Penetration of ceftaroline into epithelial lining fluid in healthy adult subjects

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16 **Abstract** [unstructured, 250 words]

17 Ceftaroline, the active metabolite of the prodrug ceftaroline fosamil, is a cephalosporin with
18 bactericidal activity against Gram-positive organisms including methicillin-resistant
19 *Staphylococcus aureus* (MRSA). This study aimed to (i) evaluate ceftaroline concentrations in
20 human plasma and epithelial lining fluid (ELF) and (ii) develop a population pharmacokinetic
21 (PK) model for plasma and ELF to be used in PK/pharmacodynamic (PD) target attainment
22 simulations. Ceftaroline concentrations in ELF and plasma at steady-state (Day 4) were
23 measured in healthy adult subjects for two dosages: 600mg q12h; 600mg q8h. Both were well
24 tolerated with no serious adverse events. The penetration of free ceftaroline into ELF, assuming
25 20% protein binding in plasma, no protein binding in ELF, was ≈23%. The population PK
26 model utilized a two-compartment model for both ceftaroline fosamil and ceftaroline.
27 Goodness-of-fit criteria revealed the model was consistent with observed data and no systematic
28 bias remained. At 600mg q12h and an MIC of 1 mg/L, 98.1% of simulated patients would be
29 expected to achieve a target *f*T >MIC in plasma of 42% and in ELF 81.7% would be expected to
30 achieve a target *f*T >MIC of 17%; at 600mg q8h, 100% were predicted to achieve a *f* T >MIC in
31 plasma of 42%, and 94.7% to achieve a *f* T >MIC of 17% in ELF. The literature and data
32 suggest the 600mg q12h dose is adequate for MICs ≤1 mg/L. There is a need for clinical data in
33 patients with MRSA pneumonia and data to correlate PK/PD relationships in ELF with clinical
34 outcomes.

35 Keywords: Ceftaroline, pharmacokinetics, ELF

36

Introduction

Ceftaroline, the active metabolite of the prodrug ceftaroline fosamil, is a cephalosporin antibiotic with bactericidal activity against Gram-positive organisms, including penicillin-resistant *Streptococcus pneumoniae* and methicillin-resistant *Staphylococcus aureus* (MRSA) (1, 2). Ceftaroline is also active in vitro against Gram-negative organisms such as *Haemophilus influenzae* and *Moraxella catarrhalis* and non-extended-spectrum β-lactamase-producing Enterobacteriaceae (1, 2). Ceftaroline fosamil is approved in the United States for the treatment of acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP), with approval in Europe for similar indications. At a dosage of 600 mg q12h, ceftaroline fosamil demonstrated non-inferiority to ceftriaxone given at 1 g q24h, in the treatment of patients with moderate to severe CABP in two Phase 3 clinical studies (clinicaltrials.gov identifiers: NCT00621504, NCT00509106) (3–5). Ceftaroline fosamil (600 mg q12h) has also been demonstrated to be superior to ceftriaxone (2 g q24h) in the treatment of Asian patients with community-acquired pneumonia (NCT01371838) (6), and in a recent meta-analysis ceftaroline fosamil was shown to be superior to ceftriaxone as empirical treatment for adult patients hospitalized with PORT risk class 3–4 community-acquired pneumonia (7). Ceftaroline fosamil has a favorable safety profile consistent with the cephalosporin class of antibiotics.

The MIC_{90} for ceftaroline against MRSA is 1 mg/L in the United States (1, 8, 9). Phase 3 clinical trials for ceftaroline fosamil in the treatment of CABP did not include *S. aureus* isolates with ceftaroline MICs of ≥1 mg/L and patients with suspected MRSA were excluded because ceftriaxone, the comparator in the clinical trials, is not active against MRSA. To assess whether

ceftaroline concentrations in the lung are adequate to cover the MIC_{90} of ceftaroline against MRSA, animal model studies of pneumonia were conducted along with a Phase 1 study to measure ceftaroline concentrations in human epithelial lining fluid (ELF). In these studies the free drug concentrations above the MIC (*f*T > MIC) was the pharmacokinetic/pharmacodynamic (PK/PD) index of interest, as with other β-lactams it is the index that correlates with efficacy for ceftaroline. In the mouse lung infection model, ceftaroline fosamil, at a human simulated dose of 600 mg q12h, was effective against *S. aureus*, the majority of which were MRSA, at MICs up to 4 mg/L (**10**). In this model, a 1-log_{10} reduction in bacterial densities after 24h was associated with free drug concentrations being above the MIC in serum for 41% of the dosing interval, and a *f*T > MIC of 16% in serum was associated with stasis. Concentrations of ceftaroline in ELF in this model were similar to serum concentrations, resulting in similar *f*T > MIC values in serum and ELF. In a rabbit model of necrotizing pneumonia, which used a panton valentine leukocidin (PVL)-positive MRSA strain with ceftaroline MIC of 1 mg/L, ceftaroline fosamil at a human simulated plasma exposure of 600 mg q12h was shown to be effective, significantly (p=0.0001) reducing bacterial titers after 48h antibiotic treatment in the lungs and spleens when compared with the control group (no antibiotic treatment) (**11**).

Presented here are data from a pharmacokinetic study in healthy adult subjects. The concentrations of ceftaroline in ELF and plasma at steady-state were measured for two ceftaroline fosamil dosage regimens (600 mg q12h and 600 mg q8h). Safety and tolerability were also assessed. These data were then used to develop a population pharmacokinetic (PK) model for ceftaroline concentrations in plasma and ELF. The population PK model was used to conduct simulations to assess the likelihood of achieving, in patients with CABP, PK/PD targets that had been previously derived from mouse lung infection models.

Methods

In this Phase 1, open-label, multiple-dose study, 53 healthy subjects were randomly assigned to receive ceftaroline fosamil IV 600 mg either as a 1-hour infusion q12h for 3 days with a single dose on Day 4 or as a 1-hour infusion q8h for 3 days with a single dose on Day 4. Subjects participated in the study for 6 days (from Day -1 to Day 5 when the last pharmacokinetic sample was taken).

