**INTRODUCTION**

- Lefamulin is a novel fluorin class penicillin antibiotic approved in the United States (US), Europe (EU), and Canada for the oral and intravenous treatment of community-acquired pneumonia (CAP) in adults caused by susceptible typical and atypical bacterial organisms, including S. aureus.
- CAP is the most common infection-related cause of death in Europe, with an incidence of 1.7 to 11.6 cases per 1000 person-years.
- S. pneumoniae is the most frequently isolated bacterial pathogen from patients with CAP, with prevalences that vary by geographic region. Other bacterial causes of CAP include Haemophilus influenzae, Moraxella catarrhalis, and Staphylococcus aureus, as well as atypical pathogens.
- Increasing resistance rates and safety concerns around available antibiotics have created the need for new CAP treatment options.
- Lefamulin is a novel penicillin antibiotic protein synthesis inhibitor with a unique mode-of-action, low potential for resistance development and has demonstrated potent clinical efficacy in global phase 3 clinical trials in CAP patients with moderate to severe pneumonia with a good safety and tolerability profile.
- This study evaluated the in vitro activity of lefamulin and susceptibility of comparator antibiotics used to treat CAP against contemporary isolates from bacterial species responsible for CAP collected in European medical centers in 2020–2021.

**MATERIALS AND METHODS**

### Bacterial isolates

- Overall, 3,345 organisms were collected within the SENTRY Surveillance Program from 35 medical centers from the following countries:
  - Belgium
  - Czech Republic
  - France
  - Germany
  - Greece
  - Israel
  - Italy
  - Poland
  - Portugal
  - Romania
  - Russia
  - Slovenia
  - Sweden
  - Switzerland
  - Turkey
  - United Kingdom
- Isolates were from infections of the respiratory tract (44.8%), skin and soft tissue (28.9%), bloodstream (18.0%), and other sites (3.8%).
- Organisms were susceptibility tested by CLSI reference broth microdilution and EUCAST breakpoints were applied when available.

### RESULTS

- Lefamulin demonstrated potent antibacterial activity against all tested CAP pathogens and was unaffected by resistance to other antibacterial classes.
- S. pneumoniae (728)
  - 100% of S. pneumoniae isolates were inhibited at lefamulin concentrations at or below the susceptible EUCAST and CLSI breakpoints of 0.06/0.25 mg/L, lefamulin displayed MIC50/90 values of 0.06/0.25 mg/L (Table 1 and Figure 1).
  - Lefamulin activity against S. pneumoniae was not adversely affected by resistance to other antibacterials and lefamulin remained fully active against resistant subsets including macrolide-, doxycycline- and penicillin-resistant isolates (Table 1 and Figure 1).
- The susceptibility rates of other antibacterials that are commonly used to treat CAP were lower:
  - S. aureus (283) 0.06/0.12 (98.2) Not tested >8/>8 (42.8) 2/>4 (40.6)
  - H. influenzae Moxifloxacin-R (214) 0.06/0.25 (98.1) Not tested >8/>8 (40.7) 4/>4 (0.0)
  - Penicillin-R (43) 0.06/0.12 (100.0) >4/>4 (0.0) >4/>4 (34.9) 0.12/0.25 (97.7) 0.12/>1 (60.5)
  - H. parainfluenzae Lefamulin was active against H. parainfluenzae, demonstrating an MIC50 of 0.06/0.12 mg/L and 99.6% susceptibility per EUCAST, CLSI, and US FDA criteria (Table 1 and Figure 2).
- The susceptibility rates of other antibacterials that are commonly used to treat CAP were lower:
  - S. aureus
    - 99.6% susceptibility per EUCAST, CLSI, and US FDA criteria (Table 1 and Figure 2).
- Lefamulin was active against H. influenzae (99.6% susceptible when applying the US FDA and CLSI susceptible breakpoint of 32 mg/L), including β-lactamase-positive strain (Table 1).
- Against H. parainfluenzae lefamulin MIC50 were 0.24 µg/mL and all isolates were inhibited at lefamulin concentrations of 54 mg/L.
- β-hemolytic and viridans group Streptococcus spp.
  - Lefamulin activity was determined against β-hemolytic and viridans group streptococci with complete inhibition of isolates at concentrations ≤0.5 mg/L, the EUCAST and CLSI breakpoint for S. agalactiae (lefamulin MIC50 of 0.03/0.06 mg/L), S. pyogenes (lefamulin MIC50 of 0.03/0.03 mg/L), and viridans group streptococci (lefamulin MIC50 of 0.12/0.25 mg/L). Table 1.

### CONCLUSIONS

- Lefamulin displayed potent in vitro activity against this contemporary collection of CAP pathogens from Europe.
- Lefamulin activity was unaffected by resistance to other antibacterial classes and particularly those commonly used to treat CAP, including fluoroquinolones, macrolides, β-lactams, and tetracyclines.
- Lefamulin represents a valuable empiric treatment option for ambulatory and hospitalized patients with CAP irrespective of the current resistance rates in the respective regions, countries or institutions.

**REFERENCES**