International Journal of Antimicrobial Agents 53 (2019) 830–837

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

# Ceftaroline fosamil therapy in patients with acute bacterial skin and skin-structure infections with systemic inflammatory signs: A retrospective dose comparison across three pivotal trials

G. Ralph Corey[a], Mark H. Wilcox[b], Jesus Gonzalez[c,1], Alena Jandourek[d], David J. Wilson[c,2], H. David Friedland[d], Shampa Das[c,3], Joseph Iaconis[e], Matthew Dryden[f,*]

[a] Department of Medicine, Duke University School of Medicine, 310 Trent Drive, Durham, NC 27710, USA
[b] Department of Medical Microbiology, Leeds Teaching Hospitals & University of Leeds, Leeds, UK
[c] AstraZeneca, Macclesfield, UK
[d] Cerexa, Inc., Oakland, CA, USA
[e] AstraZeneca, Waltham, MA, USA
[f] Hampshire Hospitals NHS Foundation Trust, Winchester, UK

ARTICLE INFO

*Article history:*
Received 2 August 2018
Accepted 27 January 2019

Editor: H. Derendorf

*Keywords:*
Ceftaroline fosamil
Skin and soft-tissue infection
Sepsis
Clinical trial

ABSTRACT

This post-hoc analysis compared the pharmacokinetics and clinical outcomes of ceftaroline fosamil 600 mg every 12 (q12h) versus every 8 hours (q8h) in patients with acute bacterial skin and skin-structure infection (ABSSSI) and signs of sepsis. Clinical outcomes at test-of-cure in patients with ABSSSI and systemic inflammatory signs/systemic inflammatory response syndrome (SIRS) as well as ceftaroline minimum inhibitory concentrations (MICs) against baseline pathogens were compared between the COVERS trial (ceftaroline fosamil 600 mg q8h, 2-h infusion) and the CANVAS 1 and 2 trials (ceftaroline fosamil 600 mg q12h, 1-h infusion). Ceftaroline exposure among patients in COVERS with or without markers of sepsis was compared using population pharmacokinetic modelling. In COVERS, 62% (312/506) and 41% (208/506) of ceftaroline fosamil-treated patients had ≥1 systemic inflammatory sign or SIRS, respectively, compared with 55% (378/693) and 22% (155/693), respectively, in the CANVAS trials. Clinical cure rates for the modified intent-to-treat population in COVERS and CANVAS were similar for ceftaroline fosamil-treated patients with ≥1 sign of sepsis [82% (255/312) and 85% (335/394)] and for those with SIRS [84% (168/199) and 85% (131/155)]. Ceftaroline MIC distributions were similar across trials. Sepsis did not affect predicted individual steady-state ceftaroline exposure. Clinical cure rates in patients with ≥1 systemic inflammatory sign or SIRS were comparable for both ceftaroline fosamil dosage regimens. Pathogen susceptibilities to ceftaroline were similar across trials. Ceftaroline exposure was not affected by disease severity. Ceftaroline fosamil 600 mg q12h is a robust dosage regimen for most ABSSSI patients with sepsis [ClinicalTrials.gov ID: NCT01499277, NCT00424190, NCT00423657].



## 1. Introduction

Acute bacterial skin and skin-structure infections (ABSSSIs) and complicated skin and soft-tissue infections (cSSTIs) include cellulitis/erysipelas, wound infection and major cutaneous abscess [1,2], imposing a substantial burden on healthcare systems. Between 2005 and 2010, the incidence of SSTI in the USA was ca. 48 per 1000 person-years [3]; currently, up to 300 000 surgical site infections occur each year, including those of the skin and subcutaneous tissue [4]. SSTIs can be serious, requiring hospitalisation and surgical procedures, and occasionally can cause bacteraemia and death [5]. Factors associated with ABSSSI onset and clinical

* Corresponding author. Present address: Department of Microbiology & Infection, Hampshire Hospitals NHS Foundation Trust, Romsey Road, Winchester, Hampshire SO22 5DG, UK. Tel.: +44 1962 824 451; fax: +44 1962 825 431.
*E-mail addresses:* matthew.dryden@phe.gov.uk, matthew.dryden@hhft.nhs.uk (M. Dryden).
[1] Present address: Block C18-1, 1 Watson Street, Manchester M3 4EF, UK.
[2] Present address: DJW STATS Consulting, 1 Market Street, Whaley Bridge, High Peak, UK.
[3] Present address: Centre for Antimicrobial Pharmacodynamics, Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool, Liverpool, UK.

https://doi.org/10.1016/j.ijantimicag.2019.01.016

failure of ABSSSI treatment include obesity and low antibiotic dosage at discharge [6,7].

Ceftaroline, the active metabolite of the prodrug ceftaroline fosamil, is a cephalosporin antibiotic with in vitro activity against many of the common bacteria associated with ABSSSI, including *Staphylococcus aureus* [both methicillin-susceptible *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA)], *Streptococcus pyogenes, Streptococcus agalactiae*, and non-extended-spectrum $\beta$-lactamase (ESBL)-producing *Escherichia coli, Klebsiella pneumoniae* and *Klebsiella oxytoca* [8,9]. In the pivotal phase III CANVAS 1 and 2 trials, ceftaroline fosamil 600 mg given as a 1-h intravenous (i.v.) infusion every 12 h (q12h) was shown to be non-inferior to vancomycin plus aztreonam for the treatment of ABSSSI [10–12]. These results supported the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approvals of ceftaroline fosamil 600 mg q12h (adjusted for renal function) for the treatment of adults with ABSSSI and cSSTI, respectively [8,9].

The presence of sepsis can impact the pharmacokinetics of some antibiotics and thus potentially affect antibiotic efficacy in patients with ABSSSI. Septic patients in the intensive care unit have shown an increased volume of distribution ($V_d$) and increased clearance. An increase in $V_d$ in these patients has been shown to be due to capillary leakage and endothelial damage, which can result in subtherapeutic dosing following administration of antibiotics. Clearance is variable and is dependent on the individual's disease state. Variable exposure to drug as a result of changes in $V_d$ and clearance can, in turn, result in variable responsiveness to treatment both in terms of efficacy and toxicity, and this can impact mortality rates in these patients [13–15].

The phase III COVERS trial was conducted to assess a ceftaroline fosamil dosage regimen of 600 mg as a 2-h infusion every 8 h (q8h) in patients with ABSSSI with systemic inflammatory response syndrome (SIRS) or underlying co-morbidities and, on average, a greater lesion size [12]. Results from COVERS showed that ceftaroline fosamil 600 mg q8h was non-inferior to vancomycin plus aztreonam in these patients [12].

The objective of this post-hoc analysis was to compare ceftaroline fosamil 600 mg q12h versus 600 mg q8h for the treatment of ABSSSI in patients with signs of sepsis, first by comparing clinical outcomes and pathogen susceptibilities in the COVERS trial with the previously published CANVAS trials, and second by using population pharmacokinetic (PK) modelling to compare ceftaroline exposure in patients with or without markers of sepsis.

