Saturday – AAR-786

Lefamulin Activity Against Respiratory Tract Pathogens Collected in the 2017 Global SENTRY Antimicrobial Surveillance Program

INTRODUCTION

- Community-acquired bacterial pneumonia (CABP) is a common infection-related cause of hospitalization and/ or death in older adults in Europe, Latin America, Asia-Pacific, and North America¹⁻⁵
- Annual CABP care costs an estimated €10.1 billion¹ ir Europe and >\$17 billion in the United States⁵
- Increasing rates of antibiotic resistance among CABPcausing pathogens and safety concerns around available antibiotics drive a worldwide need for new CABP treatment options⁶
- Lefamulin (LEF) is a first-in-class pleuromutilin antibiotic in phase 3 clinical development for intravenous (IV) and oral treatment of CABP^{7,8}
- LEF selectively inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit at the Aand P-sites in the peptidyl transferase center^{7,8} (Figure 1
- LEF was noninferior to moxifloxacin in two phase 3 trials (one IV-to-oral switch study and one oral-only study) in adults with CABP^{7,9}
- The objective of this study was to evaluate the in vitro activity of LEF and comparators against a contemporary global set of respiratory tract pathogens

Figure 1. (A) Structure of Lefamulin and (B) Lefamulin in the Peptidyl Transferase Center Overlapping With A- and P-site tRNA



METHODS

- As part of the 2017 global SENTRY Antimicrobial Surveillance Program, 3190 unique isolates (1 per patient) were collected from patients with communityacquired respiratory tract infections (77.2%) or hospitalized patients with pneumonia (22.8%)
- Isolates were collected from 109 sites in 33 countries
- 40.3% of isolates were collected from the United States, 41.1% from Europe, 10.3% from Asia Pacific, and 8.2% from Latin America
- Minimum inhibitory concentration (MIC) for LEF and comparators was determined using Clinical and Laboratory Standards Institute (CLSI) broth microdilution¹⁰; susceptibility was evaluated using the CLSI (2019) breakpoints¹¹

RESULTS

• LEF showed potent antibacterial activity against all tested CABP pathogens and its activity was not affected by resistance to other antibiotic classes (Table 1)

Streptococcus pneumoniae

- S. pneumoniae isolates showed resistance to macrolides (35.8% resistant to erythromycin), penicillin (14.4%), trimethoprim-sulfamethoxazole (18.4%), and tetracycline (24.9%), whereas they were largely susceptible (≥84%) to the tested cephalosporins and fluoroquinolones (Table 2)
- LEF inhibited 99.5% of *S. pneumoniae* isolates at $\leq 0.25 \ \mu g/mL$, with MIC_{50/90} values of 0.06/0.12 $\mu g/mL$ for multidrug-resistant and penicillin-resistant subsets and 0.12/0.25 µg/mL for the macrolide-resistant subset (Table 3)

Staphylococcus aureus

- S. aureus isolates overall, and particularly methicillinresistant S. aureus (MRSA) strains, were resistant to macrolides (40.2% and 70.2%, respectively, resistant to erythromycin) and fluoroquinolones (26.4% and 67.5%, respectively, resistant to moxifloxacin; **Table 4**)
- LEF showed potent activity against *S. aureus* as well as MRSA, with MIC_{50/90} values of 0.06/0.12 μ g/mL for both (Table 4)

Haemophilus influenzae

- *H. influenzae* isolates were largely susceptible to all antimicrobial agents except ampicillin (27.6% resistant) and trimethoprim-sulfamethoxazole (33.1% resistant; Table 5)
- LEF inhibited *H. influenzae* isolates (Table 5), including the β -lactamase-positive subset (*n*=144; data not shown), with MIC_{50/90} values of 0.5/2 μ g/mL for both

Haemophilus parainfluenzae

- *H. parainfluenzae* isolates were largely susceptible to all antimicrobial agents except ampicillin (15.2% resistant), clarithromycin (8.7% resistant), and trimethoprimsulfamethoxazole (16.3% resistant; **Table 5**)
- LEF inhibited *H. parainfluenzae* isolates at MIC_{50/90} values of 1/2 µg/mL (Table 5)

Moraxella catarrhalis

- M. catarrhalis isolates included a substantial proportion of β -lactamase producers (96.9%) and were largely susceptible to all tested antimicrobial agents (Table 5)
- LEF inhibited *M. catarrhalis* isolates at concentrations of ≤0.12 µg/mL (MIC_{50/90} values of 0.06/0.06 µg/mL; Table 5)

