# Lefamulin Demonstrates Favorable Safety and Tolerability in Adults with Community-Acquired Bacterial Pneumonia (CABP) in the Phase 3 Lefamulin Evaluation Against Pneumonia (LEAP 1) Study

David Mariano, PharmD Phone: 1-610-816-6659 Email: David.Mariano@nabriva.com

> **Nabriva Therapeutics Dublin**, Ireland www.nabriva.com

Thomas File,<sup>1</sup> Lisa Goldberg,<sup>2</sup> Anita Das,<sup>3</sup> Carolyn Sweeney,<sup>2</sup> Steven P. Gelone,<sup>2</sup> John Saviski,<sup>2</sup> Elyse Seltzer,<sup>4</sup> George H. Talbot,<sup>5</sup> Leanne B. Gasink<sup>2</sup> ¹Summa Health System, Akron, OH, USA; ²Nabriva Therapeutics US Inc., King of Prussia, PA, USA; ¹Urogen Pharma, New York, NY, USA; ⁵Talbot Advisors LLC, Anna Maria, FL, USA

# ABSTRACT

**Background:** New antibiotics for CABP with a targeted spectrum and improved tolerability are needed. Lefamulin is a novel pleuromutilin antibiotic for IV or oral use in development for treating CABP. Lefamulin binds to a highly conserved region of the ribosomal peptidyl transferase center targeting key CABP pathogens.

patients could switch to oral therapy, reaching a treatment duration of 7 days. Safety was assessed in patients

(2.2%) vs 3 [1.1%]). Lower rates of gastrointestinal (6.6% vs 13.6%), hepatobiliary (0.7% vs 1.5%), and cardiac (2.9% vs 4%) system organ class AEs were reported in the lefamulin arm. Fewer patients on lefamulin than moxifloxacing reported diarrhea (2 [0.7%] vs 21 [7.7%]). No cases of Clostridium difficile infection were reported. Laboratory values, liver function tests and ECG, were similar between groups; no patients met Hy's Law criteria. nclusions: In this first phase 3 CABP clinical trial, lefamulin monotherapy treatment of CABP in adults demonstrated favorable tolerability and safety profile compared to moxifloxacin ±linezolid.

# INTRODUCTION

- The burden of community-acquired pneumonia (CAP) is significant,<sup>1-3</sup> with annual costs approximately €10.1 billion in Europe and over \$17 billion in the United States<sup>2,4</sup>
- The most commonly isolated CAP bacterial pathogen is Streptococcus pneumoniae. Other common causes of community-acquired bacterial pneumonia (CABP) include Haemophilus influenzae, Moraxella catarrhalis, and Staphylococcus aureus<sup>5</sup>
- New therapies for CABP are needed because of the rise of antibacterial resistance and the undesirable risks and side effects associated with current treatments<sup>6-1</sup>
- Lefamulin is a novel semisynthetic pleuromutilin antibiotic in development for the treatment of CABP. Lefamulin inhibits protein synthesis by binding selectively and specifically to the peptidyl transferase center of the 50S ribosomal subunit<sup>12</sup>
- The objective of the study was to describe the safety and tolerability of lefamulin, with an intravenous (IV) to oral switch option, in the first phase 3 trial in adult patients with CABP

# METHODS

# Study Design

- LEAP 1 was a prospective, multicenter, randomized, double-blind, double-dummy phase 3 study to evaluate adult patients with CABP conducted in 18 countries at 104 study sites
- Patients were randomly assigned to receive lefamulin 150 mg IV every 12 hours (q12h) or moxifloxacin 400 mg IV every 24 hours (q24h) for 7 days of therapy
- Linezolid (600 mg IV or orally q12h) or matching placebo was added to moxifloxacin or lefamulin therapy, respectively, if methicillin-resistant S. aureus (MRSA) was suspected If MRSA was confirmed, treatment duration was 10 days
- Patients could be switched to oral therapy (lefamulin 600 mg q12h or moxifloxacin 400 mg q24h) after ≥6 IV doses of study drug (~3 days), if predefined criteria were met

