Lefamulin Activity Against Bacterial Pathogens Commonly Associated With Acute Bacterial Skin and Skin Structure Infections (ABSSSIs) Collected in the 2017 Global SENTRY Antimicrobial Surveillance Program

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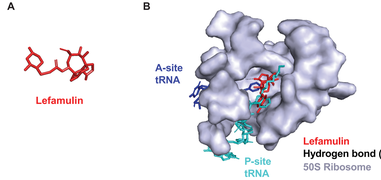
INTRODUCTION

- Acute bacterial skin and skin structure infections (ABSSSIs) comprise a variety of clinical manifestations such as abscesses, cellulitis, and wound infections that are predominantly caused by *Staphylococcus aureus* and group A and other β-hemolytic streptococci[1,2]
- Effective antibacterial treatment is integral for the optimal management of ABSSSI. Although current clinical practice guidelines recommend a range of antibiotic therapies, selecting the appropriate antibiotic can be challenging owing to increasing antibiotic resistance among pathogens and the lack of rapid and selective diagnostic assays (particularly in the case of nonpurulent cellulitis)[1-4]
  - Up to 34.1% of patients receive inappropriate treatment, resulting in prolonged hospitalization, increased risk of morbidity and mortality, and a substantial economic burden[1,2,4,5]
- Novel antimicrobials that are effective against group A, B, C, and G streptococci and staphylococci (including methicillin-resistant *S. aureus* [MRSA]) and that remain active despite high rates of antibiotic resistance are needed for the empiric treatment of ABSSSI[6]
- Lefamulin (LEF), a novel antimicrobial for intravenous (IV) and oral (PO) use in humans that inhibits bacterial protein synthesis **(Figure 1)**,[7] is in post phase 3 clinical development for the treatment of community-acquired bacterial pneumonia[8,9]
- For the treatment of ABSSSI, a phase 2 clinical trial demonstrated that LEF efficacy was comparable to that of vancomycin in patients with predominantly cellulitis or abscess with cellulitis (>80%) caused by gram-positive pathogens (MRSA and methicillin-susceptible *S. aureus* [MSSA])[10]
- This study investigated the in vitro activity of LEF and comparators against a contemporary global set of gram-positive pathogens that commonly cause ABSSSIs and blood stream infections (BSIs)

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



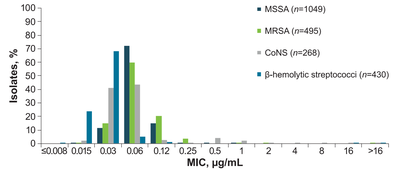
METHODS

- 2242 unique patient isolates were collected worldwide from 33 countries and 96 sites (34.1% USA, 32.7% Europe, 16.4% Asia-Pacific, and 16.8% Latin America)
  - Targeted pathogens of interest (nonprevalence-based study) were collected primarily from skin and skin structure infections (36.3%), BSIs (36.1%), pneumonia in hospitalized patients (20.6%), and other infections (7.1%)
  - Extensively drug-resistant (XDR) *Staphylococcus* spp. was defined as resistant to oxacillin, erythromycin, levofloxacin, clindamycin, and gentamicin according to the Clinical and Laboratory Standards Institute (CLSI; 2019)
- Minimum inhibitory concentration (MIC) values for LEF and comparator agents were determined using CLSI broth microdilution methodology[11]; susceptibility was determined using the CLSI (2019) breakpoints[12]

