Oral Tebipenem is Non-inferior to IV Ertapenem in Complicated Urinary Tract Infection (cUTI) and Acute Pyelonephritis (AP): *Results from the Pivotal ADAPT-PO Study*

SPERO THERAPEUTICS

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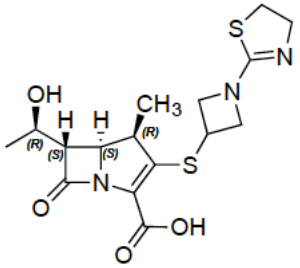
IDWeek 2020

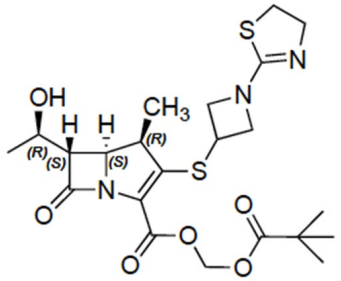
Tebipenem Pivoxil Hydrobromide (TBP-PI-HBr)

Overview

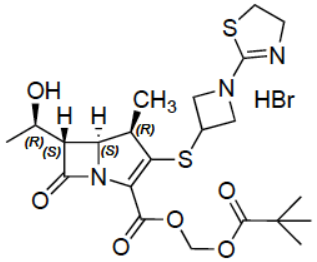
- **TBP-PI-HBr is an orally bioavailable carbapenem prodrug** that rapidly converts in enterocytes to tebipenem
- **Tebipenem has *in vitro* activity against multidrug-resistant (MDR) Gram-negative pathogens**, including extended-spectrum ß-lactamase (ESBL)-producing, fluoroquinolone-resistant, and TMP-SMX-resistant Enterobacterales
- **TBP-PI-HBr being developed as 1st oral carbapenem for treatment of cUTI/AP in the U.S.**



Tebipenem
Active drug



Tebipenem Pivoxil
Orally bioavailable prodrug of tebipenem (Orapenem® fine granules for pediatrics; Meiji Seika, Japan)

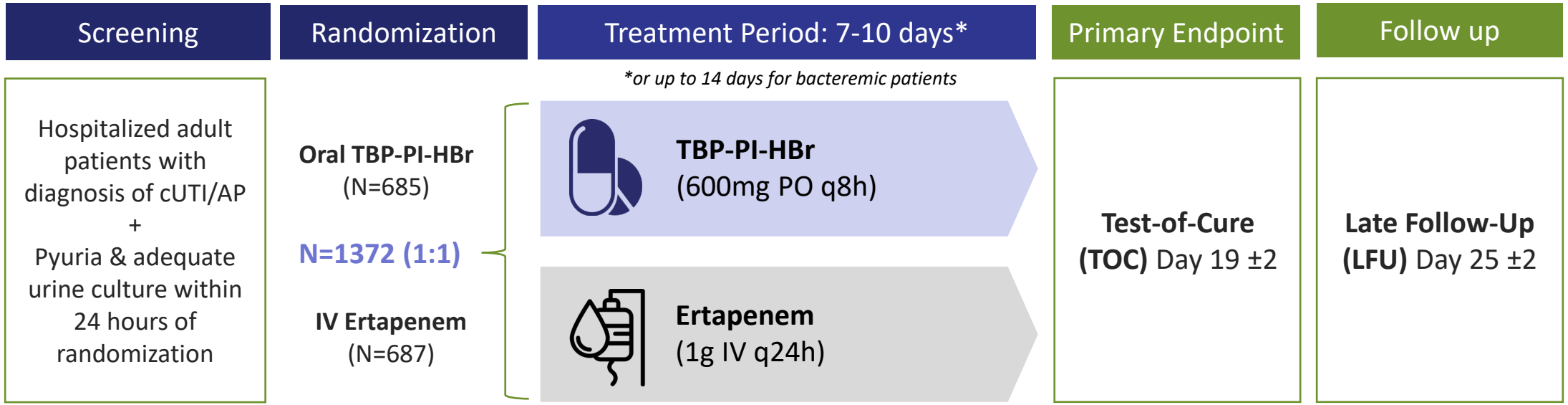


Tebipenem Pivoxil Hydrobromide
Spero's orally bioavailable prodrug + HBr salt, enabling high dosage and room temperature-stable product

