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Pharmacokinetic-Pharmacodynamic Target Attainment Analyses to Support Oral Lefamulin Dose Selection in the Treatment of Patients with Community-Acquired Bacterial Pneumonia

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ABSTRACT

Background: Lefamulin, a semi-synthetic intravenous (IV) and oral (PO) pleuromutilin antibiotic with activity against pathogens commonly associated with community-acquired bacterial pneumonia (CABP), including multi-drug resistant *Streptococcus pneumoniae* (SP) and *Staphylococcus aureus* (SA), is currently in Phase 3 development for the treatment of CABP. To provide dose selection support for CABP, an existing population PK (PPK) model, *in vitro* surveillance and non-clinical PK-PD data for SP and SA, and Monte Carlo simulation were used to assess probabilities of PK-PD target attainment for lefamulin 600 mg PO q12h.

Methods: Data used included a PPK model for IV and PO (fed and fasted) lefamulin developed using Phase 1 data, PK-PD targets based on neutropenic murine-lung infection models (ICAAC 2015, Abstr A-037) and lefamulin MIC data for SP and SA isolates from the USA and Europe (Antimicrob Agents Chemother. 57:4489-9445). The PPK model was a 3-compartment model with nonlinear protein binding and 2 parallel first-order absorption processes. Using PK parameter estimates, free-drug plasma concentration-time profiles were generated for 2,000 simulated patients following lefamulin 600 mg PO q12h under fed and fasted conditions; Day 1 free-drug AUC_{0-24} was calculated. Percent probabilities of PK-PD target attainment by MIC and overall (i.e., weighted over SP and SA MIC distributions) were determined using median free-drug plasma AUC:MIC targets associated with 1- and 2-log_{10} CFU reductions from baseline for SP and SA.

Results: Percent probabilities of PK-PD target attainment by MIC for SP and SA (**Figure 1**) were similar under fed and fasted conditions at MICs ≤ MIC_{90}. As shown in Figures 1A and 1B, percent probabilities of attaining free-drug plasma AUC:MIC ratio targets associated with a 1-log_{10} CFU reduction were 100% at the MIC_{90} (0.25 and 0.12 μg/mL for SP and SA, respectively) and ≥95.5% at the MIC_{99} (0.5 and 0.25 μg/mL for SP and SA, respectively). For free-drug plasma AUC:MIC ratio targets associated with a 2-log_{10} CFU reduction, percent probabilities were ≥91.9% at MIC_{90} values. Overall percent probabilities of attaining free-drug plasma AUC:MIC ratio targets for 1- and 2-log_{10} CFU reductions of SP or SA were ≥99.4 and ≥91.7%, respectively.

Conclusion: These data provide support for lefamulin 600 mg PO q12h for the treatment of patients with CABP and suggest that doses do not need to be taken under fasted conditions.

INTRODUCTION

- Lefamulin (BC-3781) is an antimicrobial agent of the pleuromutilin class which 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 infections (ABSSSI), such as *Streptococcus pneumoniae* and *Staphylococcus aureus*, including methicillin-resistant isolates (MRSA) [1].

- Phase 3 studies evaluating intravenous (IV) and oral (PO) formulations of lefamulin in patients with CABP are ongoing.

- Results of previous PK-PD target attainment analyses provided dose selection support for an IV lefamulin dosing regimen for patients with CABP [2]. As described herein, a similar approach was undertaken to evaluate a PO lefamulin dosing regimen for patients with CABP.

OBJECTIVE

- To assess the PK-PD target attainment of lefamulin 600 mg PO q12h under both fed and fasted conditions using a refined population PK model, non-clinical PK-PD targets for efficacy, *in vitro* surveillance data, and Monte Carlo simulation.

METHODS

Simulated Patient Population

- PK parameter estimates for 2,000 simulated patients were generated from a previously-developed population PK model for PO lefamulin [3] using NONMEM v7.1.2 .

- The population PK model was developed [3] using a previous population PK model that described the disposition of IV lefamulin [4] and PK data from a Phase 1 cross-over study [5].

  o This study assessed the bioavailability of lefamulin among healthy subjects who received singe IV or PO doses under fed or fasted conditions [5].

  o Given that non-linear protein binding was observed *in vitro* [6], saturable protein binding was incorporated into the model and all model parameters were conditioned on the unbound concentrations.

  o Results of this analysis demonstrated that the PK of PO lefamulin in plasma was best described using a three-compartment disposition model with nonlinear protein binding, two parallel first-order absorption processes [3].

