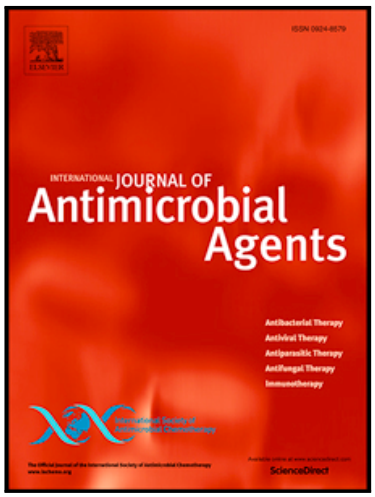


Ceftaroline Fosamil Therapy in Patients With Acute Bacterial Skin and Skin Structure Infections With Systemic Inflammatory Signs: A Retrospective Dose Comparison Across Three Pivotal Trials

G. Ralph Corey , Mark H. Wilcox , Jesus Gonzalez , Alena Jandourek , David J. Wilson , H. David Friedland , Shampa Das , Joseph Iaconis , Matthew Dryden

PII: S0924-8579(19)30023-8
DOI: https://doi.org/10.1016/j.ijantimicag.2019.01.016
Reference: ANTAGE 5639

To appear in: *International Journal of Antimicrobial Agents*

Received date: 2 August 2018
Accepted date: 27 January 2019

Please cite this article as: G. Ralph Corey , Mark H. Wilcox , Jesus Gonzalez , Alena Jandourek , David J. Wilson , H. David Friedland , Shampa Das , Joseph Iaconis , Matthew Dryden , 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, *International Journal of Antimicrobial Agents* (2019), doi: https://doi.org/10.1016/j.ijantimicag.2019.01.016

Highlights

- Ceftaroline fosamil treatment in patients with ABSSSI and sepsis
- Post hoc analysis of patients given 600 mg ceftaroline fosamil q12h or q8h
- Clinical cure rates were comparable for both ceftaroline fosamil dosage regimens
- Ceftaroline exposures were not affected by disease severity

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

Running Title: Ceftaroline: Severe Skin Infections

Author(s): G. Ralph Corey,[a] Mark H. Wilcox,[b] Jesus Gonzalez,[c†] Alena Jandourek,[d] David J. Wilson,[c‡] H. David Friedland,[d] Shampa Das,[c§] Joseph Iaconis,[e] Matthew Dryden[f,*]

Affiliation(s): [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]Royal Hampshire County Hospital, Winchester, UK

[†]Current Address: Block C18-1, 1 Watson Street, Manchester, M3 4EF, UK
[‡]Current Address: DJW STATS Consulting, 1 Market Street, Whaley Bridge, High Peak, UK
[§]Current Address: Centre for Antimicrobial Pharmacodynamics, Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool, Liverpool, UK

Author email addresses: G. Ralph Corey: g.corey@duke.edu; Mark H. Wilcox: Mark.Wilcox@nhs.net; Jesus Gonzalez: tropmedpe@yahoo.com; Alena Jandourek: ajandour@yahoo.com; David J. Wilson; david.wilson@djwstats.co.uk; H. David Friedland: hdavidf22@comcast.net; Shampa Das: shampadaspkpd@gmail.com; Joseph Iaconis: pino.joey@gmail.com; Matthew Dryden: matthew.dryden@hhft.nhs.uk

Keyword(s): ceftaroline fosamil; skin and soft tissue infection; sepsis; clinical trial

***Corresponding author:** Matthew Dryden, MA, MBBS, MD, FRCPath
Department of Microbiology & Infection
Hampshire Hospitals NHS Foundation Trust
Romsey Road
Winchester, Hampshire, SO22 5DG, UK
Ph: 44(0)1962-824451
Fax: 44(0) 44(0)1962-825431
matthew.dryden@hhft.nhs.uk

Section/Category: Original Article

Abstract (word count 250/250)

Background: Post-hoc analysis compared 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 infections (ABSSSI) and signs of sepsis.

Methods: Clinical outcomes at test-of-cure in patients with ABSSSI and systemic inflammatory signs/systemic inflammatory response (SIRS), and ceftaroline minimum inhibitory concentrations (MICs) against baseline pathogens were compared between COVERS (ceftaroline fosamil 600 mg q8h, 2-h infusion) and the CANVAS 1 and 2 trials (ceftaroline fosamil 600 mg q12h, 1-h infusion). Ceftaroline exposures among patients in COVERS with or without markers of sepsis were compared using population pharmacokinetic (PK) modeling.

Results: In COVERS, 62% (312/506) and 41% (208/506) of ceftaroline fosamil-treated patients had ≥1 systemic sign or SIRS, respectively and 55% (378/693) and 22% (152/693), respectively in the CANVAS trials. Clinical cure rates for the modified intent-to-treat (MITT) 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 exposures.

Conclusions: 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 exposures were not affected by

disease severity. Ceftaroline fosamil 600 mg q12h is a robust dosage regimen for most ABSSSI patients with sepsis.

Trial Registry Information: https://clinicaltrials.gov: (NCT01499277, NCT00424190, NCT00423657).

