P1823

Antimicrobial Activity of Lefamulin Against a Large Longitudinal Collection of Clinical Bacterial Isolates Collected Worldwide: Results From the SENTRY Antimicrobial Surveillance Programme

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INTRODUCTION & PURPOSE

- Lefamulin (LEF) is a semisynthetic pleuromutilin antibiotic in late-stage clinical development for intravenous (IV) and oral treatment of community-acquired pneumonia (CAP) and acute bacterial skin and skin structure infections (ABSSSI)
- LEF inhibits protein synthesis by binding the 50S ribosomal subunit at the A- and P-sites in the peptidyl transferase centre
- LEF has demonstrated activity against a variety of pathogens, including those commonly associated with CAP and ABSSSI, and its activity is not influenced by resistance to other antimicrobial classes
- In a recent phase 3 trial for the treatment of CAP (ClinicalTrials.gov identification number NCT02559310), LEF (150 mg IV q12h or for 5–7 days) was noninferior to moxifloxacin ± linezolid (400 mg IV q24h for 7 days) when patients initiated IV drug with optional oral switch (600 mg LEF q12h or 400 mg moxifoxacin q24h).[1] LEF noninferiority to moxifloxacin was also observed in a second phase 3 trial when patients received oral LEF 600 mg q12h for 5 days or oral moxifoxacin 400 mg q24h for 7 days (ClinicalTrials.gov identification number NCT02813694)[2]
- The objective of this investigation was to evaluate the *in vitro* activities of LEF and comparators against clinical bacteria collected worldwide during 3 years of surveillance

METHODS

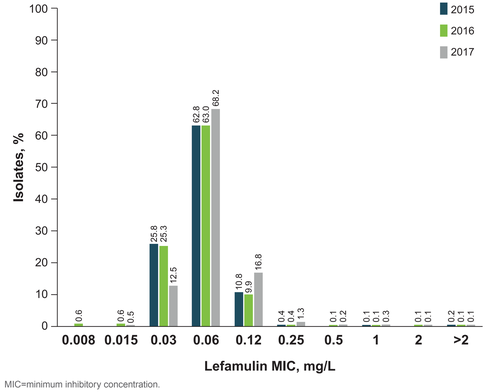
- 15,036 bacterial isolates, including 6018 *Streptococcus pneumoniae* and 4463 *Staphylococcus aureus* isolates, among others, were collected from medical centres in Europe (*n*=5712 [19 nations]), the United States (*n*=5731), the Asia-Pacific region (APAC; *n*=2132 [10 nations]), and Latin America (*n*=1461 [6 nations]) from 2015–2017 as part of the SENTRY Antimicrobial Surveillance Programme
- Susceptibility was tested against LEF and numerous comparators by reference broth microdilution method according to Clinical and Laboratory Standards Institute guidelines[3] at a central laboratory
- The following proposed LEF breakpoints were applied: ≤0.5 mg/L for *Staphylococcus* spp., viridans group streptococci, and *Moraxella catarrhalis*; ≤1 mg/L for *S. pneumoniae*; ≤0.25 mg/L for β-haemolytic streptococci; ≤4 mg/L for *Haemophilus influenzae*; and ≤8 mg/L for *Haemophilus parainfluenzae*
- LEF resistance mechanisms were evaluated by whole genome sequencing and *in silico* analysis

RESULTS

- LEF was active against *S. aureus* independent of oxacillin resistance (minimum concentration at which 50% or 90% of the isolates were inhibited [$MIC_{50/90}$], 0.06/0.12 mg/L); only 9 (0.2%) isolates exhibited LEF minimum inhibitory concentration (MIC) >1 mg/L, and oxacillin resistance varied from 22.3% (Europe) to 41.4% (United States; 32.1% overall; **Tables 1** and **2**)
- LEF activity against *S. aureus* remained very stable over the study period **(Figure 1)**
- LEF was highly active against *S. pneumoniae* ($MIC_{50/90}$, 0.06/0.12 mg/L; highest MIC, 1 mg/L; **Table 1**) and retained activity against isolates resistant to penicillin (MIC, >2 mg/L [EUCAST], *n*=311), erythromycin (*n*=2080), tetracycline (*n*=1424), and/or trimethoprim-sulfamethoxazole (*n*=1091), with $MIC_{50/90}$ of 0.06/0.12 mg/L for these subsets **(Figure 2)**
- LEF was also active against levofloxacin-resistant (MIC, >2 mg/L [EUCAST]) isolates (*n*=86; $MIC_{50/90}$, 0.06/0.25 mg/L; **Figure 2**)
- Overall rates of *S. pneumoniae* susceptibility to penicillin (at ≤0.06 mg/L), amoxicillin-clavulanate, azithromycin, and tetracycline were 65.0%, 93.5%, 65.6%, and 75.9%, respectively, and susceptibility rates were generally lower in APAC compared with other regions **(Table 1)**
- LEF exhibited similar activity against β-lactamase–positive (24.2% overall) and –negative *H. influenzae*, with $MIC_{50/90}$ of 0.5/1 mg/L for both groups (**Tables 1** and **2** show all *H. influenzae* isolates combined)
- LEF MIC values were generally low among β-haemolytic streptococci ($MIC_{50/90}$, 0.03/0.03 mg/L), with only 5 (0.6%, all *Streptococcus agalactiae*) isolates showing MIC >0.12 mg/L (**Tables 1** and **2**)
- LEF was also active against coagulase-negative staphylococci ($MIC_{50/90}$, 0.03/0.12 mg/L), viridans group streptococci ($MIC_{50/90}$, 0.06/2 mg/L), and *H. parainfluenzae* ($MIC_{50/90}$, 1/4 mg/L; **Table 1**)
- Isolates with elevated LEF MIC results (compared with the wild-type population) were rare and mainly caused by *vga*(A) in staphylococci and *lsa*(E) in streptococci (data not shown); the methyltransferase *cfr* was detected in only 2 coagulase-negative staphylococci (in 2016), whereas not a single *cfr*-positive isolate was detected in *S. aureus* in the complete 2015–2017 testing period