    ▪ Delay in absorption was modeled for the second absorption process though multiple transit compartments.

- Free-drug plasma concentration-time profiles from time 0 to 24 hours were generated for each simulated patient under fed and fasted conditions following administration of lefamulin 600 mg PO q12h on Day 1.

- Day 1 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 free-drug plasma AUC_{0-24} values were divided by MIC values ranging from 0.015 to 16 μg/mL to calculate the ratio of the AUC_{0-24} to the MIC (AUC:MIC ratio).

Non-Clinical PK-PD Targets for Efficacy

- Free-drug plasma AUC:MC ratio targets for efficacy for *S. pneumoniae* and *S. aureus* evaluated, as shown in **Table 1**, were based on data from neutropenic murine-lung infection models [7]. Emphasis was placed on the assessment of the median free-drug plasma targets associated with a 1-log_{10} CFU reduction from baseline.

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

Pathogen	Bacterial reduction endpoint (log_{10} CFU reduction from baseline)	Median free-drug plasma AUC:MIC ratio
S. pneumoniae	1	1.37
	2	2.15
S. aureus	1	2.13
	2	6.24

METHODS

Lefamulin *In Vitro* Activity

- The MIC distributions for lefamulin against *S. pneumoniae* and *S. aureus* used to interpret the percent probabilities of PK-PD target attainment by MIC and calculate overall percent probabilities of PK-PD target attainment were based on 1,237 and 4,546 isolates, respectively, collected from North America and the European Union combined [1].

Evaluation of PK-PD Target Attainment

- Percent probabilities of PK-PD target attainment by MIC and weighted over the above-described MIC distributions were determined for each of the free-drug plasma AUC:MIC ratio targets described in **Table 1** for simulated patients under fed and fasted conditions

RESULTS

- As shown in **Figure 1**, percent probabilities of attaining the free-drug plasma AUC:MIC ratio target associated with a 1-log_{10} CFU reduction from baseline at the MIC_{99} of 0.5 μg/mL for *S. pneumoniae* were 95.5 and 100% for simulated patients after administration of lefamulin 600 mg PO q12h under fed and fasted conditions, respectively.

