Lefamulin

The potential for 1 antibiotic rather than 2 in CABP

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Nabriva THERAPEUTICS

Disclosures

Mark H. Wilcox has received

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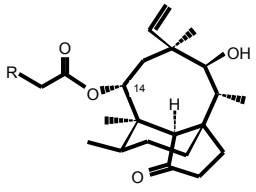
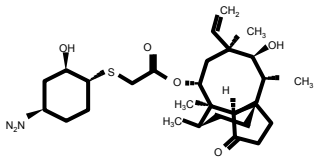
Pleuromutilin Antibacterial Agents

- **Pleuromutilin** antibiotics inhibit translation and are semisynthetic derivatives of the naturally occurring tricyclic diterpenoid pleuromutilin isolated from an edible mushroom
  - Veterinary use: **tiamulin** and **valnemulin** (oral treatment of dysentery and respiratory infections in swine and poultry)
  - Human use: **retapamulin** (topical treatment of uSSSTI caused by MSSA or *Streptococcus* spp)
- **Lefamulin** was discovered by Nabriva and is the first systemic pleuromutilin for human use
  - Developed as both an intravenous formulation (150 mg q12h) and an oral immediate-release tablet (600 mg q12h)
    - Completed phase 2 trial for treating ABSSSI: lefamulin showed comparable efficacy to vancomycin
    - 2 phase 3 trials for treating CABP: positive topline results from the first just reported



Pleuromutilin R = OH


Pleurotus mutilus (*Clitopilus scyphoides*)
Source: James Lindsey's Ecology of Commanster Site, 2006

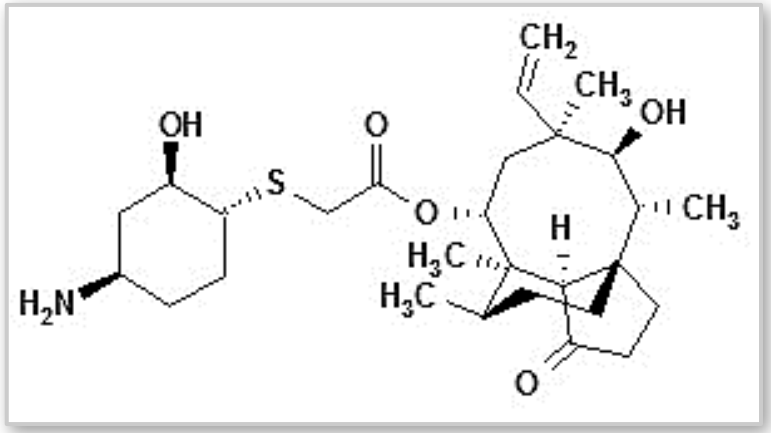


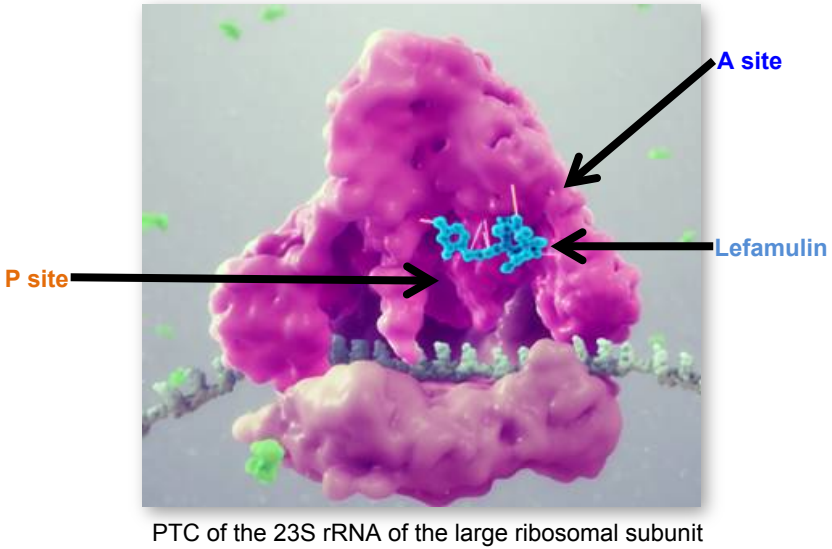
ABSSSI=acute bacterial skin and skin structure infections; CABP=community-acquired bacterial pneumonia; MSSA=methicillin-susceptible *Staphylococcus aureus*; q12h=every 12 hours; uSSSTI=uncomplicated skin and soft tissue infection

