Activity of Tebipenem Against Enterobacterales, Including Molecularly Characterized Clinical Isolates Causing Urinary Tract and Bloodstream Infections from the United States in 2023

R Kapoor[1], TB Doyle[2], Z. Kockler[2], IA Critchley[3], RE Mendes[2], M Castanheira[2], D Torumkuney[4]

[1]GSK, Collegeville, PA, USA, [2]Element Iowa City (JMI Laboratories), North Liberty, Iowa, USA, [3]Spero Therapeutics, Cambridge, MA, USA, [4]GSK-HQ, London, UK

Tebipenem demonstrated potent *in vitro* activity against the numerous subsets of molecularly characterized isolates, including those with ESBL phenotypes.

Digital poster

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Introduction

- Tebipenem is a carbapenem with broad spectrum activity against Gram-negative and Gram-positive bacteria, including multidrug resistant strains[1,2]
- A phase 3 clinical trial (PIVOT-PO) evaluating the safety and efficacy of tebipenem-pivoxil (oral prodrug) for the treatment of complicated urinary tract infection (cUTI) and acute pyelonephritis (AP) was recently completed[3].
- This study describes the *in vitro* activity of tebipenem and comparator agents against molecularly characterized Enterobacterales isolates recovered from UTIs and bloodstream infections (BSIs) in the United States (US), including extended-spectrum b-lactamase (ESBL) and carbapenemase-producing Enterobacterales isolates.

Methods

Bacterial isolates

- A total of 3,523 Enterobacterales isolates collected from 61 US sites as part of the Tebipenem Surveillance Program for 2023 were included in this study. These included 2,796 isolates of *Escherichia coli, Klebsiella pneumoniae*, and *Proteus mirabilis*.
- Isolates recovered from UTIs (2,614; 74.2%) and BSIs (909; 25.8%) were included.
- Bacterial identification was confirmed by standard algorithms supported by matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany).

Susceptibility testing

- Isolates were tested for susceptibility by broth microdilution and results were interpreted following Clinical and Laboratory Standards Institute (CLSI) guidelines[4,5].
- *E. coli*, *K. pneumoniae* isolates with aztreonam, ceftazidime, or ceftriaxone MICs of ≥2 µg/mL), and *P. mirabilis* isolates with cefpodoxime or ceftazidime MICs of ≥2 µg/mL were categorized as presumptive ESBL producers (ESBL+).
- Any isolate displaying MIC values ≥2 µg/mL for imipenem and/or meropenem, or ≥1 µg/mL for ertapenem, were categorized as carbapenem-not susceptible (CNSE). Only meropenem was used for the categorization of *Morganellaceae* due to their intrinsic decreased susceptibility to imipenem.
- ESBL+ and CNSE isolates were subjected to genome sequencing followed by β-lactamase gene screening.

Screening of β-lactamase genes

- Selected isolates had total genomic DNA extracted by the fully automated Thermo Scientific™ KingFisher™ Flex Magnetic Particle Processor (Cleveland, OH, USA), which was used to generate input material for library construction.
- DNA libraries were prepared using the Illumina DNA™ library construction protocol (Illumina, San Diego, CA, USA) following the manufacturer's instructions and were sequenced on a NextSeq Sequencer.
- FASTQ format sequencing files for each sample set were trimmed, error-corrected, and assembled using *de novo* assembler SPAdes 3.15.3. An in-house software was applied to align the assembled sequences against a comprehensive in-house database containing known β-lactamase genes.

Table 1 Activity of tebipenem and comparator agents tested against molecularly characterized Enterobacterales from the US collected in 2023