β-hemolytic and viridans group streptococci

- LEF showed potent activity against both β-hemolytic and viridans group streptococci, with MIC_{50/90} values of 0.03/0.03 µg/mL and 0.06/2 µg/mL, respectively (Table 1)
- β-hemolytic and viridans group streptococcal isolates showed resistance to clindamycin (11.1% and 23.1% respectively), erythromycin (33.3% and 46.2%, respectively), and levofloxacin (5.6% and 7.7%, respectively; data not shown)



Table 2. Activity of Lefamulin and Comparators Against S. pneumoniae





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Table 1. Activity of Lefamulin and Comparators Against CABP Pathogens

MIC _{50/90} , μg/mL											
n	Lefamulin	Amoxicillin- clavulanic acid	Azithromycin	Ceftriaxone	Moxifloxacin	Tigecycline					
1862	0.12/0.25	≤0.03/2	0.06/>4	0.03/1	0.12/0.25	0.06/0.06					
268	0.06/0.12	2/>4	>4/>4	1/2	0.12/0.25	0.06/0.12					
667	0.12/0.25	0.5/>4	>4/>4	0.5/2	0.12/0.25	0.06/0.06					
162	0.06/0.12	4/>4	>4/>4	1/2	0.12/0.25	0.06/0.12					
428	0.06/0.12	_	0.5/>32	0.25/1§	≤0.06/>4	0.12/0.12					
151	0.06/0.12	_	>32/>32	1/2§	2/>4	0.12/0.25					
550	0.5/2	1/2	1/2	0.004/0.015	0.03/0.06	0.25/0.5					
92	1/2	0.5/1	0.5/2	0.004/0.06	0.06/>2	0.25/0.5					
227	0.06/0.06	≤0.25/≤0.25	0.015/0.03	0.25/1	0.06/0.06	0.06/0.06					
18	0.03/0.03	—	0.03/8	0.06/0.06	0.12/0.25	0.06/0.06					
13	0.06/2	_	0.03/>16	0.12/0.5	0.12/0.25	0.06/0.12					
	n 1862 667 162 162 151 550 92 1227 18 13	Image: Normal Stress of Control Stress of Contrel Stress of Contrel Stress of Contrel Str	n LefamulinAmoxicillincial clavulanic acid18620.12/0.25 $\leq 0.03/2$ 2680.06/0.12 $2/>4$ 6670.12/0.25 $0.5/>4$ 1620.06/0.12 $4/>4$ 4280.06/0.12 $-$ 1510.06/0.12 $-$ 5500.5/2 $1/2$ 92 $1/2$ $0.5/1$ 92 $1/2$ $0.5/1$ 18 $0.03/0.03$ $-$ 13 $0.06/2$ $-$	Image: Mic_solve big stressImage: Nic_solve big stressImag	MIC solved in the transmission of the transmission of transmissio	MIC50090, $\mu g/mL$ <i>n</i> LefamulinAmoxicillin- clavulanic acidAzithromycinCeftriaxoneMoxifloxacin18620.12/0.25 $\leq 0.03/2$ 0.06/>40.03/10.12/0.252680.06/0.12 $2/>4$ $>4/>4$ 1/20.12/0.256670.12/0.250.5/>4 $>4/>4$ 0.5/20.12/0.251620.06/0.12 $4/>4$ $>4/>4$ 1/20.12/0.251620.06/0.12 $4/>4$ $>4/>4$ 1/20.12/0.251620.06/0.12 $4/>4$ $>4/>4$ 1/20.12/0.251630.06/0.12 $$ $0.5/>320.25/1§\leq 0.06/>41510.06/0.12>32/>321/2§2/>45500.5/21/21/20.004/0.0150.03/0.06921/20.5/10.5/20.015/0.030.25/10.06/0.26180.03/0.030.03/8II0.06/0.060.12/0.25130.06/20.03/>16II0.12/0.50.12/0.25$					

CABP=community-acquired bacterial pneumonia; CLSI=Clinical and Laboratory Standards Institute; MIC=minimun concentration: MIC₅₀=minimum concentration at which 50% of isolates were inhibited: MIC₆₀=minimum

*Applying oral CLSI breakpoint of ≥2 μg/mL. ⁺Using erythromycin breakpoint. [‡]Resistant to oral penicillin, erythromycin, and tetracycline. [§]Ceftaroline tested instead of ceftriaxone. [¶]Organisms include: Streptococcus pyogenes (n=8) and S. agalactiae (n=10). "Erythromycin tested instead of azithromycin. ^Organisms include: Streptococcus anginosus (n=1), S. anginosus group (*n*=1), *S. gallolyticus* (*n*=2), *S. mitis* group (*n*=7), *S. parasanguinis* (*n*=1), *S. salivarius/vestibularis* (*n*=1).

