T-18

Pharmacokinetic-Pharmacodynamic (PK-PD) Analyses for Efficacy Based on Data From Lefamulin-Treated Patients Enrolled in Phase 3 Studies for Community-Acquired Bacterial Pneumonia (CABP)

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INTRODUCTION & PURPOSE

- Lefamulin (LEF, BC-3781) is an intravenous (IV) and oral (PO) pleuromutilin antimicrobial agent that demonstrates *in vitro* activity against the most common pathogens causing community-acquired bacterial pneumonia (CABP), including *Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus* (including methicillin-resistant *S. aureus*), and atypical pathogens.[1,2]
- LEF is approved for the treatment of adults with CABP.[3] Evaluation of pharmacokinetic-pharmacodynamic (PK-PD) relationships for efficacy using data from patients in clinical trials provides the benefit of confirming dose selection decisions made in early-stage development.
- Using a previously developed population pharmacokinetic (PK) model for LEF[4] and data from patients with CABP receiving LEF enrolled in 2 phase 3 studies,[5,6] the objective of these analyses was to evaluate PK-PD relationships for efficacy.

METHODS

- Patients enrolled in the 2 phase 3 studies received LEF 150 mg IV every 12 hours (q12h), with an optional switch (after ≥6 doses of IV) to 600 mg PO q12h, or 600 mg PO q12h.
- Efficacy endpoints assessed included early clinical response (96±24 hours after the first dose of study drug); investigator-assessed clinical response at end of therapy (EOT), test of cure (TOC), and late follow-up (LFU); and microbiological response at EOT, TOC, and LFU.
- Using a population PK model for LEF developed using phase 1, 2, and 3 data[3] and plasma PK data from patients in the phase 3 studies, Day 1 free-drug plasma and total-drug epithelial lining fluid (ELF) area under the concentration-time curve (AUC) were determined.
- Relationships between efficacy endpoints and each of LEF Day 1 free-drug plasma and total-drug ELF AUC to minimum inhibitory concentration (MIC) (AUC:MIC ratio) were assessed among evaluable patients and patient subsets with baseline pathogens of interest using chi-square tests or Fisher's exact tests for categorical independent variables and logistic regression for continuous independent variables.
  - Given that data from previous nonclinical studies demonstrated that AUC:MIC ratio was most predictive of LEF efficacy,[7] this PK-PD index was evaluated for these analyses.

RESULTS

- As shown in **Table 1**, successful response across efficacy endpoints ranged from 87.5% to 93.5% among 92 evaluable patients and from 85.4% to 88.9% for the subset of 54 patients with *S. pneumoniae* at baseline.

RESULTS (continued)

Table 1. Summary of Successful Responses for Efficacy Endpoints by Visit for All Patients and Patients With *S. pneumoniae* at Baseline

Analysis population*	Visit	Successful responses by efficacy endpoint and visit, % (*n*/*N*)		
		Early clinical response	Investigator-assessed clinical response	Microbiological response
All patients	96±24 hours	93.5 (86/92)	—	—
	EOT	—	90.2 (83/92)	90.2 (83/92)
	TOC	—	89.8 (79/88)	89.8 (79/88)
	LFU	—	87.5 (70/80)	87.5 (70/80)
Patients with *S. pneumoniae* at baseline	96±24 hours	88.9 (48/54)	—	—
	EOT	—	87.0 (47/54)	87.0 (47/54)
	TOC	—	86.0 (43/50)	86.0 (43/50)
	LFU	—	85.4 (41/48)	85.4 (41/48)

ECR=early clinical response (96±24 hours); EOT=end of treatment (within 2 days after the last dose of study drug); LFU=late follow-up (Day 30±3 days); ME=microbiologically evaluable; MIC=minimum inhibitory concentration; PK=pharmacokinetic; TOC=test of cure (5 to 10 days after last dose of study drug).
*Based on data from patients in the ME population with a baseline pathogen and MIC value, PK data, and who were evaluable for ECR and clinical response at the EOT, TOC, or LFU visits.

- Summary statistics for free-drug plasma AUC, total-drug ELF AUC, baseline MIC, free-drug plasma AUC:MIC ratio, and total-drug ELF AUC:MIC ratio for all patients and patients with *S. pneumoniae* at baseline are provided in **Table 2**.