Phenotype (No. tested)	MIC_{50}/MIC_{90} in µg/mL (% susceptible by CLSI)								
	TBP	IMI	MER	ERT	LEV	CRO	FEP*[j]	SXT	TZP
All (3,523)	0.015/0.06 (-)	≤0.12/1 (93.5)	0.03/0.06 (99.4)	0.008/0.06 (98.6)	0.06/8 (82.5)	≤0.06/>8 (82.5)	0.06/4 (89.0)	≤0.12/>4 (75.7)	2/8 (91.7)
CSE[a] (3,467)	0.015/0.06 (-)	≤0.12/1 (94.3)	0.03/0.06 (100)	0.008/0.03 (100)	0.06/8 (83.0)	≤0.06/>8 (83.6)	0.06/4 (89.9)	≤0.12/>4 (76.2)	2/8 (92.9)
non-ESBL[b] (2,301)	0.015/0.03 (-)	≤0.12/0.5 (93.5)	≤0.015/0.03 (100)	0.008/0.015 (99.9)	0.03/4 (87.7)	≤0.06/0.12 (100)	≤0.03/0.12 (100)	≤0.12/>4 (81.7)	2/4 (97.6)
ESBL[c] (495)	0.015/0.06 (-)	≤0.12/0.5 (95.6)	0.03/0.06 (97.0)	0.03/0.25 (94.9)	2/16 (43.8)	>8/>8 (7.7)	8/>32 (29.5)	>4/>4 (31.8)	4/64 (77.0)
ESBL-pos, CSE[d] (470)	0.015/0.03 (-)	≤0.12/0.5 (98.5)	0.03/0.06 (100)	0.03/0.12 (100)	2/16 (44.9)	>8/>8 (8.1)	8/>32 (31.1)	>4/>4 (32.2)	4/32 (80.9)
CTX-M[e] (381)	0.015/0.03 (-)	≤0.12/0.25 (98.9)	0.03/0.06 (100)	0.03/0.12 (100)	8/16 (38.8)	>8/>8 (0.3)	16/>32 (16.0)	>4/>4 (24.7)	4/16 (83.5)
pAmpC[f] (45)	0.015/0.12 (-)	0.25/1 (95.6)	0.03/0.12 (100)	0.06/0.25 (100)	0.5/16 (66.7)	>8/>8 (17.8)	0.25/1 (97.8)	1/>4 (53.3)	4/64 (71.1)
Other[g] (8)	0.015/nc (-)	≤0.12/nc (87.5)	0.03/nc (100)	0.015/nc (100)	0.5/nc (50.0)	8/nc (12.5)	1/nc (87.5)	0.5/nc (50.0)	4/nc (62.5)
None[h] (36)	0.015/0.03 (-)	≤0.12/0.25 (100)	≤0.015/0.03 (100)	0.015/0.06 (100)	0.03/16 (80.6)	0.5/2 (77.8)	0.12/2 (94.4)	≤0.12/>4 (82.9)	8/>128 (69.4)
CNSE[i] (56)	1/>8 (-)	2/>8 (48.2)	1/>32 (60.7)	2/>2 (8.9)	1/32 (48.2)	>8/>8 (14.3)	16/>32 (32.1)	>4/>4 (41.1)	>128/>128 (12.5)

CSE, carbapenem-susceptible Enterobacterales; ESBL, extended-spectrum-β-lactamase; CNSE, carbapenem not susceptible Enterobacterales; TBP, tebipenem; IMI, imipenem; MER, meropenem; ERT, ertapenem; LEV, levofloxacin; CRO, ceftriaxone; FEP, cefepime; SXT, trimethoprim-sulfamethoxazole; TZP, piperacillin-tazobactam; CLSI breakpoints applied for comparator agents; "-" breakpoints not available; nc, MIC_{90} not calculated if ns10

*Susceptibility breakpoints for all agents are same for CLSI and EUCAST, except for meropenem and imipenem.

[a] Includes CSE isolates with MIC ≤1 µg/mL for imipenem (not considered for Morganellaceae) and/or meropenem, or ≤0.5 µg/mL for ertapenem.

[b] Includes *E. coli*, *K. pneumoniae,* and *P. mirabilis* isolates that did not meet the definition of ESBL phenotype.

[c] Includes *E. coli* and *K. pneumoniae* isolates (with aztreonam, ceftazidime, or ceftriaxone MICs of ≥2 µg/mL), and *P. mirabilis* isolates (with cefpodoxime or ceftazidime MICs of ≥2 µg/mL) that meeting ESBL+ phenotype definition

[d] Includes carbapenem-susceptible *E. coli, K. pneumoniae,* and *P. mirabilis* isolates that meet the definition of ESBL phenotype

[e] The following bla_{CTX-M} alleles were detected: 1 $bla_{CTX-M-1}$, 228 $bla_{CTX-M-15}$, 2 $bla_{CTX-M-3}$, 1 $bla_{CTX-M-32}$, 18 $bla_{CTX-M-55}$, 2 $bla_{CTX-M-115}$, 1 $bla_{CTX-M-89}$, 1 $bla_{CTX-M-91}$, 1 $bla_{CTX-M-134}$, 27 $bla_{CTX-M-14}$, 1 $bla_{CTX-M-174}$, 1 $bla_{CTX-M-24}$, 92 $bla_{CTX-M-27}$, 5 $bla_{CTX-M-65}$. Isolates may include additional ESBL alleles.