Keyword(s): ceftaroline fosamil; skin and soft tissue infection; sepsis; clinical trial

1. Introduction (Word count=3130/4000)

Acute bacterial skin and skin structure infection (ABSSSI) and complicated skin and soft tissue infection (cSSTI) include cellulitis/erysipelas, wound infection, and major cutaneous abscess [1, 2] and impose a substantial burden on healthcare systems. Between 2005 and 2010, the incidence of skin and soft tissue infection in the United States was approximately 48 per 1000 person-years [3]; currently, up to 300,000 surgical site infections occur each year, including those in skin and subcutaneous tissue [4]. Skin and soft tissue infections can be serious, requiring hospitalization and surgical procedures, and occasionally can cause bacteremia and death [5]. Factors associated with ABSSSI onset and clinical failures 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 *S*. *aureus* (both methicillin-susceptible [MSSA] and methicillin-resistant [MRSA]), *Streptococcus pyogenes*, *Streptococcus agalactiae*, and non-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 hour IV infusion every 12 hours (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 (PK) of some antibiotics and thus potentially affect antibiotic efficacy in patients with ABSSSI. Septic patients in the intensive care unit have shown increased volume of distribution and increased clearance. An increase in volume of distribution in these patients has been shown to be due to capillary leak and endothelial damage, which can result in sub-therapeutic 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 volumes and clearance can, in turn, result in variable responsiveness to treatment, in terms of both 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 hour infusion every 8 hours (q8h) in patients with ABSSSI with systemic inflammatory response syndrome (SIRS) or underlying comorbidities 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, firstly by comparing clinical outcomes and pathogen susceptibilities in the COVERS trial

with the previously published CANVAS trials, and secondly by using population PK modeling to compare ceftaroline exposures in patients with or without markers of sepsis.

2. Material and Methods

2.1. Study Design

COVERS (NCT01499277) and CANVAS 1 and 2 (NCT00424190 and NCT00423657) were phase 3, multicenter, randomized, double-blind, comparative safety and efficacy trials of IV ceftaroline fosamil versus vancomycin plus aztreonam for the treatment of ABSSSI [10-12]. Patients were randomized 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 (CrCl) ≤50 mL/min and vancomycin plus aztreonam dosages were adjusted according to 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 clinical cure rate at test-of-cure (TOC) in the modified intent-to-treat (MITT) and clinically evaluable (CE) patient populations.

2.2. Patient 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 hospitalization and ≥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, edema, and/or induration with surface area ≥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 presence of ≥2 of the following symptoms at baseline: temperature <36°C or >38°C; heart rate >90 beats per minute; respiratory rate >20 breaths per minute, or on blood gas, a $PaCO_2$ <32 mmHg [4.3 kPa]; white blood cells [WBCs] <4000 cells/mm^3 or >12,000 cells/mm^3, or >10% band forms [immature WBC]), and elevated C-reactive protein (CRP) levels. 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 methodology [16] by a central reference laboratory.

2.4. Clinical Outcomes

Clinical cure was defined as the 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 randomized patients that received any study medication) and CE population, a subset of the MITT population that 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 summarized for the MITT and CE populations overall, and for patient subgroups with ≥1 systemic sign of inflammation, or sepsis (fever >38°C, hypothermia <36°C, elevated WBC count [>10,000 cells/mm^3 or bands >10%]), ≥2 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 PK [18, 19], clinical cure rates were summarized by body mass index (BMI) and CrCl to compare outcomes across BMI and CrCl subgroups. Finally, clinical cure rates were also summarised by baseline pathogen. Safety was assessed in all randomized patients who received ≥1 dose of study therapy.

2.5. Population Pharmacokinetic Modeling

The ceftaroline population PK model used in this analysis was developed using a large patient PK dataset, which included data from 14 phase I trials in healthy subjects (with normal renal function or renal impairment), one phase II trial in patients with cSSTI, three phase III trials in patients with cSSTI (CANVAS 1, CANVAS 2, and COVERS) and three 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 (ie 8 hours) 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 version 7.2.0 (ICON plc, Dublin, Ireland). Details related to the PK modeling 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 curve [AUC_{ss}]) were derived from the individual predicted ceftaroline concentration-time courses from the population PK model using noncompartmental analysis. To assess whether the presence of markers of systemic inflammation, or sepsis, had any impact on ceftaroline exposures, AUC_{ss} and $C_{max,ss}$ were compared for the following patient subgroups: fever ≤38°C or >38°C, WBC ≤12,000/mm^3 or >12,000/mm^3, CRP ≤50 mg/L, >50 to ≤150 mg/L or >150 mg/L, and presence or absence of SIRS or bacteremia at baseline [29].

