



# In Vitro Activity of Lefamulin against Bacterial Pathogens Commonly Causing Community-Acquired Bacterial Pneumonia (CAP): 2015 SENTRY Data from Europe

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## INTRODUCTION & PURPOSE

**Background:** Lefamulin is the first semi-synthetic pleuromutilin antibiotic for IV and oral use in humans. It is currently in Phase 3 trials for the treatment of CAP in adults. Lefamulin effectively and selectively inhibits bacterial translation by binding to the peptidyl transferase center (PTC) at two sites. It interacts via four H-bonds and other interactions resulting in an "induced fit" whereby nucleotides in the PTC shift and further tighten the binding pocket around lefamulin (Figure 1).<sup>1,2</sup>

Lefamulin has demonstrated potent *in vitro* activity against a variety of pathogens that cause skin and soft tissue infections and respiratory tract infections caused by Gram positive, fastidious Gram-negative, and atypical bacteria including *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella pneumophila*.<sup>3,4</sup> Lefamulin showed similar efficacy to IV vancomycin in a clinical Phase 2 trial in patients with acute bacterial skin and skin structure infections.<sup>5</sup> Furthermore, lefamulin has been well tolerated in phase 1 and phase 2 trials.

CAP is the number one infectious diseases cause of death worldwide and emerging resistance complicates its treatment.<sup>6</sup> This study investigated the activity of lefamulin and comparators against a contemporary set of bacterial respiratory pathogens collected in Europe.

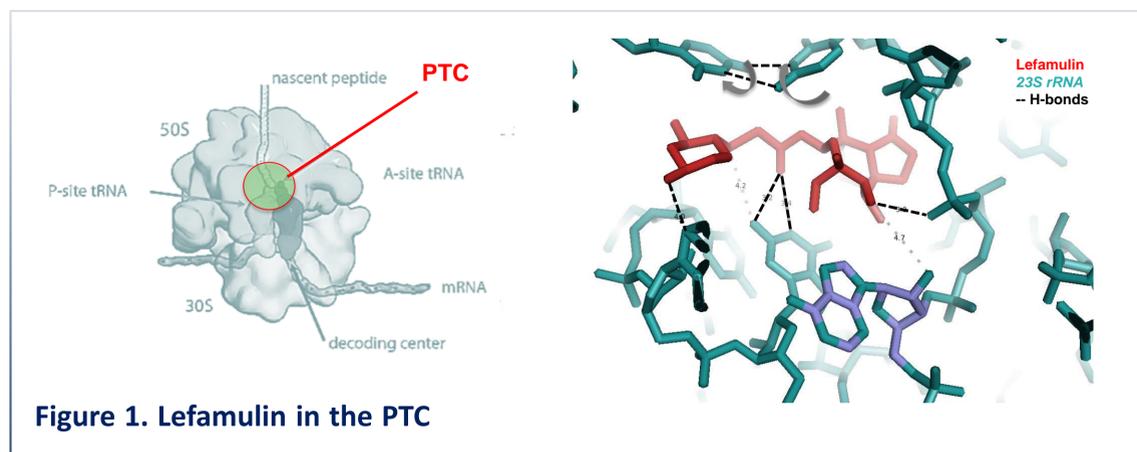


Figure 1. Lefamulin in the PTC

## METHODS

Unique patients' isolates ( $n=1040$ ) were collected in Europe (19 countries, 36 sites) from patients with respiratory tract infections (87.5%), blood stream infections (8.4%) and other infections (4.1%). Only one isolate per patient infection episode was included in surveillance.

Lefamulin and comparators were tested by CLSI broth microdilution methods and susceptibility was determined using the EUCAST (2017) breakpoints.<sup>7,8</sup> QC reference organisms were tested concurrently for lefamulin and comparator agents.

## RESULTS

- Lefamulin displayed potent antibacterial activity against this collection of respiratory pathogens with all 1040 isolates inhibited at concentrations of  $\leq 2$  mg/L (Table 1).
- Lefamulin was the most active compound against *S. pneumoniae* (MIC<sub>50/90</sub> of 0.06/0.12 mg/L) with only 3 isolates inhibited by a lefamulin concentration of  $\geq 0.5$   $\mu$ g/mL
  - S. pneumoniae* isolates were susceptible to levofloxacin (98.6%), whereas 27.6%, 24.6% and 13.2% of isolates were resistant to macrolides, tetracycline, and ceftriaxone, respectively.

