Pharmacokinetic-Pharmacodynamic Target Attainment Analyses To Evaluate *In Vitro* Susceptibility Test Interpretive Criteria for Ceftaroline against *Staphylococcus aureus* and *Streptococcus pneumoniae*

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To provide support for *in vitro* susceptibility test interpretive criteria decisions for ceftaroline against *Staphylococcus aureus* and *Streptococcus pneumoniae*, as well as dose adjustment recommendations for renal impairment, pharmacokinetic-pharmacodynamic (PK-PD) target attainment was evaluated for simulated patients administered intravenous (i.v.) ceftaroline fosamil at 600 mg twice daily (q12h) and simulated patients with renal impairment administered various dosing regimens. Using a previously developed population PK model, Monte Carlo simulation was used to generate ceftaroline plasma concentration profiles for simulated patients with normal renal function or mild, moderate, or severe renal impairment. Using these profiles, the percentage of time during the dosing interval that free-drug concentrations remained above the MIC ($f\%T > $MIC) for ceftaroline at steady state was calculated. Percentages of simulated patients achieving $f\%T > $MIC targets for *S. aureus* and *S. pneumoniae* based on murine infection models were calculated by MIC. At MICs of 2 mg/liter for *S. aureus* and 1 mg/liter for *S. pneumoniae*, the percentages of simulated patients with normal renal function and mild renal impairment following administration of ceftaroline fosamil at 600 mg q12h, moderate renal impairment following administration of ceftaroline fosamil at 400 mg q12h, and severe renal impairment following administration of ceftaroline fosamil at 300 mg q12h achieving $f\%T > $MIC targets ($\geq$26 for *S. aureus* and $\geq$44 for *S. pneumoniae*) exceeded 90%. The results of these analyses, which suggested that *in vitro* susceptibility test interpretive criteria defining susceptible could be as high as MICs of $\leq$2 and $\leq$1 mg/liter for ceftaroline against *S. aureus* and *S. pneumoniae*, respectively, provide support for current FDA and CLSI criteria, which define susceptible as MICs of 1 and 0.5 mg/liter, respectively. Recommendations for dose adjustments for patients with renal impairment were also supported by the results of these analyses.

When establishing *in vitro* susceptibility test interpretive criteria to guide effective antimicrobial therapy, a hierarchy of data is considered. This typically includes organism-drug susceptibility population statistics, pharmacokinetic-pharmacodynamic (PK-PD) data, and clinical response evaluations (1, 2, 3, 4). The application of PK-PD principles for this purpose involves the use of population PK models, which are developed using clinical PK data, and PK-PD targets for efficacy, which are based on data from preclinical infection models and/or infected patients. Using these data and Monte Carlo simulation, the impact of the PK variability on the probability of achieving PK-PD targets is assessed in the context of MIC distributions for the pathogens of interest. As described herein, such an assessment was carried out during the clinical development program for ceftaroline fosamil to support the determination of *in vitro* susceptibility test interpretive criteria and dosing regimens for patients with renal impairment.

Ceftaroline fosamil, a water-soluble prodrug of ceftaroline, is approved in the United States as an intravenous (i.v.) treatment for patients with acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP) and in Europe for similar indications (5, 6, 7). Ceftaroline exhibits *in vitro* activity against a broad spectrum of Gram-positive and common Gram-negative pathogens associated with either CABP or ABSSSI, including methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin-resistant *Streptococcus pneumoniae*.

The objective of these analyses was to evaluate PK-PD target attainment by MIC in simulated patients following i.v. administration of ceftaroline fosamil at 600 mg twice daily (q12h) in order to provide support for *in vitro* susceptibility test interpretive criteria decisions for *S. aureus* and *S. pneumoniae*. These analyses also included the evaluation of various i.v. dosing regimens for administration to simulated patients with different categories of renal impairment to support recommendations for dose adjustments of ceftaroline fosamil.

MATERIALS AND METHODS

The analyses described herein were conducted using two steps, the details of which are described in the sections below. The first step involved using Monte Carlo simulation to generate four separate patient populations, one for each renal function category (normal renal function or mild, moderate, or severe renal impairment). Steady-state ceftaroline plasma concentration-time profiles following administration of different i.v. cef-

TABLE 1 Final population PK model for ceftaroline fosamil[a]

Parameter[b]	Estimate	% SEM
CL_p (liters/h)[c]	228	2.59
CL_p-CL_{CR} power	0.147	26.5
$V_{c,p}$ (liters)[d]	10.8	8.35
$V_{c,p}$ shift for SEV_j	17.2	32.8
$V_{c,p}$ shift for POP_j	−5.81	18.8
CL_{d1p} (liters/h)	25.7	11.3
V_{p1} (liters)	363	15.2
CL_{d2p} (liters/h)	16.2	11.8
V_{p2} (liters)	3.24	6.00
F	1.23	4.96
k_a (h^{-1})	0.627	8.12
FRC	0.772	5.73
t_{lag} (h)	0.462	7.36
ω^2_{ka}	26.4% CV[e]	50.7
ω^2_{CLp}	25.7% CV	13.2
$\omega^2_{Vc,p}$	68.2% CV	13.5
ω^2_{CLd1p}	70.3% CV	24.4
σ^2 for studies 1, 2, and 3	34.2% CV	4.91
σ^2 for all other studies	36.6% CV	5.80

