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 log10 cfu reductions from baseline.

Results: Percentage probabilities of attaining the total-drug ELF AUC:MIC ratio target for a 1 log10 cfu reduction from baseline for SP were ≥99.2% at the MIC90 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 MIC99 of 0.25 mg/L. Percentage probabilities of attaining the free-drug plasma AUC:MIC target for the same endpoint at the SP MIC99 were 100% for each regimen. For the SA MIC90 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.5 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 class7 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.
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 ‘Pharmacokinetics/pharmacodynamics of lefamulin in a neutropenic murine pneumonia model with Staphylococcus aureus and Streptococcus pneumoniae’) (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 AUC0–24 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 AUC0–24 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’).

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, 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 log10 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.

In vitro surveillance data

The MIC distributions for lefamulin against S. pneumoniae and S. aureus were determined for isolates collected between 2015 and 2016. 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; MIC50 and MIC90 values were 0.06 and 0.12 mg/L, respectively. MIC values for S. aureus isolates ranged from 0.03 to >16 mg/L; MIC50 and MIC90 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’), fitted functions for the relationship between change in log10 cfu from baseline at 24 h and lefamulin total-drug ELF AUC0–24 ratio were generated for each pathogen. Total-drug ELF AUC/MIC ratios for simulated patients were generated by taking the day 1
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\(_{0-24}\) values. The percentage probability of attaining the total-drug ELF AUC\(_{0-24}\) 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\(_{0-24}\):MIC ratios for simulated patients, box-and-whisker plots of total-drug ELF AUC\(_{0-24}\):MIC ratios were then overlaid on the above-described fitted functions.

Table 1. 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) |

The percentage probability of attaining the total-drug ELF AUC\(_{0-24}\) target associated with a 1 log\(_{10}\) cfu reduction from baseline for S. pneumoniae 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\(_{99}\) value of 0.25 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\(_{0-24}\):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.

As shown in Table 3, overall percentage probabilities of PK/PD target attainment based on total-drug ELF or free-drug plasma AUC\(_{0-24}\):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.

Table 1. Summary of AUC\(_{0-24}\) ratio targets for S. pneumoniae and S. aureus efficacy

| Pathogen   | Bacterial reduction endpoint (log\(_{10}\) cfu reduction from baseline) | Median AUC\(_{0-24}\):MIC ratio target\(^a\) |
|------------|-----------------------------------------------------------------------|------------------------------------------|
| S. pneumoniae | 1                                                                      | 14.0                                    |
|            | 2                                                                      | 22.0                                    |
| S. aureus  | 1                                                                      | 21.7                                    |
|            | 2                                                                      | 63.9                                    |

\(^a\)Median AUC\(_{0-24}\):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’).
Figure 2 shows the percentage probabilities of PK/PD target attainment by MIC 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 for *S. aureus*, overlaid on the MIC distribution for *S. aureus*. A tabular summary of the percentage probabilities of PK/PD target attainment by MIC for total-drug ELF and free-drug plasma AUC:MIC targets associated with 1 and 2 log_{10} cfu reductions from baseline for *S. aureus* is provided in Table S2.

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. aureus* was 99.3% at the MIC90 value of 0.12 mg/L for the iv dosing regimen. Percentage probabilities of PK/PD target attainment at the same MIC value were 92.7% and 99.3% for the fed and fasted oral dosing regimens, respectively. For the free-drug plasma AUC:MIC ratio target associated with the same endpoint and MIC value of 0.12 mg/L, percentage probabilities exceeded 90% for the iv and oral fasted dosing regimens but not for the oral fed dosing regimen (76.0%). For the free-drug plasma AUC:MIC ratio target associated with the same endpoint and MIC value of 0.12 mg/L, percentage probabilities were ≥91.9% 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. aureus* were ≥98.5% for the iv and oral (fed and fasted) dosing regimens.

Figures 3 and 4 show the fitted functions for the relationship between change in log_{10} cfu from baseline at 24 h and lefamulin total-drug ELF AUC:MIC ratio, based on Hill-type models fit to data from the neutropenic murine lung infection models for *S. pneumoniae* and *S. aureus*, respectively. As reported previously, the coefficient of determination for each relationship was 0.65 and 0.69, respectively. Horizontal box-and-whisker plots of total-drug ELF AUC:MIC ratios based on day 1 total-drug ELF AUC values for simulated patients after the iv and oral lefamulin dosing regimens and MIC values from the global collection of isolates for each pathogen are shown overlaid on the fitted functions.

