

# In Vitro Activity of Lefamulin Against Bacterial Pathogens Causing Community-Acquired Bacterial Pneumonia: SENTRY Surveillance 2017–2018 Results From the United States

Susanne Paukner,<sup>1</sup> S. J. Ryan Arends,<sup>2</sup> Steven P. Gelone,<sup>3</sup> Helio S. Sader<sup>2</sup>

<sup>1</sup>Nabriva Therapeutics GmbH, Vienna, Austria; <sup>2</sup>JMI Laboratories, North Liberty, IA, USA; <sup>3</sup>Nabriva Therapeutics US, Inc., King of Prussia, PA, USA

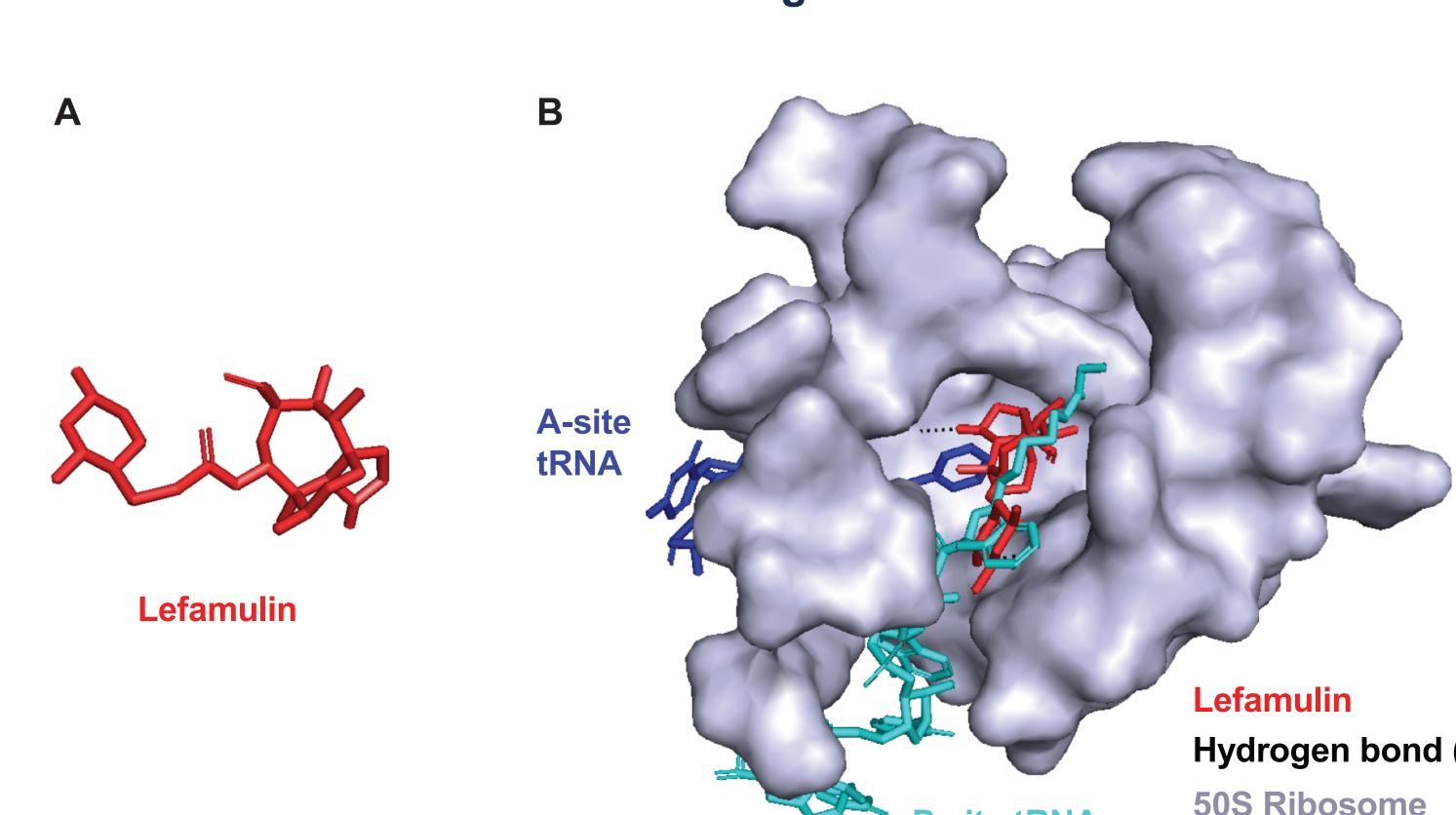
Fax: 319-665-3371

Nabriva Therapeutics Dublin, Ireland

# INTRODUCTION & PURPOSE

- Pneumonia is one of the leading causes of infection-related death in the United States (US)¹ and is associated with substantial morbidity, mortality, and economic burden<sup>2</sup>
- Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, Moraxella catarrhalis, and the atypical pathogens Mycoplasma pneumoniae, Chlamydophila pneumoniae, and Legionella pneumophila, are among the most common pathogens that cause community-acquired bacterial pneumonia (CABP) and are usually treated with macrolides, β-lactams, or fluoroquinolones<sup>2,3</sup>
- Surveillance programs have observed trends of generally decreasing antimicrobial susceptibility for *S. pneumoniae* strains in North America, including 64.1% and 56.1% susceptibility to penicillin (using oral breakpoints) and erythromycin, respectively<sup>4</sup>
- Methicillin-resistant S. aureus (MRSA) has emerged as an important CABP-causing pathogen because of its disproportionate frequency of infecting young, otherwise healthy patients<sup>5</sup>; in the US, methicillin-resistance rates range from 40.7%–54.7%, depending on the region<sup>6</sup>
- Increasing rates of antimicrobial resistance, combined with increasing safety concerns associated with fluoroguinolones,<sup>7,8</sup> have created a need for new safe and effective treatment options<sup>2</sup>
- Lefamulin (LEF) is the first antimicrobial in the pleuromutilin class approved for intravenous (IV) and oral administration in adults with CABP.9 LEF selectively inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit at the A- and P-sites in the peptidyl transferase center<sup>10,11</sup> (Figure 1)
