T-19

Pharmacokinetic-Pharmacodynamic Target Attainment Analyses to Support Lefamulin Dose Justification and Susceptibility Breakpoint Determinations for Patients With Community-Acquired Bacterial Pneumonia

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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]
- The current paradigm for selecting antimicrobial dosing regimens in clinical development involves the use of data from nonclinical pharmacokinetic-pharmacodynamic (PK-PD), population pharmacokinetic (PK), and *in vitro* surveillance studies, together with Monte Carlo simulation to assess PK-PD target attainment.[3]
  - PK-PD target attainment analyses[4] were carried out to provide support for LEF IV-to-PO and PO dosing regimens evaluated in 2 recently completed phase 3 studies in patients with CABP.[5,6]
- Evaluation of PK data from patients in clinical trials provides the benefit of confirming dose selection decisions made in early-stage development.
- As described herein, a population PK model refined based on PK data collected in phase 3,[7] nonclinical PK-PD targets for efficacy,[8] and *in vitro* surveillance data[1] were used with Monte Carlo simulation to carry out PK-PD target attainment analyses to provide dose justification for LEF IV and PO dosing regimens evaluated in phase 3 studies in patients with CABP and decision support for LEF susceptibility breakpoints against *S. pneumoniae* and *S. aureus*.

METHODS

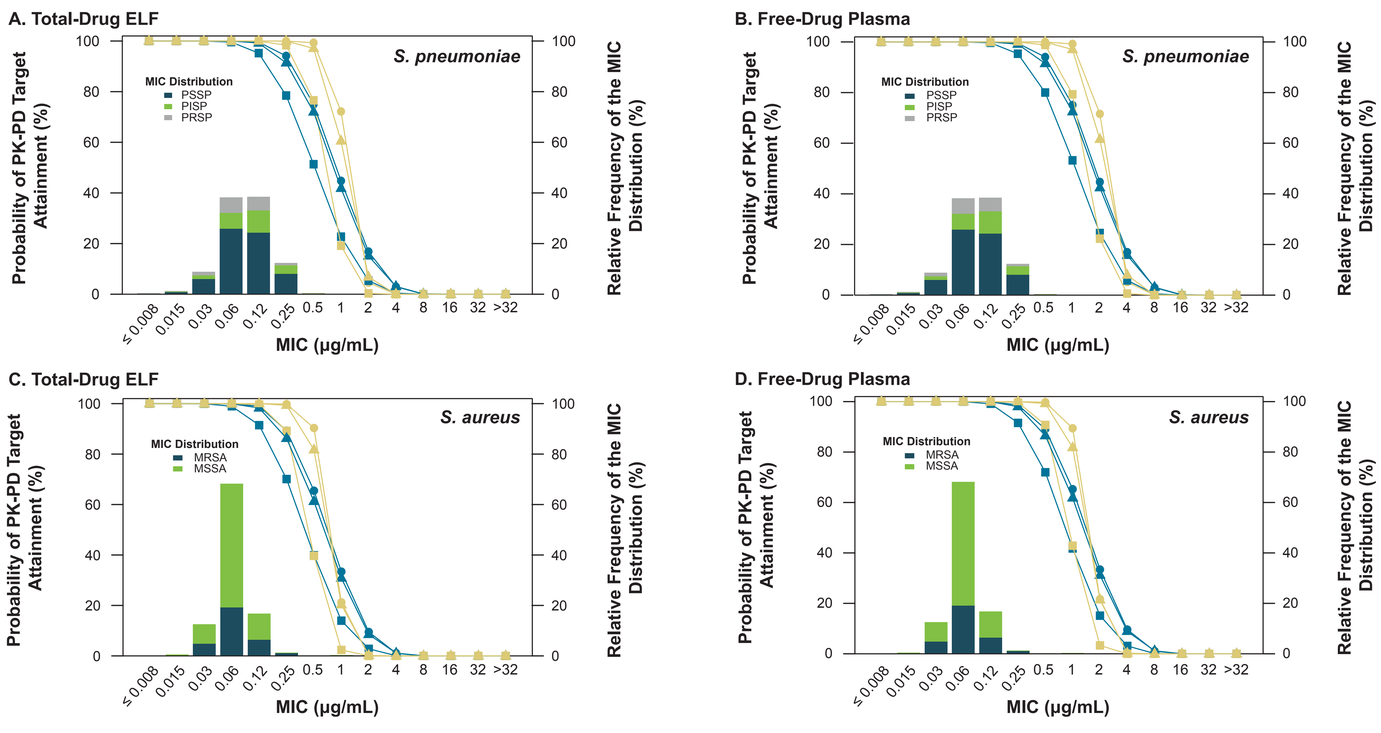
- Using a previously developed population PK model for LEF[7], LEF free-drug plasma and total-drug epithelial lining fluid (ELF) concentration-time profiles were generated for 5000 simulated patients with CABP after administration of LEF 150 mg IV every 12 hours (q12h), 600 mg PO q12h for 5 days under fasted conditions (fasted), and 600 mg PO q12h for 5 days under fed conditions (fed).
- Free-drug plasma and total-drug ELF 24-hour area under the concentration-time curve (AUC) values on Day 1 were determined using numerical integration.
- Percent probabilities of PK-PD target attainment by minimum inhibitory concentration (MIC) and overall (ie, weighted over *S. pneumoniae* and *S. aureus* MIC distributions for isolates collected worldwide)[1] were determined using Day 1 AUC values and total-drug ELF and free-drug plasma AUC:MIC ratio targets for efficacy.[8]
  - Median and randomly assigned total-drug ELF and free-drug plasma AUC:MIC ratio targets associated with a 1-$\log_{10}$ colony forming units (CFU) reduction from baseline for *S. pneumoniae* and *S. aureus* based on data from neutropenic murine-lung infection models[8] were evaluated.
    - 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] were assessed.
    - Total-drug ELF and free-drug plasma AUC:MIC ratio targets were randomly assigned for a simulated patient based on estimated log normal distributions of targets associated with each endpoint. Each distribution was truncated at ± 2 standard deviations on the log scale.