2.6. Statistical Analyses

Patient outcomes are presented using descriptive statistics and between-group outcome differences (95% CI) were determined using the Miettinen and 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 summarized in **Table 1**. Most

patients were male and white. Overall, baseline characteristics, including body mass index, comorbidities, 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 age [SD], 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; median (range) infection area was greater among ceftaroline fosamil−treated patients from COVERS compared with those from CANVAS 1 and 2 (400 [75–5040] cm^2 in COVERS vs 156 [1–3150] cm^2 in CANVAS 1 and 2). A greater proportion of ceftaroline fosamil−treated patients from COVERS also had ≥1 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 152/693 [21.9%] CANVAS 1 and 2) at baseline. Compared with CANVAS 1 and 2, a greater proportion of patients in COVERS had elevated baseline C-reactive protein levels.

3.2. Baseline Pathogens

The most common pathogens isolated at baseline in the COVERS patient population were MSSA (n=164 [39%]), MRSA (n=54 [13%]), non−extended-spectrum beta-lactamase-producing *E. coli* (n=26 [6%]), and *S. pyogenes* (n=25 [6%]). In the CANVAS trials, MSSA (n=244 [38%]), MRSA (n=164 [25%]), *S. pyogenes* (n=61 [9%]), and *Enterococcus faecalis* (n=27 [4%]) were most commonly isolated. The proportion of

patients with no baseline pathogen identified was higher in COVERS (n=378 [49.0%]) compared to the CANVAS trials (n=324 [23.2%]), reflecting the higher proportion of patients with cellulitis in the COVERS trial.

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

3.3. Clinical Outcomes (MITT 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 CrCl subgroups and overall are summarized 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 ≥1 systemic sign of inflammation, or sepsis, clinical cure was observed in 81.7% (255/312) patients in COVERS and 85.0% (335/394) patients 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 (**Supplemental Table 1**).

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 –<25, ≥25–<30 and ≥30 kg/m^2 ranged from 75.2% to 84.5% in COVERS and 84.5% to 91.2% in the CANVAS trials. A small proportion of ceftaroline fosamil-treated patients had moderate renal impairment (CrCl >30-≤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 CrCl subgroups in the CE population were similar to those in the MITT (**Supplemental Table 1**).

Clinical cure rates by baseline pathogen (ME population) are summarized 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.

3.4. Safety

In COVERS, 45.8% (232/506) of patients treated with ceftaroline fosamil experienced ≥1 adverse event (AE) compared with 45.5% (116/255) of patients treated with vancomycin plus aztreonam; 44.7% (309/692) of patients treated with ceftaroline fosamil and 47.5% (326/686) of patients treated with vancomycin plus aztreonam experienced ≥1 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 hypokalemia (3.0%). The most common AEs among ceftaroline fosamil-treated patients in CANVAS 1 and 2 (occurring in ≥3% of patients) were nausea (5.9%), headache (5.2%), diarrhea (4.9%), pruritus (3.5%), and rash (3.2%).

3.5. Population PK Modeling of Ceftaroline Exposures

Overall, the population PK modeling dataset 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 bacteremia, high WBC count and CRP levels in **Figure 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 the exposures of ceftaroline.

4. Discussion

The COVERS and CANVAS 1 and 2 trials all included 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 hour infusion, q8h, versus 600 mg as a 2 hour 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, we compared the clinical outcomes and pathogen susceptibilities. 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 (ie, >1 systemic sign of inflammation, or sepsis, fever, elevated WBC, or SIRS), were comparable to patients receiving ceftaroline fosamil q12h in the CANVAS trials. Clinical cure rates were also generally comparable for BMI and CrCl patient subgroups in the COVERS and the 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 to the CANVAS trials. This is likely due to patients generally having a more severe infection and comorbidities 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 modeling 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 PK of ceftaroline in COVERS were similar to results previously reported for subjects treated with ceftaroline fosamil q12h [18, 32], with a dose-proportional increase in exposure from the q8h dosing used in COVERS [30, 32, 33]. Ceftaroline PK therefore does not appear to be affected by disease severity, suggesting that the ceftaroline fosamil q12h regimen provides adequate exposures 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 EUCAST susceptibility breakpoints for ceftaroline fosamil 600 mg q12h [16, 34]. 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 minimum inhibitory concentration (MIC) of 2 or 4 mg/L [8]; such isolates are very rare in the US and Europe [35, 36].

Because individual study patient PK data were not analyzed in this retrospective analysis and individual patients may have different states of disease, this was not described in the CANVAS and COVERS trials. We believe that confounds that do exist in this particular patient population are valid, but given the positive findings in our 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 enrollment 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 modeling comparisons presented here, sepsis did not affect predicted individual steady state ceftaroline exposures. 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 funded by Allergan plc (Dublin, Ireland). All authors met the International Committee of Medical Journal Editors authorship criteria. Neither honoraria nor payments were made for authorship.

Declarations

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 data described herein, and were directly involved in the writing of this manuscript in their roles as authors.

*The authors have associations that may pose a conflict of interest.

Competing Interests: G. Ralph Corey has no conflicts to disclose.

Mark H. Wilcox has received consulting fees from AiCuris, AstraZeneca, Bayer, Cerexa, Durata, The Medicines Company, Menarini, Motif Biosciences, Nabriva, Paratek and

Pfizer. He has received lecture fees from Allergan, AstraZeneca and Pfizer, and grant support from Motif Biosciences, Nabriv, Paratek, and Pfizer.