[f] The following alleles were detected: 26 bla_{CMY-2}, 2 bla_{CMY-6}, 2 bla_{CMY-42}, and 15 bla_{DHA-1}. Excludes isolates with CTX-M alleles.

[g] The following alleles were detected: 1 bla_{OXA-1}, 2 bla_{SHV-12}, 1 bla_{SHV-2}, 1 bla_{SHV-27}, 2 bla_{SHV-7}, 1 bla_{VEB-6}. Excludes isolates with CTX-M or pAmpC alleles.

[h] No ESBL alleles were detected in these isolates.

[i] Includes isolates with MIC ≥2 mg/m for imipenem and/or meropenem, or ≥1 µg/mL for ertapenem. Includes 22 isolates that carried carbapenemase genes (1 bla_{KPC-65}, and bla_{NDM-5}, 1 bla_{KPC-3} and bla_{NDM-1}, 4 bla_{KPC-2}, 4 bla_{KPC-3}, 4 bla_{NDM-1}, 4 bla_{NDM-5}, 2 bla_{NDM-7}, 1 bla_{IMP-27}, and 1 bla_{OXA-48}) and 34 isolates where no carbapenemase genes were detected.

[j] Intermediate is interpreted as susceptible-dose dependent

Results

- Overall, tebipenem MIC_{50} and MIC_{90} values against all 3,523 Enterobacterales isolates from the US were 0.015 µg/mL and 0.06 µg/mL, respectively (Tables 1 and 2).
- The MIC_{50} and MIC_{90} values of 2,796 *E. coli, K. pneumoniae*, and *P. mirabilis* isolates were 0.015 and 0.03 µg/mL, respectively.
- A total of 495 (17.7%) *E. coli*, *K. pneumoniae,* and *P. mirabilis* isolates met the screening criteria for ESBL phenotype (ESBL+) (Table 1). There were 2,301 (82.3%) isolates that did not meet criteria for screening of β-lactamase genes (presumptive ESBL-negative).
- Among ESBL+ isolates, 470 (13.3% of total isolates) were carbapenem-susceptible (ESBL+, CSE).
- Tebipenem had $MIC_{50/90}$ values of 0.015/0.06 µg/mL against ESBL+ isolates.
  - The $MIC_{50/90}$ values of intravenous (IV) carbapenem agents were ≤0.12/0.5 µg/mL for imipenem (95.6% susceptible), 0.03/0.06 µg/mL for meropenem (97.0% susceptible), and 0.03/0.25 µg/mL for ertapenem (94.9% susceptible).
  - Susceptibility to other comparator agents ranged from 7.7% - 77.0%.
- Most ESBL+ and CSE isolates carried a CTX-M allele (81.1%; 381/470), whereas 9.6% (45/470) had plasmid AmpC genes without a CTX-M, 1.7% carried other ESBL genes (8/470), and 7.7% (36/470) had no acquired ESBL genes.
- The carbapenem-not susceptible Enterobacterales (CNSE) phenotype accounted for 1.6% (56/3,523) of tested isolates.
- Tebipenem had $MIC_{50/90}$ values of 1/>8 µg/mL against CNSE isolates.
  - The $MIC_{50/90}$ values of IV carbapenem agents were 2/>8 µg/mL for imipenem (48.2% susceptible), 1/>32 µg/mL for meropenem (60.7% susceptible), and 2/>2 µg/mL for ertapenem (8.9% susceptible).
  - Susceptibility to other comparator agents ranged from 12.5% - 48.2%.
- Carbapenemase genes were identified in 22/56 CNSE isolates. Of these, 10 isolates carried an NDM, 8 carried a KPC, 1 carried an IMP, 1 carried an OXA-48, and 2 carried an NDM + KPC.