Table 1. Susceptibility of CABP pathogens against lefamulin and comparators

Organism (N)	MIC <sub>50</sub>	MIC <sub>90</sub>	MIC <sub>99</sub>	Range	% Susceptible <sup>a</sup>	% Intermediate <sup>a</sup>	% Resistant <sup>b</sup>
<b><i>S. pneumoniae</i> (710)</b>							
Lefamulin	0.06	0.12	0.25	$\leq 0.008$ to 1			
Amoxicillin-clavulanic acid	$\leq 0.03$	2	>4	$\leq 0.03$ to >4			
Azithromycin	0.06	>4	>4	$\leq 0.03$ to >4	72.1	0.3	27.6
Ceftaroline	$\leq 0.008$	0.12	0.25	$\leq 0.008$ to 0.25	100.0		0.0
Ceftriaxone	0.03	1	2	$\leq 0.015$ to >2	86.8	12.5	0.7
Clindamycin	$\leq 0.12$	>1	>1	$\leq 0.12$ to >1	81.0		19.0
Erythromycin	0.03	>2	>2	$\leq 0.015$ to >2	72.3	0.1	27.6
Imipenem	$\leq 0.015$	0.25	0.5	$\leq 0.015$ to 0.5	100.0		0.0
Levofloxacin	1	1	>4	$\leq 0.12$ to >4	98.6		1.4
Penicillin	$\leq 0.06$	2	4	$\leq 0.06$ to 8	68.6	27.3	4.1 <sup>b</sup>
Tetracycline	0.25	>4	>4	$\leq 0.12$ to >4	74.8	0.6	24.6
<b><i>H. influenzae</i> (170)</b>							
Lefamulin	0.5	1	2	$\leq 0.12$ to 2			
Amoxicillin-clavulanic acid	0.5	2	4	$\leq 0.12$ to 8	97.6		2.4
Ampicillin	0.25	8	>8	0.12 to >8	84.7		15.3 <sup>c</sup>
Azithromycin	0.5	1	2	0.12 to 2	1.2	98.8	0.0
Ceftriaxone	$\leq 0.015$	$\leq 0.015$	0.06	$\leq 0.015$ to 0.06	100.0		0.0
Clarithromycin	4	8	16	1 to 16	2.4	97.6	0.0
Levofloxacin	$\leq 0.015$	$\leq 0.015$	0.5	$\leq 0.015$ to 0.5	98.2		1.8
Tetracycline	0.5	0.5	0.5	$\leq 0.12$ to >16	99.4	0.0	0.6
Trimethoprim-sulfamethoxazole	0.06	>4	>4	$\leq 0.03$ to >4	74.7	2.9	22.4
<b><i>M. catarrhalis</i> (160)</b>							
Lefamulin	0.06	0.12	0.12	$\leq 0.008$ to 0.12			
Amoxicillin-clavulanic acid	0.12	0.25	0.25	$\leq 0.03$ to 0.25	100.0		0.0
Azithromycin	0.015	0.03	0.06	0.002 to 0.06	100.0	0.0	0.0
Ceftriaxone	0.25	0.5	0.5	$\leq 0.015$ to 1	100.0	0.0	0.0
Erythromycin	0.12	0.12	0.5	$\leq 0.015$ to 1	98.8	0.6	0.6
Levofloxacin	0.03	0.06	0.06	$\leq 0.015$ to 0.5	100.0		0.0
Tetracycline	0.12	0.25	0.5	$\leq 0.03$ to 0.5	100.0	0.0	0.0

<sup>a</sup> Criteria as published by EUCAST [2017]

<sup>b</sup> Non-meningitis breakpoints applied for penicillin

<sup>c</sup>  $\beta$ -lactamase positive, reported as resistant for penicillins without inhibitors

## RESULTS (con't)

- Lefamulin's activity was not affected by resistance to other antibiotic classes.
  - MIC<sub>50/90</sub> of lefamulin against penicillin non-susceptible *S. pneumoniae* ( $n=223$ , non-meningitis breakpoint of  $>0.06$   $\mu$ g/mL) were 0.06/0.12  $\mu$ g/mL
  - 100% of *S. pneumoniae* resistant to penicillin ( $n=29$ , breakpoint  $>2$   $\mu$ g/mL) were inhibited by lefamulin concentrations of  $\leq 0.12$   $\mu$ g/mL;
    - PRSP showed high resistance rates to macrolides (93.1%), tetracycline (89.7%), amoxicillin-clavulanic acid (62.1%) and trimethoprim-sulfamethoxazole (96.6%) whereas PRSP were largely susceptible to levofloxacin (82.8%), tigecycline (100%) and vancomycin (100%).
  - 98.5% of macrolide-resistant *S. pneumoniae* ( $n=196$ ) were inhibited by  $\leq 0.25$   $\mu$ g/mL lefamulin (MIC<sub>50/90</sub> 0.06/0.12  $\mu$ g/mL, range 0.008-1  $\mu$ g/mL)
- Against the fastidious respiratory pathogens, lefamulin showed potent activity and was not affected by  $\beta$ -lactamase production.
  - H. influenzae*, MIC<sub>50/90</sub> of 0.5/1 mg/L, including 12.9% of  $\beta$ -lactamase producing strains
  - M. catarrhalis*, MIC<sub>50/90</sub> of 0.06/0.12 mg/L

## CONCLUSIONS

- Lefamulin demonstrated potent *in vitro* activity against a contemporary collection of respiratory pathogens from Europe.
- Lefamulin was active regardless of resistance phenotype to the other antibiotic classes including macrolides,  $\beta$ -lactams, tetracyclines or fluoroquinolones.
- The lefamulin activity against this contemporary collection is consistent with results obtained from previous studies including a variety of *S. pneumoniae* serotypes.<sup>9</sup>
- These data support the continued clinical development of lefamulin for the treatment of respiratory tract infections, including CAP.

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