



Impact of Underlying Comorbidities on Outcomes of Patients Treated with Ceftaroline Fosamil for Complicated Skin and Soft Tissue Infections: Pooled Results from Three Phase III Randomized Clinical Trials

Mark Wilcox · Jean Li Yan · Pedro L. Gonzalez · Matthew Dryden ·

Gregory G. Stone · Michal Kantecki

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ABSTRACT

Introduction: In three phase III randomized controlled trials, ceftaroline fosamil was shown to be non-inferior to vancomycin plus aztreonam for the treatment of complicated skin and soft tissue infections (cSSTIs). This exploratory analysis evaluated the impact of underlying comorbidities on clinical outcomes in patients with cSSTI pooled from these three studies.

Methods: CANVAS 1 and 2 and COVERS evaluated ceftaroline fosamil (600 mg every 12 h [q12h]; 600 mg every 8 h [q8h; COVERS]) versus

vancomycin plus aztreonam (1 g q12h each [CANVAS 1 and 2]; vancomycin 15 mg/kg q12h and aztreonam 1 g q8h [COVERS]) in hospitalized adults with cSSTI. The primary efficacy variable in each trial was clinical response at the test-of-cure (TOC) visit. Subgroup analyses were performed on the pooled clinically evaluable (CE) population, exploring the impact of age and various baseline comorbidities.

Results: Overall, 1808 patients were included in the CE population (1005 ceftaroline fosamil; 803 vancomycin plus aztreonam). Clinical cure rates at TOC were 89.7% (ceftaroline fosamil) and 90.8% (vancomycin plus aztreonam) (difference [95% confidence interval] – 1.13 [– 3.87, 1.67]). Clinical response rates were similar between treatment groups, regardless of age (≤ 65 years or > 65 years), and in subgroups of patients with and without diabetes mellitus, peripheral vascular disease, cancer/malignancy, renal impairment, and obesity; within these subgroups, efficacy and safety results were generally consistent with those of the overall cSSTI population.

Conclusions: This analysis provides supportive evidence of the efficacy of ceftaroline fosamil in patients with cSSTI and underlying comorbidities.

Trial Registration: CANVAS 1, NCT00424190 and CANVAS 2, NCT00423657 (both trials first posted on ClinicalTrials.gov 18/01/2007); COVERS, NCT01499277 (first posted on ClinicalTrials.gov 26/12/2011).

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M. Wilcox (✉)
Department of Microbiology, Leeds Teaching Hospitals, University of Leeds, Leeds LS1 3EX, UK
e-mail: mark.wilcox@nhs.net

J. L. Yan
Pfizer, New York, NY, USA

P. L. Gonzalez
AbbVie, Madison, NJ, USA

M. Dryden
Royal Hampshire County Hospital, Winchester, UK

G. G. Stone
Pfizer, Groton, CT, USA

M. Kantecki
Pfizer, Paris, France

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Key Summary Points

Why carry out this study?

Patients with complicated skin and soft tissue infections (cSSTIs) frequently have underlying comorbidities, which may complicate or delay treatment response, leading to increased risks of treatment failure and mortality

This exploratory analysis evaluated the impact of underlying comorbidities on clinical outcomes in patients with cSSTI treated with ceftaroline fosamil or vancomycin plus aztreonam pooled from three phase III randomized, controlled studies

What was learned from the study?

Overall clinical and microbiological response rates were similar for ceftaroline fosamil and vancomycin plus aztreonam and were generally similar between treatment groups regardless of age or comorbidity status

The pattern of adverse events within each comorbidity subgroup was similar between treatment groups

This pooled analysis provides supportive evidence of the efficacy of ceftaroline fosamil in patients with cSSTI with underlying comorbidities

The presence of underlying comorbidities may complicate or delay treatment response in patients with cSSTI, leading to increased risks of treatment failure and mortality [1, 4–6]. Consequently, patients with comorbidities have been shown to require significantly greater use of healthcare resources, such as increased time to clinical stability and longer hospital stay [4], thus adding to the healthcare burden already associated with cSSTI.