Jesus Gonzalez, David J. Wilson, Shampa Das, and Joseph Iaconis were employees of AstraZeneca at the time of study conduct and analysis.

David J. Wilson, Shampa Das, and Joseph Iaconis are shareholders in AstraZeneca.

Alena Jandourek and H. David Friedland were employees of Cerexa (now a subsidiary of Allergan) at the time of study conduct and analysis.

Matthew Dryden: has received honoraria from and attended advisory boards for Bayer, AstraZeneca, Motif-Bio, Pfizer, Matoke, and MSD.

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 center.

Author Contributions

J.G., A.J., D.J.W., H.D.F., S.D., and **J.I.** contributed to study design. **D.J.W.** made a substantial contribution to data analyses. **J.I**. made a contribution to data analysis. **M.D.** was involved in study design and data interpretation. **All authors** contributed to data interpretation and to each stage of development of the manuscript and review and approved the final version for submission.

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. Available at: http://www.fda.gov/downloads/Drugs/Guidances/ucm071185.pdf.%20Accessed%20Aug%202. Accessed November 28, 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;15:1516-8.

[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, Allergan plc, Dublin, Ireland, 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:iv41-iv51.

[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:iv53-iv65.

[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.

[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. Journal of the Intensive Care Society 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. Clinical and Laboratory Standards Institute; 2015.

[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:iii19-iii32.

[21] Low DE, File TM, Jr, Eckburg PB, Talbot GH, David Friedland H, 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:iii33-iii44.

[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;51:3612-6.

[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;54:1811-4.

[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] US National Library of Medicine. NCT00633126: Pharmacokinetics of Ceftaroline in Subjects 12 to 17 Years of Age. US National Library of Medicine. Available at:

https://clinicaltrials.gov/ct2/show/NCT00633126?term=NCT00633126&rank=1. Accessed November 27, 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 Presented at: 55th Interscience Conference on Antimicrobial Agents and Chemotherapy, September 17-21, 2015; San Diego, CA.

[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 2018.

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

[32] 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 ≤2 mg/L in ABSSSI Presented at: 55th Interscience Conference on Antimicrobial Agents and Chemotherapy, September 17-21, 2015; San Diego, CA.

[33] 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.

[34] The European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. 2017.

[35] 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.

[36] 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.

[37] Clinical and Laboratory Standards Institute. M100-S27. Performance standards for antimicrobial susceptibility testing: 27th informational supplement. Wayne, PA: Clinical and Laboratory Standards Institute; 2017.

Table 1

Patient Demographics and Baseline Characteristics (MITT Population)

	COVERS		CANVAS 1 and 2	
		Vancomycin Plus		Vancomycin Plus
	Ceftaroline Fosamil	Aztreonam	Ceftaroline Fosamil	Aztreonam
Characteristic	**n=506**	**n=255**	**n=693**	**n=685**
Age, mean (SD), y	52.6 (16.5)	53.6 (16.3)	47.5 (17.0)	48.4 (16.6)
Sex, n (%)				
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, n (%)				
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	–	–	2 (0.3)	2 (0.3)

Islander				
Multiracial/other	25 (4.9)	18 (7.1)	6 (0.9)	7 (1.0)
BMI, median (range), kg/m^2	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 CrCl (mL/min)[a]				
>30–≤50	31 (6.1)	17 (6.7)	23 (3.3)	26 (3.8)
>50–≤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 C-reactive protein, mg/L				
≤50	178 (35.2)	100 (39.2)	396 (57.1)	387 (56.5)
>50−≤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)
Comorbid conditions, n (%)				
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, median (range), cm^2	400 (75–5040)	400 (77–6048)	156 (1–3150)	150 (0.04–4950)
Prior antibiotic therapy, n (%)	240 (47.4)	116 (45.5)	276 (39.8)	260 (38.0)

≥1 systemic inflammatory sign, n (%)[b]	312 (61.7)	166 (65.1)	378 (54.5)	363 (53.0)
≥2 severe signs and/or symptoms, n (%)[c]	329 (65.0)	165 (64.7)	372 (53.7)	379 (55.3)
SIRS, n (%)[d]	208 (41.1)	113 (44.3)	155 (22.4)	163 (23.8)

BMI=body mass index; MITT=modified intent-to-treat population; SIRS=systemic inflammatory response syndrome.

[a]Eight patients had CrCl >20–<30 mL/min and 22 patients had missing CrCl data in COVERS; 4 patients had CrCl ≤30 mL/min in CANVAS 1 and 2.

[b]Systemic signs were fever >38°C, hypothermia <36°C, elevated WBC count (>10,000 cells/mm^3), or bands >10%.

[c]Severe local signs were erythema, swelling, tenderness, or warmth that was designated as "severe" by the investigator.

[d]Systemic inflammatory response syndrome criteria were defined as presence of ≥2 of the following symptoms at baseline: temperature <36°C or >38°C; heart rate >90 beats per minute; respiratory rate >20 breaths per minute, or on blood gas, a $PaCO_2$, <32 mmHg (4.3 kPa); WBCs <4000 cells/mm^3 or >12,000 cells/mm^3, or >10% band forms (immature WBC).