- In patients with CABP, LEF demonstrated noninferiority to moxifloxacin in the IV-to-oral switch Lefamulin Evaluation Against Pneumonia (LEAP) 1 phase 3 study,12 and in the LEAP 2 oral-only
- The objective of this analysis was to investigate the in vitro activity of LEF and comparators against a contemporary set of CABP-causing pathogens collected in the US in 2017 and 2018

### Figure 1. (A) Structure of Lefamulin and (B) Lefamulin in the Peptidyl Transferase Center of the Large Ribosomal Subunit



# METHODS

- As part of the SENTRY Antimicrobial Surveillance Program, 2299 unique isolates (1 per patient) were collected from 34 US medical centers in 2017 and 2018 from patients with community-acquired respiratory tract infections (1812/2299 [78.8%]) and hospitalized patients with pneumonia (487/2299 [21.2%])
- Minimum inhibitory concentration (MIC) for LEF and comparators was determined using Clinical and Laboratory Standards Institute (CLSI) broth microdilution<sup>14</sup>; susceptibility was evaluated using the CLSI (2019) breakpoints<sup>15</sup>

# RESULTS

 LEF demonstrated potent antibacterial activity against all tested CABP pathogens, and its activity was unaffected by resistance to other antibiotic classes

#### S. pneumoniae

- S. pneumoniae isolates showed considerable resistance to macrolides (45.6%), penicillin (36.8%), and tetracycline (20.4%), whereas they were largely susceptible (>85%) to the tested cephalosporins and fluoroquinolones (Table 1)
- LEF was highly active against S. pneumoniae, with a minimum concentration at which 50% or 90% of the isolates were inhibited (MIC<sub>50/90</sub>) of 0.12/0.25 µg/mL (range  $\leq$ 0.008–2 µg/mL; **Table 1**)
- LEF was effective against all tested resistant subsets (MIC<sub>50/90</sub> of 0.12/0.25 μg/mL), with 100% of penicillin- and tetracycline-resistant isolates and 99.5% of macrolide-resistant isolates inhibited at ≤0.5 µg/mL **(Table 2)**

