In Vitro Antibacterial Spectrum and Activity of Tebipenem Against Enterobacterales Clinical Isolates Causing Urinary Tract and Bloodstream Infections in the United States and United Kingdom in 2023-2024

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 contemporary Enterobacterales isolates recovered from UTI and BSI, including ESBL-producing and MDR isolates.

Digital poster

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Introduction

- Many oral agents are used to manage urinary tract infections (UTIs), but their clinical usefulness has been compromised by the increased prevalence of extended-spectrum β-lactamases (ESBLs) and the presence of co-resistance to trimethoprim-sulfamethoxazole (TMP/SMX) and quinolones[1].
- Tebipenem is a broad-spectrum carbapenem antibiotic currently in development[2-3] and is orally administered as the prodrug tebipenem-pivoxil.
- A phase 3 clinical trial (PIVOT-PO) evaluating the safety and efficacy of tebipenem for the treatment of complicated urinary tract infection (cUTI) and acute pyelonephritis (AP) was recently completed[4].
- This study assessed the *in vitro* activity of tebipenem and comparator agents against Enterobacterales isolates responsible for UTIs and bloodstream infections (BSIs) in the US and UK during 2023–2024.

Methods

Bacterial isolates

- A total of 7,694 Enterobacterales clinical isolates collected from 72 medical centers in the US (n= 7,437) and UK (n=257) were included in the Tebipenem Surveillance Program for 2023 - 2024.
- UTIs accounted for 73.5% of isolates collected (5,654), of which 54.8% (3,101) were from outpatient settings.
- Isolates recovered from BSIs accounted for 26.5% of the isolates (2,040), of which 22.4% (456) were from outpatient settings.

Susceptibility testing and interpretation

- Isolates were tested for susceptibility by broth microdilution and results were interpreted following Clinical and Laboratory Standards Institute guidelines[5,6].
- *Escherichia coli*, *Klebsiella pneumoniae* isolates with aztreonam, ceftazidime, or ceftriaxone MICs of ≥2 µg/mL), and *Proteus mirabilis* isolates with cefpodoxime or ceftazidime MICs of ≥2 µg/mL were categorized as ESBL phenotype .
- Enterobacterales displaying imipenem and/or meropenem MIC values ≥2 mg/mL, or ertapenem MIC values ≥1 mg/mL were categorized as carbapenem-not susceptible (CNSE). Only meropenem was used for the categorization of *Morganellaceae* due to their intrinsic decreased susceptibility to imipenem.
- The MDR phenotype was defined as described by Magiorakos et al.[7] as having a CLSI-not susceptible phenotype to 3 or more drug classes.

Table 1 Activity of tebipenem and comparator agents against Enterobacterales isolates from the United States and United Kingdom collected during 2023-2024 from urinary tract and bloodstream infections