Table 2

Susceptibility of Pathogens Isolated at Baseline to Ceftaroline (mMITT population)

	COVERS			CANVAS 1 and 2		
Pathogen	**Isolates (n)**	**MIC range[a]**	**MIC_{90}[a,b]**	**Isolates (n)**	**MIC range[a]**	**MIC_{90}[a]**
Gram-positive						
Staphylococcus aureus[c]	217	0.06–1	0.5	399	0.06–2	0.5
MSSA	164	0.06–0.5	0.25	235	0.06–0.5	0.25
MRSA	54	0.25–1	0.5	164	0.25–2	0.5
Streptococci						
Streptococcus pyogenes[d]	25	≤0.008	≤0.008	61	≤0.004–0.008	≤0.004
Streptococcus agalactiae[d]	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[e]						
Escherichia coli (non−ESBL-producing)	26	≤0.015–8	1	23	0.015–>16	1
Klebsiella oxytoca	8	0.03–0.25	–	11	0.03–0.25	0.25
Klebsiella pneumoniae	12	0.06–>32	>32	18	0.03–>16	>16
Morganella morganii	7	0.03–0.12	–	11	0.06–>16	>16
Proteus mirabilis	11	0.03–>32	0.12	16	≤0.008–>16	>16

ESBL=extended-spectrum beta lactamase; MIC=minimum inhibitory concentration; MRSA=methicillin-resistant *S*. *aureus*; MSSA=methicillin-susceptible *S*. *aureus*.

[a]MIC range/MIC_{90} expressed in mg/L.

[b]MIC_{90} not calculated when n<10.

[c]FDA/CLSI ceftaroline susceptible/resistant breakpoints ≤1/≥4 mg/L.

[d]FDA/CLSI ceftaroline susceptible breakpoint ≤0.5 mg/L.

[e]FDA/CLSI ceftaroline susceptible/resistant breakpoint for *Enterobacteriaceae* ≤0.5/≥2 mg/L [37].

Table 3

Clinical Cure Rates at Test-of-Cure Overall and Among Subgroups of Patients with Systemic Signs of Infection, SIRS, and BMI and baseline CrCl categories (MITT Population)

	COVERS			CANVAS 1 and 2		
Patient Population	**Ceftaroline Fosamil n/N (%)**	**Vancomycin Plus Aztreonam n/N (%)**	**Between-Group Difference (95% CI)**	**Ceftaroline Fosamil n/N (%)**	**Vancomycin Plus 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 sign[a]	255/312 (81.7)	137/166 (82.5)	−0.8 (−7.7 to 6.8)	335/394 (85.0)	326/379 (86.0)	−1.0 (−6.0 to 4.0)
≥2 severe signs 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	185/211 (87.7)	181/201 (90.0)	−2.4

			(−10.6 to 4.9)			(−8.6 to 3.8)
Elevated WBC[c]	177/224 (79.0)	75/104 (72.1)	6.9	205/246 (83.3)	213/254 (83.9)	−0.5
			(−2.8 to 17.5)			(−7.1 to 6.0)
SIRS[d]	168/199 (84.4)	83/105 (79.0)	5.4	131/155 (84.5)	140/163 (85.9)	−1.4
			(−3.5 to 15.2)			(−9.4 to 6.5)
Baseline C-reactive protein, mg/L						
≤50	149/178 (83.7)	83/100 (83.0)	0.7	346/396 (87.4)	333/387 (86.0)	1.3
			(−8.0 to 10.5)			(−3.5 to 6.1)
>50 to ≤150	136/178 (76.4)	67/80 (83.8)	−7.4	156/177 (88.1)	138/166 (83.1)	5.0
			(−16.9 to 3.8)			(−2.5 to 12.7)
>150	105/139 (75.5)	49/68 (72.1)	3.5	76/98 (77.6)	95/111 (85.6)	−8.0
			(−8.8 to 16.9)			(−18.9 to 2.5)
BMI, kg/m^2						
<18.5	8/15 (53.3)	6/9 (66.7)	−13.3	11/15 (73.3)	5/7 (71.4)	1.9
			(−48.2 to 27.4)			

≥18.5–<25	145/185 (78.4)	67/87 (77.0)	1.37 (−8.7 to 12.7)	201/238 (84.5)	182/223 (81.6)	2.8 (−4.0 to 9.8)
≥25–<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)	5.01 (−5.3 to 16.9)	186/222 (83.8)	188/227 (82.8)	1.0 (−6.0 to 7.9)
CrCl, mL/min[e]						
>30–≤50	23/31 (74.2)	10/17 (58.8)	15.37 (-11.61 to 42.57)	19/23 (82.6)	21/26 (80.8)	1.8 (−21.5 to 24.2)
>50–≤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)

BMI=body mass index; SIRS=systemic inflammatory response; 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]Systemic inflammatory response syndrome criteria were defined as presence of ≥2 of the following symptoms at baseline: temperature <36°C or >38°C; heart rate >90 beats per minute; respiratory rate >20 breaths per minute, or on blood gas, a $PaCO_2$, <32 mmHg (4.3 kPa); WBCs <4000 cells/mm^3 or >12,000 cells/mm^3, or >10% band forms (immature WBC).

