#P-1216

Gepotidacin activity against and analysis of susceptibility to oral standard-of-care antibiotics for urinary tract infections caused by *Escherichia coli* and *Klebsiella pneumoniae* collected in Europe in 2023

Gepotidacin demonstrated in vitro activity against contemporary *E. coli* and *K. pneumoniae*, including MDR and ESBL-producing isolates.

Digital poster
Supplemental data

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Introduction

- Gepotidacin, a novel, bactericidal, first-in-class triazaacenaphthylene antibacterial, inhibits bacterial DNA replication by a distinct binding site, unique mechanism of action and for most pathogens, well-balanced inhibition of two type II topoisomerases [1-3].
- Gepotidacin was recently approved by the FDA for the treatment of uncomplicated urinary tract infections (uUTI).
- This study reports a subset of data from a global surveillance study testing in vitro activity of gepotidacin and other oral antibiotics against contemporary *E. coli* and *K. pneumoniae* isolates collected from patients with UTI in Europe.

Methods

- 310 *E. coli* and 154 *K. pneumoniae* isolates were collected during 2023 from 32 medical centers located in 18 European countries.
- All Isolates were cultured from urine specimens collected from patients seen mostly (62%) in ambulatory, emergency, family practice, and outpatient services.
- All isolates were tested for susceptibility by CLSI methods [4] at a central laboratory (Element Iowa City).
- MIC results for comparator agents were interpreted per EUCAST [5] or CLSI guidelines [6] to determine % of susceptible (S), intermediate (I), and resistant (R) isolates.
  - Amoxicillin-clavulanic acid was tested at the CLSI-recommended 2:1 ratio and therefore results were interpreted by CLSI breakpoints.
- MIC results for oral antibiotics licensed for the treatment of uUTI, multidrug-resistant (MDR), and ESBL subsets were interpreted per EUCAST criteria to identify drug resistant (R) subsets.
- The extended-spectrum β-lactamase (ESBL) phenotype was characterized as isolates displaying aztreonam, ceftazidime, or ceftriaxone MIC values ≥ 2 mg/L.
- MDR phenotype was defined as having a not susceptible phenotype to 3 or more drug classes [7].

Results

- Gepotidacin displayed activity against all 310 *E. coli* isolates (Table 1).
  - An $MIC_{50/90}$ of 1/4 mg/L was observed.
  - 99.7% of all observed gepotidacin MICs were ≤16 mg/L (FDA breakpoint, Table 2).
- Susceptibility rates for *E. coli* isolates against many comparators tested were below 83% (Table 1).
  - Ciprofloxacin (73.9%)
  - Levofloxacin (75.8%)
  - Amoxicillin-clavulanic acid (81.3%)
  - Cefadroxil (30 µg disk) (82.3%)
  - Trimethoprim-sulfamethoxazole (70.6%)
- Susceptibility rates for *E. coli* isolates against some comparators tested were above 93% (Table 1).
  - Nitrofurantoin (98.4%)
  - Fosfomycin (97.4%)
  - Mecillinam (93.5%)
  - Nitroxoline (30 µg disk) (100%)
- Gepotidacin maintained similar MIC_{50} (ranging from 1 – 2 mg/L) and MIC_{90} values (ranging from 4 – 8 mg/L) against drug-resistant subsets of *E. coli* (Table 2).
- Gepotidacin remained active against the 18.7% of *E. coli* isolates that displayed an ESBL phenotype ($MIC_{50/90}$ values of 2/8 mg/L) and the 11.0% of *E. coli* isolates that displayed an MDR phenotype ($MIC_{50/90}$, 2/4 mg/L; Table 2).
- Gepotidacin displayed activity against all 154 *K. pneumoniae* isolates (Table 1).
  - An $MIC_{50/90}$ of 4/16 mg/L was observed.
  - 92.9% of all observed gepotidacin MICs were ≤16 mg/L (FDA breakpoint, Table 2).
- Susceptibility rates for *K. pneumoniae* isolates against all oral comparators tested were below 87% (Table 1).
  - Ciprofloxacin (66.9%)
  - Levofloxacin (77.1%)
  - Amoxicillin-clavulanic acid (67.3%)
  - Ampicillin (1.9%)
  - Trimethoprim-sulfamethoxazole (63.6%)
  - Mecillinam (86.4%)
  - Cefadroxil (30µg disk) (66.2%)
- Gepotidacin maintained similar MIC_{50} (ranging from 4 – 8 mg/L) and MIC_{90} values (ranging from 16 – 32 mg/L) against drug-resistant subsets of *K. pneumoniae* (Table 2).
- Gepotidacin remained active against the 35.7% and 26.6% of *K. pneumoniae* isolates that displayed ESBL or MDR phenotypes, respectively, with observed $MIC_{50/90}$ values of 8/32 mg/L for both (Table 2).