[a] Data were obtained from reference 8.
[b] CL_{d1p}, prodrug distribution clearance for the first peripheral compartment; CL_{d2p}, prodrug distribution clearance for the second peripheral compartment; CL_p, prodrug clearance; F, intramuscular bioavailability; FRC, fraction of prodrug dose in the first depot compartment; k_a, first-order absorption rate constant; ω^2, interindividual variability; σ^2, residual variability; t_{lag}, delay in the start of absorption from the second depot compartment; $V_{c,p}$, prodrug central volume of distribution; V_{p1}, prodrug volume of distribution for the first peripheral compartment; V_{p2}, prodrug volume of distribution for the second peripheral compartment.
[c] Population mean CL_p (liters/h) = 228 · $(CL_{CR}/102)^{0.147}$.
[d] Population mean $V_{c,p}$ (liters/h) = 10.8 + 17.2 · SEV_j − 5.81 · POP_j, where SEV_j is an indicator variable in the jth subject with a value of 1 if CL_{CR} < 30 ml/min/1.73 m² and 0 otherwise and POP_j is an indicator variable in the jth subject with a value of 1 for phase 2/3 patients and 0 otherwise.
[e] CV, coefficient of variation.

TABLE 2 Final population PK model for ceftaroline[a]

Parameter[b]	Estimate	% SEM	Bootstrap mean (90% confidence interval)
CL_i (liters/h)[c]	11.6	9.24	11.5 (9.61, 13.1)
CL_i-CL_{CR} power	0.441	10.8	0.443 (0.361, 0.518)
CL_i-age slope	−0.0883	17.0	−0.0902 (−0.111, −0.0698)
CL_i shift for POP_j	4.11	17.7	4.16 (3.11, 5.28)
K_m (mg/liter)	9.62	26.6	9.58 (6.79, 13.6)
CL_{lin} (liters/h)[d]	3.06	17.7	3.16 (2.09, 4.20)
CL_{lin}-CL_{CR} power	0.343	17.5	0.333 (0.206, 0.424)
Vc (liters)[e]	8.67	4.93	8.64 (8.11, 9.25)
Vc shift for POP_j	7.02	22.1	6.97 (5.01, 8.69)
CLd (liters/h)[f]	8.59	6.07	8.59 (7.39, 10.0)
CLd shift for males	4.88	17.1	5.04 (3.42, 6.90)
Vp (liters)[g]	11.7	5.02	11.6 (10.5, 12.7)
Vp shift for males	2.87	16.7	2.97 (2.05, 3.90)
ω^2_{CLi}	30.2% CV[h]	21.5	29.6% CV (23.9, 35.5)
Covariance (CL_i, K_m)	−0.0927 (r^2 = 0.196)	55.6	−0.0780 (−0.160, 0.0001)
ω^2_{Km}	67.0% CV	28.6	65.0% CV (50.5, 77.4)
ω^2_{Vc}	43.5	25.2	43.4% CV (34.7, 52.2)
ω^2_{CLd}	31.8% CV	25.8	31.8% CV (24.8, 39.1)
Covariance (CLd, Vp)	0.0643 (r^2 = 0.959)	25.5	0.0645 (0.0412, 0.0929)
ω^2_{Vp}	20.6% CV	26.7	21.2% CV (17.2, 25.4)
$\sigma^2_{Additive}$	0.0392	8.74	0.0387 (0.0331, 0.0440)
σ^2_{CCV}	0.00180	53.1	0.0019 (0.0011, 0.0031)

[a] Data were obtained from reference 8.
[b] CCV, constant coefficient of variation; CLd, distribution clearance for the peripheral compartment for ceftaroline; CL_i, intrinsic ceftaroline clearance for the saturable elimination pathway; CL_{lin}, linear ceftaroline clearance; K_m, ceftaroline concentration producing 50% of CL_i; ω^2, interindividual variability; σ^2, residual variability; Vc, ceftaroline central volume of distribution; Vp, = volume of distribution for the peripheral compartment for ceftaroline.
[c] Population mean CL_i (liters/h) = 11.6 · $(CL_{CR}/102)^{0.441}$ − 0.0883 · $(age_j − 36)$ + 4.11 · POP_j, where POP_j is an indicator variable in the jth subject with a value of 1 for phase 2/3 patients and 0 otherwise.
[d] Population mean CL_{lin} (liters/h) = 3.06 · $(CL_{CR}/102)^{0.343}$.
[e] Population mean Vc (liters) = 8.67 + 7.02 · POP_j.
[f] Population mean CLd (liters/h) = 8.59 + 4.88 · $MALE_j$, where $MALE_j$ is an indicator variable in the jth subject with a value of 1 for males and 0 for females.
[g] Population mean Vp (liters) = 11.7 + 2.87 · $MALE_j$.
[h] CV, coefficient of variation.

taroline fosamil dosing regimens were simulated using previously developed population PK models for the prodrug, ceftaroline fosamil, and the active agent, ceftaroline (8). The percentage of time during the dosing interval that free-drug ceftaroline plasma concentrations remained above the MIC (f%T>MIC) was calculated for each simulated plasma concentration-time profile.