RESULTS

- LEF demonstrated potent antibacterial activity against all tested organisms, including *S. aureus* (MSSA and MRSA), coagulase-negative *Staphylococcus* spp. (CoNS), and β-hemolytic group A, B, C, and G *Streptococcus pneumoniae*, with 97.5% of all isolates inhibited at ≤0.12 µg/mL and 99.0% at ≤0.5 µg/mL
- Among *S. aureus* isolates, 98.3% were inhibited at ≤0.12 µg/mL LEF ($MIC_{50/90}$ of 0.06/0.12 µg/mL; **Table 1, Figure 2**) irrespective of resistance phenotype to other antibacterial classes (MRSA, macrolides, fluoroquinolones, XDR, tetracyclines)
  - Susceptibility remained high for glyco- and lipopeptides (daptomycin and vancomycin, 100%) and linezolid (100%) but was substantially lower for macrolides (azithromycin, 59.6%; erythromycin, 59.2%) and fluoroquinolones (levofloxacin, 74.9%; moxifloxacin, 75.2%; **Table 1**)
  - Resistance rates to macrolides and fluoroquinolones were particularly high for MRSA: 74.1%, 70.9%, 65.3%, and 56.8% were resistant to azithromycin, erythromycin, levofloxacin, and moxifloxacin, respectively **(Table 1)**
  - Among XDR isolates, LEF remained fully active ($MIC_{50/90}$ of 0.06/0.12 µg/mL [range, 0.03–0.25 µg/mL]), as did linezolid ($MIC_{50/90}$ of 1/2 µg/mL), vancomycin ($MIC_{50/90}$ of 1/1 µg/mL), daptomycin ($MIC_{50/90}$ of 0.25/0.5 µg/mL), and tigecycline ($MIC_{50/90}$ of 0.12/0.25 µg/mL; **Table 1**)
- LEF was one of the most active compounds against CoNS isolates ($MIC_{50/90}$ of 0.06/0.5 µg/mL), including XDR CoNS ($MIC_{50/90}$ of 0.06/1 µg/mL; **Table 2**)
  - Overall, CoNS appeared to be less susceptible to comparator agents than *S. aureus*; 13.8% of CoNS were XDR **(Table 2)**, whereas only 2.98% of *S. aureus* isolates were XDR **(Table 1)**
  - XDR CoNS were largely susceptible (91.9%–100% susceptible) only to doxycycline (MIC_{90} of 1 µg/mL), linezolid (MIC_{90} of 1 µg/mL), daptomycin (MIC_{90} of 0.5 µg/mL), and vancomycin (MIC_{90} of 2 µg/mL; **Table 2**)
- LEF was highly active against β-hemolytic streptococci, including *Streptococcus pyogenes*, *Streptococcus agalactiae*, and macrolide-resistant isolates (all $MIC_{50/90}$ of 0.03/0.03 µg/mL) as well as group C and G *Streptococcus* spp. ($MIC_{50/90}$ of 0.03/0.06 µg/mL; **Table 3**)
  - All β-hemolytic streptococcal isolates were largely susceptible to all tested antimicrobials except clindamycin (12.8% resistant) and erythromycin (24.7% resistant; **Table 3**)

Figure 2. MIC Distributions of Lefamulin for *Staphylococcus aureus* Isolates Collected From Medical Centers Worldwide in 2017



CoNS=coagulase-negative *Staphylococcus* spp.; MIC=minimum inhibitory concentration; MRSA=methicillin-resistant *S. aureus*; MSSA=methicillin-susceptible *S. aureus*.

Table 1. Activity of Lefamulin and Comparator Agents Against *Staphylococcus aureus*