The study was approved by the Institutional Review Board at the study site (Pulmonary Associates; Phoenix, AZ). All subjects provided a signed informed consent form prior to any study procedures. The study complied with the International Conference on Harmonization Guidance on General Considerations for Clinical Trials, Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals, and Good Clinical Practice: Consolidated Guidance.

Inclusion and exclusion criteria

Subjects were healthy males or females between 18 and 45 years of age, with a body mass index of 18–30 kg/m^2, a supine pulse rate of 50–100 bpm, and were non-smokers (defined as never smoked or have not smoked within the previous 2 years). Female subjects had negative pregnancy tests. All subjects were required to use an effective method of contraception unless, for male subjects, they had been sterilized for a least 1 year before the start of the study or, for female subjects, they had been postmenopausal for 2 years or had tubal ligation or a hysterectomy.

Exclusion criteria included known hypersensitivity to ceftaroline or other β-lactam antimicrobial. Subjects were also excluded if they had clinically significant disease, or any abnormal or clinically significant finding on physical examination, medical history, serum chemistry, or ECG. Other exclusion criteria included supine systolic blood pressure of ≥ 140 mmHg or ≤ 90 mmHg, or supine diastolic blood pressure of ≥ 90 mmHg or ≤ 50 mmHg, as well as a positive test for HIV, hepatitis B or hepatitis C.

Sample collection and analysis

Blood samples for plasma pharmacokinetic analysis were collected from all subjects at the following time points relative to the start of the infusion on Day 4: pre-dose, during infusion at 30 and 60 min (immediately before end of infusion) and after infusion at 65 and 75 min, and 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 h. Subjects were randomly assigned to undergo bronchoalveolar lavage (BAL) for ELF collection at one of five time points (five subjects at each time point) after the last dose on Day 4: 1, 2, 4, 8, and 12 h for subjects receiving 600mg q12h and 1, 2, 4, 6, and 8 h for subjects receiving 600 mg q8h. Blood was collected into tubes containing 15 mg of sodium fluoride and 12 mg of potassium oxalate as anticoagulants.

To collect the plasma, blood samples were centrifuged within 30 mins of collection. Plasma samples were immediately flash-frozen in an isopropyl alcohol/dry ice bath and stored at -70ºC until analysis for determination of ceftaroline, ceftaroline fosamil, and ceftaroline M-1 (inactive, open-ring metabolite) concentrations.

To collect the BAL samples, topical lidocaine was used for local anesthesia. A fiber-optic bronchoscope was inserted and guided to the area of the right middle lobe bronchus. First a

50mL aliquot of sterile normal saline (0.9% wt/vol) was instilled through the bronchoscope, aspirated and discarded to prevent contamination of the lavage specimens from larger airway secretions. Then the instillation was repeated three times and these samples were pooled, immediately placed on ice, centrifuged, flash frozen and stored at -70ºC until analysis for determination of ceftaroline, ceftaroline fosamil, ceftaroline M-1, and urea concentrations was done.

Determination of ELF final concentrations

As BAL results in a dilution of ELF in the BAL fluid, ELF concentrations of ceftaroline, ceftaroline fosamil, and ceftaroline M-1 were calculated from concentrations in BAL fluid using the urea dilution method (12). Urea concentrations in plasma and BAL fluid were determined using validated LC-MS/MS methods. Concentrations of ceftaroline, ceftaroline fosamil, and ceftaroline M-1 in ELF were then determined by multiplying the concentration of each analyte in BAL fluid by the ratio of the concentration of urea in plasma to the concentration of urea in BAL fluid to correct for dilution.

The percentage penetration of free ceftaroline into ELF was calculated assuming 20% protein binding in plasma and no protein binding in ELF (13).

Determination of urea concentration

Determinations of urea concentrations in plasma and BAL were carried out at High Standard Products (now Keystone Bioanalytical) (North Wales, PA).

In plasma. Urea in plasma samples was isolated using protein precipitation with methanol. A 50 µL sample was centrifuged and the supernatant diluted in mobile phase (90:10 methanol:water). A 10 µL sample was analyzed by LC/MS-MS, using a Phenomenex Partisil 5 SI column (100 x 4.6 mm with 5-µm particle size), mobile phase flow rate of 0.7 mL/min under isocratic conditions, and positive polarity, to monitor for urea (*m/z* 61 → 44), and urea-$^{13}C,^{15}N_2$ (*m/z* 64 → 46). The lower limit of quantification for urea was 100 µg/mL and the upper limit was 3000 µg/mL. The precision of urea calibration standards in human plasma ranged from 0.82% to 2.19%, while the accuracy ranged from -1.57% to 1.53%. The precision for urea quality control samples ranged from 0.80% to 6.66%, and the accuracy from -5.97% to -1.60%.

In BAL fluid. A 100-µL sample of BAL fluid was diluted in mobile phase (0.02 N ammonium hydroxide in 75:25 methanol:water) and then injected (10 µL) into the LC/MS-MS. The system used a Thermo BDS Hypersil C18 column (100 x 3 mm with a 3-µm particle size), and flow rate of 0.4 mL/min under isocratic conditions. The ions monitored were urea (m/z 61 → 44) and urea-13C,15N2 (m/z 64 → 46). The limits of quantification for urea ranged from 0.2 µg/mL to 10 µg/mL. The precision of urea calibration standards ranged from 1.28% to 4.43%, while the accuracy ranged from -1.86% to 4.67%. The precision for urea quality control samples ranged from 1.59% to 3.17%, and the accuracy at all concentrations ranged from -8.21% to -0.46%.

Determination of drug concentration

Determinations of drug concentration were carried out at Forest Laboratories (New York, NY).

