J Antimicrob Chemother 2019; **74**: 425–431
doi:10.1093/jac/dky439 Advance Access publication 31 October 2018

Journal of Antimicrobial Chemotherapy

Ceftaroline fosamil doses and breakpoints for *Staphylococcus aureus* in complicated skin and soft tissue infections

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Received 10 May 2018; returned 13 June 2018; revised 27 September 2018; accepted 1 October 2018

Objectives: To describe the pharmacokinetic/pharmacodynamic (PK/PD) modelling and microbiological data that were used to support the recent European approval of ceftaroline fosamil 600 mg q8h by 2 h intravenous (iv) infusion for patients with complicated skin and soft tissue infections (cSSTIs) caused by *Staphylococcus aureus* with ceftaroline MICs of 2 or 4 mg/L, and the associated EUCAST MIC breakpoint update for q8h dosing (intermediate = 2 mg/L and resistant >2 mg/L).

Methods: A population PK model for ceftaroline and ceftaroline fosamil was developed using PK data from 21 clinical studies. The final model was used to simulate PTA in patients with cSSTI receiving ceftaroline fosamil 600 mg q12h by 1 h iv infusion or 600 mg q8h by 2 h iv infusion. PTA was calculated by MIC for *S. aureus* PK/PD targets derived from preclinical studies (27% $fT_{>MIC}$ for stasis, 31% $fT_{>MIC}$ for 1 $\log_{10}$ kill and 35% $fT_{>MIC}$ for 2 $\log_{10}$ kill) and compared with *S. aureus* ceftaroline MIC distributions from a 2013 global surveillance study.

Results: The final population PK model based on 951 subjects adequately described ceftaroline and ceftaroline fosamil PK. High PTA (>90%) was predicted for the ceftaroline fosamil 600 mg q12h dosage regimen against *S. aureus* isolates with ceftaroline MICs ≤2 mg/L. Greater than 90% PTA was predicted for the ceftaroline fosamil 600 mg q8h dosage regimen against *S. aureus* with ceftaroline MICs ≤4 mg/L.

Conclusions: The approved ceftaroline fosamil dosage regimens for adults and adolescents with cSSTI achieve high PTA against *S. aureus* at the associated EUCAST breakpoints.

Introduction

Staphylococcus aureus is the most common cause of complicated skin and soft tissue infections (cSSTIs) worldwide.[1] Ceftaroline, the active metabolite of the prodrug ceftaroline fosamil, demonstrates *in vitro* activity against many pathogens commonly implicated in cSSTI, including MSSA and MRSA, *Streptococcus pyogenes* and non-ESBL-producing Gram-negative species.[2,3]

Ceftaroline fosamil is approved in Europe for the treatment of cSSTI and community-acquired pneumonia (CAP), with similar indications in other regions.[2,3] Ceftaroline fosamil is not approved for patients with CAP caused by MRSA,[2,3] as these patients were excluded from the pivotal Phase 3 trials in CAP.[4,5] For adults with cSSTI and normal renal function, ceftaroline fosamil was initially approved at a single dosage of 600 mg q12h by 1 h iv infusion based on data from the Phase 3 CANVAS 1 and 2 studies (NCT00424190 and NCT00423657), which demonstrated the non-inferiority of ceftaroline fosamil 600 mg q12h to vancomycin plus aztreonam.[6,7] Ceftaroline MIC breakpoints for *S. aureus* of susceptible ≤1 mg/L and resistant >1 mg/L were established by EUCAST for the q12h dosage regimen.

Surveillance data in some regions such as Latin America and the Asia Pacific have reported ceftaroline MIC_{90} values of 2 mg/L for *S. aureus*[8,9] and rare *S. aureus* isolates with ceftaroline MICs of 4 mg/L have also been identified.[10] Therefore, an increased dose of ceftaroline fosamil may be of clinical benefit to treat infections caused by these strains. In the Phase 3 COVERS trial

(NCT01499277), an increased total daily ceftaroline fosamil dose and infusion duration (600 mg q8h by 2 h iv infusion) was evaluated in patients with cSSTI and evidence of systemic inflammation and/or underlying comorbidities.[11] The higher q8h dose was evaluated to ensure adequate exposure of ceftaroline in severe infections that may be associated with increased clearance of ceftaroline and for infections caused by *S. aureus* with ceftaroline MICs >2 mg/L. Despite various efforts during COVERS to maximize the number of *S. aureus* clinical isolates with ceftaroline MICs of ≥2 mg/L, including an MRSA-focused expansion period following the main trial, only one such isolate was identified.[11]