		µg/ml	_	CLSI*								
timicrobial Agent		MIC ₉₀	Range	%S	%	%R						
oneumoniae (n=1862)												
Lefamulin	0.12	0.25	≤0.008–1	[100.0] ⁺								
Amoxicillin-clavulanic acid	≤0.03	2	≤0.03–>4	93.1	2.2	4.8						
Azithromycin	0.06	>4	≤0.03–>4	63.7	0.6	35.7						
Ceftaroline	≤0.008	0.12	≤0.008–>1	99.9	—	_						
Ceftriaxone	0.03	1	≤0.015–>2	83.8 [‡] 94.9 [§]	11.2 4.1	5.1 1.0						
Clindamycin	≤0.25	>2	≤0.25–>2	80.8	0.4	18.8						
Erythromycin	0.03	>16	≤0.015–>16	63.7	0.4	35.8						
Levofloxacin	1	2	0.25->4	98.0	0.3	1.7						
Moxifloxacin	0.12	0.25	≤0.03–>4	98.4	1.1	0.4						
Penicillin	0.03	2	≤0.008–>4	64.9¶ 64.9∥ 94.0^	20.7 _ 5.3	14.4 35.1 0.6						
Tetracycline	0.5	>4	0.06–>4	74.8	0.3	24.9						
Tigecycline	0.06	0.06	0.015-0.25	93.7#	_	_						
Trimethoprim- sulfamethoxazole	0.25	>4	≤0.12–>4	71.4	10.2	18.4						

LSI=Clinical and Laboratory Standards Institute; I=intermediate; MIC=minimum inhibitory concentration; MIC₅₀=minimur concentration at which 50% of isolates were inhibited; MIC₉₀=minimum concentration at which 90% of isolates were inhibited; R=resistant; S=susceptible.

*Criteria as published by CLSI 2019. [†]Percentage inhibited at proposed lefamulin breakpoint of ≤1 µg/mL for S. pneumoniae shown for reference. [‡]Using meningitis breakpoints. [§]Using nonmeningitis breakpoints. [¶]Using oral

breakpoints. ^{II}Using parenteral, meningitis breakpoints. [^]Using parenteral, nonmeningitis breakpoints. [#]US Food and Drug Administration breakpoints accessed February 2018.