In plasma. Equal amounts (50 µL) of plasma sample and internal standard solution (10/10/10 µg/mL [$^2H_3$] ceftaroline/[$^2H_3$] ceftaroline fosamil/[$^2H_3$] ceftaroline M-1) were mixed and chilled methanol was added to precipitate the protein. The mixture was centrifuged and the supernatant

mixed with 20 mM ammonium formate and centrifuged again. 15 µL aliquots were injected into the LC-MS/MS, with a Waters Atlantis dC18 column (150 x 2.1 mm, 5-µm particle size), mobile phase of 100 mM ammonium formate (pH 3.25):water:methanol:isopropyl alcohol (100:780:80:40, v/v/v/v), and flow rate of 0.6 mL/min. Detection of analytes was by electrospray ionization (ESI) mass spectrometry with multiple reaction monitoring (MRM) of positive ion. The MRM used precursor → product ions of *m/z* 685.0 → 208.0, *m/z* 605.0 → 209.0, *m/z* 623.1 → 209.0, *m/z* 688.0 →211.0, *m/z* 608.1 → 212.0, and *m/z* 626.1 → 212.0 to monitor ceftaroline fosamil, ceftaroline, ceftaroline M-1, and their internal standards, [$^2H_3$] ceftaroline fosamil, [$^2H_3$] ceftaroline, and [$^2H_3$] ceftaroline M-1, respectively. Quantification was determined from the ratios of the analyte peak areas to their respective internal standard.

The range of quantification was 50–50,000 ng/mL for ceftaroline and 50–10,000 ng/mL for ceftaroline fosamil and ceftaroline M-1. In human plasma the precision and accuracy of ceftaroline standards were within 2.4% and ± 5.1%, respectively, for ceftaroline fosamil they were within 3.1% and ± 6.5%, respectively; and for ceftaroline M-1 were within 1.8% and ± 3.1%, respectively. The precision and accuracy of ceftaroline, ceftaroline fosamil, and ceftaroline M-1 quality control samples were within 4.6% and ± 9.4%, 3.8% and ± 7.7%, and 4.3% and ± 2.2% (including outliers), respectively.

In BAL fluid. The 50 µL BAL fluid sample was mixed with internal standard spiking solution (12.5/1.25/1.25 ng/mL [$^2H_3$] ceftaroline/[$^2H_3$] ceftaroline fosamil/[$^2H_3$] ceftaroline M-1) and the resulting solution was injected into the LC-MS/MS. The system used a Zorbax SB-C18 column (75 x 4.6 mm, 3.5-µm particle size) at 45°C, mobile phase of 100 mM ammonium formate buffer (pH 3.25):methanol:isopropanol:water (300:200:100:1400, v/v/v/v) and flow rate of 0.5 mL/min under isocratic conditions. Analytes were detected by ESI mass spectrometry with

MRM of positive ions. The precursor → product ions of *m/z* 605.3 → 209.0, *m/z* 685.4 → 208.0, *m/z* 623.2 → 209.0, *m/z* 608.1 → 212.0, *m/z* 688.2 → 211.0, and *m/z* 626.1 → 212.0 were used to monitor ceftaroline, ceftaroline fosamil, ceftaroline M-1 and their internal standards, [$^2H_3$] ceftaroline, [$^2H_3$] ceftaroline fosamil, and [$^2H_3$] ceftaroline M-1, respectively. As above, quantification was determined from the ratios of the analyte peak areas to their respective internal standard.

The range of quantification was 1–1,000 ng/mL for ceftaroline and 1–100 ng/mL for ceftaroline fosamil and ceftaroline M-1. In BAL fluid the precision and accuracy of ceftaroline standards were within 6.4% and ± 4.2%, respectively, for ceftaroline fosamil were within 8.0% and ± 3.9%, respectively, and for ceftaroline M-1 were within 7.7% and ± 2.7%, respectively. The precision and accuracy of ceftaroline, ceftaroline fosamil, and ceftaroline M-1 quality control samples were within 9.9% and ± 3.6%, 10.0% and ± 3.8%, and 9.4% and ± 7.7% (including outliers), respectively.

Determination of pharmacokinetic parameters

The parameters describing the pharmacokinetics of ceftaroline, ceftaroline fosamil, and ceftaroline M-1 in plasma and ELF were determined using non-compartmental analysis with Phoenix WinNonlin (version 6.1; Pharsight, Princeton, NJ) software. Area under the concentration-time curve (AUC) parameters were calculated by numeric integration using the linear trapezoidal rule in Phoenix WinNonlin. Elimination rate constants were determined by performing a regression analysis on the terminal linear phase of semilogarithmic plots of individual concentration-time data. A minimum of at least 3 points in the terminal phase were

208 required for the analysis. Concentrations below the limit of quantification were treated as 0 for
209 all noncompartmental PK calculations.

210 Plasma PK parameters were determined for each subject. However, because only one ELF
211 sample was collected per subject, PK parameters in ELF were based on a composite
212 concentration-time profile consisting of median ELF concentrations across subjects at each of
213 the five BAL time points.

214 **Safety analysis**

215 Adverse events were recorded from the time of signing the informed consent form until 30 days
216 after the last dose of ceftaroline fosamil.

217 Measurements of vital signs were carried out at screening, before the start of and end of each
218 infusion, at intervals after dosing and at the end of the study. Blood and urine samples were
219 obtained at screening and at the end of the study. A physical examination and standard 12-lead
220 ECG was also completed at these time points.

221 **Population pharmacokinetics in the lung**

222 The plasma and ELF concentration data from the current study were used to develop a
223 population PK model to describe the disposition of ceftaroline in the lung. For modeling of
224 plasma, a structural model previously developed for ceftaroline fosamil and ceftaroline based on
225 data from 10 Phase 1, one Phase 2, and four Phase 3 studies was used as a starting point (14).
226 No additional covariate modeling was performed beyond the covariates already specified in the
227 previous population PK model. However, some covariate effects and structural parameters were

fixed to their values from the original model because the data from the ELF study did not contain information on these parameters. For example, there were only healthy subjects in the ELF study, no subjects had end-stage renal disease or were on dialysis, no subjects had CrCL < 80 mL/min, and no subjects were over the age of 45.

Population PK analyses were conducted via nonlinear mixed-effects modeling with a qualified installation of the nonlinear mixed-effects modeling (NONMEN) software, version 7, level 2.0 (ICON Development Solutions, Hanover, MD). The first-order conditional estimation with η-ε interaction (FOCEI) was employed for all model runs. Concentrations that were below the limit of quantification (BQL) were ignored during the estimation process after demonstrating that ignoring BQLs had no effect when evaluating models that included BQL data using the M3 method (15). Model selection was driven by the data and guided by various goodness-of-fit criteria, including diagnostic scatter plots, plausibility of parameter estimates, precision of parameter estimates, and correlation between model parameter estimation errors <0.95. Final model parameter estimates were reported with a measure of estimation uncertainty (NONMEM 95% confidence intervals). A predictive check model evaluation step was performed to assess the performance of the final model and to assess the suitability of the final model for simulation.

