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In Vitro Activity of Gepotidacin and Comparators Against a Collection of *E. coli* and *S. saprophyticus* Urine Isolates Collected Worldwide During 2019-2021

S. J. Ryan Arends[1]; D Butler[2]; N Scangarella-Oman[2]; M Castanheira[1]; RE Mendes[1]

[1]JMI Laboratories, North Liberty, Iowa, USA; [2]GlaxoSmithKline plc., Collegeville, Pennsylvania, USA

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Introduction and Methods

– Gepotidacin is a novel, first-in-class triazaacenaphthylene antibiotic that inhibits bacterial DNA replication by a distinct mechanism of action, which confers activity against most strains of target pathogens, such as *Escherichia coli*, *Staphylococcus saprophyticus*, and *Neisseria gonorrhoeae*, including those resistant to current antibiotics. This study reports on results of the *in vitro* activity of gepotidacin when tested against contemporary *E. coli* and *S. saprophyticus* clinical isolates collected from patients with UTIs for a gepotidacin global surveillance study as part of the SENTRY Antimicrobial Surveillance Program.

Study design

– A total of 4,664 *E. coli* and 433 *S. saprophyticus* isolates were collected from 96 medical centres located in 25 countries.

– All isolates were recovered from patients with UTIs
  – 68.1% percent from ambulatory, emergency, family practice, and outpatient services

– Susceptibility tested by CLSI methods in a central laboratory (JMI Laboratories).

– MIC results for all comparators were interpreted per EUCAST or CLSI guidelines.

– The extended-spectrum β-lactamase (ESBL) phenotype in *E. coli* was characterized by isolates displaying aztreonam, ceftazidime, or ceftriaxone MIC values ≥ 2 mg/L.

Results and conclusions

- Gepotidacin activity against all *E. coli* isolates was similar across all 4 regions ($MIC_{50,}$ 2 mg/L; $MIC_{90,}$ 2-4 mg/L).
- ESBL prevalence varied by region with higher ESBL prevalence percentages were seen among LATAM (34.6%) and JPN (23.2%) isolates compared to EU (15.1%) and US (13.9%) isolates.
- Gepotidacin displayed MIC_{90} values ranging from 4-8 mg/L against ESBL isolates.
- Gepotidacin demonstrated potent in vitro activity against contemporary *E. coli* and including ESBL-producing isolates.
- Gepotidacin activity showed little variability across regions.

Activity of gepotidacin and comparators against isolates collected from urinary tract infections stratified by region

Organism (no. of isolates)	Europe		United States		Latin America		Japan	
Antimicrobial agent	$MIC_{50/90}$	%S [a]	$MIC_{50/90}$	%S	$MIC_{50/90}$	%S	$MIC_{50/90}$	%S
E. coli (4,664)	(n=1,341)		(n=2,752)		(n=272)		(n=299)	
Gepotidacin	2/2		2/2		2/4		2/2	
Ciprofloxacin	0.015/>4	75.5	0.015/>4	76.1	0.25/>4	54.4	0.12/>4	57.4
Amoxicillin-clavulanic acid [b]	8/16	79.0	4/16	81.9	8/16	74.1	4/16	88.6
Ceftriaxone [c]	≤0.06/>8	86.0	≤0.06/>8	87.1	≤0.06/>8	65.8	≤0.06/>8	77.9
Trimethoprim-sulfamethoxazole	≤0.12/>4	70.8	≤0.12/>4	70.0	1/4	50.7	≤0.12/>4	79.8
Nitrofurantoin [d]	16/32	99.0	16/32	99.0	16/32	97.4	16/32	99.3
Nitroxoline 30 µg disk [d]	-	100.0	-	99.9	-	100.0	-	100.0
Fosfomycin [e]	0.5/1	97.1	0.5/1	98.2	0.5/2	94.5	0.5/1	97.3
Mecillinam [e]	0.5/4	94.0	0.5/4	93.9	0.5/4	96.7	0.25/2	98.0
ESBL *E. coli* (746)	(n=201)		(n=382)		(n=94)		(n=69)	
Gepotidacin	2/4		2/4		2/8		1/4	
Ciprofloxacin	>4/>4	27.4	>4/>4	21.8	>4/>4	13.8	>4/>4	13.0
Amoxicillin-clavulanic acid [b]	16/32	48.8	16/32	47.4	16/32	46.6	8/32	69.6
Ceftriaxone [c]	>8/>8	7.0	>8/>8	7.3	>8/>8	1.1	>8/>8	4.3
Trimethoprim-sulfamethoxazole	>4/>4	40.8	>4/>4	38.7	>4/>4	29.8	≤0.12/>4	64.7
Nitrofurantoin [d]	16/32	97.5	16/32	96.6	16/32	95.7	16/32	98.6
Nitroxoline 30 µg disk [d]	-	100.0	-	100.0	-	100.0	-	100.0
Fosfomycin [e]	0.5/2	93.0	0.5/2	97.9	0.5/256	87.1	0.5/1	95.7
Mecillinam [e]	1/4	95.5	1/4	95.3	1/4	97.9	0.5/2	100.0