RESULTS

- **Figures 1A** and **1B** show percent probabilities of attaining median or randomly assigned total-drug ELF and free-drug plasma AUC:MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline for *S. pneumoniae*, respectively, overlaid upon MIC distributions for *S. pneumoniae* isolates collected worldwide.
  - Percent probabilities of PK-PD target attainment ranged from 91.4% to 100% at the MIC_{90} of 0.25 µg/mL for LEF 150 mg IV q12h and 600 mg PO q12h administered under fasted conditions. Under fed conditions for the PO dosing regimen, percent probabilities of PK-PD target attainment ranged from 76.6% to 98.8%.
- **Figures 1C** and **1D** show percent probabilities of attaining median or randomly assigned total-drug ELF and free-drug plasma AUC:MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline for *S. aureus*, respectively, overlaid upon MIC distributions for *S. aureus* isolates collected worldwide.
  - Percent probabilities of PK-PD target attainment ranged from 98.3% to 100% at the $MIC_{90}$of 0.12 µg/mL for LEF 150 mg IV q12h and 600 mg PO q12h administered under fasted conditions. Under fed conditions for the PO dosing regimen, percent probabilities of PK-PD target attainment ranged from 91.5% to 100%.
- Overall percent probabilities of PK-PD target attainment based on median or randomly assigned total-drug ELF and free-drug plasma AUC:MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline and the MIC distributions for *S. pneumoniae* and *S. aureus* were ≥95.1%.
- **Figures 2A** and **2B** show the fitted functions for relationships between change from baseline in $\log_{10}$ CFU at 24 hours and LEF total-drug ELF AUC:MIC ratio based on the Hill models for *S. pneumoniae* and *S. aureus*, respectively, developed using data from neutropenic murine-lung infection models.[8]
  - On each figure, horizontal box-and-whisker plots representing Day 1 total-drug ELF AUC:MIC ratio distributions for simulated patients after administration of LEF IV or PO dosing regimens are shown. MIC values were randomly assigned from the observed MIC distribution for each pathogen.
  - These data demonstrate that all simulated patients after administration of IV or PO dosing regimens would be expected to achieve total-drug ELF AUC:MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline for both pathogens. Assessments based on free-drug plasma AUC:MIC ratio demonstrated similar findings (data not shown).