## S. aureus

- S. aureus isolates overall, and particularly MRSA and fluoroquinolone-resistant strains, were commonly resistant to macrolides; 81.2% of MRSA and 80.4% of fluoroquinolone-resistant strains were resistant to erythromycin (**Table 3**)
- LEF demonstrated potent activity against *S. aureus* isolates, including methicillin-resistant, macrolide-resistant (75.0% MRSA) and fluoroquinolone-resistant (87.6% MRSA) subsets (MIC<sub>50/00</sub> of 0.06/0.12 μg/mL for each; **Table 3**)

#### H. influenzae

- *H. influenzae* isolates were largely susceptible to all comparators except ampicillin (31.4% resistant) and trimethoprim-sulfamethoxazole (35.3% resistant; **Table 4**)
- LEF demonstrated activity against H. influenzae (MIC<sub>50/90</sub> of 0.5/2 μg/mL; Table 4), with 99.2% of isolates inhibited at ≤2 μg/mL

#### M. catarrhalis

- M. catarrhalis isolates included a large proportion (97.6%) of β-lactamase producers and were susceptible (96.4%–100%) to all comparators, including amoxicillin-clavulanic acid (**Table 4**)
- LEF inhibited all M. catarrhalis isolates at concentrations of ≤0.5 μg/mL (MIC<sub>50/90</sub> of 0.06/0.12 μg/mL; Table 4

## **β-hemolytic streptococci**

• LEF effectively inhibited  $\beta$ -hemolytic streptococci (n=14), with MIC<sub>50/90</sub> values of 0.03/0.06 µg/mL (data not shown)

	(µg/mL)			CLSI*				
Antimicrobial Agent	MIC <sub>50</sub>	MIC <sub>90</sub>	Range	%S	<b>%</b> I	%R		
S. pneumoniae (n=1441)								
Lefamulin	0.12	0.25	≤0.008–2	99.8 <sup>†</sup>	_	_		
Amoxicillin-clavulanic acid‡	≤0.03	2	≤0.03->4	95.1	1.9	3.0		
Azithromycin <sup>‡</sup>	0.12	>4	≤0.03->4	53.0	1.4	45.6		
Ceftaroline	≤0.008	0.12	≤0.008-0.5	100.0	_	_		
Ceftriaxone§	0.03	1	≤0.015->2	86.0 <sup>  </sup> 97.1 <sup>¶</sup>	11.0 2.5	2.9 0.4		
Clindamycin	≤0.25	>2	≤0.25->2	85.2	0.4	14.4		
Erythromycin	0.06	>16	≤0.015->16	53.9	0.6	45.6		
Levofloxacin	1	1	0.25->4	99.2	0.1	0.7		
Moxifloxacin	0.12	0.25	≤0.03–4	99.4	0.5	0.1		
Penicillin	0.03	2	≤0.008->4	63.2^	26.0	10.8		
				63.2#	_	36.8		
				96.3**	3.1	0.7		
Tetracycline <sup>‡</sup>	0.5	>4	0.06->4	79.6	0.1	20.4		
Trimethoprim-sulfamethoxazole	0.25	>4	≤0.12->4	73.6	11.7	14.8		

CLSI=Clinical and Laboratory Standards Institute; I=intermediate; MIC<sub>50</sub>=minimum concentration at which 50% of isolates were inhibited; MIC<sub>90</sub>=minimum concentration at which 90% of isolates were inhibited; R=resistant; S=susceptible. \*2019 CLSI criteria. †2019 FDA susceptibility breakpoint of ≤0.5 μg/mL applied. ‡n=1439. §n=1440. □Using meningitis breakpoints. □Using nonmeningitis breakpoints. ^Using oral breakpoints. #Using parenteral, meningitis breakpoints. \*\*Using parenteral, nonmeningitis breakpoints Table 2. Activity of Lefamulin and Comparators Against Drug-Resistant S. pneumoniae

