Current Pharmacology Reports (2022) 8:418–426
https://doi.org/10.1007/s40495-022-00297-6

CLINICAL PHARMACOLOGY (L BRUNETTI, SECTION EDITOR)

Lefamulin: a New Hope in the Field of Community-Acquired Bacterial Pneumonia

Shubham Adhikary[1] · Meher Kaur Duggal[1] · Saraswathy Nagendran[2] · Meena Chintamaneni[1] · Hardeep Singh Tuli[3] · Ginpreet Kaur[1]

Accepted: 14 June 2022 / Published online: 6 July 2022

Abstract

Purpose of Review Community-acquired bacterial pneumonia (CABP) continues to be a worldwide health concern since it is the major cause of mortality and hospitalisation worldwide. Increased macrolide resistance among Streptococcus pneumoniae and other infections has resulted in a significantly larger illness burden, which has been exacerbated by evolving demography and a higher prevalence of comorbid disorders. Owing to such circumstances, the creation of new antibiotic classes is critical.

Recent Findings Lefamulin, also referred to as BC-3781, is the primary pleuromutilin antibiotic which has been permitted for both intravenous and oral use in humans for the remedy of bacterial infections. It has shown activity against gram-positive bacteria including methicillin-resistant strains as well as atypical organisms which as often implicated in CABP. It has a completely unique mechanism of action that inhibits protein synthesis via way of means of stopping the binding of tRNA for peptide transfer. The C(14) side chain is responsible for its pharmacodynamic and antimicrobial properties, together with supporting in overcoming bacterial ribosomal resistance and mutations improvement amplifying the number of hydrogen bonds to the target site.

Summary This review aims to highlight the pre-existing treatment options and specific purposes to shed some light upon the development of a new drug lefamulin and its specifications and explore this novel drug's superior efficacy to already existing treatment strategies.

Keywords Community-acquired bacterial pneumonia (CABP) · Lefamulin · Tablet · Pleuromutilin · Treatment

Abbreviations

CABP	Community-acquired bacterial pneumonia
COPD	Chronic obstructive pulmonary disease
LEAP 1	Lefamulin Evaluation Against Pneumonia
ELF	Epithelial lining fluid
ECR	Early clinical response
ITT	Intent-to-treat
EMA	European Medicines Agency
IACR	Investigator assessment of clinical response

Introduction

Community-acquired bacterial pneumonia (CABP) is a very common infectious disease wherein inflammation of lung parenchyma takes place due to bacterial infection and air sacs get filled with fluid or pus causing problems in breathing. It is a leading cause of morbidity and in some cases even death across the globe [1••]. It is a form of pneumonia that is contracted from outside the hospital or nursing home (CAP).

This article is part of the Topical Collection on *Clinical Pharmacology*

✉ Saraswathy Nagendran
saraswathyn@mithibai.ac.in

✉ Hardeep Singh Tuli
hardeep.biotech@gmail.com

✉ Ginpreet Kaur
ginpreet.aneja@gmail.com

[1] Department of Pharmacology, Shobhaben Pratapbhai Patel School of Pharmacy and Technology Management, SVKM'S NMIMS, Vileparle-West, Mumbai-56, India

[2] Department of Botany, SVKM's Mithibai College of Arts Chauhan Institute of Science and Amrutben Jivanlal College Of Commerce and Economics, Vile Parle (W), 400056 Mumbai, India

[3] Department of Biotechnology, Maharishi Markandeshwar (Deemed to Be University), Mullana Ambala 133207, Haryana, India

Staphylococcus aureus, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis* and *Klebsiella pneumoniae* are the most common bacterial pathogens that cause community-acquired pneumonia [2]. Some common atypical bacteria include *Mycoplasma pneumoniae*, *Chlamydia Pneumoniae* and *Legionella species*. A combination of factors such as COPD (chronic obstructive pulmonary disease), smoking, congestive heart failure, chronic liver, renal diseases, chronic alcoholism, diabetes mellitus, malignancies and use of medicines such as proton pump inhibitors furthermore enhances the chance of acquiring this infectious disease [3–6]. *S. pneumoniae* is the second largest cause of lung ailment among healthy people falling within the age bracket of 4 years to 40 years old. In India, it is estimated that 151.8 million cases are recorded each year wherein around 13.1 million cases require hospitalisation [7, 8•]. Community-acquired pneumonia contributes to 1/6th of the mortality rate of India [7]. In 2018, pneumonia was the second leading cause of hospitalisation in the world. India contributes to 23% of the global pneumonia encumbrance [9].

Some characteristic symptoms include malaise, fever and dry cough in infants whereas productive cough and purulent sputum in adults, breathlessness, fatigue, loss of appetite, chest pain or upper abdominal pain in the infected region, tachypnoea, bronchial breath sounds, dullness to percussion, nasal flaring, pleural effusion, nonexudative pharyngitis, etc. [1••]. Gastrointestinal symptoms like vomiting, diarrhoea may also be observed in some cases. It is commonly observed that the infection causes restlessness and exasperation in infants and mental confusion and prominent headaches in elderly. Extrapulmonary symptoms seen in some atypical CAP include rashes, haemoptysis, bradycardia, myalgias, ear pain and splenomegaly. These symptoms alone are not indicative of a particular causative pathogen or the accurate etiological agent; henceforth, additional testing is of immense importance to identify the correct agent which will inevitably help in the treatment; sometimes even after thorough testing, it is difficult to identify the microorganism (< 20% cases) [9].

Sneezing and coughing are the most common modes however, a small fomite has the capacity to transport more than 500 microorganisms [10]. The upper respiratory tract has several defence mechanisms which prevent the entry of the pathogens such as a cough reflex that clears the trachea, alveolar macrophages that act as protective barriers against pathogens and ciliary action and mucus production that prevent the entry of pathogens into the respiratory tract. If the immune system of the host organism is not robust enough then the chances of infection significantly increase [11]. When the microorganism enters the alveolar region, it indicates that the host's defence mechanism is not competent enough. The inflammatory action triggered by macrophages results in the production of fibrin rich exudate that further infects the alveolar spaces and they get filled with fluid or pus which inevitably causes pain and breathlessness. This further results in the proliferation of neutrophils which causes pulmonary oedema, fibrosis or pleural effusion [12]. All these complications result in difficulty in breathing as the expansion of the lungs are hindered. When respiration does not take place efficiently, the organs in our body become oxygen-deprived, and henceforth, tachycardia and the rise of carbon dioxide levels take place [13, 14].

