Pharmacokinetic-Pharmacodynamic Target Attainment Analyses Supporting Lefamulin Dose Selection for the Treatment of Patients with Community-Acquired Pneumonia

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ABSTRACT

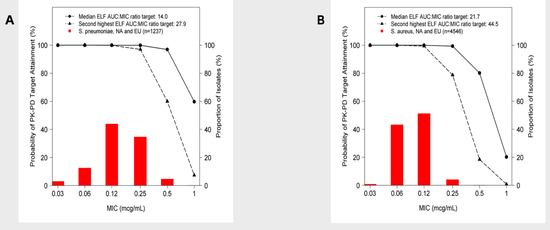
Objectives: Lefamulin is a semi-synthetic intravenous (IV) and oral pleuromutilin antibiotic entering Phase 3 clinical development for community-acquired bacterial pneumonia (CABP). Lefamulin is active against pathogens commonly associated with CABP, including multi-drug resistant (MDR) *S. pneumoniae* (SP), *M. pneumoniae*, and *S. aureus* (SA). Using *in vitro*, non-clinical pharmacokinetic-pharmacodynamic (PK-PD), and clinical pharmacokinetic (PK) data, PK-PD target attainment (TA) analyses were performed to provide support for the selection of a lefamulin dosing regimen for the treatment of patients with CABP.

Methods: Data utilized included a population PK (PPK) model describing the disposition of lefamulin developed using Phase 1 and 2 data, non-clinical PK-PD targets based on neutropenic murine-lung infection models and MIC data from isolates collected from North America (NA) and the European Union (EU) for lefamulin against SP and SA (SENTRY Program). The PPK model used was a 3-compartment model with first-order elimination with saturable protein binding. Lefamulin concentrations in epithelial lining fluid (ELF) were modeled using first-order rate constants into and out of the ELF compartment. Using the PK parameter estimates, ELF and free-drug plasma concentration-time profiles were generated for 2,000 simulated patients following lefamulin 150 mg IV q12h; Day 1 AUC_{0-24} values were calculated. Non-clinical ELF and free-plasma AUC:MIC ratio targets (median and second highest) associated with a 1-$\log_{10}$ CFU reduction from baseline for SP and SA were evaluated. Percent probabilities of PK-PD TA by MIC value and over MIC distributions for SP and SA were determined.

Results: Percent probabilities of PK-PD TA by MIC are shown for SP (A) and SA (B) for ELF targets in **Figure 1**. Percent probabilities of attaining median ELF AUC:MIC ratio targets were 97.0% at the MIC_{99} of 0.5 mcg/mL for SP and 99.4% at the MIC_{99} of 0.25 mcg/mL for SA. For the second highest targets, ≥97.0% PK-PD TA was achieved at MIC_{90} values for each pathogen. Overall percent probabilities of attaining AUC:MIC ratio targets for SP and SA based on NA and EU MIC data were ≥96.6%. Results based on plasma targets were similar for SP and SA.

Conclusions: Results of these PK-PD TA analyses for SP and SA provide support for the selection of lefamulin 150 mg IV q12h for the treatment of patients with CABP.

Figure 1. Percent probabilities of PK-PD target attainment by MIC for lefamulin 150 mg IV q12h based on the evaluation of the ELF AUC :MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline for SP isolates from NA and the EU (A) and SA overlaid on the MIC distribution for SA isolates from NA and the EU (B)



INTRODUCTION

- Lefamulin (BC-3781) is an antimicrobial agent from the pleuromutilin class that demonstrates *in vitro* microbiological activity against a wide range of bacterial pathogens including common pathogens causing community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infection (ABSSSI), such as *Streptococcus pneumoniae* and *Staphylococcus aureus*, including methicillin-resistant isolates (MRSA) [1].
- Lefamulin is entering Phase 3 clinical development for CABP as an intravenous (IV) and oral formulation, thus allowing for a potential IV to oral switch (i.e., step-down therapy) in patients with CABP, ABSSSI, and other diseases.

OBJECTIVE

- *In vitro* surveillance, non-clinical pharmacokinetic-pharmacodynamic (PK-PD), and clinical pharmacokinetic (PK) data were used together with Monte Carlo simulation to evaluate the PK-PD target attainment of a lefamulin dosing regimen of 150 mg IV every 12 hours (q12h) to provide dose selection support for the treatment of patients with CABP.