	MIC_{50}/MIC_{90} in µg/mL (% susceptible by CLSI)								
Phenotype (No. tested)	TBP	IMI	MER	ERT	LEV	CRO	FEP*	SXT	TZP
All (7,694)	0.015/0.06 (-)	≤0.12/1 (92.9)	0.03/0.06 (99.4)	≤0.008/0.06 (98.3)	0.06/8 (81.5)	≤0.06/>8 (82.7)	0.06/8 (88.3)	≤0.12/>4 (75.2)	2/8 (91.3)
United States (7,437)	0.015/0.06 (-)	≤0.12/1 (93.0)	0.03/0.06 (99.4)	≤0.008/0.06 (98.3)	0.06/8 (81.4)	≤0.06/>8 (82.5)	0.06/8 (88.2)	≤0.12/>4 (75.2)	2/8 (91.3)
United Kingdom (257)	0.015/0.12 (-)	≤0.12/1 (90.3)	≤0.15/0.06 (100)	≤0.008/0.03 (98.4)	0.03/2 (85.2)	≤0.06/>8 (87.9)	0.06/2 (90.7)	≤0.12/>4 (73.5)	2/8 (91.1)
CSE (7,617)	0.015/0.06 (-)	≤0.12/1 (93.8)	0.03/0.06 (100)	≤0.008/0.06 (99.0)	0.06/8 (81.9)	≤0.06/>8 (83.3)	0.06/4 (88.9)	≤0.12/>4 (75.5)	2/8 (91.9)
Non-ESBL (5,344)	0.015/0.03 (-)	≤0.12/0.5 (93.5)	≤0.015/0.03 (100)	≤0.008/0.015 (99.9)	0.03/4 (87.6)	≤0.06/0.12 (100)	≤0.03/0.12 (99.9)	≤0.12/>4 (80.6)	4/8 (97.4)
ESBL (1,113)	0.015/0.06 (-)	≤0.12/0.5 (95.2)	0.03/0.06 (96.8)	0.03/0.25 (93.9)	4/16 (41.5)	>8/>8 (7.9)	16/>32 (25.2)	>4/>4 (35.5)	4/64 (73.0)
ESBL, CSE (1,074)	0.015/0.06 (-)	≤0.12/0.5 (98.1)	0.03/0.06 (100)	0.03/0.25 (97.3)	2/16 (42.2)	>8/>8 (8.2)	16/>32 (26.2)	>4/>4 (36.1)	4/32 (75.7)
CNSE (77)	4/>8 (-)	4/>8 (7.8)	4/>32 (40.3)	>2/>2 (29.9)	1/32 (45.5)	>8/>8 (24.7)	16/>32 (33.8)	>4/>4 (41.6)	>128/>128 (24.7)
MDR (1,656)	0.015/0.12 (-)	≤0.12/1 (95.4)	0.03/0.06 (97.2)	0.03/0.5 (92.1)	1/16 (44.9)	>8/>8 (36.9)	2/>32 (56.0)	>4/>4 (26.3)	4/128 (64.0)
LEV-NS (1,422)	0.015/0.12 (-)	≤0.12/2 (89.5)	0.03/0.06 (97.4)	0.015/0.25 (95.1)	8/32 (0.0)	0.5/>8 (51.8)	0.25/>32 (59.8)	>4/>4 (40.7)	4/32 (78.5)
SXT-R (1,910)	0.015/0.12 (-)	≤0.12/1 (92.3)	0.03/0.06 (98.0)	0.015/0.12 (96.2)	0.5/16 (55.9)	0.12/>8 (59.5)	0.12/>32 (67.4)	>4/>4 (0.0)	2/32 (83.9)
UTI (5,654)	0.015/0.06 (-)	≤0.12/1 (92.9)	≤0.015/0.06 (99.5)	≤0.008/0.06 (98.5)	0.06/8 (82.2)	≤0.06/>8 (83.9)	0.06/4 (89.0)	≤0.12/>4 (75.1)	2/8 (92.1)
BSI (2,040)	0.015/0.12 (-)	≤0.12/1 (93.0)	0.03/0.06 (99.3)	≤0.008/0.06 (97.8)	0.06/8 (79.5)	≤0.06/>8 (79.4)	0.06/16 (86.3)	≤0.12/>4 (75.4)	16/8 (89.1)

CSE, carbapenem-susceptible Enterobacterales; ESBL, extended-spectrum-β-lactamase; CNSE, carbapenem not susceptible Enterobacterales; MDR, multidrug-resistant (resistant to ≥3 classes of drugs); NS, not susceptible; R, resistant; 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.

[a] Susceptibility breakpoints for all agents are same for CLSI and EUCAST, except for meropenem and imipenem.

[b] Intermediate is interpreted as susceptible-dose dependent

Results

- *E. coli* comprised 57.0% of all Enterobacterales pathogens included in the study, followed by *K. pneumoniae* (17.5%) and *P. mirabilis* (6.5%).
  - Other pathogens comprised 37 species or species groups (19.0%).
- Tebipenem and comparator agents displayed similar susceptibility profiles among US and UK isolate subsets (Tables 1 and 2)
- $MIC_{50/90}$ values against all Enterobacterales were: tebipenem 0.015/0.06 mg/mL, ertapenem ≤0.008/0.06 mg/mL, imipenem ≤0.12/1 mg/mL, and meropenem 0.03/0.06 mg/mL, with similar results for UTI and BSI isolates (Table 1).
- Susceptibility to other comparator agents ranged from 75.2% – 91.3% (Table 1).
- The proportions of isolates displaying ESBL, MDR, and CNSE phenotypes among Enterobacterales were 14.5%, 21.5%, and 1.0%, respectively.
- Tebipenem $MIC_{50/90}$ values among drug resistant subsets, including ESBL and MDR phenotypes, were similar to those for all isolates (Table 2)
  - $MIC_{50/90}$ values for intravenous (IV)carbapenems were also similar to those for all isolates
  - Susceptibility to the other comparator agents ranged from 0% to 83.9%
- Against CNSE, tebipenem $MIC_{50/90}$ values were 4/>8 ug/mL, and these isolates also displayed higher MICs for IV carbapenems as well as other antibacterial agents tested.