The second step of these analyses involved the determination of the percentage of simulated patients achieving f%T>MIC targets associated with efficacy for *S. aureus* and *S. pneumoniae* based on murine infection models (9) by MIC value, dosing regimen, and renal function category. These data were then evaluated in the context of MIC distributions for each of these pathogens.

Population PK model. The population PK models for the ceftaroline fosamil and ceftaroline used for these analyses were developed using NONMEM version 6.2 (10) and plasma concentration-time data obtained from phase 1 subjects with various degrees of renal function and phase 2 and 3 patients with ABSSSI. The final population PK model was later validated using data from phase 3 patients with CABP to demonstrate that ceftaroline PKs are similar between patients with CABP and ABSSSI. The results of this analysis are presented in detail elsewhere (8).

In brief, the disposition of ceftaroline fosamil after i.v. administration was best described using a three-compartment model with zero-order input and rapid first-order conversion of the prodrug to ceftaroline. The disposition of ceftaroline was best described using a two-compartment model with parallel first-order and Michaelis-Menten elimination pathways. However, ceftaroline PKs could be adequately approximated by a

two-compartment linear model within a ceftaroline fosamil dose range of 250 to 1,000 mg. The final ceftaroline fosamil and ceftaroline population PK model parameters after accounting for all statistically significant parameter-covariate relationships, as well as the magnitude of the remaining unexplained interindividual variability for each parameter, are provided in Tables 1 and 2. All model parameters were conditioned on the actual fraction of the prodrug converted to active ceftaroline (f_m), which was not estimated. Creatinine clearance (CL_{CR}) was identified as a clinically and statistically significant predictor of both the linear and intrinsic clearance terms for ceftaroline, as both parameters decreased with renal impairment. Intrinsic clearance also was shown to decrease to a lesser degree with age. Distribution clearance and peripheral volume were also increased for males relative to females. However, CL_{CR} was the only clinically important covariate that required a dose adjustment (8).

Monte Carlo simulation. A total of 2,000 patients, of whom 50% were males, were simulated in each of four renal function categories using SAS
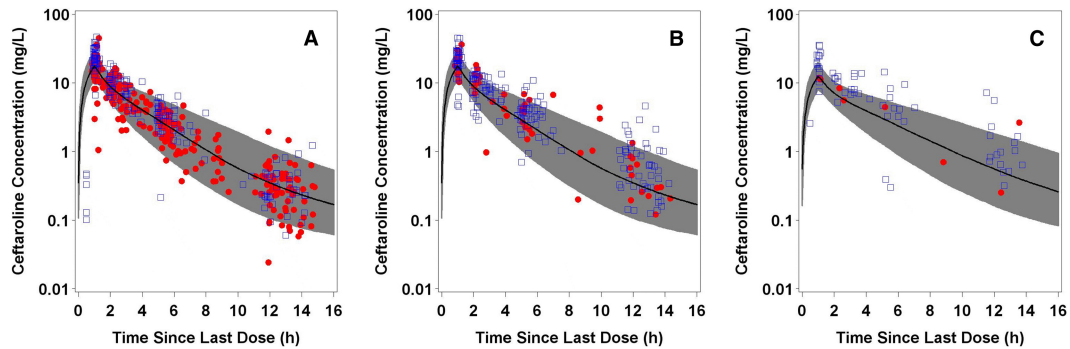
FIG 1 Steady-state ceftaroline concentrations in plasma over time for patients with ABSSSI (●) or CABP (□) with normal renal function following administration of ceftaroline fosamil at 600 mg q12h ($n = 129$) (A), mild renal impairment following administration of ceftaroline fosamil at 600 mg q12h ($n = 68$) (B), and moderate renal impairment following administration of ceftaroline fosamil at 400 mg q12h ($n = 19$) (C). The solid black line represents the 50th percentile and the gray shaded area represents the 5th and 95th percentiles of the simulated data. The symbols represent the observed data used to develop and validate the population PK model.

version 9.2 software (11). For this simulation exercise, renal function was defined by CL_{CR} calculated using the Cockcroft-Gault equation and normalized by body surface area (BSA). Renal function categories were defined as follows: normal renal function, $80 \leq CL_{CR} \leq 170$ ml/min/1.73 m²; mild renal impairment, $50 \leq CL_{CR} < 80$ ml/min/1.73 m²; moderate renal impairment, $30 \leq CL_{CR} < 50$ ml/min/1.73 m²; and severe renal impairment, $15 \leq CL_{CR} < 30$ ml/min/1.73 m². In the group with normal renal function, CL_{CR} was assigned using a truncated normal distribution with a mean (standard deviation [SD]) of 118 (30.8) ml/min/1.73 m² based on the observed data from 624 patients with ABSSSI who had a CL_{CR} of ≥80 ml/min/1.73 m² (12, 13, 14). For all other renal function categories, CL_{CR} was uniformly distributed. Age was assigned according to a normal distribution with a mean (SD) of 46.2 (16.6) years of age based on the data from 839 patients with ABSSSI studied (12, 13, 14); the simulated age distribution was truncated to include only individuals between 18 and 90 years of age.