## 2. Materials and methods

### 2.1. Study design

COVERS (NCT01499277) and CANVAS 1 and 2 (NCT00424190 and NCT00423657) were phase III, multicentre, randomised, double-blind, comparative safety and efficacy trials of i.v. ceftaroline fosamil versus vancomycin plus aztreonam for the treatment of ABSSSI [10–12]. Patients were randomised to receive ceftaroline fosamil or vancomycin plus aztreonam at a ratio of 2:1 in COVERS and 1:1 in CANVAS 1 and 2. In COVERS, ceftaroline fosamil was administered at 600 mg q8h and vancomycin was administered at 15 mg/kg q12h with aztreonam at 1 g q8h. In CANVAS 1 and 2, ceftaroline fosamil was administered at 600 mg q12h and vancomycin plus aztreonam were each administered at 1 g q12h. Ceftaroline fosamil dosages were adjusted for patients with baseline creatinine clearance ($CL_{Cr}$) $\leq$50 mL/min, and vancomycin plus aztreonam dosages were adjusted according to the respective product labelling and institutional practice guidelines. Treatments were given for 5–14 days in all trials. The primary outcome measure for all three trials was the clinical cure rate at test-of-cure (TOC) in the modified intent-to-treat (MITT) and clinically evaluable (CE) patient populations.

### 2.2. Patients and disease characteristics

The COVERS and CANVAS trials enrolled adult patients with cSSTI. The entire COVERS patient population, and a proportion of those in the CANVAS trials, met the FDA definition of ABSSSI [1]. Inclusion and exclusion criteria for the CANVAS trials have been described previously [10,11]. In brief, patients had a diagnosis of cSSTI (defined as deep extensive cellulitis, major cutaneous abscess requiring surgical drainage, or infected wound, ulcer or burn) of sufficient severity to warrant hospitalisation and $\geq$5 days of parenteral antibacterial therapy. Inclusion and exclusion criteria for COVERS were similar to the CANVAS trials, with an additional requirement of ABSSSI with surrounding area of erythema, oedema and/or induration with surface area $\geq$75 $cm^2$, reflecting regulatory guidance at the time the study was initiated [1,12]; of note, COVERS (but not CANVAS) excluded patients with diabetic foot infections. Disease characteristics assessed at baseline included systemic signs of infection, presence of SIRS [defined as the presence of at least two of the following symptoms at baseline: temperature <36°C or >38°C; heart rate >90 beats/min; respiratory rate >20 breaths/min or on blood gas, a $PaCO_2$ <32 mmHg (4.3 kPa); white blood cell (WBC) count <4000 cells/$mm^3$ or >12 000 cells/$mm^3$, or >10% band forms (immature WBCs)] and an elevated C-reactive protein (CRP) level. Patients were required to give informed consent prior to enrolment in the trials.

### 2.3. Microbiology

Baseline pathogen susceptibilities to ceftaroline [minimum inhibitory concentrations (MICs)] were determined using Clinical and Laboratory Standards Institute (CLSI) methodology [16] by a central reference laboratory.

### 2.4. Clinical outcomes

Clinical cure was defined as total resolution of all signs and symptoms of the baseline infection or improvement such that no further antimicrobial therapy was necessary. Outcome was determined at the TOC time point (8–15 days after the last dose of study drug) in the MITT population (all randomised patients who received any study medication) and CE population, a subset of the MITT population who had a diagnosis of ABSSSI, had no non-eligible infections, received a prespecified minimum of study drug, had an evaluation at the TOC (or were determined to be a clinical failure at end of therapy) and did not receive any systemically active antibacterial agents that may have affected the infection under study [12,17]. Clinical cure rates were summarised for the MITT and CE populations overall and for patient subgroups with at least one systemic sign of inflammation, or sepsis [fever >38°C, hypothermia <36°C, elevated WBC count (>10 000 cells/$mm^3$ or bands >10%)], at least two severe signs or symptoms (erythema, swelling, tenderness or warmth that was designated as 'severe' by the investigator) or SIRS. As body weight and renal function have also been shown to impact ceftaroline pharmacokinetics [18,19], clinical cure rates were summarised by body mass index (BMI) and $CL_{Cr}$ to compare outcomes across BMI and $CL_{Cr}$ subgroups. Finally, clinical cure rates were also summarised by baseline pathogen. Safety was assessed in all randomised patients who received at least one dose of study therapy.

### 2.5. Population pharmacokinetic modelling

The ceftaroline population PK model used in this analysis was developed using a large patient PK data set that included data

**Table 1**
Patient demographics and baseline characteristics of the modified intent-to-treat (MITT) population[a]

| Characteristic | COVERS | | CANVAS 1 and 2 | |
|---|---|---|---|---|
| | Ceftaroline fosamil ($n=506$) | Vancomycin + aztreonam ($n=255$) | Ceftaroline fosamil ($n=693$) | Vancomycin + aztreonam ($n=685$) |
| Age (years) (mean ± S.D.) | 52.6 ± 16.5 | 53.6 ± 16.3 | 47.5 ± 17.0 | 48.4 ± 16.6 |
| Sex | | | | |
| Female | 196 (38.7) | 107 (42.0) | 249 (35.9) | 266 (38.8) |
| Male | 310 (61.3) | 148 (58.0) | 444 (64.1) | 419 (61.2) |
| Race | | | | |
| White | 341 (67.4) | 160 (62.7) | 506 (73.0) | 512 (74.7) |
| Black or African–American | 13 (2.6) | 13 (5.1) | 48 (6.9) | 41 (6.0) |
| Asian | 126 (24.9) | 64 (25.1) | 6 (0.9) | 5 (0.7) |
| American Indian or Alaska Native | 1 (0.2) | 0 | 6 (0.9) | 4 (0.6) |
| Native Hawaiian or other Pacific Islander | – | – | 2 (0.3) | 2 (0.3) |
| Multiracial/other/unknown | 25 (4.9) | 18 (7.1) | 125 (18.0) | 121 (17.7) |
| BMI (kg/m$^2$) [median (range)] | 26.6 (15.0–50.0) | 26.6 (14.0–50.0) | 26.9 (14.1–74.1) | 27.4 (16.6–66.5) |
| Baseline $CL_{Cr}$ (mL/min)[b] | | | | |
| >30 to ≤50 | 31 (6.1) | 17 (6.7) | 23 (3.3) | 26 (3.8) |
| >50 to ≤80 | 91 (18.0) | 46 (18.0) | 99 (14.3) | 98 (14.3) |
| >80 | 362 (71.5) | 183 (71.8) | 569 (82.1) | 559 (81.6) |
| Baseline CRP (mg/L)[c] | | | | |
| ≤50 | 178 (35.2) | 100 (39.2) | 396 (57.1) | 387 (56.5) |
| >50 to ≤150 | 178 (35.2) | 80 (31.4) | 177 (25.5) | 166 (24.2) |
| >150 | 139 (27.5) | 68 (26.7) | 98 (14.1) | 111 (16.2) |
| Primary diagnosis of cellulitis | 300 (59.3) | 136 (53.3) | 249 (35.9) | 273 (39.9) |
| Co-morbid conditions | | | | |
| Diabetes mellitus | 84 (16.6) | 38 (14.9) | 122 (17.6) | 120 (17.5) |
| Peripheral vascular disease | 27 (5.3) | 11 (4.3) | 93 (13.4) | 93 (13.6) |
| Infection area (cm$^2$) [median (range)] | 400 (75–5040) | 400 (77–6048) | 156 (1–3150) | 150 (0.04–4950) |
| Prior antibiotic therapy | 240 (47.4) | 116 (45.5) | 276 (39.8) | 260 (38.0) |
| ≥1 systemic inflammatory sign[d] | 312 (61.7) | 166 (65.1) | 378 (54.5) | 363 (53.0) |
| ≥2 severe signs and/or symptoms[e] | 329 (65.0) | 165 (64.7) | 372 (53.7) | 379 (55.3) |
| SIRS[f] | 199 (39.3) | 105 (41.2) | 155 (22.4) | 163 (23.8) |