Scientists tested the innovative semisynthetic pleuromutilin lefamulin, formerly known as BC3781, for systemic injection in humans for the first time in 2006 [15]. Lefamulin in an oral and intravenous (IV) formulation showed clinical efficacy and an acceptable safety profile in the treatment of CABP in two large Phase III clinical trials, (Lefamulin Evaluation Against Pneumonia) LEAP 1 and 2 [16••, 17, 18].

LEAP 1 was a randomised, double-blind, double-dummy, active-controlled, parallel-group research in which 551 CABP patients were randomly allocated (1:1) to receive lefamulin or moxifloxacin, and LEAP 2 was a 738-person, randomised, non-inferiority, double-blind, double-dummy, multicentre, parallel-group research. In both studies, participants had to satisfy the following requirements to be considered: people over the age of 18, pneumonia-related radiographic imaging, Pneumonia Outcomes Research Team (PORT) risk class III or higher, an illness that began within 7 days of enrolment, and three or more CABP symptoms [19, 20••]. The FDA's main goal was an early clinical response (ECR) in the ITT (intent-to-treat) population 96 h following the first study medication dosage. Lefamulin was shown to be non-inferior to moxifloxacin in the EMA (European Medicines Agency) main endpoint of the IACR (Investigator assessment of clinical response) in both studies [20••].

Lefamulin was approved by the US Food and Drugs Administration (FDA) for the treatment of CABP in August of 2019 [21]. It has high antimicrobial action against fastidious Gram-negative pathogens (*Moraxella catarrhalis, Neisseria spp. & Haemophilus influenzae*) and Gram-positive (*Streptococcus pneumoniae & Staphylococcus aureus*), as well as intracellular organisms and mycoplasmas including *Chlamydia spp.* and *Legionella pneumophila* [22]. Lefamulin's antibacterial activity has also been tested for the most common bacteria that cause sexually transmitted infections. It was particularly effective against *Neisseria gonorrhoeae*, *Mycoplasma genitalium* and *Chlamydia trachomatis*, even against multidrug-resistant strains [23–26].

Current Strategies

Antibiotic therapy is most commonly administered when a person is infected by S. pneumoniae or some atypical bacterial microorganisms [27–29]. Macrolides, fuoroquinolones, tetracyclines and -lactams (alone or in combination) are common empiric antimicrobial therapies for CABP; however, bacterial resistance to these medicines is rising. The duration of this

therapy lasts for around 5–7 days depending on the severity of the infection [28]. The antibiotics administered are Amoxicillin 1 g thrice a day or Doxycycline 100 mg twice daily or clarithromycin 500 mg twice daily or Azithromycin 500 mg twice daily. In the flu season, doctors also prescribe drugs like Zanamivir or Baloxavir to patients who show pneumonia-like symptoms [27]. Another strategy is the use of biomarkers, where it helps monitor therapeutic response and could also decrease the need for antibiotics in unfavourable conditions [30, 31]. Lastly, PCV13 (pneumococcal conjugate vaccine) vaccination is recommended for infants 2 months to 2 years old, and those with immunosuppressive diseases under the age of 19 are also recommended to be vaccinated [32]. Adults above 65 years of age are recommended PPSV23 (Pneumococcal Polysaccharide Vaccine) to prevent themselves from acquiring CABP [33]. A major concern related to the treatment of patients with CABP include adverse effects as well as collateral damage to the microbiome with an associated risk of *Clostridium difcile* infection [34, 35]. The limitations of current antibiotic therapies for CABP led to the discovery of novel agents. Individuals in locations with a high frequency of drug-resistant Streptococcus pneumoniae, community-associated MRSA (methicillin-resistant Staphylococcus aureus), patients at increased risk of fluoroquinolone-related side effects, and patients with a history of *C. difficile* or multiple antibiotic intolerances may benefit from lefamulin over standard treatments.

Xenleta (Lefamulin): Recent Novelty Launched in the Market

It is the first pleuromutilin antibacterial used for the treatment of CAP and is a semi synthetic agent and can be administered both via the oral as well as intravenous route [36].

Chemistry

Pleuromutilins are natural compounds that impede the growth of *S. aureus* and were initially identified in the 1950s from *Clitophilus scyphoides* (previously known as *Pleurotus mutilus*), an edible mushroom [37]. It is actually a tricyclic diterpenoid molecule that occurs naturally. A naturally occurring chemical change in the molecule at the C14 position led to the development of two semisynthetic pleuromutilins licenced for veterinary use, tiamulin (1979) and valnemulin (in 1999). Retapamulin, a lipophilic, topically applied pleuromutilin ointment licenced in 2007 for the topical treatment of impetigo caused by methicillin susceptible S aureus (MSSA) or Streptococcus pyogenes, was the first pleuromutilin licenced for human use [38]. Lefamulin (Fig. 1) was created after thorough side chain alteration at position C14 [39, 40•].

Mechanism of Action

The first pleuromutilin antibiotic to be licenced for the systemic treatment of bacterial infections in humans is lefamulin [40•]. Pleuromutilin antibiotics work by forming multiple contacts, including four hydrogen bonds, with the peptidyl transferase core of the 50S ribosome [41]. Through a unique model of tight-fit binding to the A and P sites of the 50S ribosomal subunit, lefamulin suppresses bacterial protein synthesis by interfering with peptidyl transfer, preventing peptide bond formation and chain elongation. Lefamulin is deemed ineffective after elongation has begun [42]. Pleuromutilins suppress bacterial protein translation with excellent specificity (Fig. 2), but has no effect on eukaryotic protein synthesis, as shown by in vitro transcription/translation assays using bacterial ribosomes [43]. This unique mechanism is thought to reduce the tendency to develop bacterial resistance and explain the lack of cross-resistance with other antibacterial classes. In Fig. 3, we can see the advantages of lefamulin over other therapeutics [42]. It demonstrates both bactericidal and bacteriostatic activity against gram-positive, fastidious gram-negatives, atypical pathogens and some gram-negative anaerobes [44].