- Percent probabilities of attaining the free-drug plasma AUC:MIC ratio target associated with a 2-log_{10} CFU reduction from baseline were 99.4 and 100%, for simulated patients evaluated under fed and fasted conditions, respectively, at the MIC_{90} of 0.25 μg/mL for *S. pneumoniae*.
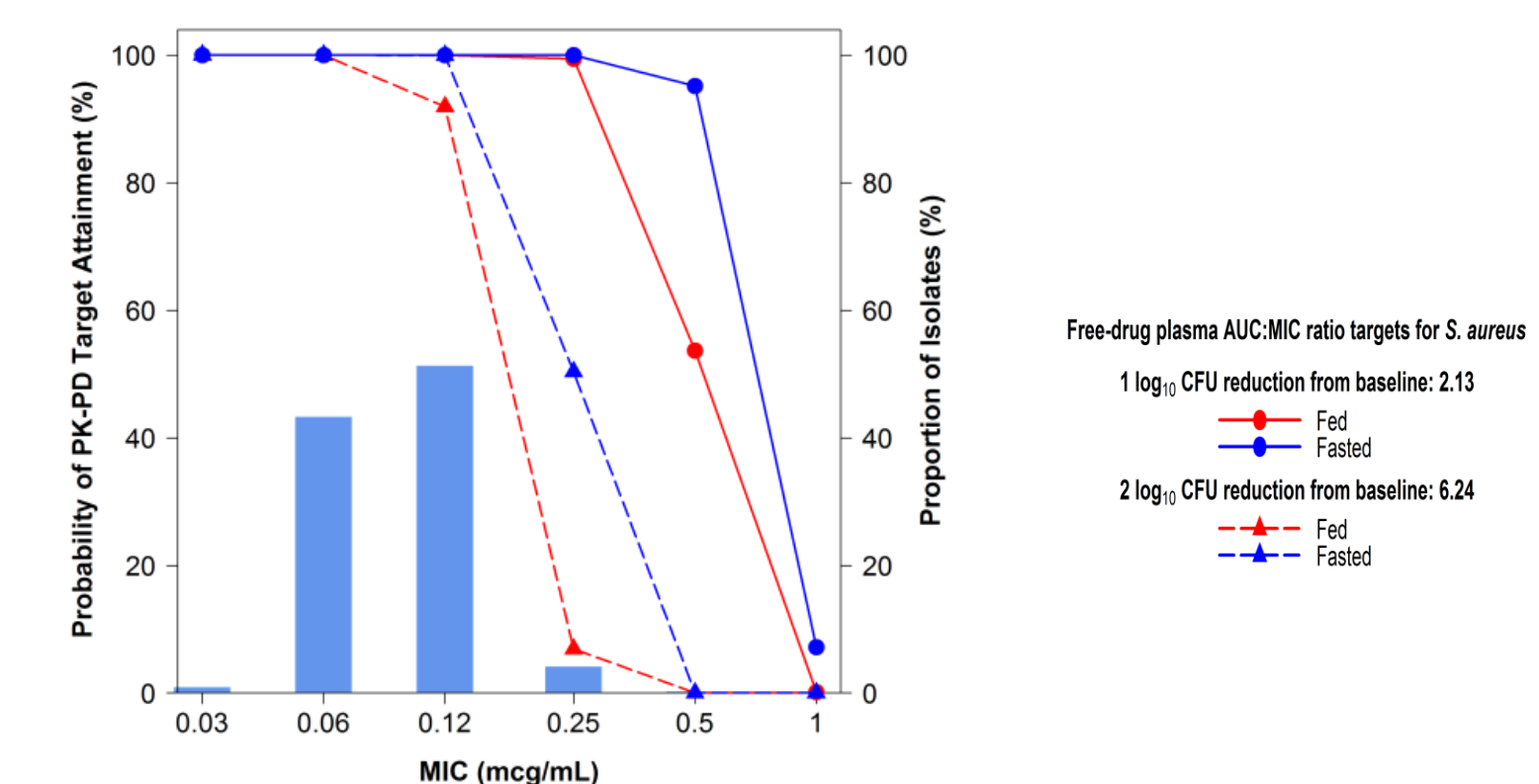
Figure 1. Percent probabilities of PK-PD target attainment by MIC for lefamulin 600 mg PO q12h based on the evaluation of the free-drug plasma AUC:MIC ratio targets for *S. pneumoniae* overlaid on the MIC distribution for *S. pneumoniae*
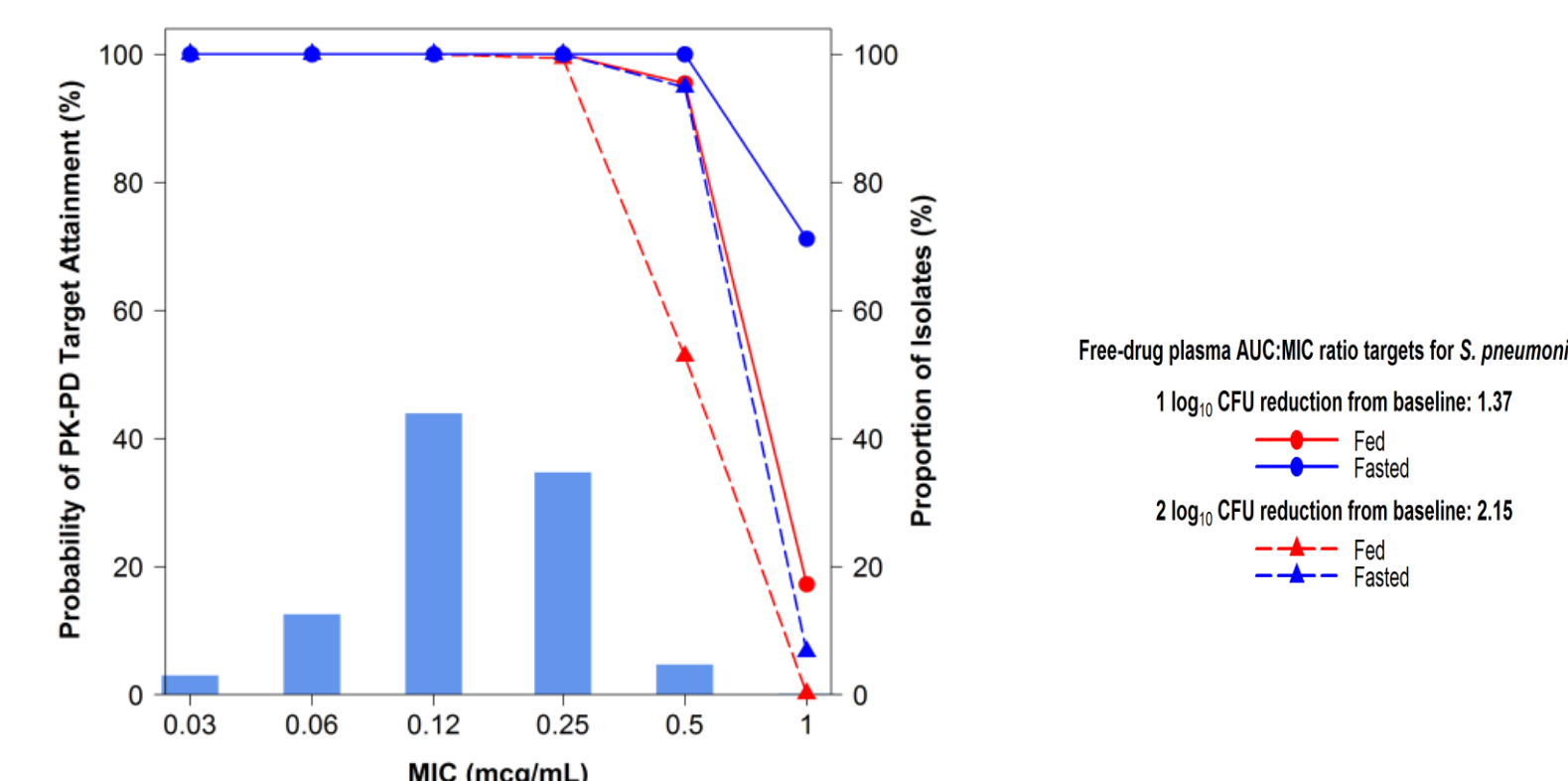
- As shown in **Figure 2**, percent probabilities of attaining the free-drug plasma AUC:MIC ratio target associated with a 1-log_{10} CFU reduction from baseline at the MIC_{99} of 0.25 μg/mL for *S. aureus* were 99.5 and 100% for simulated patients after administration of lefamulin 600 mg PO q12h under fed and fasted conditions, respectively.