### Discussion

The objectives of these analyses were to use 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*’ and a previously developed population PK model (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’), in vitro surveillance data and Monte Carlo simulation to assess the PK/PD

Table 3. Overall percentage probabilities of PK/PD target attainment for lefamulin dosing regimens based on the evaluation of total-drug ELF or free-drug plasma AUC:MIC ratio targets associated with a 1 log_{10} cfu reduction from baseline for *S. pneumoniae* and *S. aureus*

| Pathogen | Exposure matrix | iv | fed | fasted |
|----------|----------------|----|-----|-------|
| *S. pneumoniae* | total-drug ELF | 99.6 | 98.3 | 99.5 |
| *S. aureus* | total-drug ELF | 100 | 99.9 | 100 |
| | free-drug plasma | 99.5 | 98.5 | 99.4 |
| | free-drug plasma | 99.7 | 99.7 | 99.7 |

aBased on the MIC distributions for *S. pneumoniae* or *S. aureus* isolates collected as part of the 2015–16 SENTRY Antimicrobial Surveillance Program from global regions.
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 study and 144 plasma concentrations and 12 ELF concentrations from 12 subjects enrolled in the Phase 1 tissue penetration study. 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, 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 log10 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 log10 cfu reduction from baseline increased for a given dosing regimen, so too did the probability of gaining regulatory approval for that same dosing regimen.

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’) 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 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, 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 previously, the lack of consideration of effect site exposures can lead to poorly determined dosing regimens and even failure of the drug development programme.
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 and oral dosing regimens, respectively, at the MIC_{90} of 0.25 mg/L. For the free-drug plasma and oral dosing regimens under fed and fasted conditions, re-

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.

