# Xenleta™ (lefamulin)
## ICD-10 Coordination and Maintenance Meeting Presentation

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Nabriva THERAPEUTICS

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# XENLETA™: The First Systemic (IV and Oral) Pleuromutilin Treatment for Community Acquired Bacterial Pneumonia (CABP)

- Key Attributes of Xenleta
- New pleuromutilin antibiotic with unique mechanism of action
  - Inhibits bacterial protein synthesis through interactions (hydrogen bonds, hydrophobic interactions, and Van der Waals forces) with both the A- and P-sites of the PTC in domain V of the 23s rRNA of the 50s subunit
- Empiric monotherapy that provides targeted antimicrobial activity against the most common causative pathogens of CABP, including resistant strains
- Demonstrated *in vitro* and *in vivo* activity against Gram-positive, fastidious Gram-negative, and atypical bacteria
- Potential to offer a short-course empiric monotherapy for the treatment of CABP, with an oral-only option or conversion from IV to PO administration
- Designated by FDA as a Qualified Infectious Disease Product (QIDP) with Fast Track review
- FDA approval received on August 19, 2019
  - NDA based on two phase 3 pivotal clinical trials (LEAP 1 and LEAP 2) in CABP, which met the primary and secondary endpoints by demonstrating non-inferiority to moxifloxacin

# Pneumonia: A Leading Cause of Morbidity, Mortality and Healthcare Cost

- There are 5 million cases annually in the United States[5]
  - The CDC has deemed drug-resistant *S. pneumoniae* a serious public health threat[6,7]
- Morbidity and Mortality
  - #1 cause of infectious death[8]
  - #3 cause of hospital readmissions[9]
  - #5 cause of total hospitalizations[10]
  - Mortality rate is approximately 15%[11] in a hospital and ~25-30% in an ICU[12,13]
- Direct costs of pneumonia reach approximately $17 billion[14]

5: National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS) 2009 - 2010. *6: Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States. 2013. www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf. Accessed October 10, 2019. 7: Kim L, et al. Clin Microbiol Rev. 2016;29:525-552. https://www.cdc.gov/nchs/data/ahcd/combined_tables/2009-2010_combined_web_table01.pdf (Last Accessed June 21, 2019). 8: el Bcheraoui C, Mokdad AH, Dwyer-Lindgren L, et al. Trends and Patterns of Differences in Infectious Disease Mortality Among US Counties, 1980-2014. JAMA. 2018;319(12):1248–1260. doi:10.1001/jama.2018.2089 9: Fingar K, Washington R. Trends in hospital readmissions for four high-volume conditions, 2009-2013: Statistical Brief #196. Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Rockville, MD: Agency for Healthcare Research and Quality; November 2015. http//www.hcup-us.ahrq.gov/reports/statbriefs/sb196-Readmissions-Trends-High-Volume-Conditions.pdf. Accessed February 23, 2016. \ 10: HCUP Fast Stats - Most Common Diagnoses for Inpatient Stays – 2015 https://www.hcup-us.ahrq.gov/faststats/NationalDiagnosesServlet 11: 2017 CHARTBOOK STATIC ANALYSES - Trends in mortality rates following admission for acute myocardial infarction, chronic obstructive pulmonary disease, heart failure, pneumonia, and acute ischemic stroke. Prepared for CMS by Yale New Haven Health Services Corporation - Center for Outcomes Research and Evaluation (YNHHSC/CORE) September 2017 12 Joya-Montosa Critical Care 2015 19(Suppl 1):P19. 13: AlOtair Journal of Taibah University Medical Sciences Volume 10, Issue 3, Sept. 2015, Pages 293-299. 14: File TM Jr, Marrie TJ. Burden of community-acquired pneumonia in North American adults. Postgrad Med.* 2010;122:130–41.



Nabriva THERAPEUTICS

# Lefamulin: A New Pleuromutilin Antibacterial

- Pleuromutilin antibiotics are semisynthetic derivatives of pleuromutilin, isolated from an edible mushroom
- Extensive evaluation with 27 clinical studies (24 Phase 1; 1 proof of concept phase 2 study of acute bacterial skin and skin structure infections [ABSSSI] and 2 phase 3 pivotal registrational trials for the treatment of CABP.
- Available in IV and oral formulations
  - 600 mg of lefamulin in a blue, oval, film-coated tablet
  - 150 mg of lefamulin in a 15 mL single use vial intended for dilution in 250 mL of 10 mM citrate buffered 0.9% sodium chloride

Data on File. Nabriva Therapeutics, US, Inc. 2019.

