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In Vitro Activity of Gepotidacin, a Novel Triazaacenaphthylene Bacterial Topoisomerase Inhibitor, against a Broad Spectrum of Bacterial Pathogens

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Gepotidacin inhibits bacterial DNA replication through a mode different from that of fluoroquinolones. Gepotidacin and comparators were tested by broth and agar dilution against clinical isolates. The *in vitro* activities of gepotidacin were comparable against methicillin-susceptible and -resistant *Staphylococcus aureus* (MSSA and MRSA, respectively) isolates (MIC_{90}, 0.5 μg/ml). The gepotidacin MIC_{90}s were as follows (in micrograms per milliliter) for the indicated bacteria: *Streptococcus pyogenes*, 0.25; *Escherichia coli*, 2; *Moraxella catarrhalis*, ≤0.06; *Streptococcus pneumoniae* (0.25), *Haemophilus influenzae*, 1; *Clostridium perfringens*, 0.5; and *Shigella* spp., 1, including levofloxacin-resistant subsets. Gepotidacin warrants further investigation for clinical development.

Research and discovery programs targeting bacterial topoisomerases continue to evolve and are being sought to circumvent resistance to fluoroquinolones (1, 2). Gepotidacin (formerly GSK2140944), a novel triazaacenaphthylene bacterial type II topoisomerase inhibitor in clinical development, is currently being evaluated for oral and intravenous treatment of infections, including those caused by pathogens resistant to currently used antimicrobials. Gepotidacin selectively inhibits bacterial DNA gyrase and topoisomerase IV by a unique mechanism not utilized by any currently approved therapeutic agent (3). Structural data with type II topoisomerase/DNA gyrase reveals a novel binding mode that distinguishes the class from quinolones (3). Gepotidacin has *in vitro* activity against target pathogens carrying resistance determinants to fluoroquinolones (4). This study assessed the *in vitro* activities of gepotidacin and comparators against specified species from a global collection of clinical isolates.

Clinical isolates from a global collection with one isolate per patient were included. Organism identification was confirmed by a reference laboratory (IHMA). *Shigella* species identification was by latex agglutination (Wellcolex Color Shigella; Remel Europe Ltd., Dartford, United Kingdom). A total of 4,027 isolates were collected from 696 sites in 67 countries in Europe (n = 1597), North America (n = 1460), Latin America (n = 393), the Asia-Pacific (n = 304), and Africa-Middle East (n = 273). Species included *Streptococcus pneumoniae* (n = 549), *Haemophilus influenzae* (n = 981), *Moraxella catarrhalis* (n = 158), *Streptococcus pyogenes* (199), *Staphylococcus aureus* (n = 1,008), *Escherichia coli* (n = 1,010), *Shigella* spp. (n = 21), and *Clostridium perfringens* (n = 101). Isolates (82.5%) were mostly collected during the years 2010 to 2012. *H. influenzae* and *M. catarrhalis* isolates were collected between 2008 and 2012, and *Shigella* spp. were collected from 1997 to 2011. Vancomycin-nonsusceptible *S. aureus* isolates were obtained from NARSA (Eurofins Medinet, Inc.). Isolates were collected from lower respiratory (1,395), bloodstream (1,023), skin and skin structure (875), genitourinary (691), and other sources.

Gepotidacin and comparator agents were provided by their respective pharmaceutical companies or obtained from commercial manufacturers. MIC values were determined by broth microdilution and agar dilution for *C. perfringens* according to the Clinical and Laboratory Standards Institute (CLSI) guidelines and interpretations (5–7). FDA breakpoint criteria were used for tigecycline (8). No susceptibility breakpoint criteria have been proposed for gepotidacin.

Multidrug-resistant (MDR) *S. aureus* isolates were defined as methicillin-resistant *S. aureus* (MRSA) isolates resistant to three or more of the following antimicrobials: levofloxacin, azithromycin, clindamycin, linezolid, daptomycin, ceftaroline, vancomycin, and trimethoprim-sulfamethoxazole. Inducible clindamycin resistance was determined using the D-test. A screening extended-spectrum β-lactamase (ESBL)-positive phenotype was assigned to *Escherichia coli* isolates with ceftriaxone MICs of ≥2 μg/ml (7). Susceptibility testing of *C. perfringens* was performed according to CLSI methods (9). Quality control (QC) testing was performed each day of testing as specified by CLSI, using appropriate ATCC strains. CLSI-approved QC ranges reported by Ross et al. were used for validation of gepotidacin MIC testing (10).

