MAJOR ARTICLE

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

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Background. Methicillin-resistant *Staphylococcus aureus* (MRSA) is a common cause of complicated skin and skin-structure infection (cSSSI). Increasing antimicrobial resistance in cSSSI has led to a need for new safe and effective therapies. Ceftaroline was evaluated as treatment for cSSSI in 2 identical phase 3 clinical trials, the pooled analysis of which is presented here. The primary objective of each trial was to determine the noninferiority of the clinical cure rate achieved with ceftaroline monotherapy, compared with that achieved with vancomycin plus aztreonam combination therapy, in the clinically evaluable (CE) and modified intent-to-treat (MITT) patient populations.

Methods. Adult patients with cSSSI requiring intravenous therapy received ceftaroline (600 mg every 12 h) or vancomycin plus aztreonam (1 g each every 12 h) for 5–14 days.

Results. Of 1378 patients enrolled in both trials, 693 received ceftaroline and 685 received vancomycin plus aztreonam. Baseline characteristics of the treatment groups were comparable. Clinical cure rates were similar for ceftaroline and vancomycin plus aztreonam in the CE (91.6% vs 92.7%) and MITT (85.9% vs 85.5%) populations, respectively, as well as in patients infected with MRSA (93.4% vs 94.3%). The rates of adverse events, discontinuations because of an adverse event, serious adverse events, and death also were similar between treatment groups.

Conclusions. Ceftaroline achieved high clinical cure rates, was efficacious against cSSSI caused by MRSA and other common cSSSI pathogens, and was well tolerated, with a safety profile consistent with the cephalosporin class. Ceftaroline has the potential to provide a monotherapy alternative for the treatment of cSSSI.

Trial registration. ClinicalTrials.gov identifiers: NCT00424190 for CANVAS 1 and NCT00423657 for CANVAS 2.

Complicated skin and skin-structure infections (cSSSIs) are predominantly caused by *Staphylococcus aureus* or *Streptococcus pyogenes* [1–5] and various other gram-positive and gram-negative bacteria [4, 6], depending on infection etiology, host characteristics, and anatomical location. The increasing frequency of methicillin-resistant *S. aureus* (MRSA) presents difficulties in the prevention and treatment of hospital- and community-acquired infections [7, 8]. The prevalence of methicillin resistance among community-associated *S. aureus* isolates from surveillance studies and patients in emergency departments in the United States is nearly 60% [9, 10]. First-line treatment of cSSSI caused by MRSA includes vancomycin, linezolid, or daptomycin; oral options for outpatients include clindamycin, doxycycline, or sulfamethoxazole-trimethoprim. The utility of

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these drugs can be limited by a narrow spectrum of activity, resistance, the need for monitoring of serum concentration, and/or adverse effects [11–13].

Pathogenic streptococci are also showing signs of increasing resistance. Although *S. pyogenes* remains susceptible to most β-lactams, macrolide resistance has increased; recent global estimates range from 6.8% in the United States to >95% in China [14–17]. In addition, 7.5% of isolates in Belgium were reported to be resistant to fluoroquinolones [18]. Non–group A and non–group B β-hemolytic streptococci have demonstrated resistance to erythromycin, fluoroquinolones, tetracycline, and clindamycin [19]. These factors suggest a need for additional safe and efficacious therapies with a spectrum consistent with commonly encountered cSSSI pathogens.

Ceftaroline fosamil (hereafter, *ceftaroline*) is a novel, broad-spectrum cephalosporin prodrug, the active metabolite of which exhibits bactericidal activity against gram-positive organisms (including MRSA), vancomycin-intermediate *S. aureus* strains, and macrolide-resistant *S. pyogenes*, as well as potential gram-negative pathogens, including non–extended-spectrum β-lactamase (ESBL)–producing *Klebsiella pneumoniae* and *Escherichia coli* [20–24]. Ceftaroline is in development for treatment of hospitalized patients with cSSSI. A phase 2 trial initially investigated the efficacy and safety of ceftaroline in the treatment of cSSSI [25].

This article describes the integrated findings of CANVAS 1 and CANVAS 2 (Ceftaroline versus Vancomycin in Skin and Skin-Structure Infection), 2 phase 3 clinical trials that compared ceftaroline monotherapy with vancomycin plus aztreonam combination therapy for the treatment of adults with cSSSI.

METHODS

Study design and treatment. CANVAS 1 (NCT00424190) and CANVAS 2 (NCT00423657) are phase 3, international, multicenter, randomized, double-blind, comparative efficacy and safety studies, with identical designs and protocols, of intravenous ceftaroline versus intravenous vancomycin plus aztreonam for 5–14 days in adults with cSSSI. The studies were designed to allow pooling of results for a larger database of pathogens and safety information. A total of 111 study centers in Europe, Latin America, and the United States participated.

Study participants were randomized to receive 600 mg of ceftaroline followed by normal saline placebo or 1 g of vancomycin followed by 1 g of aztreonam. All doses were masked within a yellow bag to maintain blinding. The ceftaroline dose was adjusted by unblinded pharmacy or study staff to 400 mg for patients with creatinine clearance >30 and ≤50 mL/min. The vancomycin dose was adjusted according to institutional guidelines or local prescribing practices. Treatments were administered intravenously in 250 mL of sodium chloride (0.9%) over 60 min every 12 h for 5–14 days. Therapy was deemed to be complete on the basis of investigator determination that all signs and symptoms of infection had resolved or improved such that no further antimicrobial therapy was necessary. If a gram-negative pathogen was neither identified nor suspected, the blinded investigator could decide to discontinue aztreonam (or placebo in the ceftaroline group). It was not mandatory for culture results to be obtained before randomization. Test-of-cure and late follow-up visits occurred 8–15 and 21–35 days, respectively, after the last dose of study drug.