ADAPT-PO (Study SPR994-301)

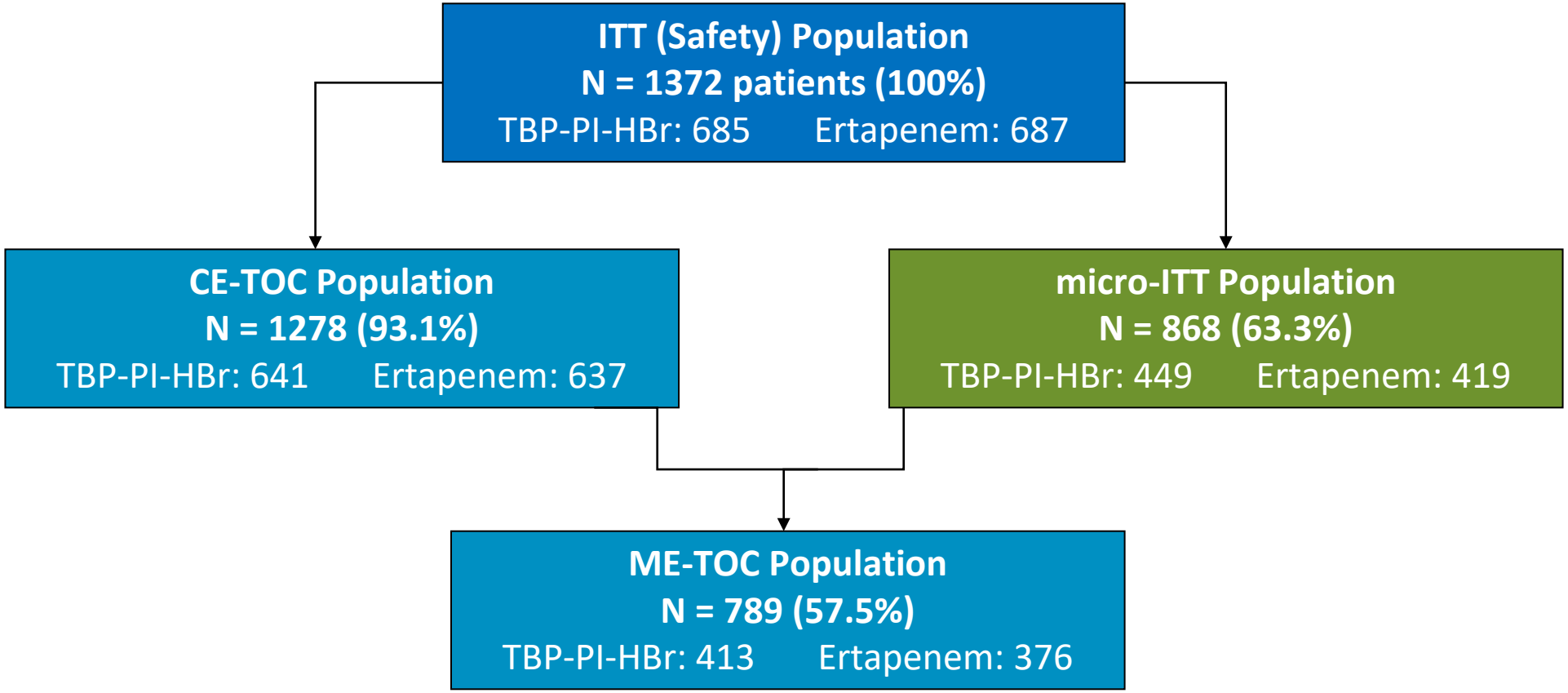
Study Design

- **Global, randomized, double-blind/double-dummy, Phase 3 study**
- **Oral TBP-PI-HBr vs. IV ertapenem in hospitalized adult patients with cUTI or AP**
- **101 sites in 15 countries:** U.S., Central/Eastern Europe, South Africa
- **Primary efficacy endpoint:** Overall response (composite clinical cure plus microbiologic eradication) at TOC in the micro-ITT population (12.5% NI margin)



ADAPT-PO: Phase 3 cUTI/AP Trial

Analysis Populations



CE-TOC = Clinically Evaluable at Test-of-Cure; ITT = Intent-to-Treat (randomized); ME-TOC = Microbiologically Evaluable at Test-of-Cure; micro-ITT = Microbiological Intent-to-Treat.