Lefamulin

Mechanism of Action

- Novel mechanism of action with 4 distinctive binding sites in highly conserved core of the ribosomal PTC





PTC of the 23S rRNA of the large ribosomal subunit

PTC=peptidyl transferase center; rRNA=ribosomal RNA

Lefamulin

In Vitro Spectrum of Activity

>22,500 clinical isolates tested, including with excellent coverage of key skin and respiratory pathogens

- >11,000 staphylococci, including HA-MRSA and CA-MRSA
- >7000 *Streptococcus pneumoniae*
- SENTRY surveillance studies 2010/2015/2016 (~80% isolates from United States and Europe)

Excellent activity against community-acquired respiratory pathogens

- *S. pneumoniae, Moraxella catarrhalis, Haemophilus influenzae, Staphylococcus aureus*
- *Legionella pneumophila, Chlamydia pneumoniae,* and *Mycoplasma pneumoniae*

Potent activity against skin pathogens

- *S. aureus* (HA-MRSA and CA-MRSA), coagulast-negative staphylococci, group A and group B Streptococci

Active against the following anaerobic organisms:

- Spore-formers like *Clostridium* spp, non-spore formers like *Propionibacteriaceae* spp, other Gram-positive cocci like *Peptostreptococcus* spp and selected Gram-negative rods

Active against *Enterococcus faecium*, in particular VRE, but not against *Enterococcus faecalis* and Enterobacteriaceae

Excellent activity against STI organisms

- *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, mycoplasma species, including MDR strains

CA-MRSA=community-acquired MRSA; HA-MRSA=hospital-acquired MRSA; MDR=multidrug resistant; MRSA=methicillin-resistant *Staphylococcus aureus;* STI=sexually transmitted infection; VRE=vancomycin-resistant enterococci

Lefamulin Spectrum of *In Vitro* Activity Is Well Suited for CABP

Organism	*n*	MIC_{90}, mg/L
*Streptococcus pneumoniae**	2886	0.12
*Moraxella catarrhalis**	779	0.06
*Haemophilus influenzae**	1108	1
Staphylococcus aureus (including HA-MRSA, CA-MRSA, and MSSA)	3077	0.12
Legionella pneumophila	30	0.5
Chlamydia pneumoniae	50	0.04
Mycoplasma pneumoniae†	50	0.002

- Extensively investigated against most prevalent CABP pathogens
- Lefamulin's activity is not affected by antibiotic resistance in CABP pathogens
  - MRSA
  - Cephalosporin or fluoroquinolone or macrolide or penicillin-resistant *S. pneumoniae*
  - Macrolide-resistant *Mycoplasma* spp

Note: *S. pneumoniae* resistant to macrolides or to levofloxacin showed 100% susceptibility to lefamulin (SENTRY 2015-16 surveillance with *S. pneumoniae* isolates collected world-wide)
*Data from SENTRY 2015–2016 world-wide surveillance program
†Waites KB, et al. ASM-Microbe Meeting, June 19, 2016; Abstract #3972
CABP=community-acquired bacterial pneumonia; CA-MRSA=community-acquired MRSA; HA-MRSA=hospital-acquired MRSA; MDR=multi-drug resistant; MIC_{90}=minimum inhibitory concentration for 90% of isolates; MRSA=methicillin-resistant *Staphylococcus aureus*; MSSA=methicillin-susceptible *S. aureus*

