BRIEF REPORT

Post Hoc Assessment of Time to Clinical Response Among Adults Hospitalized with Community-Acquired Bacterial Pneumonia Who Received Either Lefamulin or Moxifloxacin in 2 Phase III Randomized, Double-Blind, Double-Dummy Clinical Trials

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Time to clinical response, a proxy for hospital "discharge readiness," was compared between CABP inpatients who received lefamulin or moxifloxacin in the Lefamulin Evaluation Against Pneumonia (LEAP) trials. The analysis included 926 inpatients. A short and comparable median time to clinical response (4 days) was observed in both treatment groups.

Keywords: community-acquired bacterial pneumonia; fluoroquinolones; lefamulin; patient discharge; time to clinical response.

Lefamulin is a new pleuromutilin antibiotic approved for the treatment of adult patients with community-acquired bacterial pneumonia (CABP) [1–3]. Lefamulin was shown to be noninferior to moxifloxacin based on an assessment of the 4 cardinal symptoms of CABP (ie, cough, shortness of breath, chest pain, and sputum production) at 96 ± 24 hours after initiation of therapy (early clinical response) [4] in 2 phase III clinical trials (Lefamulin Evaluation Against Pneumonia [LEAP] 1 and 2) [1, 5]. Although this end point provides critical information on the presence or absence of symptom improvement [6], its practical importance to patient care and health care delivery has not been fully established. In the current US health care

system, there is an increased emphasis on how new therapies and technologies affect the quality and efficiency of health care delivery [7]. One of the most important efficiency metrics for patients with CABP is hospital length of stay (LOS), as it is the primary driver of health care costs [8–11]. Unfortunately, the design of the LEAP trials [1, 5] (ie, fixed therapy durations and no predefined criteria for hospital discharge) precluded clinically meaningful hospital LOS comparisons between treatment groups. However, it is possible to make inferences regarding hospital LOS among hospitalized patients in phase III CABP trials by comparing time with clinical response [12]. Data show that hospital LOS varies as a direct function of time to clinical response, and time to clinical response is a widely accepted tool to guide the switch from intravenous (IV) to oral antibiotic therapy and to assess hospital discharge readiness [13–17]. This analysis sought to quantify time to clinical response [12, 14–19] among CABP inpatients who received lefamulin or moxifloxacin in the LEAP trials.

METHODS

Study Design and Population

A post hoc analysis was performed using the pooled data from 2 completed and similar phase III clinical trials, NAB-BC-3781-3101 (LEAP 1) and NAB-BC-3781-3102 (LEAP 2) [1, 5]. Patients were included in this analysis from the LEAP trials if they (1) were randomized; (2) met CABP disease and other study criteria in the LEAP 1 and LEAP 2 trials; (3) had a Pneumonia Outcomes Research Team (PORT) risk class [20] of II, III, or IV at baseline; (4) started treatment as inpatients; and (5) received at least 24 hours of randomized study drug therapy (unless due to death).

Outcomes

The 3 outcomes evaluated were time to clinical response, time to clinical stability, and time to clinical improvement.

Clinical response was achieved when the following criteria were met: (1) clinical stability (see below); (2) improvement in at least 2 of the 3 or 4 cardinal symptoms of CABP the patient presented with at baseline (improvement is defined as a decrease by at least 1 level of severity); (3) no worsening of any of the 4 cardinal symptoms of CABP (worsening is defined as an increase by at least 1 level of severity for any symptom); and (4) no receipt of a concomitant antibiotic (other than adjunctive linezolid in the moxifloxacin group, as allowed by the study protocol) for treatment of the current episode of CABP.

Clinical stability was achieved when the following criteria were met: (1) temperature ≤38.0°C and ≥35.0°C measured orally, ≤38.5°C and ≥35.5°C measured tympanically, ≤39.0°C and ≥36.0°C measured rectally, or ≤37.5°C and ≥34.4°C by

axillary measurement; (2) heart rate ≤100 beats/min; (3) systolic blood pressure ≥90 mm Hg; (4) respiratory rate ≤24 breaths/min; and (5) oxygen saturation ≥90% or pO2 ≥60 mm Hg on room air.

Clinical improvement was achieved when the following criteria were met: (1) improvement in at least 2 of the 3 or 4 cardinal symptoms of CABP the patient presented with at baseline; (2) no worsening of any of the 4 cardinal symptoms of CABP; and (3) no receipt of a concomitant antibiotic (other than adjunctive linezolid in the moxifloxacin group, as allowed by the study protocol) for treatment of the current episode of CABP.