### **Patients**

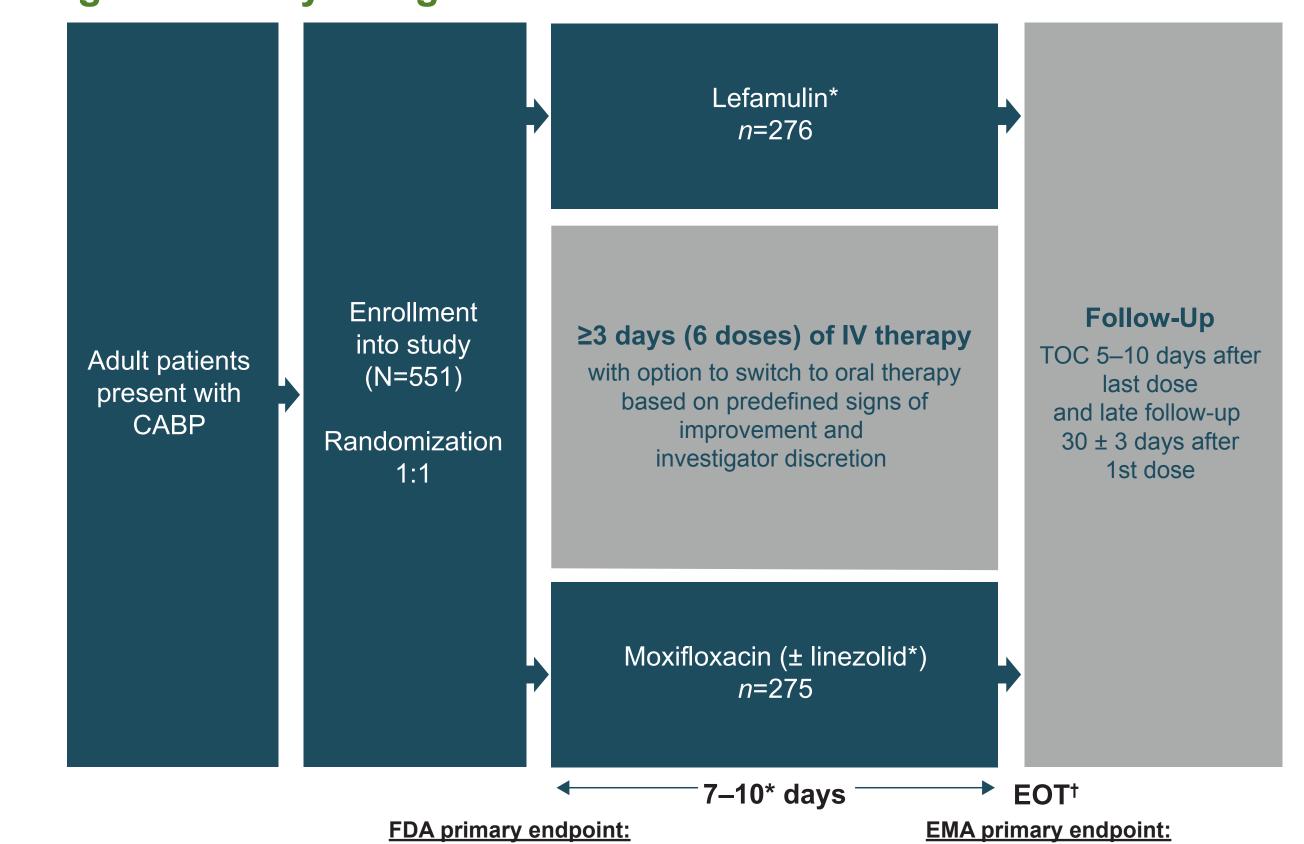
- Patients ≥18 years of age with CABP (Pneumonia Outcomes Research Team [PORT] risk class III [limited to 75%], IV, or V) were eligible
- A single dose of short-acting antibiotic (as requiring >1 dose per day) within 24 hours of randomization was allowed in up to 25% of the population
- Informed consent and approval of study procedures were obtained in accordance with local regulations before enrollment