Administration

When administered orally, it is available as an oval film-coated blue tablet containing 671 mg of lefamulin acetate as the active ingredient [45•]. The excipients consist of: colloidal silicon dioxide, ferrosoferric oxide, magnesium stearate mannitol, croscarmellose sodium, polyethylene glycol, microcrystalline cellulose FD&C Blue No 2-aluminium lake, polyvinyl alcohol (partially hydrolysed), shellac glaze, povidone K30, titanium dioxide and talc. In Table 1, we can see the different properties of Lefamulin [45•].

Pharmacokinetics and Pharmacodynamics

A new antimicrobial agent's road to drug approval begins with non-clinical infection models that identify PK/PD effectiveness targets. To generate dose regimens, these targets are combined with in vitro monitoring data, a population PK (PPK) model constructed using phase I and II data, and Monte Carlo simulation [46]. Wicha and colleagues used a neutropenic murine model for pneumonia to establish non-clinical PK/PD targets for lefamulin effectiveness against *S. pneumoniae* and *S. aureus*. Lefamulin was tested in mouse macrophages, and the PK of lefamulin was determined in Bagg albino mice treated with subcutaneous lefamulin (35 or 70 mg/kg) and intraperitoneal cyclophosphamide before being challenged with S. aureus or S. pneumoniae strains

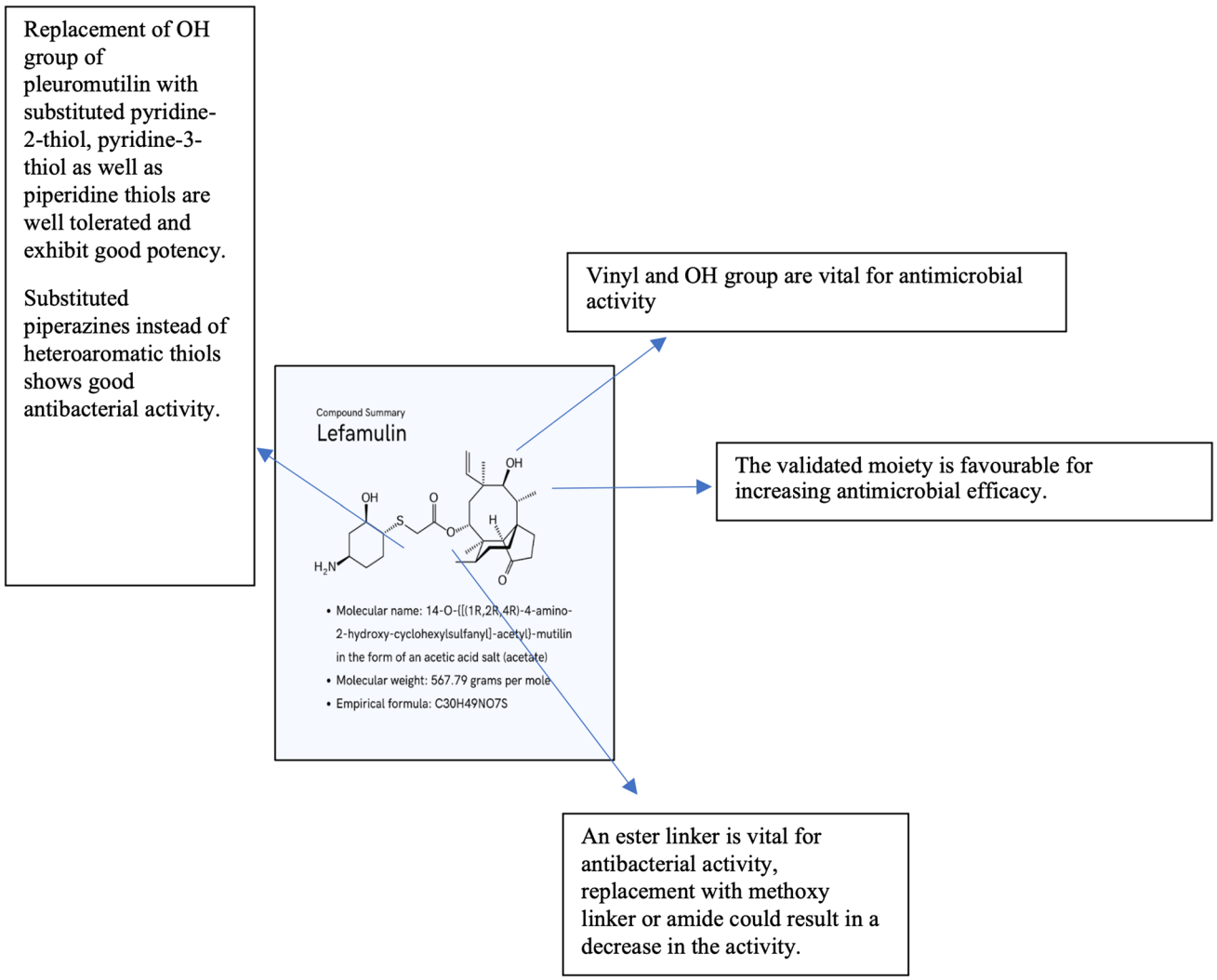

Fig. 1 Chemistry and structure activity relationship of Lefamulin

[46]. Hill models were used to characterise changes in log(10) colony-forming units and the area under the plasma drug concentration–time curve (AUC)/MIC ratios (CFUs). The fast transport of lefamulin from plasma to epithelial lining fluid (ELF) in this neutropenic mouse model demonstrated a doubling of lefamulin exposure in the ELF over 5 h. The mean plasma AUC/MIC ratios associated with 1 and 2 log10 CFU reductions from baseline for S. aureus and S. pneumoniae, respectively, were 2.13 and 6.24 for S. aureus and 1.37 and 2.15 for S. pneumoniae. The ELF results were equally impressive, with AUC/MIC ratios associated with 1 and 2 log10 CFU decreases from baseline of 21.7 and 63.9 for S. aureus and 14.0 and 22.0 for S. pneumoniae, respectively, indicating that lefamulin has favourable PK/PD targets that are generally predictive of clinical efficacy in CABP [46].