Resistant S. pn	Resistant S. pneumoniae					ua/mLCLSI*						H. influenzae, H. parainfluenzae, and M. catarrhalis								
		μg/mL			CLSI*				P9/						µg/mL		nL	CLSI		
Antimicrobial Agent		MIC ₉₀	Range	%S	%	%R	Antimicrobial Agent	MIC ₅₀	MIC ₉₀	Range	%S	%	%R	Antimicrobial Agent	MIC	MIC	Range	%S	%	%R
Penicillin-resistant [†] S. pne	umonia	e (<i>n</i> =26	8)				S_{i} aureus (n=428)												/01	
Lefamulin	0.06	0.12	0.015–0.5	[100.0] [‡]										H. influenzae (n=550)						
Amoxicillin-clavulanic acid	2	>4	1—>4	51.7	15.0	33.3	Lefamulin	0.06	0.12	0.015–1	[99.5]†			Lefamulin	0.5	2	0.015–4	[100.0]†		
Azithromycin	>4	>4	≤0.03->4	15.7	0.7	83.6	Azithromycin	0.5	>32	0.06_>32	56.8	0.0	13.2	Amoxicillin-clavulanic acid	1	2	≤0.06–16	98.9	_	1.1
Cettaroline	0.12	0.25	0.03->1	99.3 5.28	-	-	Azitinomycin	0.5	- 52	0.00->32	50.0	0.0	43.2		0.5	~		67.2	E 1	07.6
Centraxone	I	2	0.25-2	5.∠³ 66.0¶	27.6	6.3	Ceftaroline	0.25	1	≤0.06–4	92.5 [‡]	7.5	0.0	Ampicillin	0.5	>8	≤0.12 - 28	67.3	5.1	27.0
Clindamycin	>2	>2	≤0.25–>2	46.3	0.7	53.0	Clindomyoin	0.06	>2	<0.02 >2	01.2	0.0	10 7	Azithromycin	1	2	≤0.12–>8	99.1	—	-
Erythromycin	>16	>16	≤0.015–>16	15.7	0.0	84.3	Cindantycin	0.00	~2	≤0.032	01.3	0.0	10.7	Cefepime	0.12	0.25	≤0.015–>2	99.8	-	-
Levofloxacin	1	2	0.5–>4	96.6	0.0	3.4	Doxycycline	0.12	1	≤0.06–>8	95.1	3.0	1.9	Ceftriaxone	0.004	0.015	≤0.002–0.25	100.0	_	_
Moxifloxacin	0.12	0.25	0.06->4	97.4	1.1	1.5		0.05	> 0		50.0	25	40.0	Ciprofloyagin	0.015	0.015	0.009 >1	08.0		
Penicillin	2	4	2–>4	0.0 0.0 [^]	0.0	100.0	Erythromycin	0.25	>8	≤0.06>8	56.3	3.5	40.2	Cipronoxacin	0.015	0.015	0.000-21	90.9	_	_
				58.6#	36.9	4.5	Gentamicin	≤1	>8	≤1–>8	88.3	0.7	11.0	Clarithromycin	8	16	≤0.12–>16	80.5	17.6	1.8
Tetracycline	>4	>4	0.25–>4	38.4	0.0	61.6								Moxifloxacin	0.03	0.06	≤0.008–>2	99.1	_	-
Tigecycline	0.06	0.12	0.015-0.12	89.6**	—	-	Levofloxacin	0.25	>4	0.12–>4	69.9	0.2	29.9	Tetracvcline	0.5	1	0.12–>8	98.4	0.2	1.5
Trimethoprim- sulfamethoxazole	>4	>4	≤0.12–>4	24.3	11.2	64.6	Linezolid	1	2	0.25-4	100.0	_	0.0	Tigoovolino	0.25	0.5	0.02.2	96 0t		
Macrolide-resistant ⁺⁺ S. pneu	imoniae	(<i>n</i> =667)												пдесусппе	0.23	0.5	0.03–2	00.∠⁺	_	_
Lefamulin	0.12	0.25	0.015–1	[100.0]‡			Moxifloxacin	≤0.06	>4	≤0.06–>4	70.3	3.3	26.4	Trimethoprim- sulfamethoxazole	0.12	>4	≤0.06–>4	62.9	4.0	33.1
Amoxicillin-clavulanic acid	0.5	>4	≤0.03–>4	83.8	5.6	10.7	Oxacillin	0.5	>2	0.25->2	64.7	-	35.3	H narainfluenzae (n=92)						
Azithromycin	>4	>4	≤0.03–>4	0.6	0.9	98.5	Tigoovolino	0.12	0 1 2		100.08			n. parannuenzae (n–52)					ĺ	
Ceftaroline	0.06	0.12	≤0.008–>1	99.7	-	-	пдесусппе	0.12	0.12	≤0.015−0.5	100.03	_	_	Lefamulin	1	2	≤0.008–8	[100.0] ⁺		
Ceftriaxone	0.5	2	≤0.015–>2	62.0§ 86.2¶	24.2 11.3	13.8	Trimethoprim-	≤0.5	≤0.5	≤0.5–>16	97.9	-	2.1	Amoxicillin-clavulanic acid	0.5	1	≤0.06–8	98.9	-	1.1
Clindamycin	>2	>2	≤0.25–>2	46.5	1.2	52.3	sulfamethoxazole							Ampicillin	0.5	>8	≤0.12–>8	81.5	3.3	15.2
Erythromycin	>16	>16	1–>16	0.0	0.0	100.0	Vancomycin	1	1	0.5–2	100.0	0.0	0.0	Azithromycin	0.5	2	<0.12 \2	05 7		
Levofloxacin	1	2	0.5–>4	97.8	0.3	1.9								Azitinomycin	0.5	2	20.12-20	95.7	_	_
Moxifloxacin	0.12	0.25	≤0.03–>4	98.4	0.9	0.7	MRSA (<i>n</i> =151)							Cefepime	0.06	2	≤0.015–>2	96.7	-	-
Penicillin	0.5	4	≤0.008–>4	28.0	38.1	33.9	Lefamulin	0.06	0.12	0.03-0.25	[98.6]†			Ceftriaxone	0.004	0.06	≤0.002–>2	98.9	-	-
				28.0 85.5 [#]	_ 12.7	1.8								Ciprofloxacin	0.015	>1	≤0.004–>1	88.0	_	_
Tetracycline	>4	>4	0.12–>4	39.7	0.1	60.1	Azithromycin	>32	>32	0.12–>32	26.5	0.0	73.5	Clarithromycin	8	16	0 5_>16	68 5	22.8	87
Tigecycline	0.06	0.06	0.015-0.25	92.4**	—	_	Ceftaroline	1	2	0 25-4	78 8‡	21.2	0.0		0	10	0.0	00.5	22.0	0.7
Trimethoprim-	1	>4	≤0.12–>4	49.5	17.3	33.2	Certaronne		2	0.20 4	10.0	<i>∠</i> 1. <i>∠</i>	0.0	Moxifloxacin	0.06	>2	≤0.008–>2	85.7	—	-
Sulfametnoxazole		(10-162)					Clindamycin	0.06	>2	≤0.03–>2	53.6	0.0	46.4	Tetracycline	0.5	1	0.25->8	92.4	0.0	7.6
Multidrug-resistant ⁺⁺ 3. prieu		(11-102)	0.015 0.25	[100 0]±			Doxycycline	0.12	8	<0.06_>8	86.8	86	4.6	Tigecycline	0.25	0.5	0.06–1	_	_	_
Amovicillin-clayulanic acid	0.00	>/	1_>4	/2 0	18.6	38.5	Doxycycline	0.12	0	<u> </u>	00.0	0.0	T. 0	Trimethoprim-	≤0.06	4	≤0.06–>4	79.3	43	16.3
Arithromycin	4 >4	>4	1->4	42.9	12	98.8	Erythromycin	>8	>8	≤0.06–>8	26.5	3.3	70.2	sulfamethoxazole	-0.00		-0.00 - 1	10.0	110	1010
Ceftaroline	0.12	0.25	0.06-0.5	100.0	_	_	Gentamicin	<1	>8	<1 >8	76.8	20	21.2	M. catarrhalis (n=227)						
Ceftriaxone	1	2	0.5–>2	4.3 [§]	46.3	49.4	Gentamicin		20	21-20	70.0	2.0	21.2	Lofomulin	0.06	0.06		[100 0]†		
				50.6¶	41.4	8.0	Levofloxacin	>4	>4	0.12->4	24.5	0.0	75.5		0.00	0.00	20.000-0.12			
Clindamycin	>2	>2	≤0.25->2	21.0	1.2	77.8	Lipozolid	1	2	05.2	100.0		0.0	Amoxicillin-clavulanic acid	≤0.25	≤0.25	≤0.25–2	100.0	-	0.0
Erythromycin	>16	>16	1->16	0.0	0.0	100.0	LINEZOIIO	I	2	0.5–2	100.0	-	0.0	Azithromycin	0.015	0.03	≤0.004-0.06	100.0	-	-
Levofloxacin	1	2	0.06 >4	95.7	0.0	4.3	Moxifloxacin	2	>4	≤0.06–>4	25.2	7.3	67.5	Ceftriaxone	0.25	1	≤0.002–>2	99.6	_	_
Penicillin	0.12	0.25 A	0.00	90.9	0.0	1.2					0.0		100.0	Clarithramuain	<0.12	<0.12	<0.12.0.5	100.0		
	4	4	2	0.0	_	100.0	Oxacıllın	>2	>2	>2_>2	0.0	-	100.0	Clantinomycin	<u>≥</u> 0.12	<u></u> ⊃0.12	-0.12-0.5	100.0	_	_
				45.1#	48.8	6.2	Tigecycline	0.12	0.25	0.03-0.5	100.0§	_	_	Moxifloxacin	0.06	0.06	0.015-0.12	—	—	—
Time available	>4	>4	>4->4	0.0	0.0	100.0								Tetracycline	0.25	0.5	≤0.06–>8	99.1	0.0	0.9
Trimothonrim	0.06	0.12	<0.12	80.8°°	-	-	Trimethoprim-	≤0.5	≤0.5	≤0.5–>16	95.4	-	4.6	Tigecycline	0.06	0.06	≤0.015–0.12	_	_	_
sulfamethoxazole		-4			10.0		Vancomvcin	1	1	0.5-2	100.0	0.0	0.0	Trimethoprim-	0.25	0.5	≤0.06–2	94.7	5.3	0.0