Gepotidacin demonstrated activity against *S. aureus*, including MRSA and levofloxacin-resistant (FQR) isolates and those with MDR phenotypes, with MIC_{50} and MIC_{90} values of 0.25 and 0.5 μg/ml, respectively (Table 1). Macrolide, clindamycin (inducible and constitutive), linezolid, ceftaroline, daptomycin, and vancomycin resistance did not affect gepotidacin *in vitro* MICs (Table 2).

The *in vitro* activities of gepotidacin against *S. pneumoniae*, *S. pyogenes*, *H. influenzae*, and *M. catarrhalis*, including those resis-

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TABLE 1 *In vitro* activities of gepotidacin and comparator agents against pathogens associated with respiratory tract, urinary tract, and skin and skin structure infections

Organism (*n*)	Drug[a]	MIC (μg/ml)			% of isolates[b]		
		50%	90%	Range	Susceptible	Intermediate	Resistant
S. aureus (1,008)	Gepotidacin	0.25	0.5	≤0.06 to 2	NA	NA	NA
	Levofloxacin	0.5	>2	≤0.06 to >2	57.6	0.3	42.1
	Moxifloxacin	0.12	>1	0.03 to >1	58.0	0.1	41.9
	Ceftaroline	0.25	1	≤0.06 to >2	95.3	4.5	0.2
	Azithromycin	2	>4	≤0.25 to >4	51.5	1.9	46.6
	Linezolid	2	4	≤0.5 to >4	99.8	0.0	0.2
	Daptomycin	1	1	≤0.06 to >1	98.7	0.0	1.3
	Vancomycin	≤2	≤2	≤2 to >8	98.8	0.2	1.0
	Trim-sulfa	≤0.5	≤0.5	≤0.5 to >2	95.9	0.0	4.1
	Tigecycline	0.12	0.25	0.03 to 0.5	100	0.0	0.0
MRSA (490)	Gepotidacin	0.25	0.5	≤0.06 to 1	NA	NA	NA
	Levofloxacin	>2	>2	0.25 to >2	22.9	0.6	76.5
	Moxifloxacin	>1	>1	0.03 to >1	23.3	0.0	76.7
	Ceftaroline	0.5	1	0.25 to >2	90.4	9.2	0.4
	Azithromycin	>4	>4	1 to >4	23.1	2.0	74.9
	Linezolid	2	4	≤0.5 to >4	99.6	0.0	0.4
	Daptomycin	1	1	0.5 to >1	97.4	0.0	2.7
	Vancomycin	≤2	≤2	≤2 to >8	97.6	0.4	2.0
	Trim-sulfa	≤0.5	1	≤0.5 to >2	93.9	0.0	6.1
	Tigecycline	0.12	0.25	0.06 to 0.5	100	0.0	0.0
MSSA (518)	Gepotidacin	0.5	0.5	0.12 to 2	NA	NA	NA
	Levofloxacin	0.25	1	≤0.06 to >2	90.5	0.0	9.5
	Moxifloxacin	0.06	0.25	0.03 to >1	90.9	0.2	8.9
	Ceftaroline	0.25	0.25	≤0.06 to 1	100	0.0	0.0
	Azithromycin	2	>4	≤0.25 to >4	78.4	1.7	19.9
	Linezolid	2	4	≤0.5 to 4	100	0.0	0.0
	Daptomycin	1	1	≤0.06 to 1	100	0.0	0.0
	Vancomycin	≤2	≤2	≤2	100	0.0	0.0
	Trim-sulfa	≤0.5	≤0.5	≤0.5 to >2	97.9	0.0	2.1
	Tigecycline	0.12	0.25	0.03 to 0.5	100	0.0	0.0
Levofloxacin-resistant *S. aureus* (424)	Gepotidacin	0.25	0.5	≤0.06 to 1	NA	NA	NA
	Levofloxacin	>2	>2	>2	0.0	0.0	100
	Moxifloxacin	>1	>1	0.12 to >1	0.7	0.2	99.1
	Ceftaroline	0.5	2	0.12 to >2	88.9	10.6	0.5
	Azithromycin	>4	>4	1 to >4	21.7	2.4	75.9
	Linezolid	2	4	≤0.5 to >4	99.5	0.0	0.5
	Daptomycin	1	1	0.5 to >1	97.2	0.0	2.8
	Vancomycin	≤2	≤2	≤2 to >8	97.2	0.5	2.4
	Trim-sulfa	≤0.5	1	≤0.5 to >2	93.2	0.0	6.8
	Tigecycline	0.12	0.25	0.03 to 0.5	100	0.0	0.0
S. pneumoniae (549)	Gepotidacin	0.12	0.25	0.03 to 1	NA	NA	NA
	Levofloxacin	1	1	≤0.25 to >4	95.8	0.2	4.0
	Moxifloxacin	0.12	0.12	≤0.03 to >2	95.8	2.2	2.0
	Penicillin	≤0.06	2	≤0.06 to >8	69.6	14.8	15.7
	Amox-clav	0.03	2	≤0.015 to >4	90.7	1.3	8.0
	Ceftaroline	≤0.015	0.12	≤0.015 to 0.5	100	NA	NA
	Erythromycin	0.06	>0.5	≤0.015 to >0.5	70.5	0.2	29.3
	Linezolid	0.5	1	≤0.12 to 1	100	NA	NA
	Trim-sulfa	0.5	>2	≤0.06 to >2	70.1	6.9	23.0
	Tigecycline	0.015	0.03	≤0.008 to 0.06	100	NA	NA
Penicillin-susceptible *S. pneumoniae* (382)	Gepotidacin	0.12	0.25	0.03 to 1	NA	NA	NA
	Levofloxacin	1	1	≤0.25 to >4	98.2	0.3	1.6
	Moxifloxacin	0.12	0.12	≤0.03 to >2	98.2	0.5	1.3
	Penicillin	≤0.06	≤0.06	≤0.06	100	0.0	0.0
	Amox-clav	≤0.015	0.03	≤0.015 to >4	99.5	0.3	0.3