Lefamulin PD parameters from a dose-escalation trial were generated using a neutropenic murine thigh infection model. S. pneumoniae ATCC 10,813 or S. aureus ATCC 25,923 were used to infect neutropenic mice [47]. To modify the PK/PD indices, lefamulin dosages ranging from 5 to 160 mg/kg were fractionated into one, two, four or eight doses. After 1 day of therapy, mice were slaughtered and the thighs were taken and processed for CFU determination. The free-drug AUC24/MIC ratio was shown to be the most critical metric driving efficacy, followed by the percentage of time free-drug concentrations surpassed the MIC. A bacteriostatic total 24-h AUC/MIC ratio of 70 was selected to be the efficacy objective based on their findings [48, 49]

The quantity of bacteria (S. pneumoniae or S. aureus) in the thigh at the conclusion of 24 h of medication was correlated with the (1) Cmax/MIC ratio; (2) 24-h AUC/MIC ratio; and (3)

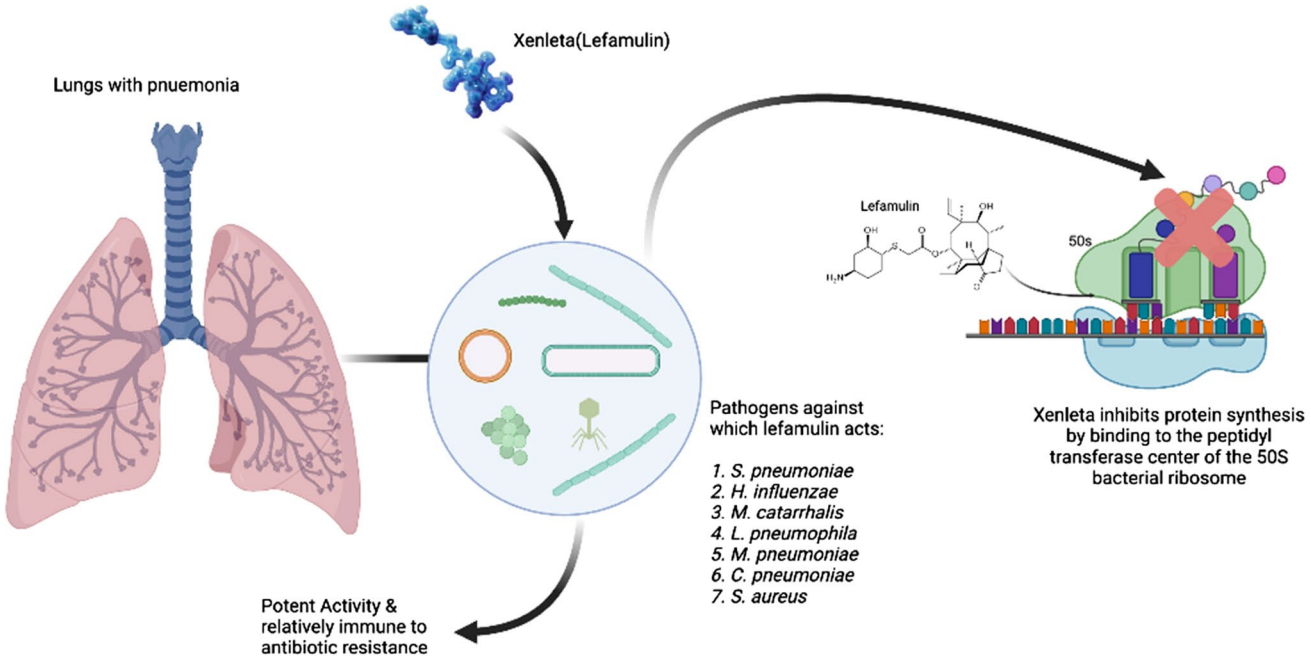

Fig. 2 Binding of Lefamulin with protein peptidyl transferase as promising inhibitor of protein synthesis

$T_{>MIC}$; $\%T_{>MIC}$ in a subsequent study in neutropenic mice. The authors discovered that the free-drug AUC24/MIC ratio was the most important index driving lefamulin efficacy, followed by the percentage of time that free-drug concentrations exceeded the MIC, implying that fAUC/MIC targets in mice could be combined with PK data from human studies to predict doses and regimens, resulting in a free-drug AUC/MIC ratio of 14 (8–16.5), which would be sufficient to treat most patients [46].

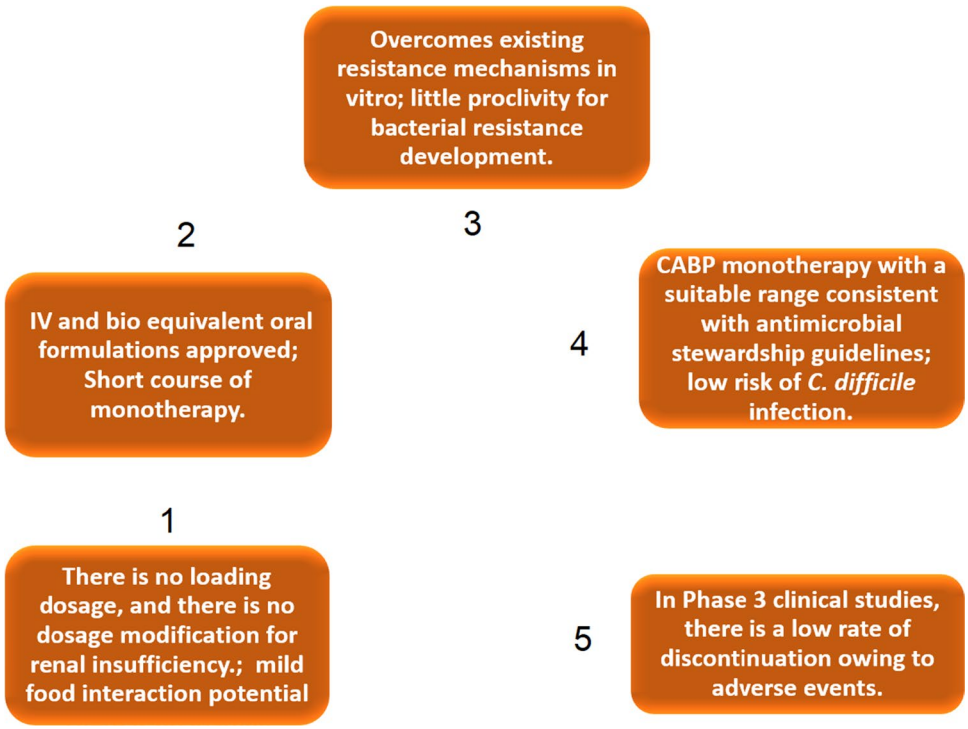

Fig. 3 Various advantages of Xenleta over other therapeutic drugs

Table 1 Bird eye view of metabolic and excretion properties of Lefamulin

Class	Plueromutilin antibiotic
Formulations	150 mg single dose vials; 600 mg tablets
Route	IV & PO
Bioavailability	PO: 25%
Tmax	P.O: 0.88–2 h
Metabolism	Primarily for CYP3A4
Excretion	IV: faeces (77.3%); urine (15.5%) PO: faeces (88.5%); urine (5.3%)
Half life	8 h