ADAPT-PO: Phase 3 cUTI/AP Trial

Demographic & Baseline Characteristics (Safety Population)

	TBP-PI-HBr (n=685)	Ertapenem (n=687)	Overall (n=1372)
Age (years)			
Mean (SD)	56.7 (18.68)	57.2 (18.23)	56.9 (18.45)
>=65 to <75 years	186 (27.2%)	201 (29.3%)	387 (28.2%)
>=75	112 (16.4%)	99 (14.4%)	211 (15.4%)
Sex, n (%)			
Male	317 (46.3%)	298 (43.4%)	615 (44.8%)
Female	368 (53.7%)	389 (56.6%)	757 (55.2%)
Baseline Diagnosis, n (%)			
AP	333 (48.6%)	332 (48.3%)	665 (48.5%)
cUTI	352 (51.4%)	355 (51.7%)	707 (51.5%)
Creatinine clearance, n (%)			
≤30 mL/min	4 (0.6%)	8 (1.2%)	12 (0.9%)
>30 to ≤50 mL/min	70 (10.2%)	69 (10.0%)	139 (10.1%)
>50 mL/min	611 (89.2%)	610 (88.8%)	1221 (89.0%)
Bacteremia at Baseline, n (%)	50 (7.3%)	56 (8.2%)	106 (7.7%)
Modified SIRS criteria at baseline, n (%)	139 (20.3%)	123 (17.9%)	262 (19.1%)
Received prior systemic antibiotics, n (%)	37 (5.4%)	47 (6.8%)	84 (6.1%)

SIRS = Systemic inflammatory response syndrome.

ADAPT-PO: Phase 3 cUTI/AP Trial

Uropathogens Isolated from Urine and/or Blood at Baseline (micro-ITT)

Baseline Pathogen*	TBP-PI-HBr (N=449)	Ertapenem (N=419)	Total (N=868)
Enterobacterales	397 (88.4%)	386 (92.1%)	783 (90.2%)
Escherichia coli	287 (63.9%)	270 (64.4%)	557 (64.2%)
Klebsiella pneumoniae	53 (11.8%)	71 (16.9%)	124 (14.3%)
Proteus mirabilis	35 (7.8%)	23 (5.5%)	58 (6.7%)
Enterobacter cloacae	11 (2.4%)	8 (1.9%)	19 (2.2%)
Citrobacter freundii	4 (0.9%)	3 (0.7%)	7 (0.8%)
Citrobacter koseri	3 (0.7%)	4 (1.0%)	7 (0.8%)
Klebsiella oxytoca	4 (0.9%)	3 (0.7%)	7 (0.8%)
Providencia rettgeri	4 (0.9%)	3 (0.7%)	7 (0.8%)
Klebsiella variicola	2 (0.4%)	4 (1.0%)	6 (0.7%)
Serratia marcescens	4 (0.9%)	2 (0.5%)	6 (0.7%)
Morganella morganii	4 (0.9%)	1 (0.2%)	5 (0.6%)
Gram-positive cocci	76 (16.9%)	51 (12.2%)	127 (14.6%)
Enterococcus faecalis	58 (12.9%)	36 (8.6%)	94 (10.8%)
Staphylococcus aureus	5 (1.1%)	8 (1.9%)	13 (1.5%)
S. saprophyticus	4 (0.9%)	6 (1.4%)	10 (1.2%)
Enterococcus faecium	5 (1.1%)	2 (0.5%)	7 (0.8%)

*Only pathogens representing ≥ 5 isolates across both treatment groups are presented.