Simulations to assess PK/PD target attainment

The final combined population PK model for plasma and ELF for ceftaroline fosamil and ceftaroline was used to simulate plasma and ELF concentration-time data to evaluate the effect of a variety of doses, dosing intervals, and infusion lengths on % *f*T>MIC in plasma and ELF. For each treatment, concentration-time profiles for 1000 patients (with normal renal function) were simulated at steady state. Covariances between age, weight and nCRCL were determined

from ceftaroline data from CABP Phase 3 clinical trials (NCT00621504, NCT00509106) and used to simulate a range of data across a multivariate normal distribution. The % *f*T>MIC in plasma and ELF for a range of MICs (0.125, 0.25, 0.5, 1, and 2 mg/L) were determined for each simulated patient. The percentage of patients greater than or equal to a set of %*f*T > MIC target values (17%, 20%, 25%, 40%, 42%, 45%, and 50%) were summarized.

Results

A total of 53 subjects were enrolled with 50 completing the study (25 subjects in each treatment group). A summary of demographics of enrolled subjects is shown in Table 1.

Pharmacokinetics in bronchial ELF and plasma

Ceftaroline fosamil was rapidly converted to ceftaroline and the maximum concentration of ceftaroline in plasma was achieved before the end of infusion in both treatment groups (Supplemental Figure 1). PK parameters could therefore not be determined for the pro-drug, ceftaroline fosamil. Maximum concentrations of ceftaroline occurred around the end of the infusion of ceftaroline fosamil in both plasma and ELF, and ceftaroline was eliminated from ELF and plasma at a similar rate (Table 2). In both treatment groups the percentage penetration of free ceftaroline into ELF, assuming 20% protein binding in plasma and no protein binding in ELF, was approximately 23% (Table 2). Exposure of the inactive metabolite ceftaroline M-1 was about 20-25% of the exposure to ceftaroline in both plasma and ELF (based on AUC, data not shown).

The concentrations of ceftaroline in plasma and ELF over time, after the last dose of ceftaroline fosamil, are shown in Table 3 and Figure 1. All subjects had measurable ceftaroline concentrations in plasma and ELF at 1, 2, and 4 hours. At 8 hours all subjects had a measureable ceftaroline concentration in plasma and the concentrations of ceftaroline in ELF exceeded 1 mg/L at 1 and 2 h in both treatment groups. For subjects receiving 600 mg q12h, 4/5 subjects had measurable concentrations in ELF at 8 hours. The same result was seen for subjects receiving 600 mg q8h with 4/5 subjects having measureable concentrations of ceftaroline in

277 ELF at 8 hours. Ceftaroline was not measurable in the ELF of the five subjects who underwent
278 BAL at 12 h.

279 **Safety and tolerability**

280 Three subjects withdrew from the study because of adverse events, all of which were mild to
281 moderate in intensity and resolved without treatment when ceftaroline fosamil was stopped. One
282 subject, who received ceftaroline 600 mg q12h, withdrew because of emesis after receiving two
283 full doses and one partial dose. The other two subjects both received ceftaroline 600 mg q8h:
284 one withdrew following one full and one partial dose because of emesis, light-headedness and
285 headache, and the second withdrew because of hypersensitivity (rhinorrhea and dry cough) on
286 Day 1, after receiving one partial dose of ceftaroline fosamil.

287 Treatment-emergent adverse events (TEAE) were reported for 11/26 (42.3%) subjects receiving
288 600 mg q12h and 10/27 (37.0%) subjects receiving 600 mg q8h. The most common TEAE were
289 headache (five subjects) and nausea (four subjects). No severe or serious adverse events were
290 reported.

291 There were no clinically significant vital sign abnormalities, no abnormal physical examination
292 findings, or abnormal ECG measurements. Changes in clinical laboratory values were minor.

293 **Population pharmacokinetics in the lung**

294 PK data from the 50 healthy subjects that completed the ELF study contributed 856 measurable
295 plasma concentrations (210 ceftaroline fosamil and 646 ceftaroline) and 49 measurable ELF
296 concentrations (6 ceftaroline fosamil and 43 ceftaroline) for inclusion in the population PK

297 analysis. The study population consisted of 42 males and eight females with ages ranging from
298 20 to 45 years and weights ranging from 58 to 102 kg. The population PK model for ceftaroline
299 fosamil and ceftaroline developed previously was applied to the data from the present study.
300 The updated model utilized a two-compartment model for ceftaroline fosamil and a two-
301 compartment model for ceftaroline. The parameters of the population PK model included
302 ceftaroline fosamil and ceftaroline clearance (CLcf and CLc, respectively), ceftaroline fosamil
303 and ceftaroline central volume of distribution (Vccf and Vcc, respectively), intercompartmental
304 clearance for central and peripheral compartment for ceftaroline fosamil and ceftaroline (Q1cf
305 and Qc, respectively), the peripheral volume of distribution for ceftaroline fosamil and
306 ceftaroline (Vp1cf and Vpc, respectively), and the absorption rate constant for ceftaroline
307 fosamil (ka1cf). Population PK parameters are shown in full in Supplemental Table 1 and model
308 equations are provided in Supplemental Equation 1. The model included effects of creatinine
309 clearance (normalized by body surface area, nCRCL) for those subjects with a nCRCL of less
310 than 80 mL/min, age, and patient status (patients with an infection versus healthy subjects) on
311 CLc; and the effect of patient status on Vcc.

312 A review of the ceftaroline plasma and ceftaroline ELF concentrations demonstrated that they
313 declined in a parallel manner (Figure 1) indicating that an additional distribution compartment
314 for ELF would likely not be appropriate and would not be identifiable. Due to this parallel
315 decline, the final population PK model was adjusted to allow the ELF concentrations to be part
316 of the ceftaroline central compartment with a partition coefficient accounting for the distribution
317 into ELF. The parameter describing the distribution of ceftaroline into ELF had a point estimate
318 (95% CI) of 0.193 (0.171, 0.215) indicating that ceftaroline ELF concentrations were
319 approximately 20% of total drug concentration in the plasma and 25% of the free drug

concentrations in plasma. This is consistent with the percentage of ELF penetration calculated with PK parameters derived from noncompartmental analysis.