Study populations. Inclusion and exclusion criteria are listed in Table 1. The modified intent-to-treat (MITT) population included all randomized patients who received any treatment. The microbiological modified intent-to-treat (mMITT) population included MITT patients who met clinical disease criteria for cSSSI and had ≥1 bacterial pathogen isolated from blood or the cSSSI site at baseline. The clinically evaluable (CE) population included MITT patients who met clinical disease criteria for cSSSI, received a prespecified minimum amount of study drug, and for whom outcome information was available. The microbiologically evaluable (ME) population included CE patients with ≥1 bacterial pathogen isolated from blood or the cSSSI site at baseline. Patients were excluded from the ME population if baseline culture revealed monomicrobial *Pseudomonas aeruginosa* or anaerobic infection.

Efficacy assessments. At the test-of-cure visit, 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. Microbiological eradication was defined as absence of the baseline pathogen. Eradication was presumed if an adequate source specimen was not available for culture and the patient was assessed to have achieved clinical cure. At the late follow-up visit, relapse was noted if a patient considered to be clinically cured at the test-of-cure visit exhibited a return of symptoms and/or signs of infection. Microbiological recurrence or reinfection was defined as isolation of a baseline or new pathogen from the original cSSSI site in patients who had clinical evidence of relapse.

Safety assessments. Safety assessments (MITT population) included physical examination, electrocardiogram, clinical chemistry and hematology parameters, coagulation tests, and reporting of adverse events (AEs) and serious AEs (SAEs). One patient randomized to ceftaroline received vancomycin plus aztreonam for the full course of therapy and thus was analyzed in the comparator group. Treatment-emergent AEs were defined as AEs with onset or worsening severity at or after the first dose of study drug through the test-of-cure visit (for all AEs) or the late follow-up visit (for SAEs only).

Statistical methods. Sample size was calculated using the Farrington-Manning method [26]. Assuming a point estimate for the primary outcome measure of a clinical cure rate of 85% in both treatment groups, a noninferiority margin of 10%, power

Table 1. Inclusion and Exclusion Criteria

Inclusion criteria	Exclusion criteria
Age ⩾18 years	Received >24 h of antimicrobial treatment within 96 h before randomization, unless there was evidence of clinical and microbiological failure after ⩾48 h of therapy
cSSSI of severity substantial enough to require initial hospitalization or treatment in an emergency department and ⩾5 days of intravenous antimicrobial therapy; hospitalization was not required if the patient was suitable for outpatient parenteral antimicrobial therapy	Current pathogen was known or suspected to be resistant to vancomycin or aztreonam
⩾3 clinical signs of infection (purulent or seropurulent drainage or discharge, erythema, fluctuance, heat or localized warmth, pain or tenderness to palpation, temperature >38°C or hypothermia, WBC count >10,000 cells/μL, or >10% immature neutrophils irrespective of WBC count)	Creatinine clearance ⩽30 mL/min
cSSSI that met either of the following criteria: (1) involved deep soft tissue or required significant surgical intervention, such as wound infection with purulent or seropurulent drainage or ⩾5 cm of surrounding cellulitis, major abscess surrounded by ⩾2 cm of cellulitis, infected ulcer, or cellulitis with surface area of ⩾10 cm^2; (2) cellulitis or abscess of a lower extremity in patients with diabetes mellitus (requiring insulin, insulin analogues, or oral hypoglycemic agents) or well-documented peripheral vascular disease	cSSSI known or suspected to be caused by *Pseudomonas aeruginosa* or an anaerobic, fungal, parasitic, or viral pathogen
Patients had to provide written informed consent	Decubitus ulcer, diabetic foot ulcer, or ulcer associated with peripheral vascular disease accompanied by osteomyelitis or likely to require amputation or revascularization within 60 days
…	Required surgical intervention that could not be performed within 48 h
…	Third-degree burn or burn covering >5% of the body
…	Human or animal bite (arthropod bites were allowed)
…	Necrotizing fasciitis or gangrene
…	Endocarditis, osteomyelitis, or septic arthritis
…	Required concomitant antimicrobial therapy or high-dose corticosteroid therapy

NOTE. cSSSI, complicated skin and skin-structure infection; WBC, white blood cell.