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TABLE 1 (Continued)

Organism (*n*)	Drug[a]	MIC (μg/ml)			% of isolates[b]		
		50%	90%	Range	Susceptible	Intermediate	Resistant
	Ceftaroline	≤0.015	≤0.015	≤0.015 to 0.25	100	NA	NA
	Erythromycin	0.06	>0.5	≤0.015 to >0.5	84.6	0.3	15.2
	Linezolid	0.5	1	≤0.12 to 1	100	NA	NA
	Trim-sulfa	0.25	1	≤0.06 to >2	88.5	4.7	6.8
	Tigecycline	0.015	0.03	≤0.008 to 0.06	100	NA	NA
Penicillin-intermediate *S. pneumoniae* (81)	Gepotidacin	0.12	0.25	0.03 to 0.5	NA	NA	NA
	Levofloxacin	1	1	≤0.25 to >4	95.1	0.0	4.9
	Moxifloxacin	0.12	0.12	0.06 to >2	95.1	2.5	2.5
	Penicillin	0.25	1	0.12 to 1	0.0	100	0.0
	Amox-clav	0.12	2	≤0.015 to >4	96.3	1.2	2.5
	Ceftaroline	≤0.015	0.06	≤0.015 to 0.25	100	NA	NA
	Erythromycin	0.06	>0.5	≤0.015 to >0.5	56.8	0.0	43.2
	Linezolid	0.5	1	0.25 to 1	100	NA	NA
	Trim-sulfa	1	>2	0.12 to >2	46.9	17.3	35.8
	Tigecycline	0.03	0.03	≤0.008 to 0.03	100	NA	NA
Penicillin-resistant *S. pneumoniae* (86)	Gepotidacin	0.12	0.25	0.06 to 0.5	NA	NA	NA
	Levofloxacin	1	>4	0.5 to >4	86.1	0.0	14.0
	Moxifloxacin	0.12	2	≤0.03 to >2	86.1	9.3	4.7
	Penicillin	4	4	2 to >8	0.0	0.0	100
	Amox-clav	4	>4	≤0.015 to >4	46.5	5.8	47.7
	Ceftaroline	0.12	0.25	≤0.015 to 0.5	100	NA	NA
	Erythromycin	>0.5	>0.5	≤0.015 to >0.5	20.9	0.0	79.1
	Linezolid	0.5	1	≤0.12 to 1	100	NA	NA
	Trim-sulfa	>2	>2	≤0.06 to >2	10.5	7.0	82.6
	Tigecycline	0.03	0.03	≤0.008 to 0.06	100	NA	NA
Levofloxacin-nonsusceptible *S. pneumoniae* (23)	Gepotidacin	0.25	0.5	0.06 to 0.5	NA	NA	NA
	Levofloxacin	>4	>4	4 to >4	0.0	4.4	95.7
	Moxifloxacin	2	>2	2 to >2	0.0	52.2	47.8
	Penicillin	2	4	≤0.06 to >8	30.4	17.4	52.2
	Amox-clav	2	>4	≤0.015 to >4	60.9	4.4	34.8
	Ceftaroline	0.06	0.25	≤0.015 to 0.5	100	NA	NA
	Erythromycin	>0.5	>0.5	≤0.015 to >0.5	13.0	0.0	87.0
	Linezolid	0.5	1	≤0.12 to 1	100	NA	NA
	Trim-sulfa	>2	>2	0.12 to >2	17.4	8.7	73.9
	Tigecycline	0.03	0.03	≤0.008 to 0.06	100	NA	NA
S. pyogenes (199)	Gepotidacin	0.25	0.25	0.03 to 0.5	NA	NA	NA
	Levofloxacin	0.5	1	≤0.25 to 4	99.5	0.5	0
	Ceftriaxone	0.03	0.03	≤0.015 to 0.12	100	NA	NA
	Ceftaroline	≤0.015	≤0.015	≤0.015	100	NA	NA
	Erythromycin	≤0.015	0.06	≤0.015 to >0.5	92.5	0.0	7.5
	Linezolid	0.5	0.5	0.5 to 1	100	NA	NA
	Daptomycin	0.12	0.12	≤0.03 to 0.5	100	NA	NA
	Vancomycin	0.25	0.5	0.25 to 0.5	100	NA	NA
	Tigecycline	0.015	0.03	≤0.008 to 0.06	100	NA	NA
H. influenzae (981)	Gepotidacin	0.5	1	≤0.015 to 8	NA	NA	NA
	Levofloxacin	0.015	0.03	≤0.004 to >2	99.8	0.0	0.2
	Moxifloxacin	0.015	0.03	≤0.004 to >1	99.8	0.0	0.2
	Flucloxacillin	>8	>8	≤1 to >8	9.9	0.0	90.1
	Amox-clav	≤1	2	≤1 to 8	99.5	0.0	0.5
	Cefuroxime	1	2	≤0.12 to >8	99.3	0.5	0.2
	Ceftriaxone	≤0.03	≤0.03	≤0.03 to >2	99.8	0.0	0.2
	Ceftaroline	≤0.015	0.03	≤0.015 to 2	99.8	0.0	0.2
	Azithromycin	≤0.5	1	≤0.5 to >4	98.9	0.0	1.1
	Trim-sulfa	0.06	>2	≤0.015 to >2	73.2	3.8	23.0
	Tigecycline	0.25	0.5	≤0.03 to >0.5	55.4	0.0	44.7

