events and laboratory abnormalities was similar in both treatment groups and was representative of the carbapenem class, with few cases of premature treatment discontinuation due to adverse events.

Potential limitations of the trial include the mandated inpatient 7-to-10-day course of antibiotic therapy (up to 14 days for patients with bacteremia), since this may not directly reflect the standard of care for complicated urinary tract infection or acute pyelonephritis in the United States. Patients were excluded for immunocompromise, severe renal impairment, and confirmed or suspected carbapenem-resistant pathogens. Trial sites were located in the United States, South Africa, and Europe (the latter to enrich for resistant pathogens); accordingly, most patients were enrolled from Central and Eastern Europe, and most were White. Although the pathophysiology of complicated urinary tract infection or acute pyelonephritis and predominant pathogens is generally consistent around the world, the specific strains and resistance mechanisms that were observed in this trial may differ from those observed in other regions. In addition, patients underwent randomization on the basis of clinical criteria and evidence of pyuria before confirmation of a baseline pathogen in order to limit previous antibiotic therapy as a confounding variable for efficacy. The representativeness of the patients in this trial is summarized in Table S12.

Tebipenem pivoxil hydrobromide addresses the need for an oral antibiotic with activity against resistant gram-negative pathogens, including ESBL-producing and fluoroquinolone-resistant strains.[13,38] Recent trials of the transition from intravenous to oral antibiotics for bone and joint infections or infective endocarditis showed no difference in outcomes.[39,40] The ADAPT-PO trial provides a comparison of an oral carbapenem with an intravenous therapy in the treatment of a gram-negative bacterial infection.

Oral tebipenem pivoxil hydrobromide was noninferior to intravenous ertapenem in patients with complicated urinary tract infection or acute pyelonephritis and had a similar safety profile. In the absence of other effective oral agents, tebipenem pivoxil hydrobromide may provide an option for the treatment of complicated urinary tract infection and acute pyelonephritis due to antibiotic-resistant uropathogens.

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APPENDIX

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