Lefamulin

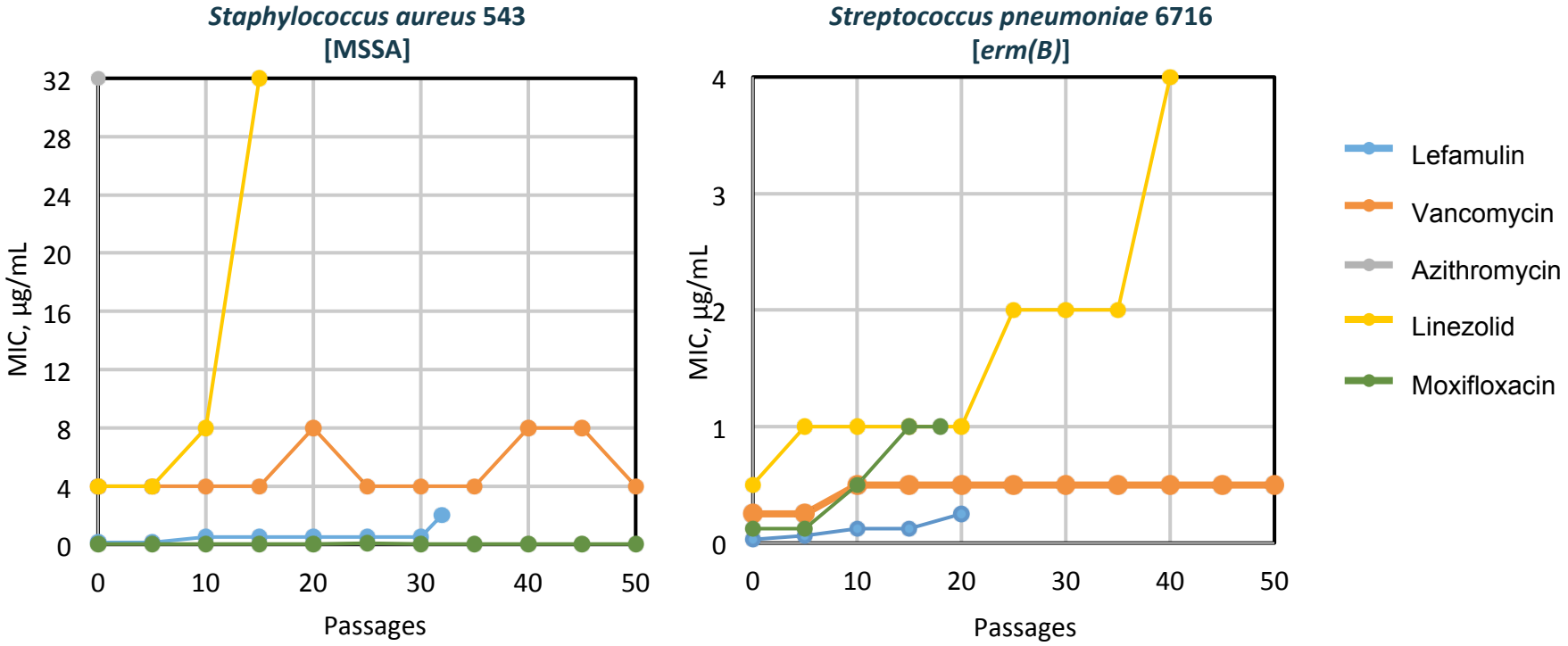
Summary of Potential for Cross-resistance

- No cross-resistance observed with bacteria resistant to
  - Aminoglycosides
  - ß-lactams
  - EF-G inhibitors (eg, fusidic acid)
  - Folate synthesis inhibitors (TMP-SMX)
  - Glycopeptides
  - Isoleucine t-RNA synthetase inhibitors (eg, pseudomonic acid/mupirocin)
  - MLSB antibiotics
  - Quinolones
  - Tetracyclines
- Affected by Cfr-mediated resistance to $PHLOPS_A$ antibiotics and Vga(A) efflux pump
  - Low incidences observed in recent surveillance studies (SENTRY 2010/2015/2016)
- No antagonism observed *in vitro* when combined with other antibacterial classes
  - Synergy vs *Staphylococcus aureus* observed when combined with doxycycline

EF-G=elongation factor G; Cfr= chloramphenicol-florfenicol resistance gene/ rRNA methyltransferase; MLSB=macrolide-lincosamide-streptogramin B; $PHLOPS_A$=phenicol-lincosamide-oxazolidinone-pleuromutilin-streptogramin A; TMP-SMX=trimethoprim sulfamethoxazole; Vga(A) efflux pump=plasmid-encoded ABC protein conferring resistance to A compounds of virginiamycin-like antibiotics

Lefamulin

Low *In Vitro* Propensity for Development of Resistance



erm(B)=erythromycin resistance gene B; MIC=minimum inhibitory concentration; MSSA=methicillin-susceptible *Staphylococcus aureus*