Management of cSSTI/ABSSSI typically includes surgical debridement/drainage and antibiotic therapy. Antimicrobial treatment options for cSSTI/ABSSSI cases involving possible/confirmed methicillin-resistant *Staphylococcus aureus* (MRSA) include vancomycin, linezolid, ceftaroline fosamil, and daptomycin [2, 7].

In the pivotal phase III CANVAS 1 and 2 studies, ceftaroline fosamil 600 mg every 12 h (q12h) by 1-h intravenous (IV) infusions (doses adjusted for patients with moderate or severe renal impairment) was shown to be non-inferior to vancomycin plus aztreonam in hospitalized adults with cSSTI [1, 8]. In a further phase III randomized controlled study (COVERS), a 50% higher dose of ceftaroline fosamil (600 mg every 8 h [q8h] by 2-h IV infusions, again adjusted for renal function) was shown to be non-inferior to vancomycin plus aztreonam in patients with cSSTI with extensive cutaneous involvement, including evidence of systemic inflammation or underlying comorbidities associated with impaired immune response [9].

A previous pharmacokinetic study in healthy volunteers found, as expected, ceftaroline fosamil q8h dosing to result in increased drug exposure and higher pharmacokinetic/pharmacodynamic target attainment rates versus q12h dosing, particularly with minimum inhibitory concentrations > 1 mg/l; however, high interindividual variability in relevant pharmacokinetic parameters was observed. The clinical implications of these findings were considered limited, with q12h dosing deemed likely sufficient for the treatment of infections caused by the vast majority of pathogens [10]. Although the CANVAS 1 and 2 and COVERS studies differed with respect to ceftaroline fosamil doses, as well as with respect to patients' overall

INTRODUCTION

Complicated skin and soft tissue infections (cSSTIs), also known as acute bacterial skin and skin structure infections (ABSSSIs), are among the most common infections encountered in the healthcare setting [1, 2]. Patients with cSSTI frequently have underlying comorbidities [3, 4].

disease severity and extent of comorbidities, a comparative subgroup analysis demonstrated generally equivalent outcomes for ceftaroline fosamil q12h and q8h when patients with similar comorbidities and/or disease severity were compared [11]. In conjunction with the similar study designs, this finding supports pooling of the CANVAS and COVERS data for further analysis.

The current exploratory analysis evaluated the impact of underlying comorbidities on clinical outcomes in patients with cSSTI pooled from the CANVAS 1, CANVAS 2, and COVERS studies.

METHODS

Study Design and Patient Population

The CANVAS 1 (NCT00424190), CANVAS 2 (NCT00423657), and COVERS (NCT01499277) studies were all phase III, multicenter, randomized, double-blind, comparative safety and efficacy trials of IV ceftaroline fosamil vs. vancomycin plus aztreonam for the treatment of adults with cSSTI (Table S1 in the Supplementary Material). Ethics approval of the study protocols and any amendments from the relevant IRB/IECs, and written informed consent, were obtained for each trial [1, 8, 9], and all trials were conducted in accordance with the Helsinki Declaration of 1964, and its later amendments.

Full details of the methods used in each of the studies have been previously described [1, 8, 9]. In brief, CANVAS 1 and 2 included patients with cSSTI (defined as deep extensive cellulitis, major cutaneous abscess needing surgical drainage, or infected wound, ulcer, or burn) requiring hospitalization and ≥ 5 days of parenteral antibiotic therapy. Inclusion criteria for COVERS were similar to the CANVAS studies, but in addition required cSSTI with surrounding area of erythema, edema, and/or induration with a surface area ≥ 75 cm², and patients had to have one or more sign/symptom of systemic inflammation or comorbidities. In COVERS, patients with diabetic foot infections were excluded. Full eligibility criteria for each of

the studies are provided in the Supplementary Material.

In each of the three studies, patients were randomized to receive ceftaroline fosamil or vancomycin plus aztreonam for 5–14 days. Randomization and blinding information is provided in the Supplementary Material. Details of the treatment regimens and the numbers of patients included in the studies are provided in Table S1 in the Supplementary Material. An overview of study design is shown in Fig. S1 in the Supplementary Material.

