IDWEEK 2020 | Poster#1262

Antimicrobial Activity of Gepotidacin Against Clinical Isolates of *Escherichia coli* and *Staphylococcus saprophyticus* Collected Worldwide in 2019

S. J. Ryan Arends[1], Deborah Butler[2], Nicole E. Scangarella-Oman[2], Mariana Castanheira, Rodrigo E. Mendes

[1] JMI Laboratories, North Liberty, Iowa, USA

[2] GlaxoSmithKline, Collegeville, PA

Introduction

- Gepotidacin (GSK2140944) is a novel triazaacenaphthylene bacterial type II topoisomerase inhibitor in Phase 3 clinical development for the treatment of uncomplicated urinary tract infections (UTI) and gonorrhea
- Gepotidacin inhibits bacterial DNA gyrase and topoisomerase IV by a unique mechanism
- This study reports on interim results from a global surveillance program to monitor the *in vitro* activity of gepotidacin and comparator agents when tested against contemporary *Escherichia coli* and *Staphylococcus saprophyticus* clinical isolates collected from patients with UTIs worldwide as part of the SENTRY Antimicrobial Surveillance Program

Materials and Methods

- A total of 1,467 *E. coli* and 92 *S. saprophyticus* isolates were collected from 73 medical centers located in the US (38 centers), Europe (27 centers in 14 countries), Asia-Pacific region (4 centers in Japan), and Latin America (4 centers in 3 countries)
- Isolates were from urinary tract infections, 70% of which were isolated from ambulatory, emergency, family practice, and outpatient medical services commonly associated with community acquired UTI
- Isolates were tested for susceptibility by CLSI reference methods in a central laboratory (JMI Laboratories)
- Susceptibility to mecillinam and fosfomycin was determined by agar dilution, and the latter included glucose-6-phosphate (25 µg/mL)
- MICs for comparators were interpreted, where available, according to CLSI and EUCAST criteria
- The extended-spectrum β-lactamase (ESBL) phenotype in *E. coli* was characterized by isolates displaying ceftriaxone MIC values ≥2µg/mL

Results

- Gepotidacin ($MIC_{50/90}$, 2/4 µg/mL) displayed activity against 1,467 *E. coli* isolates (Tables 1 and 4)
- Susceptibility rates of trimethoprim-sulfamethoxazole ($MIC_{50/90}$, ≤0.12/>16 µg/mL), ciprofloxacin ($MIC_{50/90}$, 0.015/>4 µg/mL), and amoxicillin-clavulanate ($MIC_{50/90}$, 8/16 µg/mL) were 67.1%, 72.9%, and 78.6% (CLSI), respectively (Table 1)
- Susceptibility rates of 99.0% for fosfomycin ($MIC_{50/90}$, 0.5/1 µg/mL), 97.4% for nitrofurantoin ($MIC_{50/90}$, 16/32 µg/mL), and 100% for meropenem (≤0.015/0.03 µg/mL) were seen against *E. coli* isolates (Table 1)
- Gepotidacin ($MIC_{50/90}$, 0.06/0.12 µg/mL) also was active against 92 *S. saprophyticus* isolates, with 100% of isolates inhibited at ≤0.25 µg/mL (Table 2)
- Susceptibility of *S. saprophyticus* isolates to trimethoprim-sulfamethoxazole, ciprofloxacin, or nitrofurantoin was 98.9-100% (CLSI), while fosfomycin showed little activity ($MIC_{50/90}$, 64/>256 µg/mL; 1.1% susceptible [EUCAST]) (Table 2)
- An ESBL phenotype was observed in 15.2% of *E. coli* isolates, and gepotidacin ($MIC_{50/90}$, 2/4 µg/mL) remained active against these isolates with activity similar to that obtained against non-ESBL *E. coli* ($MIC_{50/90}$, 2/2 µg/mL; Table 3)
- Activities of ciprofloxacin ($MIC_{50/90}$, >4/>4 µg/mL; 16.6% susceptible), cefazolin ($MIC_{50/90}$, >32/>32 µg/mL; 0.0% susceptible) and trimethoprim/sulfamethoxazole ($MIC_{50/90}$ >16/>16 µg/mL; 39.0% susceptible) were limited against ESBL isolates (Table 3)
- The oral drugs fosfomycin ($MIC_{50/90}$, 0.5/1 µg/mL; 96.9% susceptible) and nitrofurantoin ($MIC_{50/90}$, 16/32 µg/mL; 92.4% susceptible) remained active against ESBL isolates (Table 3)
- Similar MIC distributions and activities for gepotidacin were observed for isolates collected from outpatient and inpatient settings with 98.2% of all observed MIC results at ≤4 µg/mL (Table 4)