In the absence of clinical data for the treatment of pathogens with higher MICs, pharmacokinetic/pharmacodynamic (PK/PD) analyses using population PK models in Monte Carlo simulations to determine PTA are important to support dose recommendations and determine clinical breakpoints. The European label for ceftaroline fosamil was recently expanded to recommend an increased dose of 600 mg q8h by 2 h iv infusion for the treatment of patients with cSSTI caused by *S. aureus* with ceftaroline MICs of 2 or 4 mg/L.[2] The approval of the q8h dose led EUCAST to introduce an intermediate category of MIC = 2 mg/L for ceftaroline against *S. aureus*, per EUCAST current practice,[12] and defined the resistant category for the q8h dose as MIC >2 mg/L,[13] with the breakpoints for the q12h dose remaining unchanged.[13] This paper describes the PK/PD modelling and microbiological data that were used together with clinical data from COVERS to support updates to the European product labelling for ceftaroline fosamil and associated EUCAST breakpoints.

Methods

Ceftaroline PK/PD targets for S. aureus

The duration of time that free drug plasma concentration exceeds the MIC of the target organism (%$fT_{>MIC}$) is an established PK/PD index for ceftaroline.[14,15] Ceftaroline *S. aureus* PK/PD targets were derived from three preclinical models: an *in vivo* neutropenic murine thigh infection model,[14] an *in vitro* single-compartment dilutional PK model[16] and an *in vitro* hollow-fibre model.[17] In total, 24 *S. aureus* isolates with ceftaroline MICs ranging from 0.12 to 4 mg/L and a wide range of genotypes, including different MLST and staphylococcal cassette chromosome *mec* (SCC*mec*) types, and isolates with genetic variations in the PBP2a domain, were assessed in these studies to: (i) include representative clinical isolates with molecular characteristics most widely prevalent in different geographic regions; and (ii) compensate for limited efficacy data on clinical trial isolates with ceftaroline MIC values ≥2 mg/L. The mean %$fT_{>MIC}$ values across the 24 isolates were used to derive *S. aureus* PK/PD targets for the PTA analysis of 27% $fT_{>MIC}$ for stasis, 31% $fT_{>MIC}$ for 1 $\log_{10}$ kill and 35% $fT_{>MIC}$ for 2 $\log_{10}$ kill (Table 1).

Population PK model development

Population PK models of ceftaroline and ceftaroline fosamil were developed and updated with clinical trial data throughout the clinical development programme (see footnote to Table S1, available as Supplementary data at *JAC* Online). In this analysis, the population PK model dataset comprised data from 21 clinical studies [14 Phase 1 studies in healthy subjects and patients with end-stage renal disease (ESRD), 1 Phase 2 and 3 Phase 3 studies in patients with cSSTI and 3 Phase 3 studies in CAP; Table S1].[4–7,11,18–26] Ceftaroline fosamil was given as an iv infusion in these studies, apart from in one study in which ceftaroline fosamil was administered intramuscularly.[20]

First-order conditional estimation with interaction method in NONMEM version 7.2.0 was used to develop the population PK model. Full details of the covariate analysis are provided in the Supplementary Methods. In brief, the previous model (unpublished data; J. Li, S. Das, D. Zhou and N. Al-Huniti) was adapted as the basis to re-evaluate the significance of previously identified significant covariates: age, patient status (healthy volunteers versus patients) and creatinine clearance normalized by body surface area (NCL_{CR}) on ceftaroline CL and patient status on the central volume of distribution of ceftaroline (V_{cc}). These covariates were re-evaluated with the pooled dataset by a backward elimination procedure to obtain a full model. The full model was subsequently used as a base model to evaluate the effect of the race and gender covariate on ceftaroline CL and V_{cc} using a forward selection and backward elimination procedure to obtain the final model. The final model was evaluated by standard goodness-of-fit plots and visual predictive check.