# Pleuromutilins - Distinctive Mechanism of Action and Low Propensity to Develop Bacterial Resistance

- Lefamulin's distinctive MoA inhibits bacterial protein synthesis through interactions with the A- and P-sites of the peptidyl transferase center (PTC)
  - Binds with high affinity and specificity with 4 distinctive binding interactions in highly conserved core of the ribosomal PTC
  - Binding pocket closes around the mutilin core for an induced fit at molecular sites that are differentiated from those of other antibiotic classes
- This has important potential clinical benefit because lefamulin has a:
  - Low potential for cross-resistance to other classes (e.g., macrolides, ß-lactams, fluoroquinolones, tetracyclines, vancomycin)
  - Low propensity to develop resistance as seen in in vitro single and multi-step mutation resistance studies
    - Resistance frequency to lefamulin due to spontaneous mutations in vitro at 2-8 times the MIC was $2 \times 10^{-9}$ to $<2 \times 10^{-11}$ for *S. aureus*, $<1 \times 10^{-9}$ to $<3 \times 10^{-10}$ for *S. pneumoniae*, and $<4 \times 10^{-9}$ to $<2 \times 10^{-10}$ for *S. pyogenes*.
    - Resistance development at sub-MIC concentrations required greater than 1 mutational step with no resistant clones detected at ≥4-times MIC.


1. Data on File. Nabriva Therapeutics US, Inc 2019
2. Paukner S; Riedl R. *Cold Spring Harbor perspectives in medicine;*2017:2157-1422
3. Waites KB, et al. *Antimicrob Agents Chemother.* 2017;61:pii: e02008-16.

# Lefamulin- Bacterial Spectrum of Activity Targeted for CABP*

## Lefamulin has activity against pathogens that most commonly cause CABP*

| Etiology[1,2] | Frequency (median percentage)[2] |
|---|---|
| **Outpatients** | |
| *Mycoplasma pneumoniae* | 16 |
| Respiratory viruses | 15 |
| *Streptococcal pneumoniae* | 14 |
| *Chlamydophila pneumoniae* | 12 |
| *Legionella* species** | 2 |
| *Haemophilus influenzae* | 1 |
| Unknown | 44 |

**Lefamulin is active against *Legionella pneumophila*

| Etiology[1,2] | Frequency (median percentage)[2] |
|---|---|
| **Inpatients not admitted to ICU** | |
| *S. pneumoniae* | 25 |
| Respiratory viruses | 10 |
| *M. pneumoniae* | 6 |
| *H. influenzae* | 5 |
| *C. pneumoniae* | 3 |
| *Legionella* species** | 3 |
| Unknown | 37 |

| Etiology[1,2] | Frequency (median percentage)[2] |
|---|---|
| **Inpatients admitted to ICU** | |
| *S. pneumoniae* | 17 |
| *Legionella* species** | 10 |
| Gram-negative bacilli | 5 |
| *Staphylococcus aureus* | 5 |
| Respiratory viruses | 4 |
| *H. influenzae* | 3 |
| Unknown | 41 |

*Lefamulin is not active against Enterobacteriaceae or *Pseudomonas aeruginosa*

1. Watkins RR, Lemonovich TL. *Am Fam Physician.* 2011;83(11):1299-306. 2. Mandell et al. *Clin Infect Dis.* 2007;44(suppl 2):S27-S72.