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TABLE 1 (Continued)

Organism (*n*)	Drug[a]	MIC (μg/ml)			% of isolates[b]		
		50%	90%	Range	Susceptible	Intermediate	Resistant
M. catarrhalis (158)	Gepotidacin	≤0.06	≤0.06	≤0.06 to 0.12	NA	NA	NA
	Levofloxacin	≤0.06	0.12	≤0.06 to 0.5	100	0.0	0.0
	Flucloxacillin	>4	>4	≤0.25 to >4	16.5	0.0	83.5
	Amox-clav	0.12	0.25	≤0.06 to 1	100	0.0	0.0
	Cefuroxime	1	2	≤0.25 to 4	100	0.0	0.0
	Ceftriaxone	≤0.5	≤0.5	≤0.5 to 2	100	0.0	0.0
	Erythromycin	≤1	≤1	≤1 to >4	98.7	0.0	1.3
	Azithromycin	≤0.06	≤0.06	≤0.06 to >4	98.7	0.0	1.3
	Trim-sulfa	≤0.25	0.5	≤0.25 to 4	94.9	4.4	0.6
E. coli (1,010)	Gepotidacin	2	2	≤0.03 to >32	NA	NA	NA
	Levofloxacin	0.06	>4	≤0.004 to >4	72.5	1.6	25.9
	Moxifloxacin	0.06	>4	≤0.004 to >4	NA	NA	NA
	Ceftriaxone	0.06	>4	≤0.015 to >4	82.3	0.1	17.6
	Ceftaroline	0.12	>2	≤0.015 to >2	74.6	3.6	21.8
	Pip-tazo	4	32	≤0.25 to >64	89.7	4.5	5.8
	Fosfomycin	≤2	8	≤2 to >256	98.9	0.8	0.3
	Nitrofurantoin	16	32	≤2 to >64	94.5	4.9	0.6
	Trim-sulfa	≤0.5	>32	≤0.5 to >32	62.3	0.0	37.7
	Tigecycline	0.25	0.5	0.03 to 2	100	0.0	0.0
Levofloxacin-susceptible *E. coli* (732)	Gepotidacin	2	2	≤0.03 to 16	NA	NA	NA
	Levofloxacin	0.03	0.5	≤0.004 to 2	100	0.0	0.0
	Moxifloxacin	0.06	0.5	≤0.004 to 4	NA	NA	NA
	Ceftriaxone	0.06	0.12	≤0.015 to >4	94.5	0.0	5.5
	Ceftaroline	0.06	1	≤0.015 to >2	86.9	3.3	9.8
	Pip-tazo	2	8	≤0.25 to >64	95.6	1.2	3.2
	Fosfomycin	≤2	4	≤2 to >4	99.0	1.0	0.0
	Nitrofurantoin	16	32	≤2 to >64	97.3	2.6	0.1
	Trim-sulfa	≤0.5	>32	≤0.5 to >32	74.2	0.0	25.8
	Tigecycline	0.25	0.5	0.03 to 2	100	0.0	0.0
Levofloxacin-nonsusceptible *E. coli* (278)	Gepotidacin	2	4	0.06 to >32	NA	NA	NA
	Levofloxacin	>4	>4	4 to >4	0.0	5.8	94.2
	Moxifloxacin	>4	>4	0.5 to >4	NA	NA	NA
	Ceftriaxone	1	>4	≤0.015 to >4	50.0	0.4	49.6
	Ceftaroline	>2	>2	0.03 to >2	42.5	4.3	53.2
	Pip-tazo	4	>64	≤0.25 to >64	74.0	13.0	13.0
	Fosfomycin	≤2	8	≤2 to >256	98.6	0.3	1.1
	Nitrofurantoin	16	64	8 to >64	87.4	10.8	1.8
	Trim-sulfa	>32	>32	≤0.5 to >32	30.9	0.0	69.1
