J Antimicrob Chemother 2019; **74** Suppl 3: iii2–iii4
doi:10.1093/jac/dkz084

Journal of Antimicrobial Chemotherapy

Introduction: lefamulin and pharmacokinetic/pharmacodynamic rationale to support the dose selection of lefamulin

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Lefamulin is the first semisynthetic pleuromutilin being developed for oral and intravenous administration. The drug selectively inhibits prokaryotic ribosomal protein synthesis by binding to the peptidyl transferase centre via four H-bonds and other interactions, resulting in an 'induced fit' that tightens the binding pocket around lefamulin. This unique mechanism of action has been associated with a low probability of cross-resistance to other antimicrobial classes commonly used to treat community-acquired bacterial pneumonia (CABP). This Supplement, entitled 'Pharmacokinetic and pharmacodynamic analyses and dose rationale for lefamulin, a novel pleuromutilin antibiotic, for the treatment of community-acquired bacterial pneumonia', is intended to be a valuable resource for both clinicians and researchers. It provides the essential pharmacokinetic and pharmacodynamic data on lefamulin that were used to support the optimal dose selection of lefamulin for the safe and effective treatment of CABP in adults.

Pleuromutilins were discovered as natural antimicrobial products more than 60 years ago in the 1950s.[1–4] These diterpene antibiotics were isolated from the basidiomycete fungi *Clitopilus scyphoides* (formerly *Pleurotus mutilus*) and *Clitopilus passeckerianus* (formerly *Pleurotus passeckerianus*). Pleuromutilins are also produced by *Psathyrella conopilus* (formerly *Drosophila subatrata*) and other *Clitopilus* species. The first two semisynthetic derivatives that were developed and subsequently used in veterinary medicine were tiamulin in 1979 and valnemulin in 1999. The first commercial pleuromutilin developed for human use was retapamulin, which became available in 2007 as a 1% ointment for the topical treatment of uncomplicated skin infections, such as impetigo, and secondarily infected traumatic lesions due to methicillin-susceptible *Staphylococcus aureus* and *Streptococcus pyogenes*.

Lefamulin (formerly known as BC-3781) is a novel, semisynthetic pleuromutilin being developed for oral and intravenous administration. The drug inhibits prokaryotic ribosomal protein synthesis by binding to the peptidyl transferase centre (PTC) of the 50S subunit of the bacterial ribosome. Lefamulin inhibits translation by binding to the A- and P-site of the PTC 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.[1] Lefamulin selectively inhibits bacterial ribosomal translation but does not affect eukaryotic ribosomal translation. This unique mechanism of action has been associated with a low probability of cross-resistance to other antimicrobial classes based on *in vitro* studies.[5–7] Lefamulin exhibits potent *in vitro* antibacterial activity against important respiratory pathogens, including Gram-positive species, such as *Streptococcus pneumoniae* and *S. aureus* (methicillin-susceptible and methicillin-resistant isolates); the fastidious Gram-negative organisms *Haemophilus influenzae* and *Moraxella catarrhalis*; and the atypical pathogens *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae* and *Legionella pneumophila*.[5–8] Lefamulin has also displayed potent *in vitro* activity against Gram-positive organisms commonly associated with acute bacterial skin and skin structure infections (ABSSSIs), including MRSA, coagulase-negative staphylococci, β-haemolytic streptococci, viridans group streptococci and *Enterococcus faecium* (including vancomycin-non-susceptible strains).[8,9] A Phase 2 clinical study has provided proof of concept for the potential use of lefamulin for the treatment of patients with ABSSSIs.[10]

Two multicentre, randomized, double-blind, double-dummy, Phase 3 trials—Lefamulin Evaluation Against Pneumonia (LEAP 1 and LEAP 2)—evaluated lefamulin as monotherapy for the treatment of adult patients with community-acquired bacterial pneumonia (CABP).[11,12] LEAP 1 evaluated the safety and efficacy of intravenous lefamulin 150 mg twice daily versus intravenous moxifloxacin 400 mg once daily (with or without linezolid) in adults with moderate to severe CABP [Pneumonia Patient Outcomes Research Team (PORT) Risk Class ≥III], with the option of switching to oral administration if prespecified improvement criteria were met. LEAP 2 compared the safety and efficacy of 600 mg of oral lefamulin twice daily for 5 days versus

400 mg of oral moxifloxacin once daily for 7 days in adult patients with moderate CABP (PORT Risk Class II–IV, no more than 50% of enrolled patients meeting PORT Risk Class II status). Both clinical trials met efficacy endpoints for non-inferiority and provided evidence that lefamulin was generally well tolerated, with serious treatment-emergent adverse events occurring in <5% of patients.

Pharmacokinetic and pharmacodynamic evaluations are integral parts of drug development programmes for antimicrobial agents.[13–16] Pharmacokinetic/pharmacodynamic target attainment analyses using *in vitro* surveillance data, non-clinical pharmacokinetic/pharmacodynamic targets for efficacy, population pharmacokinetic models and Monte Carlo simulations are critical components for determining an optimal dosing regimen. The application of exposure–response analyses has become the standard practice in translational research and provides the greatest opportunity to accelerate a drug development programme and mitigate risks for a new antimicrobial agent.

This Supplement offers essential information about the pharmacokinetics and pharmacodynamics of lefamulin for oral and intravenous administration, reporting preclinical study results for establishing pharmacodynamic targets for different dosing strategies and outlining how incorporation of these data provides support for the optimal dose selection of lefamulin.[17–19] Importantly, this Supplement provides descriptions of the pharmacokinetics of single and repeated dosing of lefamulin, demonstrates evidence for the bioequivalence of intravenous and oral administration in the fasted versus fed state, and delineates population pharmacokinetic modelling and parameter determination.[20,21] These data were essential for pharmacokinetic/pharmacodynamic target attainment analyses of plasma and epithelial lining fluid concentrations to support dose selection decisions and optimal use of lefamulin during the early and late stages of the clinical drug development programme.[19] This collection of articles is intended to provide a valuable resource for both clinicians and researchers, providing a pharmacokinetic/pharmacodynamic rationale to support the dose selection of lefamulin for the safe and effective treatment of CABP in adults.

Funding

This work was supported by Nabriva Therapeutics. Copyediting support for this manuscript was funded by Nabriva Therapeutics.

Transparency declarations

Keith A. Rodvold has served as a consultant on advisory boards to Nabriva Therapeutics. Dr Rodvold prepared and composed the article, and provided critical revisions to the article for intellectual content. The author received no financial compensation for the preparation of this article. Copyediting support for this article was supplied by Lycely del C. Sepulveda-Torres, PhD, and Michael S. Mcnamara, MS, at C4 MedSolutions, LLC (Yardley, PA), a CHC Group company, and funded by Nabriva Therapeutics.

This article forms part of a Supplement sponsored by Nabriva Therapeutics US, Inc.

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