# XENLETA Administration

- For the treatment of adults with CABP, the recommended dosage of XENLETA* is as follows:

| Formulation | Dosage | Treatment Duration |
|---|---|---|
| XENLETA injection<br>For intravenous use | 150 mg every 12 hours by intravenous infusion over 60 minutes* | 5 to 7 days |
| XENLETA tablets<br>For oral use | 600 mg orally every 12 hours | 5 days |

*With the option to switch to XENLETA Tablets 600 mg every 12 hours to complete the treatment course

*Precautions

- In patients with severe hepatic impairment, reduce the dosage of XENLETA Injection to 150 mg infused over 60 minutes every 24 hours. XENLETA Tablets are not recommended in patients with moderate or severe hepatic impairment due to insufficient information to provide dosing recommendations.
- Avoid XENLETA Injection and Tablets with concomitant strong or moderate CYP3A or P-gp inducers. Monitor for reduced efficacy of XENLETA.
- Avoid XENLETA Tablets with strong CYP3A or P-gp inhibitors



XENLETA™ (lefamulin) [package insert]. King of Prussia, PA: Nabriva Therapeutics; 2019.

# LEAP 1 and LEAP 2 Overview: The Phase 3 CABP Program

## LEAP 1 (IV to Oral) Trial

- 551 adult patients with PORT Risk Class III-V
- Lefamulin vs. Moxifloxacin ± Linezolid
- Rx for 5-7 days Lefamulin vs. 7 days Moxifloxacin (10 days for MRSA)
- PORT Risk Class III vs. IV and V stratification
- ≥25% of patients with PORT Risk Class IV or V

## LEAP 2 (Oral) Trial

- 738 adult patients with PORT Risk Class II-IV
- Lefamulin vs. Moxifloxacin
- Rx for 5 days Lefamulin vs. 7 days Moxifloxacin
- PORT Risk Class II vs. III and IV stratification
- ≥50% of patients with PORT Risk Class III or IV

File TM Jr, et al. *Clin Infect Dis.* 2019 Feb 13;69(11):1856-1867. doi: 10.1093/cid/ciz090
Alexander E, et. Al. JAMA. 2019;322(17):1661-1671. doi: 10.1001/jama.2019.15468.

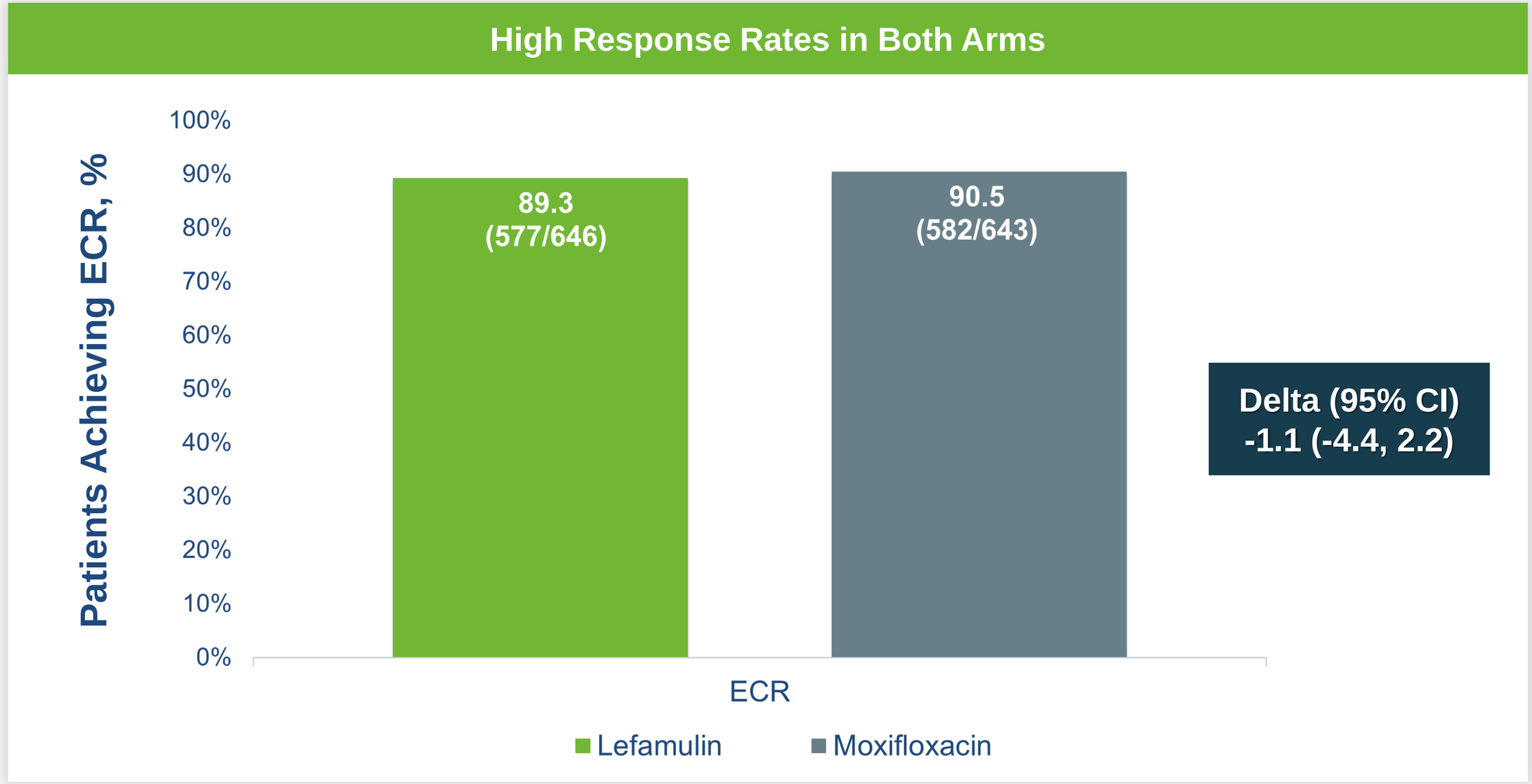
# Pooled LEAP 1 and 2 Patient Demographics and Baseline Characteristics: ITT Population