PTA analysis

The final model was used to simulate ceftaroline plasma concentration–time courses in 5000 patients with cSSTI receiving ceftaroline fosamil 600 mg q12h by 1 h iv infusion or 600 mg q8h by 2 h iv infusion by renal function category (doses adjusted for renal function as described below). Covariates for the PTA simulation (including age, sex, body weight and NCL_{CR}) were based on patients with cSSTI in one Phase 2 and three Phase 3 studies,[6,7,11,19] and subjects from four renal impairment studies.[18,25] Individual PK parameters were simulated from the population mean PK parameters, associated individual covariates from the multivariate covariate distribution and inter-subject variability from the final model. The residual error was fixed to zero in the simulation of individual ceftaroline time courses. For subjects with normal renal function (CL_{CR} >80 mL/min), individual covariates of 5000 subjects were sampled with replacement from the baseline covariates in patients included in the final model. For simulations of subjects in renal impairment categories, covariates were simulated from the multivariate covariate distribution and bounded by the appropriate upper and lower limits observed in the dataset. CL_{CR} values were assumed to follow a uniform distribution within the designated range for each category.

The %$fT_{>MIC}$ at steady-state was calculated for subjects with normal renal function or mild renal impairment (CL_{CR} 50–80 mL/min) receiving ceftaroline fosamil 600 mg q12h by 1 h iv infusion or q8h by 2 h iv infusion. Doses were adjusted to 400 mg, 300 mg or 200 mg for simulations of patients with moderate renal impairment (CL_{CR} 30–50 mL/min), severe renal impairment (CL_{CR} 15–30 mL/min) and ESRD (CL_{CR} 5–15 mL/min), respectively.[2,3] An 80% unbound fraction of plasma concentration was applied for calculating %$fT_{>MIC}$.[2,3] PTA was calculated as the percentage of 5000 simulated subjects with cSSTI who met the *S. aureus* PK/PD targets described above at ceftaroline MICs of 0.015, 0.03, 0.06, 0.125, 0.25, 0.5, 1, 2, 4 and 8 mg/L. PTA was also calculated by MIC for non-species-specific %$fT_{>MIC}$ targets ranging from 10%–100%.

To evaluate whether the doses provided adequate coverage for susceptibility profiles of *S. aureus* isolates encountered in clinical practice, PTAs were compared with ceftaroline MIC frequency distributions of *S. aureus* clinical isolates collected during 2013 as part of the Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) surveillance study in medical centres in Europe and the Asia Pacific region. The methodology used in the AWARE surveillance programme has been published elsewhere; in brief, isolates were tested at a central laboratory using reference CLSI broth microdilution methods and susceptibility was interpreted according to CLSI/EUCAST/FDA breakpoints.[9,27,28]

Results

Final population PK model

The final population PK model dataset included 2575 ceftaroline fosamil concentrations and 8174 ceftaroline concentrations from 951 subjects. Demographic covariate data for the final modelling dataset are summarized in Table S2. The dataset comprised 501

Table 1. Summary of preclinical studies used to derive ceftaroline *S. aureus* PK/PD targets for PTA analysis

Study	PK/PD model	No. of isolates	MIC range (mg/L)	PK/PD target [mean (SD) %$fT_{>MIC}$ at 24 h]		
				stasis	1 $\log_{10}$ kill	2 $\log_{10}$ kill
Andes and Craig (2006)[14]	neutropenic murine thigh infection model	4[a]	0.12–1	26 (8)	33 (9)	45 (13)
MacGowan *et al.* (2013)[16]	*in vitro* single-compartment dilutional PK model	8[b]	0.125–2	24.5 (8.9)	27.8 (9.5)	27.7 (5.7)
Singh *et al.* (2017)[17]	*in vitro* hollow-fibre model	12[c]	2–4	28 (7)	31 (6)	35 (6)
		Total	MIC range	Mean[d] (SD)		
		24	0.12–4	26.8 (7.7)	30.7 (8.0)	34.7 (9.4)

[a]Included two MSSA and two MRSA strains.
[b]Included four MSSA and four MRSA strains.
[c]Included 12 molecularly characterized MRSA strains: 10 isolates with one to four mutations in the non-penicillin binding domain (nPBD) or WT characteristics and two isolates with one mutation each in nPBD and PBD. SCC*mec* types included nine isolates of Type I–II and three isolates of Type III.
[d]Overall mean of individual isolates from the three data sources.