Resistant 5. pneumoniae						µg/mL			CLSI*		H. influenzae, h	1. para	influen	zae, and <i>M</i> .	catarrhalis					
Antimicrobial Agent	MIC	µg/m	IL Range	%\$		%R	Antimicrobial Agent	MIC	MIC	Range	%\$	%	%R			µg/ı	nL	C	LSI*	
Ponicillin-resistant [†] S. nne		$p_{0}(n=268)$		/00	/01	701						/01		Antimicrobial Agent		MIC ₉₀	Range	%S	%	%R
L efamulin			0.015_0.5	[100 0]‡			<i>S. aureus (n</i> =428)							H. influenzae (n=550)		· · · · ·				
Amoxicillin-clavulanic acid	2	>4	1->4	51.7	15.0	33.3	l efamulin	0.06	0 12	0 015_1	[99 5]†			Lofomulin	0.5	2	0.015 /	[100 0]t		
Azithromycin	>4	>4	≤0.03–>4	15.7	0.7	83.6		0.00	0.12	0.013-1	[33.3]			Letamulin	0.5	2	0.015-4	[100.0]		
Ceftaroline	0.12	0.25	0.03–>1	99.3	_	_	Azithromycin	0.5	>32	0.06–>32	56.8	0.0	43.2	Amoxicillin-clavulanic acid	1	2	≤0.06–16	98.9	—	1.1
Ceftriaxone	1	2	0.25->2	5.2 [§]	60.8	34.0		0.05	4	<0.00 1	00.5+	7 5	0.0	Ampicillin	0.5	>8	≤0.12–>8	67.3	5.1	27.6
				66.0¶	27.6	6.3	Cettaroline	0.25	1	≤0.06−4	92.5+	1.5	0.0	Azithromycin	1	2	<0.12_>8	99.1		
Clindamycin	>2	>2	≤0.25->2	46.3	0.7	53.0	Clindamycin	0.06	>2	≤0.03–>2	81.3	0.0	18.7			2	-0.12 -0	00.1		
Erythromycin	>16	>16	≤0.015->16	15.7	0.0	84.3								Cetepime	0.12	0.25	≤0.015–>2	99.8	-	-
Moviflovacin	1 0 12	0.25	0.06_>4	90.0 07 <i>1</i>	0.0	3.4 1.5	Doxycycline	0.12	1	≤0.06–>8	95.1	3.0	1.9	Ceftriaxone	0.004	0.015	≤0.002–0.25	100.0	-	-
Penicillin	2	4	2_>4	97. 4 0.0"	0.0	100.0	Ervthromvcin	0.25	>8	≤0.06–>8	56.3	3.5	40.2	Ciprofloxacin	0.015	0.015	0.008–>1	98.9	_	_
	2			0.0^	-	100.0								Clarithromyoin	0	16	<0.12 \16	<u> </u>	176	1 0
– <i>1</i>				58.6#	36.9	4.5	Gentamicin	≤1	>8	≤1–>8	88.3	0.7	11.0	Clantinomycin	0	10	≤0.12 - ->10	00.0	17.0	1.0
	>4	>4	0.25->4	38.4	0.0	61.6	Levofloyacin	0.25	>1	0 12_>/	60.0	0.2	20.0	Moxifloxacin	0.03	0.06	≤0.008–>2	99.1	—	-
Trimothonrim	0.06	0.12	0.015-0.12	89.6**	-	-	Levonoxacin	0.23	~4	0.12-24	09.9	0.2	29.9	Tetracycline	0.5	1	0.12–>8	98.4	0.2	1.5
sulfamethoxazole	~4	-4	≤0.12	24.3	11.2	04.0	Linezolid	1	2	0.25-4	100.0	—	0.0	Tigecycline	0 25	0.5	0.03–2	86 2‡	_	_
/lacrolide-resistant ⁺⁺ S. pneu	umoniae	(<i>n</i> =667)						<0.00			70.0	0.0	00.4		0.40			00.0	4.0	004
Lefamulin	0.12	0.25	0.015–1	[100.0] [‡]			Moxifloxacin	≤0.06	>4	≤0.06–>4	70.3	3.3	26.4	Irimethoprim- sulfamethoxazole	0.12	>4	≤0.06–>4	62.9	4.0	33.1
Amoxicillin-clavulanic acid	0.5	>4	≤0.03–>4	83.8	5.6	10.7	Oxacillin	0.5	>2	0.25->2	64.7	_	35.3							
Azithromycin	>4	>4	≤0.03–>4	0.6	0.9	98.5								H. parainfluenzae (n=92)		· ·				
Ceftaroline	0.06	0.12	≤0.008–>1	99.7	_	_	Tigecycline	0.12	0.12	≤0.015–0.5	100.0§	—	—	Lefamulin	1	2	≤0.008–8	[100.0]†		
Ceftriaxone	0.5	2	≤0.015–>2	62.0§	24.2	13.8	Trimethoprim-	≤0.5	≤0.5	≤0.5–>16	97.9	_	2.1	Amoxicillin-clavulanic acid	0.5	1	≤0.06–8	98 9	_	11
				86.2¶	11.3	2.6	sulfamethoxazole	-0.0	-0.0	-0.0 10	07.0		2.1		0.0		-0.00 0	00.0		