Steady-state ceftaroline concentrations in plasma were simulated every 0.1 h during the dosing interval for patients in each renal function group after i.v. administration of the following ceftaroline fosamil dosing regimens infused over 1 h: normal renal function and mild renal impairment, 600 mg q12h; moderate renal impairment, 300 mg q12h, 400 mg q12h, 600 mg q12h, and 600 mg q24h; and severe renal impairment, 300 mg q12h, 400 mg q12h, 600 mg q12, 600 mg q24h, and 800 mg q24h. These dosing regimens were previously evaluated to determine which regimen(s) provides comparable steady-state ceftaroline maximum concentration (C_{max}) and area under the concentration-time curve (AUC) values among simulated patients in each of the above-described renal function groups (8). To confirm the reliability of the simulations, a visual predictive check was performed in which percentiles (5th, 50th, and 95th) of the simulated data following administration of 600 mg ceftaroline fosamil q12h were overlaid upon the observed plasma ceftaroline concentration-time data in patients with ABSSSI or CABP with either normal renal function or mild renal impairment receiving this same dose. Similarly, a visual predictive check was carried out for the ceftaroline fosamil dosing regimen of 400 mg q12h administered to phase 2/3 ABSSSI and CABP patients with moderate renal impairment, a dosing regimen which provided exposures similar to those for patients with normal renal function administered ceftaroline fosamil at 600 mg q12h (12, 13, 14, 15, 16).

Calculation of ceftaroline exposures. Free-drug (f) ceftaroline concentrations in plasma were calculated by multiplying the total-drug concentration by 0.8 based on a concentration-independent plasma protein binding estimate of 20% (6). For each simulated profile, $f\%T>MIC$ was calculated by MIC values ranging from 0.008 to 32 mg/liter.

PK-PD target attainment analyses. For each dosing regimen and renal function group, the percentage of simulated patients achieving PK-PD targets was assessed by MIC value. PK-PD targets were based on $f\%T>MIC$, the PK-PD index associated with efficacy for ceftaroline (9). Specific $f\%T>MIC$ targets associated with various levels of bacterial reduction from baseline for *S. aureus* and *S. pneumoniae* based on data from a neutropenic murine thigh infection model were assessed. For bacterial reduction endpoints of net bacterial stasis and 1- and 2-log₁₀ CFU reductions from baseline, $f\%T>MIC$ targets for *S. aureus* were 26, 36, and 51, respectively. For *S. pneumoniae*, $f\%T>MIC$ targets associated with these endpoints were 35, 44, and 51, respectively. These studies evaluated four *S. aureus* isolates (including one MRSA isolate) and five *S. pneumoniae* isolates (one penicillin susceptible, one with intermediate sensitivity, and three penicillin resistant) (9). Nonclinical PK-PD targets associated with net bacterial stasis and 90% animal survival have been shown to be correlated with a high percentage of successful outcomes in patients with ABSSSI and pneumonia, respectively (17). Given these data, focus was given to results based on achieving an $f\%T>MIC$ target of 26 for *S. aureus*, which was associated with net bacterial stasis. An $f\%T>MIC$ target of ≥44 for *S. pneumoniae*, which was associated with a 1-log₁₀ CFU reduction from baseline, was chosen for evaluation rather than the target for net bacterial stasis given the higher bacterial burden typically associated with pneumonia compared to ABSSSI.

The percentage of simulated patients among each renal function group achieving the above-described $f\%T>MIC$ targets was assessed over an MIC range of 0.008 to 32 mg/liter for each dosing regimen evaluated. Percentages of PK-PD target attainment were also assessed in the context of MIC distributions for ceftaroline against *S. aureus* and *S. pneumoniae* based on contemporary surveillance data (18, 19). These data, which included ceftaroline MIC values for 3,965 and 894 *S. aureus* and *S. pneumoniae* isolates, respectively, were collected from medical centers in the United States. MIC values for the 3,965 *S. aureus* isolates were stratified by MRSA and methicillin-susceptible *S. aureus* (MSSA) isolates. The minimum MIC, the MIC inhibiting 50% of isolates (MIC₅₀), the MIC inhibiting 90% of isolates (MIC₉₀), and the maximum MIC were 0.12, 1, 1, and 2 mg/liter, respectively, for the 2,254 MRSA isolates collected and ≤0.008, 0.25, 0.25, and 0.5 mg/liter, respectively, for the 1,711 MSSA isolates collected. For the 894 *S. pneumoniae* isolates collected, these values were ≤0.008, 0.015, 0.12, and 0.5 mg/liter, respectively.