3. prieumomae		(µg/mL)			CLSI*	
Antimicrobial Agent	MIC <sub>50</sub>	MIC <sub>90</sub>	Range	%S	%l	%R
Penicillin-resistant <sup>†</sup> <i>S. pneumon</i>		- 50				
Lefamulin	0.12	0.25	0.015-0.25	100.0‡	_	_
Amoxicillin-clavulanic acid	2	>4	1->4	55.1	17.3	27.6
Azithromycin	>4	>4	0.06->4	5.8	0.0	94.2
Ceftaroline	0.12	0.25	0.06-0.5	100.0	_	_
Ceftriaxone	1	2	0.5->2	5.8§	67.9	26.3
				73.7 <sup>  </sup>	22.4	3.8
Clindamycin	≤0.25	>2	≤0.25->2	57.7	0.6	41.7
Erythromycin	16	>16	0.03->16	5.8	0.0	94.2
Levofloxacin	1	1	0.5->4	98.7	0.0	1.3
Moxifloxacin	0.12	0.25	0.06–2	99.4	0.6	0.0
Penicillin	2	4	2->4	PO.0	0.0	100.0
				0.0^	_	100.0
				65.4#	28.2	6.4
Tetracycline	1	>4	0.12->4	50.0	0.0	50.0
Trimethoprim-sulfamethoxazole	>4	>4	≤0.12->4	26.3	5.1	68.6
//acrolide-resistant** <i>S. pneumo</i>	niae (n=657	<b>')</b>				
Lefamulin	0.12	0.25	0.015–2	99.5‡	-	-
Amoxicillin-clavulanic acid	0.25	4	≤0.03->4	89.5	4.0	6.5
Azithromycin	>4	>4	0.06->4	0.2	1.4	98.5
Ceftaroline	0.06	0.12	≤0.008-0.5	100.0	_	_
Ceftriaxone	0.25	1	≤0.015->2	71.5§	22.1	6.4
				93.6 <sup>  </sup>	5.5	0.9
Clindamycin	≤0.25	>2	≤0.25->2	67.9	8.0	31.4
Erythromycin	8	>16	1->16	0.0	0.0	100.0
Levofloxacin	1	1	0.5->4	99.2	0.2	0.6
Moxifloxacin	0.12	0.25	≤0.03–2	99.5	0.5	0.0
Penicillin	0.25	2	≤0.008->4	33.0 <sup>¶</sup>	44.6	22.4
				33.0^	_	67.0
				91.8#	6.7	1.5
Tetracycline	0.5	>4	0.06->4	60.0	0.0	40.0
Trimethoprim-sulfamethoxazole	0.5	>4	≤0.12->4	53.9	18.9	27.2
etracycline-resistant <i>S. pneumo</i>	•					
Lefamulin	0.12	0.25	0.015-0.5	100.0 <sup>‡</sup>	-	_
Amoxicillin-clavulanic acid	0.25	>4	≤0.03->4	79.9	6.5	13.7
Azithromycin <sup>††</sup>	>4	>4	≤0.03->4	6.8	2.1	91.1
Ceftaroline	0.06	0.12	≤0.008–0.5	100.0	_	_
Ceftriaxone	0.25	2	≤0.015->2	71.3§	15.7	13.0
	_	_		87.0 <sup>  </sup>	11.6	1.4
Clindamycin	>2	>2	≤0.25->2	33.1	1.4	65.5
Erythromycin	>16	>16	≤0.015—>16	9.2	1.0	89.8
Levofloxacin	1	2	0.5->4	99.0	0.3	0.7
Moxifloxacin	0.12	0.25	0.06–2	99.7	0.3	0.0
Penicillin	0.25	4	≤0.008->4	21.2¶	52.2	26.6
				21.2^	40.0	78.8
				83.6#	13.3	3.1
Tetracycline	>4	>4	4->4	0.0	0.0	100.0
Trimethoprim-sulfamethoxazole	1	>4	≤0.12->4	39.6	24.9	35.5

CLSI=Clinical and Laboratory Standards Institute; I=intermediate; MIC=minimum inhibitory concentration; MIC<sub>50</sub>=minimum concentration at which 50% of isolates were inhibited; MIC<sub>90</sub>=minimum concentration at which 90% of isolates were inhibited; R=resistant; S=susceptible. \*2019 CLSI criteria. †Penicillin MIC ≥2 μg/mL for oral breakpoint. ‡2019 FDA susceptibility breakpoint of ≤0.5 μg/mL applied. §Using meningitis breakpoints. Using nonmeningitis breakpoints. Using oral breakpoints. Using parenteral, meningitis breakpoints. Using parenteral, nonmeningitis breakpoints. \*\*Using erythromycin breakpoints. ††n=292.

