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Health-Related Quality of Life as Measured by the 12-Item Medical Outcomes Study Short-Form Among Adults With Community-Acquired Bacterial Pneumonia Who Received Either Lefamulin or Moxifloxacin in Two Phase 3 Randomized, Double-Blind, Double-Dummy Clinical Trials (LEAP 1 and 2)

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INTRODUCTION & PURPOSE

- Patient-reported outcomes (PROs) have been recognized by the US Food and Drug Administration-National Institute of Health Biomarker Working Group for Endpoints and other Tools as an important part of the benefit-risk assessment for new drug approvals across all therapeutic domains[1]
- Patient-centeredness is also a growing area of focus in the healthcare sector and is a major component of the personal and community engagement quality domain in the Centers for Medicare & Medicaid Services Hospital Value-Based Purchasing Program[2,3]
- Lefamulin (LEF) is the first pleuromutilin developed for systemic use and was recently approved for the treatment of adults with community-acquired bacterial pneumonia (CABP).[4] LEF was shown to be noninferior to moxifloxacin (MOX) based on the standard early and posttreatment clinical response endpoints in 2 phase 3 clinical trials (Lefamulin Evaluation Against Pneumonia [LEAP] 1 and LEAP 2)[5,6]
- Given the increasingly important role of PROs in the development and evaluation of new medicines, health-related quality of life (HRQoL) measures, a type of PRO, were prospectively incorporated and evaluated in both LEAP 1 and LEAP 2 via the acute form (4-week recall) of the 12-Item Medical Outcomes Study Short-Form Health Survey (SF-12) v2
  - The SF-12 is a general survey that measures HRQoL in 8 domains (physical function, role limitations due to physical problems, bodily pain, general health, vitality, social function, role limitations due to emotional problems, and mental health; **Table 1**)[7]
  - The SF-12 has been used extensively and has been broadly demonstrated to be reliable and well validated across most health and clinical contexts
- The intent of this analysis was to describe and compare HRQoL outcomes as measured by the SF-12 administered to patients with CABP who received either LEF or MOX using the pooled data from LEAP 1 and LEAP 2

Table 1. SF-12 Items and Scales

Question No.	Description of Question	Response Options	Domain
1	General health	1–5	General health
2a	Health affect moderate activities	1–3	Physical functioning
2b	Health affect step climbing	1–3	Physical functioning
3a	Physical health affected ability to accomplish	1–5	Role physical
3b	Physical health affected kind of work or other activities	1–5	Role physical
4a	Emotional health affected ability to accomplish	1–5	Role emotional
4b	Emotional health affected kind of work or other activities	1–5	Role emotional
5	Pain interfere with normal work	1–5	Bodily pain
6a	Felt calm and peaceful	1–5	Mental health
6b	Have a lot of energy	1–5	Vitality
6c	Felt downhearted or depressed	1–5	Mental health
7	Amount of time physical or emotional problems interfere with social activities	1–5	Social functioning

SF-12=12-Item Medical Outcomes Study Short-Form Health Survey.

METHODS

Study Design and Population

- A post hoc analysis using the pooled data from 2 completed and similar phase 3 clinical trials NAB-BC-3781-3101 (LEAP 1)[5] and NAB-BC-3781-3102 (LEAP 2)[6]
- Patients randomized from LEAP 1 and LEAP 2 who received any amount of the study drug were included in this analysis, with the following additional requirements:
  - Meet CABP disease and other study criteria in LEAP trials
  - Pneumonia Outcomes Research Team (PORT) risk class of II, III, or IV at baseline
  - Received ≥24 hours of therapy (unless death occurred sooner)

Health-Related Quality of Life

- The acute form of the SF-12, used to measure HRQoL, was administered to patients in both LEAP 1 and LEAP 2 at baseline (within 24 hours before the first dose of study drug) and at the test-of-cure (TOC) visit (5–10 days after the last dose of study drug)
- The 12 items of the SF-12 and the 8 domains to which they correspond are detailed in **Table 1**
- The 8 individual domain scores and 2 component summary (Physical Component Summary [PCS] and Mental Component Summary [MCS]) scores were evaluated using Optum's QualityMetric (QualityMetric Incorporated, Lincoln, RI, USA) proprietary software v5.1[8,9]
  - All scores were normalized against the 2009 US population reference scores. A score of 50 for any of the SF-12 domains or component summaries is equivalent to the reference population mean, and the standard deviation is set at 10
  - The minimal clinically important difference for the MCS, PCS, and 8 domains are as follows: MCS, 3; PCS, 2; General Health, 2; Physical Functioning, 3; Role Physical, 3; Bodily Pain, 3; Vitality, 2; Social Functioning, 3; Role Emotional, 4; Mental Health, 3