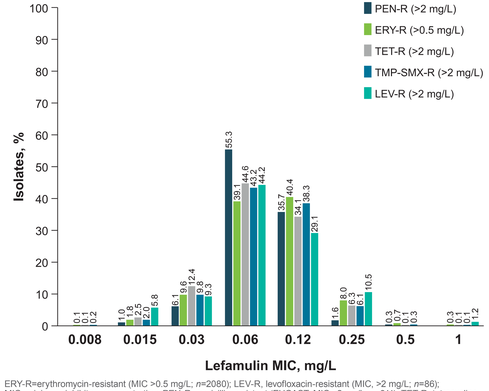
RESULTS (continued)

Figure 1. Lefamulin MIC Distribution for *S. aureus* Stratified by Year



MIC=minimum inhibitory concentration.

Figure 2. Lefamulin MIC Distribution for *S. pneumoniae*–Resistant Subsets



ERY-R=erythromycin-resistant (MIC >0.5 mg/L; *n*=2080); LEV-R, levofloxacin-resistant (MIC, >2 mg/L; *n*=86); MIC=minimum inhibitory concentration; PEN-R=penicillin-resistant (EUCAST; MIC >2 mg/L; *n*=311); TET-R=tetracycline-resistant (MIC >2 mg/L; *n*=1424); TMP-SMX-R, trimethoprim-sulfamethoxazole-resistant (MIC, >2 mg/L; *n*=1091).

Table 1. Lefamulin MIC Distribution for the Organisms and Main Resistant Subsets, 2015–2017

Organism/Organism Group (Isolates)	*n*	Lefamulin MIC, mg/L, Cumulative %										mg/L	
		≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8	MIC_{50}	MIC_{90}
S. pneumoniae	6018	1.7	11.0	52.8	91.4	99.6	99.9	100.0					0.06	0.12
Penicillin-resistant (>2 mg/L)	311	1.0	7.1	62.4	98.1	99.7	100.0						0.06	0.12
S. aureus	4463		21.5	86.3	98.8	99.5	99.6	99.8				100.0	0.06	0.12
Methicillin-resistant	1433		22.8	75.4	97.1	99.1	99.2	99.5				100.0	0.06	0.12
H. influenzae	1656				2.1	19.2	65.0	90.8	99.3	99.9	100.0		0.5	1
M. catarrhalis	897	3.2	14.3	89.9	99.9	100.0							0.06	0.12
β-haemolytic streptococci	819	26.4	94.1	98.3	99.4	99.4	99.4	99.4	99.4	99.4	99.6	100.0	0.03	0.03
CoNS	544	9.2	55.0	89.0	91.7	92.5	95.0	96.5	97.4	98.3	99.1	100.0	0.03	0.12
Viridans group streptococci	327	17.1	27.2	52.9	70.0	79.5	86.5	89.6	96.0	99.1	99.4	100.0	0.06	2
H. parainfluenzae	312				8.7	17.3	32.7	55.1	84.6	97.8	100.0		1	4

CoNS=coagulase-negative staphylococci; MIC=minimum inhibitory concentration; MIC_{50}=minimum concentration at which 50% of the isolates were inhibited; MIC_{90}=minimum concentration at which 90% of the isolates were inhibited.

Table 2. Antimicrobial Activity of Lefamulin and Comparators Stratified by Geographic Region, 2015–2017