	Tigecycline	0.5	1	0.12 to 2	100	0.0	0.0

[a] Trim-sulfa, trimethoprim-sulfamethoxazole. For this drug combination, the data are expressed as the trimethoprim concentration only; it was tested as a 1:19 ratio of trimethoprim-sulfamethoxazole. Amox-clav, amoxicillin-clavulanic acid. For this drug combination, the data are expressed as the amoxicillin concentration only; it was tested as a 2:1 ratio of amoxicillin-clavulanic acid. Pip-tazo, piperacillin-tazobactam.

[b] Susceptibilities/phenotypes are defined by CLSI document M100-S25 (7), where available. For tigecycline, susceptibility is defined by FDA breakpoints; NA, no breakpoints defined.

tant to penicillin, macrolides, and levofloxacin, are also shown in Table 1. The MIC_{90} of gepotidacin against *S. pneumoniae* and *S. pyogenes* was 0.25 μg/ml. A single MIC_{90} doubling dilution increase to 0.5 μg/ml for gepotidacin was observed against levofloxacin-nonsusceptible (MIC, ≥4 μg/ml) *S. pneumoniae* isolates ($n = 23$). The gepotidacin MIC_{90} remained 0.25 μg/ml regardless of the penicillin susceptibility of the isolate. The highest MIC of gepotidacin was for an *S. pneumoniae* isolate from the United States (gepotidacin MIC, 1 μg/ml). Regardless of beta-lactamase production, the MIC_{90} of gepotidacin was 1 μg/ml against *H. influenzae*. The MIC_{90} of gepotidacin was ≤0.06 μg/ml against *M. catarrhalis*.

Gepotidacin demonstrated an MIC_{90} of 2 μg/ml against the *E. coli* isolates tested, and among levofloxacin-nonsusceptible isolates, the MIC_{90} of gepotidacin increased to 4 μg/ml (Table 1). Gepotidacin MIC_{90}s increased from 2 to 4 μg/ml against nitrofurantoin-nonsusceptible, fosfomycin-nonsusceptible, and ESBL screen-positive populations (Table 2). Nearly 75% of the ESBL screen-positive *E. coli* isolates were resistant to levofloxacin. The MIC_{90} of gepotidacin was 4 μg/ml against this subset (Table 2). The gepotidacin MIC against five geographically unrelated *E. coli* isolates was ≥16 μg/ml.