S.D., standard deviation; BMI, body mass index; $CL_{Cr}$, creatinine clearance; CRP, C-reactive protein; WBC, white blood cell; SIRS, systemic inflammatory response syndrome.
[a] Data are *n* (%) unless otherwise stated.
[b] 9 patients had $CL_{Cr}$ >20 to <30 mL/min and 22 patients had missing $CL_{Cr}$ data in COVERS; 4 patients had $CL_{Cr}$ ≤30 mL/min in CANVAS 1 and 2.
[c] 18 patients had missing CRP data in COVERS; 43 patients had missing CRP data in CANVAS 1 and 2.
[d] Systemic inflammatory signs were fever >38°C, hypothermia <36°C, elevated WBC count (>10 000 cells/mm$^3$) or bands >10%.
[e] Severe local signs were erythema, swelling, tenderness or warmth that was designated as 'severe' by the investigator.
[f] SIRS criteria were defined as the presence of at least two of the following symptoms at baseline: temperature <36°C or >38°C; heart rate >90 beats/min; respiratory rate >20 breaths/min, or on blood gas, a $PaCO_2$, <32 mmHg (4.3 kPa); WBC count <4000 cells/mm$^3$ or >12 000 cells/mm$^3$, or >10% band forms (immature WBCs).

from 14 phase I trials in healthy subjects (with normal renal function or renal impairment), 1 phase II trial in patients with cSSTI, 3 phase III trials in patients with cSSTI (CANVAS 1, CANVAS 2 and COVERS) and 3 phase III trials in patients with community-acquired pneumonia [10–12,19–28]. Patient PK data were obtained in COVERS and in a subset of 45 patients in CANVAS 1 and 2 trials by sparse PK sampling over a single dosing interval (i.e. 8 h) on Day 3, with intensive PK samples taken in a subset of patients [29]. The population PK model was derived from first-order conditional estimation with the interaction model using the software program NONMEM v.7.2.0 (ICON plc, Dublin, Ireland). Details related to the PK modelling have been previously described [30]. Ceftaroline PK profiles were estimated for individual patients in COVERS with available ceftaroline PK data. Steady-state ceftaroline exposures [maximum plasma concentration ($C_{max,ss}$) and area under the concentration–time curve ($AUC_{ss}$)] were derived from the individual predicted ceftaroline concentration–time courses from the population PK model using non-compartmental analysis. To assess whether the presence of markers of systemic inflammation or sepsis had any impact on ceftaroline exposures, AUCss and Cmax,ss were compared for the following patient subgroups: fever ≤38°C or >38°C; WBC count ≤12 000/mm$^3$ or >12 000/mm$^3$; CRP ≤50 mg/L, >50 mg/L to ≤150 mg/L or >150 mg/L; and presence or absence of SIRS or bacteraemia at baseline [29].

### 2.6. Statistical analyses

Patient outcomes are presented using descriptive statistics, and between-group outcome differences (95% confidence interval) were determined using the Miettinen & Nurminen method [31]. Full details of the statistical analyses used in the COVERS and CANVAS 1 and 2 trials have previously been described [10,11].

## 3. Results

### 3.1. Patient demographics and baseline characteristics

Patient demographics and baseline characteristics are summarised in Table 1. Most patients were male and white. Overall, baseline characteristics, including BMI, co-morbidities and prior antibiotic therapy, were similar between the patient populations in COVERS and the CANVAS trials. Patients were slightly older in COVERS compared with the CANVAS trials (mean ± standard deviation age, 52.6 ± 16.5 years vs. 47.5 ± 17.0 years for ceftaroline fosamil-treated patients) and there was a greater proportion of patients with a primary cSSTI diagnosis of cellulitis in COVERS [300 (59.3%) vs. 249 (35.9%) for ceftaroline fosamil-treated patients].

As expected based on inclusion criteria, more severe ABSSSI was observed in patients in COVERS; the median (range) infection area was greater among ceftaroline fosamil-treated patients from COVERS [400 (75–5040) cm$^2$] compared with those from CANVAS 1 and 2 [156 (1–3150) cm$^2$]. A greater proportion of ceftaroline fosamil-treated patients from COVERS also had at least one systemic inflammatory sign [312/506 (61.7%) COVERS vs. 378/693 (54.5%) CANVAS 1 and 2] and SIRS [208/506 (41.1%) COVERS vs. 155/693 (22.4%) CANVAS 1 and 2] at baseline. Compared with

**Table 2**
Susceptibility to ceftaroline of pathogens isolated at baseline in the modified intent-to-treat (MITT) population

| Pathogen | COVERS | | | CANVAS 1 and 2 | | |
|---|---|---|---|---|---|---|
| | Isolates ($n$)[a] | MIC range[b] | $MIC_{90}$[b,c] | Isolates ($n$)[a] | MIC range[b] | $MIC_{90}$[b] |
| Gram-positive bacteria | | | | | | |
| *Staphylococcus aureus*[d,e] | 217 | 0.06–1.0 | 0.5 | 399 | 0.06–2.0 | 0.5 |
| MSSA | 164 | 0.06–0.5 | 0.25 | 235 | 0.06–0.5 | 0.25 |
| MRSA | 54 | 0.25–1.0 | 0.5 | 164 | 0.25–2.0 | 0.5 |
| Streptococci | | | | | | |
| *Streptococcus pyogenes*[f] | 25 | ≤0.008 | ≤0.008 | 61 | ≤0.004–0.008 | ≤0.004 |
| *Streptococcus agalactiae*[f] | 16 | ≤0.008–0.015 | 0.015 | 22 | 0.008–0.015 | 0.015 |
| *Streptococcus dysgalactiae* | 12 | ≤0.008–0.06 | 0.015 | 13 | ≤0.004–0.008 | 0.008 |
| *Streptococcus anginosus* group | 21 | ≤0.008–0.03 | 0.03 | 14 | ≤0.004–0.06 | 0.03 |
| *Enterococcus faecalis* | 13 | 0.5–64 | 8 | 27 | 0.25–16 | 8 |
| Gram-negative bacteria[g] | | | | | | |
| *Escherichia coli* (non-ESBL-producing) | 26 | ≤0.015–8 | 1.0 | 23 | 0.015 to >16 | 1.0 |
| *Klebsiella oxytoca* | 8 | 0.03–0.25 | – | 11 | 0.03–0.25 | 0.25 |
| *Klebsiella pneumoniae* | 12 | 0.06 to >32 | >32 | 18 | 0.03 to >16 | >16 |
| *Morganella morganii* | 7 | 0.03–0.12 | – | 11 | 0.06 to >16 | >16 |
| *Proteus mirabilis* | 11 | 0.03 to >32 | 0.12 | 16 | ≤0.008 to >16 | >16 |

MIC, minimum inhibitory concentration; $MIC_{90}$, MIC required to inhibit 90% of the isolates; FDA, US Food and Drug Administration; CLSI, Clinical and Laboratory Standards Institute; MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; ESBL, extended-spectrum $\beta$-lactamase.
[a] Some pathogens that were isolated were not able to be tested.
[b] MIC range and $MIC_{90}$ expressed in mg/L.
[c] $MIC_{90}$ not calculated when $n < 10$.
[d] Patients with both MRSA and MSSA were counted only once.
[e] FDA/CLSI ceftaroline susceptible/resistant breakpoints ≤1/≥4 mg/L.
[f] FDA/CLSI ceftaroline susceptible breakpoint ≤0.5 mg/L.
[g] FDA/CLSI ceftaroline susceptible/resistant breakpoint for Enterobacteriaceae ≤0.5/≥2 mg/L [32].