Table 1: **Activity of gepotidacin and other oral agents tested against *E. coli* and *K. pneumoniae* UTI isolates collected from medical centers in Europe during 2023**

Organism (No. isolates)	mg/L			EUCAST [a]		
Antimicrobial agent	MIC_{50}	MIC_{90}	MIC range	%S	%I	%R
E. coli (310)						
Gepotidacin [h]	1	4	0.12 to 32	99.7	0.3	0.0
Ciprofloxacin [c]	0.015	>4	0.004 to >4	73.9	2.6	23.5
Levofloxacin	0.03	8	≤0.015 to >32	75.8	1.0	23.2
Amoxicillin-clavulanic acid [d]	4	16	1 to >32	81.3	10.6	8.1
Ampicillin	>64	>64	≤1 to >64	49.0		51.0
Nitrofurantoin [e]	16	32	≤2 to >128	98.4		1.6
Trimethoprim-sulfamethoxazole	≤0.12	>4	≤0.12 to >4	70.6	0.6	28.7
Fosfomycin [e, f]	0.5	2	≤0.12 to >256	97.4		2.6
Mecillinam [e, f]	0.25	4	0.06 to >32	93.5		6.5
Nitroxoline [g]				100.0		0.0
Cefadroxil [e, g]				82.3		17.7
K. pneumoniae (154)						
Gepotidacin [h]	4	16	2 to 64	92.9	5.2	1.9
Ciprofloxacin [c]	0.03	>4	0.004 to >4	66.9	7.1	26.0
Levofloxacin	0.06	8	≤0.015 to >32	77.1	6.5	16.3
Amoxicillin-clavulanic acid [d]	4	32	0.5 to >32	67.3	19.0	13.7
Ampicillin	64	>64	8 to >64	1.9		98.1
Trimethoprim-sulfamethoxazole	0.25	>4	≤0.12 to >4	63.6	2.6	33.8
Mecillinam [e, f]	0.5	32	0.06 to >32	86.4		13.6
Cefadroxil [e, g]				66.2		33.8

[a] Interpreted by EUCAST breakpoints.
[b] Breakpoints not established.
[c] Using breakpoints for indications other than meningitis.
[d] Tested at 2:1 ratio and therefore interpreted by CLSI breakpoints.
[e] Using uncomplicated urinary tract infection only breakpoints.
[f] Tested by agar dilution.
[g] Tested by disk diffusion.
[h] Using FDA breakpoints.

Table 2: **Activity of gepotidacin and comparator agents against FQ-S and FQ-NS *E. coli* and *K. pneumoniae***