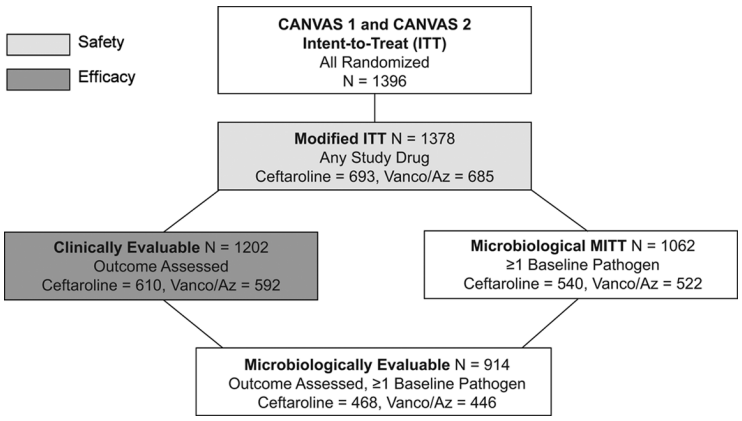

Figure 1. Disposition of patients in studies of ceftaroline versus vancomycin plus aztreonam (Vanco/Az) for the treatment of complicated skin and skin-structure infections. Eighteen patients were excluded from the modified intent-to-treat (MITT) population because they did not receive study drug; 334 patients were excluded from the microbiological MITT population because a baseline pathogen was not isolated, the minimal disease definition was not met, or they did not receive study drug; 194 patients were excluded from the clinically evaluable (CE) population, the most common reasons for which were indeterminate assessment at the test-of-cure visit ($n = 112$), breaking of the blind ($n = 20$), and receipt of a potentially effective concomitant antimicrobial ($n = 14$). Patients from the CE population were included in the microbiologically evaluable (ME) population if they met the assessment criteria, a baseline pathogen was isolated, and they did not have only anaerobic infection or monomicrobial *Pseudomonas aeruginosa* isolated from the infection site (482 patients were excluded from the ME population).

of 90%, and a 20% nonevaluable rate, a sample size of 690 patients (345 per treatment group) was required for each study.

The primary outcome measure in each study, as well as the integrated analysis, was the per-patient clinical cure rate at the test-of-cure visit in the CE and MITT populations (coprimary analysis). Secondary efficacy analyses included per-patient microbiological response and per-pathogen clinical and microbiological response at the test-of-cure visit and relapse and reinfection/recurrence rates at the late follow-up visit.

A 2-sided 95% confidence interval (CI) for the observed difference in the primary outcome measure between treatment groups was calculated using the Miettinen-Nurminen method [27], stratified by study. Noninferiority was concluded if the lower limit of the 95% CI was above −10%. For per-patient microbiological response and clinical cure within subgroups of patients, 95% CIs were calculated using the same method and are provided for descriptive purposes.

RESULTS

Patient disposition and analysis populations. Of the 1396 randomized patients in the ITT population, 1378 received study drug (for ceftaroline, $n = 693$; for vancomycin plus aztreonam, $n = 685$) (Figure 1).

Patient demographics and baseline medical characteristics. The patient population was predominantly white and male (Table 2), and 78.2% were hospitalized at study entry. The median patient age was 48 years; 18.1% and 7.5% were aged 65 and 75 years or older, respectively. Both treatment groups had similar demographic characteristics, type and site of cSSSI, and relevant medical or surgical history. Moderate renal impairment (creatinine clearance >30 and ⩽50 mL/min) was present in 3.6% of patients. In 54.5% of cases, patients had ⩾2 signs or symptoms (erythema, swelling, tenderness, or warmth) classified as severe; 36.3% had leukocytosis, and 29.9% were febrile. Bacteremia was present in 4.0% of patients. Infection types occurred at similar frequencies in the ceftaroline and vancomycin plus aztreonam groups, with cellulitis, major abscess, and infected wound accounting for the majority (Figure 2). The median infection area was 156 cm^2 for the ceftaroline group and 150 cm^2 for the vancomycin plus aztreonam group. All abscesses were required to contain loculated fluid and be surrounded by ⩾2 cm of erythema. In addition, >88% had ⩾1 dimension >5 cm. The mean treatment duration in the CE population was ~8 days for both groups. A pathogen was isolated from 76.1% of patients; the most common pathogen isolated from the primary infection site was *S. aureus*, with MRSA accounting for 40% in the ceftaroline group and 34% in the vancomycin plus aztreonam group (Table 3). Gram-negative potential pathogens were isolated from the primary infection site in 16.3% of patients; gram-negative bacteria alone were recovered from 5.9% of patients. Polymicrobial infections that included a gram-positive potential pathogen occurred in 20.6% of patients.

Clinical outcomes. In the integrated analysis, the efficacy of ceftaroline was similar to that of vancomycin plus aztreonam in the CE and MITT populations (Table 4). The lower limit of the 95% CI was above −10%, which was the predefined requirement for noninferiority in each trial. Similarly, each of the 2 trials met the primary objective of noninferiority in the clinical cure rate for ceftaroline versus vancomycin plus aztreonam

Table 2. Demographic and Baseline Characteristics (Modified Intent-to-Treat Population)

Characteristic	Ceftaroline (n = 693)	Vancomycin plus aztreonam (n = 685)
Age, median years (range)	48.0 (18–93)	48.0 (18–96)
Male sex, no. (%)	444 (64.1)	419 (61.2)
Race, no. (%)		
White	506 (73.0)	512 (74.7)
Nonwhite	62 (8.9)	52 (7.6)
Other/unknown	125 (18.0)	121 (17.7)
Region of enrollment, no. (%)		
EU	147 (21.2)	145 (21.2)
Non-EU Europe	187 (27.0)	188 (27.4)
Latin America	56 (8.1)	53 (7.7)
United States	303 (43.7)	299 (43.6)
BMI		
Median (range)	26.9 (14.1–74.1)	27.4 (16.6–66.5)
>30, no. (%)	222 (32.0)	227 (33.1)
Duration of therapy, mean days ± SD	8.3 ± 3.2	8.4 ± 3.3
Comorbid conditions, no. (%)		
Diabetes mellitus	122 (17.6)	120 (17.5)
Peripheral vascular disease	93 (13.4)	93 (13.6)
Injection drug use	46 (6.6)	59 (8.6)
Bacteremia, no. (%)	29 (4.2)	26 (3.8)
Site of primary infection, no. (%)		
Lower limb	338 (48.8)	339 (49.5)
Head/neck	45 (6.5)	33 (4.8)
Other	310 (44.7)	313 (45.7)
Prior antimicrobial therapy, no. (%)	276 (39.8)	260 (38.0)
Infection measurements		
Length, median cm (range)	15.00 (0.4–65.0)	15.00 (0.2–99.0)
Width, median cm (range)	10.00 (0.5–55.0)	10.00 (0.2–61.3)
Surgical procedures on primary infection site ⩽48 h after enrollment,[a] no. (%)		
⩾1 procedure	97 (14.0)	108 (15.8)
Incision and drainage	46 (6.6)	51 (7.4)
Debridement	31 (4.5)	29 (4.2)

NOTE. BMI, body mass index (calculated as the weight in kilograms divided by the square of height in meters); EU, European Union; SD, standard deviation.