Assessments

In each study, the primary endpoint was clinical cure at the test-of-cure (TOC) visit (8–15 days after last dose of study drug), in the modified intention-to-treat (MITT) and clinically evaluable (CE) populations. Per-pathogen microbiological response rates were assessed at TOC for the microbiological MITT (mMITT) population. Safety assessments included adverse event (AE) monitoring, vital signs, physical examinations, and clinical chemistry/laboratory tests up to the late follow-up visit (21–35 days after the last dose of study drug) in the safety population. Definitions of analysis populations are provided in the Supplementary Material.

Statistical Analysis

Statistical methods for the key primary and secondary endpoints and safety assessments, including sample size calculations and non-inferiority, have been reported previously [1, 8, 9].

Exploratory subgroup analyses assessing the impact of baseline characteristics and comorbidities on clinical outcomes at TOC were performed for the pooled CE population. Subgroups were defined programmatically from patients' baseline information and medical history as recorded in the study case report forms and included age group (≤ 65 years or > 65 years) and presence/absence of diabetes mellitus, peripheral vascular disease (PVD), cancer/malignancy, renal impairment (mild impairment/normal renal function: estimated creatinine clearance [CL_{CR}] > 50 ml/min;

moderate impairment: $CL_{CR} > 30$ to ≤ 50 ml/min; severe impairment: $CL_{CR} > 20$ to ≤ 30 ml/min), and body mass index (BMI; < 18.5 kg/m², ≥ 18.5 to < 25 kg/m², ≥ 25 to < 30 kg/m², and ≥ 30 kg/m²).

The 95% CIs for the observed difference in the outcome measure between the ceftaroline fosamil and vancomycin plus aztreonam groups were calculated using the method of Miettinen and Nurminen [12].

RESULTS

Patient Characteristics and Baseline Pathogens

Patient disposition is shown in Fig. S2 in the Supplementary Material. The pooled MITT population included 2139 patients (ceftaroline fosamil, $n = 1199$; vancomycin plus aztreonam, $n = 940$ [difference in numbers between the two groups is a result of the 2:1 ceftaroline fosamil: vancomycin plus aztreonam randomization ratio in the COVERS study]). One patient in the CANVAS 2 study who was randomized to receive ceftaroline fosamil was given vancomycin plus aztreonam in error. Per protocol, this patient was grouped according to actual treatment received in the safety population, which thus comprised 2139 patients (ceftaroline fosamil, $n = 1198$; vancomycin plus aztreonam, $n = 941$). The pooled CE population included 1808 patients (ceftaroline fosamil, $n = 1005$; vancomycin plus aztreonam, $n = 803$). Baseline and demographic characteristics were generally similar between treatment arms (Table 1).

The most frequently isolated pathogens at baseline (infection site and blood) were methicillin-sensitive *S. aureus* (MSSA; 352/787 [44.7%] and 319 [48.4%] for ceftaroline fosamil and vancomycin plus aztreonam, respectively), MRSA (210/787 [26.7%] and 174 [26.4%], respectively), and *Streptococcus pyogenes* (81/787 [10.3%] and 69/659 [10.5%], respectively). In vitro activity of the most common baseline pathogens (isolated from ≥ 10 patients in either treatment group) to ceftaroline fosamil and

vancomycin or aztreonam is summarized in Table 2.

Clinical Outcomes

Overall clinical cure rates at TOC (CE population) were similar for ceftaroline fosamil ($n = 901/1005$ [89.7%]) and for vancomycin plus aztreonam ($n = 729/803$ [90.8%]); difference (95% CI) -1.13% ($-3.87, 1.67$). Clinical cure rates at TOC were similar for ceftaroline fosamil and vancomycin plus aztreonam, regardless of age or comorbidity status (Fig. 1). However, in patients with cancer/malignancy, clinical cure rates were 88.9% ($n = 24/27$) for ceftaroline fosamil vs. 78.9% ($n = 15/19$) for vancomycin plus aztreonam (difference [95% CI] 9.94% [$-11.66, 34.31$]). In patients without cancer/malignancy, cure rates were 89.7% ($n = 877/978$) vs. 91.1% ($n = 714/784$), respectively (treatment difference [95% CI] -1.40% [$-4.15, 1.41$]).