CANVAS 1 and 2, a greater proportion of patients in COVERS had elevated baseline CRP levels.

### 3.2. Baseline pathogens

The most common pathogens isolated and tested at baseline in the COVERS patient population were MSSA ($n = 164$; 39%), MRSA ($n = 54$; 13%), non-ESBL-producing *E. coli* ($n = 26$; 6%) and *S. pyogenes* ($n = 25$; 6%). In the CANVAS trials, MSSA ($n = 235$; 36%), MRSA ($n = 164$; 25%), *S. pyogenes* ($n = 61$; 9%) and *Enterococcus faecalis* ($n = 27$; 4%) were the most commonly isolated pathogens. The proportion of patients with no baseline pathogen identified was higher in COVERS ($n = 378$; 49.0%) compared with the CANVAS trials ($n = 324$; 23.2%), reflecting the higher proportion of patients with cellulitis in the COVERS trial.

The ceftaroline susceptibility of pathogens isolated at baseline were generally similar between the COVERS and CANVAS trials (Table 2). Both in COVERS and the CANVAS trials, the ceftaroline MIC (range) and $MIC_{90}$ (MIC required to inhibit 90% of the isolates) for MSSA isolates were 0.06–0.5 mg/L and 0.25 mg/L, respectively. Ceftaroline susceptibility among MRSA isolates was as follows: COVERS MIC range, 0.25–1.0 mg/L, $MIC_{90}$, 0.5 mg/L; and CANVAS MIC range, 0.25–2.0 mg/L, $MIC_{90}$, 0.5 mg/L. The ceftaroline MIC range and $MIC_{90}$ of *S. pyogenes* isolates from COVERS were both ≤0.008 mg/L; the ceftaroline MIC range and $MIC_{90}$ of *S. pyogenes* isolates from the CANVAS trials were <0.004–0.0008 mg/L and ≤0.004 mg/L, respectively.

### 3.3. Clinical outcomes (modified intent-to-treat population)

Overall clinical cure rates at TOC for ceftaroline fosamil were 78.3% (396/506) in the COVERS trial and 85.9% (595/693) in the CANVAS trials. For patients treated with vancomycin plus aztreonam, overall clinical cure rates were 79.2% (202/255) in the COVERS trial and 85.5% (586/685) in the CANVAS trials. Clinical cure rates by inflammatory sign, BMI and $CL_{Cr}$ subgroups and overall are summarised in Table 3. Clinical cure rates for ceftaroline fosamil-treated patients across all subgroups with systemic inflammatory signs or SIRS were broadly similar in the COVERS and CANVAS trials, ranging from 79% to 85% in COVERS and from 83% to 89% in the CANVAS trials. For comparison, the clinical cure rates for vancomycin plus aztreonam ranged from 72% to 88% in the COVERS trial and from 84% to 90% in the CANVAS trials. Among ceftaroline fosamil-treated patients with at least one systemic sign of inflammation, or sepsis, clinical cure was observed in 81.7% of patients (255/312) in COVERS and 85.0% (335/394) in CANVAS 1 and 2. Among ceftaroline fosamil-treated patients with SIRS, clinical cure was observed in 84.4% (168/199) from COVERS and 84.5% (131/155) from CANVAS 1 and 2. Clinical cure rates by inflammatory sign and overall for the CE population were similar to those in the MITT population (Supplementary Table S1).

Clinical cure rates were generally comparable between ceftaroline fosamil-treated BMI subgroups in the COVERS and CANVAS trials, with the exception of a small number of patients with BMI <18.5 kg/m$^2$ [clinical cure rate 8/15 (53.3%) in COVERS compared with 11/15 (73.3%) in CANVAS]. Clinical cure rates for ceftaroline fosamil-treated patient subgroups with BMI ≥18.5 to <25, ≥25 to <30 and ≥30 kg/m$^2$ ranged from 75.2% to 84.5% in COVERS and from 84.5% to 91.2% in the CANVAS trials. A small proportion of ceftaroline fosamil-treated patients had moderate renal impairment ($CL_{Cr}$ >30 to ≤50 mL/min) at baseline in the COVERS and CANVAS trials [31 (6.1%) and 23 (3.3%), respectively]. Clinical cure rates for ceftaroline fosamil-treated patients with moderate renal impairment were 23/31 (74.2%) in COVERS and 19/23 (82.6%) in the CANVAS trials. Clinical cure rates for BMI and $CL_{Cr}$ subgroups in the CE population were similar to those in the MITT population (Supplementary Table S1).

Clinical cure rates by baseline pathogen (medically evaluable population) are summarised in Table 4. Among ceftaroline fosamil-treated patients with infections caused by MSSA, clinical cure rates were 93.6% (88/94) and 93.0% (212/228) in COVERS and CANVAS 1 and 2, respectively. Clinical cure was observed 84.0% (21/25) and 93.4% (142/152) of ceftaroline fosamil-treated patients with infections caused by MRSA from COVERS and CANVAS 1 and 2, respectively; all MRSA isolates from COVERS and CANVAS 1 and 2 had a ceftaroline MIC of ≤1 mg/L and ≤2 mg/L, respectively.

**Table 3**
Clinical cure rates at test-of-cure overall and among subgroups of patients with systemic signs of infection, systemic inflammatory response syndrome (SIRS), and body mass index (BMI) and baseline creatinine clearance ($CL_{Cr}$) categories in the modified intent-to-treat (MITT) population