Clindamycin	>2	>2	≤0.25->2	46.5	1.2	52.3					4000			Ampicillin	0.5	>8	≤0.12–>8	81.5	3.3	15.2
Erythromycin	>16	>16	1->16	0.0	0.0	100.0	Vancomycin	1	1	0.5–2	100.0	0.0	0.0	Azithromycin	0.5	2	≤0.12–>8	95.7	-	-
Moviflovacin	0 12	0.25	0.5-24	97.0	0.3	1.9	MRSA (<i>n</i> =151)							Cefepime	0.06	2	≤0.015–>2	96.7	_	_
Penicillin	0.12	4	<0.03->4	28 0 [∥]	38.1	33.9								Ceftriavone	0.004	0.06	<0 002_>2	08.0	_	_
	0.0		-0.000 / 1	28.0 [^]	_	72.0	Lefamulin	0.06	0.12	0.03-0.25	[98.6] [†]			Certinazone	0.004	0.00	20.002-2	50.5		
— · ·				85.5#	12.7	1.8	Azithromycin	>32	>32	0 12_>32	26.5	0.0	73 5	Ciprofloxacin	0.015	>1	≤0.004–>1	88.0	-	-
Time	>4	>4	0.12->4	39.7	0.1	60.1		- 02	- 02	0.12 - 02	20.0	0.0	70.0	Clarithromycin	8	16	0.5–>16	68.5	22.8	8.7
Trimethonrim	0.06	0.06	0.015-0.25	92.4**	-	-	Ceftaroline	1	2	0.25–4	78.8 [‡]	21.2	0.0	Moxifloxacin	0.06	>2	≤0.008–>2	85.7	_	_
sulfamethoxazole	1	-4	≤0.1Z - -24	49.5	17.5	JJ.Z	Clindomyoin	0.06	>2	<0.02 >2	52.6	0.0	16.4	Totroovalina	0.5	1	0.25 >8	02.4	0.0	76
/lultidrug-resistant ^{‡‡} S. pneเ	umoniae	(<i>n</i> =162)					Cindamycin	0.00	~2	≤0.032	53.0	0.0	40.4	retracycline	0.5	I	0.25-20	92.4	0.0	7.0
Lefamulin	0.06	0.12	0.015-0.25	[100.0]‡			Doxycycline	0.12	8	≤0.06–>8	86.8	8.6	4.6	Tigecycline	0.25	0.5	0.06–1	-	-	-
Amoxicillin-clavulanic acid	4	>4	1->4	42.9	18.6	38.5					00 5	0.0	70.0	Trimethoprim-	≤0.06	4	≤0.06–>4	79.3	4.3	16.3
Azithromycin	>4	>4	1->4	0.0	1.2	98.8	Erythromycin	>8	>8	≤0.06–>8	26.5	3.3	70.2	sulfamethoxazole						
Ceftaroline	0.12	0.25	0.06-0.5	100.0	_	—	Gentamicin	≤1	>8	≤1–>8	76.8	2.0	21.2	<i>M. catarrhalis (n=227)</i>						
Ceftriaxone	1	2	0.5–>2	4.3§	46.3	49.4								Lefamulin	0.06	0.06	≤0.008–0.12	[100.01 ⁺		
Clindomycin	>2	>2	<0.25 >2	50.6	41.4	8.0	Levofloxacin	>4	>4	0.12–>4	24.5	0.0	75.5		<0.05	<0.05	<0.05.0	100.0		0.0
Erythromycin	>16	>16	1 >16	21.0	1.2	100.0	Linezolid	1	2	0.5–2	100.0	_	0.0	Amoxicillin-clavulanic acid	≥0.25	≥0.25	≥0.25-2	100.0	_	0.0
Levofloxacin	-10	2	0 5_>4	95.7	0.0	4.3			2	0.0 2	10010		0.0	Azithromycin	0.015	0.03	≤0.004–0.06	100.0	-	-
Moxifloxacin	0.12	0.25	0.06->4	96.9	1.9	1.0	Moxifloxacin	2	>4	≤0.06–>4	25.2	7.3	67.5	Ceftriaxone	0.25	1	≤0.002–>2	99.6	_	-
Penicillin	4	4	2->4	0.0	0.0	100.0	Ovacillin	>2	>2	>2 >2	0.0		100.0	Clarithromycin	<0.12	<0.12	<0.12-0.5	100.0	_	_
				0.0^	-	100.0	Oxaciiiii	~2	~2	~~_	0.0	_	100.0		-0.12	-0.12		10010		
Totrogualing				45.1*	48.8	6.2	Tigecycline	0.12	0.25	0.03-0.5	100.0§	_	_	IVIOXITIOXACIN	0.06	0.06	0.015-0.12	_	-	-
Tigogyeline	>4	>4 0.12	24-24 0.015 0.12	0.0	0.0	100.0	T ·							Tetracycline	0.25	0.5	≤0.06–>8	99.1	0.0	0.9
Trimethonrim-	>4	>4	<0.013-0.12	18.5	13.6	679	sulfamethoxazole	≤0.5	≤0.5	≤0.5–>16	95.4	—	4.6	Tigecycline	0.06	0.06	≤0.015–0.12	_	_	_
sulfamethoxazole	rds Institute	e: I=interme		num inhibito		otration:	Vancomycin	1	1	0.5–2	100.0	0.0	0.0	Trimethoprim- sulfamethoxazole	0.25	0.5	≤0.06–2	94.7	5.3	0.0