[a] Includes patients with surgical procedures performed <24 h before first dose or randomization and <48 h after first dose.

(95% CIs in CANVAS 1, −6.6 to 2.1 for CE and −4.1 to 6.2 for MITT; 95% CIs in CANVAS 2, −4.4 to 4.5 for CE and −5.8 to 5.0 for MITT). The efficacy of ceftaroline and of vancomycin plus aztreonam against polymicrobial and monomicrobial infections was similar (Table 4). Clinical cure rates by baseline pathogen are presented in Table 5.

Clinical cure rates in subgroups of patients (CE) were similar between treatment groups (Table 6). Infection type did not affect clinical cure rates between treatment groups. Of note, clinical cure was reported in 91.1% and 94.1% of patients with a major abscess in the ceftaroline and vancomycin plus aztreonam groups, respectively. When major abscesses were excluded from analysis (CE), the clinical cure rate remained similar both overall and between treatment groups (for ceftaroline, 91.9%; for vancomycin plus aztreonam, 92.1%). Clinical cure rates were similar between treatment groups for subgroups of patients with diabetes mellitus (for ceftaroline, 87.3%; for vancomycin plus aztreonam, 90.9%) or peripheral vascular disease (for ceftaroline, 88.9%; for vancomycin plus aztreonam, 89.3%).

Clinical cure rates among the 47 patients with bacteremia (CE) were 84.6% (22 of 26) for ceftaroline versus 100% (21 of 21) for vancomycin plus aztreonam (Table 6). Of note, more patients in the ceftaroline group than the comparator group experienced staphylococcal bacteremia (18 vs 9, respectively), whether caused by methicillin-susceptible *S. aureus* (11 vs 7) or MRSA (7 vs 2). The remaining bacteremias were predominantly caused by *S. pyogenes* (2 vs 3), gram-negative bacilli (2 vs 5), and other streptococci. Among patients with *S. aureus* bacteremia, the ceftaroline group had an 88.9% clinical cure rate. Similar cure rates were found among patients infected with MRSA. Four of the 26 patients in the ceftaroline-treated bacteremia group were classified as having experienced clinical

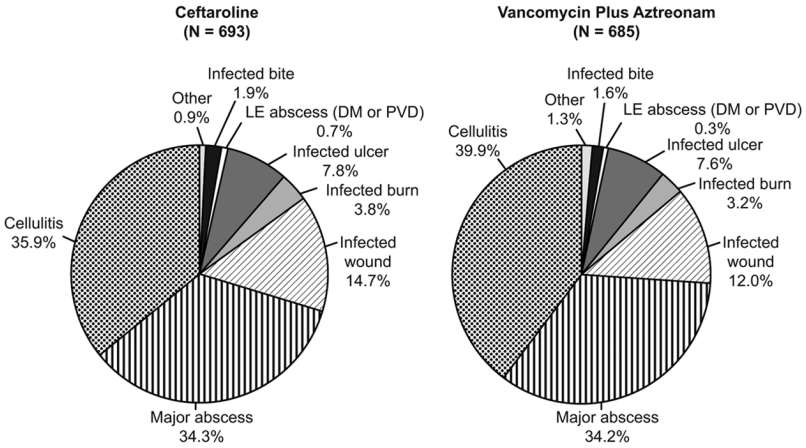

Figure 2. Infection type at baseline (modified intent-to-treat population). DM, diabetes mellitus; LE, lower extremity; PVD, peripheral vascular disease.

failure: 2 due to a treatment-limiting AE leading to withdrawal of study drug (1 episode of *Clostridium difficile*–associated diarrhea and 1 allergic rash), 1 because of the need for surgical intervention on study day 7, and 1 due to a resistant copathogen (*P. aeruginosa*) and failure to timely perform surgical intervention. The organisms isolated from these patients were *S. aureus* (2 patients), an organism from the *Streptococcus anginosus* group (1 patient), and *P. aeruginosa* and *Morganella morganii* as copathogens (1 patient). Follow-up blood cultures indicated clearance in all 4 patients; for the 3 patients with staphylococcal or streptococcal bacteremia, sterilization of blood cultures was achieved during continued ceftaroline therapy.

Clinical relapse at the late follow-up visit was noted in 1.1% (6 of 559) of patients in the ceftaroline group, compared with 0.9% (5 of 549) of patients in the vancomycin plus aztreonam group (CE).