| Patient population | COVERS | | | CANVAS 1 and 2 | | |
|---|---|---|---|---|---|---|
| | Ceftaroline fosamil [*n*/*N* (%)] | Vancomycin + aztreonam [*n*/*N* (%)] | Between-group difference (95% CI) | Ceftaroline fosamil [*n*/*N* (%)] | Vancomycin + aztreonam [*n*/*N* (%)] | Between-group difference (95% CI) |
| Overall | 396/506 (78.3) | 202/255 (79.2) | −1.0 (−6.9 to 5.4) | 595/693 (85.9) | 586/685 (85.5) | 0.3 (−3.4 to 4.0) |
| ≥1 systemic inflammatory sign[a] | 255/312 (81.7) | 137/166 (82.5) | −0.8 (−7.7 to 6.8) | 335/378 (88.6) | 326/363 (89.8) | −1.0 (−6.0 to 4.0) |
| ≥2 severe signs and/or symptoms[b] | 259/329 (78.7) | 137/165 (83.0) | −4.3 (−11.3 to 3.3) | 330/372 (88.7) | 332/379 (87.6) | 1.1 (−3.6 to 5.8) |
| Fever | 179/211 (84.8) | 104/118 (88.1) | −3.3 (−10.6 to 4.9) | 185/211 (87.7) | 181/201 (90.0) | −2.4 (−8.6 to 3.8) |
| Elevated WBC count[c] | 177/224 (79.0) | 75/104 (72.1) | 6.9 (−2.8 to 17.5) | 205/246 (83.3) | 213/254 (83.9) | −0.5 (−7.1 to 6.0) |
| SIRS[d] | 168/199 (84.4) | 83/105 (79.0) | 5.4 (−3.5 to 15.2) | 131/155 (84.5) | 140/163 (85.9) | −1.4 (−9.4 to 6.5) |
| Baseline CRP (mg/L) | | | | | | |
| ≤50 | 149/178 (83.7) | 83/100 (83.0) | 0.7 (−8.0 to 10.5) | 346/396 (87.4) | 333/387 (86.0) | 1.3 (−3.5 to 6.1) |
| >50 to ≤150 | 136/178 (76.4) | 67/80 (83.8) | −7.4 (−16.9 to 3.8) | 156/177 (88.1) | 138/166 (83.1) | 5.0 (−2.5 to 12.7) |
| >150 | 105/139 (75.5) | 49/68 (72.1) | 3.5 (−8.8 to 16.9) | 76/98 (77.6) | 95/111 (85.6) | −8.0 (−18.9 to 2.5) |
| BMI ($kg/m^2$)[e,f] | | | | | | |
| <18.5 | 8/15 (53.3) | 6/9 (66.7) | −13.3 (−48.2 to 27.4) | 11/15 (73.3) | 5/7 (71.4) | 1.9 |
| ≥18.5 to <25 | 145/185 (78.4) | 67/87 (77.0) | 1.4 (−8.7 to 12.7) | 201/238 (84.5) | 182/223 (81.6) | 2.8 (−4.0 to 9.8) |
| ≥25 to <30 | 115/153 (75.2) | 71/86 (82.6) | −7.4 (−17.5 to 3.8) | 197/216 (91.2) | 210/227 (92.5) | −1.3 (−6.7 to 3.9) |
| ≥30 | 125/148 (84.5) | 58/73 (79.5) | 5.0 (−5.3 to 16.9) | 186/222 (83.8) | 188/227 (82.8) | 1.0 (−6.0 to 7.9) |
| $CL_{Cr}$ (mL/min)[g] | | | | | | |
| >30 to ≤50 | 23/31 (74.2) | 10/17 (58.8) | 15.4 (−11.6 to 42.6) | 19/23 (82.6) | 21/26 (80.8) | 1.8 (−21.5 to 24.2) |
| >50 to ≤80 | 71/91 (78.0) | 38/46 (82.6) | −4.6 (−17.6 to 10.7) | 83/99 (83.8) | 88/98 (89.8) | −6.0 (−15.8 to 3.7) |
| >80 | 288/362 (79.6) | 149/183 (81.4) | −1.9 (−8.6 to 5.5) | 492/569 (86.5) | 475/559 (85.0) | 1.5 (−2.6 to 5.6) |

CI, confidence interval; WBC, white blood cell.
[a] Systemic signs were fever >38°C, hypothermia <36°C, elevated WBC count (>10 000 cells/$mm^3$) or bands >10%.
[b] Severe local signs were erythema, swelling, tenderness or warmth that was designated as 'severe' by the investigator.
[c] >10 000 cells/$mm^3$.
[d] SIRS criteria were defined as presence of at least two of the following symptoms at baseline: temperature <36°C or >38°C; heart rate >90 beats/min; respiratory rate >20 breaths/min, or on blood gas, a $PaCO_2$, <32 mmHg (4.3 kPa); WBC count <4000 cells/$mm^3$ or >12 000 cells/$mm^3$, or >10% band forms (immature WBCs).
[e] BMI data were missing from 5 patients in COVERS and from 3 patients in CANVAS 1 and 2.
[f] CIs were calculated when the sample size for a pathogen was ≥10 patients in each treatment group using the Miettinen & Nurminen method for stratified designs (stratified by study) [31].
[g] Ceftaroline fosamil dosage regimens were adjusted for patients with $CL_{Cr}$ >30 to ≤50 mL/min. Clinical cure rates for patients with $CL_{Cr}$ >20 to <30 mL/min ($n = 8$) and patients with missing $CL_{Cr}$ data ($n = 22$) in COVERS are not shown.

**Table 4**
Clinical cure rate by baseline pathogen in the medically evaluable population

| Pathogen | COVERS | | | CANVAS 1 and 2 | | |
|---|---|---|---|---|---|---|
| | Ceftaroline fosamil [*n*/*N* (%)] | Vancomycin + aztreonam [*n*/*N* (%)] | Between-group difference (95% CI) | Ceftaroline fosamil [*n*/*N* (%)] | Vancomycin + aztreonam [*n*/*N* (%)] | Weighted[a] between-group difference (95% CI) |
| Gram-positive bacteria | | | | | | |
| *Staphylococcus aureus*[b] | 109/119 (91.6) | 61/71 (85.9) | 5.7 (−3.3 to 16.5) | 352/378 (93.1) | 336/356 (94.4) | −1.3 (−4.9 to 2.4) |
| MSSA | 88/94 (93.6) | 49/57 (86.0) | 7.7 (−1.9 to 19.7) | 212/228 (93.0) | 225/238 (94.5) | −1.6 (−6.3 to 2.9) |
| MRSA | 21/25 (84.0) | 12/15 (80.0) | 4.0 (−19.8 to 32.2) | 142/152 (93.4) | 115/122 (94.3) | −0.9 (−7.0 to 5.5) |
| Streptococci | | | | | | |
| *Streptococcus pyogenes* | 14/15 (93.3) | 7/7 (100.0) | −6.7 (−30.5 to 30.8) | 56/56 (100.0) | 56/58 (96.6) | 3.9 (−2.3 to 12.6) |
| *Streptococcus agalactiae* | 5/6 (83.3) | 7/9 (77.8) | 5.6 (−41.2 to 44.9) | 21/22 (95.5) | 18/18 (100.0) | N/A[c] |
| *Streptococcus dysgalactiae* | 9/9 (100.0) | 0/0 (0) | N/A | 13/13 (100.0) | 15/16 (93.8) | N/A[c] |
| *Streptococcus anginosus* group | 16/18 (88.9) | 4/4 (100.0) | −11.1 (−33.4 to 40.6) | 12/13 (92.3) | 15/16 (93.8) | N/A[c] |
| *Enterococcus faecalis* | 4/6 (66.7) | 4/5 (80.0) | −13.3 (−59.6 to 41.6) | 20/25 (80.0) | 22/24 (91.7) | −12.6 (−34.1 to 8.0) |
| Gram-negative bacteria | | | | | | |
| *Escherichia coli* | 11/12 (91.7) | 9/10 (90.0) | 1.7 (−28.5 to 34.7) | 20/21 (95.2) | 19/21 (90.5) | N/A[c] |
| *Klebsiella oxytoca* | 4/4 (100.0) | 1/1 (100.0) | N/A | 10/12 (83.3) | 6/6 (100.0) | N/A[c] |
| *Klebsiella pneumoniae* | 5/7 (71.4) | 3/4 (75.0) | −3.6 (−51.1 to 52.1) | 17/18 (94.4) | 13/14 (92.9) | N/A[c] |
| *Morganella morganii* | 4/4 (100.0) | 2/2 (100.0) | N/A | 11/12 (91.7) | 5/6 (83.3) | N/A[c] |
| *Proteus mirabilis* | 6/7 (85.7) | 2/2 (100.0) | −14.3 (−53.5 to 58.4) | 10/15 (66.7) | 20/21 (95.2) | N/A[c] |

CI, confidence interval; MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; N/A, not applicable.
[a] Weighted difference in clinical cure rates stratified by study.
[b] Patients with MRSA and MSSA were counted only once.
[c] CIs were calculated when the sample size for a pathogen was ≥10 patients in each treatment group using the Miettinen & Nurminen method for stratified designs (stratified by study) [31].