Table 2. PTA for 5000 simulated cSSTI patients with normal renal function achieving PK/PD targets for *S. aureus* by MIC following administration of ceftaroline fosamil 600 mg q12h 1 h iv infusion

Ceftaroline MIC (mg/L)	PTA (%)		
	stasis (27% $fT_{>MIC}$)	1 $\log_{10}$ kill (31% $fT_{>MIC}$)	2 $\log_{10}$ kill (35% $fT_{>MIC}$)
0.015	100	100	100
0.03	100	100	100
0.06	100	100	100
0.125	100	100	100
0.25	100	100	100
0.5	100	100	100
1	100	100	100
2	98.9	96.1	92.5
4	66.5	49.5	37.1
8	4.84	2.14	1.04
16	0.04	0	0

male and 450 female subjects with a median age of 50 years (range 12–93 years) and a median body weight of 73 kg (range 40–134 kg). Of the 951 subjects, 267 (28%) were healthy volunteers and 684 (72%) were patients, including 214 patients with CAP, 463 patients with cSSTI and 7 patients with suspected infection. The ceftaroline fosamil and ceftaroline concentration–time courses were simultaneously modelled as two-compartment disposition PK models with an assumption of 100% conversion of ceftaroline fosamil into ceftaroline. As one study included intramuscular delivery of ceftaroline fosamil, a zero-order absorption component of ceftaroline fosamil after intramuscular administration of ceftaroline fosamil was included in the model. The impact of body weight on CL and *V* of both ceftaroline and ceftaroline fosamil were modelled allometrically.

Age, participant status (patients versus healthy volunteers) and NCL_{CR} were significant covariates on CL of ceftaroline; participant status was a significant covariate on V_{cc}. The overall CL of ceftaroline increased as CL_{CR} increased, and decreased as age increased. Race and gender were not considered significant covariates of ceftaroline CL and V_{cc}. The final population PK model adequately described observed concentrations of both ceftaroline and ceftaroline fosamil and the covariate relationships in patients with cSSTI, judging from standard goodness-of-fit plots and visual predictive checks showing that simulations from the final model were consistent with the observed data (data not shown). All parameter estimates of the final model exhibited small relative standard errors (Table S3).

Ceftaroline in vitro activity against S. aureus isolates collected in the AWARE 2013 surveillance study

A total of 5380 *S. aureus* clinical isolates (2815 MRSA) were collected in Europe and 2595 *S. aureus* isolates (1574 MRSA) were collected in the Asia Pacific region. In Europe, the overall ceftaroline MIC_{90} against all *S. aureus* isolates including MRSA was 1 mg/L; in the individual countries, ceftaroline MIC_{90} values were $\leq$1 mg/L, except in Italy, Poland, Romania, Russia and Turkey, where a ceftaroline MIC_{90} of 2 mg/L was reported. In the Asia Pacific region, the ceftaroline MIC_{90} against all *S. aureus* isolates including MRSA was 2 mg/L. The ceftaroline MIC_{90} was $\leq$2 mg/L in all individual countries, except in Thailand where an MIC_{90} of 4 mg/L was reported. Isolates with ceftaroline MICs >2 mg/L comprised 9 MRSA isolates collected from Thailand with MICs of 8 mg/L and 33 isolates collected from South Korea (4 isolates) and Thailand (29 isolates) with MICs of 4 mg/L.

PTA by MIC for patients with normal renal function given ceftaroline fosamil 600 mg q12h by 1 h iv infusion

PTAs by MIC for the *S. aureus* PK/PD targets in 5000 simulated cSSTI patients with normal renal function given ceftaroline fosamil 600 mg q12h by 1 h iv infusion are shown in Table 2. Ceftaroline fosamil 600 mg q12h is predicted to achieve >95% PTA for the 1 $\log_{10}$ kill target (31% $fT_{>MIC}$) and >90% PTA for the 2 $\log_{10}$ kill target (35% $fT_{>MIC}$) against *S. aureus* testing with ceftaroline MICs $\leq$2 mg/L. PTA by MIC overlaid with the AWARE 2013 ceftaroline MIC frequency distribution for *S. aureus* shows that ceftaroline fosamil 600 mg q12h provides >90% PTA for the MIC distributions of *S. aureus* isolates with a ceftaroline MIC $\leq$2 mg/L in both Europe

Table 3. PTA for 5000 simulated cSSTI patients with normal renal function achieving PK/PD targets for *S. aureus* by MIC following administration of ceftaroline fosamil 600 mg q8h 2 h iv infusion

