**In Vitro Bactericidal Activity of Lefamulin Against Streptococcus pneumoniae Isolates**

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**INTRODUCTION & PURPOSE**

- Lefamulin, the first pleuromutilin antibiotic for IV or oral use in humans, recently completed phase 3 trials for the treatment of community-acquired bacterial pneumonia (CABP). In the initial study, lefamulin demonstrated non-inferiority to moxifloxacin in linezolid and showed favorable tolerability and safety profile.

- In a non-inferiority phase 2 study, lefamulin showed similar efficacy to vancomycin for the treatment of acute bacterial skin and skin structure infections (ABSSSI).

- Like all pleuromutilin antibiotics, lefamulin specifically inhibits prokaryotic protein synthesis by binding to the A-site in the peptidyl transferase center by way of 4-hydroxy-bonds and other interactions that result in tight binding via an induced fit mechanism.

- Lefamulin is highly active in vitro against pathogens that commonly cause CAP, including Streptococcus pneumoniae, Neisseria meningitidis, Moraxella catarrhalis, Staphylococcus aureus, Mycoplasma pneumoniae, and Legionella pneumophila, and its activity is not influenced by resistance to other antibiotic classes.

**METHODS**

- Finally, the MIC was determined at 8-hour post-exposure to lefamulin.

- The killing curves for S. pneumoniae clinical strain B1378, and reference strain ATCC29212 were demonstrated that lefamulin concentrations 1- to 3-fold the MIC (0.06–1.9 µg/mL) were bactericidal, resulting in ≥5 log reduction in living cell counts (Figure 2).

- The average concentration required for in vitro bactericidal activity at 8 hours was 0.5 µg/mL lefamulin.

- Concentrations reported in previous pharmacokinetic analyses in human plasma and tissue were below the minimum concentration of lefamulin to have occurred the value.

**RESULTS**

- Lefamulin displayed bactericidal activity against all strains tested with dependency on concentration and time of incubation.

- Living cell counts of all strains were reduced by 2 log units within 8 hours of incubation at 5- to 16-fold lefamulin MIC corresponding to 0.12–1.92 mg/L (Figure 1).

- At 4-fold MIC, lefamulin was bactericidal against 9 of 10 strains with a mean kill rate of 5.7 ± 0.29 log CFU/mL.

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**CONCLUSIONS**

- Lefamulin demonstrated bactericidal activity against all 10 S. pneumoniae isolates tested as was observed for Mucocystis pneumoniae in an earlier in vitro study.

- 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.

**REFERENCES**


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