Table 2. Summary Statistics for Free-Drug Plasma and Total-Drug ELF AUC, Baseline MIC, and Free-Drug Plasma and Total-Drug ELF AUC:MIC Ratio for All Patients and Patients With *S. pneumoniae* at Baseline

Analysis population	Variable	Free-drug plasma AUC* (mg•h/L)	Total-drug ELF AUC* (mg•h/L)	MIC (μg/mL)	Free-drug plasma AUC:MIC ratio*	Total-drug ELF AUC:MIC ratio*
All patients (*N*=92)†	Mean (%CV)	4.22 (63.6)	20.54 (61.9)	—	18.76 (96.2)	91.38 (94.9)
	Median or $MIC_{50/90}$ (min, max)	3.68 (1.39, 24.65)	18.54 (6.62, 116.3)	0.25/1 (0.03, 8)	13.35 (0.57, 98.59)	66.37 (2.51, 465.0)
Patients with *S. pneumoniae* at baseline (*n*=54)	Mean (%CV)	4.24 (75.6)	20.78 (72.8)	—	20.53 (84.1)	100.7 (82.9)
	Median or $MIC_{50/90}$ (min, max)	3.68 (1.39, 24.65)	18.65 (6.62, 116.3)	0.25/0.5 (0.06, 0.5)	15.38 (4.72, 98.59)	76.53 (24.14, 465.0)

AUC=area under the concentration-time course; ELF=epithelial lining fluid; MIC=minimum inhibitory concentration; $MIC_{50/90}$=MIC at which 50% and 90% of isolates were inhibited; %CV=percent coefficient of variation.
*Based on the free-drug plasma or total-drug ELF AUC over 0 to 24 hours.
†Median (min, max) values for free-drug plasma AUC, free-drug plasma AUC:MIC ratio, total-drug ELF AUC, and total-drug ELF AUC:MIC ratio for the 15 patients with *S. aureus* at baseline in each group were as follows: 3.67 (1.73, 5.25), 27.28 (13.44, 43.72), 17.55 (8.59, 26.02), and 127.99 (66.83, 210.94), respectively.

- As shown in **Table 3**, assessed relative to nonclinical AUC:MIC ratio targets for efficacy based on PK-PD data from neutropenic murine-lung infection models,[8] 100% of patients with *S. pneumoniae* or *S. aureus* achieved such targets.

Table 3. Summary of the Percentage of Patients With *S. pneumoniae* or *S. aureus* at Baseline Achieving Nonclinical Free-Drug Plasma or Total-Drug ELF AUC:MIC Ratio Targets

Endpoint for free-drug plasma or total-drug ELF AUC:MIC ratio targets	Patients with all baseline cultures, % (*n*/*N*)	
	Patients with *S. pneumoniae* at baseline	Patients with *S. aureus* at baseline
1-log_{10} CFU reduction from baseline*	100 (54/54)	100 (15/15)
2-log_{10} CFU reduction from baseline†	100 (54/54)	100 (15/15)

AUC=area under the concentration-time course; CFU=colony-forming unit; ELF=epithelial lining fluid; MIC=minimum inhibitory concentration.
*Based on the assessment of median free-drug plasma and total-drug ELF AUC:MIC ratio targets associated with a 1-log_{10} CFU reduction from baseline of 1.37 and 14.0, respectively, for *S. pneumoniae* and 2.13 and 21.7, respectively, for *S. aureus*.[8]
†Based on the assessment of median free-drug plasma and total-drug ELF AUC:MIC ratio targets associated with a 2-log_{10} CFU reduction from baseline of 2.15 and 22.0, respectively, for *S. pneumoniae* and 6.24 and 63.9, respectively for *S. aureus*.[8]

- Results of PK-PD analyses for efficacy failed to demonstrate statistically significant and biologically plausible univariable relationships between efficacy endpoints and AUC:MIC ratio.
  - The limited sample size of the analysis dataset and number of failures observed potentially hindered the identification of PK-PD relationships for efficacy.

CONCLUSIONS

- While statistically significant and biologically plausible PK-PD relationships based on data from patients receiving LEF were not identified, all patients with *S. pneumoniae* and *S. aureus* at baseline achieved free-drug plasma AUC:MIC ratios that were above nonclinical PK-PD targets.
  - These findings suggest that free-drug plasma and total-drug ELF AUC:MIC ratios achieved among patients receiving LEF were on the plateau of nonclinical PK-PD relationships for efficacy.
- The results of these analyses provide support for the LEF 150 mg IV q12h and 600 mg PO q12h dosing regimens evaluated in adult patients with CABP.

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Acknowledgments & Disclosures

This analysis was supported by Nabriva Therapeutics. Editorial and creative assistance for poster formatting services was provided by C4 MedSolutions, LLC (Yardley, PA, USA), a CHC Group company and funded by Nabriva Therapeutics. Sujata M. Bhavnani, Jeffrey P. Hammel, Nikolas J. Onufrak, Kathryn Liolios, Christopher M. Rubino, and Paul G. Ambrose are employees of the Institute for Clinical Pharmacodynamics, which was contracted by Nabriva Therapeutics to perform the analyses described herein. Wolfgang W. Wicha, Susanne Paukner, Elizabeth Alexander, Jennifer Schranz, and Steven P. Gelone are employees of/ stockholders in Nabriva Therapeutics plc.

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