In patients with moderate renal impairment, clinical cure rates were 84.8% ($n = 39/46$) for ceftaroline fosamil vs. 78.4% ($n = 29/37$) for vancomycin plus aztreonam (difference [95% CI]: 6.40% [$-10.43, 24.29$]) (Fig. 1).

In patients with BMI < 18.5 kg/m², clinical cure rates were 69.2% ($n = 18/26$) for ceftaroline fosamil vs. 90.9% for vancomycin plus aztreonam ($n = 10/11$) (difference [95% CI] -21.68% [$-44.09, 10.98$]). Respective clinical cure rates for BMI ≥ 18.5 to < 25 kg/m² were 91.0% ($n = 312/343$) vs. 89.9% ($n = 232/258$) (difference [95% CI] 1.04 [$-3.66, 6.06$]), for BMI ≥ 25 to < 30 kg/m² 90.9% ($n = 288/317$) vs. 93.6% ($n = 263/281$) (difference [95% CI] -2.74 [$-7.14, 1.66$]), and for BMI ≥ 30 kg/m² 89.2% ($n = 281/315$) vs. 88.5% ($n = 223/252$) (difference [95% CI] 0.71 [$-4.47, 6.15$]) (Fig. 1).

Overall favorable microbiological response rates for the most commonly isolated pathogens at TOC (mMITT population) were similar for ceftaroline fosamil and vancomycin plus aztreonam (MSSA: 318/352 [90.3%] and 283/319 [88.7%], respectively; MRSA: 178/210 [84.8%] and 135/174 [77.6%], respectively; and *S. pyogenes*: 72/81 [88.9%] and 64/69 [92.8%], respectively). Favorable microbiological

Table 1 Baseline demographic characteristics and comorbidities (CE population)

	Number (%) of patients		
	Ceftaroline fosamil (<i>n</i> = 1005)	Vancomycin + aztreonam (<i>n</i> = 803)	Total (<i>N</i> = 1808)
Demographic characteristic			
Age (years)			
Mean	49.7	50.2	49.9
Median (range)	16.9 (18–93)	16.5 (18–96)	16.7 (18–96)
Age group (years), <i>n</i> (%)			
≥ 18 to < 65	805 (80.1)	626 (78.0)	1431 (79.1)
≥ 65 to < 75	112 (11.1)	114 (14.2)	226 (12.5)
≥ 75	88 (8.8)	63 (7.8)	151 (8.4)
Sex, <i>n</i> (%)			
Female	372 (37.0)	322 (40.1)	694 (38.4)
Comorbidity/analysis subgroup, <i>n</i> (%)			
Age > 65 years	188 (18.7)	162 (20.2)	350 (19.4)
Diabetes mellitus	173 (17.2)	139 (17.3)	312 (17.3)
Peripheral vascular disease	113 (11.2)	94 (11.7)	207 (11.4)
Cancer/malignancy	27 (2.7)	19 (2.4)	46 (2.5)
Renal status (estimated CL_{CR} , ml/min) ^a			
Severe impairment (> 20 to ≤ 30)	4 (0.4)	1 (0.1)	5 (0.3)
Moderate impairment (> 30 to ≤ 50)	46 (4.6)	37 (4.6)	83 (4.6)
Mild impairment or normal (> 50)	946 (94.1)	759 (94.5)	1705 (94.3)
Body mass index (kg/m ²) ^b			
< 18.5	26 (2.6)	11 (1.4)	37 (2.0)
≥ 18.5 to < 25	343 (34.1)	258 (32.1)	601 (33.2)
≥ 25 to < 30	317 (31.5)	281 (35.0)	598 (33.1)
≥ 30	315 (31.3)	252 (31.4)	567 (31.4)

CE clinically evaluable, CL_{CR} creatinine clearance

^aData not collected for nine patients in the ceftaroline group and six patients in the vancomycin plus aztreonam group

^bData not collected for four patients in the ceftaroline group and one patient in the vancomycin plus aztreonam group

Table 2 In vitro activity of ceftaroline, vancomycin, and aztreonam against pathogens isolated from patients with cSSTI (mMITT population)

