



Oral tebipenem pivoxil hydrobromide vs intravenous imipenem-cilastatin in patients with complicated urinary tract infections or acute pyelonephritis: efficacy and safety results from the phase 3 PIVOT-PO study

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On behalf of the PIVOT-PO study group

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Disclosures

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- The authors declare the following real or perceived conflicts of interest during the last 3 years in relation to this presentation: **NB, IAC, MG, AH** and **DKH** are employed by, and hold financial equities in, Spero Therapeutics, Inc.; **KAH** is employed by Spero Therapeutics, Inc; **SA, AM, TO, AP, YS-P, AJS, MS** and **DT** are employed by, and hold financial equities in, GSK; **LBG** is a consultant for Spero Therapeutics, Inc; **DS** and **KW** received consultancy compensation from Spero Therapeutics, Inc as principal investigators for this study
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Introduction

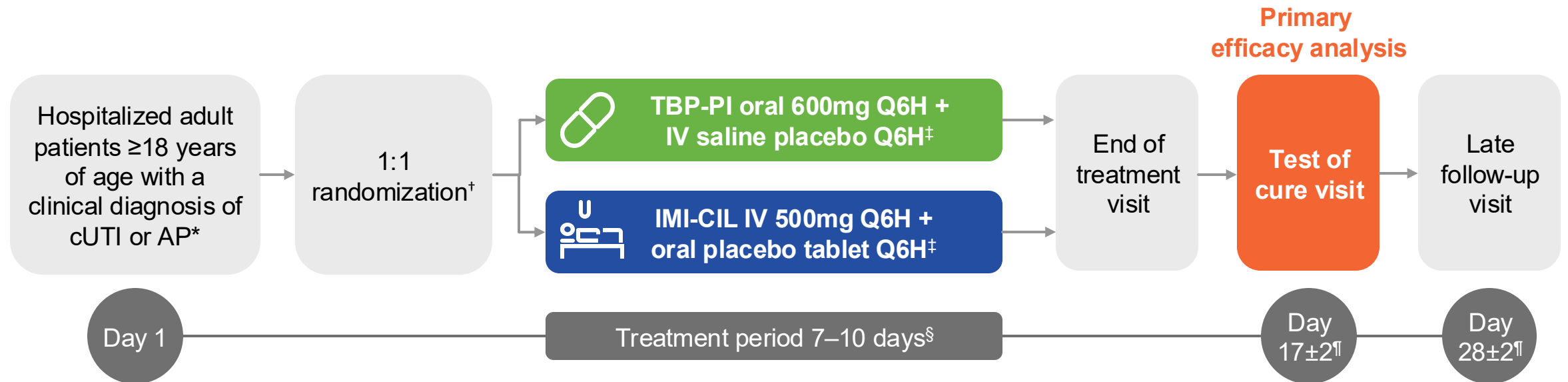
- cUTI is a common infection with ~3 million cases estimated annually in the US¹
- Effective oral treatment options for cUTI are becoming increasingly limited due to rising antimicrobial resistance²
- IV antibiotics often require longer hospital stays, associated with complications and higher costs, compared with oral therapy³
- There is an unmet need for oral treatment options for antimicrobial-resistant cUTIs⁴
- Tebipenem pivoxil (TBP-PI) is an oral carbapenem tablet with activity against antimicrobial-resistant Enterobacterales, and some gram-positive pathogens^{5,6}
- TBP-PI is under investigation for the treatment of cUTI including AP;⁷ results from the Phase 3 PIVOT-PO study are presented here

AP, acute pyelonephritis; cUTI, complicated urinary tract infection; IV, intravenous; TBP-PI, tebipenem pivoxil.