The combined ceftaroline fosamil and ceftaroline population PK ELF model provided a good description of the observed data. Goodness-of-fit criteria revealed that the model was consistent with the observed data and no systematic bias remained. Observed ceftaroline concentrations in plasma and ELF versus population predictions and individual predictions are shown in Figure 2. Visual predictive checks for ceftaroline plasma concentrations are shown in Supplemental Figure 2 (q12h regimen) and Figure 3 (q8h regimen), and demonstrate that the majority of observed data fall within the 90% prediction intervals for each dosing regimen.

Simulations to assess PK/PD target attainment

The percent of simulated subjects achieving %*f* T > MIC targets in plasma and ELF at MICs of 0.125 – 2 mg/L are given in Table 4 and Table 5, respectively. At an MIC of 1 mg/L for subjects receiving 600 mg q12h, more than 98% of simulated patients would be expected to achieve a target *f*T > MIC in plasma of 42% (Table 4), which was associated with 1-log kill of *S. aureus* in the murine lung infection model, and 100% of simulated patients would achieve 17% *f*T>MIC, which was associated with stasis. Approximately 82%, 71%, and 14% of simulated patients would be expected to achieve target *f*T > MIC values of 17%, 20%, and 42%, respectively, in ELF (Table 5). In the case of subjects receiving 600 mg q8h, all subjects (100%) were predicted to achieve a *f* T > MIC value in plasma of 42% for an MIC of 1 mg/L (Table 4), and 95%, 91%, and 53% were predicted to achieve target *f*T > MIC values of 17%, 20%, and 42%, respectively, in ELF (Table 5).

Discussion

Ceftaroline fosamil, at a dosage of 600 mg q12h, has been shown to be effective in the treatment of CABP (3–6). A meta-analysis of three randomized, active controlled, double blinded clinical studies showed the superiority of ceftaroline fosamil at a dosage of 600 mg q12h over ceftriaxone for the treatment of CABP (7).

The data presented in this report demonstrate that ceftaroline, when administered as ceftaroline fosamil at a dose of 600mg q12h or q8h, is able to penetrate into ELF and that the concentrations of ceftaroline in ELF are higher than the MIC_{90} for ceftaroline against MRSA in the US (1 mg/L) at 1 and 2 hours after the start of infusion in healthy subjects. Both treatment regimens were well tolerated with no serious adverse events reported.

Ceftaroline rapidly penetrated into ELF with maximum concentrations occurring at the end of infusion, and was eliminated from ELF at a similar rate to its elimination from plasma. The penetration of ceftaroline into human ELF relative to plasma was approximately 23% which is similar to that reported for other β-lactams (16–18). This result was in agreement with the simultaneous population PK analysis of the plasma and ELF data.

In a murine model of staphylococcal pneumonia Bhalodi et al. showed that a *f*T>MIC of 42% was required for a 1 $\log_{10}$ kill of *S. aureus* and 17% *f*T>MIC was associated with stasis, with concentrations of ceftaroline in ELF similar to the concentrations in serum (10). These values are consistent with PK/PD targets reported in other studies that were associated with efficacy of ceftaroline against *S. aureus*. For example, Keel et al. found that *f*T>MIC in serum of approximately 20% to 30% was needed for a 1 $\log_{10}$ CFU/mL reduction in bacterial density

when studying human simulated exposures of 600 mg q12h ceftaroline fosamil in the murine thigh infection model (19). This model utilized a broad range of MSSA and MRSA isolates with ceftaroline MICs of 0.125 to 4 mg/L. In another murine thigh infection model against *S. aureus*, Andes and Craig showed that 33% and 26% *f*T>MIC in serum were required for 1-log kill and stasis, respectively (20), and an in vitro model presented by MacGowan et al. reported 28% and 24.5% *f*T>MIC for a 1-log kill and stasis, respectively (21). Since the work of Bhalodi et al was the only nonclinical lung infection model with ceftaroline that also measured serum and ELF concentrations, this work was used as the basis for target attainment simulations in the current analyses.

Based on simulations using the population PK model described herein, at a ceftaroline fosamil dose of 600 mg q12h, more than 98% of patients would be expected to achieve a target plasma *f*T>MIC of 42% for *S. aureus* with an MIC of 1 mg/L, and more than 80% of patients would achieve the mouse stasis target in ELF (17%) at an MIC of 1 mg/L. For the 600 mg q8h dose, 100% of simulated patients were predicted to achieve an *f* T > MIC value in plasma of 42% at an MIC of 1 mg/L, and 95% were predicted to achieve a *f* T > MIC value of 17% in ELF at an MIC of 1 mg/L. The clinical significance of this difference in predicted target attainment in ELF with the q8h as compared with the q12h dosing regimen remains uncertain. In addition, there are currently no clinical data to suggest whether stasis or 1-log kill PK/PD targets in ELF derived from animal models are more appropriate for predicting clinical outcomes in CABP patients.

An in vitro pharmacodynamic model simulating ELF concentrations of ceftaroline following the 600 mg q12h and 600 mg q8h doses demonstrated efficacy for both regimens against *S. aureus*; however 600 mg q8h demonstrated greater antibacterial activity compared with ceftaroline 600 mg q12h (22). Monte Carlo simulations of q12h administration of ceftaroline fosamil conducted

by Justo et al using a population PK model developed with data from normal weight to obese healthy subjects found that in the case of MRSA the cumulative fractions of response were >90% for 30% and 40% *f*T>MIC targets, and 87.5% was predicted for 50% *f*T>MIC (23). The study concluded that the 600 mg q12h regimen was adequate against most clinical isolates; however, more frequent dosing (i.e. q8h) or the use of combination therapy may be more suitable for serious, deep seated, infections due to MRSA. In addition, a literature based analysis of pharmacokinetic and microbiological data by Canut et al. concluded that in patients with normal renal function 600 mg q12h should be adequate to treat CABP caused by a number of organisms, including MSSA (24). However, in the case of MRSA they concluded that ceftaroline fosamil at 600 mg q8h as a 2h infusion may be more appropriate.