Organism/Antimicrobial Agent	Susceptibility (EUCAST*) by Region, %			
	USA	EUR	APAC	LATAM
S. aureus*, *n	**1593**	**1566**	**653**	**651**
Lefamulin*	**[99.6]**	**[99.6]**	**[99.7]**	**[99.5]**
Azithromycin	43.0	71.9	68.8	56.1
Ceftaroline	97.7	96.7	89.1	91.4
Clindamycin	81.7	93.6	82.8	82.6
Doxycycline	96.7	96.3	83.2	96.6
Levofloxacin	63.3	79.8	75.2	79.3
TMP-SMX	97.7	99.7	95.3	98.8
Oxacillin	58.6	77.7	62.6	72.5
MRSA, *n*	**660**	**350**	**244**	**179**
Lefamulin*	**[99.2]**	**[98.9]**	**[99.2]**	**[99.4]**
Azithromycin	11.8	38.3	34.4	27.4
Ceftaroline	94.4	85.4	70.9	68.5
Doxycycline	95.9	93.7	61.9	95.5
Levofloxacin	27.0	24.0	37.7	34.6
TMP-SMX	95.2	99.4	88.1	96.1
S. pneumoniae*, *n	**2367**	**2613**	**735**	**303**
Lefamulin*	**[100.0]**	**[100.0]**	**[100.0]**	**[100.0]**
Amoxicillin-clavulanate	80.3	84.1	69.7	85.1
Azithromycin	54.7	75.7	55.4	70.2
Ceftriaxone	87.1	87.3	75.2	87.1
Levofloxacin	99.2	98.0	97.8	100.0
Tetracycline	80.5	77.6	57.1	70.5
TMP-SMX	80.2	78.9	70.2	70.0
Penicillin-resistant† *S. pneumoniae*, *n*	**82**	**126**	**80**	**23**
Lefamulin*	**[100.0]**	**[100.0]**	**[100.0]**	**[100.0]**
Amoxicillin-clavulanate	0.0	0.0	0.0	0.0
Azithromycin	0.0	23.0	0.0	0.0
Ceftriaxone	0.0	0.0	1.2	0.0
Levofloxacin	98.8	94.4	90.0	100.0
Tetracycline	6.1	28.6	1.2	26.1
TMP-SMX	4.9	4.0	26.2	0.0

Organism/Antimicrobial Agent	Susceptibility (EUCAST*) by Region, %			
	USA	EUR	APAC	LATAM
β-haemolytic streptococci, *n*	**265**	**265**	**152**	**137**
Lefamulin*	**[100.0]**	**[100.0]**	**[98.0]**	**[98.5]**
Ceftriaxone	100.0	100.0	100.0	100.0
Erythromycin	64.9	76.6	81.6	79.6
Levofloxacin	100.0	98.9	94.7	92.0
Penicillin	100.0	100.0	100.0	100.0
CoNS, *n*	**166**	**165**	**103**	**110**
Lefamulin*	**[93.4]**	**[97.0]**	**[95.1]**	**[94.5]**
Azithromycin	32.1	38.8	50.5	27.3
Clindamycin	62.7	81.8	71.8	57.3
Doxycycline	83.7	89.1	90.3	95.5
Levofloxacin	55.4	40.0	65.0	45.5
TMP-SMX	71.1	60.6	64.1	54.5
Oxacillin	38.0	27.3	30.1	22.7
H. influenzae*, *n	**618**	**618**	**271**	**149**
Lefamulin*	**[100.0]**	**[100.0]**	**[100.0]**	**[99.3]**
Amoxicillin-clavulanate	93.7	95.6	84.5	94.0
Azithromycin	99.4	99.7	98.5	94.6
Ceftriaxone	99.4	100.0	93.4	100.0
Levofloxacin	98.1	98.9	95.9	98.7
Tetracycline	98.7	98.9	95.9	97.3
TMP-SMX	65.3	67.8	55.4	67.8
Viridans group streptococci, *n*	**106**	**124**	**59**	**38**
Lefamulin*	**[86.8]**	**[84.7]**	**[88.1]**	**[89.5]**
Ceftriaxone	96.2	95.2	89.8	92.1
Clindamycin	87.7	86.3	91.5	89.5
Penicillin	88.7	87.9	81.4	76.3

APAC=Asia-Pacific region; CoNS=coagulase-negative staphylococci; EUR=Europe; LATAM=Latin America; MRSA=methicillin-resistant *S. aureus*; TMP-SMX=trimethoprim-sulfamethoxazole.

*Percentages inhibited at proposed lefamulin breakpoint of ≤0.5 mg/L *Staphylococcus* spp. and viridans group streptococci, ≤1 mg/L for *S. pneumoniae*, ≤0.25 mg/L for β-haemolytic streptococci, and ≤4 mg/L for *H. influenzae* are shown in brackets for comparison purpose only.

†Penicillin MIC >2 mg/L for indications other than pneumonia.

CONCLUSIONS

- LEF displayed stable and potent *in vitro* activity against a large, 3-year, contemporary worldwide collection of bacterial isolates regardless of resistance phenotype to other antibiotic classes, including β-lactams, tetracyclines, macrolides and fluoroquinolones, among others
- Percentages of isolates with elevated LEF MIC values (putative resistant) were very low and primarily caused by target protection by ATP-binding cassette F (ABC-F) proteins such as *vga*(A, E), *lsa*(E), and *sal*(A), respectively, whereas *cfr* has hardly been detected (2 of >15,000 total tested isolates)
- The coverage of CAP pathogens including resistant isolates (this study) and atypical respiratory pathogens (demonstrated in other studies) supports the ongoing clinical development of LEF as an empiric IV and oral monotherapy for the treatment of CAP and other respiratory tract infections

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