RESULTS

As shown in Fig. 1, steady-state plasma ceftaroline concentrations over time for simulated patients with either normal renal function or mild renal impairment following administration of 600 mg ceftaroline fosamil q12h, as well as for simulated patients with moderate renal impairment following administration of 400 mg ceftaroline fos-
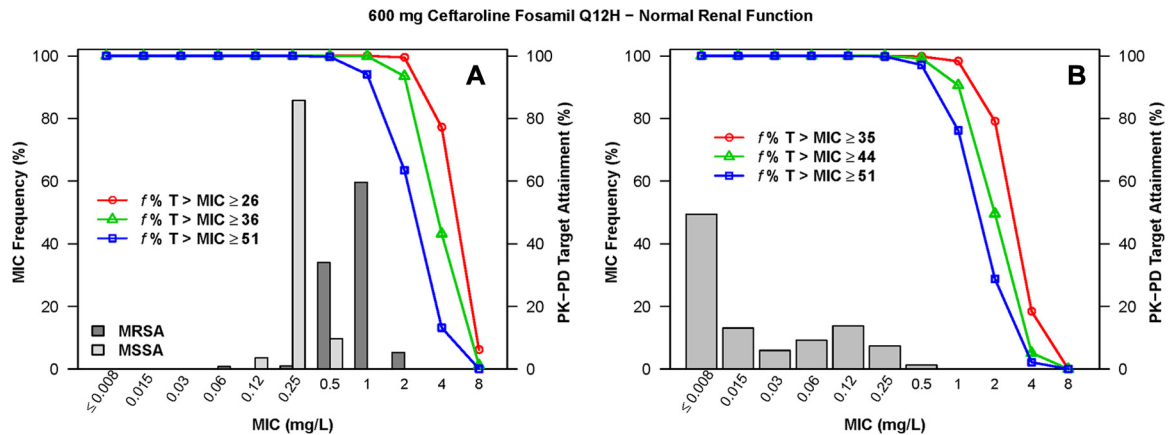
FIG 2 Percentages of simulated patients with normal renal function ($80 \leq \mathrm{CL_{CR}} \leq 170$ ml/min/1.73 m^2) achieving $f\%T{>}$MIC targets by MIC following administration of ceftaroline fosamil at 600 mg q12h, overlaid on a histogram showing the MIC distribution for *S. aureus* (A) or *S. pneumoniae* (B).

amil q12h, agreed well with the observed data collected from patients with ABSSSI and CABP in each of these renal function groups. This evaluation demonstrated that the population PK model used in PK-PD target attainment simulations was adequate.

The percentages of simulated patients with normal renal function and mild renal impairment following administration of ceftaroline fosamil at 600 mg q12h who achieved $f\%T{>}$MIC targets by MIC for *S. aureus* and *S. pneumoniae* are shown in Table S1 in the supplemental material. The percentages of simulated patients with moderate and severe renal impairment following administration of the various dosing regimens evaluated who achieved each of these $f\%T{>}$MIC targets by MIC are shown in Tables S2 and S3 in the supplemental material, respectively. The percentages of simulated patients with normal renal function and mild renal impairment following administration of ceftaroline fosamil at 600 mg q12h who achieved $f\%T{>}$MIC targets by MIC, overlaid on MIC distributions for *S. aureus* or *S. pneumoniae*, are shown in Fig. 2 and 3, respectively. Similar data are presented for simulated patients with moderate renal impairment following administration of ceftaroline fosamil at 400 mg q12h in Fig. 4 and for those with severe renal impairment following administration of ceftaroline fosamil at 300 mg q12h in Fig. 5.

When examining PK-PD target attainment for *S. aureus*, the percentages of simulated patients achieving $f\%T{>}$MIC targets of ≥ 26 (net bacterial stasis) and ≥ 36 (1-log$_{10}$ CFU reduction from baseline) were $\geq 99.4\%$ and $\geq 92.4\%$, respectively, at an MIC of 1 mg/liter across all renal function groups for all dosing regimens evaluated, with the exception of the dosing regimen of ceftaroline fosamil at 600 mg q24h in simulated patients with moderate renal impairment. For this population and dosing regimen, 96.5% and 74.1% of simulated patients achieved an $f\%T{>}$MIC of ≥ 26 and ≥ 36, respectively (see Table S2 in the supplemental material). At an MIC value of 2 mg/liter, the percentages of simulated patients with normal renal function and mild renal impairment following administration of 600 mg ceftaroline fosamil q12h achieving an $f\%T{>}$MIC of ≥ 26 were 95.9% and 99.5%, respectively (see Table S1 in the supplemental material). For simulated patients with moderate renal impairment following administration of ceftaroline fosamil at 400 mg q12h and with severe renal impairment following ceftaroline fosamil at 300 mg q12h, these percentages were 96.1% and 92.2%, respectively (see Tables S2 and S3 in the supplemental material, respectively).

When examining PK-PD target attainment for *S. pneumoniae*, the percentages of simulated patients achieving $f\%T{>}$MIC tar-
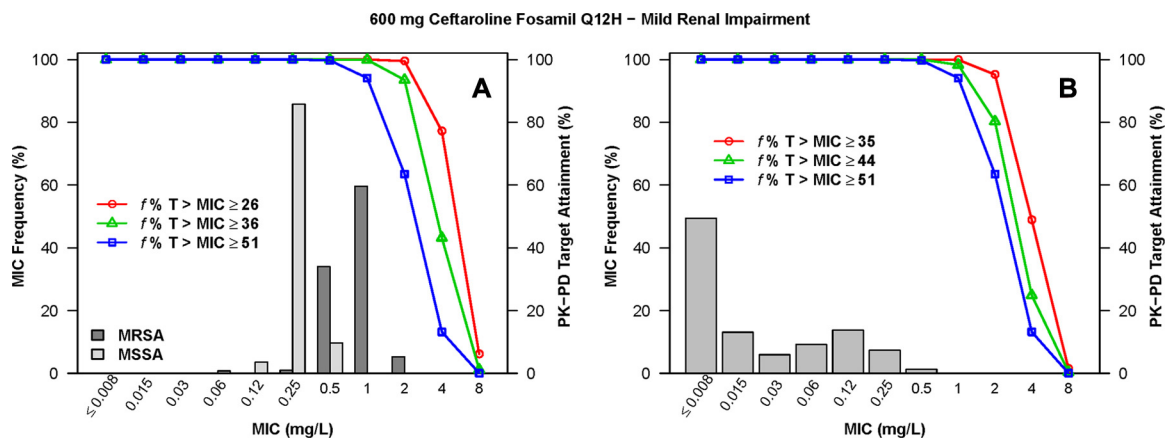