## Assessments

- Screening occurred within 24 hours before the first dose of study drug
- Efficacy was assessed with 2 measures: Early Clinical Response (ECR) and Investigator Assessment of Clinical Response (IACR)
- ECR was assessed in the intent-to-treat (ITT) population 72–120 hours after the first dose of study drug
- IACR was evaluated at the test-of-cure (TOC) assessment 5–10 days after the last dose of study drug in the modified ITT (mITT) population (patients who received any amount of study drug) and in the clinically evaluable (CE) population (patients who met predefined specified criteria related to adherence to the protocol)
- Adverse events (AEs) were monitored throughout the trial at each study visit and by patient reporting, as needed. AEs and clinically significant abnormal laboratory tests were evaluated by the study investigator or a monitoring physician, at which time their relationship to the study drug treatment was evaluated
- Laboratory tests were performed at baseline and throughout the study at predefined time points. Blood tests were sent to a central laboratory for analysis
- For cardiac evaluations, triplicate 12-lead electrocardiograms were performed within a 5-minute interval at screening and on days 1 and 3

# METHODS (continued)

## Figure 1. Study Design



of clinical response (IACR) (assessed 72–120 hours after first dose) (assessed 5–10 days after last dose) Improvement in ≥2 of 4 CABP Improvement or resolution in CABP signs/symptoms such that no additional signs/symptoms,<sup>‡</sup> no worsening ir any sign/symptom, alive, did not receive antibacterial therapy was required to treat CABP, mITT and CE-TOC nonstudy antibacterial for CABP, populations, 10% noninferiority margin ITT population, 12.5% noninferiority margin

\*If MRSA was suspected, linezolid or placebo was added to moxifloxacin or lefamulin therapy, respectively; if MRSA was confirmed,

**Investigator assessment** 

Early clinical response (ECR)

# RESULTS

†EOT assessment was within 2 days after the last dose of study drug

moxifloxacin ± linezolid groups, respectively

<sup>‡</sup>Dyspnea, cough, production of purulent sputum, chest pain.

## **Patients**

- Of the 551 patients enrolled, 276 were randomly assigned to receive lefamulin and 275 to receive moxifloxacin ± linezolid. 273 patients in each group received the assigned drug and were included in the safety analysis
- Patient characteristics were similar between the 2 groups; however, patients in the lefamulin group were older (aged ≥75 years: lefamulin, 21% [58/276] vs moxifloxacin ± linezolid, 15% [42/275]). The mean age (range) of patients was 61.0 (19–91) and 59.6 (20–90) years in the lefamulin and moxifloxacin ± linezolid groups, respectively
- Full patient demographic details are available in poster #682<sup>13</sup> Mean duration of therapy was 7.2 and 7.1 days for patients in the lefamulin and
- Switch from IV to oral therapy was made in 38.1% (104/273) and 44.3% (121/273) of patients receiving lefamulin and moxifloxacin ± linezolid, respectively

## Clinical Success

- Lefamulin was noninferior to moxifloxacin ± linezolid when assessed by the US Food and Drug Administration primary endpoint (ECR) in the ITT population, or by the European Medicines Agency co-primary endpoint (IACR) in the mITT and CE-TOC populations
- Please refer to the accompanying companion poster #682 for additional details regarding lefamulin efficacy in the LEAP 1 trial<sup>13</sup>

#### Overview of AEs

Safety and Tolerability

- The overall rate of treatment-emergent AEs (TEAEs) was similar in the lefamulin (38.1%) and the moxifloxacin (37.7%) treatment groups (Table 1)
- A similar percentage of patients receiving lefamulin (15.0%) or moxifloxacin ± linezolid (14.3%) experienced a treatment-related TEAE. Most were mild or moderate in severity (Table 1)
- Lower rates of gastrointestinal system organ class TEAEs were reported in the lefamulin group compared with the moxifloxacin ± linezolid group (6.6% [18/273] vs 13.6% [37/273], respectively) Substantially fewer patients taking lefamulin reported diarrhea compared with those taking moxifloxacin ± linezolid (0.7% [2/273] vs 7.7% [21/273]; **Table 1**)
- No cases of Clostridium difficile infection were reported in either group

# RESULTS (continued)

- More patients receiving lefamulin than moxifloxacin ± linezolid reported infusion site pain (2.9% [8/273] vs 0%) and infusion site phlebitis (2.2% [6/273] vs 1.1% [3/273]; **Table 1**)
- Of the few infusion site-related TEAEs reported, only 1 in each treatment group led to study drug discontinuation: 1 patient taking lefamulin and 1 patient taking moxifloxacin ± linezolid discontinued because of infusion site phlebitis and infusion site erythema,
- 7.0% (19/273) of patients taking lefamulin and 4.8% (13/273) taking moxifloxacin ± linezolid experienced a treatment-emergent serious AE (SAE), of which 1.1% (3/273) and 0.4% (1/273) were judged by the investigator as related to study treatment (Table 1)
- Though uncommon, the most frequently occurring treatment-emergent SAEs by system organ class and preferred term were typical of the disease and patient population being studied (Table 3). SAEs generally occurred in no more than 1 patient, with the exception of pneumonia (n=4 for lefamulin and n=1 for moxifloxacin  $\pm$  linezolid)

