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Pharmacokinetic/pharmacodynamic target attainment analyses to support intravenous and oral lefamulin dose selection for the treatment of patients with community-acquired bacterial pneumonia

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Objectives: Lefamulin is a semi-synthetic intravenous (iv) and oral pleuromutilin antibiotic active against community-acquired bacterial pneumonia (CABP) pathogens. Pharmacokinetic/pharmacodynamic (PK/PD) target attainment analyses were carried out to evaluate lefamulin 150 mg iv q12h and 600 mg orally q12h under fed and fasted conditions for the treatment of patients with CABP.

Methods: The analyses undertaken used a population PK model based on Phase 1 PK data, non-clinical PK/PD targets for efficacy and *in vitro* surveillance data for *Streptococcus pneumoniae* (SP) and *Staphylococcus aureus* (SA), and Monte Carlo simulation. Percentage probabilities of PK/PD target attainment by MIC on day 1 were determined using median total-drug epithelial lining fluid (ELF) and free-drug plasma AUC:MIC ratio targets associated with 1 and 2 $\log_{10}$ cfu reductions from baseline.

Results: Percentage probabilities of attaining the total-drug ELF AUC:MIC ratio target for a 1 $\log_{10}$ cfu reduction from baseline for SP were $\geq$99.2% at the MIC_{90} of 0.12 mg/L and 96.7%, 82.1% and 96.3% for iv and oral dosing regimens under fed and fasted conditions, respectively, at the MIC_{99} of 0.25 mg/L. Percentage probabilities of attaining the free-drug plasma AUC:MIC target for the same endpoint at the SP MIC_{99} were 100% for each regimen. For the SA MIC_{90} of 0.12 mg/L and AUC:MIC ratio targets for the same endpoint, percentage probabilities were 92.7%–100% for iv and oral dosing regimens.

Conclusions: These data provide support for lefamulin 150 mg iv q12h and 600 mg orally q12h for the treatment of patients with CABP and suggest that doses may not need to be taken under fasted conditions.

Introduction

Community-acquired bacterial pneumonia (CABP) is a leading cause of infection-related hospitalization and mortality, and is associated with increased burden in certain populations, including the elderly.[1–4] Among those with CABP, *Streptococcus pneumoniae* is the most common causative pathogen.[1,2] Given the current prevalence of *S. pneumoniae* resistance to β-lactams, macrolides and older-generation tetracyclines,[5] the treatment of CABP can be challenging. In the USA, the estimated numbers of hospitalizations and deaths per year that have been attributed to antibiotic-resistant *S. pneumoniae* are 19000 and 7000, respectively.[6] Given these data, the availability of additional treatment choices for patients with CABP, especially oral therapy, is needed.

Lefamulin (BC-3781) is an antimicrobial agent from the pleuromutilin class[7] that demonstrates *in vitro* microbiological activity against a wide range of bacterial pathogens, including common pathogens causing CABP and acute bacterial skin and skin structure infections. These pathogens include *S. pneumoniae* and *Staphylococcus aureus*, including MRSA.[8–12] Two Phase 3 clinical studies, LEAP1 and LEAP2, one evaluating intravenous (iv) to oral lefamulin and the other evaluating oral lefamulin for the treatment of CABP, were recently completed. For each study, lefamulin met the FDA primary endpoint of non-inferiority compared with moxifloxacin for early clinical response assessed 72–120 h following initiation of therapy in the intent-to-treat (ITT) patient population. Lefamulin also met the EMA primary endpoint for non-inferiority

(10.0% margin) compared with moxifloxacin based on an investigator assessment of clinical response 5–10 days following the completion of study drug dosing in the modified ITT and clinically evaluable at test of cure patient populations.[13,14]