Microbiological efficacy. Favorable microbiological response (ME) was observed in 92.3% (432 of 468) of patients in the ceftaroline group, compared with 93.7% (418 of 446) of patients in the vancomycin plus aztreonam group (difference, −1.4%; 95% CI, −4.8% to 2.0%). For patients with infection caused by ⩾1 gram-positive pathogen, a favorable microbiological response was achieved in 93.5% (403 of 431) of patients in the ceftaroline group, compared with 93.8% (396 of 422) of patients in the vancomycin plus aztreonam group (difference, −0.3%; 95% CI, −3.7% to 3.1%). For infections in which ⩾1 potential gram-negative pathogen was present, a favorable per-pathogen microbiological response was achieved in 86.3% (82 of 95) of patients

Table 3. Minimum Inhibitory Concentration (MIC) Ranges and MIC_{90} Values for Selected Baseline Isolates from the Primary Infection Site (Microbiologically Evaluable Population)

	Ceftaroline					
	No. of	μg/mL		No. of	μg/mL	
Isolate	isolates	MIC range	MIC_{90}	isolates	MIC range	MIC_{90}
Gram-positive organisms					Vancomycin	
Staphylococcus aureus	377	0.06 to 2	0.5	357	⩽0.25 to 2	1
MRSA	150	0.25 to 2	1	121	0.5 to 2	1
MSSA	227	0.06 to 0.5	0.25	236	⩽0.25 to 2	1
Streptococcus pyogenes	55	⩽0.004 to 0.008	⩽0.004	58	0.25 to 1	0.5
Streptococcus agalactiae	20	0.008 to 0.015	0.015	18	0.25 to 0.5	0.5
Enterococcus faecalis	25	0.25 to 16	4	24	0.5 to 2	2
Gram-negative organisms					Aztreonam	
Pseudomonas aeruginosa	16	4 to >16	>16	18	1 to >32	>32
Escherichia coli	21	0.015 to >16	1	21	⩽0.03 to 0.5	0.12
Klebsiella pneumoniae	18	0.03 to >16	>16	14	⩽0.03 to >32	>32
Proteus mirabilis	15	⩽0.008 to >16	>16	21	⩽0.03 to 16	0.06

NOTE. MIC_{90}, MIC value for which 90% of isolates are susceptible; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*.

Table 4. Clinical Cure Rates by Analysis Population at the Test-of-Cure Visit

Population, type of infection	Cure rate, no. of patients cured/total no. of patients (%)		
	Ceftaroline	Vancomycin plus aztreonam	Difference,[a] % (95% CI)
Clinically evaluable	559/610 (91.6)	549/592 (92.7)	−1.1 (−4.2 to 2.0)
MITT	595/693 (85.9)	586/685 (85.5)	0.3 (−3.4 to 4.0)
Microbiologically evaluable	434/468 (92.7)	421/446 (94.4)	−1.7 (−4.9 to 1.6)
Gram positive only	348/371 (93.8)	330/350 (94.3)	−0.5 (−4.1 to 3.1)
Gram negative only	29/34 (85.3)	24/24 (100)	−15.6 (−31.6 to −1.2)
Mixed gram positive and negative	57/63 (90.5)	67/72 (93.1)	−2.6 (−13.4 to 7.2)
Polymicrobial infection	125/136 (91.9)	134/139 (96.4)	−4.2 (−10.5 to 1.5)

NOTE. CI, confidence interval; MITT, modified intent-to-treat.

[a] Ceftaroline monotherapy minus vancomycin plus aztreonam combination therapy.

in the ceftaroline group, compared with 93.6% (88 of 94) of patients in the vancomycin plus aztreonam group (difference, −7.4%; 95% CI, −16.6% to 1.3%).

Safety and tolerability. Incidences of treatment-emergent AEs, regardless of relationship to study drug, were similar between study groups (Table 7). Diarrhea occurred in 4.9% of patients in the ceftaroline group and in 3.8% of patients in the vancomycin plus aztreonam group (MITT population). *C. difficile* infection occurred in 2 patients in the ceftaroline group and in 1 patient in the vancomycin plus aztreonam group. These infections were successfully managed. AEs considered to be related to study drug in ⩾3% of patients were pruritus, nausea, and diarrhea. Pruritus occurred more often with vancomycin plus aztreonam than with ceftaroline (8.2% vs 3.5%). The most common reason for premature discontinuation of study drug was possible allergic reactions (for ceftaroline, 1.9%; for vancomycin plus aztreonam, 2.9%).

An SAE occurred in 4.3% of patients in the ceftaroline group and in 4.1% of patients in the vancomycin plus aztreonam group. Important medical events related to ceftaroline therapy, such as neutropenia, thrombocytopenia, and liver failure, were not observed in these studies. Possible allergic reaction occurred in 2.0% and 4.1% of patients in the ceftaroline and vancomycin plus aztreonam groups, respectively. Three patients in the ceftaroline group died during the 2 studies. The causes of death were respiratory failure, neck cancer, and cardiopulmonary insufficiency; none of the deaths was assessed by an investigator as related to either study drug or the cSSSI.

As observed with cephalosporins, a higher incidence of Coombs test positivity was recorded in the ceftaroline group than in the comparator group; however, no laboratory or clinical manifestations of hemolytic anemia were identified. Fewer than 2% of patients in each group had a clinically significant electrocardiogram abnormality; the majority of these patients entered the study with an underlying condition that may have been associated with cardiac irregularities. No difference in abnormal physical findings or vital signs was identified between treatment groups.