Lefamulin

Summary of *In Vitro* Activities

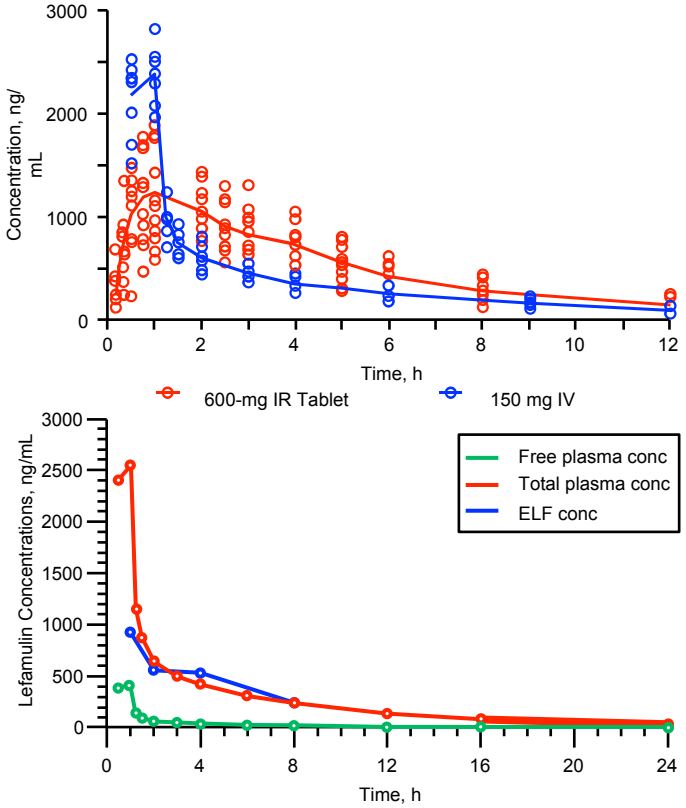
- Lefamulin inhibits protein synthesis by specifically targeting the peptidyl transferase center
- Lefamulin is active *in vitro* against CABP pathogens
- Lefamulin's activity is unaffected by an organism's resistance to other antibiotics
- The *in vitro* development of antimicrobial resistance is low for lefamulin

CABP=community-acquired bacterial pneumonia

Lefamulin

Pharmacokinetics (PK) – Lefamulin Shows Rapid and Predictable Tissue Penetration

PK Parameter	150 mg x 2 (IV 1-h Infusion) Mean ± SD	600 mg x 2 (IR Tablet) Mean ± SD
$C_{max,}$ mg/L	2.42 ± 0.52	1.46 ± 0.44
C_{min}, mg/L	0.24 ± 0.09	0.36 ± 0.21
Total body clearance, L/h	21.6 ± 5.4	
$t_{½}$, h	10.6 ± 0.7	9.09 ± 1.30
AUC_{24h}, mg·h/L	14.1 ± 5.8	
$AUC_{0\text{-}12h,ss}$, mg·h/L	8.27 ± 3.11	10.8 ± 4.2
AUC_{∞}, mg·h/L	7.28 ± 1.62	8.25 ± 2.31
Fraction unbound, % range [conc.]	12.1–27.3 [1–10 mg/L]	12.1–27.3 [1–10 mg/L]
Volume of distribution, L/kg	160 ± 43	
Accumulation, ratio of AUC ELF/$Plasma_{free}$(day 1)	5.8	

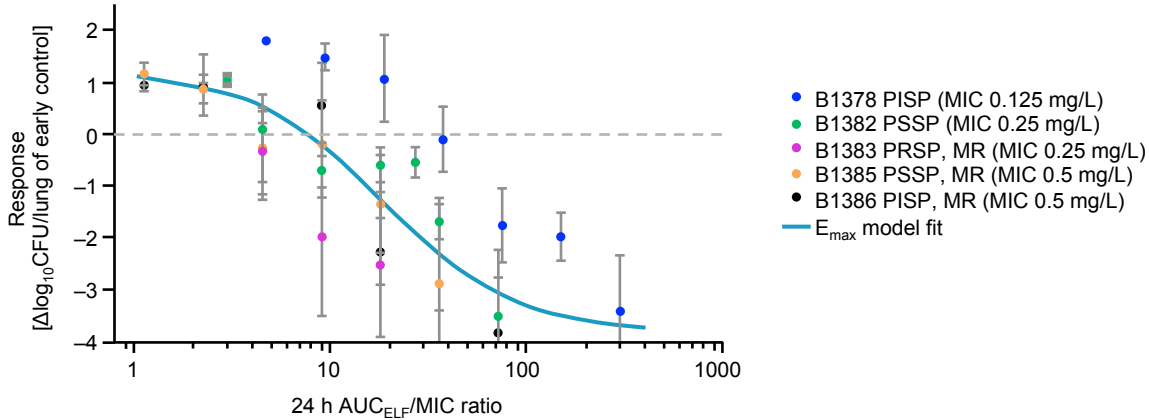


AUC=area under the concentration-time curve; ELF=epithelial lining fluid; IR=immediate release; IV=intravenous