The current paradigm for the development of antimicrobial agents involves the use of non-clinical infection models that characterize pharmacokinetic/pharmacodynamic (PK/PD) relationships for efficacy. Studies using such models enable the identification of the PK/PD index associated with efficacy and calculation of the magnitudes of this index required to achieve various levels of reduction in bacterial burden (i.e. PK/PD targets).[15] The application of these PK/PD targets for efficacy, together with a population PK model developed using Phase 1 and/or 2 data, *in vitro* surveillance data and Monte Carlo simulation, enables the evaluation of dosing regimens for future Phase 3 studies.[16–18] The evaluation of non-clinical PK/PD targets for efficacy with early clinical PK data is now advocated in contemporary regulatory guidance documents, such as the infectious disease-specific FDA guidance documents for developing drugs and the EMA guidance for developing antibacterial agents.[19–21]

In the analyses described herein, non-clinical PK/PD targets for efficacy for *S. pneumoniae* and *S. aureus* (see article in this Supplement entitled 'Pharmacokinetics/pharmacodynamics of lefamulin in a neutropenic murine pneumonia model with *Staphylococcus aureus* and *Streptococcus pneumoniae*'[22]), a population PK model developed based on Phase 1 PK data (see article in this Supplement entitled, 'Prediction of lefamulin epithelial lining fluid penetration after intravenous and oral administration using Phase 1 data and population pharmacokinetics methods'[23]), *in vitro* surveillance data[12] and Monte Carlo simulation were used to assess the PK/PD target attainment of lefamulin 150 mg iv q12h and 600 mg orally q12h for the treatment of patients with CABP.

Methods

Simulated patient population

Monte Carlo simulation was performed using a previously described population PK model for lefamulin developed using Phase 1 data (see article in this Supplement entitled 'Prediction of lefamulin epithelial lining fluid penetration after intravenous and oral administration using Phase 1 data and population pharmacokinetics methods'[23]) and NONMEM® version 7.1.2[24] (ICON Development Solutions, Ellicott City, MD, USA). The population PK model describing the disposition of lefamulin was a three-compartment model with non-linear protein binding and two parallel first-order absorption processes. The only significant covariate relationships identified for the plasma PK were the effect of food on the rate and extent of absorption after oral administration. First-order rate constants were used to describe lefamulin transfer into and out of the epithelial lining fluid (ELF) compartment from plasma. As described below, given the food effect findings, data from simulated patients who received oral lefamulin under fed and fasted conditions were evaluated.

Using the mean parameter vector and the variance–covariance matrix from the above-described population PK model, PK parameter estimates were simulated for 2000 patients. These population PK parameter estimates were used to generate total-drug ELF and free-drug plasma concentration–time profiles from 0–24 h on day 1 for each simulated patient following lefamulin 150 mg iv q12h and 600 mg orally q12h under fed and fasted conditions. Day 1 total-drug ELF and free-drug plasma AUC_{0-24} values were calculated using the linear trapezoidal rule. These exposures

were then divided by MIC values ranging from 0.015 to 16 mg/L to calculate the ratio of the AUC_{0-24} to the MIC (AUC:MIC ratio), the PK/PD index of primary interest for lefamulin (see article in this Supplement entitled '*In vivo* pharmacodynamics of lefamulin, the first systemic pleuromutilin for human use, in a neutropenic murine thigh infection model'[25]).

Non-clinical PK/PD targets for efficacy

Median total-drug 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, as described earlier in this Supplement,[22] are summarized in Table 1. The bacterial reduction endpoints of interest for the AUC:MIC ratio targets for *S. pneumoniae* and *S. aureus* were 1 and 2 $\log_{10}$ cfu reductions from baseline. Greater emphasis was given to PK/PD target attainment results based on the former, the basis for which was guided by the results of a recent assessment that evaluated the relationship between the probability of PK/PD target attainment using this endpoint and the probability of obtaining regulatory approval for an antibacterial dosing regimen for patients with pneumonia. Results of this analysis, which were based on data for 19 development programmes for antibacterial agents for pneumonia, demonstrated that, as the probability of PK/PD target attainment for a given dosing regimen in the context of that agent's MIC distribution for the relevant pathogen increased, so too did the probability of regulatory approval for the same dosing regimen.[26]