METHODS

Simulated Patient Population

- PK parameter estimates for 2,000 simulated patients were generated from a previously-developed population PK model for IV lefamulin [2] using NONMEM v7.1.2.
  - The PK of lefamulin in plasma were described using a 3-compartment model with first order elimination [2].
  - Saturable protein binding, based on non-linear protein binding observed *in vitro* [3], was incorporated into the model and all model parameters were conditioned on the unbound concentrations.
- Lefamulin concentrations in epithelial lining fluid (ELF) were modeled using first-order rate constants into and out of the ELF compartment.
  - ELF PK was constructed using data from ELF samples from normal, healthy volunteers after administration of a single, IV dose of lefamulin 150 mg (n=12) [3]. Since the population PK model did not have inter-individual variability (IIV) in the ELF parameters, 25% IIV in the first order rate constants was added to better approximate the ELF PK in patients with CABP.
- ELF and free-drug plasma concentration-time profiles from time 0 to 24 hours were generated for each simulated patient following administration of lefamulin 150 mg IV q12h on Day 1. Day 1 ELF and free-drug plasma area under the concentration-time curve from time 0 to 24 hours (AUC_{0-24}) were calculated using the linear trapezoidal rule.
- Day 1 ELF and free-drug plasma AUC_{0-24} values were divided by MIC values ranging from 0.015 to 16 mcg/mL to calculate the ratio of the AUC_{0-24} to the MIC (AUC:MIC) ratio for each exposure.

Non-Clinical PK-PD Targets for Efficacy

- ELF and free-drug plasma AUC:MIC ratio targets for *S. pneumoniae* and *S. aureus* efficacy based on data from a neutropenic murine-lung infection model [4] are summarized in **Table 1**.
  - The bacterial reduction endpoint of interest for lefamulin against *S. pneumoniae* and *S. aureus* was 1-$\log_{10}$ CFU reduction from baseline since higher percentages of response in patients with CABP who attained the PK-PD indices associated with this endpoint have been observed than those with lower PK-PD indices [5].
  - In addition to evaluating the median ELF and free-drug plasma AUC:MIC ratio targets among the isolates studied, PK-PD target attainment was assessed for the second highest AUC:MIC ratio targets to evaluate the impact of variability around the targets (i.e., for a sensitivity analysis).

Table 1. Summary of AUC:MIC ratio targets for *S. pneumoniae* and *S. aureus* efficacy

Pathogen	Bacterial reduction endpoint ($\log_{10}$ CFU reduction from baseline)	ELF		Free-drug plasma	
		Median	Second highest	Median	Second highest
S. pneumoniae	1	14.0	27.9	1.37	2.73
	2	22.0	40.5	2.15	3.96
S. aureus	1	21.7	44.5	2.13	4.35
	2	63.9	85.7	6.24	8.39

Lefamulin *In Vitro* Activity

- The MIC distributions for lefamulin against *S. pneumoniae* and *S. aureus* were obtained during 2010 from 37 North America (NA), 25 European Union (EU), 10 Latin American, and 12 Asian-Pacific medical centers [1].
  - A total of 1,473 *S. pneumoniae* isolates were tested (NA/EU = 793/444). MIC values ranged from ≤0.0008 to 1 mcg/mL; the $MIC_{50/90}$ was 0.12/0.25 mcg/mL for all regions combined and NA and the EU separately.
  - A total of 5,527 *S. aureus* isolates were tested (NA/EU = 3,043/1,503). MIC values ranged from 0.015 to >16 mcg/mL; the $MIC_{50/90}$ was 0.12/0.12 mcg/mL for all regions combined and NA and the EU separately.

Evaluation of PK-PD Target Attainment

- Percent probabilities of PK-PD target attainment by MIC and weighted over MIC distributions based on ELF and free-drug plasma exposures for lefamulin were determined for each of the AUC:MIC ratio targets described in **Table 1**.
  - Percent probabilities of overall PK-PD target attainment were determined for each AUC:MIC ratio target and each MIC distribution. For a given AUC:MIC ratio target, percent probabilities represented the sum of the product of the percent probability of PK-PD target attainment at a given MIC and the proportion of isolates in the collection with a MIC corresponding to that value for all MIC values at which there is observed data.

RESULTS

PK-PD Target Attainment for *S. pneumoniae*

- **Figure 1** shows the percent probabilities of PK-PD target attainment by MIC based on ELF and free-drug plasma AUC:MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline for *S. pneumoniae* overlaid on the MIC distribution for *S. pneumoniae* from NA and the EU.
  - Percent probabilities of attaining the median ELF and free-drug plasma AUC:MIC ratio targets were 97.0 and 97.9%, respectively, at the MIC_{99} value of 0.5 mcg/mL.
  - For second highest ELF and free-drug plasma AUC:MIC ratio targets, percent probabilities were 97.0 and 97.9%, respectively, at the MIC_{90} value of 0.25 mcg/mL.
- High probabilities of PK-PD target attainment were also seen for ELF and free-drug plasma AUC:MIC ratio targets associated with a 2-$\log_{10}$ CFU reduction from baseline.
  - Percent probabilities of attaining the median ELF and free-drug plasma AUC:MIC ratio targets were 99.4 and 99.6%, respectively, at the MIC_{99} value of 0.25 mcg/mL.
  - For second highest ELF and free-drug plasma AUC:MIC ratio targets, percent probabilities were 99.7 and 99.8%, respectively, at the MIC_{90} value of 0.12 mcg/mL. Percent probabilities were 85.0 and 87.4%, respectively, at the MIC_{90} value of 0.25 mcg/mL.