Statistical Analysis Plan

- Treatment group comparisons for all SF-12 domain and summary scores were performed at baseline and TOC
- Changes in SF-12 domain and summary scores from baseline to TOC (score at TOC – score at baseline) were compared between treatment groups
  - The overall difference in the change in each SF-12 score between treatment groups was assessed using a linear model, adjusted for the corresponding baseline SF-12 score

RESULTS

- Patient demographics and baseline disease characteristics are summarized in **Table 2**
- At baseline, all mean SF-12 scores (domain, PCS, and MCS) were well below the average US norm level of 50, indicating lower HRQoL in the LEF and MOX treatment groups compared with the general population (**Figure A**)
- At TOC, the mean SF-12 scores in both the LEF and MOX treatment groups were generally close to the average US population norm score of 50, indicating similar HRQoL to the general population (**Figure B**)
- Clinically meaningful and statistically significant improvements in all mean SF-12 scores were observed from baseline to TOC in both treatment groups (**Figure C**)
  - The greatest magnitude of improvements was observed in the domain of general health, which showed improvements of 15.6 points for LEF and 15.8 points for MOX
  - The least substantial improvement in HRQoL was seen in the domain of mental health, which showed improvements of 11.2 points for LEF and 11.5 points for MOX
- No clinical or statistically significant differences were observed in least squares mean score improvements in HRQoL from baseline to TOC between LEF and MOX

Table 2. Demographics and Baseline Disease Characteristics

Parameter	LEF (*n*=607)	MOX (*n*=608)	Overall (*N*=1215)
Age, y, mean (SD)	58.8 (16.3)	58.4 (15.5)	58.6 (15.9)
Male, *n* (%)	354 (58.3)	325 (53.5)	679 (55.9)
Race, *n* (%)			
White	490 (80.7)	486 (79.9)	976 (80.3)
Asian	65 (10.7)	63 (10.4)	128 (10.5)
Black or African American	25 (4.1)	32 (5.3)	57 (4.7)
American Indian or Alaska Native	21 (3.5)	17 (2.8)	38 (3.1)
Native Hawaiian or other Pacific Islander	0	0	0
Other	6 (1.0)	10 (1.6)	16 (1.3)
Weight, kg, mean (SD)	75.5 (19.2)	74.0 (18.3)	74.7 (18.8)
BMI, kg/m^2, mean (SD)	26.5 (5.8)	26.4 (5.9)	26.5 (5.9)
Renal status,* *n* (%)			
Severe impairment	6 (1.0)	4 (0.7)	10 (0.8)
Moderate impairment	111 (18.3)	125 (20.6)	236 (19.4)
Mild impairment	190 (31.3)	181 (29.8)	371 (30.5)
Normal function	299 (49.3)	298 (49.0)	597 (49.1)
Missing	1 (0.2)	0	1 (0.1)
PORT risk class,† *n* (%)			
II	174 (28.7)	181 (29.8)	355 (29.2)
III	327 (53.9)	322 (53.0)	649 (53.4)
IV	106 (17.5)	105 (17.3)	211 (17.4)
CURB-65 score,‡ *n* (%)			
0	106 (17.5)	106 (17.4)	212 (17.4)
1	308 (50.7)	303 (49.8)	611 (50.3)
2	162 (26.7)	163 (26.8)	325 (26.7)
3	31 (5.1)	32 (5.3)	63 (5.2)
4	0	4 (0.7)	4 (0.3)
5	0	0	0
Met minor ATS severity criteria,§ *n* (%)	80 (13.2)	78 (12.8)	158 (13.0)
Met modified ATS severity criteria,‖ *n* (%)	47 (7.7)	53 (8.7)	100 (8.2)
Met SIRS criteria,¶ *n* (%)	587 (96.7)	579 (95.2)	1166 (96.0)
Bacteremia, *n* (%)	12 (2.0)	12 (2.0)	24 (2.0)
Prior antibiotic use,# *n* (%)	137 (22.6)	134 (22.0)	271 (22.3)
Comorbidities, median (IQR)	2 (1–4)	2 (1–4)	2 (1–4)

ATS=American Thoracic Society; BMI=body mass index; BUN=blood urea nitrogen; CrCl=creatinine clearance; eCRF=electronic case report form; IQR=interquartile range; LEF=lefamulin; MOX=moxifloxacin; PORT=Pneumonia Outcomes Research Team; SIRS=systemic inflammatory response syndrome; WBC=white blood cell.