[e]Ceftaroline fosamil dosage regimens were adjusted for patients with CrCl >30-≤50 mL/min. Clinical cure rates for patients with CrCl >20–<30 mL/min (n=8) and patients with missing CrCl data (n=22) in COVERS not shown.

Table 4

Clinical Cure Rate by Baseline Pathogen (ME Population)

	COVERS			CANVAS 1 and 2		
Pathogen	**Ceftaroline Fosamil n/N (%)**	**Vancomycin Plus Aztreonam n/N (%)**	**Between-Group Difference (95% CI)**	**Ceftaroline Fosamil n/N (%)**	**Vancomycin Plus Aztreonam n/N (%)**	**Between-Group Difference (95% CI)**
Gram-positive						
Staphylococcus aureus[a]	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)	22/238 (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)	–6.7 (–30.5 to 30.8)	56/56 (100)	56/58 (96.6)	3.9 (–2.3 to 12.6)
Streptococcus	5/6 (83.3)	7/9 (77.8)	5.6	21/22 (95.5)	18/18 (100)	N/A

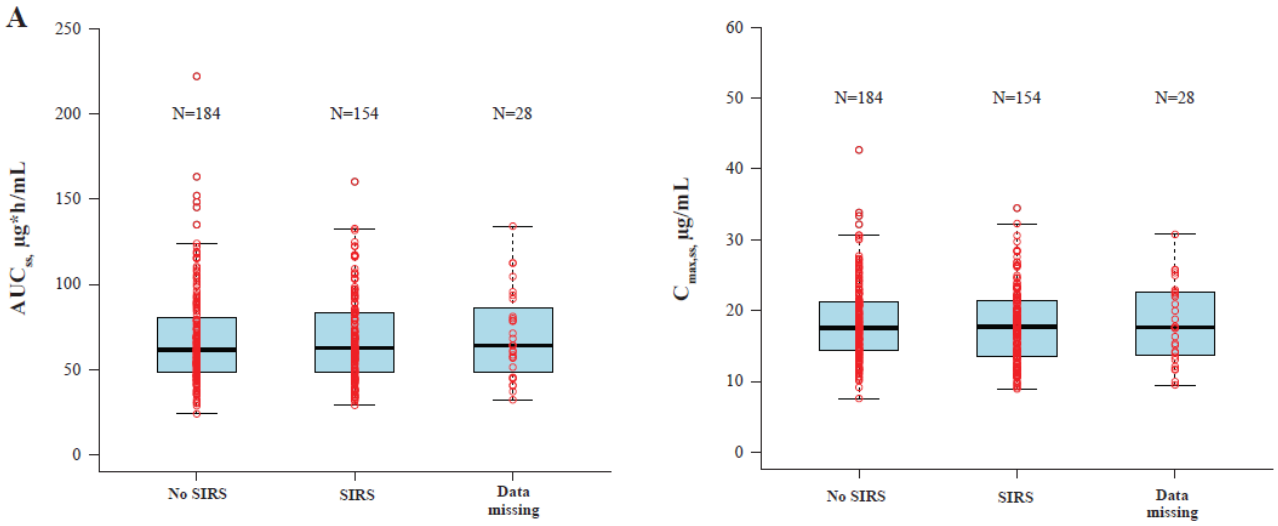
agalactiae			(–41.2 to 44.9)			
Streptococcus dysgalactiae	9/9 (100.0)	0/0 (0)	N/A	13/13 (100)	15/16 (93.8)	N/A
Streptococcus anginosus group	16/18 (88.9)	4/4 (100)	–11.1 (–33.4 to 40.6)	12/13 (92.3)	15/16 (93.8)	N/A
Enterococcus faecalis	4/6 (66.7)	4/5 (80.0)	–13.3 (–59.6 to 41.6)	20/25 (80.0)	22/24 (91.7)	–12.6 (–34.1 to 8.0)
Gram-negative						
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
Klebsiella oxytoca	4/4 (100.0)	1/1 (100)	N/A	10/12 (83.3)	6/6 (100)	N/A
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
Morganella morganii	4/4 (100)	2/2 (100)	N/A	11/12 (91.7)	5/6 (83.3)	N/A
Proteus mirabilis	6/7 (85.7)	2/2 (100)	–14.3 (–53.5 to 58.4)	10/15 (66.7)	20/21 (95.2)	N/A