References
1 File TM, Marrie TJ. Burden of community-acquired pneumonia in North American adults. Postgrad Med 2010; 122: 130–41.
2 Welte T, Torres A, Nathwani D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. Thorax 2012; 67: 71–9.
3 World Health Organization. Antimicrobial Resistance: Global Report on Surveillance. 2014. http://apps.who.int/iris/bitstream/10665/112642/1/9789241564748_eng.pdf.
4 Violi F, Cangemi R, Falcone M et al. Cardiovascular complications and short-term mortality risk in community-acquired pneumonia. Clin Infect Dis 2017; 64: 1486–93.
5 Pfaller MA, Farrell DJ, Sader HS et al. AWARE Ceftaroline Surveillance Program (2008-2010): trends in resistance patterns among Streptococcus
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pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis in the United States. Clin Infect Dis 2012; 55: S187–93.
6 Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States, 2013. https://www.cdc.gov/drugresistance/threat-report-2013/index.html.
7 Paukner S, Riedl R. Pleuromutilins: potent drugs for resistant bugs-mode of action and resistance. Cold Spring Harb Perspect Med 2017; 7: a027110.
8 Sader HS, Paukner S, Ivezic-Schoenfeld Z et al. Antimicrobial activity of the novel pleuromutilin antibiotic BC-3781 against organisms isolated in the community-acquired respiratory tract infections (CARTIs). J Antimicrob Chemother 2012; 67: 1170–5.
9 Sader HS, Biedenbach DJ, Paukner S. Antimicrobial activity of the investigational pleuromutilin compound BC-3781 tested against gram-positive organisms commonly associated with acute bacterial skin and skin structure infections. Antimicrob Agents Chemother 2012; 56: 1619–23.
10 Paukner S, Sader HS, Ivezic-Schoenfeld Z et al. Antimicrobial activity of the pleuromutilin antibiotic BC-3781 against bacterial pathogens isolated in the SENTRY Antimicrobial Surveillance Program in 2010. Antimicrob Agents Chemother 2012; 57: 4489–95.
11 Paukner S, Streit JM, Flamm RK et al. In vitro activity of lefamulin against bacterial pathogens commonly causing acute bacterial skin and skin structure infections (ABSSSI) and bloodstream infections (BSI): global SENTRY surveillance 2016. In: ASM Microbe, Atlanta, GA, USA, 2018. Abstract 6852.
12 Paukner S, Gelone SP, Arends SJR et al. Antibacterial activity of lefamulin against pathogens most commonly causing community-acquired bacterial pneumonia: SENTRY antimicrobial surveillance program (2015–2016). Antimicrob Agents Chemother 2019; doi:10.1128/AAC.02161-18.
13 Alexander E, Goldberg L, Das A et al. Oral lefamulin is safe and effective in the treatment of adults with community-acquired bacterial pneumonia (CABP): results of Lefamulin Evaluation Against Pneumonia (LEAP 2) study. In: IDWeek, San Francisco, CA, USA, 2018. Abstract 74297.
14 File TM Jr, Goldberg L, Das A et al. Efficacy and safety of iv-to-oral lefamulin, a pleuromutilin antibiotic, for treatment of community-acquired bacterial pneumonia: the phase 3 LEAP 1 trial. Clin Infect Dis 2019; doi: 10.1093/cid/ciz090.
15 Craig WA. Pharmacodynamics of antimicrobials: general concepts and applications. In: CH Nightingale, AG Ambrose, GL Drusano, eds. Antimicrobial Pharmacodynamics in Theory and Clinical Practice. New York, NY, USA: Marcel Dekker, 2007; 1–19.
16 Drusano GL, Preston SL, Hardaco C et al. Use of preclinical data for selection of a phase II/III dose for evernimicin and identification of a preclinical MIC breakpoint. Antimicrob Agents Chemother 2001; 45: 13–22.
17 Bhavnani SM, Hammel JP, Cininnone BB et al. Use of pharmacokinetic-pharmacodynamic target attainment analyses to support phase 2 and 3 dosing strategies for doripenem. Antimicrob Agents Chemother 2005; 49: 3944–7.
18 Trang M, Dudley MN, Bhavnani SM. Use of Monte Carlo simulation and considerations for PK-PD targets to support antibacterial dose selection. Curr Opin Pharmacol 2017; 36: 107–13.
19 European Medicines Agency. Guidance on the Use of Pharmacokinetics and Pharmacodynamics in the Development of Antimicrobial Medicinal Products. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/07/WC500210982.pdf.
20 US Food and Drug Administration. Guidance for Industry. Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment. US Department of Health and Human Services. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM123686.pdf.
21 US Food and Drug Administration. Guidance for Industry. Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment. US Department of Health and Human Services. https://www.fda.gov/downloads/Drugs/…/Guidances/ucm071185.pdf.
22 Wicha WW, Strickmann DB, Paukner S. Pharmacokinetics/pharmacodynamics of lefamulin in a neutropenic murine pneumonia model with Staphylococcus aureus and Streptococcus pneumoniae. J Antimicrob Chemother 2019; 74 Suppl 3.
23 Zhang L, Wicha WW, Bhavnani SM et al. Prediction of lefamulin epithelial lining fluid penetration after intravenous and oral administration using Phase 1 data and population pharmacokinetics methods. J Antimicrob Chemother 2019; 74 Suppl 3.
24 Bauer RJ. NONMEM 7, Version 7.1.2. Elicott City, MD, USA: ICON Development Solutions, 2010.
25 Wicha WW, Craig WA, Andes D. In vivo pharmacodynamics of lefamulin, the first systemic pleuromutilin for human use, in a neutropenic murine thigh infection model. J Antimicrob Chemother 2019; 74 Suppl 3.
26 Bulik C, Bhavnani S, Hammel J et al. Relationship between regulatory approval and pharmacokinetic-pharmacodynamic target attainment: focus on community- and hospital-acquired pneumonia. In: 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Denver, CO, USA, 2013. Abstract A-295.
27 Wicha WW, Leil C, Seltzer E et al. Pharmacokinetics and safety of an oral, immediate-release (IR) tablet formulation of lefamulin in fed and fasted healthy subjects. In: ECCMID, Vienna, Austria, 2017. Abstract P1336.
28 Zeitlinger M, Schwameis R, Burian A et al. Simultaneous assessment of the pharmacokinetics of a pleuromutilin, lefamulin, in plasma, soft tissues and pulmonary epithelial lining fluid. J Antimicrob Chemother 2016; 71: 1022–6.
29 Rubino CM, Xue B, Bhavnani SM et al. Population pharmacokinetic analyses for BC-3781 using phase 2 data from patients with acute bacterial skin and skin structure infections. Antimicrob Agents Chemother 2015; 59: 282–8.
30 Rubino CM, Forrest A, Bhavnani SM et al. Population pharmacokinetics of BC-3781 using phase 1 data. In: 50th Interscience Conference on Antimicrobial Agents and Chemotherapy, Boston, MA, USA, 2010. Abstract A1-018.
31 Rodvold KA, Hope WW, Boyd SE. Considerations for effect site pharmacokinetics to estimate drug exposure: concentrations of antibiotics in the lung. Curr Opin Pharmacol 2017; 36: 114–23.
32 Ambrose PG, Bhavnani SM, Ellis-Grosse EJ et al. Pharmacokinetic-pharmacodynamic considerations in the design of hospital-acquired or ventilator-associated bacterial pneumonia studies: look before you leap! Clin Infect Dis 2010; 51: S103–10.
33 Ambrose PG. Antibacterial drug development program successes and failures: a pharmacometric explanation. Curr Opin Pharmacol 2017; 36: 1–7.