*National Kidney Foundation categories of renal impairment determined by Cockcroft-Gault[10] using baseline central laboratory serum creatinine. When baseline central laboratory serum creatinine was not available, local serum creatinine results were used. Renal impairment categories: normal [CrCl ≥90 mL/min], mild [CrCl 60 to <90 mL/min], moderate [CrCl 30 to <60 mL/min], and severe [CrCL<30 mL/min].

†PORT risk class was calculated programmatically using data obtained at the site and reported in the eCRF and was not always consistent with the site-reported PORT risk class used for enrollment/stratification.

‡Defined as confusion of new onset, BUN >19 mg/dL, respiratory rate ≥30 breaths/min, systolic blood pressure <90 mm Hg or diastolic blood pressure ≤60 mm Hg, and age ≥65 years.

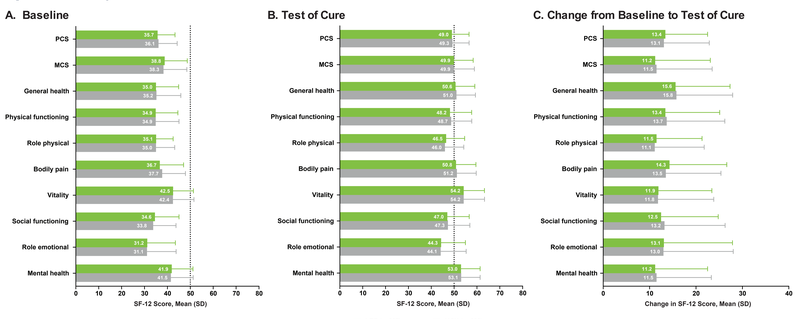
§Defined as presence of ≥3 of the following 9 criteria at baseline: respiratory rate ≥30 breaths/min, O_2 saturation <90% or PaO_2 <60 mm Hg, BUN ≥20 mg/dL, WBC <4000 cells/mm^3, confusion, multilobar infiltrates, platelets <100,000 cells/mm^3, temperature <36°C, or systolic blood pressure <90 mm Hg.[11]

‖Defined as presence of ≥3 of the following 6 criteria at baseline: respiratory rate ≥30 breaths/min, SpO_2/FiO_2 <274 where $SpO_2/FiO_2 = 64+0.84\ (PaO_2/FiO_2)$, BUN ≥20 mg/dL, confusion, age ≥65 years, or multilobar infiltrates.

¶Defined as having ≥2 of the following 4 criteria at baseline: temperature <36°C or >38°C; heart rate >90 bpm; respiratory rate >20 breaths/min; and WBC <4000 cells/mm^3, WBC >12,000 cells/mm^3, or immature polymorphonuclear neutrophils >10%.[12]

#Patients received a single dose of short-acting systemic antibacterial medication within 72 hours before randomization; randomization was stratified and capped such that no more than 25% of the total intent-to-treat population (all randomized patients) met these criteria as reported.

Figure. Summary of SF-12 Scores



HRQoL=health-related quality of life; LEF=lefamulin; MCS=mental component summary; MOX=moxifloxacin; PCS=physical component summary; SF-12=12-Item Medical Outcomes Study Short-Form Health Survey.
Higher scores indicate better HRQoL. Dotted lines indicate the 2009 US population reference mean of 50.

CONCLUSIONS

- Patients' HRQoL improved from well below the general population average at baseline to similar to the general population at TOC
- Patients who received LEF had comparable improvements in HRQoL relative to those who received MOX
- Combined with phase 3 efficacy and safety data, these findings have implications for clinical practice, as analyses suggest that LEF provides an effective new intravenous (IV) and oral monotherapy option for empiric treatment of adults with CABP
- For patients with CABP, there is a clear clinical need for new antibiotics with comparable IV and oral formulations that result in similar HRQoL improvements as fluoroquinolones but without the associated safety concerns

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Acknowledgments

Funding for editorial and creative assistance for poster formatting services was provided by Nabriva Therapeutics to C4 MedSolutions, LLC (Yardley, PA), a CHC Group company.

Disclosures

Elizabeth Alexander, Daniel S. Stein, David Fitts, Lisa Goldberg, and Jennifer Schranz are employees of/stockholders in Nabriva Therapeutics plc. Thomas Lodise has served as a consultant for Nabriva Therapeutics. Sam Colman is an employee of Covance Market Access, which was contracted by Nabriva Therapeutics to create the statistical analysis plan and to conduct and oversee the analyses presented here.

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