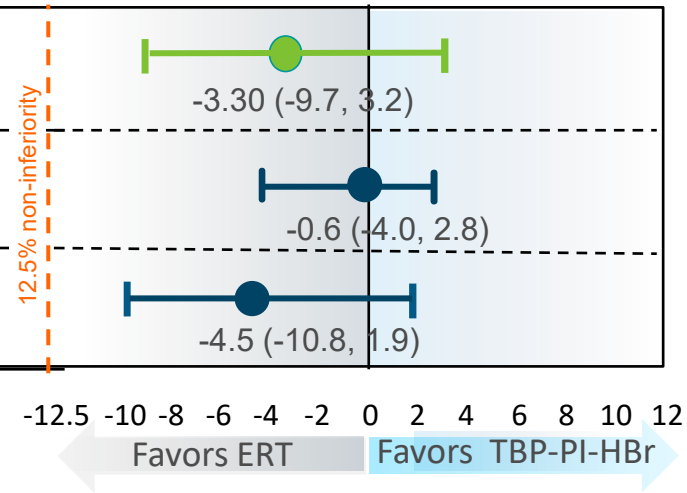
- **90% patients in micro-ITT were infected with Enterobacterales**
- **Infections caused by resistant Enterobacterales strains were common**

Enterobacterales Resistance phenotype[1]	TBP-PI-HBr	Ertapenem
ESBL+	26.5%	22.0%
FQ-non-susceptible	40.2%	37.8%
TMP-SMX-resistant	42.4%	43.5%

[1] Per CLSI screening criteria: ESBL+ = ceftazidime MIC ≥2 µg/mL; fluoroquinolone (FQ)-non-susceptible = levofloxacin MIC ≥ 1 µg/mL; trimethoprim-sulfamethoxazole (TMP/SMX)-resistant = TMP-SMX MIC ≥ 4/76 µg/mL.

ADAPT-PO Met the Primary Efficacy Endpoint

Endpoint (micro-ITT Population)	TBP-PI-HBr N = 449	Ertapenem N = 419	Treatment Difference (%) (TBP-PI-HBr minus ertapenem, 95% CI)
Overall response at TOC (%/n)	58.8% 264	61.6% 258	-3.30 (-9.7, 3.2)
Clinical cure at TOC (%/n)	93.1% 418	93.6% 392	-0.6 (-4.0, 2.8)
Microbiological eradication at TOC (%/n)	59.5% 267	63.5% 266	-4.5 (-10.8, 1.9)



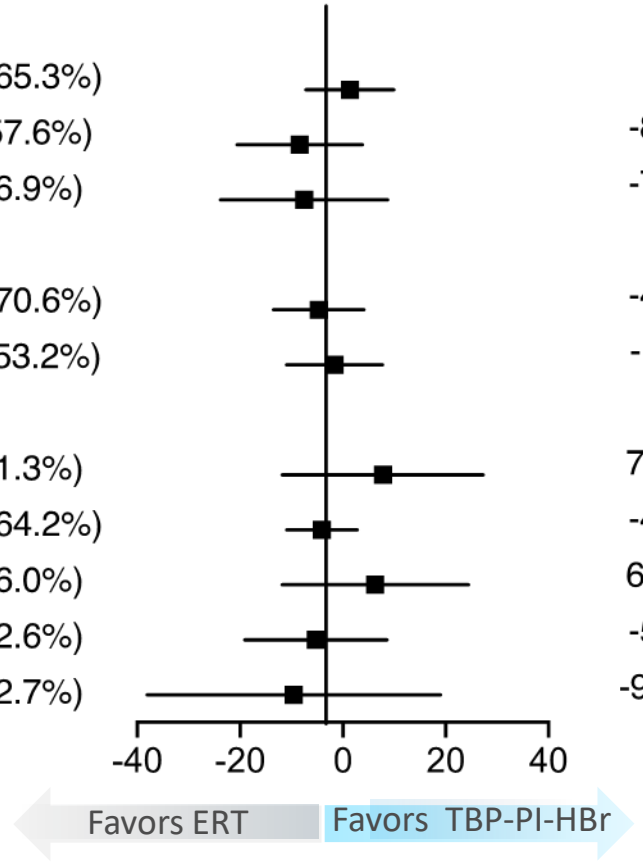
micro-ITT = microbiological Intent-to Treat; TOC = Test-of-Cure.