#### Table 1. Overview of Patients Experiencing ≥1 TFAF

	Pa	Patients, <i>n</i> (%)		
TEAEs*,†	Lefamulin n=273	Moxifloxacin ± Linezolid n=273		
All TEAEs	104 (38.1)	103 (37.7)		
Mild	56 (20.5)	62 (22.7)		
Moderate	34 (12.5)	28 (10.3)		
Severe	14 (5.1)	13 (4.8)		
Serious TEAEs	19 (7.0)	13 (4.8)		
Treatment-related TEAEs	41 (15.0)	39 (14.3)		
Mild	28 (10.3)	30 (11.0)		
Moderate	9 (3.3)	6 (2.2)		
Severe	4 (1.5)	3 (1.1)		
Serious treatment-related TEAEs	3 (1.1)	1 (0.4)		
TEAEs leading to death	6 (2.2)	5 (1.8)		
TEAEs occurring in >2% of patients	104 (38.1)	103 (37.7)		
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		
Infusion site phlebitis	6 (2.2)	3 (1.1)		
Alanine aminotransferase increase	5 (1.8)	6 (2.2)		
Hypertension	2 (0.7)	6 (2.2)		
Diarrhea	2 (0.7)	21 (7.7)		

\*TEAE is defined as an AE that starts or worsens at or during the time of or after the first study drug administration Per protocol, sites were instructed to report nonserious AEs through the test-of-cure visit and serious AEs through late follow-up.

AE=adverse event: TEAE=treatment-emergent AE

- Discontinuation of the study drug or study due to a TEAE was less common with lefamulin than moxifloxacin ± linezolid (Table 2)
- Discontinuation of study drug due to a TEAE occurred in 2.9% (8/273) of patients receiving lefamulin and 4.4% (12/273) of patients receiving moxifloxacin ± linezolid, and distributions by preferred term were generally similar for both treatment groups (Table 2) TEAEs most commonly leading to discontinuation in the lefamulin and moxifloxacin
- ± linezolid groups, respectively, were electrocardiogram QT prolonged (0.4% [1/273] and 1.1% [3/273]) and infectious pleural effusion (0.4% [1/273] and 0.7% [2/273]; **Table 2**) • TEAEs leading to study discontinuation occurred in 1.8% (5/273) of patients taking lefamulin and 4.0% (11/273) taking moxifloxacin ± linezolid

# Table 2. TEAEs Leading to Discontinuation of Study Drug

Lefamulin n=273	Moxifloxacin ± Linezolid n=273
8 (2.9)	12 (4.4)
0	1 (0.4)
1 (0.4)	0
1 (0.4)	0
0	1 (0.4)
1 (0.4)	0
0	1 (0.4)
1 (0.4)	2 (0.7)
1 (0.4)	1 (0.4)
1 (0.4)	0
1 (0.4)	3 (1.1)
0	1 (0.4)
0	1 (0.4)
1 (0.4)	0
0	1 (0.4)
0	1 (0.4)
0	1 (0.4)
0	1 (0.4)
	8 (2.9) 0 1 (0.4) 1 (0.4) 0 1 (0.4) 0 1 (0.4) 1 (0.4) 1 (0.4) 1 (0.4) 1 (0.4) 0 0 1 (0.4) 0 0 0 0 0 0 0

Patients, *n* (%)

TEAE=treatment-emergent adverse event. \*A patient could have >1 TEAE leading to discontinuation of study drug.