Antibacterial Agent	µg/mL			CLSI		
	MIC_{50}	MIC_{90}	Range	%S*	%I	%R
***S. aureus*, total (*n*=1544)**						
Lefamulin	**0.06**	**0.12**	**0.015–>16**	**[99.5]†**		
Azithromycin	0.5	>32	0.06–>32	59.6	0.4	40.0
Ceftaroline	0.25	1	≤0.06–4	95.5‡	4.5	0.0
Clindamycin	0.06	>2	≤0.03–>2	87.8	0.2	12.0
Daptomycin	0.25	0.25	≤0.12–1	100.0	–	–
Doxycycline	0.12	0.5	≤0.06–>8	97.2	1.8	1.0
Erythromycin	0.25	>8	≤0.06–>8	59.2	4.1	36.7
Levofloxacin	0.25	>4	0.06–>4	74.9	0.1	24.9
Linezolid	1	2	0.25–4	100.0	–	0.0
Moxifloxacin	≤0.06	4	≤0.06–>4	75.2	3.4	21.4
Oxacillin	0.5	>2	0.12–>2	67.9	–	32.1
Tigecycline	0.06	0.12	≤0.015–0.5	100.0§	–	–
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5–>16	98.3	–	1.7
Vancomycin	1	1	0.25–2	100.0	0.0	0.0
MRSA (*n*=495)						
Lefamulin	**0.06**	**0.12**	**0.015–>16**	**[98.6]†**		
Azithromycin	>32	>32	0.06–>32	25.9	0.0	74.1
Ceftaroline	0.5	2	0.25–4	85.8‡	14.2	0.0
Clindamycin	0.06	>2	≤0.03–>2	67.7	0.2	32.1
Daptomycin	0.25	0.5	≤0.12–1	100.0	–	–
Doxycycline	0.12	2	≤0.06–>8	92.5	4.8	2.6
Erythromycin	>8	>8	≤0.06–>8	25.5	3.6	70.9
Levofloxacin	>4	>4	0.12–>4	34.7	0.0	65.3
Linezolid	1	2	0.25–4	100.0	–	0.0
Moxifloxacin	2	>4	≤0.06–>4	35.2	8.1	56.8
Oxacillin	>2	>2	>2–>2	0.0	–	100.0
Tigecycline	0.06	0.25	0.03–0.5	100.0§	–	–
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5–>16	95.6	–	4.4
Vancomycin	1	1	0.25–2	100.0	0.0	0.0
XDR *S. aureus*† (*n*=46)						
Lefamulin	**0.06**	**0.12**	**0.03–0.25**	**[100.0]†**		
Azithromycin	>32	>32	32–>32	0.0	0.0	100.0
Ceftaroline	2	4	0.25–4	45.7‡	54.3	0.0
Clindamycin	>2	>2	>2–>2	0.0	0.0	100.0
Daptomycin	0.25	0.5	≤0.12–0.5	100.0	–	–
Doxycycline	1	>8	≤0.06–>8	58.7	19.6	21.7
Erythromycin	>8	>8	>8–>8	0.0	0.0	100.0
Levofloxacin	>4	>4	4–>4	0.0	0.0	100.0
Linezolid	1	2	0.5–2	100.0	–	0.0
Moxifloxacin	4	>4	0.5–>4	2.2	2.2	95.7
Oxacillin	>2	>2	>2–>2	0.0	–	100.0
Tigecycline	0.12	0.25	0.03–0.5	100.0§	–	–
Trimethoprim-sulfamethoxazole	≤0.5	4	≤0.5–>16	87.0	–	13.0
Vancomycin	1	1	0.5–2	100.0	0.0	0.0

CLSI=Clinical and Laboratory Standards Institute; I=intermediate; MIC_{50}=minimum concentration at which 50% of the isolates were inhibited; MIC_{90}=minimum concentration at which 90% of the isolates were inhibited; MRSA=methicillin-resistant *S. aureus*; R=resistant; S=susceptible; XDR=extensively drug resistant.
*Criteria as published by CLSI 2019.
†Percentages inhibited at proposed lefamulin breakpoint of ≤0.5 µg/mL for *S. aureus* shown for reference.
‡Intermediate interpreted as susceptible-dose dependent.
§US Food and Drug Administration breakpoints accessed February 2018.
¶Resistant to oxacillin, erythromycin, levofloxacin, clindamycin, and gentamicin.

Table 2. Activity of Lefamulin and Comparator Agents Against Coagulase-Negative *Staphylococcus* spp.