### 3.4. Safety

In COVERS, 45.8% (232/506) of patients treated with ceftaroline fosamil experienced at least one adverse event (AE) compared with 45.5% (116/255) of patients treated with vancomycin plus aztreonam; and 44.7% (309/692) of patients treated with ceftaroline fosamil and 47.5% (326/686) of patients treated with vancomycin plus aztreonam experienced at least one AE in the CANVAS trials. The most common AEs among ceftaroline fosamil-treated patients in COVERS (occurring in ≥3% of patients) were nausea (4.0%), headache (3.4%) and hypokalaemia (3.0%). The most common AEs among ceftaroline fosamil-treated patients in CANVAS 1 and 2

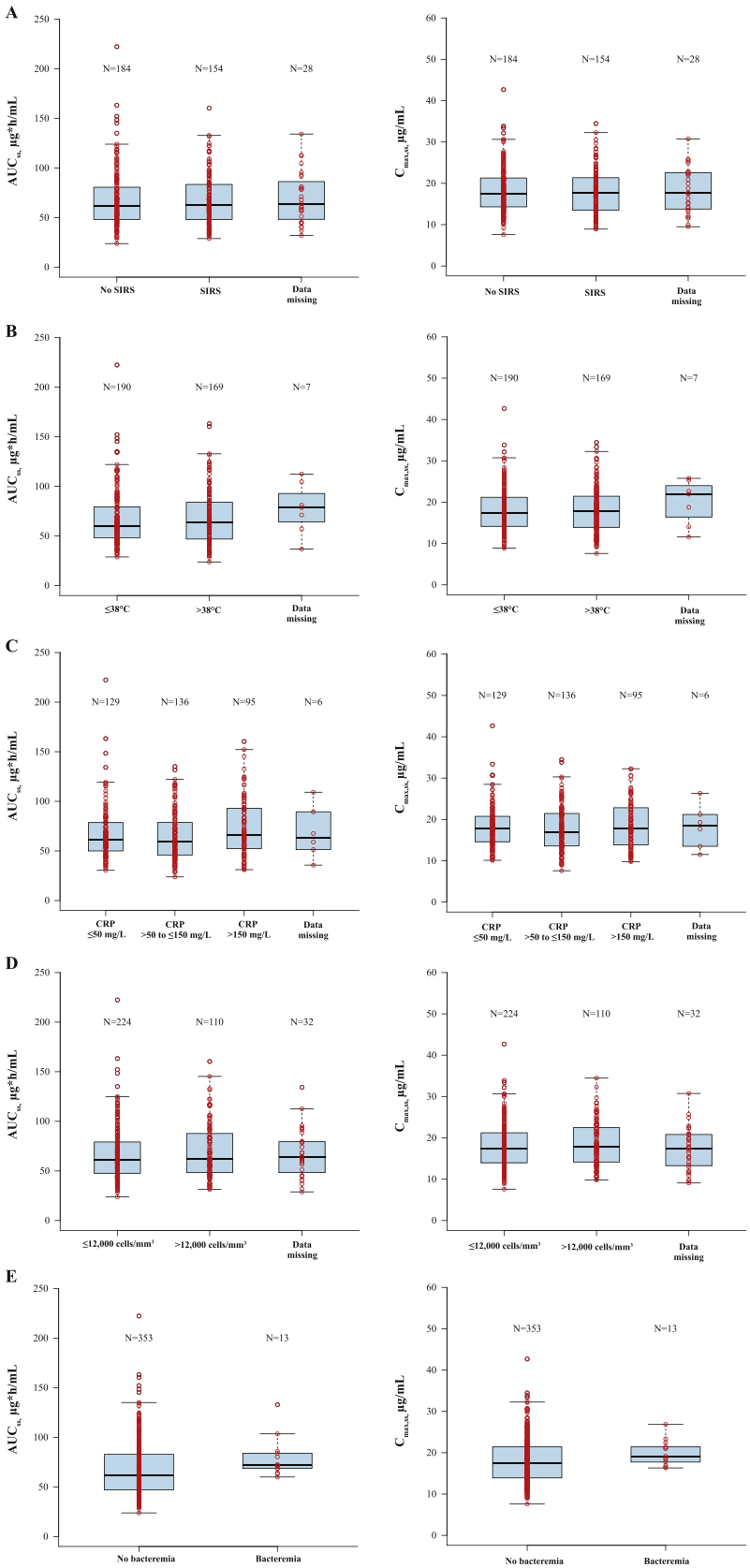


**Fig. 1.** Comparison of predicted steady-state ceftaroline fosamil exposures ($AUC_{ss}$ and $C_{max,ss}$) in individual acute bacterial skin and skin-structure infection (ABSSSI) patients from COVERS (A) with and without systemic inflammatory response syndrome (SIRS), (B) with and without fever, (C) with and without high C-reactive protein (CRP), (D) with and without high white blood cell count and (E) with and without bacteraemia. $AUC_{ss}$, area under the concentration–time curve at steady-state; $C_{max,ss}$, maximum plasma concentration at steady-state.

(occurring in ≥3% of patients) were nausea (5.9%), headache (5.2%), diarrhoea (4.9%), pruritus (3.5%) and rash (3.2%).

### 3.5. Population pharmacokinetic modelling of ceftaroline exposure

Overall, the population PK modelling data set included data from 951 subjects, of which 463 were patients with cSSTI. The model described the observed ceftaroline concentration data well and was considered suitable to calculate exposure parameters for individual patients in COVERS. PK data were available from 371 patients in COVERS for whom a full ceftaroline plasma concentration time course could be calculated. Individual predictions of $AUC_{ss}$ and $C_{max,ss}$ for these patients are summarised by the presence or absence of fever, SIRS or bacteraemia, high WBC count and CRP levels in Fig. 1. The individual, median and range $AUC_{ss}$ and $C_{max,ss}$ values demonstrated clear evidence of overlap in patients within the respective disease severity parameters, indicating that these parameters had little effect on ceftaroline exposure.

## 4. Discussion

The COVERS and CANVAS 1 and 2 trials included all patients with systemic signs of inflammation, or sepsis, and SIRS, allowing for an informative comparison of the clinical outcomes associated with ceftaroline fosamil 600 mg as a 1-h infusion q8h versus 600 mg as a 2-h infusion q12h in patients with severe ABSSSI. Because the pathogens isolated and their associated ceftaroline susceptibilities in the COVERS trial were similar to the CANVAS trials, the clinical outcomes and pathogen susceptibilities were compared. This provides further rationale for the comparison of clinical outcomes between the trials. Moreover, a patient-rich population ceftaroline PK model, which included data from over 900 subjects, allowed evaluation of predicted ceftaroline exposures for patients with and without sepsis, complementing the clinical data comparisons between the trials.