Organism (No. isolates)	No. and cumulative % of isolates inhibited at gepotidacin MIC of:									Gepotidacin	
Phenotypic subset[a]	≤0.25	0.5	1	2	4	8	16	32	64	MIC_{50}	MIC_{90}
E. coli (310)	4 1.3%	28 10.3%	126 51.0%	110 86.5%	30 96.1%	4 97.4%	7 99.7%	1 100%		1	4
ESBL positive (58)	0 0.0%	2 3.4%	25 46.6%	20 81.0%	4 87.9%	3 93.1%	4 100%			2	8
MDR (34)		0 0.0%	15 44.1%	13 82.4%	3 91.2%	2 97.1%	1 100%			2	4
Fluoroquinolone-I+R[b] (81)	2 2.5%	6 9.9%	34 51.9%	26 84.0%	7 92.6%	1 93.8%	4 98.1%	1 100%		1	4
Amox-clav-I+R[c] (58)	1 1.7%	4 8.6%	20 43.1%	26 87.9%	5 96.6%	1 98.3%	1 100%			2	4
Ampicllin-R (158)	2 1.3%	15 10.8%	59 48.1%	54 82.3%	16 92.4%	4 94.9%	7 99.4%	1 100%		2	4
Fosfomycin-R[d,e] (8)	0 0.0%	1 12.5%	4 62.5%	2 87.5%	0 87.5%	1 100%				ND	ND
Mecillinam-R[d,e] (20)	1 5.0%	3 20.0%	5 45.0%	8 85.0%	3 100%					2	4
Nitrofurantoin-R [d] (5)		0 0.0%	2 40.0%	3 100%						ND	ND
Trim-sulfa-I+R (91)	2 2.2%	10 13.2%	38 54.9%	21 78.0%	14 93.4%	3 96.7%	2 98.9%	1 100%		1	4
Cefadroxil-R[d,f] (55)	0 0.0%	1 1.8%	25 47.3%	20 83.6%	3 89.1%	3 94.5%	3 100%			2	8
K. pneumoniae (154)			0 0.0%	6 3.9%	76 53.2%	38 77.9%	23 92.9%	8 98.1%	3 100%	4	16
ESBL positive (55)			0 0.0%	5 9.0%	13 35.7%	14 66.3%	17 88.4%	6 100%		8	32
MDR (41)			0 0.0%	5 12.2%	10 36.6%	11 63.4%	10 87.8%	5 100%		8	32
Fluoroquinolone-I+R[b] (51)			0 0.0%	5 9.8%	11 31.4%	11 52.9%	14 80.4%	7 94.1%	3 100%	8	32
Amox-clav-I+R[c] (50)			0 0.0%	5 10.0%	15 40.0%	15 70.0%	11 92.0%	4 100%		8	16
Mecillinam-R[d,e] (21)			0 0.0%	3 9.1%	8 29.5%	3 60.5%	4 85.9%	2 95.0%	1 100%	4	32
Trim-sulfa-I+R (56)			0 0.0%	4 7.1%	18 39.3%	12 60.7%	14 85.7%	8 100%		8	32
Cefadroxil-R[d,f] (52)			0 0.0%	5 9.6%	12 32.7%	13 57.7%	16 88.5%	6 100%		8	32

ND, not determined due to small number of isolates; I, intermediate; R, resistant.
[a] Interpreted by EUCAST breakpoints.
[b] FQ-I+R defined for isolates with levofloxacin MIC values corresponding to I or R breakpoints (≥ 1 mg/L) or ciprofloxacin MIC values corresponding to I or R breakpoints for indications other than meningitis (≥ 0.5 mg/L).
[c] Tested at 2:1 ratio and therefore interpreted by CLSI breakpoints.
[d] Using uncomplicated urinary tract infection only breakpoints.
[e] Tested by agar dilution.
[f] Tested by disk diffusion.

Abbreviations

CLSI, Clinical and Laboratory Standards Institute
ESBL, extended-spectrum β-lactamase
EUCAST, European Committee on Antimicrobial Susceptibility Testing
I, Susceptible, increased exposure
MDR, multidrug resistance
MIC, Minimal inhibitory concentration
ND, not determined
S, susceptible
R, resistant
UTI, urinary tract infection

Acknowledgements

This project has been funded in whole or in part with federal funds from the U.S. Department of Health and Human Services; Administration for Strategic Preparedness and Response; Biomedical Advanced Research and Development Authority under contract HHSO100201300011C.

Disclosures

This study at Element Iowa City was supported by GSK. Element Iowa City received compensation fees for services in relation to preparing the poster.

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Conclusions

- Gepotidacin demonstrated in vitro activity against contemporary *E. coli* and *K. pneumoniae* UTI isolates from Europe.
  - 99.7% of *E. coli* and 92.9% of *K. pneumo*niae isolates were inhibited by gepotidacin at or below the FDA approved breakpoint of ≤16 mg/L.
- This activity remained mostly unaffected by resistance to other oral standard-of-care antibiotics with $MIC_{50/90}$ values within 1-dilution of those described for the overall population.
- Of the comparator agents tested, only nitrofurantoin, fosfomycin, mecillinam, and nitroxoline had susceptibility rates greater than 90% against European *E. coli* isolates while no agents had susceptibility rates greater than 87% against European *K. pneumoniae* UTI isolates.

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