FIG 3 Percentages of simulated patients with mild renal impairment ($50 \leq \mathrm{CL_{CR}} < 80$ ml/min/1.73 m^2) achieving $f\%T{>}$MIC targets by MIC following administration of ceftaroline fosamil at 600 mg q12h, overlaid on a histogram showing the MIC distribution for *S. aureus* (A) or *S. pneumoniae* (B).
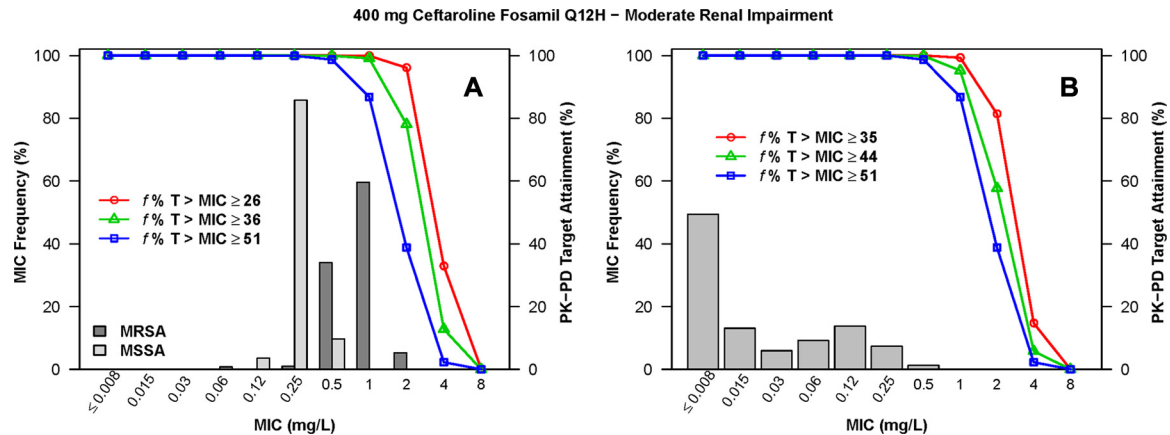
FIG 4 Percentages of simulated patients with moderate renal impairment ($30 \leq CL_{CR} < 50$ ml/min/1.73 m^2) achieving $f\%T>MIC$ targets by MIC following administration of ceftaroline fosamil at 400 mg q12h, overlaid on a histogram showing the MIC distribution for *S. aureus* (A) or *S. pneumoniae* (B).

gets of ≥35 (net bacterial stasis) and ≥44 (1-log$_{10}$ CFU reduction from baseline) were ≥99.6% and ≥95.8%, respectively, at an MIC of 0.25 mg/liter across all renal function groups for all dosing regimens evaluated. At an MIC value of 0.5 mg/liter, the percentages of simulated patients achieving an $f\%T>MIC$ of ≥35 and ≥44 were ≥99.3% and ≥94.3%, respectively, across renal function groups for all dosing regimens, with the exception of the dosing regimen of ceftaroline fosamil at 600 mg q24h in simulated patients with moderate renal impairment. The percentages of simulated patients achieving an $f\%T>MIC$ of ≥35 and ≥44 for this population and dosing regimen were 95.6% and 80.7%, respectively (see Table S2 in the supplemental material). At an MIC value of 1 mg/liter, the percentages of simulated patients with normal renal function and mild renal impairment following administration of 600 mg q12h achieving an $f\%T>MIC$ of ≥44 were 90.6% and 98.3%, respectively (see Table S1 in the supplemental material). For simulated patients with moderate renal impairment following administration of 400 mg q12h and with severe renal impairment following administration of 300 mg q12h, these percentages were 95.2% and 95.0%, respectively (see Tables S2 and S3 in the supplemental material, respectively).

DISCUSSION

The objective of the analyses described herein was to evaluate PK-PD target attainment by MIC in simulated patients following administration of ceftaroline fosamil at 600 mg q12h, with the goal of providing support for *in vitro* susceptibility test interpretive criteria decisions for *S. aureus* and *S. pneumoniae*. As part of this evaluation, PK-PD target attainment was assessed for various ceftaroline fosamil dosing regimens within various renal function categories to support recommendations for dose adjustments in patients with renal impairment.