PK-PD Target Attainment for *S. aureus*

- **Figure 2** shows the percent probabilities of PK-PD target attainment by MIC based on ELF and free-drug plasma AUC:MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline for *S. aureus* overlaid on the MIC distribution for *S. aureus* from NA and the EU.
  - Percent probabilities of attaining the median ELF and free-drug plasma AUC:MIC ratio targets were 99.4 and 99.6%, respectively, at the MIC_{99} value of 0.25 mcg/mL.
  - For second highest ELF and free-drug plasma AUC:MIC ratio targets, percent probabilities were 99.4 and 99.7%, respectively, at the MIC_{90} value of 0.12 mcg/mL.
- High probabilities of PK-PD target attainment were also seen for ELF and free-drug plasma AUC:MIC ratio targets associated with a 2-$\log_{10}$ CFU reduction from baseline.
  - Percent probabilities of attaining the median ELF and free-drug plasma AUC:MIC ratio targets were 95.3 and 96.6%, respectively, at the MIC_{90} value of 0.12 mcg/mL.
  - For second highest ELF and free-drug plasma AUC:MIC ratio targets, percent probabilities were 99.5 and 99.7%, respectively, at a MIC value of 0.06 mcg/mL. Percent probabilities were 83.9 and 86.5%, respectively, at the MIC_{90} value of 0.12 mcg/mL.

Overall PK-PD Target Attainment for *S. pneumoniae* and *S. aureus*

- **Table 2** provides the percent probabilities of overall PK-PD target attainment for the ELF and free-drug plasma AUC:MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline and MIC distributions for *S. pneumoniae* and *S. aureus* isolates collected from NA and the EU regions combined and regions worldwide.

Table 2. Summary of percent probabilities of overall PK-PD target attainment for *S. pneumoniae* and *S. aureus* by geographic region and AUC:MIC ratio target

Pathogen	Geographic region for the MIC distribution	Percent probabilities of overall PK-PD target attainment based on the ELF or free-drug plasma AUC:MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline			
		ELF		Free-drug plasma	
		Median	Second highest	Median	Second highest
S. pneumoniae	NA/EU	99.5	96.6	99.6	97.2
	Worldwide	99.5	96.7	99.6	97.2
S. aureus	NA/EU	99.8	98.5	99.8	98.8
	Worldwide	99.7	98.1	99.7	98.5

RESULTS

Figure 1. Percent probabilities of PK-PD target attainment by MIC for lefamulin 150 mg IV q12h based on the evaluation of the ELF (A) and free-drug plasma (B) AUC:MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline for *S. pneumoniae* overlaid on the MIC distribution for *S. pneumoniae* from NA and the EU

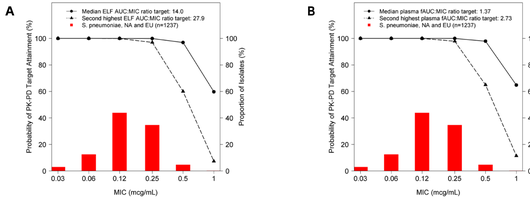
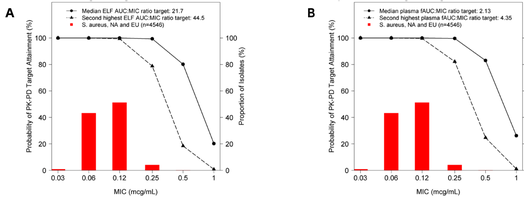


Figure 2. Percent probabilities of PK-PD target attainment by MIC for lefamulin 150 mg IV q12h based on the evaluation of the ELF (A) and free-drug plasma (B) AUC:MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline for *S. aureus* overlaid on the MIC distribution for *S. aureus* from NA and the EU



CONCLUSIONS

- Results of PK-PD target attainment analyses provide dose selection support for lefamulin 150 mg IV q12h for CABP. This conclusion is supported by the following:
  - Percent probabilities of attaining the median ELF AUC:MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline by MIC were 97.0% at a MIC of 0.5 mcg/mL for *S. pneumoniae* and 99.4% at a MIC of 0.25 mcg/mL for *S. aureus* (thus, covering ≥99.5% of NA and the EU or worldwide isolates for either pathogen).
    - At the MIC_{90} values for *S. pneumoniae* and *S. aureus* (0.25 and 0.12 mcg/mL, respectively), percent probabilities of PK-PD target attainment were ≥99.9%.
    - Sensitivity analyses based on the evaluation of the second highest AUC:MIC ratio targets revealed percent probabilities of PK-PD target attainment of ≥97.0% at MIC values that were one dilution lower and which represent the MIC_{90} for each pathogen.
  - Overall percent probabilities of attaining ELF AUC:MIC ratio targets associated with a 1-$\log_{10}$ CFU reduction from baseline for *S. pneumoniae* and *S. aureus* based on robust surveillance data for both pathogens from NA and the EU or worldwide were ≥96.6%.
  - Similar PK-PD target attainment results as those for ELF exposures were obtained for the evaluation of free-drug plasma AUC:MIC ratio targets.

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