#### Table 3. Serious TEAEs by System Organ Class

	Patients, <i>n</i> (%)	
Serious TEAEs by System Organ Class*	Lefamulin <i>n</i> =273	Moxifloxacin ± Linezolio n=273
Serious TEAE	19 (7.0)	13 (4.8)
Cardiac disorders <sup>a</sup>	3 (1.1)	3 (1.1)
Gastrointestinal disorders <sup>b</sup>	0	1 (0.4)
General disorders and administration site conditions <sup>c</sup>	1 (0.4)	1 (0.4)
Infections and infestations <sup>d</sup>	8 (2.9)	4 (1.5)
Investigations <sup>e</sup>	2 (0.7)	0
Metabolism and nutrition disorders	0	1 (0.4)
Neoplasms benign, malignant, and unspecified <sup>9</sup>	2 (0.7)	1 (0.4)
Nervous system disorders <sup>h</sup>	0	1 (0.4)
Respiratory, thoracic, and mediastinal disorders <sup>i</sup>	4 (1.5)	3 (1.1)
Skin and subcutaneous tissue disorders <sup>j</sup>	0	1 (0.4)
Vascular disorders <sup>k</sup>	0	1 (0.4)

\*If a patient had multiple occurrences of an AE, the patient is presented only once in the respective patient count, Preferred terms, within each system organ class, included ( $n \le 1$  for all terms, except for pneumonia [n = 4 for lefamulin and n = 1for moxifloxacin ± linezolid]): acute myocardial infarction, atrial fibrillation, cardiac arrest, cardiac failure congestive, cardiogenic shock, myocardial infarction, myocardial ischemia, ventricular arrhythmia; bhematemesis; cdeath, injection site reaction; dinfectious pleural effusion, lung abscess, pneumonia, pulmonary tuberculosis, sepsis, urinary tract infection, viral pharyngitis; ealanine aminotransferase increased, liver function test increased; hypokalemia; bronchial carcinoma, lung neoplasm, squamous cell carcinoma of lung, testicular seminoma (pure); herebrovascular accident; acute respiratory failure, bronchial disorder, chronic obstructive pulmonary disease, pleurisy, pulmonary embolism, pulmonary necrosis; angioedema; shock hemorrhagic.

## Liver and Renal Function

- Fewer patients receiving lefamulin (0.7%) reported a hepatobiliary system organ class AE compared with moxifloxacin ± linezolid (1.5%)
- Elevations in liver transaminases (alanine aminotransferase and aspartate aminotransferase) were uncommon and comparable across both treatment groups (Table 4)
- No patients met the laboratory criteria for Hy's law, an indicator of drug-induced liver injury Changes from baseline in creatinine levels were comparable across both groups during treatment, with 0.8% and 0% of patients in the lefamulin and moxifloxacin ± linezolid arms reporting both >2 × the upper limit of normal and >100% increase from baseline in

#### Table 4 Maximum Postbaseline Flevation in Liver Enzymes

Laboratory Measurement	Pa	Patients,* <i>n</i> (%)	
	Lefamulin <i>n</i> =268	Moxifloxacin ± Linezolid n=267	
Any postbaseline ALT			
>3 × ULN	19 (7.1)	17 (6.4)	
>5 × ULN	6 (2.2)	5 (1.9)	
>10 × ULN	1 (0.4)	0	
Any postbaseline AST			
>3 × ULN	11 (4.1)	7 (2.6)	
>5 × ULN	2 (0.7)	2 (0.7)	
>10 × ULN	1 (0.4)	0	
Any postbaseline total bilirubin			
>1.5 × ULN	3 (1.1)	3 (1.1)	
>2 × ULN	0	2 (0.7)	
Any postbaseline alkaline phosphatase			
>2 × ULN	5 (1.9)	5 (1.9)	

#### **Cardiac Evaluations**

- Low rates of cardiac system organ class AEs were reported for lefamulin (2.9%) and moxifloxacin ± linezolid (4.0%)
- Potentially clinically significant changes of concern in QT interval were uncommon
- No patients that received lefamulin or moxifloxacin ± linezolid reported a post-baseline increase in QT interval of >60 msec that resulted in a value of >500 msec

## Table 5 Maximum Postdose QTcF Change (Day 3)

Table 3. Maximum 1 03tabse & for onlinge (bay 3)				
QTcF	Lefamulin n=263	Moxifloxacin ± Linezoli <i>n</i> =260		
Maximum postdose increase 30–60 msec, n (%)	12 (4.6)	14 (5.4)		
Maximum postdose increase >60 msec, n (%)	0	1 (0.4)		
Maximum postdose value >500 msec,* n (%)	1 (0.4)	1 (0.4)		
Mean (SD) change from baseline, msec <sup>†</sup>	13.75 (19.8)	16.35 (21.4)		

QTcF=QT interval, Fridericia correctio Lefamulin (n=264) and moxifloxacin  $\pm$  linezolid (n=262) <sup>†</sup>Lefamulin (*n*=273) and moxifloxacin ± linezolid (*n*=273).