A dosing regimen of 600 mg q8h has been shown to be effective and well-tolerated in a prospective clinical trial (NCT01499277) of patients with acute bacterial skin and skin structure infections (25). In a comparison of the results from that study with studies administering ceftaroline fosamil every 12 hours (NCT00424190, NCT00423657), the efficacy of ceftaroline fosamil administered every 8 hours was demonstrated to be comparable to that observed in patients to whom ceftaroline fosamil was administered every 12 hours, including those infected with MRSA (26).

Although PK/PD target attainment in ELF was < 90% for the 600 mg q12h dose, it should be noted that PK/PD targets in ELF have not to date been shown to be correlated with clinical or microbiological outcomes in patients with pneumonia in clinical studies. In contrast, the more meaningful relationships have been shown to occur between PK/PD targets derived from plasma data and clinical outcomes in CABP and hospital acquired pneumonia (HAP)/ventilator associated pneumonia (VAP) (27–29). In addition, Kiem & Schentag have reported that plasma

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PK/PD indices can be an effective surrogate when concentrations at the site of infection, such as ELF, are not available (30). However, when an antibiotic has no detectable concentration in ELF, such as daptomycin, it should not be used to treat pulmonary infections (31).

Another factor to consider when interpreting the ELF data is methodology limitations. The use of BAL to determine ELF drug concentrations is a commonly used approach; however, large differences in antibiotic ELF concentrations using this method have been observed (32, 33). Using results from healthy subjects may also underestimate antibiotic concentrations at the site of infection, because penetration of antibiotics into the lung of pneumonia patients may be higher as a result of the increased permeability of inflamed lung tissue (32, 34). The methodology used to evaluate antibiotic concentrations in the lung continues to develop and serves as a valuable tool in evaluating antibiotics for the treatment of pneumonia. To date exposure-response relationships between PK/PD indices and patient outcomes in pneumonia are limited to PK/PD targets based on plasma concentrations (27).

The efficacy of ceftaroline 600 mg q12h has been demonstrated in pivotal clinical studies of ceftaroline fosamil in patients with CABP (3-6); however, ceftaroline has yet to be evaluated in a controlled clinical trial in patients with CABP associated with MRSA infections. A number of reports in the literature specifically looked at respiratory infections due to MRSA and provide further support for the 600 mg q12h dose of ceftaroline fosamil. Results from CAPTURE, a registry study of adult patients treated with ceftaroline fosamil, gave a clinical success rate of 66% (42/64) for patients with CABP due to MRSA and 74% (17/23) for patients with CABP due to MSSA (35). The majority of patients (>75%) received ceftaroline fosamil 600mg q12h. In a study of CAPTURE data from patients with MRSA HAP or VAP the clinical success rate was 57.9% (11/19) (36). An analysis of more recent data from CAPTURE reported a clinical

success rate of 62% (13/21) for patients with MRSA HAP or VAP (37). Most patients in this study (93%) received ceftaroline fosamil every 12 h. In addition, in a case series, ceftaroline fosamil at 600 mg q12h showed efficacy in patients with nosocomial pneumonia due to MRSA, with clinical success achieved in 6/10 patients (38). Three patients expired due to non-infectious causes, and one patient relapsed.

In summary, the current study demonstrates that ceftaroline penetrates into ELF and achieves maximum concentrations above the MIC_{90} of MRSA when administered either every 12 or every 8 hours. While predicted target attainment in ELF versus *S. aureus* at an MIC of 1 mg/L is somewhat higher with q8h administration, the clinical significance of this finding is uncertain. Taking into consideration the demonstrated efficacy of ceftaroline fosamil in treating patients with CABP in active controlled, blinded, randomized studies, these data suggest that ceftaroline fosamil, at a dosing regimen of 600 mg q12h, which achieves greater than 90% target attainment in plasma should be effective in treating MRSA pneumonia with a ceftaroline MIC of ≤1 mg/L. Additional data to correlate PK/PD indices in ELF with clinical and microbiological outcomes in patients with pulmonary infections are needed

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604 **Figure legends**

605 Figure 1. Mean (± SD) ceftaroline concentration versus time in plasma and epithelial lining fluid
606 (ELF) of healthy subjects at steady-state following the last dose of 600 mg ceftaroline fosamil
607 q12h and q8h

608

609 Figure 2. Observed versus population or individual predicted ceftaroline concentrations (mg/L)
610 in plasma and ELF. Values are indicated by black squares, the line of identity appears as a solid
611 black line

612

613 **Table 1. Summary of demographics of enrolled subjects**

Demographic variable	600mg q12h (n=26)	600 mg q8h (n=27)
Race, n (%)		
White	18 (69.2)	25 (92.6)
Black, African American	5 (19.2)	2 (7.4)
Asian	2 (7.7)	0
American Indian, Alaska Native	1 (3.8)	0
Sex, n (%)		
Male	24 (92.3)	19 (70.4)
Age, years		
Mean (±SD)	34.6 (±6.9)	33.1 (±7.9)
Range	21–44	19–45

614 SD, standard deviation

615

Table 2. Mean (± SD) plasma and epithelial lining fluid (ELF) pharmacokinetic parameters for ceftaroline in healthy subjects following last IV infusion on Day 4

Parameter	Plasma (n=25)[a]	ELF (n=25)[b]
600 mg q12h		
C_{max}, mg/L	19.7 ± 2.72	3.38
T_{max}, h[c]	1.0 (0.97–1.10)	1.0
$T_{½}$, h	2.41 ± 0.29	1.95
$AUC_{0–\tau}$ mg•h/L	45.0 ± 7.32	8.09
Percentage penetration[d]	N/A	22.5
600 mg q8h		
C_{max}, mg/L	22.3 ± 3.23	3.56
T_{max}, h[c]	1.0 (0.98–1.13)	1.0
$T_{½}$, h	2.48 ± 0.31	1.81
$AUC_{0–\tau}$ mg•h/L	53.0 ± 7.16	9.36
Percentage penetration[d]	N/A	23.6

Abbreviations: AUC = area under the concentration versus time curve; $AUC_{0-\tau}$ = area under the concentration versus time curve from time 0 to the end of the dosing interval, τ; C_{max} = maximum drug concentration; ELF = epithelial lining fluid; q8h = every 8 hours; q12h = every 12 hours; T_{max} = time of maximum drug concentration; $T_{½}$ = terminal elimination half-life.