The gepotidacin MIC_{50} and MIC_{90} values against *C. perfringens* were 0.12 and 0.5 μg/ml, respectively, and those against *Shigella*

TABLE 2 Frequency distribution of gepotidacin tested against drug-resistant phenotypes of *S. aureus* and *E. coli*

Organism and phenotype (*n*)[a]	No. of isolates with indicated gepotidacin MIC (cumulative %)[b]										
	≤0.06[c]	0.12	0.25	0.5	1	2	4	8	16	32	>32
S. aureus											
All isolates (1,008)	1 (0.1)	71 (7.1)	481 (54.9)	**425 (97.0)**	29 (99.9)	1 (100)					
MDR-MRSA (183)	1 (0.6)	19 (10.9)	92 (61.2)	**67 (97.8)**	4 (100)						
Ceftaroline NS (47)	0 (0.0)	10 (21.3)	24 (72.3)	**12 (97.9)**	1 (100)						
Daptomycin-NS (13)	0 (0.0)	1 (7.7)	6 (53.9)	**6 (100)**							
VISA/VRSA (12)	0 (0.0)	1 (8.3)	**10 (91.7)**	1 (100)							
Constitutive clindamycin resistant (161)	0 (0.0)	4 (2.5)	85 (55.3)	**67 (96.9)**	5 (100)						
Inducible clindamycin resistant (122)	0 (0.0)	8 (6.6)	64 (59.0)	**49 (99.2)**	1 (100)						
E. coli											
All isolates (1,010)	7 (0.7)	4 (1.1)	3 (1.4)	54 (6.7)	397 (46.0)	**445 (90.1)**	72 (97.2)	23 (99.5)	2 (99.7)	2 (99.9)	1 (100)
Nitrofurantoin NS (55)	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.5)	17 (36.4)	26 (83.6)	**4 (90.9)**	3 (96.4)	0 (96.4)	1 (98.2)	1 (100)
Fosfomycin NS (11)	0 (0.0)	0 (0.0)	0 (0.0)	1 (9.1)	3 (36.4)	4 (72.7)	**2 (90.9)**	1 (100)			
ESBL (179)[d]	0 (0.0)	0 (0.0)	0 (0.0)	10 (5.6)	60 (39.1)	77 (81.1)	**19 (92.7)**	10 (98.3)	1 (98.9)	1 (99.4)	1 (100)

[a] Phenotypes are defined by CLSI document M100-S25 (7). NS, nonsusceptible; MDR, multidrug-resistant *S. aureus*; VISA, vancomycin-intermediate *S. aureus*; VRSA, vancomycin-resistant *S. aureus*.
[b] MIC_{90} values are in bold.
[c] MICs in micrograms per milliliter.
[d] ESBL phenotype based upon a ceftriaxone MIC value of ≥2 μg/ml (CLSI).

species were 0.5 and 1 μg/ml, respectively. None of the 21 *Shigella* species isolates tested were resistant to ciprofloxacin, gentamicin, or ceftriaxone. Resistance to ampicillin, trimethoprim-sulfamethoxazole, and tetracycline ranged from 47.6% to 66.7%. The MICs of gepotidacin were not affected by the presence of these resistance mechanisms and remained in the wild-type distribution.

Gepotidacin is a broad-spectrum antibacterial agent with a novel mechanism of action. Initial phase I studies with escalating oral dosing have demonstrated a safety profile consistent with other marketed antibiotics, and significant changes in cardiac parameters were not shown for this compound (11). Gepotidacin has progressed into a phase II study that is examining the treatment of subjects with suspected or confirmed Gram-positive acute bacterial skin and skin structure infections (http://clinicaltrials.gov). Pharmacodynamic profiling of gepotidacin in a murine lung infection model supports further investigation of this compound for treating respiratory infections (12).

As gepotidacin continues to progress through clinical development, careful monitoring of its continued *in vitro* activity against target pathogens is warranted to determine if changes in resistance trends affects this drug's activity (1, 4, 12). In this current study, gepotidacin demonstrated *in vitro* activity against a robust collection of fastidious, nonfastidious, aerobic, and anaerobic Gram-positive and -negative species, including many isolates resistant to levofloxacin and drugs of other classes. These *in vitro* data support further investigation of gepotidacin for the treatment of infections caused by *S. aureus*, *H. influenzae*, *S. pneumoniae*, *S. pyogenes*, *E. coli*, *M. catarrhalis*, *Shigella* spp., or *C. perfringens*, including, where applicable, those caused by isolates exhibiting drug-resistant phenotypes.

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