- Percent probabilities of attaining the free-drug plasma AUC:MIC ratio target associated with a 2-log_{10} CFU reduction from baseline were 91.9 and 100%, for simulated patients evaluated under fed and fasted conditions, respectively, at the MIC_{90} of 0.12 μg/mL for *S. aureus*.

RESULTS

Figure 2. Percent probabilities of PK-PD target attainment by MIC for lefamulin 600 mg PO q12h based on the evaluation of the free-drug plasma AUC:MIC ratio targets for *S. aureus* overlaid on the MIC distribution for *S. aureus*

- As shown in **Table 2**, overall percent probabilities of PK-PD target attainment for the free-drug plasma AUC:MIC ratio targets associated with a 1- or 2-log_{10} CFU reduction from baseline exceed 90% among simulated patients evaluated under fed and fasted conditions.

Table 2. Overall probabilities of PK-PD target attainment for *S. pneumoniae* and *S. aureus*

Pathogen	Overall percent probabilities of PK-PD target attainment[a]			
	Fed		Fasted	
	1-log_{10} CFU reduction	2-log_{10} CFU reduction	1-log_{10} CFU reduction	2-log_{10} CFU reduction
S. pneumoniae	99.4	97.2	99.7	99.4
S. aureus	99.8	91.7	99.9	97.6

a. Based on the MIC distributions for *S. pneumoniae* or *S. aureus* isolates collected from NA and EU regions combined.

CONCLUSIONS

- Regardless of food intake, percent probabilities of PK-PD target attainment based on the free-drug plasma AUC:MIC ratio targets associated with a 1-log_{10} CFU reduction from baseline were ≥95.5% for both *S. pneumoniae* and *S. aureus* at a MIC values covering ≥99.5% of isolates in NA and the EU for both pathogens.

- These data provide support for lefamulin 600 mg PO q12h for the treatment of patients with CABP and suggest that doses can be administered irrespective of food.

- Results of these PK-PD target attainment analyses are similar to those observed with an IV lefamulin dosing regimen for patients with CABP [2], which included assessment of ELF exposures in humans and murine ELF PK-PD targets for efficacy and that demonstrated comparable PK-PD target attainment to that based on plasma exposures.

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