In vitro surveillance data

The MIC distributions for lefamulin against *S. pneumoniae* and *S. aureus* were determined for isolates collected between 2015 and 2016.[12] A total of 3923 *S. pneumoniae* isolates were collected from 122 medical centres worldwide (60 in the USA, 38 in Europe and the Mediterranean region, 15 in the Asia-Pacific region, 9 in Latin America). For *S. aureus*, a total of 2919 isolates were collected from 124 medical centres worldwide (62 in the USA, 38 in Europe and the Mediterranean region, 14 in the Asia-Pacific region, 10 in Latin America). MIC values for *S. pneumoniae* isolates ranged from ≤0.008 to 1 mg/L; MIC_{50} and MIC_{90} values were 0.06 and 0.12 mg/L, respectively. MIC values for *S. aureus* isolates ranged from 0.03 to >16 mg/L; MIC_{50} and MIC_{90} values for all isolates and the MRSA subset (n=1981) were 0.06 and 0.12 mg/L.

Evaluation of PK/PD target attainment

Percentage probabilities of PK/PD target attainment by MIC value and weighted over the above-described MIC distributions based on total-drug ELF and free-drug plasma exposures for lefamulin were determined for each of the AUC:MIC ratio targets described in Table 1.

Using total-drug ELF and free-drug plasma AUC:MIC ratio targets for *S. pneumoniae* and *S. aureus* and MIC distributions for each pathogen, overall percentage probabilities of PK/PD target attainment were determined by multiplying the percentage probability of PK/PD target attainment for the AUC:MIC ratio target at a given MIC value by the probability of occurrence of that MIC value. The sum of these percentages (i.e. the overall PK/PD target attainment) was then determined.

Evaluation of non-clinical PK/PD relationships for efficacy relative to simulated total-drug ELF AUC:MIC ratios

Using parameter estimates from Hill models constructed using data from murine lung-infection models for *S. aureus* and *S. pneumoniae* (see article in this Supplement entitled, 'Pharmacokinetics/pharmacodynamics of lefamulin in a neutropenic murine pneumonia model with *Staphylococcus aureus* and *Streptococcus pneumoniae*'[22]), fitted functions for the relationship between change in $\log_{10}$ cfu from baseline at 24 h and lefamulin total-drug ELF AUC:MIC ratio were generated for each pathogen. Total-drug ELF AUC:MIC ratios for simulated patients were generated by taking the day 1

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)	Median AUC:MIC ratio target[a]	
		total-drug ELF	free-drug plasma
S. pneumoniae	1	14.0	1.37
	2	22.0	2.15
S. aureus	1	21.7	2.13
	2	63.9	6.24

[a]Median AUC:MIC ratio targets were determined based on the evaluation of data for five *S. pneumoniae* and five *S. aureus* isolates using a neutropenic murine lung infection model described in this Supplement (see 'Pharmacokinetics/pharmacodynamics of lefamulin in a neutropenic murine pneumonia model with *Staphylococcus aureus* and *Streptococcus pneumoniae*'[22]).

Table 2. Summary statistics for day 1 AUC_{0-24} values among simulated patients after administration of lefamulin iv and oral dosing regimens

Lefamulin dosing regimen (mg)	Route of administration	Food status	Exposure matrix	Mean (%CV)	Median (range)
150	iv	fasted	total-drug plasma	13.2 (13.5)	13.1 (8.76–19.5)
			free-drug plasma	1.67 (13.9)	1.65 (1.06–2.45)
			total-drug ELF	9.46 (47.6)	8.58 (2.06–33.4)
600	oral	fasted	total-drug plasma	13.4 (19.6)	13.3 (6.49–23.6)
			free-drug plasma	1.59 (22.2)	1.56 (0.69–3.04)
			total-drug ELF	8.92 (49.6)	8.00 (1.20–40.9)
		fed	total-drug plasma	10.1 (23.1)	9.94 (4.13–18.3)
			free-drug plasma	1.12 (25.5)	1.10 (0.42–2.17)
			total-drug ELF	6.07 (51.4)	5.38 (0.788–28.0)

total-drug ELF AUC values for each simulated patient after administration of iv and oral lefamulin dosing regimens and dividing this AUC value by an MIC value that was randomly assigned from the observed distribution for the global collection of isolates for each pathogen. To interpret the non-clinical PK/PD relationships for efficacy relative to total-drug ELF AUC:MIC ratios for simulated patients, box-and-whisker plots of total-drug ELF AUC:MIC ratios were then overlaid on the above-described fitted functions.