Table 5. Clinical Cure Rates for Selected Baseline Isolates at the Test-of-Cure Visit

Organism	Cure rate, no. of patients cured/total no. of patients (%)			
	Isolates identified in ME population		Isolates identified in mMITT population	
	Ceftaroline	Vancomycin plus aztreonam	Ceftaroline	Vancomycin plus aztreonam
Staphylococcus aureus	352/378 (93.1)	336/356 (94.4)	377/425 (88.7)	356/409 (87.0)
MRSA	142/152 (93.4)	115/122 (94.3)	155/179 (86.6)	124/151 (82.1)
MSSA	212/228 (93.0)	225/238 (94.5)	221/245 (90.2)	233/258 (90.3)
Streptococcus pyogenes	56/56 (100)	56/58 (96.6)	56/63 (88.9)	57/62 (91.9)
Streptococcus agalactiae	21/22 (95.5)	18/18 (100)	25/27 (92.6)	19/21 (90.5)
Enterococcus faecalis	20/25 (80.0)	22/24 (91.7)	20/28 (71.4)	23/28 (82.1)
Escherichia coli	20/21 (95.2)	19/21 (90.5)	21/23 (91.3)	19/21 (90.5)
Pseudomonas aeruginosa	NA	NA	20/25 (80.0)	22/25 (88.0)
Proteus mirabilis	10/15 (66.7)	20/21 (95.2)	11/16 (68.8)	20/23 (87.0)
Klebsiella pneumoniae	17/18 (94.4)	13/14 (92.9)	17/18 (94.4)	14/19 (73.7)

NOTE. ME, microbiologically evaluable; mMITT, microbiological modified intent-to-treat; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; NA, not applicable.

Table 6. Clinical Cure Rates by Type of Infection, Underlying Comorbidity, or Bacteremia Status (Clinically Evaluable Population) at the Test-of-Cure Visit

Clinical diagnosis	Cure rate, no. of patients cured/total no. of patients (%)		
	Ceftaroline	Vancomycin plus aztreonam	Difference,[a] % (95% CI)
Cellulitis	213/229 (93.0)	222/243 (91.4)	1.7 (−3.4 to 6.7)
Major abscess	184/202 (91.1)	177/188 (94.1)	−3.0 (−8.5 to 2.3)
Infected wound	73/84 (86.9)	65/73 (89.0)	−2.2 (−12.8 to 8.7)
Infected ulcer	48/53 (90.6)	47/50 (94.0)	−3.5 (−15.7 to 8.3)
Infected burn	25/25 (100)	18/18 (100)	0.0 (−13.6 to 17.9)
Infected bite	9/9 (100)	9/9 (100)	0.0
Other	4/5 (80.0)	9/9 (100)	−20.0
Underlying comorbidity			
Diabetes mellitus	96/110 (87.3)	100/110 (90.9)	−3.5 (−12.2 to 5.0)
Peripheral vascular disease	80/90 (88.9)	75/84 (89.3)	−0.2 (−10.0 to 9.7)
Bacteremia	22/26 (84.6)	21/21 (100)	−15.4 (−33.8 to 1.5)
Staphylococcus aureus	16/18 (88.9)	9/9 (100)	−11.1 (−33.2 to 5.7)
MRSA	6/7 (85.7)	2/2 (100)	−14.3 (−53.5 to 58.4)

NOTE. CI, confidence interval; MRSA, methicillin-resistant *S. aureus*.

[a] Ceftaroline monotherapy minus vancomycin plus aztreonam combination therapy.

DISCUSSION

The data from this integrated analysis demonstrate that ceftaroline monotherapy is efficacious for the treatment of cSSSI, with a clinical cure rate comparable to that of vancomycin plus aztreonam. The cure rates consistently exceeded 93% in the ME population. The overall cure rate for ceftaroline-treated patients with staphylococcal infection was 93.1% (93.4% for patients with cSSSI caused by MRSA). The efficacy of ceftaroline monotherapy was consistently demonstrated in the relevant populations (CE, MITT, ME, and mMITT). In addition, clinical cure rates were similar between patients infected with single or multiple pathogens, across infection types (including cellulitis, major abscess, and infected wound), and between patients with common comorbidities, such as diabetes mellitus and peripheral vascular disease.

The proportions of causative pathogens isolated in these studies are consistent with the broader epidemiologic picture of cSSSI. The majority of cSSSIs are caused by gram-positive pathogens [4], as reflected in these studies. Additionally, 40% of *S. aureus* isolates in the ceftaroline group and 34% in the

Table 7. Summary of Treatment-Emergent Adverse Events in the Safety Population

Category	Ceftaroline (n = 692)	Vancomycin plus aztreonam (n = 686)
Adverse event		
Nausea	41 (5.9)	35 (5.1)
Headache	36 (5.2)	31 (4.5)
Diarrhea	34 (4.9)	26 (3.8)
Pruritus	24 (3.5)	56 (8.2)
Rash	22 (3.2)	17 (2.5)
Vomiting	20 (2.9)	18 (2.6)
Constipation	18 (2.6)	18 (2.6)
Insomnia	17 (2.5)	17 (2.5)
Generalized pruritus	15 (2.2)	19 (2.8)
Dizziness	14 (2.0)	8 (1.2)
Transaminases increased	15 (2.2)	25 (3.6)
Hypokalemia	10 (1.4)	15 (2.2)
Pyrexia	9 (1.3)	16 (2.3)
Any	309 (44.7)	326 (47.5)
Discontinuation because of an adverse event	21 (3.0)	33 (4.8)

NOTE. Shown are treatment-emergent adverse events occurring in ⩾2% of patients.

vancomycin plus aztreonam group were methicillin resistant, which is representative of the rate seen across countries with varying MRSA epidemiology [9, 10, 28–32]. As such, the CANVAS studies provide efficacy data in the context of the current endemicity of this important cSSSI pathogen.