Although the ceftaroline fosamil q8h dosage regimen was efficacious in COVERS, clinical outcomes among ceftaroline fosamil-treated patient subgroups with more severe disease (i.e. more than one systemic sign of inflammation, or sepsis, fever, elevated WBC count or SIRS) were comparable with patients receiving ceftaroline fosamil q12h in the CANVAS trials. Clinical cure rates were also generally comparable for BMI and $CL_{Cr}$ patient subgroups in the COVERS and CANVAS trials. Differences in clinical cure rates for ceftaroline fosamil versus vancomycin plus aztreonam were broadly similar across the trials; for both treatment groups, clinical cure rates were generally numerically lower in COVERS compared with the CANVAS trials. This is likely due to patients generally having more severe infection and co-morbidities that are not captured in a single subgroup category. Ceftaroline fosamil was well tolerated in both trials, with AEs representative of the cephalosporin class. Hence, the q12h regimen appears robust for the majority of patients with ABSSSI, regardless of the presence of systemic inflammatory signs.

These clinical data are aligned with population PK modelling of individual patients within the COVERS trial, which showed that steady-state exposures of ceftaroline were comparable across patients with and without signs of sepsis. The pharmacokinetics of ceftaroline in COVERS was similar to results previously reported for subjects treated with ceftaroline fosamil q12h [18,33], with a dose-proportional increase in exposure from the q8h dosing used in COVERS [30,33,34]. Ceftaroline pharmacokinetics therefore does not appear to be affected by disease severity, suggesting that the ceftaroline fosamil q12h regimen provides adequate exposure in ABSSSI patients with severe disease. Pathogen susceptibilities to ceftaroline were similar between the COVERS and CANVAS trials, with both dosage regimens providing broad coverage against commonly isolated ABSSSI pathogens. The MICs of >95% of baseline isolates across the three trials were at or below respective CLSI and European Committee on Antimicrobial Susceptibility Testing (EUCAST) susceptibility breakpoints for ceftaroline fosamil 600 mg q12h [16,35]. Clinical response rates were generally comparable across the COVERS and CANVAS trials for key ABSSSI pathogens, including *S. aureus*. MRSA isolated from COVERS and CANVAS 1 and 2 had ceftaroline MICs of ≤1 mg/L and ≤2 mg/L, respectively. Probability of target attainment (PTA) analyses using the ceftaroline population PK model described above have shown that >95% PTA is predicted with the 600 mg q12h dose regimen for *S. aureus* isolates with MICs up to 2 mg/L [30]. With the 600 mg q8h dosage regimen, >95% PTA is predicted for *S. aureus* isolates with MICs up to 4 mg/L [30]. In 2017, the EMA label was updated to recommend the use of ceftaroline fosamil 600 mg q8h for cSSTI patients where the causative pathogen is *S. aureus* with a ceftaroline MIC of 2 mg/L or 4 mg/L [8]; such isolates are very rare in the USA and Europe [36,37].

Because individual study patient PK data were not analysed in this retrospective analysis and individual patients may have different disease states, this was not described in the CANVAS and COVERS trials. We believe that confounders that do exist in this particular patient population are valid but, given the positive findings in this study, do not appear to play a substantial role in the efficacy or toxicity of ceftaroline treatment. In addition, because this analysis is a retrospective cross-trial comparison, it is limited by the inability to completely control for population differences between trials. Similarly, as enrolment for COVERS and the CANVAS trials occurred in different geographic locations, regional differences in care may have affected the results. However, given that the population PK analyses support the conclusions from the cross-trial comparison, the data overall support that ceftaroline fosamil 600 mg q12h is a robust dosage regimen for the great majority of patients with ABSSSI, including those with sepsis and SIRS.

## 5. Conclusions

On the basis of the clinical, microbiological and population PK modelling comparisons presented here, sepsis did not affect predicted individual steady-state ceftaroline exposure. Ceftaroline fosamil 600 mg q12h is a well-tolerated, efficacious dosage regimen for the majority of patients with severe ABSSSI, regardless of the extent of sepsis.

## Acknowledgments

Writing and editorial assistance was provided to the authors by Todd J. Waldron, PhD, and John E. Fincke, PhD, of Complete Healthcare Communications, LLC (Chadds Ford, PA) and was funded by Allergan plc (Dublin, Ireland).

## Funding

The CANVAS 1 and 2 trials were sponsored by Forest Laboratories, Inc., a subsidiary of Allergan Inc. The COVERS trial was originally sponsored by AstraZeneca, and is now sponsored by Pfizer. AstraZeneca's rights to ceftaroline fosamil were acquired by Pfizer in December 2016. This work was supported by Allergan plc (Dublin, Ireland). Employees of Allergan and AstraZeneca plc were involved in the preparation of the data described herein and were directly involved in the writing of this manuscript in their roles as authors.

## Competing interests

MHW has received consulting fees from AiCuris, AstraZeneca, Bayer, Cerexa, Durata, The Medicines Company, Menarini, Motif Bio, Nabriva, Paratek and Pfizer, lecture fees from Allergan, AstraZeneca and Pfizer, and grant support from Motif Biosciences, Nabriva, Paratek and Pfizer; JG, DJW, SD and JI were employees of AstraZeneca at the time of study conduct and analysis; DJW, SD and JI are shareholders in AstraZeneca; AJ and HDF were employees of Cerexa (now a subsidiary of Allergan) at the time of study conduct and analysis; MD has received honoraria from and attended advisory boards for Bayer, AstraZeneca, Motif Bio, Pfizer, Matoke and MSD. GRC declares no competing interests.

## Ethical approval

For each trial, the clinical study protocol was approved before enrolment of any patient into the trial, including approved by or notification to the national regulatory authority, as required by local regulations. Ethical approval was obtained from the local ethical committee at each study centre.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2019.01.016.

## References


[1] US Department of Health and Human Services, US Food and Drug Administration, Center for Drug Evaluation and Research (CDER). *Guidance for industry. Acute bacterial skin and skin structure infections: developing drugs for treatment*. http://www.fda.gov/downloads/Drugs/Guidances/ucm071185.pdf.%20Accessed%20Aug%202 [accessed 28 November 2018].

[2] Edelsberg J, Taneja C, Zervos M, Haque N, Moore C, Reyes K, et al. Trends in US hospital admissions for skin and soft tissue infections. Emerg Infect Dis 2009;15:1516–18.

[3] Miller LG, Eisenberg DF, Liu H, Chang CL, Wang Y, Luthra R, et al. Incidence of skin and soft tissue infections in ambulatory and inpatient settings, 2005–2010. BMC Infect Dis 2015;15:362.

[4] Anderson DJ, Podgorny K, Berrios-Torres SI, Bratzler DW, Dellinger EP, Greene L, et al. Strategies to prevent surgical site infections in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol 2014;35:605–27.

[5] Carratala J, Roson B, Fernandez-Sabe N, Shaw E, del Rio O, Rivera A, et al. Factors associated with complications and mortality in adult patients hospitalized for infectious cellulitis. Eur J Clin Microbiol Infect Dis 2003;22:151–7.

[6] Theofiles M, Maxson J, Herges L, Marcelin A, Angstman KB. Cellulitis in obesity: adverse outcomes affected by increases in body mass index. J Prim Care Community Health 2015;6:233–8.

[7] Halilovic J, Heintz BH, Brown J. Risk factors for clinical failure in patients hospitalized with cellulitis and cutaneous abscess. J Infect 2012;65:128–34.

[8] *Zinforo (ceftaroline fosamil)*. Full prescribing information. AstraZeneca AB; 2016.

[9] *Teflaro (ceftaroline fosamil)*. Full prescribing information. Dublin, Ireland: Allergan plc; 2016.