Results

Summary of simulated exposures

Table 2 provides the summary statistics for day 1 AUC_{0-24} values among simulated patients after administration of lefamulin iv and oral dosing regimens.

Evaluation of PK/PD target attainment

Figure 1 shows the percentage probabilities of PK/PD target attainment by MIC on day 1 for lefamulin dosing regimens based on the evaluation of the total-drug ELF and free-drug plasma AUC:MIC ratio targets associated with a 1 $\log_{10}$ cfu reduction from baseline, overlaid on the MIC distribution for *S. pneumoniae*. A tabular summary of percentage probabilities of PK/PD target attainment by MIC for total-drug ELF and free-drug plasma AUC:MIC ratio targets associated with 1 and 2 $\log_{10}$ cfu reductions from baseline for *S. pneumoniae* is provided in Table S1 (available as Supplementary data at *JAC* Online).
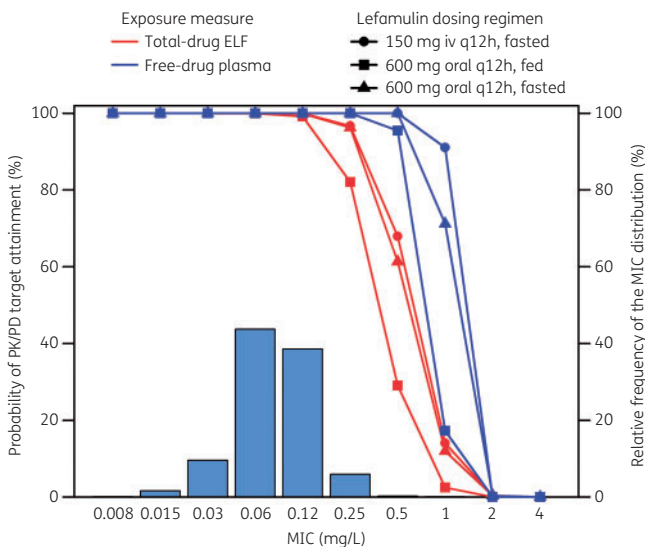
The percentage probability of attaining the total-drug ELF AUC:MIC ratio target associated with a 1 $\log_{10}$ cfu reduction from baseline for *S. pneumoniae* at the MIC_{99} value of 0.25 mg/L was 96.7% for the iv dosing regimen. Percentage probabilities of PK/PD target attainment at the same MIC value were 82.1% and 96.3% for the fed and fasted oral dosing regimens, respectively. At the MIC_{90} value of 0.12 mg/L for *S. pneumoniae*, percentage probabilities of PK/PD target attainment ranged from 99.2% to 100% for the iv and oral dosing regimens. For the free-drug plasma AUC:MIC ratio target associated with the same endpoint and an MIC value of 0.25 mg/L, percentage probabilities were 100% for each dosing regimen.

The percentage probability of attaining the total-drug ELF AUC:MIC ratio target associated with a 2 $\log_{10}$ cfu reduction from baseline for *S. pneumoniae* was 99.2% at an MIC_{90} value of 0.12 mg/L for the iv dosing regimen. Percentage probabilities were 92.3% and 99.2% for the fed and fasted oral dosing regimens, respectively, at the same MIC value. For the free-drug plasma AUC:MIC ratio target associated with the same endpoint and an MIC value of 0.12 mg/L, percentage probabilities were 100% for each dosing regimen.