In healthy individuals, lefamulin plasma protein binding degrees from 94.8% at 2.35 mcg/mL to 97.1% at 0.25 mcg/mL. After the management of lefamulin injection, the mean (min to max) steady-nation quantity of distribution of lefamulin is 86.1 L (34.2 to 153 L). The highest concentrations of lefamulin in the epithelial lining fluid (ELF) were observed following a single IV injection of 150 mg lefamulin in healthy subjects. Mean AUC08 ELF and plasma values were 3.87 µg·h/ml and 5.27 µg·h/ml, respectively. The calculated ELF AUC to unbound plasma AUC ratio is around 15. CYP3A4 is the enzyme that largely metabolises lefamulin [50].

Adverse reactions and Contraindications

Common adverse reactions through the IV route(injection) include hepatic enzyme elevation, hypokalaemia, administration site reactions, nausea, insomnia and headache. From the oral route (tablet), hepatic enzyme elevation, diarrhoea, vomiting and nausea are observed. Less common adverse reactions include atrial fibrillation, anemia, thrombocytopenia, oropharyngeal and vulvovaginal candidiasis, anxiety and urinary retention [51, 52].

Lefamulin is contraindicated in patients with a known hypersensitivity to pleuromutilin drugs or to any of the agent's excipients. CYP3A4 substrates that lengthen the QT interval should also not be utilised with lefamulin tablets because lefamulin is known to prolong the QT interval. In individuals with a history of ventricular arrhythmias, particularly torsades de pointes, lefamulin should be avoided. Amiodarone, macrolides, verapamil, azoles and protease inhibitors are all CYP3A4 inhibitors; therefore, they are to be avoided. Lastly, coadministration of lefamulin with any of the following agents should be avoided: class IA and class III antiarrhythmics, antipsychotics, tricyclic antidepressants and fluoroquinolones [44, 53, 54].

Dosage, Drug Interactions and Special Population

Lefamulin is indicated for the treatment of adults with CABP caused by the following susceptible microorganisms: S. pneumoniae, S. aureus (methicillin susceptible isolates), *H. influenzae*, *L. pneumophila*, *M. pneumoniae* and *C. pneumoniae*. The suggested dose of lefamulin for the treatment of CABP is 150 mg administered intravenously over 60 min every 12 h for 5–7 days. Alternatively, the medicine can be taken orally in doses of 600 mg every 12 h for 5 days. The oral pills should be taken 1 h before or 2 h after meals and consumed whole with 170–200 mL of water [55].

The effect of lefamulin on pregnant women has not been studied; however, the potential teratogenicity has been depicted in animal studies of lefamulin [56]. Furthermore, pregnancy surveillance studies are ongoing. Its administration during pregnancy has been linked to ossification, stillbirth and other foetal abnormalities in animal studies [57]. The label says that women who may become pregnant should take effective contraceptive measures during the period of taking Lefamulin and within 2 days after stopping the drug. Breastfeeding mothers should pump and discard breast milk during therapy with lefamulin and within 2 days after the final dosage since it might cause significant adverse effects in the infant, including a prolonged QT interval [58•].

Challenges and Future Perspective

Despite FDA approval in August 2019 and European Medicines Agency approval in July 2020, no real-world post-marketing evidence on efficacy or tolerance has been published. There are no case reports or case series descriptive studies available, which is surprising. Instead, after receiving regulatory approval, publications have been limited to a variety of analyses based on subgroup level data from investigator-sponsored studies or in vitro research that evaluates previously reported similar known data. Lefamulin's adoption and use for CABP may be limited due to a lack of studies. Regulatory approval before and during the coronavirus disease 2019 (COVID-19) pandemic may have contributed to the lack of post-marketing research.

Patients with severe and greatest risk categorization of CABP by CURB-65 scores may assist to further understand CABP efficacy since the majority of patients in the LEAP studies had reduced mortality risk (scores = 1-2) [52, 59]. Having stated that, the most recent ATS/IDSA recommendations (American Journal of Critical Care Medicine Volume 200 Number 7 October 1 2019) suggest using the PORT/PSI index as a clinical prediction tool rather than the CURB-65.

In addition to this, taking note of the pooled analysis of LEAP 1&2 by Dr File, we can infer that the comorbidity of the patients was severe and commensurate to that seen in clinical practice [60]. Additional data to support use in younger patients (< 65 years old) could help clarify that different efficacy results observed in this younger subgroup (LEAP 1) were likely confounded by low ATS severity criteria, and further validate findings from the LEAP 2 trial, which found no significant differences in this younger cohort [61, 62].

Since more large-scale investigator-sponsored trials are unlikely due to considerable financial concerns, real-world clinical investigations are critical for future acceptance of lefamulin, including the discovery of other therapeutic functions. Post-marketing studies are needed to better define the role of lefamulin in terms of (1) tolerability of the oral lefamulin formulation in terms of diarrhoea occurrence and severity, (2) resistance mutation and/or treatment failure observed with long-term use, (3) effectiveness and safety profile for the treatment of ABSSSIs caused by streptococci and staphylococci, as well as STIs caused by ceftriaxone-resistant *N. gonorrhoea* and (4) occurrence of C. difficile infection when compared to other therapeutic classes.