| Category | Lefamulin N=646 / n (%) | Moxifloxacin N=643 / n (%) |
|---|---|---|
| *Mean (SD) age, y* | 58.9 (16.5) | 58.5 (15.7) |
| *Age Group, n (%)* | | |
| 18-64 | 378 (58.5%) | 394 (61.3%) |
| 65-74 | 152 (23.5%) | 145 (22.6%) |
| ≥75 | 116 (18.0) | 104 (16.2%) |
| *Demographics* | | |
| Male | 377 (58.4%) | 340 (52.9%) |
| Mean (SD) BMI (kg/m$^2$) | 26.5 (5.8) | 26.4 (6.0) |
| Race (White) | 513 (79.4%) | 509 (79.2%) |
| *Renal Status* | | |
| Normal function (CrCl ≥90 mL/min) | 311 (48.1%) | 312 (48.5%) |
| *Comorbidities* | | |
| Hypertension | 244 (37.8%) | 247 (38.4%) |
| Diabetes | 80 (12.4%) | 88 (13.6%) |
| Chronic Obstructive Pulmonary Disease | 76 (11.8%) | 60 (9.3%) |

**CrCl=creatinine clearance**

File TM Jr, et al. *Clin Infect Dis.* 2019 Feb 13;69(11):1856-1867. doi: 10.1093/cid/ciz090
Alexander E, et. Al. JAMA. 2019;322(17):1661-1671. doi: 10.1001/jama.2019.15468.