As shown in Table 3, overall percentage probabilities of PK/PD target attainment based on total-drug ELF or free-drug plasma AUC:MIC ratio targets associated with a 1 $\log_{10}$ cfu reduction from baseline for *S. pneumoniae* were ≥98.3% for the iv and oral (fed and fasted) dosing regimens.

Figure 2. Percentage probabilities of PK/PD target attainment by MIC for lefamulin iv and oral dosing regimens based on the evaluation of the total-drug 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*.
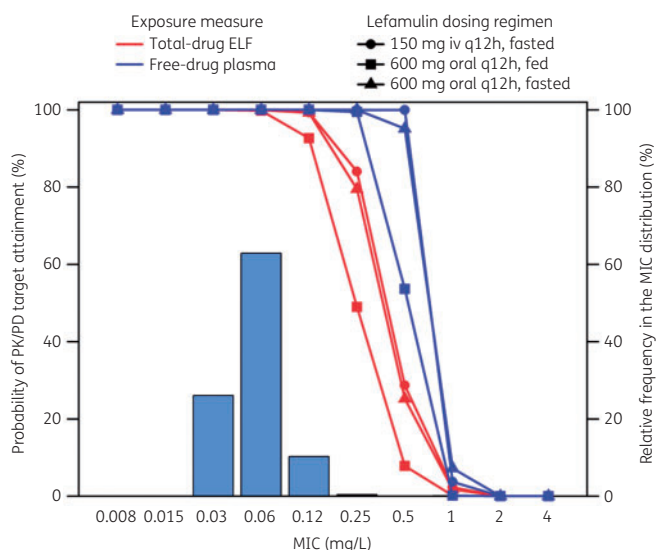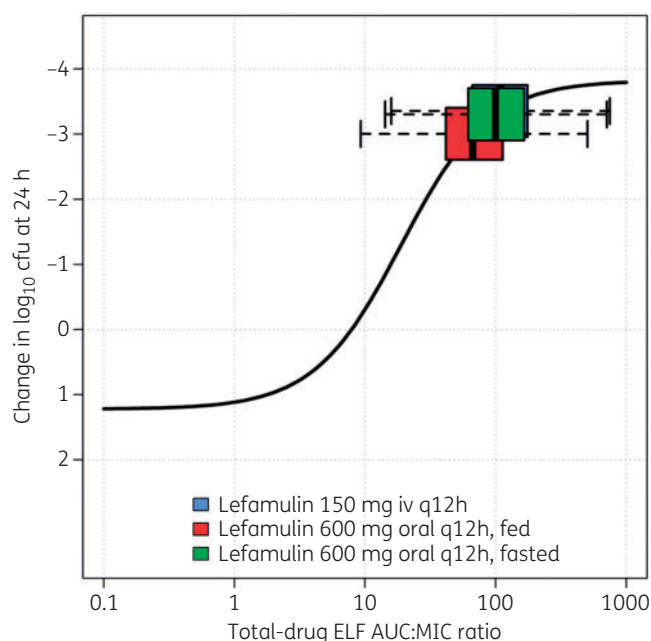

Figure 3. Non-clinical PK/PD relationship for efficacy for *S. pneumoniae*, overlaid with box-and-whisker plots of total-drug ELF AUC:MIC ratios for simulated patients after administration of lefamulin iv and oral dosing regimens. Horizontal box-and-whisker plots of total-drug ELF AUC:MIC ratios for simulated patients after iv and oral (under fed and fasted conditions) dosing regimens are shown overlaid on the PK/PD relationship based on data from a neutropenic murine-lung infection model for *S. pneumoniae*. For each boxplot, the edge of the box represents the 25th and 75th percentiles of the distribution for total-drug ELF AUC:MIC ratio. The line within the box represents the median total-drug ELF AUC:MIC ratio. The whiskers extend to the nearest value among those represented by 1.5×IQR of the box edges, where IQR is the distribution of total-drug ELF AUC:MIC ratio from the 25th to the 75th percentiles. Note: the box-and-whisker plot for the distribution of total-drug ELF AUC:MIC ratios for lefamulin 150 mg iv q12h shown in blue is obscured by that for lefamulin 600 mg orally q12h administered under fasted conditions, shown in green.

target attainment of lefamulin 150 mg iv q12h and 600 mg orally q12h for the treatment of patients with CABP.