The combination of vancomycin plus aztreonam demonstrated higher favorable microbiological response rates than did ceftaroline monotherapy against gram-negative infection. The efficacy of ceftaroline against non–ESBL-producing *E. coli* and *K. pneumoniae* infection was comparable to that of aztreonam; however, the efficacy of aztreonam against *P. aeruginosa* and *Proteus mirabilis* infection was better than that of ceftaroline. These results are not surprising, given in vitro data previously reported for ceftaroline [33]. Interestingly, despite the reported low in vitro activity against *P. aeruginosa*, ceftaroline therapy in the CANVAS trials demonstrated a high cure rate for this organism when found in combination with another pathogen. Given the difficulty of differentiating causative from colonizing pathogens in polymicrobial infections, it is not surprising that ceftaroline appears to be effective against infections from which ceftaroline-resistant organisms such as *P. aeruginosa* are isolated.

There was a trend toward a higher clinical cure rate among patients with bacteremia treated with vancomycin plus aztreonam; because of the small numbers of such cases (with greater numbers and more staphylococci in the ceftaroline group), this observation is of unknown significance. Of note, sterilization of blood cultures was achieved during continued therapy in the 3 ceftaroline-treated patients with staphylococcal or streptococcal bacteremia who were assessed as experiencing clinical failure. This finding confirms the designation of clinical failure as a result of reasons other than a lack of microbiological efficacy.

Safety and tolerability of new antibiotics are of primary concern, especially in light of the limitations demonstrated by several currently available anti-MRSA agents. Data from >1300 patients in this analysis demonstrated that ceftaroline monotherapy was generally safe and well tolerated, consistent with the safety profile of the cephalosporin class. The incidence of treatment-emergent AEs was similar between treatment groups. No cardiac, hepatic, or renal toxicity signal was identified.

The inclusion of a significant number of cutaneous abscesses in cSSSI trials is controversial. It is recognized that many small, uncomplicated cutaneous abscesses can be treated with incision and drainage alone [34]. Antimicrobial therapy is recommended when abscesses are large, surrounded by extensive cellulitis, or accompanied by systemic symptoms [35]. By design, abscesses in these studies fulfilled several or all of these criteria. In addition, the CANVAS trials were similar to other recent studies of antimicrobial treatment of cSSSI [36, 37], which also included a high proportion of abscesses. Most importantly, significant efficacy was maintained in both groups when abscesses were excluded from analyses, with ceftaroline being comparable to vancomycin plus aztreonam.

Potential limitations of these analyses include small numbers of black, Asian, and elderly (>75 years old) patients and the exclusion of patients <18 years old; these are typical of registrational trials of new antimicrobials. Future studies involving such important populations as patients with diabetic foot infection will be needed to supplement the current understanding of the safety and efficacy profile of ceftaroline.

In conclusion, ceftaroline administered intravenously to adults at a dosage of 600 mg every 12 h for 5–14 days was efficacious and well tolerated for the treatment of cSSSI. In light of these analyses, ceftaroline has the potential to provide a monotherapy alternative for the treatment of cSSSI.

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References

1. Ho RC, Ho EC, Mak A. Cutaneous complications among i.v. buprenorphine users. J Dermatol **2009**; 36:22–29.
2. Lamagni TL, Darenberg J, Luca-Harari B, et al. Epidemiology of severe *Streptococcus pyogenes* disease in Europe. J Clin Microbiol **2008**; 46: 2359–2367.
3. Lamagni TL, Neal S, Keshishian C, et al. Severe *Streptococcus pyogenes* infections, United Kingdom, 2003–2004. Emerg Infect Dis **2008**; 14: 202–209.
4. Moet GJ, Jones RN, Biedenbach DJ, et al. Contemporary causes of skin and soft tissue infections in North America, Latin America, and Europe: report from the SENTRY Antimicrobial Surveillance Program (1998–2004). Diagn Microbiol Infect Dis **2007**; 57:7–13.
5. Rennie RP, Jones RN, Mutnick AH; SENTRY Program Study Group (North America). Occurrence and antimicrobial susceptibility patterns of pathogens isolated from skin and soft tissue infections: report from the SENTRY Antimicrobial Surveillance Program (United States and Canada, 2000). Diagn Microbiol Infect Dis **2003**; 45:287–293.
6. Chang CM, Lee HC, Lee NY, et al. Community-acquired *Klebsiella pneumoniae* complicated skin and soft-tissue infections of extremities: emphasis on cirrhotic patients and gas formation. Infection **2008**; 36: 328–334.
7. Grundmann H, Aires-de-Sousa M, Boyce J, et al. Emergence and resurgence of methicillin-resistant *Staphylococcus aureus* as a public-health threat. Lancet **2006**; 368:874–885.
8. Nubel U, Roumagnac P, Feldkamp M, et al. Frequent emergence and limited geographic dispersal of methicillin-resistant *Staphylococcus aureus.* Proc Natl Acad Sci U S A **2008**; 105:14130–14135.
9. Moran GJ, Krishnadasan A, Gorwitz RJ, et al; EMERGEncy ID Net Study Group. Methicillin-resistant *S. aureus* infections among patients in the emergency department. N Engl J Med **2006**; 355:666–674.