Zeitlinger M, et al. *J Antimicrob Chemother*. 2016 Apr;71(4):1022-1026

Lefamulin

Pharmacokinetics/Pharmacodynamics – Target Attainment



Wicha WW, et al. 55th ICAAC. San Diego, CA. September 17-21, 2015. Abstract #A-037

	% Probabilities of Overall PK-PD Target Attainment Based on the Day 1 AUC:MIC Ratio Targets Associated With a 1-log_{10} CFU Reduction From Baseline				
	Region	IV AUC:MIC		PO AUC:MIC (fasted/fed)	
Pathogen	SENTRY 2015	ELF	Plasma	ELF	Plasma
Streptococcus pneumoniae	Global	99.6	100	99.6 / 98.3	100 / 99.9
Staphylococcus aureus	Global	99.6	99.7	99.5 / 99.7	99.7 / 99.7

Bhavnani SM, et al. IDWeek. New Orleans, LA. October 26-30, 2016. Poster #1976

AUC=area under the concentration-time curve; CFU=colony-forming unit; ELF=epithelial lining fluid; E_{max}=maximum effect; IV=intravenous; MIC=minimum inhibitory concentration; PD=pharmacodynamics; PISP=penicillin-intermediate *Streptococcus pneumoniae*; PK=pharmacokinetics; PRSP=penicillin-resistant *S. pneumoniae*; PSSP=penicillin-susceptible *S. pneumoniae*; PO=oral; MR=methicillin-resistant

Lefamulin Evaluation Against Pneumonia

LEAP 2 Enrollment Completed in December 2017
Top-Line Results Expected in Spring 2018

LEAP 1 (IV to Oral) Trial

- 551 adult patients with PORT risk class ≥III (moderate to severe)
- Lefamulin vs moxifloxacin ± linezolid
- Prescription for 7 days (10 days for MRSA)
- PORT risk class III vs IV and V
  - ≥25% of patients with PORT risk class IV or V

LEAP 2 (Oral) Trial

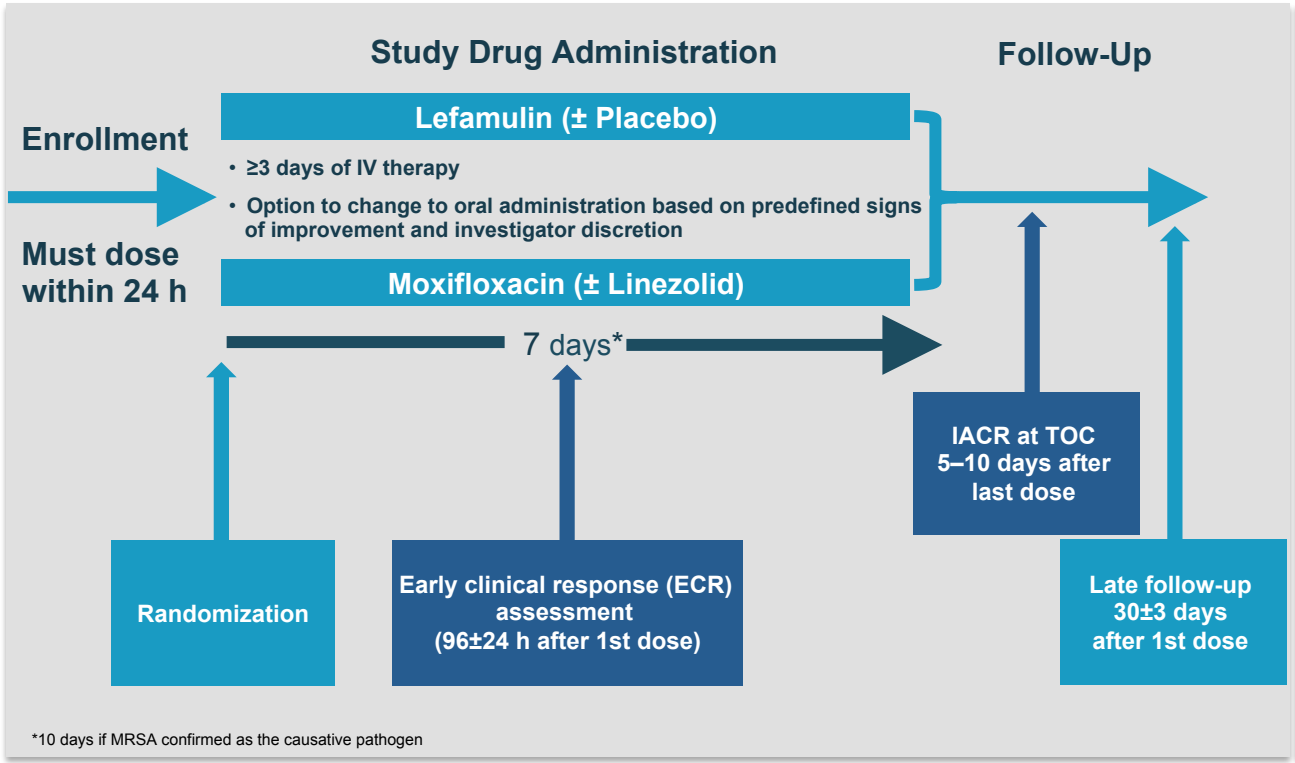
- 738 adult patients with PORT risk class II–IV (moderate)
- Lefamulin vs moxifloxacin
- Prescription for 5 days lefamulin vs 7 days moxifloxacin
- PORT risk class II vs III and IV
  - ≥50% of patients with PORT risk class III or IV