MIC₅₀=minimum concentration at which 50% of isolates were inhibited; MIC₉₀=minimum concentration at which 90% of isolates were inhibited: R=resistant; S=susceptible CLSI=Clinical and Laboratory Standards Institute: I=intermediate: MIC=minimum inhibitory concentration MIC₅₀=minimum concentration at which 50% of isolates were inhibited; MIC₉₀=minimum concentration at *2019 CLSI criteria. *Penicillin MIC $\geq 2 \mu g/mL$ using the oral breakpoint. *Percentages inhibited at propose which 90% of isolates were inhibited; MRSA=methicillin-resistant S. aureus; R=resistant; S=susceptible lefamulin breakpoint of $\leq 1 \mu g/mL$ for S. pneumoniae shown for reference. [§]Using meningitis breakpoin [¶]Using nonmeningitis breakpoint. [|]Using oral breakpoint. [^]Using parenteral, meningitis breakpoints. [#]Using *2019 CLSI criteria. [†]Percentages inhibited at proposed lefamulin breakpoint of ≤0.5 µg/mL for S. aureus parenteral, nonmeningitis breakpoints. **US Food and Drug Administration breakpoints accessed February shown for reference. [‡]Intermediate interpreted as susceptible-dose dependent. [§]US Food and Drug 2018. ⁺⁺Using erythromycin breakpoint. ⁺⁺Resistant to oral penicillin, erythromycin, and tetracycline. Administration breakpoints accessed February 2018.