The population PK model used for these analyses was developed using a data set that contained 959 plasma concentrations from 20 subjects enrolled in a Phase 1 food-effect study[27] and 144 plasma concentrations and 12 ELF concentrations from 12 subjects enrolled in the Phase 1 tissue penetration study.[28] A three-compartment model with non-linear protein binding and two parallel first-order absorption processes, which was consistent with the results of previous population PK analyses of Phase 1 and 2 data,[29,30] provided precise and unbiased estimates of lefamulin plasma concentration–time profiles. Covariate analyses demonstrated that the absorption rate was slower and bioavailability was decreased after a high-fat/high-calorie meal compared with the fasted condition. When applied to the data from the tissue penetration study, the model provided an unbiased fit to the plasma data after iv administration. The ELF data from these 12 subjects were well described using first-order rate constants into and out of the ELF compartment.

AUC:MIC ratio targets for both *S. pneumoniae* and *S. aureus* were identified using PK/PD relationships for efficacy based on data from a neutropenic murine lung infection model, a model that is appropriate for translations to patients with CABP. AUC:MIC ratio targets associated with a 1 $\log_{10}$ cfu reduction from baseline for *S. pneumoniae* and *S. aureus* represented the model endpoint of focus. This choice is supported by the results of a recent assessment of the relationship between the probability of PK/PD target attainment for antibacterial dosing regimens in patients with pneumonia, including those with CABP, and the probability of obtaining regulatory approval for that same dosing regimen. As described earlier, these data demonstrated that, as the probability of attaining the non-clinical PK/PD target associated with a 1 $\log_{10}$ cfu reduction from baseline increased for a given dosing

regimen, so too did the probability of gaining regulatory approval for that same dosing regimen.[26]

The use of a neutropenic murine lung infection model and the collection of ELF PK from mice (see article in this Supplement entitled 'Pharmacokinetics/pharmacodynamics of lefamulin in a neutropenic murine pneumonia model with *Staphylococcus aureus* and *Streptococcus pneumoniae*'[22]) allowed the estimation of AUC:MIC ratio targets based on drug exposures at the effect site. Given the above-described availability of ELF data from healthy subjects and the ability to estimate ELF exposures in simulated patients, the PK/PD target attainment of lefamulin iv and oral dosing regimens was evaluated based on total-drug ELF exposures and total-drug ELF AUC:MIC ratio targets for efficacy. Although the results of PK/PD target attainment analyses based on both total-drug ELF and free-drug plasma AUC:MIC ratio targets were examined, emphasis was placed on the results for the former. As described previously,[18,31,32] the lack of consideration of effect site exposures can lead to poorly determined dosing regimens and even failure of the drug development programme. As described
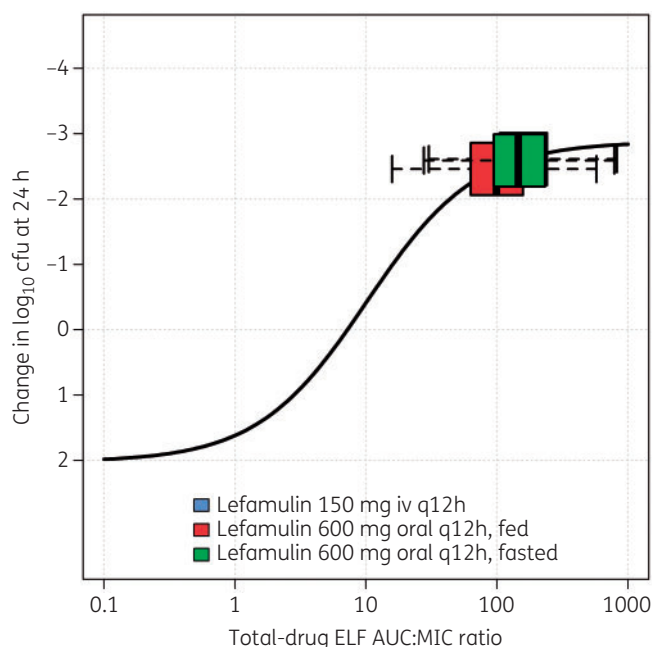
Figure 4. Non-clinical PK/PD relationship for efficacy for *S. aureus*, overlaid with box-and-whisker plots of total-drug ELF AUC:MIC ratios for simulated patients after administration of lefamulin iv and oral dosing regimens. Horizontal box-and-whisker plots of total-drug ELF AUC:MIC ratios for simulated patients after iv and oral (under fed and fasted conditions) dosing regimens are shown overlaid on PK/PD relationship based on data from a neutropenic murine-lung infection model for *S. aureus*. For each boxplot, the edges of the box represent the 25th and 75th percentiles of the distribution for total-drug ELF AUC:MIC ratio. The line within the box represents the median total-drug ELF AUC:MIC ratio. The whiskers extend to the nearest value among those represented by 1.5×IQR of the box edges, where IQR is defined by the distribution of total-drug ELF AUC:MIC ratio from the 25th to the 75th percentiles. Note: the box-and-whisker plot for the distribution of total-drug ELF AUC:MIC ratios for lefamulin 150 mg iv q12h shown in blue is obscured by that for lefamulin 600 mg orally q12h administered under fasted conditions, shown in green.