Table 2 Frequency distribution of tebipenem MIC values against Enterobacterales isolates from the United States and United Kingdom collected during 2023-2024 from urinary tract and bloodstream infections

Phenotype/genotype	No. and cumulative % of isolates inhibited at a tepotidacin MIC (mg/L) of:													Tebipenem	
(No. tested)	≤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 (7,694)	22 0.3%	1551 20.4%	3935 71.6%	982 84.4%	484 90.6%	488 97%	126 98.6%	37 99.1%	20 99.4%	10 99.5%	4 99.5%	4 99.6%	31 100%	0.015	0.06
United States (7,437)	21 0.3%	1482 20.2%	3813 71.5%	962 84.4%	465 90.7%	471 97.0%	117 98.6%	37 99.1%	20 99.3%	10 99.5%	4 99.5%	4 99.6%	31 100.0%	0.015	0.06
United Kingdom (257)	1 0.4%	69 27.2%	122 74.7%	20 82.5%	19 89.9%	17 96.5%	9 100.0%							0.015	0.12
CSE (7,617)	22 0.3%	1551 20.7%	3931 72.3%	978 85.1%	478 91.4%	486 97.8%	122 99.4%	33 99.8%	12 99.9%	4 100%				0.015	0.06
Non-ESBL (5,344)	19 0.4%	1409 26.7%	2950 81.9%	476 90.8%	181 94.2%	244 98.8%	61 99.9%	3 99.9%	1 100%					0.015	0.03
ESBL (1,113)	2 0.2%	69 6.4%	643 64.2%	225 84.4%	71 90.7%	38 94.2%	11 95.1%	9 96%	9 96.8%	7 97.4%	3 97.7%	1 97.8%	25 100%	0.015	0.06
ESBL, CSE (1,074)	2 0.2%	69 6.6%	643 66.5%	225 87.4%	71 94%	38 97.6%	11 98.6%	9 99.4%	4 99.8%	2 100%				0.015	0.06
CNSE (77)		0 0%	4 5.2%	4 10.4%	6 18.2%	2 20.8%	4 26%	4 31.2%	8 41.6%	6 49.4%	4 54.5%	4 59.7%	31 100%	4	>8
MDR (1,656)	2 0.1%	189 11.5%	849 62.8%	261 78.6%	157 88%	78 92.8%	24 94.2%	31 96.1%	17 97.1%	9 97.6%	4 97.9%	4 98.1%	31 100%	0.015	0.12
LEV-NS (1,422)	3 0.2%	220 15.7%	713 65.8%	184 78.8%	93 85.3%	98 92.2%	43 95.2%	19 96.6%	11 97.3%	7 97.8%	2 98%	3 98.2%	26 100%	0.015	0.12
SXT-R (1,910)	6 0.3%	349 18.6%	1037 72.9%	233 85.1%	85 89.5%	99 94.7%	35 96.5%	14 97.3%	12 97.9%	8 98.3%	4 98.5%	4 98.7%	24 100%	0.015	0.12
UTI (5,654)	16 0.3%	1227 22%	2931 73.8%	667 85.6%	322 91.3%	327 97.1%	89 98.7%	28 99.2%	14 99.4%	6 99.5%	4 99.6%	2 99.6%	21 100%	0.015	0.06
BSI (2,040)	6 0.3%	324 16.2%	1004 65.4%	315 80.8%	162 88.8%	161 96.7%	37 98.5%	9 98.9%	6 99.2%	4 99.4%	0 99.4%	2 99.5%	10 100%	0.015	0.12

CSE, carbapenem-susceptible Enterobacterales; ESBL, extended-spectrum-β-lactamase; CNSE, carbapenem not susceptible Enterobacterales; MDR, multidrug-resistant (resistant to ≥3 classes of drugs); NS, not susceptible; R, resistant; LEV, levofloxacin; SXT, trimethoprim-sulfamethoxazole.

Conclusions

- Tebipenem demonstrated potent *in vitro* activity against Enterobacterales pathogens recovered from UTIs or BSIs in the US and UK.
- The *in vitro* $MIC_{50/90}$ values for tebipenem, which can be administered orally, were similar to those of the IV drugs ertapenem, imipenem and meropenem .
- Tebipenem activity remained consistent against drug-resistant isolates, including those with ESBL and MDR phenotypes, with the exception of carbapenem-not susceptible isolates.
- These data support the further clinical development of tebipenem as a treatment for cUTI and AP infections caused by Enterobacterales, including for infections caused by common drug-resistant isolates where other oral treatment options are limited.

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 b-lactamase; US, United States; UTI, Urinary Tract Infection

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