	PTA (%)		
Ceftaroline MIC (mg/L)	stasis (27% $fT_{>MIC}$)	1 $\log_{10}$ kill (31% $fT_{>MIC}$)	2 $\log_{10}$ kill (35% $fT_{>MIC}$)
0.015	100	100	100
0.03	100	100	100
0.06	100	100	100
0.125	100	100	100
0.25	100	100	100
0.5	100	100	100
1	100	100	100
2	100	100	100
4	98.7	96.8	93.6
8	42.9	33.1	23.4
16	0.72	0.38	0.22

and the Asia Pacific region (Figure 1). For PK/PD targets up to and including 50% $fT_{>MIC}$ (beyond the 35% $fT_{>MIC}$ required for 2 $\log_{10}$ kill), >90% PTA was achieved for an MIC of 1 mg/L (Table S4). At a target of 60% $fT_{>MIC}$, PTA was 78.7% for an MIC of 1 mg/L.

PTA by MIC for patients with normal renal function given ceftaroline fosamil 600 mg q8h by 2 h iv infusion

PTAs by MIC for the *S. aureus* PK/PD targets in 5000 simulated cSSTI patients with normal renal function (CL_{CR} >80 mL/min) given ceftaroline fosamil 600 mg q8h by 2 h iv infusion are shown in Table 3. Ceftaroline fosamil 600 mg q8h is predicted to achieve >95% PTA for the 1 $\log_{10}$ kill target (31% $fT_{>MIC}$) and >90% PTA for the 2 $\log_{10}$ kill target against *S. aureus* isolates with ceftaroline MICs ≤4 mg/L (Table 3). PTA by MIC overlaid with the AWARE 2013 ceftaroline MIC frequency distributions for *S. aureus* in Europe and the Asia Pacific region shows that ceftaroline fosamil 600 mg q8h provides >90% PTA for the MIC distribution of *S. aureus* with ceftaroline MICs ≤4 mg/L in both regions (Figure 2). For an MIC of 2 mg/L, >90% PTA was maintained for targets as high as 60% $fT_{>MIC}$ (Table S5). At an MIC of 4 mg/L, PTA was 86% for a target of 40% $fT_{>MIC}$.

PTA by MIC for patients with renal impairment receiving adjusted q12h and q8h doses

Similar PTA analyses were conducted for patients with mild renal impairment receiving ceftaroline fosamil 600 mg q12h or q8h, and in patients with moderate renal impairment, severe renal impairment and ESRD receiving the recommended dosage adjustments.[2,3] PTAs by MIC were generally similar or higher in patients with renal impairment compared with subjects with normal renal function (Tables S6 and S7).

Discussion

Ceftaroline PK/PD targets against *S. aureus* were initially derived based on a single *in vivo* study against four *S. aureus* isolates with ceftaroline MICs ranging from 0.12 to 1 mg/L.[14] The mean (SD) %$fT_{>MIC}$ values for stasis, 1 $\log_{10}$ kill and 2 $\log_{10}$ kill in that study were 26% (8), 33% (9) and 45% (13). Since then, ceftaroline PK/PD against *S. aureus* have been evaluated in two further *in vitro* studies.[16,17] The PK/PD targets for *S. aureus* used in this analysis were derived from these three studies using 24 isolates with a wider range of ceftaroline MICs (0.12–4 mg/L) and genotypes than in the single *in vivo* study alone. It is expected that there would be some variation in the PK/PD data obtained from *in vitro* and *in vivo* approaches; however, the %$fT_{>MIC}$ values across the three models were generally in good concordance. Using data from across three different models provides a robust basis to determine the *S. aureus* PK/PD targets for use in PTA analysis to support dosage recommendations and breakpoint determination, as each model may compensate for limitations in the others. The ceftaroline *S. aureus* PK/PD targets for stasis, 1 $\log_{10}$ kill and 2 $\log_{10}$ kill were thus better characterized and defined as 27%, 31% and 35% $fT_{>MIC}$, respectively.

An early population PK model based on data from 185 healthy subjects and 92 patients with cSSTI was used to support the initial approvals of the ceftaroline fosamil 600 mg q12h dosage regimen.[29,30] The population PK model reported here was based on a more substantial clinical dataset comprising 951 subjects, including 463 patients with cSSTI. Similar to the earlier model,[30] age, participant status (patients versus healthy volunteers) and NCL_{CR} were identified as significant covariates impacting ceftaroline and ceftaroline fosamil PK. Critical illness caused by severe infection can affect antibiotic PK, resulting in low exposures and a higher risk of not achieving PK/PD targets compared with non-critically ill patients.[31] The inclusion of patient PK data from the COVERS study [which included patients with systemic inflammatory response syndrome (SIRS) and bacteraemia][11] ensured that a broad range of comorbid conditions and disease severity covariates were included in the dataset. This provides reassurance that the PTA estimates from this model will be relevant for patients with more severe infections.