~40% of Patients in LEAP 1 Switched to Oral Lefamulin During Trial

IV=intravenous; PORT=Patient Outcomes Research Team Score; MRSA=methicillin-resistant *Staphylococcus aureus*

LEAP 1 Phase 3 Trial Design

IV Initiation With Option for Switch to Oral Administration



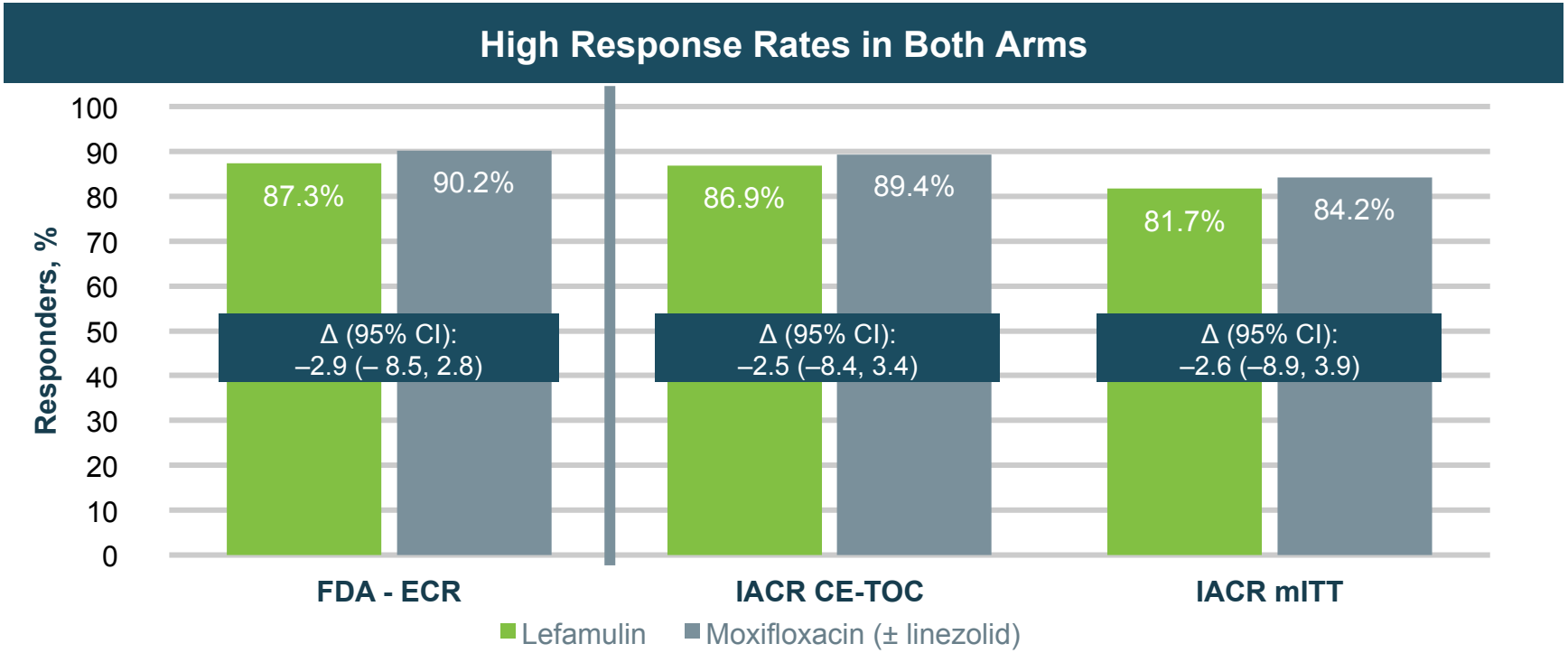
LEAP 2 Design

- Oral only
- No option to add linezolid
- 5 days lefamulin vs 7 days moxifloxacin
- ECR and IACR at TOC measured at the same time as in LEAP 1

ECR=early clinical response; IACR=investigator assessment of clinical response; IV=intravenous; MRSA=methicillin-resistant *Staphylococcus aureus*; TOC=test of cure

LEAP 1 Trial Efficacy Results

Lefamulin Met Both FDA and EMA Primary Endpoints



CE=clinically evaluable; ECR=early clinical response; EMA=European Medicines Agency; FDA=US Food and Drug Administration; IACR=investigator assessment of clinical response; mITT=modified intent to treat; TOC=test of cure

LEAP 1

Overview of Adverse Events

- Overall, comparable rates of adverse events were observed in both groups
  - Adverse events, TEAEs, related adverse events, and related serious adverse events
- Discontinuation of study drug or withdrawal of a patient from the study due to an adverse event
  - ~4% and ~2% discontinued in the moxifloxacin and lefamulin groups, respectively

Gastrointestinal System Organ Class (SOC)

- TEAEs in 6.6% and 13.0% of patients receiving lefamulin and moxifloxacin (± linezolid), respectively
- No cases of *Clostridium difficile* infection were reported in either treatment group
- Diarrhea was observed in 0.7% and 7.7% of patients receiving lefamulin and moxifloxacin (± linezolid), respectively

Hepatobiliary SOC

- TEAEs in 0.7% and 1.5% of patients receiving lefamulin and moxifloxacin (± linezolid), respectively