Antibacterial Agent	µg/mL			CLSI		
	MIC_{50}	MIC_{90}	Range	%S*	%I	%R
CoNS† (*n*=268)						
Lefamulin	**0.06**	**0.5**	**0.015–>16**	**[94.0]‡**		
Azithromycin	32	>32	0.06–>32	37.5	0.4	62.2
Ceftaroline	0.25	1	≤0.06–4	–	–	–
Clindamycin	0.06	>2	≤0.03–>2	71.3	1.1	27.6
Daptomycin	0.25	0.5	≤0.12–1	100.0	–	–
Doxycycline	0.25	4	≤0.06–>8	91.8	4.5	3.7
Erythromycin	>8	>8	≤0.06–>8	36.9	1.9	61.2
Levofloxacin	0.5	>4	0.06–>4	53.7	1.5	44.8
Linezolid	1	1	0.25–>8	98.9	–	1.1
Moxifloxacin	0.12	4	≤0.06–>4	57.8	10.8	31.3
Oxacillin	>2	>2	≤0.06–>2	29.9	–	70.1
Tigecycline	0.12	0.25	0.03–0.5	–	–	–
Trimethoprim-sulfamethoxazole	≤0.5	16	≤0.5–>16	60.8	–	39.2
Vancomycin	2	2	≤0.12–4	100.0	0.0	0.0
XDR CoNS§ (*n*=37)						
Lefamulin	**0.06**	**1**	**0.03–16**	**[89.2]‡**		
Azithromycin	>32	>32	>32–>32	0.0	0.0	100.0
Ceftaroline	0.5	1	0.25–2	–	–	–
Clindamycin	>2	>2	>2–>2	0.0	0.0	100.0
Daptomycin	0.25	0.5	0.25–0.5	100.0	–	–
Doxycycline	0.5	1	≤0.06–>8	91.9	5.4	2.7
Erythromycin	>8	>8	>8–>8	0.0	0.0	100.0
Levofloxacin	>4	>4	4–>4	0.0	0.0	100.0
Linezolid	0.5	1	0.25–2	100.0	–	0.0
Moxifloxacin	2	>4	0.5–>4	5.4	29.7	64.9
Oxacillin	>2	>2	2–>2	0.0	–	100.0
Tigecycline	0.12	0.25	0.03–0.5	–	–	–
Trimethoprim-sulfamethoxazole	8	16	≤0.5–>16	10.8	–	89.2
Vancomycin	2	2	0.5–2	100.0	0.0	0.0

CLSI=Clinical and Laboratory Standards Institute; CoNS=coagulase-negative *Staphylococcus* spp.; I=intermediate; MIC_{50}=minimum concentration at which 50% of the isolates were inhibited; MIC_{90}=minimum concentration at which 90% of the isolates were inhibited; R=resistant; S=susceptible; XDR=extensively drug resistant.
*Criteria as published by CLSI 2019.
†Organisms include *Staphylococcus capitis* (22), *S. cohnii* (5), *S. epidermidis* (143), *S. haemolyticus* (36), *S. hominis* (26), *S. lugdunensis* (21), *S. pettenkoferi* (1), *S. pseudintermedius* (1), *S. saprophyticus* (7), *S. simulans* (3), and *S. warneri* (3).
‡Percentages inhibited at proposed lefamulin breakpoint of ≤0.5 µg/mL for CoNS shown for reference. The proposed breakpoint is based on *S. aureus* nonclinical pharmacokinetic-pharmacodynamic cut-off.
§Resistant to oxacillin, erythromycin, levofloxacin, clindamycin, and gentamicin. Organisms include *Staphylococcus capitis* (2), *S. epidermidis* (28), *S. haemolyticus* (5), and *S. hominis* (2).

Table 3. Activity of Lefamulin and Comparator Agents Against β-Hemolytic *Streptococcus* spp.