Whilst the susceptible breakpoint for the ceftaroline fosamil 600 mg q12h dose is ≤1 mg/L, high PTA (>90%) was predicted for patients with cSSTI treated with the q12h dosage regimen against *S. aureus* with ceftaroline MICs up to and including 2 mg/L. Ceftaroline fosamil 600 mg q8h is predicted to achieve high PTA (>90%) for *S. aureus* MICs up to and including 4 mg/L. Whilst the resistant breakpoint for the ceftaroline fosamil q8h dose is MIC >2 mg/L, both the European label and EUCAST indicate that ceftaroline fosamil 600 mg q8h can be used for the treatment of cSSTI caused by rare *S. aureus* isolates with MICs of 4 mg/L. For both dosage frequencies, similar or higher PTAs are still achieved in cSSTI patients with renal impairment receiving adjusted doses for renal function compared with patients with normal renal function.

The achievement of therapeutic antibiotic concentrations at the infection site is an important consideration for breakpoint setting and dosing recommendations. In line with the PTA results presented here, comparison of ceftaroline PK following administration of ceftaroline 600 mg q12h or q8h in healthy volunteers found that calculated %$fT_{>MIC}$ values in the plasma, muscle and subcutis exceeded the *S. aureus* PK/PD targets for both dosage regimens up to an MIC of 2 mg/L, while the q8h dosage regimen provided %$fT_{>MIC}$ values ranging from 26.2%–43.0% across the three compartments for an MIC of 4 mg/L.[32]

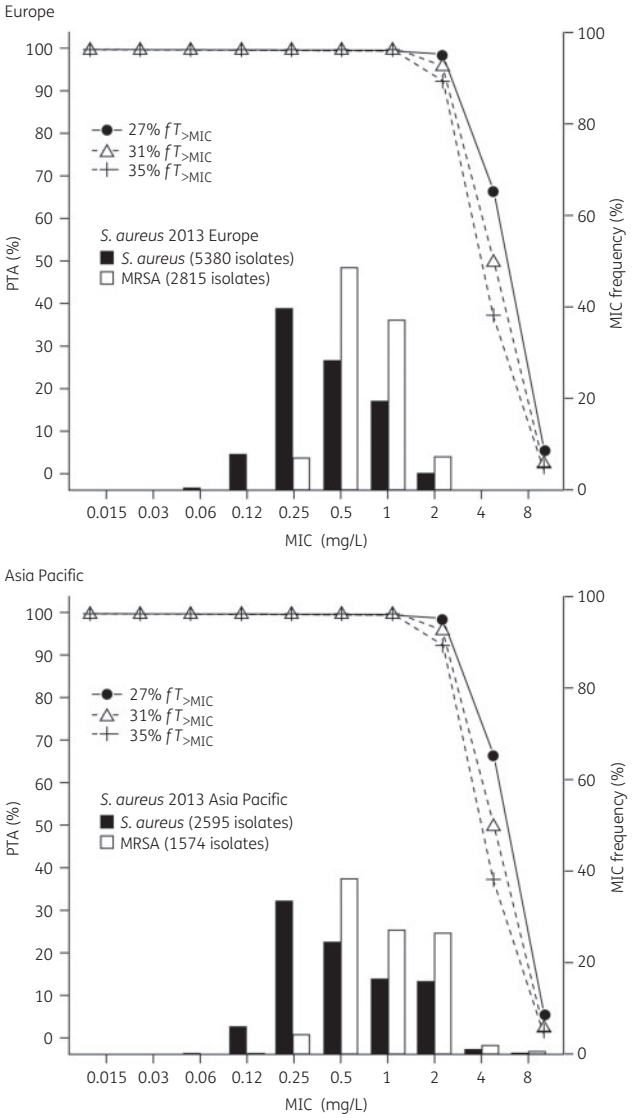

Figure 1. PTA for 5000 simulated cSSTI patients with normal renal function achieving PK/PD targets for *S. aureus* by MIC following administration of ceftaroline fosamil 600 mg q12h 1 h iv infusion, overlaid with ceftaroline MIC distributions for *S. aureus* collected from the 2013 AWARE surveillance study in Europe and the Asia Pacific region. The ceftaroline MIC_{90} values for all *S. aureus* isolates and the MRSA subset were 1 mg/L and 2 mg/L in Europe and the Asia Pacific region, respectively.