# CONCLUSIONS

- Lefamulin demonstrated high response rates for ECR and IACR that were noninferior to the comparator, moxifloxacin ± linezolid
- The overall rate of AEs was similar for the 2 treatment groups, as were the rates of treatment-related AEs (15.0% for lefamulin vs 14.3% for moxifloxacin ± linezolid); treatment-related SAEs
- The overall rates of TEAEs, as well as severity and relatedness, were similar in the lefamulin and moxifloxacin ± linezolid groups
- The incidence of gastrointestinal system organ class AEs was lower in the lefamulin group, driven mainly by fewer patients on lefamulin compared with moxifloxacin ± linezolid reporting diarrhea (0.7% vs 7.7%)
- More patients receiving lefamulin reported infusion site-related TEAEs (pain or phlebitis) compared with those receiving moxifloxacin ± linezolid (2.9% vs 0% and 2.2% vs 1.1%,
- Fewer patients taking lefamulin discontinued the study drug or withdrew from the study due to a TEAE, compared with those taking moxifloxacin ± linezolid
- Liver, renal, and cardiac function evaluations were comparable between the 2 treatment groups
- Lefamulin shows promise as a safe and well-tolerated targeted monotherapy for the treatment of CABP in adults

# REFERENCES

- ) Broulette J, et al. Am Health Drug Benefits. 2013;6(8):494-503.
- 2) Welte T, et al. *Thorax*. 2012;67(1):71-79.
- (3) Gibson J. The European Lung White Book: Respiratory Health and Disease in Europe. 2nd ed. Sheffield: European Respiratory Society: 2013.
- (4) File TM and Marrie TJ. *Postgrad Med.* 2010;122(2):130-141.
- (5) Mandell LA, et al. *Clin Infect Dis.* 2007;44(suppl 2):S27-S72.
- (6) Pereyre S, et al. Front Microbiol. 2016;7:974
- 7) Cunha BA. *Chest*. 2004;125(5):1913-1919 (8) Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States. 2013. Available at: https://www.cdc.gov/drugresistance/threat-report-2013/index.html. Accessed March 23, 2018.
- (9) Shehab N. et al. *Clin Infect Dis.* 2008:47(6):735-743.
- (10) US Food and Drug Administration. FDA Drug Safety Communication: FDA updates warnings for oral and injectable fluoroquinolone antibiotics due to disabling side effects. Available at: https://www.fda.gov/Drugs/DrugSafety/ ucm511530.htm. Accessed March 23, 2018.
- (11) Brown KA, et al. Antimicrob Agents Chemother. 2013;57(5):2326-2332.
- (12) Eyal Z, et al. Sci Rep. 2016;6:39004
- (13) File T, et al. Lefamulin Is Non-inferior to Moxifloxacin in Adults with Community-Acquired Bacterial Pneumonia (CABP): The Phase 3 Lefamulin Evaluation Against Pneumonia (LEAP 1) Study [abstract 6306]. Presented at: ASM Microbe 2018 Meeting (Atlanta, GA).

### **Acknowledgments & Disclosures**

The authors thank David Mariano for his input during the development of this poster. Funding for development of this poster was provided by Nabriva to C4 MedSolutions, LLC (Yardley, PA), a CHC Group company.

Lisa Goldberg, Carolyn Sweeney, Steven P. Gelone, John Saviski, Elyse Seltzer, and Leanne B. Gasink are or were employees of Nabriva when the study was performed. Anita Das and George H. Talbot served as consultants for Nabriva during design and execution of the study, and George H Talbot is a member of Nabriva's Board of Directors. Thomas File has served as a consultant for Motif BioSciences, Allergan, Shionogi, Merck, Nabriva, Paratek, and

Scan this QR code with your electronic device to receive a PDF file of the poster or visit posters.c4medsolutions.com/ASMMicrobeLEAP1Safet

