P0276

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

Thomas File[1], Lisa Goldberg[2], Anita Das[3], Carolyn Sweeney[2], Steven P. Gelone[2], John Saviski[2], Elyse Seltzer[4], George H. Talbot[5], Leanne B Gasink[2]

[1]Summa Health System, Akron, OH, USA; [2]Nabriva Therapeutics, King of Prussia, PA, USA; [3]Das Consulting, Guerneville, CA, USA; [4]Urogen Pharma, New York, NY, USA; [5]Talbot Advisors LLC, Anna Maria, FL, USA

Nabriva Therapeutics
Vienna, Austria
and King of Prussia, PA, USA
www.nabriva.com

INTRODUCTION

- The burden of community-acquired pneumonia (CAP) is significant,[1-3] with annual costs approximately €10.1 billion in Europe and over $17 billion in the United States[2,4]
- 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*[5]
- New therapies for CABP are needed because of the rise of antibacterial resistance and the undesirable risks and side effects associated with current treatments[6-11]
- 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[12]

OBJECTIVE

- 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 **(Figure 1)**
- 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

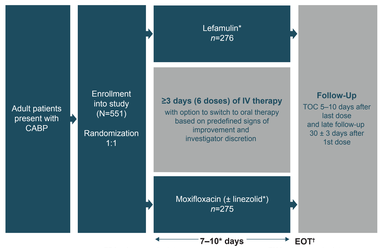
- Patients ≥18 years of age with CABP (Pneumonia Outcomes Research Team [PORT] risk class III [limited to 75%], IV, or V) were eligible
- A single dose of short-acting antibiotic (as requiring >1 dose per day) within 24 hours of randomization was allowed in up to 25% of the population
- Informed consent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



CABP=community-acquired bacterial pneumonia; CE-TOC=clinically evaluable at TOC; EMA=European Medicines Agency; EOT=end of treatment; FDA=US Food and Drug Administration; ITT=intent to treat; IV=intravenous; mITT= modified ITT; MRSA=methicillin-resistant *Staphylococcus aureus*; TOC=test of cure.
*If MRSA was suspected, linezolid or placebo was added to moxifloxacin or lefamulin therapy, respectively; if MRSA was confirmed, treatment duration was 10 days.
†EOT assessment was within 2 days after the last dose of study drug.
‡Dyspnea, cough, production of purulent sputum, chest pain.

RESULTS

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 #P0277[13]
- Mean duration of therapy was 7.2 and 7.1 days for patients in the lefamulin and moxifloxacin ± linezolid groups, respectively
- 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 #P0277 for additional details regarding lefamulin efficacy in the LEAP 1 trial[13]

Safety and Tolerability

Overview of AEs

- 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)**

RESULTS (continued)

- 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
- 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, respectively **(Table 2)**
- 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 ± linezolid)

Table 1. Overview of Patients Experiencing ≥1 TEAE

TEAEs*,†	Patients, *n* (%)	
	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)

AE=adverse event; TEAE=treatment-emergent AE.
*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.

- 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

RESULTS (continued)

Table 2. TEAEs Leading to Discontinuation of Study Drug

Preferred Term	Patients, *n* (%)	
	Lefamulin *n*=273	Moxifloxacin ± Linezolid *n*=273
TEAEs leading to discontinuation of study drug*	**8 (2.9)**	**12 (4.4)**
Atrial fibrillation	0	1 (0.4)
Bradycardia	1 (0.4)	0
Cardiac failure congestive	1 (0.4)	0
Infusion site erythema	0	1 (0.4)
Infusion site phlebitis	1 (0.4)	0
Cystitis	0	1 (0.4)
Infectious pleural effusion	1 (0.4)	2 (0.7)
Pneumonia	1 (0.4)	1 (0.4)
Pulmonary tuberculosis	1 (0.4)	0
Electrocardiogram QT prolonged	1 (0.4)	3 (1.1)
Confusional state	0	1 (0.4)
Acute respiratory failure	0	1 (0.4)
Chronic obstructive pulmonary disease	1 (0.4)	0
Pulmonary embolism	0	1 (0.4)
Angioedema	0	1 (0.4)
Hypertension	0	1 (0.4)
Shock hemorrhagic	0	1 (0.4)

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

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

TEAE=treatment-emergent adverse event.
*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*≥1 for all terms, except for pneumonia [*n*=4 for lefamulin and *n*=1 for moxifloxacin ± linezolid]): [a]acute myocardial infarction, atrial fibrillation, cardiac arrest, cardiac failure congestive, cardiogenic shock, myocardial infarction, myocardial ischemia, ventricular arrhythmia; [b]hematemesis; [c]death, injection site reaction; [d]infectious pleural effusion, lung abscess, pneumonia, pulmonary tuberculosis, sepsis, urinary tract infection, viral pharyngitis; [e]alanine aminotransferase increased, liver function test increased; [f]hypokalemia; [g]bronchial carcinoma, lung neoplasm, squamous cell carcinoma of lung, testicular seminoma (pure); [h]cerebrovascular accident; acute respiratory failure, bronchial disorder, chronic obstructive pulmonary disease, pleurisy, pulmonary embolism, pulmonary necrosis; [i]angioedema; [j]shock hemorrhagic.

RESULTS (continued)

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 creatinine values

Table 4. Maximum Postbaseline Elevation in Liver Enzymes

Laboratory Measurement	Patients,* *n* (%)	
	Lefamulin *n*=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)

ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal.
*Safety population.

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 **(Table 5)**
- 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)

QTcF	Lefamulin *n*=263	Moxifloxacin ± Linezolid *n*=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†	13.75 (19.8)	16.35 (21.4)

QTcF=QT interval, Fridericia correction.
*Lefamulin (n=264) and moxifloxacin ± linezolid (n=262).
†Lefamulin (n=273) and moxifloxacin ± linezolid (n=273).

CONCLUSIONS

- Lefamulin demonstrated high response rates for ECR and IACR that were noninferior to the competitor, 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 were uncommon
- 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%, respectively)
- 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

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