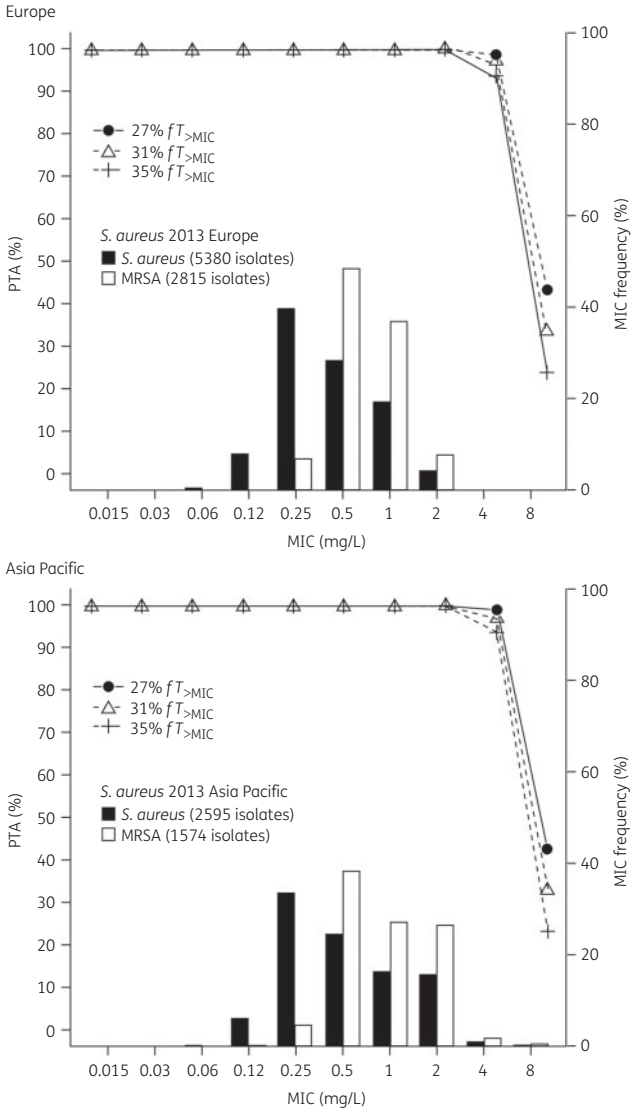

Figure 2. PTA for 5000 simulated cSSTI patients with normal renal function achieving PK/PD targets for *S. aureus* by MIC following administration of ceftaroline fosamil 600 mg q8h 2 h iv infusion, overlaid with ceftaroline MIC distributions for *S. aureus* collected from the 2013 AWARE surveillance study in Europe and the Asia Pacific region. The ceftaroline MIC_{90} values for all *S. aureus* isolates and the MRSA subset were 1 mg/L and 2 mg/L in Europe and the Asia Pacific region, respectively.

The susceptibility of *S. aureus* to ceftaroline varies geographically.[8,9,33,34] In the AWARE 2013 surveillance study data presented here, ceftaroline MIC_{90}s of 1 mg/L and 2 mg/L were reported for *S. aureus* (including MRSA) in Europe and the Asia Pacific region, respectively. Whilst a low frequency of *S. aureus* isolates were identified with an MIC of 2 mg/L in Europe, ceftaroline MIC_{90}s of 2 mg/L were reported in Italy, Poland, Romania, Russia and Turkey. In the Asia Pacific region there was a much higher frequency of isolates with a ceftaroline MIC of 2 mg/L: in most countries the MIC_{90} was 2 mg/L, except in Thailand where the MIC_{90} was 4 mg/L. Ceftaroline 600 mg q12h was shown to provide high PTA across the MIC distributions of real-life *S. aureus* isolates with ceftaroline MICs $\leq$2 mg/L, while the ceftaroline 600 mg q8h dosage regimen provides high PTA for *S. aureus* isolates with ceftaroline MICs $\leq$4 mg/L.