1. Carreno JJ, et al. Open Forum Infect Dis. 2019;6(11):ofz446. 2. Gupta K. Acute complicated urinary tract infection (including pyelonephritis) in adults and adolescents. (2025). Available online at: <https://www.uptodate.com/contents/acute-complicated-urinary-tract-infection-including-pyelonephritis-in-adults> (accessed October 1, 2025). 3. Cyriac JM and James E. J Pharmacol Pharmacother. 2014;5(2):83–7. 4. Critchley IA, et al. J Glob Antimicrob Res. 2020;23:439–44. 5. Sodhi V, et al. Pharmacotherapy. 2021;41:748–61. 6. Cotroneo N, et al. Antimicrob Agents Chemother. 2020;64:e02240-19. 7. ClinicalTrials.gov. NCT06059846.

PIVOT-PO study design

PIVOT-PO (NCT06059846) was a global, randomized, double-blind, double-dummy, non-inferiority (10% non-inferiority margin), phase 3 trial that evaluated the efficacy, safety and PK of oral TBP-PI compared with IV IMI-CIL in hospitalized adult patients with cUTI including AP



*Those with defined signs/symptoms of cUTI/AP were included. †Randomization stratified by age at informed consent (≥18 to <65 years vs ≥65 years), baseline diagnosis (cUTI vs AP), and presence or absence of urinary tract instrumentation at baseline. ‡Patients with moderate renal insufficiency (baseline creatinine clearance, >30 to ≤50mL/min) received 300mg of oral TBP-PI or one placebo tablet Q6H. IMI-CIL dose adjustment for patients with impaired renal function (baseline creatinine clearance, <90mL/min) was consistent with product labeling. §7–10 days therapy. ¶From 1st dose.

AP, acute pyelonephritis; cUTI, complicated urinary tract infection; IMI-CIL, imipenem-cilastatin; IV, intravenous; PK, pharmacokinetics; Q6H, every 6 hours; TBP-PI, tebipenem pivoxil.

Primary endpoint: overall response at test of cure in the micro-ITT population



Primary analysis
population: micro-ITT

All randomized participants with a baseline urine culture demonstrating $\geq 10^5$ CFU/mL of an Enterobacterales uropathogen that was IMI-susceptible*

Overall
response
at test of
cure visit

=

Clinical cure

- Complete resolution or clinically significant alleviation of baseline signs and symptoms of cUTI or AP
- No new symptoms, such that no further antimicrobial therapy was warranted
- Participant was alive



Microbiologic eradication

- Reduction of baseline uropathogens to $< 10^3$ CFU/mL
- Negative repeat blood culture if a culture was positive at baseline
- Participant was alive