A patient was considered to have achieved the outcome of interest on a given day if all components of the outcome of interest were achieved on that day. Patients who died or did not show clinical improvement between day 2 and end of treatment (EOT) were right-censored at the last evaluable outcome assessment. Patients who received a concomitant antibiotic, except for linezolid in the moxifloxacin group in LEAP 1, for treatment of the current episode of CABP were right-censored at the earlier of either the date of concomitant antibiotic for treatment or the last evaluable outcome assessment.

Statistical Analysis Plan

Kaplan-Meier time-to-event analyses were conducted for time to clinical response, time to clinical stability, and time to clinical improvement. Cox proportional hazards models were conducted to estimate the hazards of time to clinical response, controlling for baseline characteristics with a variation of ≥10% between treatment groups.

RESULTS

There were 926 patients (lefamulin: n = 468; moxifloxacin: n = 458) from the LEAP trials who met the selection criteria and were included in the study population, which represents 72% of the original randomized population (total: n = 1289; lefamulin: n = 646; moxifloxacin: n = 643). Most patients who were excluded from the study population did not start treatment as inpatients (289/363, 80%), and they were predominantly from the oral-only LEAP 2 trial. Baseline characteristics of the study population are summarized in Supplementary Table 1. There were no notable differences between the study population and the original randomized population.

Of the 926 patients included, we were able to assess time to clinical response in 918, clinical stability in 925, and clinical improvement in 923. Kaplan-Meier analyses showed that time to clinical response was nearly identical between treatment groups (Figure 1A). The median (interquartile range [IQR]) time from treatment initiation to clinical response was 4 (3–4) days for lefamulin and 4 (3–5) days for moxifloxacin (P = .730, log rank test). In the Cox regression, there was no difference in time to clinical response between treatments after adjustment for

baseline covariates (adjusted hazard ratio, 1.04; 95% confidence interval, 0.91–1.20; P = .532). Supplementary Table 2 presents the results of the subgroup analyses on median time to clinical response.

The median (IQR) time from treatment initiation to clinical stability was 3 (2–4) days in both the lefamulin and moxifloxacin groups (P = .659, log rank test) (Figure 1B). The median (IQR) time from treatment initiation to clinical improvement was 3 (2–4) days in both the lefamulin and moxifloxacin groups (P = .985, log rank test) (Figure 1C).

DISCUSSION

As a number of studies have demonstrated that there is a clear link between time to clinical response and subsequent hospital discharge and efficacy outcomes among hospitalized patients with suspected or documented CABP, the collective findings indicate that lefamulin was associated with a comparable time to clinical response, a proxy for time to "discharge readiness," relative to moxifloxacin in the phase III LEAP trials. While several options exist for transition from IV to oral therapy, including from 1 beta-lactam to another or from cephalosporin plus macrolide combination therapy to macrolide monotherapy, fluoroquinolones remain widely used in CABP [21] due to their interchangeable IV and oral formulations and robust efficacy [22]. Despite these advantages, there is increased recognition of their safety risks, as reflected in the recent updates to their product labeling [23–26]. There is a clear clinical need for new antibiotics for patients with CABP that result in similar real-world outcomes as fluoroquinolones without the safety concerns, and the current analyses suggest that lefamulin may be a potential fluoroquinolone replacement agent. As such, lefamulin monotherapy represents another option in the transition of care.

Several issues should be taken into consideration when interpreting these findings. We applied a post hoc adjudication algorithm to the data collected in the LEAP trials. To minimize the potential biases associated with this approach, we constructed a set of objective criteria for time to clinical response, a proxy for "discharge readiness," before conducting the study and made the "discharge readiness" definition include and depend on the early clinical response assessment variable specified in the current FDA CABP guidance document. Multivariate analyses were also performed to control for any residual baseline differences. This study was constrained by the original clinical trial study design, which only required collection of daily clinical information during the duration of therapy among inpatients. As patients who started treatment in the outpatient setting are not evaluable for discharge readiness, these patients were excluded from the analyses.