Oral TBP-PI-HBr was non-inferior to IV ertapenem in overall response at TOC

ADAPT-PO: Phase 3 cUTI/AP Trial

Overall Response at TOC by Baseline Characteristics (micro-ITT)

Subgroup	TBP-PI-HBr n/N (%)	Ertapenem n/N (%)	Difference (%) (95% CI)
Age at informed consent			
≥18 to <65 years	164/246 (66.7%)	145/222 (65.3%)	1.4% (-7.2, 9.9)
≥65 to <75 years	60/122 (49.2%)	76/132 (57.6%)	-8.4% (-20.6, 3.8)
≥75	40/81 (49.4%)	37/65 (56.9%)	-7.5% (-23.8, 8.7)
Baseline Diagnosis			
AP	149/226 (65.9%)	142/201 (70.6%)	-4.7% (-13.5, 4.1)
cUTI	115/223 (51.6%)	116/218 (53.2%)	-1.6% (-11.0, 7.7)
Creatinine clearance categories			
>30 to ≤50	26/53 (49.1%)	19/46 (41.3%)	7.8% (-11.8, 27.3)
>50	237/394 (60.2%)	235/366 (64.2%)	-4.1% (-10.9, 2.8)
Bacteremia at Baseline	34/47 (72.3%)	35/53 (66.0%)	6.3% (-11.8, 24.4)
Met modified SIRS criteria	66/98 (66.3%)	53/73 (72.6%)	-5.3% (-19.1, 8.6)
Received any prior systemic antibiotics	12/19 (63.2%)	16/22 (72.7%)	-9.6% (-38.1, 19.0)



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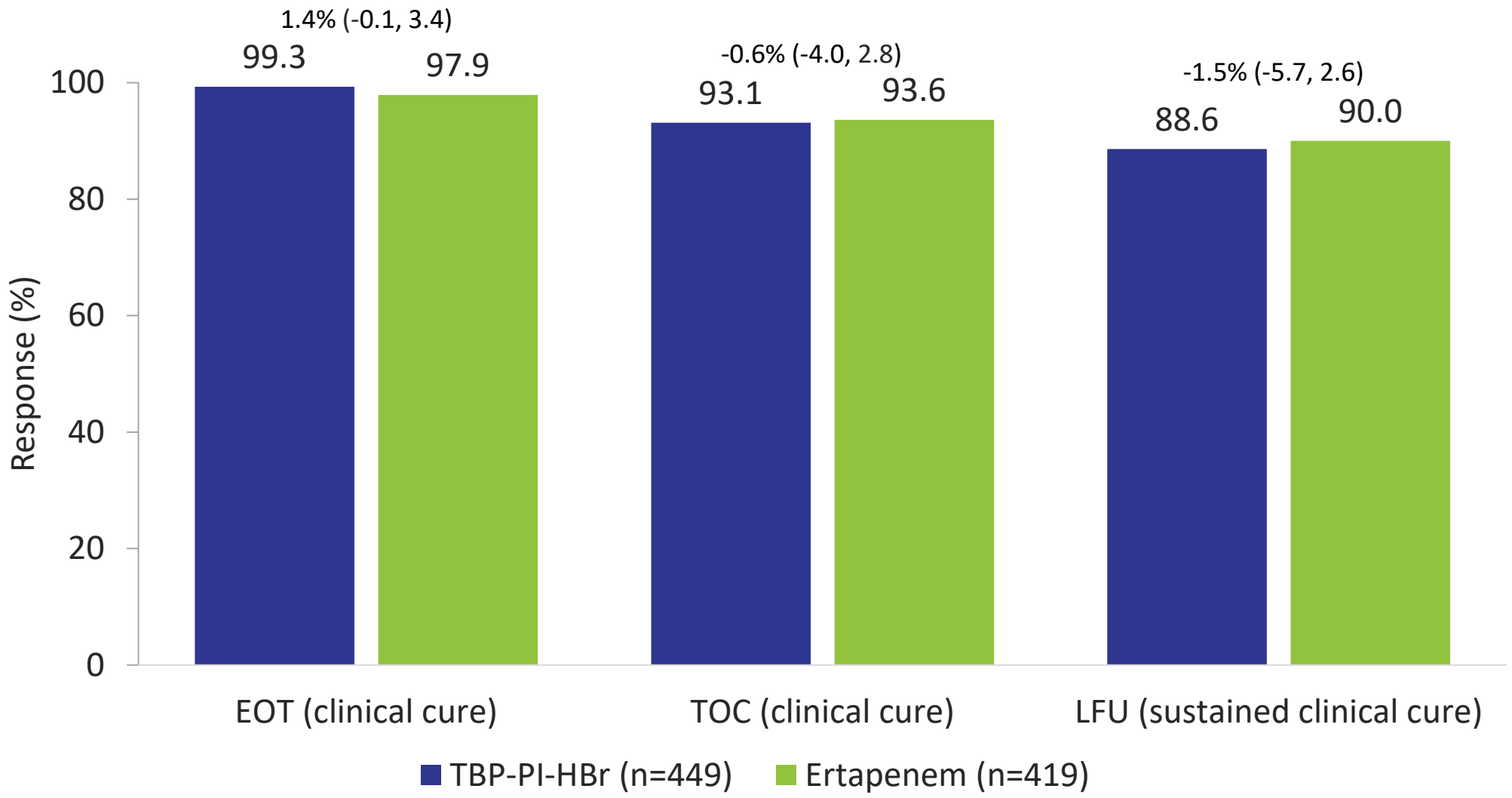
Favorable Clinical Response by Visit (micro-ITT)