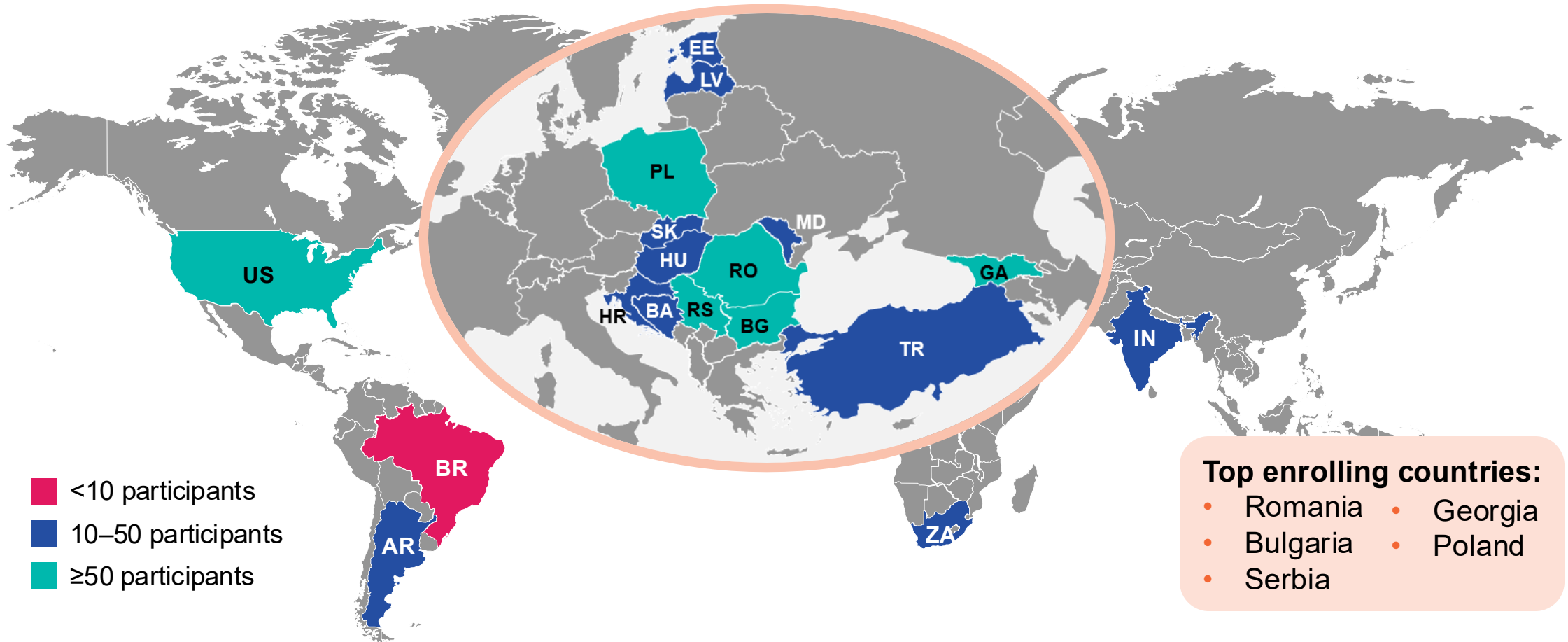
A pre-specified unblinded interim analysis for efficacy and futility was conducted by an Independent Data Monitoring Committee

At interim analysis, the stopping criteria for efficacy was met (where efficacy = non-inferiority), the study was stopped, and non-inferiority declared*

*No additional pathogens were permitted other than an additional Enterobacterales species, *Enterococcus faecalis*, *Staphylococcus aureus*, or *Staphylococcus saprophyticus* identified in the baseline urine culture at $\geq 10^5$ CFU/mL (or the same pathogen is present concurrently in blood cultures and in urine). In addition, where *Enterococcus faecalis*, *Staphylococcus aureus*, or *Staphylococcus saprophyticus* isolates were identified, imipenem must have had antibacterial activity. No more than two microorganisms identified in the baseline urine culture, regardless of colony count, were permitted. AP, acute pyelonephritis; CFU, colony-forming unit; cUTI, complicated urinary tract infection; IMI, imipenem; micro-ITT, microbiological intent-to-treat.

Participants were enrolled from 96 sites in 18 countries

(N=1690, ITT population)



Baseline characteristics were evenly distributed between groups

Micro-ITT population

	TBP-PI (N=446)	IMI-CIL (N=483)	Total (N=929)
Age, years, mean (SD)	64.7 (14.6)	64.2 (14.8)	64.4 (14.7)
Female, n (%)	245 (54.9)	292 (60.5)	537 (57.8)
White race, n (%)	431 (96.6)	473 (97.9)	904 (97.3)
Hispanic or Latino ethnicity, n (%)	23 (5.2)	31 (6.4)	54 (5.8)
BMI, kg/m ² , mean (SD)	29.5 (5.2)	28.9 (5.2)	29.2 (5.2)
Bacteremia, n (%)	32 (7.2)	34 (7.0)	66 (7.1)
Infection type, n (%)			
AP only	154 (34.5)	165 (34.2)	319 (34.3)
cUTI (with or without AP)	292 (65.5)	318 (65.8)	610 (65.7)
cUTI with AP	105 (23.5)	102 (21.1)	207 (22.3)
cUTI without AP	187 (41.9)	216 (44.7)	403 (43.4)