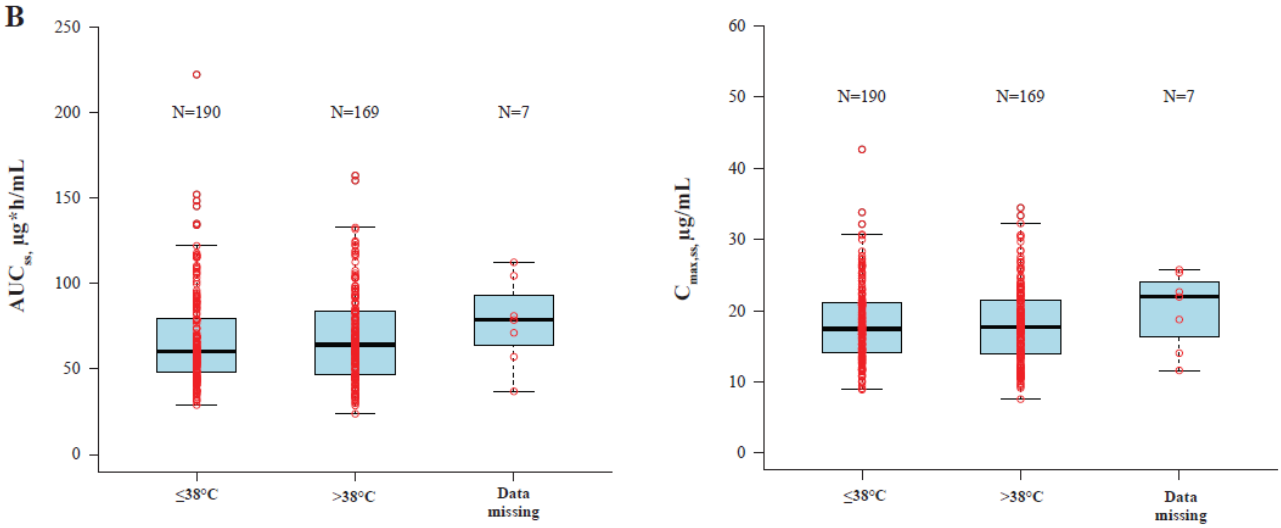
ESBL=extended-spectrum beta lactamase; ME=medically evaluable; MIC=minimum inhibitory concentration; MRSA=methicillin-resistant *S. aureus*; MSSA=methicillin-susceptible *S. aureus*; N/A=not applicable.

[a]Patients with MRSA and MSSA were counted only once.

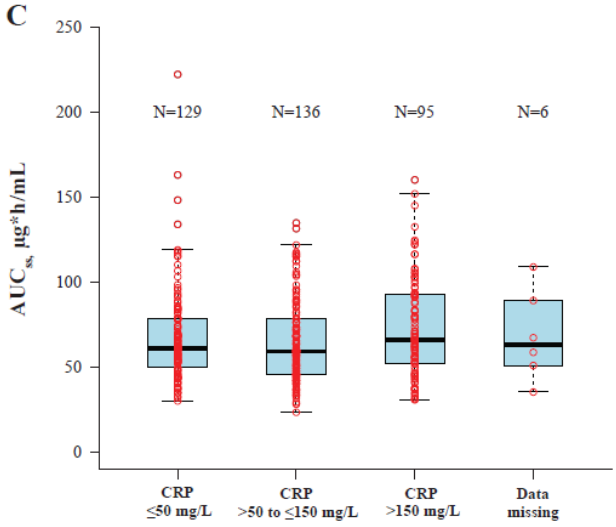
Figure Legend

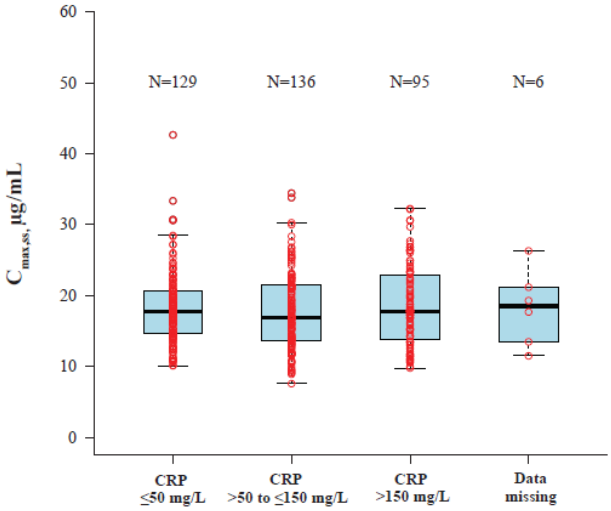
Figure 1. Comparison of predicted steady-state ceftaroline fosamil exposures (AUC_{ss} and $C_{max,ss}$) in individual ABSSSI patients from COVERS (A) with and without SIRS (B) with and without fever (C) with and without high CRP (D) with and without high WBC count and (E) with and without bacteremia. ABSSSI=acute bacterial skin and skin structure infections, CRP=C-reactive protein, SIRS=systemic inflammatory response syndrome.