[a] Interpretations per EUCAST guidelines (2021).
[b] Using CLSI oral breakpoints for uncomplicated UTI; tested in a 2:1 ratio.
[c] Using non-meningitis breakpoints
[d] Uncomplicated UTI only, *E. coli*.
[e] Uncomplicated UTI only, *E. coli* (oral); tested by agar dilution.

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In Vitro Activity of Gepotidacin and Comparators Against a Collection of *E. coli* and *S. saprophyticus* Urine Isolates Collected Worldwide During 2019-2021

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Introduction

- Gepotidacin is a novel, first-in-class triazaacenaphthylene antibiotic that inhibits bacterial DNA replication by a distinct mechanism of action, which confers activity against most strains of target pathogens, such as *Escherichia coli*, *Staphylococcus saprophyticus*, and *Neisseria gonorrhoeae*, including those resistant to current antibiotics.
- Gepotidacin (GSK2140944) is in Phase 3 clinical development for the treatment of gonorrhea and uncomplicated urinary tract infections (UTIs).
- This study reports on results of the in vitro activity of gepotidacin and comparator agents when tested against contemporary *E. coli* and *S. saprophyticus* clinical isolates collected from patients with UTIs for a gepotidacin global surveillance study as part of the SENTRY Antimicrobial Surveillance Program.

Materials and Methods

- A total of 4,664 *E. coli* and 433 *S. saprophyticus* isolates were collected from 96 medical centres located in 25 countries.
  - Europe (EU), 17 countries, United States (US), Latin America (LATAM) 6 countries, and Japan (JPN).
  - All isolates were recovered from patients with UTIs, 68.1% percent from ambulatory, emergency, family practice, and outpatient services.
- Susceptibility tested by CLSI methods in a central laboratory (JMI Laboratories).
- MIC results for all comparators except amoxicillin-clavulanic acid were interpreted per EUCAST guidelines.
- Amoxicillin-clavulanic acid was tested at a 2:1 ratio and MICs were interpreted using CLSI breakpoints.
- Susceptibility to fosfomycin and mecillinam was determined by agar dilution.
- Fosfomycin testing was supplemented with glucose-6-phosphate (25 mg/L).
- The extended-spectrum β-lactamase (ESBL) phenotype in *E. coli* was characterized by isolates displaying aztreonam, ceftazidime, or ceftriaxone MIC values ≥ 2 mg/L.

Disclosures

This study at JMI Laboratories was supported by GlaxoSmithKline. JMI Laboratories received compensation fees for services in relation to preparing the poster.

Acknowledgments

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Gepotidacin demonstrated potent *in vitro* activity against contemporary *E. coli*, including ESBL-producing isolates, and *S. saprophyticus*.

Gepotidacin activity showed little variability across regions.

Table 1 Activity of gepotidacin and comparators against *E. coli* isolates collected from urinary tract infections stratified by region

Organism (no. of isolates)	Europe		United States		Latin America		Japan	
Antimicrobial agent	$MIC_{50/90}$	%S [a]	$MIC_{50/90}$	%S	$MIC_{50/90}$	%S	$MIC_{50/90}$	%S
E. coli (4,664)	(n=1,341)		(n=2,752)		(n=272)		(n=299)	
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Trimethoprim-sulfamethoxazole	≤0.12/>4	70.8	≤0.12/>4	70.0	1/4	50.7	≤0.12/>4	79.8
Nitrofurantoin [d]	16/32	99.0	16/32	99.0	16/32	97.4	16/32	99.3
Nitroxoline 30 µg disk [d]	-	100.0	-	99.9	-	100.0	-	100.0
Fosfomycin [e]	0.5/1	97.1	0.5/1	98.2	0.5/2	94.5	0.5/1	97.3
Mecillinam [e]	0.5/4	94.0	0.5/4	93.9	0.5/4	96.7	0.25/2	98.0
ESBL *E. coli* (746)	(n=201)		(n=382)		(n=94)		(n=69)	
Gepotidacin	2/4		2/4		2/8		1/4	
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Trimethoprim-sulfamethoxazole	>4/>4	40.8	>4/>4	38.7	>4/>4	29.8	≤0.12/>4	64.7
Nitrofurantoin [d]	16/32	97.5	16/32	96.6	16/32	95.7	16/32	98.6
Nitroxoline 30 µg disk [d]	-	100.0	-	100.0	-	100.0	-	100.0
Fosfomycin [e]	0.5/2	93.0	0.5/2	97.9	0.5/256	87.1	0.5/1	95.7
Mecillinam [e]	1/4	95.5	1/4	95.3	1/4	97.9	0.5/2	100.0