Gepotidacin demonstrated potent *in vitro* activity against contemporary *E. coli* and *S. saprophyticus* isolates causing UTI worldwide

Gepotidacin retained *in vitro* activity against phenotypic ESBL *E. coli* where some oral and intravenous options were limited

Table 1 Activity of gepotidacin and comparator antimicrobial agents tested against 1,467 *Escherichia coli* isolates

Antimicrobial agent	No. of isolates [a]	µg/L			CLSI[b]			EUCAST[b]		
		MIC_{50}	MIC_{90}	MIC range	%S	%I	%R	%S	%I	%R
Gepotidacin	1,467	2	4	0.06 to 32	—	—	—	—	—	—
Ciprofloxacin	1,466	0.015	>4	≤0.002 to >4	72.9	1.8	25.2	72.9	1.8	25.2
Levofloxacin	1,458	0.03	16	≤0.015 to >32	74.1	0.9	25.0	74.1	0.9	25.0
Fosfomycin	1,467	0.5	1	≤0.12 to >256	99.0 [c]	0.3	0.6	96.9 [d]		3.1
Mecillinam	1,467	0.5	8	0.06 to >32	92.9 [c]	1.6	5.5	92.9 [d]		7.1
Nitrofurantoin[i]	1,466	16	32	≤2 to >128	97.4	1.4	1.2	98.8 [d]		1.2
Trimethoprim-Sulfamethoxazole[i]	1,464	≤0.12	>16	≤0.12 to >16	67.1		32.9	67.1	0.8	32.1
Trimethoprim	1,466	0.5	>8	0.03 to >8	66.2		33.8	66.0 [d]		34.0
Sulfisoxazole	1,466	128	>256	≤4 to >256	59.6		40.4	—	—	—
Ampicillin	1,466	>64	>64	≤1 to >64	45.6	0.5	53.9	45.6 [d]		54.4
Amoxicillin-clavulanate										
IV	1,316	8	16	0.5 to >32	78.6	15.5	5.9	78.6		21.4
ORAL					78.6	15.5	5.9	98.4 [d]		1.6
Piperacillin-Tazobactam	1,461	2	4	0.25 to >128	97.5	1.2	1.3	94.9	2.7	2.5
Ceftazidime-Avibactam	1,465	0.12	0.25	≤0.015 to 1	100.0		0.0	100.0		0.0
Ceftolozane-Tazobactam	1,465	0.25	0.5	≤0.12 to >16	99.5	0.3	0.2	99.5		0.5
Cefazolin										
IV	1,314	2	>32	≤0.5 to >32	58.8 [e]	12.9	28.3		71.7 [f,g]	28.3
uUTI					80.1 [h]		19.9		71.7 [f,g]	28.3
Ceftriaxone	1,465	≤0.06	>8	≤0.06 to >8	84.6	0.1	15.2	84.6	0.1	15.2
Meropenem	1,465	≤0.015	0.03	≤0.015 to 1	100.0	0.0	0.0	100.0	0.0	0.0
Amikacin	1,465	2	8	≤0.25 to >32	99.7	0.1	0.3	98.5 [i]		1.5
Gentamicin	1,465	0.5	4	≤0.12 to >16	90.3	0.2	9.5	89.8 [i]		10.2

[a] Not all isolates were tested against all drugs at time of publication and represents interim data
[b] Criteria as published by CLSI (2020) and EUCAST (2020).
[c] Using oral breakpoints for urinary tract infection caused by *E. coli*.
[d] Using oral breakpoints for uncomplicated urinary tract infection.
[e] Using parenteral breakpoints for infection other than uncomplicated urinary tract.
[f] Intermediate can be interpreted as susceptible if drug exposure can be increased with a higher dosing regimen or higher concentration at the infection site (EUCAST 2020).
[g] Using parenteral breakpoints for urinary tract infection caused by *E. coli*.
[h] Using parenteral breakpoints for urinary tract infection.
[i] For infections originating from the urinary tract.
[j] Used only or for primarily treating UTIs.