10. Tillotson GS, Draghi DC, Sahm DF, et al. Susceptibility of *Staphylococcus aureus* isolated from skin and wound infections in the United States 2005–07: laboratory-based surveillance study. J Antimicrob Chemother **2008**; 62:109–115.
11. LoVecchio F, Perera N, Casanova L, et al. Board-certified emergency physicians' treatment of skin and soft tissue infections in the community-acquired methicillin-resistant *Staphylococcus aureus* era. Am J Emerg Med **2009**; 27:68–70.
12. Napolitano LM. Early appropriate parenteral antimicrobial treatment of complicated skin and soft tissue infections caused by methicillin-resistant *Staphylococcus aureus*. Surg Infect (Larchmt) **2008**; 9(suppl 1): s17–s27.
13. Sievert DM, Rudrik JT, Patel JB, et al. Vancomycin-resistant *Staphylococcus aureus* in the United States, 2002–2006. Clin Infect Dis **2008**;46: 668–674.
14. Gracia M, Diaz C, Coronel P, et al. Antimicrobial susceptibility of *Streptococcus pyogenes* in Central, Eastern, and Baltic European Countries, 2005 to 2006: the cefditoren surveillance program. Diagn Microbiol Infect Dis **2009**; 64:52–56.
15. Liu X, Shen X, Chang H, et al. High macrolide resistance in *Streptococcus pyogenes* strains isolated from children with pharyngitis in China. Pediatr Pulmonol **2009**; 44:436–441.
16. Montagnani F, Stolzuoli L, Croci L, et al. Erythromycin resistance in *Streptococcus pyogenes* and macrolide consumption in a central Italian region. Infection **2009**; 37:353–357.
17. Richter SS, Heilmann KP, Beekmann SE, et al. Macrolide-resistant *Streptococcus pyogenes* in the United States, 2002–2003. Clin Infect Dis **2005**; 41:599–608.
18. Malhotra-Kumar S, Van Heirstraeten L, Lammens C, et al. Emergence of high-level fluoroquinolone resistant in emm6 *Streptococcus pyogenes* and in vitro resistance selection with ciprofloxacin, levofloxacin and moxifloxacin. J Antimicrob Chemother **2009**; 63:886–894.
19. Broyles LN, van Beneden C, Beall B, et al. Population-based study of invasive disease due to β-hemolytic streptococci of groups other than A and B. Clin Infect Dis **2009**; 48:706–712.
20. Ge Y, Biek D, Talbot GH, Sahm DF. In vitro profiling of ceftaroline against a collection of recent bacterial clinical isolates from across the United States. Antimicrob Agents Chemother **2008**; 52:3398–3407.
21. Iizawa Y, Nagai J, Ishikawa T, et al. In vitro antimicrobial activity of T-91825, a novel anti-MRSA cephalosporin, and in vivo anti-MRSA activity of its prodrug, TAK-599. J Infect Chemother **2004**; 10:146–156.
22. Jacqueline CJ, Caillon V, Le Mabecque AF, et al. In vivo efficacy of ceftaroline (PPI-0903), a new broad-spectrum cephalosporin, compared with linezolid and vancomycin against methicillin-resistant and vancomycin-intermediate *Staphylococcus aureus* in a rabbit endocarditis model. Antimicrob Agents Chemother **2007**; 51:3397–3400.
23. Mushtaq S, Warner M, Ge Y, et al. In vitro activity of ceftaroline (PPI-0903M, T-91825) against bacteria with defined resistance mechanisms and phenotypes. J Antimicrob Chemother **2007**; 60:300–311.
24. Sader HS, Fritsche TR, Jones RN. Antimicrobial activities of ceftaroline and ME1036 tested against clinical strains of community-acquired methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother **2008**; 52:1153–1155.
25. Talbot GH, Thye D, Das A, et al. Phase 2 study of ceftaroline versus standard therapy in treatment of complicated skin and skin structure infections. Antimicrob Agents Chemother **2007**; 51:3612–3616.
26. Farrington CP, Manning G. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference of non-unity relative risk. Stat Med **1990**; 9:1447–1454.
27. Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med **1985**; 4:213–226.
28. Frazee BW, Lynn J, Charlebois ED, et al. High prevalence of methicillin-resistant *Staphylococcus aureus* in emergency department skin and soft tissue infections. Ann Emerg Med **2005**; 45:311–320.
29. Kaplan SL, Hulten KG, Gonzalez BE, et al. Three-year surveillance of community-acquired *Staphylococcus aureus* infections in children. Clin Infect Dis **2005**; 40:1785–1791.
30. Miller LG, Perdreau-Remington F, Bayer AS, et al. Clinical and epidemiologic characteristics cannot distinguish community-associated methicillin-resistant *Staphylococcus aureus* infection from methicillin-susceptible *S. aureus* infection: a prospective investigation. Clin Infect Dis **2007**; 44:471–482.
31. Moran GJ, Amii RN, Abrahamian FM, et al. Methicillin-resistant *Staphylococcus aureus* in community-acquired skin infections. Emerg Infect Dis **2005**; 11:928–930.
32. Young DM, Harris HW, Charlebois ED, et al. An epidemic of methicillin-resistant *Staphylococcus aureus* soft tissue infections among medically underserved patients. Arch Surg **2004**; 139:947–951.
33. Sader HS, Fritsche TR, Kaniga K, et al. Antimicrobial activity and spectrum of PPI-0903M (T-91825), a novel cephalosporin, tested against a worldwide collection of clinical strains. Antimicrob Agents Chemother **2005**; 49:3501–3512.
34. Hankin A, Everett WW. Are antibiotics necessary after incision and drainage of a cutaneous abscess? Ann Emerg Med **2007**; 50:49–51.
35. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. Clin Infect Dis **2005**; 41:1373–1406.
36. Noel GJ, Strauss RS, Amsler K, et al. Results of a double-blind, randomized trial of ceftobiprole treatment of complicated skin and skin structure infections caused by gram-positive bacteria. Antimicrob Agents Chemother **2008**; 52:37–44.
37. Stryjewski ME, Graham DR, Wilson SE, et al; Assessment of Telavancin in Complicated Skin and Skin-Structure Infections Study. Telavancin versus vancomycin for the treatment of complicated skin and skin-structure infections caused by gram-positive organisms. Clin Infect Dis **2008**; 46:1683–1693.