Antibacterial Agent	µg/mL			CLSI		
	MIC_{50}	MIC_{90}	Range	%S*	%I	%R
β-hemolytic *Streptococcus* spp.† (*n*=430)						
Lefamulin	**0.03**	**0.03**	**≤0.008–>32**	**[99.5]‡**		
Ceftriaxone	0.03	0.06	≤0.015–0.5	100.0	–	–
Clindamycin	≤0.25	>2	≤0.25–>2	84.4	2.8	12.8
Erythromycin	0.03	>16	≤0.015–>16	74.2	1.2	24.7
Levofloxacin	1	1	0.25–>4	97.4	0.0	2.6
Penicillin	0.015	0.06	≤0.008–0.12	100.0	–	–
Trimethoprim-sulfamethoxazole	≤0.12	0.25	≤0.12–>4	–	–	–
Vancomycin	0.5	0.5	0.12–1	100.0	–	–
***Streptococcus pyogenes* (*n*=180)**						
Lefamulin	**0.03**	**0.03**	**≤0.008–0.06**	**[100.0]‡**		
Ceftriaxone	0.03	0.03	≤0.015–0.5	100.0	–	–
Clindamycin	≤0.25	≤0.25	≤0.25–>2	96.1	0.0	3.9
Erythromycin	0.03	0.5	≤0.015–>16	88.9	1.1	10.0
Levofloxacin	0.5	1	0.25–>4	99.4	0.0	0.6
Penicillin	≤0.008	0.015	≤0.008–0.12	100.0	–	–
Trimethoprim-sulfamethoxazole	≤0.12	0.25	≤0.12–0.5	–	–	–
Vancomycin	0.5	0.5	0.12–1	100.0	–	–
***Streptococcus agalactiae* (*n*=180)**						
Lefamulin	**0.03**	**0.03**	**≤0.008–>32**	**[98.9]‡**		
Ceftriaxone	0.06	0.06	≤0.015–0.5	100.0	–	–
Clindamycin	≤0.25	>2	≤0.25–>2	71.7	5.0	23.3
Erythromycin	0.06	>16	≤0.015–>16	58.3	1.1	40.6
Levofloxacin	1	1	0.5–>4	94.4	0.0	5.6
Penicillin	0.03	0.06	≤0.008–0.12	100.0	–	–
Trimethoprim-sulfamethoxazole	≤0.12	0.25	≤0.12–1	–	–	–
Vancomycin	0.5	0.5	0.25–1	100.0	–	–
***Streptococcus dysgalactiae* (*n*=70)**						
Lefamulin	**0.03**	**0.06**	**0.015–0.12**	**[100.0]‡**		
Ceftriaxone	0.03	0.06	≤0.015–0.06	100.0	–	–
Clindamycin	≤0.25	0.5	≤0.25–>2	87.1	4.3	8.6
Erythromycin	0.06	8	0.03–>16	77.1	1.4	21.4
Levofloxacin	0.5	1	0.25–2	100.0	0.0	0.0
Penicillin	0.015	0.015	≤0.008–0.03	100.0	–	–
Trimethoprim-sulfamethoxazole	≤0.12	≤0.12	≤0.12–>4	–	–	–
Vancomycin	0.25	0.5	0.25–0.5	100.0	–	–
Macrolide-resistant β-hemolytic *Streptococcus* spp.§ (*n*=106)						
Lefamulin	**0.03**	**0.03**	**≤0.008–16**	**[99.1]‡**		
Ceftriaxone	0.06	0.06	≤0.015–0.5	100.0	–	–
Clindamycin	1	>2	≤0.25–>2	39.6	9.4	50.9
Erythromycin	8	>16	1–>16	0.0	0.0	100.0
Levofloxacin	1	2	0.25–>4	95.3	0.0	4.7
Penicillin	0.03	0.06	≤0.008–0.12	100.0	–	–
Trimethoprim-sulfamethoxazole	≤0.12	0.25	≤0.12–0.25	–	–	–
Vancomycin	0.5	0.5	0.25–1	100.0	–	–

CLSI=Clinical and Laboratory Standards Institute; I=intermediate; MIC_{50}=minimum concentration at which 50% of the isolates were inhibited; MIC_{90}=minimum concentration at which 90% of the isolates were inhibited; R=resistant; S=susceptible.
*Criteria as published by CLSI 2019.
†Organisms include *Streptococcus agalactiae* (180), *S. dysgalactiae* (70), and *S. pyogenes* (180).
‡Percentages inhibited at proposed lefamulin breakpoint of ≤0.25 µg/mL for β-hemolytic *Streptococcus* spp. shown for reference.
§Applying the CLSI breakpoint for erythromycin. Organisms include *Streptococcus agalactiae* (73), *S. dysgalactiae* (15), and *S. pyogenes* (18).

CONCLUSIONS

- LEF demonstrated potent in vitro activity against this contemporary collection of pathogens that commonly cause ABSSSI and BSI
- The activity of LEF was not affected by resistance to other classes of antibiotics and fully covered XDR isolates, which are resistant to at least 5 antibiotic classes
- These data support the continued development of LEF for the treatment of ABSSSI and further exploration of LEF activity in BSI

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Disclosures

Susanne Paukner and Steven P. Gelone are employees of and hold stock in Nabriva Therapeutics plc. S.J. Ryan Arends and Helio S. Sader are employees of JMI Laboratories, which was contracted by Nabriva Therapeutics to conduct the susceptibility testing.

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