Table 2 Activity of gepotidacin and comparator antimicrobial agents tested against 92 *Staphylococcus saprophyticus* isolates

Antimicrobial agent	No. of isolates	µg/mL			CLSI[a]			EUCAST[a]		
		MIC_{50}	MIC_{90}	MIC range	%S	%I	%R	%S	%I	%R
Gepotidacin	92	0.06	0.12	≤0.03 to 0.25						
Ciprofloxacin	92	0.25	0.5	0.25 to 0.5	100.0	0.0	0.0	[b]	100.0	0.0
Levofloxacin	92	0.5	0.5	0.25 to 1	100.0	0.0	0.0	[b]	100.0	0.0
Nitrofurantoin	92	16	32	8 to 32	100.0	0.0	0.0	100.0 [c]		0.0
Vancomycin	92	1	2	0.5 to 2	100.0	0.0	0.0	100.0		0.0
Trimethoprim-Sulfamethoxazole	92	≤0.5	≤0.5	≤0.5 to >16	98.9		1.1	98.9	0.0	1.1
Trimethoprim	92	0.25	0.5	0.12 to >8				95.7 [c]		4.3
Sulfisoxazole	92	32	256	8 to >256						
Penicillin	92	0.25	0.5	0.12 to >2	1.1		98.9			
Fosfomycin	92	64	>256	32 to >256				1.1 [d]		98.9

[a] Criteria as published by CLSI (2020) and EUCAST (2020).
[b] An arbitrary susceptible breakpoint of ≤0.001 µg/mL has been published by EUCAST indicating that susceptible should not be reported for this organism-agent combination and intermediate should be interpreted as "susceptible increased exposure" (EUCAST 2020).
[c] Using uncomplicated urinary tract infection only breakpoints.
[d] Administered via IV formulation

Table 3. Distribution of MIC values for gepotidacin and comparator antimicrobial agents tested against ESBL and non-ESBL *Escherichia coli*