The effect of the EUCAST MIC breakpoint change on the interpretation of *S. aureus* susceptibility to ceftaroline was explored in a recent analysis of MRSA isolates from cSSTI patients collected through the AWARE 2015–16 surveillance programme.[35] The percentage of isolates categorized as resistant to ceftaroline across Europe, Latin America, Middle East/Africa and the Asia/South Pacific regions decreased from 3.1%–7.6% when using the q12h breakpoints (resistant >1 mg/L) to 0.0%–1.3% when using the q8h breakpoints (intermediate = 2 mg/L, resistant >2 mg/L). This was

most notable in the Latin America and Asia/South Pacific regions, where isolates with a ceftaroline MIC of 2 mg/L are more prevalent and are now classified in the intermediate category. These findings indicate that the frequency of *S. aureus* resistant to ceftaroline (MIC >2 mg/L) remains low globally.

A limitation of this analysis is the lack of clinical outcomes data available for cSSTI caused by *S. aureus* with high ceftaroline MICs. The results from COVERS demonstrated the non-inferiority of ceftaroline fosamil 600 mg q8h with respect to vancomycin plus aztreonam in patients with cSSTI and no new safety signals were identified.[11] Importantly, clinical outcomes in patient subgroups with more severe infection were comparable between COVERS and the CANVAS studies; clinical cure rates in patients with one or more sign of systemic inflammation in the clinically evaluable population were 88.0% (219/249) in COVERS versus 91.1% (308/338) in CANVAS 1 and 2.[36] Consistent with this finding, predicted ceftaroline exposures (AUC_{ss} and $C_{max,\ ss}$) were comparable between COVERS patients with and without signs of severe infection, such as high white blood cell count, high C-reactive protein levels and the presence of fever, SIRS or bacteraemia.[37] Together with the findings presented here, these data support that ceftaroline fosamil 600 mg q12h is a robust dosage regimen for most patients with cSSTI, with the 600 mg q8h regimen offering an additional treatment option for patients with cSSTI caused by *S. aureus* with ceftaroline MICs of 2 or 4 mg/L.

Conclusions

S. aureus with ceftaroline MICs of 2–4 mg/L represent the upper end of the MIC distribution and clinical outcomes data are limited for cSSTI caused by *S. aureus* isolates with high ceftaroline MICs. Population PK modelling based on an extensive patient dataset and using robustly characterized PK/PD targets indicates that ceftaroline fosamil 600 mg q12h achieves >90% PTA against *S. aureus* at the EUCAST susceptible breakpoint of 1 mg/L as well as for a ceftaroline MIC of 2 mg/L, and that ceftaroline fosamil 600 mg q8h achieves >90% PTA for ceftaroline MICs ≤4 mg/L. These results provide reassurance that the approved ceftaroline fosamil dosage regimens for cSSTI achieve high PTA against *S. aureus* at the associated EUCAST MIC breakpoints.

Acknowledgements

We would like to thank all the investigators and patients involved in the ceftaroline fosamil clinical trials and Jennifer Hammond, Pfizer, Collegeville, PA, USA for her review and critical input on the manuscript.
These data were presented in part at the 55th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) 2015, San Diego, CA, USA (abstracts A-456 and A-455) and at the 25th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) 2015, Copenhagen, Denmark (poster P1384).

Funding

The population PK modelling and PTA analysis and the global (excluding the US) AWARE surveillance programme were funded by AstraZeneca. Of the studies included in this population PK analysis, NCT01499277, NCT01371838, NCT01458743, NCT01612507 and NCT01664065 were originally sponsored by AstraZeneca and are now sponsored by Pfizer. All other studies included in the population PK analysis were sponsored by Allergan. AstraZeneca's rights to ceftaroline fosamil were acquired by Pfizer in December 2016.
Medical writing support was provided by Sirisha Bulusu, MBiochem of Prime, Knutsford, Cheshire, UK, funded by Pfizer. Ultimate responsibility for opinions, conclusions and data interpretation lies with the authors.

Transparency declarations

J. I., S. D. and J. L. are former employees of and shareholders in AstraZeneca. G. G. S. is a former employee of and shareholder in AstraZeneca and is currently an employee of and shareholder in Pfizer. D. Z. is an employee of and shareholder in AstraZeneca. D. M. is a former employee of Allergan. J. L. Y. is an employee of and shareholder in Pfizer.

Supplementary data

Methods and Tables S1 to S7 appear as Supplementary data at *JAC* Online.

Data sharing

Upon request, and subject to certain criteria, conditions and exceptions see (https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (i) for indications that have been approved in the US and/or EU or (ii) in programmes that have been terminated (i.e. development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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