28th ECCMID EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES
Madrid, Spain
21 – 24 April 2018

P0250 In vitro bactericidal activity of lefamulin against Streptococcus pneumoniae isolates

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Background: Targeted antibiotics that are effective against key pathogens causing community-acquired bacterial pneumonia (CABP) are needed. Lefamulin, the first pleuromutilin antibiotic for IV and oral use in humans, is currently in Phase 3 trials for the treatment of CABP. Lefamulin specifically inhibits bacterial protein synthesis by binding to the PTC via 4 H-bonds and other interactions at the A- and P-site resulting in an "induced fit." Lefamulin is highly active *in vitro* against pathogens causing CABP including *S. pneumoniae* (the leading cause of CABP in adults), *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus*, as well as atypical pathogens such as *Mycoplasma pneumoniae*. This study investigated the bactericidal activity of lefamulin against *S. pneumoniae* by growth kill-curve determinations.

Materials/methods: Kill-curves were determined for lefamulin at concentrations 1-, 2-, 4-, 8- and 16-fold the MIC and measured by broth microdilution according to Clinical and Laboratory Standards Institute guidelines. Azithromycin served as the control at 1x MIC. *S. pneumoniae* strains assayed included ATCC49619, ATCC6303, and 8 clinical isolates collected in 2010 showing lefamulin MICs of 0.015–0.12 mg/L. The maximum duration of incubation was 8 hours due to autolysis observed for the growth controls at 24 hours.

Results: Lefamulin displayed potent bactericidal activity against all strains tested and showed dependency on concentration and time of incubation. Living cell counts of all strains were rapidly reduced and reached ≥3 $\log_{10}$ within 8 hours of incubation at 8- to 16-fold MIC corresponding to 0.12–1.92 mg/L. At 4-fold MIC, lefamulin was bactericidal against 9 of 10 strains with a mean kill rate of –3.35 $\log_{10}$ CFU/mL (Figure). The concentration required for bactericidal activity at 8 hours was 0.5 mg/mL, which is significantly lower than plasma and epithelial lining fluid concentrations achieved with the clinical dose of 150 mg IV or 600 mg PO in humans.

Conclusions: Lefamulin demonstrated rapid bactericidal activity against all *S. pneumoniae* isolates tested. Killing was dependent on the lefamulin concentration and time of incubation. These results correlate with *in vivo* data supporting AUC:MIC as the primary pharmacokinetic/pharmacodynamic index and support the development of lefamulin for the treatment of CABP.

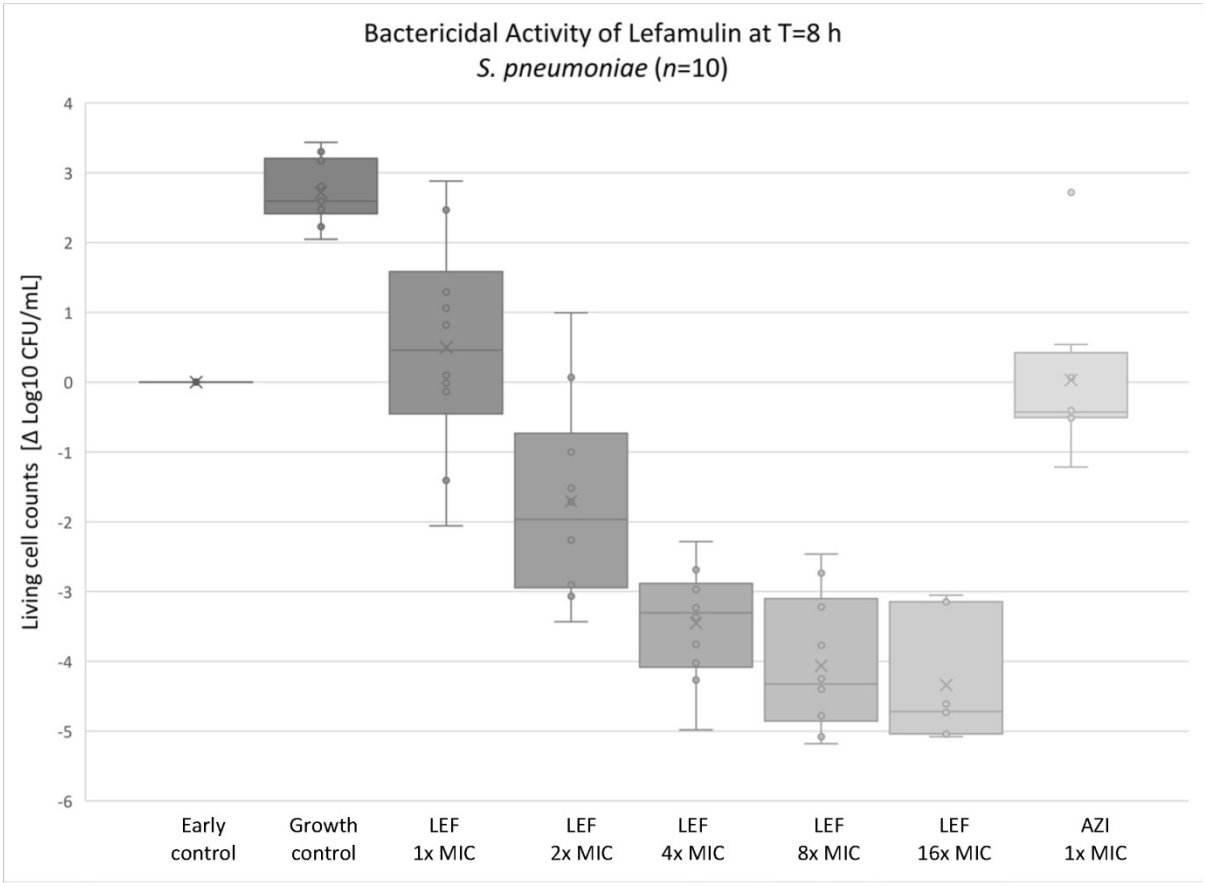

Figure. Concentration Response of Lefamulin against *S. pneumoniae*