Table 3 Activity of Lefamulin and Comparators Against S aurous

Table 3. Activity of Lefan		(µg/mL		CLSI*			
Antimicrobial Agent	MIC <sub>50</sub>	MIC <sub>90</sub>	Range	%S	<b>%</b> I	%R	
S. aureus (n=297)	00						
Lefamulin	0.06	0.12	0.03-0.25	100.0 <sup>†</sup>	_	-	
Azithromycin	32	>32	0.12->32	46.5	0.3	53.2	
Ceftaroline	0.25	1	≤0.06–2	94.3 <sup>‡</sup>	5.7	0.0	
Clindamycin	0.06	>2	≤0.03->2	79.5	0.0	20.5	
Doxycycline	0.12	0.5	≤0.06>8	98.0	1.7	0.3	
Erythromycin	4	>8	≤0.06>8	46.5	5.1	48.5	
Gentamicin	≤1	≤1	≤1->8	96.6	0.3	3.0	
Levofloxacin	0.25	>4	0.12->4	62.0	0.0	38.0	
Linezolid	1	2	0.25-4	100.0	_	0.0	
Moxifloxacin	≤0.06	>4	≤0.06->4	62.0	5.4	32.7	
Oxacillin	1	>2	0.12->2	55.2	_	44.8	
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5->16	98.7	_	1.3	
Vancomycin	1	1	0.25–2	100.0	0.0	0.0	
MRSA ( <i>n</i> =133)							
Lefamulin	0.06	0.12	0.03-0.25	100.0 <sup>†</sup>	_	_	
Azithromycin	>32	>32	0.12->32	14.3	0.0	85.7	
Ceftaroline	1	2	0.25–2	87.2 <sup>‡</sup>	12.8	0.0	
Clindamycin	0.06	>2	≤0.03->2	58.6	0.0	41.4	
Doxycycline	0.12	1	≤0.06–8	97.0	3.0	0.0	
Erythromycin	>8	>8	≤0.06>8	14.3	4.5	81.2	
Gentamicin	≤1	≤1	≤1>8	94.7	0.0	5.3	
Levofloxacin	>4	>4	0.12->4	26.3	0.0	73.7	
Linezolid	1	2	0.25–2	100.0	_	0.0	
Moxifloxacin	2	>4	≤0.06>4	26.3	9.8	63.9	
Oxacillin	>2	>2	>2->2	0.0	_	100.0	
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5->16	97.0	_	3.0	
Vancomycin	1	1	0.5–2	100.0	0.0	0.0	
Macrolide-resistant <sup>§</sup> S. aureus (n							
Lefamulin	0.06	0.12	0.03-0.25	100.0 <sup>†</sup>	_	_	
Azithromycin	>32	>32	8->32	0.0	0.0	100.0	
Ceftaroline	0.5	2	≤0.06–2	88.2 <sup>‡</sup>	11.8	0.0	
Clindamycin	0.06	>2	≤0.03->2	57.6	0.0	42.4	
Doxycycline	0.12	1	≤0.06–>8	96.5	2.8	0.7	
Erythromycin	>8	>8	8->8	0.0	0.0	100.0	
Gentamicin	≤1	≤1	≤1–>8	94.4	0.0	5.6	
Levofloxacin	>4	>4	0.12->4	35.4	0.0	64.6	
Linezolid	1	2	0.25–2	100.0	-	0.0	
Moxifloxacin	2	>4	≤0.06->4	35.4	10.4	54.2	
Oxacillin	>2	>2	0.25->2	25.0	-	75.0	
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5–>16	98.6	_	1.4	
Vancomycin	1	1	0.5–2	100.0	0.0	0.0	
Fluoroquinolone-resistant <sup>∥</sup> <i>S. au</i>	reus (n=97)						
Lefamulin	0.06	0.12	0.03-0.25	100.0 <sup>†</sup>	_	_	
Azithromycin	>32	>32	0.25->32	14.4	1.0	84.5	
Ceftaroline	1	2	0.12–2	82.5 <sup>‡</sup>	17.5	0.0	
Clindamycin	>2	>2	≤0.03->2	47.4	0.0	52.6	
Doxycycline	0.12	1	≤0.06–8	96.9	3.1	0.0	
Erythromycin	>8	>8	≤0.06>8	14.4	5.2	80.4	
Gentamicin	≤1	≤1	≤1->8	92.8	0.0	7.2	
Levofloxacin	>4	>4	4->4	0.0	0.0	100.0	
Linezolid	1	2	0.5–2	100.0	_	0.0	
Moxifloxacin	>4	>4	2->4	0.0	0.0	100.0	
Oxacillin	>2	>2	0.25->2	12.4	_	87.6	
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5->16	95.9	_	4.1	

