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Pharmacokinetic-Pharmacodynamic Analyses for Efficacy of Ceftaroline Fosamil in Patients with Community-Acquired Bacterial Pneumonia

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Pharmacokinetic-pharmacodynamic (PK-PD) analyses for efficacy using phase III trial data from patients treated with a ceftaroline fosamil dosing regimen of 600 mg intravenously (i.v.) every 12 h (q12h) for 5 to 7 days for community-acquired bacterial pneumonia (CABP) were conducted. High clinical and microbiological success rates (84.7 and 86.3%, respectively) and percentages of time during the dosing interval that free-drug steady-state concentrations remained above the MIC (*f*%*T*>MIC) (98.4% had *f*%*T*>MIC values of ≥63.3) were observed among 124 microbiologically evaluable patients. As a result, significant PK-PD relationships could not be identified. These data provide support for the use of a ceftaroline fosamil dosing regimen of 600 mg i.v. q12h to treat patients with CABP.

Results of pharmacokinetic (PK)-pharmacodynamic (PD) analyses have increasingly been used to support drug development, both early in development to make decisions about dosing regimens and then in late-stage development to confirm these decisions (1). Such analyses were carried out for ceftaroline fosamil, a water-soluble prodrug of ceftaroline (2). Ceftaroline is a broad-spectrum cephalosporin with activity against pathogens commonly associated with acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP), including methicillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumoniae*, respectively. Ceftaroline fosamil is approved by the FDA for the treatment of patients with ABSSSI and CABP and for similar such indications in Europe (3, 4, 5).

By using data from ceftaroline-treated patients with ABSSSI enrolled in two phase II and two phase III studies, PK-PD efficacy analyses were carried out (2). The results of these analyses demonstrated a relationship between ceftaroline exposure, as measured by the percentage of time during the dosing interval that free-drug steady-state concentrations remained above the MIC (*f*%*T*>MIC) and microbiological response. Given that a ceftaroline fosamil dosing regimen of 600 mg given intravenously (i.v.) every 12 h (q12h) provided exposures associated with the upper plateau of the PK-PD relationship identified for efficacy, these data provided support for the use of this dosing regimen for the treatment of patients with ABSSSI. The objective of the analyses described herein was to conduct similar such PK-PD analyses for efficacy by using data from two phase III studies of patients with CABP (ClinicalTrials.gov registration numbers NCT00621504 and NCT00509106) in which the efficacy and safety of a ceftaroline fosamil dosing regimen of 600 mg i.v. q12h were evaluated (6, 7).

In each of the above-described phase III studies, patients received two consecutive infusions of 300 mg of ceftaroline fosamil i.v. q12h, each infused over 30 min for a total dose of 600 mg and a total infusion time of 60 min, with dose adjustments for patients with moderate renal impairment. The total duration of treatment was 5 to 7 days. Patients were eligible for inclusion if they were at least 18 years of age with CABP and if they required initial hospitalization or emergency room care and treatment with i.v. antimicrobial agents. Patients were also required to have radiographic evidence of pneumonia, to have acute illness with at least three clinical signs or symptoms consistent with lower respiratory tract infection, and to be in Patient Outcome Research Team (PORT) risk class III or IV. Additional details regarding the inclusion and exclusion criteria for these studies are provided elsewhere (6, 7).

Patient clinical and microbiological responses were evaluated at the test-of-cure visit, which occurred 8 to 15 days posttherapy. Clinical response was classified as a cure if there was total resolution of all signs and symptoms of CABP or improvement such that further antimicrobial therapy was not necessary. Clinical response was classified as a failure if persistence, incomplete resolution, or worsening of signs and symptoms of CABP that required further antimicrobial therapy or discontinuation of study medication or death, wherein CABP was considered causative, occurred. Microbiological response was classified as favorable if the baseline pathogen was eradicated or presumed eradicated and unfavorable if the baseline pathogen persisted or was presumed to persist.

Plasma ceftaroline fosamil and ceftaroline concentrations were measured on day 3 of therapy (approximately 15 min prior to the administration of a dose, within 5 min following the end of the second consecutive 30-min infusion, and between 1 and 3 h and between 4 and 8 h after the end of the second infusion) from a subset of patients who participated in each of the two phase III studies. The final population PK models for ceftaroline fosamil and ceftaroline (8) were used to generate steady-state ceftaroline concentrations during the 12-h dosing interval. Free-drug concentrations of ceftaroline were determined by using a protein

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binding estimate of 20% (4) and used in the calculation of *f*%*T*>MIC, the PK-PD index most predictive of ceftaroline efficacy based on preclinical data (9). It should be noted that only 28 CABP patients with PK data collected were in the microbiologically evaluable (ME) population. In order to utilize data for all patients with CABP in the ME population for the PK-PD analyses, *f*%*T*>MIC values were also calculated for patients without PK data ($n = 96$) by using the population PK models for ceftaroline fosamil and ceftaroline and patient covariate data as prior information.