***E. coli* was the most common baseline Enterobacterales uropathogen; drug-resistant phenotypes were well represented and balanced between groups**

Micro-ITT population

	TBP-PI (N=446)	IMI-CIL (N=483)	Total (N=929)
Most common baseline Enterobacterales, n (%)*			
<i>E. coli</i>	333 (74.7)	348 (72.0)	681 (73.3)
<i>K. pneumoniae</i>	81 (18.2)	106 (21.9)	187 (20.1)
<i>E. cloacae</i> complex	11 (2.5)	11 (2.3)	22 (2.4)
Antimicrobial-resistant Enterobacterales, n (%)			
Enterobacterales pathogens [†]	N=459	N=494	N=953
ESBL+	161 (35.1)	192 (38.9)	353 (37.0)
FQ-NS	201 (43.8)	214 (43.3)	415 (43.5)
TMP-SMX-R	184 (40.1)	207 (41.9)	391 (41.0)
MDR‡	218 (47.5)	236 (47.8)	454 (47.6)

A participant may have had >1 baseline pathogen. Multiple isolates of same species from same participant are only counted once for each row. *n = number of baseline pathogens isolated from urine and/or blood from participants in the micro-ITT population with susceptibility data. †N = number of baseline pathogens isolated from urine and/or blood from participants in the micro-ITT population with susceptibility data, n = number of baseline pathogens with indicated phenotype.

‡MDR defined as non-susceptibility (i.e., resistant or intermediate) to ≥1 agent in ≥3 antimicrobial classes.

E. coli, *Escherichia coli*; *E. cloacae*, *Enterobacter cloacae*; ESBL+, extended-spectrum β-lactamase–positive; FQ-NS, fluoroquinolone-not susceptible (intermediate or resistant to levofloxacin); IMI-CIL, imipenem-cilastatin; *K. pneumoniae*, *Klebsiella pneumoniae*; MDR, multi-drug resistant; micro-ITT, microbiological intent-to-treat; TBP-PI, tebipenem pivoxil; TMP-SMX-R, trimethoprim-sulfamethoxazole–resistant.

Oral TBP-PI was non-inferior to IV IMI-CIL for the treatment of cUTI including AP

Overall response at test of cure: micro-ITT population

Response	TBP-PI (N=446) n (%)	IMI-CIL (N=483) n (%)	Treatment Difference (TBP-PI – IMI-CIL) % (95% CI)*
Responder	261 (58.5)	291 (60.2)	–1.3 (–7.5, 4.8)
Non-responder or Indeterminate	185 (41.5)	192 (39.8)	
Non-responder	171 (38.3)	179 (37.1)	
Indeterminate	14 (3.1)	13 (2.7)	

Non-inferiority Z Statistic: 2.773
(Efficacy boundary: >2.384)