Table 2 Frequency distribution of tebipenem MIC values against molecularly characterized Enterobacterales from the US collected in 2023

Phenotype/genotype (No. tested)	No. and cumulative % of isolates inhibited at a gepotidacin MIC (mg/L) of:													Tebipenem	
	≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8	MIC_{50}	MIC_{90}
All (3,523)	6 0.2%	798 22.8%	1779 73.3%	418 85.2%	196 90.7%	223 97.1%	53 98.6%	18 99.1%	6 99.3%	7 99.5%	0 99.5%	2 99.5%	17 100%	0.015	0.06
CSE[a] (3,467)	6 0.2%	798 23.2%	1778 74.5%	416 86.5%	190 92%	215 98.2%	50 99.6%	11 99.9%	2 99.9%	1 100%				0.015	0.06
non-ESBL[b] (2,301)	5 0.2%	709 31%	1208 83.5%	169 90.9%	67 93.8%	113 98.7%	26 99.8%	3 99.9%	1 100%					0.015	0.03
ESBL[c] (495)	0 0%	38 7.7%	304 69.1%	88 86.9%	25 91.9%	15 94.9%	4 95.8%	3 96.4%	2 96.8%	3 97.4%	0 97.4%	1 97.6%	12 100%	0.015	0.06
ESBL-pos, CSE[d] (470)	0 0%	38 8.1%	304 72.8%	88 91.5%	22 96.2%	13 98.9%	3 99.6%	1 99.8%	1 100%					0.015	0.03
CTX-M[e] (381)	0 0%	30 7.9%	251 73.8%	75 93.4%	15 97.4%	8 99.5%	2 100%							0.015	0.03
pAmpC[f] (45)	0 0%	3 6.7%	20 51.1%	11 75.6%	5 86.7%	4 95.6%	0 95.6%	1 97.8%	1 100%					0.015	0.12
Other[g] (8)		0 0%	5 71.4%	1 85.7%	1 100%									0.015	nc
None[h] (36)	0 0%	5 13.9%	27 88.9%	1 91.7%	1 94.4%	1 97.2%	1 100%							0.015	0.03
CNSE[i] (56)		0 0%	1 1.8%	2 5.4%	6 16.1%	8 30.4%	3 35.7%	7 48.2%	4 55.4%	6 66.1%	0 66.1%	2 69.6%	17 100%	1	>8

[a] Includes CSE isolates with MIC ≤1 µg/mL for imipenem (not considered for Morganellaceae) and/or meropenem, or ≤0.5 µg/mL for ertapenem.

[b] Includes *E. coli*, *K. pneumoniae,* and *P. mirabilis* isolates that did not meet the definition of ESBL phenotype.

[c] Includes all *E. coli* and *K. pneumoniae* isolates (with aztreonam, ceftazidime, or ceftriaxone MICs of ≥2 µg/mL), and *P. mirabilis* isolates (with cefpodoxime or ceftazidime MICs of ≥2 µg/mL) that meet the definition of ESBL phenotype

[d] Includes carbapenem-susceptible *E. coli, K. pneumoniae,* and *P. mirabilis* isolates that meet the definition of ESBL phenotype

[e] The following bla_{CTX-M} alleles were detected: 1 $bla_{CTX-M-1}$, 228 $bla_{CTX-M-15}$, 2 $bla_{CTX-M-3}$, 1 $bla_{CTX-M-32}$, 18 $bla_{CTX-M-55}$, 2 $bla_{CTX-M-115}$, 1 $bla_{CTX-M-89}$, 1 $bla_{CTX-M-91}$, 1 $bla_{CTX-M-134}$, 27 $bla_{CTX-M-14}$, 1 $bla_{CTX-M-174}$, 1 $bla_{CTX-M-24}$, 92 $bla_{CTX-M-27}$, 5 $bla_{CTX-M-65}$. Isolates may include additional ESBL alleles.

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Conclusions

- Tebipenem demonstrated potent *in vitro* activity against Enterobacterales causing UTI and BSI in the US, including ESBL+ isolates.
- These data support the development of tebipenem as an oral treatment option for cUTI and AP.

Abbreviations

AP, acute pyelonephritis; BSI, Bloodstream Infection; CLSI, Clinical and Laboratory Standards Institute; CNSE, carbapenem not susceptible; CPE, carbapenemase-producing Enterobacterales; cUTI, complicated urinary tract infection; ESBL, extended-spectrum β-lactamase; US, United States; UTI, Urinary Tract Infection

References

1. Critchley et al. Open Forum Infect Dis. 2019;6:S534-5.
2. Eckburg et al. N Engl J Med. 2022;386(14):1327-1338.
3. GSK. PIVOT-PO phase III study for tebipenem HBr stopped early for efficacy following review by Independent Data Monitoring Committee. 2025
4. M07Ed12. Clinical and Laboratory Standards Institute, 2024.
5. M100Ed35. Clinical and Laboratory Standards Institute, 2025.

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Presenting author: Timothy B. Doyle, tim.doyle@element.com