[a] Interpretations per EUCAST guidelines (2021).
[b] Using CLSI oral breakpoints for uncomplicated UTI; tested in a 2:1 ratio.
[c] Using non-meningitis breakpoints
[d] Uncomplicated UTI only, *E. coli.*
[e] Uncomplicated UTI only, *E. coli* (oral); tested by agar dilution.

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Results

- Gepotidacin activity against all *E. coli* isolates was similar across all 4 regions (Table 1).
  - MIC_{50} values were 2 mg/L.
  - MIC_{90} values ranged from 2 to 4 mg/L.
- Among *E. coli* isolates, lower susceptibilities and larger variation were observed for some comparators while other comparators remained active.
  - Amoxicillin-clavulanic acid ($MIC_{50/90}$, 4-8/16 mg/L, 74.1-88.6%S).
  - Ciprofloxacin ($MIC_{50/90}$, 0.015-0.25/>4 mg/L, 54.4-76.1%S).
  - Trimethoprim-sulfamethoxazole ($MIC_{50/90}$, ≤0.12-1/>4 mg/L, 50.7-79.8%S).
  - Fosfomycin ($MIC_{50/90}$, 0.5/1-2 mg/L; 94.5-98.2%S).
  - Mecillinam ($MIC_{50/90}$, 0.25-0.5/2-4 mg/L; 93.9-98.0%S).
  - Nitrofurantoin ($MIC_{50/90}$, 16/32 mg/L; 97.4-99.3%S).
  - Nitroxoline (99.9-100.0%S).
- ESBL prevalence varied by region (Table 1).
  - Higher ESBL prevalence percentages were seen among LATAM (34.6%) and JPN (23.2%) isolates compared to EU (15.1%) and US (13.9%) isolates.
- Gepotidacin displayed MIC_{50} values ranging from 1-2 mg/L and MIC_{90} values of 4 mg/L for all regions, except LATAM ($MIC_{90,}$ 8 mg/L) against ESBL isolates.
- Activities of ciprofloxacin (13.0-27.4%S), amoxicillin-clavulanic acid (46.6-69.6%S), and trimethoprim-sulfamethoxazole (29.8-64.7%S) were limited against ESBL *E. coli* isolates.

Table 2 Activity of gepotidacin and comparators against 433 *S. saprophyticus* isolates collected from urinary tract infections stratified by region

Organism (no. of isolates)	Europe		United States		Latin America		Japan	
Antimicrobial agent	$MIC_{50/90}$	%S [a]	$MIC_{50/90}$	%S	$MIC_{50/90}$	%S	$MIC_{50/90}$	%S
S. saprophyticus (433)	(n=123)		(n=238)		(n=28)		(n=44)	
Gepotidacin	0.06/0.12		0.06/0.12		0.06/0.12		0.06/0.12	
Ciprofloxacin [b]	0.25/0.5	100.0	0.5/0.5	100.0	0.5/0.5	96.4	0.25/0.5	95.5
Trimethoprim-sulfamethoxazole	≤0.5/≤0.5	97.6	≤0.5/≤0.5	99.2	≤0.5/16	82.1	≤0.5/≤0.5	97.7
Nitrofurantoin [c]	16/16	100.0	16/16	100.0	16/16	100.0	16/16	100.0

[a] Interpretations per EUCAST guidelines (2021).
[b] Interpreted as I – Susceptible, Increased exposure.
[c] Uncomplicated UTI only, *Staphylococcus saprophyticus.*

- Gepotidacin was active against *S. saprophyticus* isolates, with observed $MIC_{50/90}$ values of 0.06/0.12 mg/L for all regions (Table 2).
- Regardless of region, >95% of *S. saprophyticus* isolates were susceptible to ciprofloxacin (95.5-100.0%S) or nitrofurantoin (100.0%S).

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Contact

S. J. Ryan Arends, Ph.D.
JMI Laboratories
345 Beaver Kreek Centre, Suite A
North Liberty, Iowa 52317
Phone: (319) 665-3370
Fax: (319) 665-3371
Email: ryan-arends@jmilabs.com