In conclusion, the findings from this post hoc examination of the clinical data collected from the LEAP trials
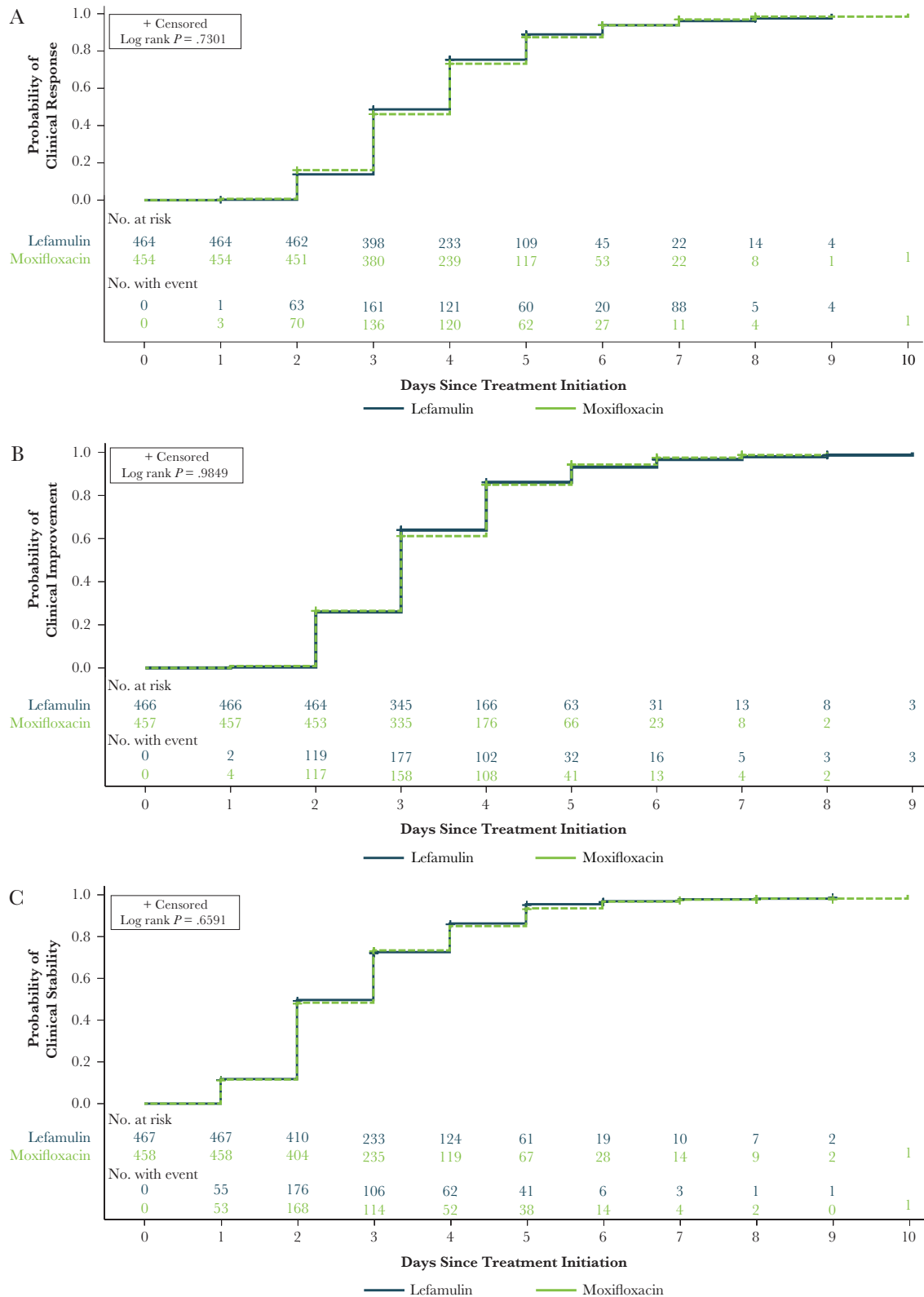
Figure 1. Kaplan-Meier time-to-event analyses. A, Time to clinical response. B, Time to clinical stability. C, Time to clinical improvement.

show that patients who received lefamulin had a comparable and relatively rapid time to meeting the criteria for clinical response, a proxy for "discharge readiness," relative to those who received moxifloxacin. Given the clear link between time to clinical response and hospital discharge [14–17], these findings have implications for

clinical practice, as analyses suggest that lefamulin provides an effective new IV and oral monotherapy option for empiric treatment of adults with CABP that enables short-course therapy and early discharge.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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