Conclusion

Lefamulin is a new pleuromutilin antibiotic that exhibits good efficacy against a variety of gram-positive and gram-negative bacteria, including the respiratory infections linked to CABP. Given the seeming lack of interest for giant pharmaceutical corporations to find novel antibiotics, the approval of an antibiotic after a long absence of more than a decade is a positive trend. Lefamulin gives doctors the option of administering an IV or PO formulation depending on the patient's needs, and it is a better alternative to fluoroquinolones and other typical front-line antimicrobials for the treatment of CABP. There is a great need for post-marketing clinical data to better define lefamulin's efficacy and safety in the treatment of different infections and disease states for which it has shown in vitro and/or early clinical trial activity. Data from post-marketing trials may help to further identify lefamulin's therapeutic niche, as well as the amount to which it is adopted and used in the future.

Author Contribution SA, MKD and SN visualized the presented idea, did the literature review and prepared the manuscript. MC, HST and GK supervised the project and corrected, revised and approved the manuscript. All authors contributed to the article and approved the submitted version.

Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. ••Tomiyama Y, Tomono K, Kohno S. Community-acquired pneumonia. 2022:400–403. https://doi.org/10.7326/AITC202204190. **Article tells us about pathogenesis of CABP**.
2. Lanks CW, Musani AI, Hsia DW. Community-acquired pneumonia and hospital-acquired pneumonia. Medical Clinics. 2019;103(3):487–501. https://doi.org/10.1016/J.MCNA.2018.12.008.
3. Brunetti VC, Ayele HT, Yu OHY, Ernst P, Filion KB. Type 2 diabetes mellitus and risk of community-acquired pneumonia: a systematic review and meta-analysis of observational studies. Can Med Assoc Open Access J. 2021;9(1):E62–70. https://doi.org/10.9778/CMAJO.20200013.
4. Bellinghausen C, et al. Chronic liver disease negatively affects outcome in hospitalised patients with community-acquired pneumonia. Gut. 2021;70(1):221–2. https://doi.org/10.1136/GUTJNL-2020-320876.
5. Bordon J, et al. Hospitalization due to community-acquired pneumonia in patients with chronic obstructive pulmonary disease: incidence, epidemiology and outcomes. Clin Microbiol Infect. 2020;26(2):220–6. https://doi.org/10.1016/J.CMI.2019.06.025.
6. Cavallazzi R, Ramirez J. Community-acquired pneumonia in chronic obstructive pulmonary disease. Curr Opin Infect Dis. 2020;33(2):173–81. https://doi.org/10.1097/QCO.0000000000000639.
7. Ghia CJ, Dhar R, Koul PA, Rambhad G, Fletcher MA. Streptococcus pneumoniae as a cause of community-acquired pneumonia in Indian adolescents and adults: a systematic review and meta-analysis. Clin Med Insights Circ Respir Pulm Med. 2019;13:1179548419862790. https://doi.org/10.1177/1179548419862790.
8. • Yadav RK, Kumar D, Singh A, Ziauddin M, Singh DK. Clinical and microbial spectrum of community-acquired pneumonia in children of north India. Trop Doct. 2021;51(1):71–7. https://doi.org/10.1177/0049475520971595. **Paper gives us the Indian context on the disease burden of CABP**.
9. Eshwara VK, Mukhopadhyay C, Rello J. Community-acquired bacterial pneumonia in adults: an update. Indian J Med Res. 2020;151(4):287. https://doi.org/10.4103/IJMR.IJMR_1678_19.
10. Smith-Vaughan H, Crichton F, Beissbarth J, Morris PS, Leach AJ. Survival of pneumococcus on hands and fomites. BMC Res Notes. 2008;1(1):1–4. https://doi.org/10.1186/1756-0500-1-112/FIGURES/1.
11. Mizgerd JP. "Respiratory infection and the impact of pulmonary immunity on lung health and disease," 186(9):824–829 2012. https://doi.org/10.1164/RCCM.201206-1063PP.
12. Musher DM and Thorner AR. "Community-acquired pneumonia," 371(17):1619–1628. 2014. https://doi.org/10.1056/NEJMRA1312885.
13. Alcón A, Fàbregas N, Torres A. "Pathophysiology of pneumonia," *Clinics in Chest Medicine*, 26(1). W.B. Saunders. 39–46, 2005. https://doi.org/10.1016/j.ccm.2004.10.013.