[a] Based on total drug concentration in plasma.

[b] Based on median ELF concentration at each time point, n = 5 subjects per time point.

[c] Median (min-max).

[d] Based on the ratio of AUC0-τ in ELF to $AUC_{0-\tau}$ in plasma assuming 20% protein binding in plasma and no protein binding in ELF.

627 **Table 3. Plasma and epithelial lining fluid (ELF) concentrations (median, min, max) of**

628 **ceftaroline in healthy subjects**

Time point, h	Total plasma concentration, mg/L		ELF concentration, mg/L		Ratio[b]
	(n=25 per treatment)		(n=5 per time point, per treatment)		
	Median	min, max	Median	min, max	
600 mg q12h[a]					
1	18.73	14.8, 25.7	3.38	2.08, 7.63	0.23
2	8.47	5.49, 11.4	1.60	1.08, 3.45	0.24
4	3.27	2.2, 4.9	0.54	0.36, 1.26	0.20
8	0.9	0.4, 1.2	0.18	0.00, 0.22	0.25
12	0.27	0.11, 0.43	0.00	0.00, 0.00	0.00
600 mg q8h[a]					
1	21.31	16.7, 28.9	3.56	2.69, 5.07	0.21
2	9.46	7.85, 12.0	2.57	0.61, 3.2	0.34
4	3.56	2.85, 5.49	0.58	0.39, 0.98	0.20
6	1.74	1.28, 3.29	0.27	0.17, 0.52	0.19
8	0.99	0.20, 1.74	0.26	0.00, 0.70	0.32

629 max = maximum; min = minimum; q8h = every 8 hours; q12h = every 12 hours.

630 [a] For subjects receiving 600 mg q12h, 4/5 subjects had measurable concentrations in ELF at 8 hours. The same result was seen

631 for subjects receiving 600 mg q8h with 4/5 subjects having measureable concentrations of ceftaroline in ELF at 8 hours.

632 Ceftaroline was not measurable in the ELF of the five subjects who underwent BAL at 12 h.

633 [b] Ratio of free drug assuming 20% protein binding in plasma and no protein binding in epithelial lining fluid.

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636 **Table 4. Percentage of simulated patients achieving *f*T>MIC targets in plasma**

***f*T>MIC target %**	**MIC, mg/L**				
	0.125	**0.25**	**0.5**	**1**	**2**
600 mg q12h, 1 h infusion					
17	100	100	100	100	100
20	100	100	100	100	99.9
42	100	100	100	98.1	69.0
50	100	100	99.3	92.0	38.1
60	100	99.6	96.4	68.5	15.5
70	99.8	97.7	85.4	40	4.1
600 mg q8h, 1 h infusion					
17	100	100	100	100	100
20	100	100	100	100	100
42	100	100	100	100	97.9
50	100	100	100	99.8	93.4
60	100	100	100	98.7	80.1
70	100	100	99.8	95.6	58.0

637 *f* T > MIC = time that free drug concentration is above the MIC during a dosing interval; MIC= minimum inhibitory
638 concentration;
639 q8h = every 8 hours; q12h= every 12 hours.
640
641

642 **Table 5. Percentage of simulated patients achieving *f*T>MIC targets in epithelial lining**

643 **fluid**

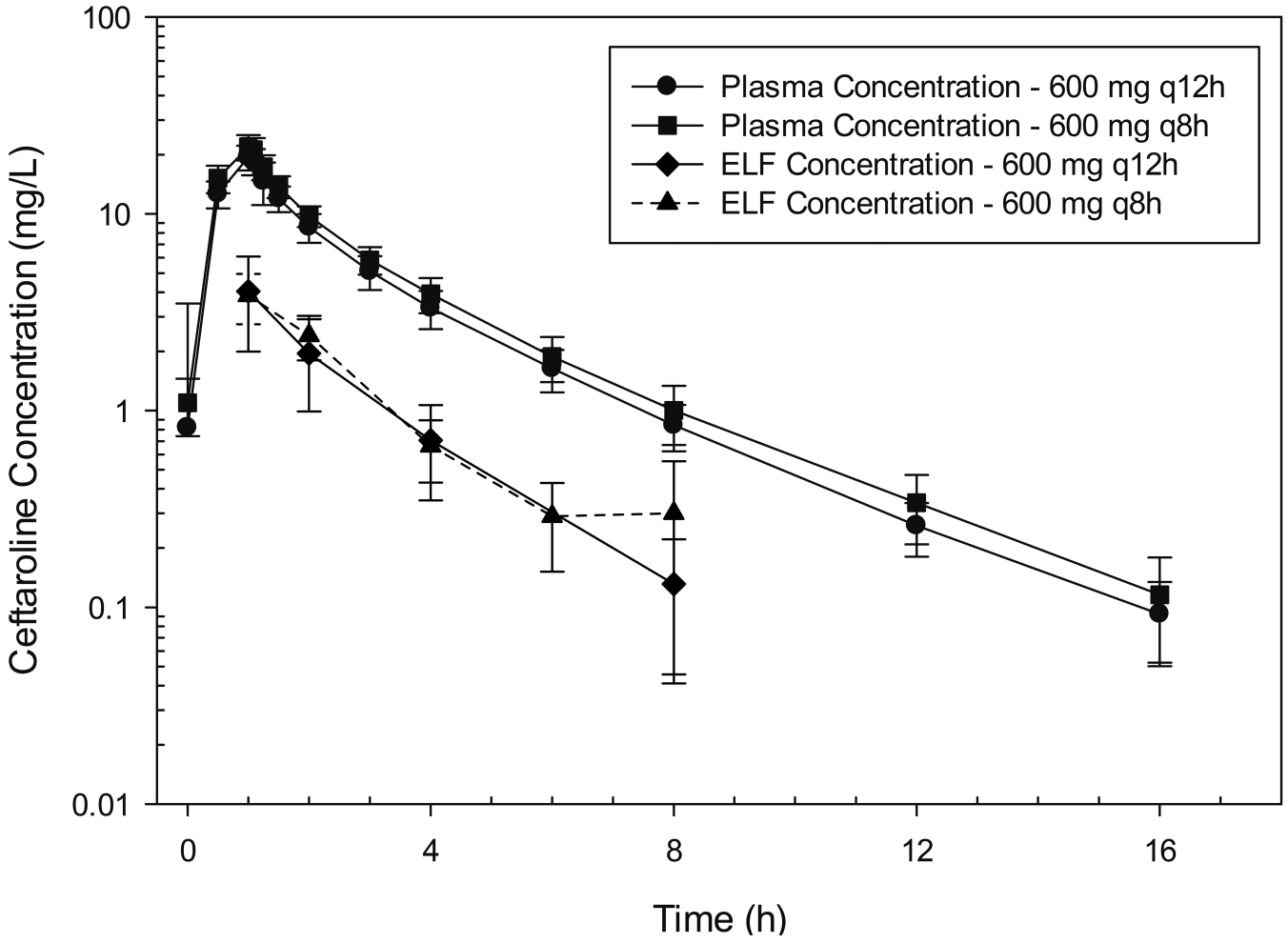
***f*T>MIC target %**	**MIC, mg/L**				
	0.125	**0.25**	**0.5**	**1**	**2**
600 mg q12h, 1 h infusion					
17	100	100	98.7	81.7	26.8
20	100	100	97.8	71.1	17.7
25	100	99.9	93.3	56.1	9.5
40	99.8	95.2	65.6	16.6	1.4
42	99.7	93.3	61.7	13.9	0.9
600 mg q8h, 1 h infusion					
17	100	100	99.9	94.7	58.5
20	100	100	99.8	91.4	47.4
25	100	100	99.2	85.0	33.5
40	100	99.8	92.5	57.0	9.8
42	100	99.7	90.9	52.5	8.0