ASM Microbe 2019: June 20–24, San Francisco, CA, USA

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which 90% of isolates were inhibited; R=resistant; S=susceptible. Administration breakpoints accessed February 2018.

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CLSI=Clinical and Laboratory Standards Institute: I=intermediate; MIC=minimum inhibitory concentration MIC₅₀=minimum concentration at which 50% of isolates were inhibited; MIC₉₀=minimum concentration a

*2019 CLSI criteria. [†]Percentages inhibited at proposed lefamulin breakpoints of ≤4 µg/mL for *H. influenz* ≤8 µg/mL for *H. parainfluenzae*, and ≤0.5 µg/mL for *M. catarrhalis* shown for reference. [‡]US Food and D

CONCLUSIONS

- LEF demonstrated potent in vitro activity against this contemporary (2017) collection of community-acquired bacterial pathogens collected worldwide from patients with respiratory tract infections and hospitalized patients with pneumonia compared with the most potent comparator agents used to treat CABP
- LEF activity was unaffected by resistance to other antibiotic classes, including macrolides, fluoroquinolones, and tetracyclines
- These in vitro data suggest that LEF may offer an important empiric monotherapy treatment option for CABP, in particular, where resistance to antimicrobials commonly used for CABP is high

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Acknowledgments

Funding for development of this poster was provided by Nabriva Therapeutics to C4 MedSolutions, LLC (Yardley, PA), a CHC Group company.

Disclosures

Susanne Paukner and Steven P. Gelone are employees/stockholders of Nabriva Therapeutics plc. S.J. Ryan Arends and Helio S. Sader are employees of JMI Laboratories, which was contracted by Nabriva Therapeutics to conduct these analyses



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