14. Cillóniz C, Cardozo C, García-Vidal C. Epidemiology, pathophysiology, and microbiology of community-acquired pneumonia. Annals Res Hosp. 2018;2:1–1. https://doi.org/10.21037/arh.2017.12.03.
15. Eraikhuemen N, Julien D, Kelly A, Lindsay T, Lazaridis D. Treatment of community-acquired pneumonia: a focus on lefamulin. Infect Dis Ther. 2021;10(1):149–63. https://doi.org/10.1007/s40121-020-00378-3.
16. ••File TM, et al. Efficacy and safety of intravenous-to-oral lefamulin, a pleuromutilin antibiotic, for the treatment of community-acquired bacterial pneumonia: the Phase III Lefamulin Evaluation Against Pneumonia (LEAP 1) trial. Clin Infect Dis. 2019;69(11):1856–67. https://doi.org/10.1093/cid/ciz090. **Paper tells us about the clinical trials of lefamulin**.
17. Zhanel GG et al. "Lefamulin: a novel oral and intravenous pleuromutilin for the treatment of community-acquired bacterial pneumonia," Drugs, 81(2). Adis, pp. 233–256:2021. https://doi.org/10.1007/s40265-020-01443-4.
18. Dillon C, Guarascio AJ, Covvey JR. Lefamulin: a promising new pleuromutilin antibiotic in the pipeline. Expert Rev Anti Infect Ther. 2019;17(1):5–15. https://doi.org/10.1080/14787210.2019.1554431.
19. File TM, et al. Lefamulin efficacy and safety in a pooled phase 3 clinical trial population with community-acquired bacterial pneumonia and common clinical comorbidities. BMC Pulm Med. 2021;21(1):1–10. https://doi.org/10.1186/S12890-021-01472-Z/TABLES/2.
20. ••Paukner S, et al. Pooled microbiological findings and efficacy outcomes by pathogen in adults with community-acquired bacterial pneumonia from the Lefamulin Evaluation Against Pneumonia (LEAP) 1 and LEAP 2 phase 3 trials of lefamulin versus moxifloxacin. J Global Antimicrob Resist. 2021. https://doi.org/10.1016/J.JGAR.2021.10.021. **Paper tells us about the clinical trials information of Lefamulin**.
21. Lee YR, Jacobs KL. Leave it to lefamulin: a pleuromutilin treatment option in community-acquired bacterial pneumonia. Drugs. 2019;79(17):1867–76. https://doi.org/10.1007/S40265-019-01219-5.
22. "Nabriva Therapeutics Announces European Medicines Agency (EMA) Validation of Marketing Authorization Application for Lefamulin Nasdaq:NBRV." https://www.globenewswire.com/news-release/2019/06/24/1873292/0/en/Nabriva-Therapeutics-Announces-European-Medicines-Agency-EMA-Validation-of-Marketing-Authorization-Application-for-Lefamulin.html (accessed Apr. 22, 2021).
23. Sader HS, Biedenbach DJ, Paukner S, Ivezic-Schoenfeld Z, Jonesa RN. Antimicrobial activity of the investigational pleuromutilin compound BC-3781 tested against gram-positive organisms commonly associated with acute bacterial skin and skin structure infections. Antimicrob Agents Chemother. 2012;56(3):1619–23. https://doi.org/10.1128/AAC.05789-11.
24. ••Paukner S, Sader HS, Ivezic-Schoenfeld Z, Jonesb RN. Antimicrobial activity of the pleuromutilin antibiotic BC-3781 against bacterial pathogens isolated in the SENTRY antimicrobial surveillance program in 2010. Antimicrobial Agents and Chemotherapy. 2013;57(9):4489–95. https://doi.org/10.1128/AAC.00358-13. **Paper talks about the antimicrobial activity of Lefamulin**.
25. Paukner S, Gruss A, Jensen JS. In vitro activity of lefamulin against sexually transmitted bacterial pathogens. Antimicrob Agents Chemother. 2018;62(5):e02380–17. https://doi.org/10.1128/AAC.02380-17
26. Jacobsson S, Paukner S, Golparian D, Jensen JS, and Unemo M. "In vitro activity of the novel pleuromutilin lefamulin (BC-3781) and effect of efflux pump inactivation on multidrug-resistant and extensively drug-resistant neisseria gonorrhoeae," Antimicrob Agents Chemother. Nov. 2017;61(11). https://doi.org/10.1128/AAC.01497-17.
27. Mathur S, Fuchs A, Bielicki J, van den Anker J, and Sharland M. "Antibiotic use for community-acquired pneumonia in neonates and children: WHO evidence review," Dec. 2018. 38;S66–S75. https://doi.org/10.1080/20469047.2017.1409455.
28. Garnacho-Montero J, Barrero-García I, de Gómez-Prieto MG, Martín-Loeches I. Severe community-acquired pneumonia: current management and future therapeutic alternatives. Expert Rev Anti Infect Ther. 2018;16(9):667–77. https://doi.org/10.1080/14787210.2018.1512403.
29. Peyrani P, Mandell L, Torres A, Tillotson GS. The burden of community-acquired bacterial pneumonia in the era of antibiotic resistance. Expert Rev Respir Med. 2018;13(2):139–52. https://doi.org/10.1080/17476348.2019.1562339.
30. Fernandes CD et al. Host inflammatory biomarkers of disease severity in pediatric community-acquired pneumonia: a systematic review and meta-analysis. Open Forum Infect Dis. 2019;6(12). https://doi.org/10.1093/OFID/OFZ520.
31. Savvateeva EN, Rubina AY, Gryadunov Da. Biomarkers of community-acquired pneumonia: a key to disease diagnosis and management. BioMed Res Int. 2019;2019. https://doi.org/10.1155/2019/1701276.
32. Theilacker C, Fletcher MA, Jodar L, Gessner BD. PCV13 vaccination of adults against pneumococcal disease: what we have learned from the community-acquired pneumonia immunization trial in adults (CAPiTA). Microorganisms. 2022;10:127.
33. Chandler T, Furmanek S, Carrico R, Balcom D, Arnold F, Ramirez J. 23-valent pneumococcal polysaccharide vaccination does not prevent community-acquired pneumonia hospitalizations due to vaccine-type Streptococcus pneumoniae. Microorganisms. 2022;10(3):560. https://doi.org/10.3390/MICROORGANISMS10030560.
34. Yi SH, et al. 519. Longer length of antibiotic therapy for community-acquired pneumonia and risk of clostridium difficile infection. Open Forum Infect eases. 2018;5(suppl_1):S192–S192. https://doi.org/10.1093/OFID/OFY210.528.
35. Rhodes NJ et al. Characterizing risk factors for clostridioides difficile infection among hospitalized patients with community-acquired pneumonia. Antimicrobial Agents and Chemotherapy. 2021;65(7). https://doi.org/10.1128/AAC.00417-21/SUPPL_FILE/AAC.00417-21-S0001.PDF.
36. Chahine EB and Sucher AJ. "Lefamulin: the first systemic pleuromutilin antibiotic," *Annals of Pharmacotherapy*, vol. 54, no. 12. SAGE Publications Inc., pp. Dec. 2020;1203–1214. https://doi.org/10.1177/1060028020932521.
37. Paukner S, Riedl R. Pleuromutilins: potent drugs for resistant bugs-mode of action and resistance. Cold Spring Harb Perspect Med. 2017;7(1). https://doi.org/10.1101/cshperspect.a027110.
38. Label (PDF)-FDA. XENLETA (Lefamulin). Highlights of prescribing information. [(accessed on 25 June 2022)]; Available online: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211672s000,211673s000lbl.pdf.
39. Tang Y-Z, Liu Y-H, Chen J-X. Pleuromutilin and its derivatives-the lead compounds for novel antibiotics. Mini-Rev Med Chem. 2011;12(1):53–61. https://doi.org/10.2174/138955712798868968.
40. • Eyal Z, et al. A novel pleuromutilin antibacterial compound, its binding mode and selectivity mechanism. Sci Rep. 2016;6(1):1–8. https://doi.org/10.1038/srep39004. **Paper talks about the chemistry of Lefamulin**.
41. Long KS, Hansen LH, Jakobsen L, Vester B. Interaction of Pleuromutilin Derivatives with the Ribosomal Peptidyl Transferase Center. Antimicrob Agents Chemother 2006;50:1458. https://doi.org/10.1128/AAC.50.4.1458-1462.2006.
42. Leowattana W, Leowattana P, Leowattana T. Pleuromutilin and its derivatives: promising novel anti-infective agents.