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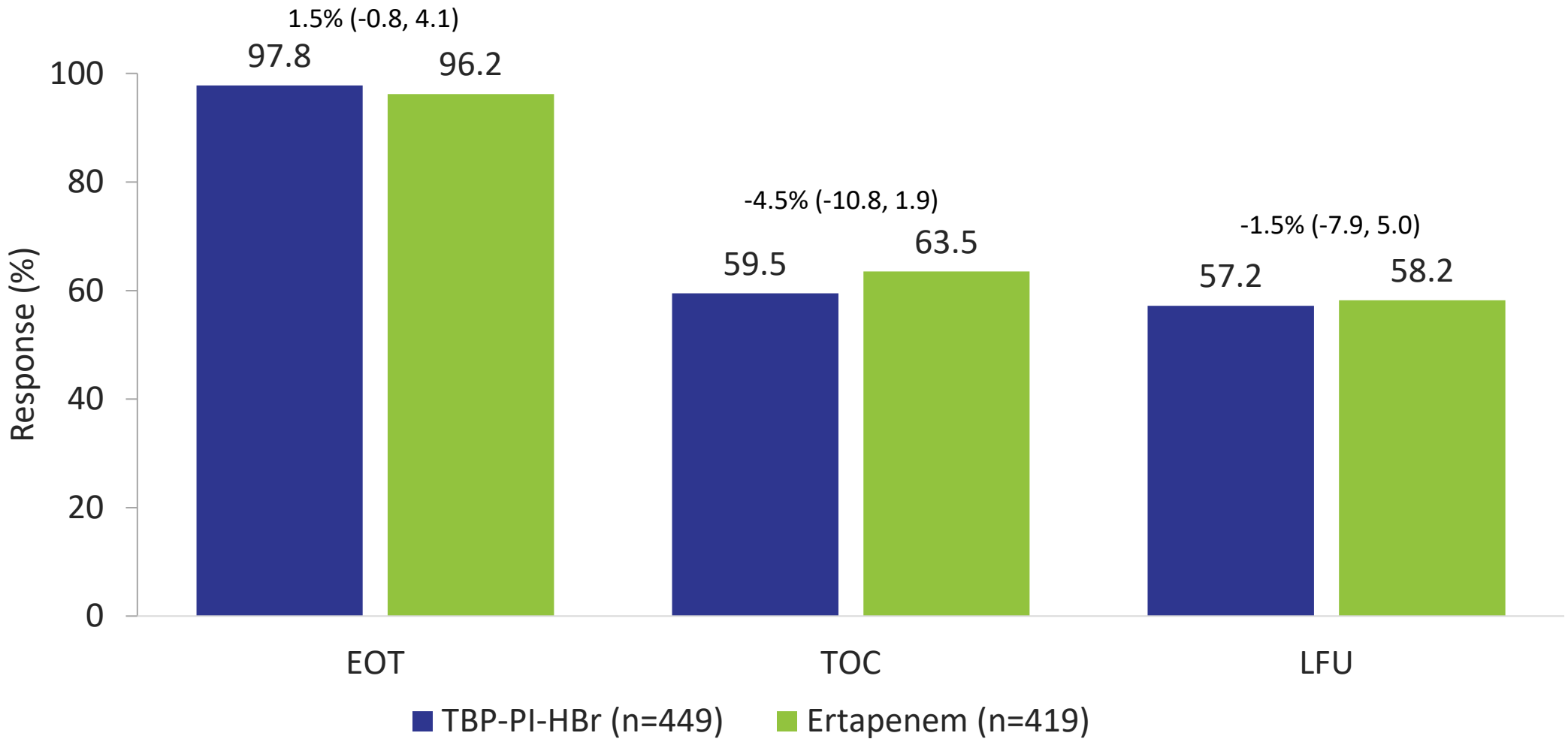
Favorable Per-Patient Microbiological Response by Visit (micro-ITT)



