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P1828 *In vitro* activity of lefamulin against isolates commonly causing community-acquired bacterial pneumonia collected during the SENTRY surveillance programme 2017 in Europe

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Background: Lefamulin, a novel pleuromutilin in development for use as intravenous and oral monotherapy, recently demonstrated noninferiority to moxifloxacin and a favourable tolerability profile in two phase 3 trials in adults with community-acquired bacterial pneumonia (CABP). Lefamulin inhibits protein synthesis by selectively binding to a highly conserved region on the peptidyl transferase centre of the 50S ribosome. This study investigated lefamulin's activity against bacterial pathogens that commonly cause CABP collected in Europe in 2017.

Materials/methods: As part of the SENTRY Surveillance Programme, isolates (*n*=1766, 1/patient) were collected in Europe (18 countries, 38 sites) from patients with community-acquired respiratory tract infections (62.5%), bloodstream infections (16.4%), pneumonia (hospitalised patients, 10.5%), skin/soft tissue infections (10.0%), and other infections (0.6%). Lefamulin and comparators were tested by CLSI broth microdilution. Susceptibility was determined using the CLSI (2018) and EUCAST (2018) breakpoints.

Results: Lefamulin demonstrated potent antibacterial activity against all pathogens and was unaffected by resistance to other antibiotic classes (**Table**). *Streptococcus pneumoniae* isolates were largely susceptible (>80%) to most comparators; however, 23.3% and 22.2% demonstrated resistance to macrolides and tetracycline, respectively. Lefamulin inhibited *S. pneumoniae*, with all isolates inhibited at ≤0.5 mg/L and resistant subsets showing $MIC_{50/90}$ of 0.06/0.12 mg/L for multidrug-resistant and penicillin-nonsusceptible isolates and 0.06/0.25 mg/L for macrolide-resistant isolates. *Staphylococcus aureus* overall, and particularly methicillin-resistant *S. aureus* (MRSA) strains, were commonly resistant (R) to macrolides (55.7% R). An $MIC_{50/90}$ of 0.06/0.12 mg/L for lefamulin was observed for macrolide-resistant *S. aureus* (43.8% MRSA). *Haemophilus influenzae* isolates were susceptible to all comparators except for ampicillin (26.2% R) and trimethoprim-sulfamethoxazole (33.3% R). Beta-lactamase-positive and trimethoprim-sulfamethoxazole–resistant *H. influenzae* displayed $MIC_{50/90}$ of 0.5/1 mg/L and 0.5/2 mg/L for lefamulin, respectively. Lastly, *Moraxella catarrhalis* isolates were susceptible to all comparators.

Conclusions: Lefamulin demonstrated potent *in vitro* activity against pathogens that commonly cause CABP collected in Europe in 2017. Its activity was unaffected by resistance to macrolides, β-lactams, fluoroquinolones, and tetracyclines. These data and the favourable efficacy in phase 3 trials support the continued development of lefamulin for the empiric treatment of CABP.

$MIC_{50/90}$ of Lefamulin and Comparators

	$MIC_{50/90}$ (mg/L)					
Organism (*n*)	Lefamulin	Amoxicillin/ Clavulanic acid	Azithromycin	Ceftriaxone/ Ceftaroline*	Moxifloxacin	Tetracycline/ Doxycycline‖
S. pneumoniae (950)	0.06/0.25	≤0.03/2	0.06/>4	0.03/1	0.12/0.25	0.5/>4
Penicillin nonsusceptible† (52)	0.06/0.12	>4/>4	>4/>4	2/2	0.12/0.5	>4/>4
Macrolide resistant‡ (221)	0.06/0.25	0.5/>4	>4/>4	0.5/2	0.12/0.25	>4/>4
Multidrug resistant§ (63)	0.06/0.12	2/>4	>4/>4	1/2	0.12/0.5	>4/>4
S. aureus (506)	0.06/0.12	ND	0.5/>32	0.25/0.5	≤0.06/2	0.12/0.25
MRSA (88)	0.06/0.12	ND	32/>32	1/2	2/>4	0.12/2
H. influenzae (225)	0.5/2	0.5/2	1/1	0.004/0.015	0.03/0.03	0.5/1
M. catarrhalis (85)	0.06/0.06	≤0.25/≤0.25	0.015/0.03	0.25/1	0.06/0.06	0.25/0.5

MRSA=methicillin-resistant *S. aureus*; ND=not determined.

*Ceftaroline for *S. aureus*; ceftriaxone for *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*; †Penicillin MIC ≥4 mg/L for nonmeningitis breakpoint; ‡Using the erythromycin breakpoint; §Multidrug resistant defined as resistant to tetracycline, erythromycin and trimethoprim-sulfamethoxazole; ‖Tetracycline for *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*; doxycycline for *S. aureus*.