[10] Corey GR, Wilcox MH, Talbot GH, Thye D, Friedland D, Baculik T, et al. CANVAS 1: the first phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. J Antimicrob Chemother 2010;65(Suppl 4):iv41–51.

[11] Wilcox MH, Corey GR, Talbot GH, Thye D, Friedland D, Baculik T, et al. CANVAS 2: the second phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. J Antimicrob Chemother 2010;65(Suppl 4):iv53–65.

[12] Dryden M, Zhang Y, Wilson D, Iaconis JP, Gonzalez J. A phase III, randomized, controlled, non-inferiority trial of ceftaroline fosamil 600 mg every 8 h versus vancomycin plus aztreonam in patients with complicated skin and soft tissue infection with systemic inflammatory response or underlying comorbidities. J Antimicrob Chemother 2016;71:3575–84.

[13] Droege ME, Van Fleet SL, Mueller EW. Application of antibiotic pharmacodynamics and dosing principles in patients with sepsis. Crit Care Nurse 2016;36:22–32.

[14] Shah S, Barton G, Fischer A. Pharmacokinetic considerations and dosing strategies of antibiotics in the critically ill patient. J Intensive Care Soc 2015;16:147–53.

[15] Veiga RP, Paiva J-A. Pharmacokinetics–pharmacodynamics issues relevant for the clinical use of $\beta$-lactam antibiotics in critically ill patients. Crit Care 2018;22:233.

[16] Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing; twenty-fifth informational supplement, Wayne, PA: CLSI; 2015. Document M100-S25.

[17] Corey GR, Wilcox M, Talbot GH, Friedland HD, Baculik T, Witherell GW, et al. Integrated analysis of CANVAS 1 and 2: phase 3, multicenter, randomized, double-blind studies to evaluate the safety and efficacy of ceftaroline versus vancomycin plus aztreonam in complicated skin and skin-structure infection. Clin Infect Dis 2010;51:641–50.

[18] Justo JA, Mayer SM, Pai MP, Soriano MM, Danziger LH, Novak RM, et al. Pharmacokinetics of ceftaroline in normal body weight and obese (classes I, II, and III) healthy adult subjects. Antimicrob Agents Chemother 2015;59:3956–65.

[19] Riccobene T, Jakate A, Rank D. A series of pharmacokinetic studies of ceftaroline fosamil in select populations: normal subjects, healthy elderly subjects, and subjects with renal impairment or end-stage renal disease requiring hemodialysis. J Clin Pharmacol 2014;54:742–52.

[20] File TM Jr, Low DE, Eckburg PB, Talbot GH, Friedland HD, Lee J, et al. FOCUS 1: a randomized, double-blinded, multicentre, phase III trial of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in community-acquired pneumonia. J Antimicrob Chemother 2011;66(Suppl 3):iii19–32.

[21] Low DE, File TM Jr, Eckburg PB, Talbot GH, Friedland HD, Lee J, et al. FOCUS 2: a randomized, double-blinded, multicentre, phase III trial of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in community-acquired pneumonia. J Antimicrob Chemother 2011;66(Suppl 3):iii33–44.

[22] Talbot GH, Thye D, Das A, Ge Y. Phase 2 study of ceftaroline versus standard therapy in treatment of complicated skin and skin structure infections. Antimicrob Agents Chemother 2007;51:3612–16.

[23] Yang L, Sunzel M, Xu P, Edeki T, Wilson D, Li J, et al. Evaluation of the pharmacokinetics and safety of single and multiple ceftaroline fosamil infusions in healthy Chinese and Western subjects. Int J Clin Pharmacol Ther 2015;53:681–91.

[24] Panagiotidis G, Backstrom T, Asker-Hagelberg C, Jandourek A, Weintraub A, Nord CE. Effect of ceftaroline on normal human intestinal microflora. Antimicrob Agents Chemother 2010;54:1811–14.

[25] Sunzel M, Learoyd M, Li J, Li Y, Ngo N, Edeki T. An open-label, non-randomised, phase 1, single-dose study to assess the pharmacokinetics of ceftaroline in patients with end-stage renal disease requiring intermittent haemodialysis. Int J Antimicrob Agents 2015;46:682–8.

[26] Riccobene TA, Su SF, Rank D. Single- and multiple-dose study to determine the safety, tolerability, and pharmacokinetics of ceftaroline fosamil in combination with avibactam in healthy subjects. Antimicrob Agents Chemother 2013;57:1496–504.

[27] Zhong NS, Sun T, Zhuo C, D'Souza G, Lee SH, Lan NH, et al. Ceftaroline fosamil versus ceftriaxone for the treatment of Asian patients with community-acquired pneumonia: a randomised, controlled, double-blind, phase 3, non-inferiority with nested superiority trial. Lancet Infect Dis 2015;15:161–71.

[28] ClinicalTrials.gov. *NCT00633126: Pharmacokinetics of ceftaroline in subjects 12 to 17 years of age*. https://clinicaltrials.gov/ct2/show/NCT00633126?term=NCT00633126&rank=1 [accessed 27 November 2018].

[29] Zhou D, Dryden M, Gonzalez J, Melnick D, Wilson D, Li J, et al. Impact of disease severity on ceftaroline pharmacokinetics (PK) in patients with ABSSSI: phase III COVERS trial. In: 55th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), 17–21 September 2015, San Diego, CA. Washington, DC. ASM Press; 2015.

[30] Das S, Li J, Iaconis J, Zhou D, Stone GG, Yan JL, et al. Ceftaroline fosamil doses and breakpoints for *Staphylococcus aureus* in complicated skin and soft tissue infections. J Antimicrob Chemother 2019;74:425–31.

[31] Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4:213–26.

[32] Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing. 27th ed. Wayne, PA: CLSI; 2017. CLSI supplement M100.

[33] Iaconis JP, Critchley I, Zhou D, Li J, Das S. Ceftaroline fosamil 600 mg every 12 h (q12h) can provide adequate exposure against *Staphylococcus aureus* with ceftaroline MICs $\leq$2 mg/L in ABSSSI. In: 55th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), 17–21 September 2015, San Diego, CA. Washington, DC. ASM Press; 2015.

[34] Bhavnani SM, Hammel JP, Van Wart SA, Rubino CM, Reynolds DK, Forrest A, et al. Pharmacokinetic–pharmacodynamic analysis for efficacy of ceftaroline fosamil in patients with acute bacterial skin and skin structure infections. Antimicrob Agents Chemother 2015;59:372–80.

[35] European Committee on Antimicrobial Susceptibility Testing. *Breakpoint tables for interpretation of MICs and zone diameters*. Version *7.1*, 2017. http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_7.1_Breakpoint_Tables.pdf [accessed 20 March 2019].

[36] Sader HS, Flamm RK, Streit JM, Farrell DJ, Jones RN. Ceftaroline activity against bacterial pathogens frequently isolated in U.S. medical centers: results from five years of the AWARE surveillance program. Antimicrob Agents Chemother 2015;59:2458–61.

[37] Karlowsky JA, Biedenbach DJ, Bouchillon SK, Iaconis JP, Reiszner E, Sahm DF. In vitro activity of ceftaroline against bacterial pathogens isolated from skin and soft tissue infections in Europe, Russia and Turkey in 2012: results from the Assessing Worldwide Antimicrobial Resistance Evaluation (AWARE) surveillance programme. J Antimicrob Chemother 2016;71:162–9.