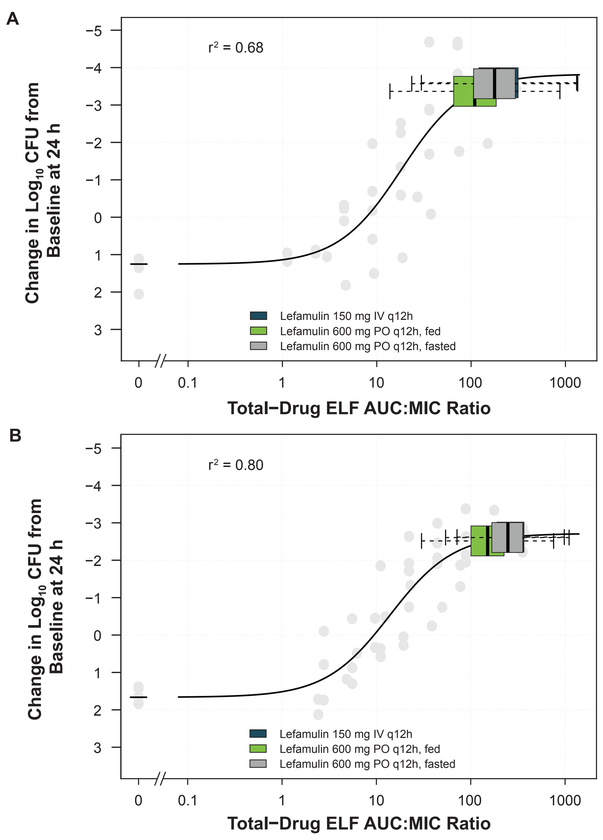
RESULTS (continued)

Figure 1. Assessment of PK-PD Target Attainment by MIC on Day 1 Based on Median or Randomly Assigned Total-Drug ELF and Free-Drug Plasma AUC:MIC Ratio Targets Associated with a 1-$\log_{10}$ CFU Reduction from Baseline for *S. pneumoniae* (A and B, respectively) and *S. aureus* (C and D, respectively), Overlaid Upon MIC Distributions for Isolates Collected Worldwide



AUC=area under the concentration-time curve; CFU=colony forming unit; ELF=epithelial lining fluid; IV=intravenous; MIC=minimum inhibitory concentration; MRSA=methicillin-resistant *S.aureus*; MSSA=methicillin-susceptible *S. aureus*; PISP=penicillin-intermediate *S. pneumoniae*; PK-PD=pharmacokinetic-pharmacodynamic; PO=oral; PRSP=penicillin-resistant *S. pneumoniae*; PSSP=penicillin-susceptible *S. pneumoniae*; q12h=every 12 hours.

Figure 2. Nonclinical PK-PD Relationships for Efficacy for *S. pneumoniae* (A) and *S. aureus* (B) Overlaid With Box-and-Whisker Plots of Day 1 Total-Drug ELF AUC:MIC Ratios*



*Based on randomly assigned MIC values for simulated patients after administration of lefamulin IV and PO dosing regimens.

AUC=area under the concentration-time curve; CFU=colony forming unit; ELF=epithelial lining fluid; IV=intravenous; MIC=minimum inhibitory concentration; PK-PD=pharmacokinetic-pharmacodynamic; PO=oral; q12h=every 12 hours.

CONCLUSIONS

- Results of these analyses provide support for LEF 150 mg IV q12h and 600 mg PO q12h for the treatment of patients with CABP and provide justification for administering PO doses without regard to food.
- The data described herein are also useful to support LEF susceptibility breakpoint determinations for *S. pneumoniae* and *S. aureus*.

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