herein, the results of the analyses for lefamulin based on both exposure measures were similar.

Percentage probabilities of attaining the total-drug ELF AUC:MIC ratio target associated with a 1 log$_{10}$ cfu reduction from baseline for *S. pneumoniae* were ≥99.2% at the MIC$_{90}$ value of 0.12 mg/L and 96.7%, 82.1% and 96.3% for the iv dosing regimen and oral dosing regimens under fed and fasted conditions, respectively, at the MIC$_{99}$ of 0.25 mg/L. For the free-drug plasma AUC:MIC ratio target associated with the same endpoint and an MIC value of 0.5 mg/L, percentage probabilities were ≥95.5% for each dosing regimen. Percentage probabilities of PK/PD target attainment for total-drug ELF and free-drug plasma AUC:MIC ratio targets associated with a 1 log$_{10}$ cfu reduction from baseline for *S. aureus* were also high at the MIC$_{90}$ value of 0.12 mg/L, ranging from 92.7% to 100% for the iv and oral dosing regimens. Overall percentage probabilities of PK/PD target attainment based on total-drug ELF or free-drug plasma AUC:MIC ratio targets associated with 1 and 2 log$_{10}$ cfu reductions from baseline and MIC distributions for each pathogen collected from regions worldwide were ≥98.3%.

Finally, evaluation of fitted functions for the non-clinical PK/PD relationships based on Hill-type models fit to data from the neutropenic murine lung infection models for *S. pneumoniae* and *S. aureus* relative to distributions of total-drug ELF AUC:MIC ratios for simulated patients after administration of lefamulin iv and oral dosing regimens also provided dose selection support. The distribution of simulated total-drug ELF AUC:MIC ratios relative to where maximal bacterial kill is observed on the Hill function is consistent with that observed for other antibacterial agents for which clinical trials demonstrated high rates of efficacy.[33]

In conclusion, results of these analyses provide support for the selection of lefamulin 150 mg iv q12h and 600 mg orally q12h for the treatment of patients with CABP and suggest that doses may not need to be taken under fasted conditions. Future efforts to collect PK data for lefamulin from patients with CABP will enable refinement of the population PK model and confirmation that the lefamulin exposures generated for the simulated patient population receiving the iv and oral dosing regimens, as described herein, reflect those of the target patient population with CABP.

Supplementary data

Tables S1 and S2 are available as Supplementary data at *JAC* Online.

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