644 *f* T > MIC = time that free drug concentration is above the MIC during a dosing interval; MIC= minimum inhibitory

645 concentration;

646 q8h = every 8 hours; q12h= every 12 hours.

647



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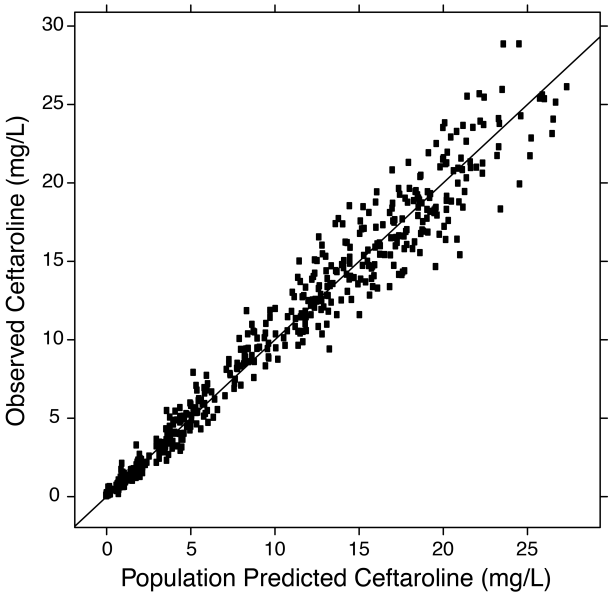
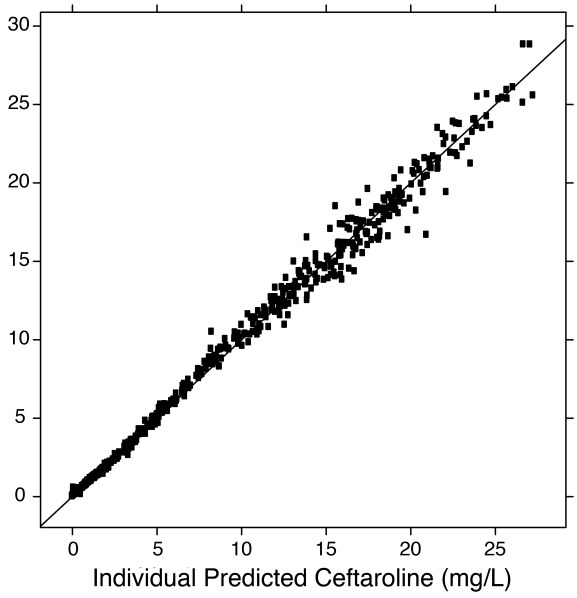
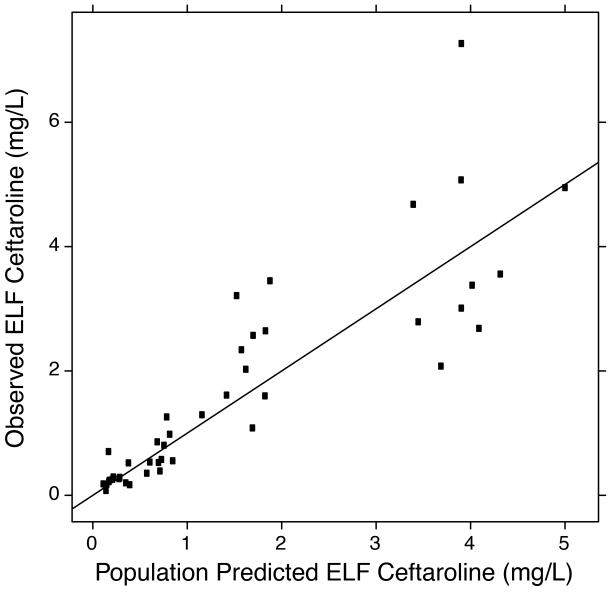
A. Observed versus population predicted ceftaroline concentrations (mg/L) in plasma



B. Observed versus individual predicted ceftaroline concentrations (mg/L) in plasma



C. Observed versus population predicted ceftaroline concentrations (mg/L) in ELF



D. Observed versus individual predicted ceftaroline concentrations (mg/L) in ELF