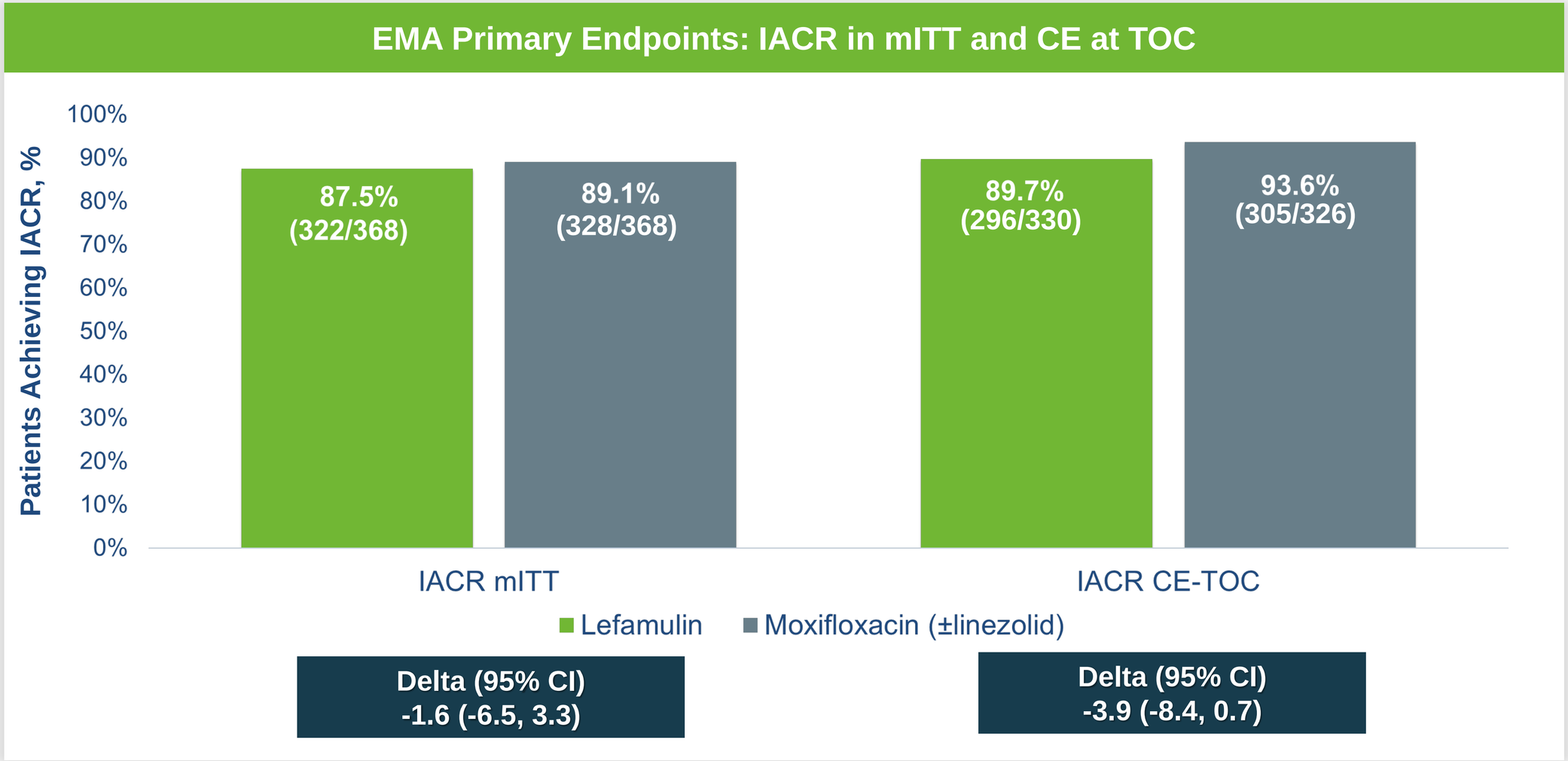
# Pooled LEAP 1 and 2 Efficacy Results
# Lefamulin Met FDA Primary Endpoint of ECR in the ITT Analysis Set




ECR=early clinical response

File TM Jr, et al. *Clin Infect Dis.* 2019 Feb 13;69(11):1856-1867. doi: 10.1093/cid/ciz090
Alexander E, et. Al. JAMA. 2019;322(17):1661-1671. doi: 10.1001/jama.2019.15468.

# LEAP 2 Efficacy Results: Lefamulin Met FDA Secondary Endpoints




CE=clinically evaluable; IACR=investigator assessment of clinical response; mITT=modified intent-to-treat; TOC=test of cure

Alexander E, et. Al. JAMA. 2019;322(17):1661-1671. doi: 10.1001/jama.2019.15468.