- Low incidence of liver enzyme elevation in both treatment groups consistent with CABP patient population

Cardiac Disorders SOC

- TEAEs in 2.9% and 4.0% of patients receiving lefamulin and moxifloxacin (± linezolid), respectively
- Changes in QT interval of potential clinical concern were uncommon and of similar frequency between treatment groups

Maximum Postdose QTcF Changes – Day 3, *n* (%)

Parameter	Lefamulin	Moxifloxacin ± Linezolid
Postdose increase 30–60 ms	12 (4.6)	14 (5.4)
Postdose increase >60 ms	0 (0.0)	1 (0.4)
Postdose value >500 ms	1 (0.4)	1 (0.4)

CABP=community-acquired bacterial pneumonia; SOC=system organ class; TEAE=treatment-emergent adverse event

TEAEs > 2% for Study Medication: Safety Population

Lefamulin was Well Tolerated with a Lower Incidence of Diarrhea

Preferred Term	Lefamulin (n=273)	Moxifloxacin (±linezolid) (n=273)
Hypokalemia	8 (2.9%)	6 (2.2%)
Nausea	8 (2.9%)	6 (2.2%)
Insomnia	8 (2.9%)	5 (1.8%)
Infusion Site Pain	8 (2.9%)	0 (0.0%)
Infusion Site Phlebitis	6 (2.2%)	3 (1.1%)
ALT Increase	5 (1.8%)	6 (2.2%)
Hypertension	2 (0.7%)	6 (2.2%)
Diarrhea	2 (0.7%)	21 (7.7%)

Summary

- Lefamulin has several attributes that facilitate improved antimicrobial stewardship
- Active against both typical and atypical CABP pathogens
- Has respiratory tract pathogen “targeted” activity (without encompassing off-target bacteria such as Enterobacteriaceae)
- Activity is not influenced by resistance to other antibacterial classes
- Available for step-down (IV to oral) therapy
- In a recent phase 3 trial for CABP, lefamulin was noninferior to moxifloxacin, with a favorable safety and tolerability profile

CABP=community-acquired bacterial pneumonia; IV=intravenous