To support the use of population mean predicted *f*%*T*>MIC values as a surrogate for individual predicted *f*%*T*>MIC values, the bias and precision of these exposure measures were examined for all patients with PK data by assessing the distribution of the percent predicted error (PE%) and the absolute predicted error (|PE%|), respectively (10). The PE% was calculated as the population mean predicted *f*%*T*>MIC value minus the individual predicted *f*%*T*>MIC value multiplied by 100 and then divided by the individual predicted *f*%*T*>MIC. Among the 28 patients in the ME population with PK data, the median (range) PE% and |PE%| were 0% (−19.59 to 9.09%) and 0% (0 to 19.59%), respectively. The coefficient of determination (r^2) of the relationship between the population mean predicted and individual predicted *f*%*T*>MIC values was 0.974. Given these findings, the population mean predicted *f*%*T*>MIC represented a reasonable surrogate for the individual predicted *f*%*T*>MIC for those ME patients who did not have PK data. Thus, using individual predicted and population mean predicted *f*%*T*>MIC values, PK-PD analyses were carried out with data from all of the ME patients ($n = 124$).

Among the 124 ME patients evaluated, the median (range) age, creatinine clearance, and weight were 59 (21 to 99) years, 69.0 (30.2 to 188) ml/min/1.73 m^2, and 70.0 (36.0 to 160) kg, respectively. The percentages of patients in PORT risk classes III and IV were 59.7 and 40.3%, respectively. A total of 35 patients had *S. pneumoniae* isolated at the baseline. Other pathogens isolated at the baseline included members of the family *Enterobacteriaceae* ($n = 45$) and *Haemophilus influenzae* or *Haemophilus parainfluenzae* ($n = 30$). The percentages of successful clinical and microbiological responses were 84.7 and 86.3%, respectively. A total of 108 (87.1) patients had an *f*%*T*>MIC value of 100, 91.1% of the patients had *f*%*T*>MIC values of ≥91.7, and 98.4% of the patients had *f*%*T*>MIC values of ≥63.3. The minimum, MIC_{50}, MIC_{90}, and maximum values upon which the *f*%*T*>MIC values were based were ≤0.004, 0.03, 0.5, and 16 mg/liter, respectively.

PK-PD analyses were conducted with the software program R, version 2.4.1 (11). The chi-square test or Fisher's exact test for *f*%*T*>MIC assessed as categorical independent variables and logistic regression for *f*%*T*>MIC assessed as a continuous independent variable were used to evaluate univariable relationships for clinical and microbiological responses. Categorical variables for *f*%*T*>MIC were constructed by using classification and regression tree analysis to derive dichotomous variables. Breakpoint pairs that split continuous *f*%*T*>MIC values into three groups were also assessed to investigate potential nonlinearity, with an optimal pair chosen on the basis of that which achieved the greatest statistical significance when comparing three groups of at least 10 patients each.

Despite the evaluation of all of the patients in the ME population, the results of univariable analyses failed to demonstrate significant relationships between clinical or microbiological response and *f*%*T*>MIC. However, given the limited number of failures and predominantly high *f*%*T*>MIC values, PK-PD relationships for efficacy, even if present, would have been difficult to identify. Given these findings and that the rate of bactericidal activity of β-lactams has been shown to be maximized at low multiples of the MIC (approximately four to eight times the MIC) based on historical *in vivo* (12) and prospective clinical data from infected patients described by Tam et al. (13), additional univariable analyses were carried out by using the percentages of time during the dosing interval that free-drug steady-state concentrations remained above various threshold values (*f*%*T*>threshold). The threshold values represented multiples of the MIC. Those chosen for further evaluation, 4 to 64 times the MIC, were selected to achieve a reasonable scatter of data across the *f*%*T*>threshold range of 0 to 100%. However, the results of these analyses also failed to reveal significant PK-PD relationships.

In conclusion, high percentages of clinical and microbiological success and high *f*%*T*>MIC values were observed among ME patients. The failure to identify relationships between *f*%*T*>MIC values and responses was not surprising, since the exposure range based on the ceftaroline fosamil dosing regimen administered and the MIC distribution for pathogens resulted in a narrow range of high *f*%*T*>MIC values; the majority of patients (91.1%) had *f*%*T*>MIC values ranging from 91.7 to 100. The results described herein, together with nonclinical *f*%*T*>MIC targets for *S. pneumoniae* (9), suggest that patients had exposures associated with the upper plateau of the PK-PD relationship for efficacy. Thus, these data provide support for the adequacy of 600 mg of ceftaroline fosamil i.v. q12h for the treatment of patients with CABP.

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