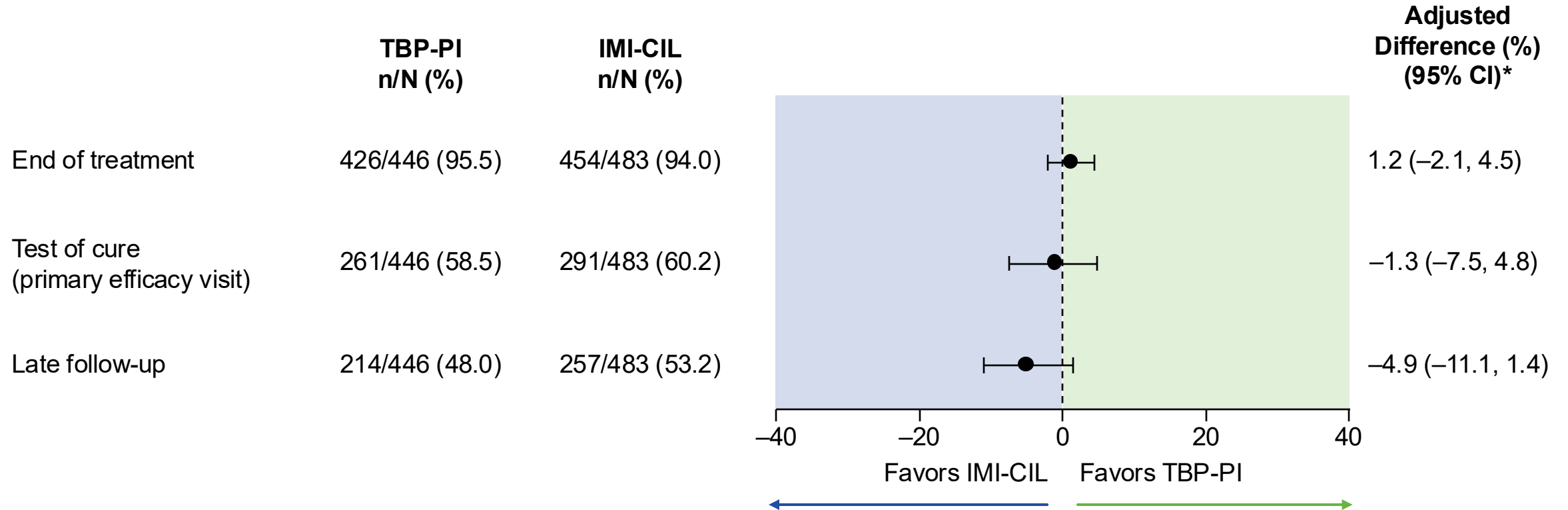
Non-inferiority p-value (one-sided): 0.003
(Efficacy boundary: <0.009)

*Adjusted treatment differences (TBP-PI – IMI-CIL) and 95% CI were calculated using the Miettinen-Numminen score method stratified by actual age at informed consent (≥18 to <65 years vs ≥65 years), baseline diagnosis (AP vs cUTI), and presence or absence of urinary tract instrumentation at baseline.

AP, acute pyelonephritis; CI, confidence interval; cUTI, complicated urinary tract infection; IMI-CIL, imipenem-cilastatin; IV, intravenous; micro-ITT, microbiological intent-to-treat; TBP-PI, tebipenem pivoxil.