The results of the PK-PD target attainment analyses support susceptibility test interpretive criteria which define susceptible as MICs of ≤2 and ≤1 mg/liter for ceftaroline against *S. aureus* and *S. pneumoniae*, respectively. At these MIC values, the percentage of simulated patients who achieved $f\%T>MIC$ targets associated with bacterial reduction endpoints linked with a high percentage of successful outcomes in patients with ABSSSI and pneumonia (17) exceeded 90% for the following ceftaroline fosamil dosing regimens: 600 mg q12h in patients with normal renal function and mild renal impairment, 400 mg q12h in patients with moderate
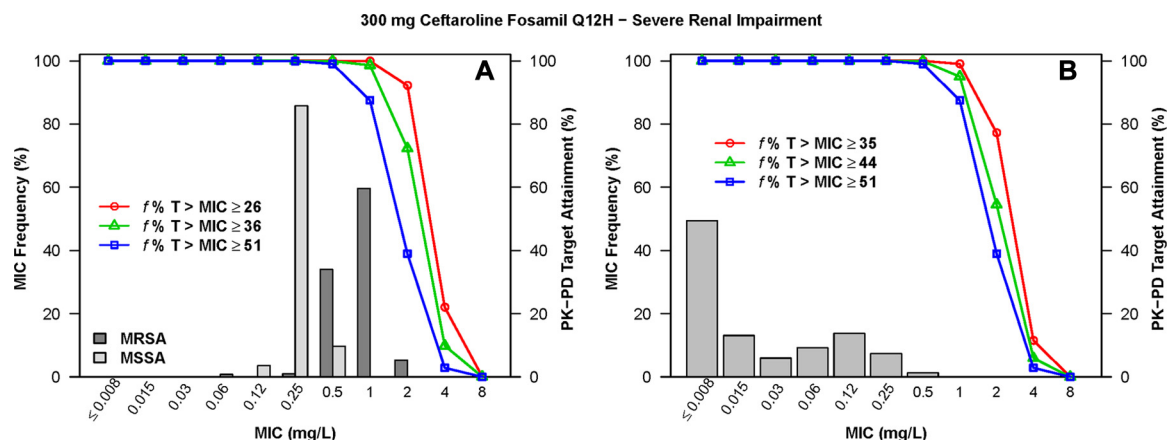

FIG 5 Percentages of simulated patients with severe renal impairment ($15 \leq CL_{CR} < 30$ ml/min/1.73 m^2) achieving $f\%T>MIC$ targets by MIC following administration of ceftaroline fosamil at 300 mg q12h, overlaid on a histogram showing the MIC distribution for *S. aureus* (A) and *S. pneumoniae* (B).

TABLE 3 Percentages of clinical and microbiological success by MIC for ceftaroline fosamil-treated patients against *S. aureus* in the ME population for the pooled phase 3 ABSSSI studies

Ceftaroline MIC (mg/liter)	N	Clinical success, n/N (%)	Microbiological success (eradicated/presumed eradicated), n/N (%)
0.06	3	3/3 (100)	3/3 (100)
0.12	79	72/79 (91.1)	73/79 (92.4)
0.25	156	148/156 (94.9)	149/156 (95.5)
0.5	109	102/109 (93.6)	102/109 (93.6)
1	11	11/11 (100)	11/11 (100)
2	4	2/4 (50)	2/4 (50)
Total	362	338/362 (93.4)	340/362 (93.9)

TABLE 4 Percentages of clinical and microbiological success by MIC for ceftaroline fosamil-treated patients against *S. pneumoniae* in the ME population for the pooled phase 3 CABP studies

Ceftaroline MIC (mg/liter)	N	Clinical success, n/N (%)	Microbiological success (eradicated/presumed eradicated), n/N (%)
≤0.004	4	4/4 (100)	4/4 (100)
0.008	20	16/20 (80)	16/20 (80)
0.015	8	6/8 (75)	6/8 (75)
0.03	2	2/2 (100)	2/2 (100)
0.06	1	1/1 (100)	1/1 (100)
0.25	1	1/1 (100)	1/1 (100)
Total	36	30/36 (83.3)	30/36 (83.3)

renal impairment, and 300 mg q12h in patients with severe renal impairment.

Although PK-PD analyses have been conducted based on clinical data from ceftaroline fosamil-treated patients with ABSSSI and *S. aureus* at baseline or CABP and *S. pneumoniae* at baseline (20, 21), the results of the analyses described herein were based on nonclinical $f\%T{>}MIC$ targets for each of these organisms. While PK-PD analyses of patients with ABSSSI and *S. aureus* isolated at baseline, which were conducted using data from two phase 2 and two phase 3 studies, revealed significant relationships between microbiological response and $f\%T{>}MIC$ evaluated continuously or categorically, there was a high degree of uncertainty around the identified PK-PD relationships (20). This was likely due to the high percentage of patients with microbiological success (and hence, the low number of failures) in this analysis population. Although these data did provide support for the adequacy of the dosing regimen of 600 mg q12h, the uncertainty around the PK-PD relationships for microbiological response precluded reliable identification of $f\%T{>}MIC$ targets for efficacy. Thus, nonclinical $f\%T{>}MIC$ targets were chosen for evaluation in the analyses described herein.