# Pooled LEAP 1 and 2 Efficacy Results: Post-hoc Assessment of Discharge Readiness in Hospitalized Patients in LEAP 1 and LEAP 2 Studies

- > 95% of patients in each analysis achieved the endpoint in each arm between treatment initiation and end of therapy.
- No difference seen between treatment arms regardless of baseline characteristics and demographics.

| Median time (interquartile range, IQR), days | Lefamulin | Moxifloxacin |
|---|---|---|
| Time to Clinical Response | 4 days (3-4) | 4 days (3-5) |
| Time to Clinical Stability | 3 days (2-4) | 3 days (2-4) |
| Time to Clinical Improvement | 3 days (2-4) | 3 days (2-4) |

- Clinical Response: alive, Clinical stability (temperature ≤38.0°C and ≥35.0°C, heart rate ≤100 bpm, systolic blood pressure ≥90 mmHg, respiratory rate ≤24 breaths/min, oxygen saturation ≥90%, arterial PaO2≥60 mmHg), improvement in at least 2 cardinal CABP symptoms (i.e., cough, shortness of breath, chest pain, or sputum production) and none worsening, and no receipt of a concomitant antibiotic (other than adjunctive linezolid) for treatment of the current episode of CABP
- Clinical Stability: temperature ≤38.0°C and ≥35.0°C, heart rate ≤100 bpm, systolic blood pressure ≥90 mmHg, respiratory rate ≤24 breaths/min, oxygen saturation ≥90%, arterial PaO2≥60 mmHg
- Clinical Improvement: Improvement in at least 2 cardinal CABP symptoms (i.e., cough, shortness of breath, chest pain, or sputum production) and none worsening

Lodise, et al. Poster Presentation at 22nd Annual Making a Difference in Infectious Diseases (MAD-ID) Meeting; May 8–11, 2019; Orlando, FL, USA.

# Pooled LEAP 1 and 2 Safety Results
# Overall Summary of Adverse Events (Safety Population)

| | Lefamulin<br>150 mg IV / 600 mg Oral<br>N=641 / n (%) | Moxifloxacin<br>400 mg IV / 400 mg Oral<br>N=641 / n (%) |
|---|---|---|
| **Treatment-emergent adverse events (TEAE)** | | |
| Any TEAE | 224 (34.9) | 195 (30.4) |
| Related TEAE | 99 (15.4) | 68 (10.6) |
| Severe TEAE | 27 (4.2) | 23 (3.6) |
| TEAE leading to death | 11 (1.7) | 8 (1.2) |
| Related TEAE leading to death | 0 | 0 |
| **Serious adverse events (SAE)** | | |
| Treatment-emergent SAE | 36 (5.6) | 31 (4.8) |
| Related treatment-emergent SAE | 3 (0.5) | 2 (0.3) |
| **Discontinuation of study drug due to AE** | | |
| TEAE | 20 (3.1) | 21 (3.3) |
| Related TEAE | 7 (1.1) | 8 (1.2) |

File TM Jr, et al. *Clin Infect Dis.* 2019 Feb 13;69(11):1856-1867. doi: 10.1093/cid/ciz090
Alexander E, et. Al. JAMA. 2019;322(17):1661-1671. doi: 10.1001/jama.2019.15468.

# XENLETA

*Summary*

**XENLETA, a pleuromutilin, represents the first intravenous (IV) and oral treatment option from a novel class of antibiotics for the treatment of CABP in adults. Due to its distinctive mechanism of action, it has activity against the pathogens that cause the majority of CABP, including certain resistant strains. XENLETA offers empiric monotherapy for the treatment of CABP, facilitating transition of care with conversion from IV to oral administration.**

***The FDA has designated XENLETA as a qualified infectious disease product (QIDP)***

**XENLETA is a first-in-class systemic pleuromutilin antibiotic**

- Novel mechanism of action
- *In vitro* activity against Gram-positive, fastidious Gram-negative, and atypical bacteria
- Low propensity for resistance
- Low probability of cross-resistance to other antibiotic classes

**XENLETA offers a short-course empiric monotherapy with an option for oral administration or switch from IV to PO administration**

- Facilitates transition of care and discharge readiness
- Aligned with antimicrobial stewardship principles

**XENLETA was found to be non-inferior to moxifloxacin in the LEAP1 and LEAP2 clinical trials evaluating IV to oral and oral only**

- Primary FDA endpoint of ECR
- Secondary endpoints of IACR at the test of cure (TOC) visit in both mITT and CE populations
- Generally safe and well tolerated

**A unique ICD-10-PCS code will help identify and track the use of XENLETA for the treatment of CABP and related outcomes data and is needed to identify qualifying cases, if granted NTAP**