Overall response by visit was similar between groups

Micro-ITT population

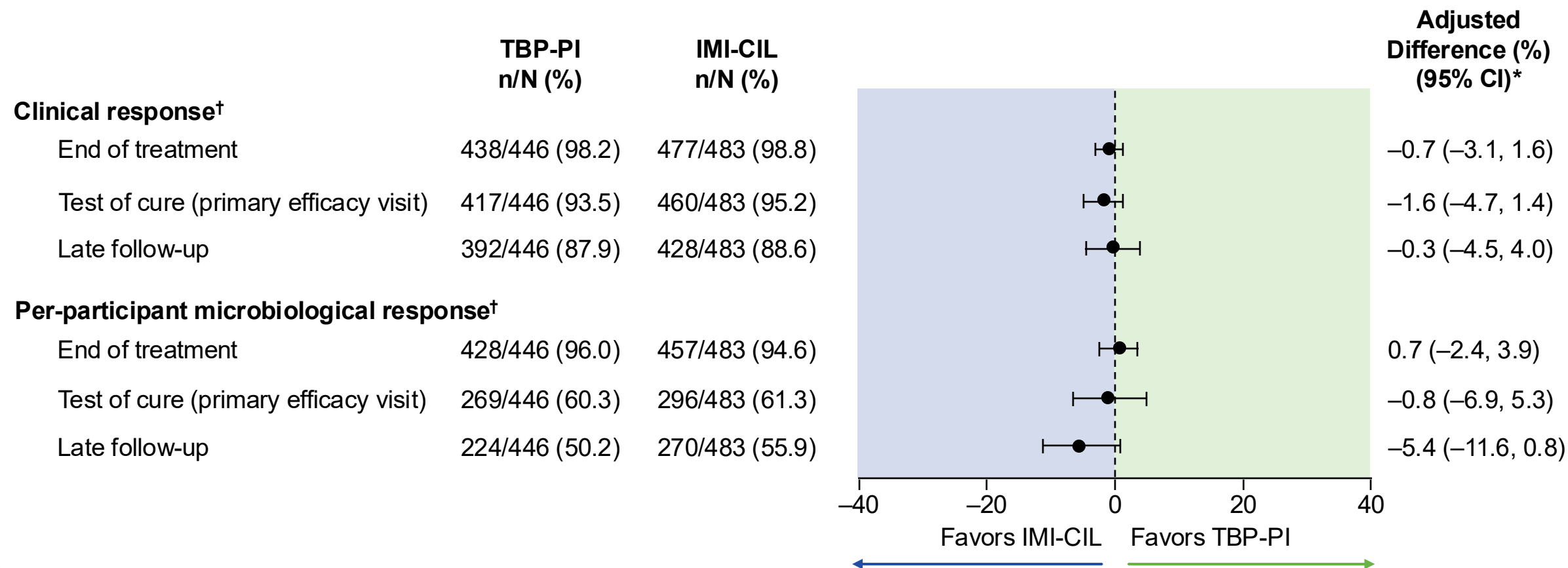


*Adjusted treatment differences (TBP-PI – IMI-CIL) and 95% CI were calculated using the Miettinen-Numminen score method stratified by actual age at informed consent (≥ 18 to < 65 years vs ≥ 65 years), baseline diagnosis (AP vs cUTI), and presence or absence of urinary tract instrumentation at baseline.

AP, acute pyelonephritis; CI, confidence interval; cUTI, complicated urinary tract infection; IMI-CIL, imipenem-cilastatin; micro-ITT, microbiological intent-to-treat; TBP-PI, tebipenem pivoxil.

Clinical cure rates were >90% at test of cure and sustained through late follow-up; microbiological eradication rates by visit were similar between groups