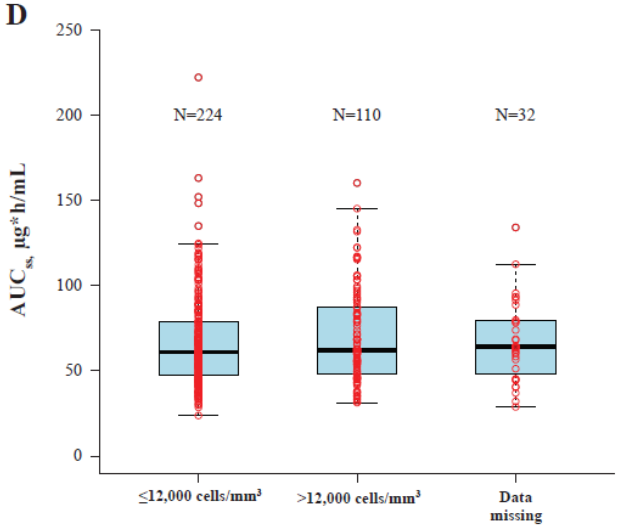

B
AUC$_{ss}$, µg*h/mL
250
200
150
100
50
0
N=190
N=169
N=7
≤38°C
>38°C
Data missing
C$_{max,ss}$, µg/mL
60
50
40
30
20
10
0
N=190
N=169
N=7
≤38°C
>38°C
Data missing

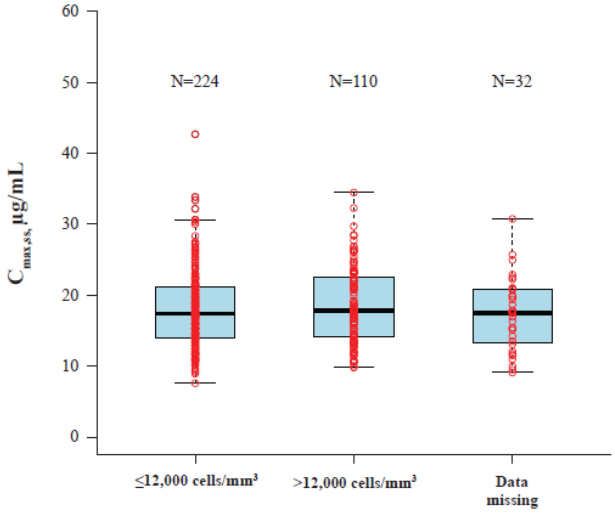
C


250
200
150
100
50
0
AUCss, µg*h/mL
N=129
N=136
N=95
N=6
CRP ≤50 mg/L
CRP >50 to ≤150 mg/L
CRP >150 mg/L
Data missing

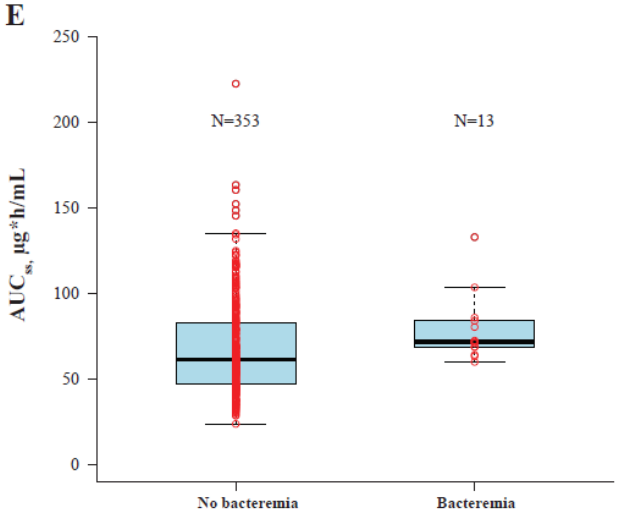

60
50
40
30
20
10
0
Cmax,ss, µg/mL
N=129
N=136
N=95
N=6
CRP ≤50 mg/L
CRP >50 to ≤150 mg/L
CRP >150 mg/L
Data missing

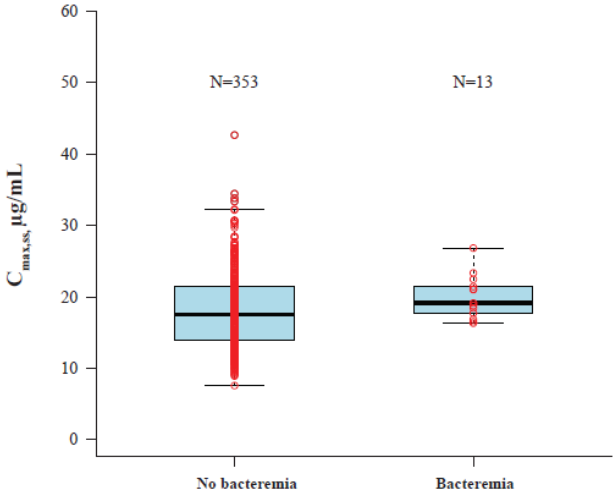
D


250
200
150
100
50
0
AUC$_{ss}$, µg*h/mL
N=224
N=110
N=32
≤12,000 cells/mm³
>12,000 cells/mm³
Data missing


60
50
40
30
20
10
0
C$_{max,ss}$, µg/mL
N=224
N=110
N=32
≤12,000 cells/mm³
>12,000 cells/mm³
Data missing

E


250
200
150
100
50
0
AUC$_{ss}$, µg*h/mL
N=353
N=13
No bacteremia
Bacteremia


60
50
40
30
20
10
0
C$_{max,ss}$, µg/mL
N=353
N=13
No bacteremia
Bacteremia