CLSI=Clinical and Laboratory Standards Institute; I=intermediate; MIC<sub>50</sub>=minimum concentration at which 50% of isolates were inhibited; MIC<sub>00</sub>=minimum concentration at which 90% of isolates were inhibited; MRSA=methicillin-resistant S. aureus; MSSA=methicillin-susceptible S. aureus; R=resistant; S=susceptible.

\*2019 CLSI criteria. †2019 FDA susceptibility breakpoint for MSSA of ≤0.25 µg/mL applied. ‡Intermediate interpreted as susceptible-dose dependent §Using erythromycin breakpoints. Using moxifloxacin breakpoints.

Table 4. Activity of Lefamulin and Comparators Against *H. influenzae* and M. catarrhalis

and W. Catarrians									
	(µg/mL)			CLSI*					
Antimicrobial Agent	MIC <sub>50</sub>	MIC <sub>90</sub>	Range	%S	<b>%</b> I	%R			
H. influenzae (n=382)									
Lefamulin	0.5	2	0.015–8	99.2 <sup>†</sup>	_	_			
Amoxicillin-clavulanic acid	0.5	2	≤0.06->8	99.2	_	8.0			
Ampicillin	0.5	>8	≤0.12>8	65.4	3.1	31.4			
Azithromycin	1	2	≤0.12>8	98.4	_	_			
Cefepime	0.12	0.25	≤0.015->2	99.7	_	_			
Ceftriaxone	0.004	0.015	≤0.002-0.25	100.0	_	_			
Ciprofloxacin	0.015	0.015	0.008->1	98.7	-	_			
Clarithromycin	8	16	≤0.12->16	80.9	16.2	2.9			
Moxifloxacin	0.03	0.06	0.015->2	99.0	-	_			
Tetracycline	0.5	1	0.12->8	99.0	0.0	1.0			
Trimethoprim-sulfamethoxazole	0.12	>4	≤0.06->4	62.0	2.6	35.3			
<i>M. catarrhalis (n</i> =165)									
Lefamulin	0.06	0.12	≤0.008–0.12	_	_	_			
Amoxicillin-clavulanic acid	≤0.25	≤0.25	≤0.25–0.5	100.0	_	0.0			
Azithromycin	≤0.03	≤0.03	≤0.03-0.06	100.0	_	_			
Ceftriaxone	0.25	1	0.004–2	100.0	_	_			
Clarithromycin	≤0.12	≤0.12	≤0.12–0.5	100.0	_	_			
Moxifloxacin	0.06	0.06	0.015-0.12	_	_	_			
Tetracycline	0.25	0.5	0.12->8	99.4	0.0	0.6			
Trimethoprim-sulfamethoxazole	0.12	0.25	≤0.06–2	96.4	3.6	0.0			
LSI=Clinical and Laboratory Standards Institu				which 50% of isc	lates were inhibit	ted;			

MIC<sub>00</sub>=minimum concentration at which 90% of isolates were inhibited; R=resistant; S=susceptible

\*2019 CLSI criteria. †2019 FDA susceptibility breakpoint of ≤2 µg/mL applied.

## CONCLUSIONS

- LEF demonstrated potent in vitro activity against this contemporary (2017–2018) set of pathogens collected in the US from patients with respiratory tract infections and hospitalized patients with pneumonia
- LEF activity was comparable with the most common antimicrobial agents used to treat CABP and was unaffected by resistance to other antibiotic classes, including macrolides, fluoroquinolones, β-lactams, and tetracyclines
- These in vitro data, as well as the high efficacy in CABP patients from phase 3 clinical trials (LEAP 1 and 2),<sup>12,13</sup> suggest that LEF may offer an important empiric monotherapy treatment option for CABP, particularly where resistance to antimicrobial agents commonly used to treat CABP is high

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

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