Micro-ITT population

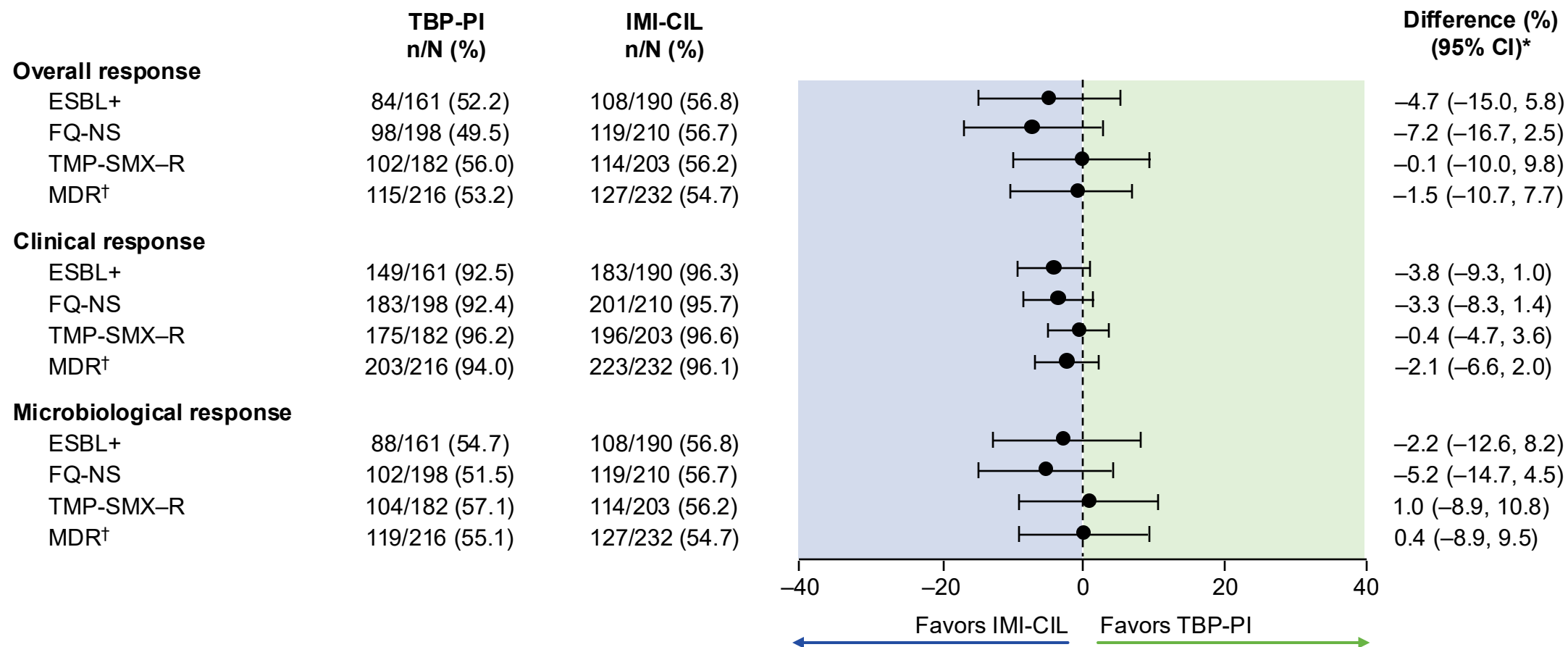


*Adjusted treatment differences (TBP-PI – IMI-CIL) and 95% CI were calculated using the Miettinen-Numminen score method stratified by actual age at informed consent (≥ 18 to < 65 years vs ≥ 65 years), baseline diagnosis (AP vs cUTI), and presence or absence of urinary tract instrumentation at baseline. [†]If a participant was assessed as a clinical failure/microbiological persistent at end of treatment, they were automatically considered a clinical failure/microbiological persistent at the test of cure and late follow-up visits. If a participant was assessed as a clinical failure/microbiological persistent at test of cure, they were automatically considered a clinical failure/microbiological persistent at the late follow-up visit.

AP, acute pyelonephritis; CI, confidence interval; cUTI, complicated urinary tract infection; IMI-CIL, imipenem-cilastatin; micro-ITT, microbiological intent-to-treat; TBP-PI, tebipenem pivoxil.

Overall, clinical and microbiological response rates in participants with infections caused by antimicrobial-resistant Enterobacterales were consistent with the primary analysis population

Test of cure visit; micro-ITT population



*Treatment differences (TBP-PI – IMI-CIL) and 95% CI were calculated using unstratified Miettinen-Numminen score method.

†MDR defined as non-susceptibility (i.e., resistant or intermediate) to ≥1 agent in ≥3 antimicrobial classes.