Antimicrobial Agent	No. of Isolates[a]	MIC (µg/mL) ≤0.12	0.25	0.5	1	2	4	8	16	32	64	128	256
Non-ESBL E. coli isolates													
Gepotidacin	1,242	3 0.2%	10 1.0%	41 4.3%	374 34.5%	696 90.5%	106 99.0%	10 99.8%	2 100.0%				
Ciprofloxacin	1,242	973 78.3%	58 83.0%	19 84.5%	7 85.1%	3 85.3%	5 85.7%	177[b] 100.0%					
Trimethoprim/ sulfamethoxazole	1,241	783 63.1%	58 67.8%	42 71.2%	7 71.7%	6 72.2%	9 72.9%	6 73.4%	2 73.6%	328[b] 100.0%			
Amoxicillin/ clavulanic acid	1,116		0 0.0%	3 0.3%	20 2.1%	143 14.9%	438 54.1%	327 83.4%	140 96.0%	35 99.1%	10[b] 100.0%		
Meropenem	1,242	1241 99.9%	99.9%	1 100.0%									
Cefazolin	1,114			2 0.2%	342 30.9%	428 69.3%	170 84.6%	69 90.8%	42 94.5%	32 97.4%	29[b] 100.0%		
Ceftriaxone	1,242	1203 96.9%	26 99.0%	6 99.4%	5 99.8%	2 100.0%							
Fosfomycin	1,241	2 0.2%	66 5.5%	783 68.6%	312 93.7%	48 97.6%	7 98.1%	6 98.6%	1 98.7%	3 99.0%	6 99.4%	4 99.8%	3[b] 100.0%
Nitrofurantoin	1,241					14 1.1%	35 3.9%	300 28.1%	700 84.5%	171 98.3%	11 99.2%	7 99.8%	3[b] 100.0%
Amikacin	1,242		2 0.2%	1 0.2%	55 4.7%	651 57.1%	444 92.8%	86 99.8%	3 100.0%				
ESBL E. coli isolates													
Gepotidacin	223	0 0%	0 0.0%	12 5.4%	69 36.3%	100 81.2%	28 93.7%	6 96.4%	5 98.7%	3 100.0%			
Ciprofloxacin	223	31 13.9%	6 16.6%	8 20.2%	2 21.1%	2 22.0%	4 23.8%	170[b] 100.0%					
Trimethoprim/ sulfamethoxazole	223	75 33.6%	8 37.2%	2 38.1%	1 38.6%	1 39.0%	2 39.9%	2 40.8%	132[b] 100.0%				
Amoxicillin/ clavulanic acid	200				0 0.0%	2 1.0%	35 18.5%	68 52.5%	63 84.0%	21 94.5%	11[b] 100.0%		
Meropenem	223	222 99.6%	0 99.6%	0 99.6%	1 100.0%								
Cefazolin	200									0 0.0%	200[b] 100.0%		
Ceftriaxone	223					0 0.0%	6 2.7%	4 4.5%	213[b] 100.0%				
Fosfomycin	223	0 0.0%	6 2.7%	143 66.8%	52 90.1%	8 93.7%	2 94.2%	2 95.1%	1 95.1%	1 95.5%	3 96.9%	1 97.3%	6[b] 100.0%
Nitrofurantoin	223					1 0.4%	2 1.3%	65 30.5%	111 80.3%	27 92.4%	9 96.4%	7 99.6%	1[b] 100.0%
Amikacin	223		0 0.0%	1 0.4%	9 4.5%	83 41.7%	68 72.2%	43 91.5%	14 97.8%	1 98.2%	4[b] 100.0%		

Shading indicates breakpoints according to CLSI (2020) with susceptible highlighted in green, intermediate in yellow, resistant in red. Concentrations not tested are represented in gray.
[a] Not all isolates were tested against all drugs at time of publication and represents interim data
[b] Represent MIC values greater than the highest concentration tested

Table 4 Distribution of MIC values for gepotidacin tested against *Escherichia coli* isolates from ambulatory, emergency, family practice, and outpatient or other medical services

Antimicrobial Agent	No. of isolates[a]	MIC (µg/mL) ≤0.25	0.5	1	2	4	8	16	32	MIC_{50}	MIC_{90}
Ambulatory, emergency, family practice, and outpatient											
Gepotidacin	1,008[a]	6 0.6%	37 4.3%	304 34.4%	550 89.0%	93 98.2%	11 99.3%	5 99.8%	2 100.0%	2	4
Other[b]											
Gepotidacin	459[a]	7 1.5%	16 5.0%	140 35.5%	247 89.3%	41 98.3%	5 99.3%	2 99.8%	1 100.0%	2	4

[a] EBSL rates observed for ambulatory, emergency, family practice, and outpatient isolates were 12.8% compared to 20.5% for other isolates.
[b] Other medical services include: cardiothoracic/pulmonary, dialysis, general/GI, geriatrics, hematology/oncology, infectious disease, intensive care unit, internal medicine, long term care, neurology, neurosurgery, obstetrics/gynecology, orthopedics, pediatrics/neonate, rehabilitation, renal, surgery, transplant, trauma, urology/prostate

Acknowledgements

This study at JMI Laboratories was supported by GlaxoSmithKline plc. JMI Laboratories received compensation fees for services in relation to preparing the poster. This project has been funded in whole or in part with federal funds from the Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority, under OTAAgreement No. HHSO100201300011C.

References

Clinical and Laboratory Standards Institute (2020). *M100Ed30. Performance standards for antimicrobial susceptibility testing: 29th informational supplement.* Wayne, PA: CLSI.

Clinical and Laboratory Standards Institute (2018). *M07Ed11. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard: eleventh edition.* Wayne, PA: CLSI.

EUCAST (2020). Breakpoint tables for interpretation of MICs and zone diameters. Version 10.0, July 2020.

Contact Information

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