For the PK-PD analyses of patients with CABP (21), which were based on data from two phase 3 studies, 124 microbiologically evaluable (ME) patients were assessed (35 of whom had *S. pneumoniae* isolated at baseline). The percentages of clinical and microbiological success in these two populations were ≥82.9%. Among the 124 patients, the majority of patients (91.1%) had $f\%T{>}MIC$ values ranging from 91.7 to 100; 98.4% of patients had $f\%T{>}MIC$ values of ≥63.3. All 35 patients with *S. pneumoniae* had an $f\%T{>}MIC$ equal to 100. Thus, given the high percentages of patients achieving successful clinical or microbiological responses and the large proportion of patients with high $f\%T{>}MIC$ values, it was anticipated that there would be some difficulty in identifying reliable PK-PD relationships for efficacy. Indeed, such relationships could not be identified based on these data as evidenced by the fact that $f\%T{>}MIC$ values were well above nonclinical $f\%T{>}MIC$ targets, thus suggesting that the majority of patients with CABP receiving the dosing regimen of ceftaroline fosamil at 600 mg q12h achieved exposures associated with the upper plateau of the PK-PD relationship for efficacy. Given the limitations of the PK-PD analyses based on the data from patients with CABP, nonclinical $f\%T{>}MIC$ targets for *S. pneumoniae* were chosen for evaluation in the analyses described herein.

While the PK-PD target attainment analyses undertaken did consider two of the three data sources typically required to establish *in vitro* susceptibility test interpretive criteria (i.e., organism drug susceptibility population statistics and PK-PD data), clinical response evaluations represent an important third data source. Although the results of PK-PD target attainment analyses in the context of surveillance data allow for predictions of efficacy by MIC beyond the MIC range observed in the clinical studies, examination of clinical response by MIC remains an important evaluation which is used to balance predictions relative to current clinical experience. Given these considerations, an MIC value at which there are an insufficient number of clinical outcomes is not usually selected to define *in vitro* susceptibility test interpretive criteria. Clinical and microbiological response data by MIC, summarized in Tables 3 and 4, were considered for ceftaroline during the U.S. Food and Drug Administration (FDA) Advisory Committee Meeting held on 7 September 2010 (data on file at Forest Research Institute, Inc.).

As shown in Table 3, the number of ceftaroline fosamil-treated ABSSSI patients with *S. aureus* at baseline with an MIC of 2 mg/liter based on the two pivotal phase 3 studies pooled was very low ($n = 4$). While the number of cases was also low for an MIC of 1 mg/liter ($n = 11$), the percentage of clinical and microbiological success was not different than for that for patients with an MIC of ≤0.5 mg/liter. Thus, the definition of susceptible based on an MIC of 1 mg/liter for ceftaroline against *S. aureus* was supported by both the results of PK-PD target attainment analyses and the observed clinical data.

As shown in Table 4, the number of ceftaroline fosamil-treated CABP patients with *S. pneumoniae* at baseline was low based on the two pivotal phase 3 studies. However, given the high percentages of clinical and microbiological success at each observed MIC value and the fact that there were patients with *S. pneumoniae* isolates at baseline with MIC values of <0.25 mg/liter, these data were supportive of a definition of susceptible of 0.25 mg/liter for ceftaroline against *S. pneumoniae*. As described herein, the results of PK-PD target attainment analyses provided support for a susceptibility breakpoint that was two dilutions higher (1.0 mg/liter).

Although there are differences in the assessment approach and perhaps the weighting of data sources, *in vitro* susceptibility test interpretive criteria determinations for *S. aureus* and *S. pneumoniae* made by the U.S. FDA (22), the Clinical and Laboratory Standards Institute (CLSI) (23), and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (24) were similar. Each defined susceptible for ceftaroline against *S. aureus* as an MIC of ≤1 mg/liter. While the U.S. FDA and EUCAST defined susceptible for ceftaroline against *S. pneumoniae* as an MIC of

≤0.25 mg/liter, the CLSI definition was one dilution higher (MIC ≤of 0.5 mg/liter). Recently, the FDA definition for susceptible for ceftaroline against *S. pneumoniae* was revised, and it is now an MIC of ≤0.5 mg/liter (6).

The PK-PD target attainment analyses carried out were used not only to provide support for *in vitro* susceptibility test interpretive criteria decisions for *S. aureus* and *S. pneumoniae* but also to evaluate the adequacy of ceftaroline fosamil dosing recommendations for patients with renal impairment. PK-PD data have been increasingly used to support dose selection during early and late stages of drug development. Metrics based on these principles provide a useful approach to assess both the dose and frequency of administration with regard to predicted probabilities of efficacy. The results of the analyses described herein, in conjunction with those conducted to identify matching exposures for patients with renal impairment to those with normal renal function, provide further support for ceftaroline fosamil dose adjustment recommendations for patients with renal impairment described in the U.S. product label (6).

In conclusion, the results of PK-PD target attainment analyses carried out for ceftaroline are consistent with FDA, CLSI, and EUCAST *in vitro* susceptibility test interpretive criteria for *S. aureus* and *S. pneumoniae*. These data also provide support for the U.S. FDA labeled ceftaroline fosamil dosing regimens of 600 mg q12h for patients with normal renal function and mild renal impairment, 400 mg q12h for patients with moderate renal impairment, and 300 mg q12h for patients with severe renal impairment.

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