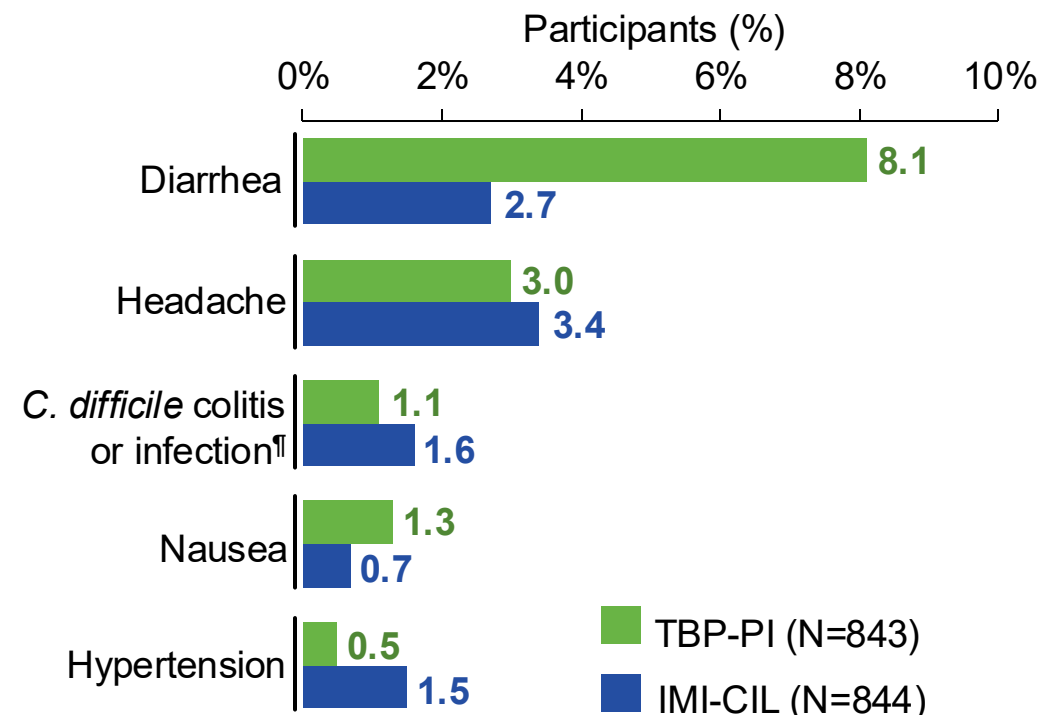
CI, confidence interval; ESBL+, extended-spectrum β-lactamase-positive; FQ-NS, fluoroquinolone-not susceptible (intermediate or resistant to levofloxacin); IMI-CIL, imipenem-cilastatin; micro-ITT, microbiological intent-to-treat; MDR, multi-drug resistant; TBP-PI, tebipenem pivoxil; TMP-SMX-R, trimethoprim-sulfamethoxazole-resistant.

The safety profile of TBP-PI was overall comparable to IMI-CIL

Safety population*

Participants with ≥1 TEAE† n (%)	TBP-PI (N=843)	IMI-CIL (N=844)
Any TEAE	235 (27.9)	201 (23.8)
Serious TEAE	29 (3.4)	22 (2.6)
TEAE related to study treatment	105 (12.5)	79 (9.4)
TEAE leading to study withdrawal	2 (0.2)	1 (0.1)
TEAE leading to drug discontinuation	5 (0.6)	7 (0.8)
TEAE leading to death‡	2 (0.2)	2 (0.2)

All causality TEAEs occurring in >1% of participants§



- Transient decreases in carnitine levels in the TBP-PI treatment group were not associated with TEAEs

*The safety population included all participants who received ≥1 dose of study treatment. †Participants with multiple TEAEs in a category were counted only once in that category. ‡All deaths in the study were unrelated to study treatment per investigator. §Events were coded using MedDRA Version 26.0. ¶All *C. difficile* colitis or *C. difficile* infection events were mild or moderate in severity (in both treatment groups). *C. difficile*, *Clostridioides difficile*; IMI-CIL, imipenem-cilastatin; MedDRA, Medical Dictionary for Regulatory Activities; TBP-PI, tebipenem pivoxil; TEAE, treatment-emergent adverse event.

Conclusions

- **Oral TBP-PI was non-inferior to IV IMI-CIL for the treatment of cUTI including AP**
 - Clinical cure rates with TBP-PI were >90% at test of cure and were sustained through late follow up
 - Microbiological eradication rates were similar between treatment groups across visits
 - Across drug-resistant phenotypes of clinical importance (including ESBL+), treatment differences for overall, clinical, and microbiological response at each visit were consistent with the primary analysis population (micro-ITT)
- **The safety profile of TBP-PI was overall comparable to IMI-CIL**
 - The two most frequent TEAEs were diarrhea and headache across treatment groups
- **TBP-PI may be an effective oral antibiotic treatment option for cUTI including AP**

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