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Per-Pathogen Microbiological Eradication at TOC (micro-ITT)

Baseline Pathogen	TBP-PI-HBr N=449 % (n/N1)	Ertapenem N=419 % (n/N1)
Enterobacterales*	320/508 (63.0%)	337/511 (65.9%)
E. coli	230/355 (64.8%)	229/352 (65.1%)
K. pneumoniae	35/65 (53.8%)	52/78 (66.7%)
P. mirabilis	23/42 (54.8%)	21/31 (67.7%)
E. cloacae	7/12 (58.3%)	4/8 (50.0%)
Resistant Enterobacterales Phenotypes		
ESBL+	57/105 (54.3%)	53/85 (62.4%)
FQ-NS	86/159 (54.1%)	90/146 (61.6%)
TMP-SMX-R	96/168 (57.1%)	108/168 (64.3%)

*Only pathogens with ≥ 5 isolates in either treatment group are presented.
ESBL+ = Expended-spectrum β-lactamase-producing; FQ-NS = fluoroquinolone-nonsusceptible; TMP-SMX-R = trimethoprim-sulfamethoxazole-resistant.

ADAPT-PO: Phase 3 cUTI/AP Trial

Safety Overview (Safety Population)

Number of patients who experienced at least one:	TBP-PI-HBr N = 685 n/N (%)	Ertapenem N=687 n/N (%)
TEAE*	176 (25.7%)	176(25.6%)
Diarrhea	39 (5.7%)	30 (4.4%)
Headache	26 (3.8%)	26 (3.8%)
Nausea	10 (1.5%)	6 (0.9%)
TEAE leading to premature discontinuation of study drug	1 (0.1%)	8 (1.2%)
TEAE leading to study withdrawal	1 (0.1%)	1 (0.1%)
TEAEs associated with *Clostridioides difficile*	0	3 (0.4%)
SAEs	9 (1.3%)	12 (1.7%)
Drug-related SAE	0	2 (0.3%)
Deaths	0	0

*Only TEAEs occurring in >1% patients in either treatment group are shown.
TEAE = treatment-emergent adverse event; SAE = serious adverse event.

ADAPT-PO: Phase 3 cUTI/AP Trial

Overall Conclusions

- **Oral TBP-PI-HBr (600mg PO q8h) was non-inferior to ertapenem (1g IV q24h) in the treatment of hospitalized adult patients with cUTI/AP**
- **ADAPT-PO achieved all primary and secondary objectives**
  - These effects were seen consistently across patient subsets
- **TBP-PI-HBr had a favorable tolerability profile, comparable to IV ertapenem**
  - Low TEAE/SAE rates, types of TEAEs consistent with carbapenem and β-lactam class effects
- **Spero expects that data from this single pivotal trial will support submission of an NDA**

Thank You!

- **Patients and Investigators**
- **PSI Study Team and Vendors**:
  - Over 1300 MDs, RNs, pharmacists, laboratory technicians, and others
  - 101 sites in 15 countries
- **External Partners**:
  - Meiji Seika
  - BARDA*

SPR994-301 Study Team

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