Anti-Infective Agents. 2018;20(2). https://doi.org/10.2174/2211352519666211130111723.
43. Veve MP and Wagner JL. "Lefamulin: review of a promising novel pleuromutilin antibiotic," *Pharmacotherapy*, vol. 38, no. 9. Pharmacotherapy Publications Inc., Sep. 2018;935–946. https://doi.org/10.1002/phar.2166.
44. Rodvold KA. Introduction: Lefamulin and pharmacokinetic/pharmacodynamic rationale to support the dose selection of lefamulin. J Antimicrob Chemother. 2019;74(Supplement_3):III2–4. https://doi.org/10.1093/jac/dkz084.
45. • Wicha WW, Strickmann DB, Paukner S. Pharmacokinetics/pharmacodynamics of lefamulin in a neutropenic murine pneumonia model with Staphylococcus aureus and Streptococcus pneumoniae. J Antimicrob Chemother. 2019;74(3):III11–8. https://doi.org/10.1093/JAC/DKZ086. **Paper gives an overview on PK/PD properties of Lefamulin**.
46. Wicha WW, Craig WA, Andes D. In vivo pharmacodynamics of lefamulin, the first systemic pleuromutilin for human use, in a neutropenic murine thigh infection model. J Antimicrob Chemother. 2019;74(3):III5–10. https://doi.org/10.1093/JAC/DKZ085.
47. Wicha WW, et al. Pharmacokinetics and safety of lefamulin after single intravenous dose administration in subjects with impaired-hepatic function. Pharmacother : J Human Pharmacol and Drug Therapy. 2021;41(5):457–62.
48. McCarthy MW. Clinical pharmacokinetics and pharmacodynamics of lefamulin. Clin Pharmacokinet. 2021;60(11):1387–94. https://doi.org/10.1007/S40262-021-01056-4.
49. Alp E, Güven M, Yildiz O, Aygen B, Voss A, and Doganay M. "Incidence, risk factors and mortality of nosocomial pneumonia in intensive care units: a prospective study," Annals of Clinical Microbiology and Antimicrobials, Sep. 2004;3. https://doi.org/10.1186/1476-0711-3-17.
50. Prince WT, et al. Phase II clinical study of BC-3781, a pleuromutilin antibiotic, in treatment of patients with acute bacterial skin and skin structure infections. Antimicrob Agents Chemother. 2013;57(5):2087–94. https://doi.org/10.1128/AAC.02106-12.
51. File TM, et al. Efficacy and safety of intravenous-to-oral lefamulin, a pleuromutilin antibiotic, for the treatment of community-acquired bacterial pneumonia: the Phase III lefamulin Evaluation Against Pneumonia (LEAP 1) trial. Clin Infect Dis. 2019;69(11):1856–67. https://doi.org/10.1093/cid/ciz090.
52. Dubey AP, Maggo S, Karan A, Singh NK, Bhaskaran S. Lefamulin: novel pleuromutilin drug for community-acquired bacterial pneumonia. Int J Basic Clin Pharmacol. 2019;8(12):2783. https://doi.org/10.18203/2319-2003.ijbcp20195297.
53. Eraikhuemen N, Julien D, Kelly A, Lindsay T, and Lazaridis D. "Treatment of community-acquired pneumonia: a focus on lefamulin," Infectious Diseases and Therapy, Mar. 01, 2021; 10(1). Adis, pp. 149–163. https://doi.org/10.1007/s40121-020-00378-3.
54. Perry W, Golan Y. Therapeutic potential of lefamulin in the treatment of community-acquired pneumonia. Future Microbiol. 2019;14(11):927–39. https://doi.org/10.2217/FMB-2019-0027.
55. Mercuro NJ, Veve MP. Clinical utility of lefamulin: if not now, when? Curr Infect Dis Reports. 2020;22(9):1–13. https://doi.org/10.1007/S11908-020-00732-Z/TABLES/3.
56. Indiraa Priyadharshini VKMMG. Lefamulin – upgrading our arsenal against community-acquired pneumonia. Archives of Pharmacy Practice, Department of Clinical Pharmacology, SRM Medical College Hospital and Research Centre, Chennai, Tamil Nadu. 2020. (https://archivepp.com/article/lefamulin-upgrading-our-arsenal-against-community-acquired-pneumonia).
57. Wicha WW, LCOF et al. An age and gender study investigating the safety, tolerance and pharmacokinetics of BC-3781. 50th Interscience Conference on Antimicrobial Agents and Chemotherapy. 2010. Abstract A1-019. (https://www.nabriva.com/Portals/_default/Skins/ProfessionalUs/pdfs/2010-age-gender-study-with-bc-3781.pdf).
58. • Alexander E, et al. Oral lefamulin vs moxifloxacin for early clinical response among adults with community-acquired bacterial pneumonia: the LEAP 2 randomized clinical trial. JAMA. 2019;322(17):1661–71. https://doi.org/10.1001/JAMA.2019.15468. **Paper tells us about efficacy of Lefamulin in comparison to Moxifloxacin**.
59. File TM, Gelone SP, Schranz J, Alexander E. Reply to Tang and Lai. Clin Infect Dis. 2020;71(6):1583. https://doi.org/10.1093/CID/CIZ1174.
60. File TM, et al. Lefamulin efficacyand safety in adults with community-acquired bacterial pneumonia: pooled analysis of the lefamulin evaluation against pneumoni (LEAP) 1 and LEAP 2 in patients with multilobar or unilobar pneumonia. Chest Infections. 2021;160(4):A522-3.
61. Tang HJ, Lai CC. Lefamulin for treating community-acquired bacterial pneumonia in adult patients aged. Clin Infect Dis. 2020;71(6):1582. https://doi.org/10.1093/CID/CIZ1173.
62. Tang H-J, Lai C-C, Chao C-M. The clinical efficacy of lefamulin in the treatment of elderlypatients with community-acquired bacterial pneumonia. J Thorac Dis. 2020;12(8):4588–90.