Baseline pathogen	Ceftaroline (N = 787)			Vancomycin (N = 659)			Aztreonam (N = 659)		
	Isolates (n)	MIC range	MIC ₉₀	Isolates (n)	MIC range	MIC ₉₀	Isolates (n)	MIC range	MIC ₉₀
Gram-positive organisms									
<i>Staphylococcus aureus</i>	535	0.06 to 2	0.5	461	≤ 0.25 to 2	1	–	–	–
<i>MSSA</i>	105	0.06 to 0.5	0.25	59	≤ 0.25 to 1	1	–	–	–
<i>MRSA</i>	32	0.25 to 1	1	22	0.5 to 1	1	–	–	–
<i>Streptococcus pyogenes</i>	80	≤ 0.004 to 0.008	≤ 0.008	68	≤ 0.25 to 1	0.5	–	–	–
<i>Streptococcus dysgalactiae</i>	13	≤ 0.004 to 0.008	0.008	17	0.25 to 0.5	0.25	–	–	–
<i>Enterococcus faecalis</i>	41	0.25 to 64	8	33	0.5 to 2	2	–	–	–
<i>Streptococcus agalactiae</i>	30	≤ 0.008 to 0.015	0.015	29	≤ 0.25 to 0.5	0.5	–	–	–
<i>Streptococcus anginosus group</i>	24	≤ 0.004 to 0.008	0.03	3	0.5 to 0.5	0.5	–	–	–
<i>Streptococcus dysgalactiae subspecies dysgalactiae</i>	11	≤ 0.008 to 0.015	0.015	1	1 to 1	1	–	–	–
<i>Finegoldia magna</i>	13	≤ 0.06 to 64	0.5	1	0.25 to 0.25	0.25	1	32 to 32	32
Gram-negative organisms									
<i>Escherichia coli</i>	42	0.015 to > 32	16	–	–	–	31	≤ 0.03 to 0.5	0.12
<i>Acinetobacter calcoaceticus</i>	10	2 to > 32	> 32	–	–	–	5	1 to > 32	> 32
<i>Klebsiella pneumoniae</i>	26	0.03 to > 32	> 16	–	–	–	23	≤ 0.03 to > 32	> 32
<i>Klebsiella oxytoca</i>	18	0.03 to 0.25	0.25	–	–	–	9	≤ 0.03 to 0.5	0.5

Table 2 continued

Baseline pathogen	Ceftaroline (N = 787)			Vancomycin (N = 659)			Aztreonam (N = 659)		
	Isolates (n)	MIC range	MIC ₉₀	Isolates (n)	MIC range	MIC ₉₀	Isolates (n)	MIC range	MIC ₉₀
<i>Proteus mirabilis</i>	23	≤ 0.008 to > 16	> 16	–	–	–	27	≤ 0.03 to 16	0.25
<i>Enterobacter cloacae</i>	11	0.06 to 1	1	–	–	–	19	≤ 0.03 to > 32	16
<i>Pseudomonas aeruginosa</i>	32	1 to > 32	> 16	–	–	–	26	1 to > 32	> 32
<i>Morganella morganii</i>	15	0.03 to > 16	> 16	–	–	–	10	≤ 0.03 to 4	4

Includes pathogens isolated from ≥ 10 patients in either treatment group. MIC range and MIC₉₀ are in mg/l

The mMITT population consisted of patients in the MITT population who met the minimal disease criteria and had ≥ 1 bacterial pathogen

cSSTI complicated skin and soft tissue infection, MIC minimum inhibitory concentration, MIC₉₀ minimum inhibitory concentration required to inhibit the growth of 90% of organisms, mMITT microbiological modified intention to treat, MRSA methicillin-resistant *Staphylococcus aureus*, MSSA methicillin-sensitive *Staphylococcus aureus*, n number of isolates, N number of patients

response rates were generally consistent within and between age and comorbidity subgroups (Table 3). Given that in each of the individual studies microbiological outcomes were largely inferred from clinical outcomes, the results for ME population were generally similar to those of the mMITT population.

Safety

Mean (standard deviation [SD]) study duration of exposure (safety population) was 8.27 (3.3) days for ceftaroline fosamil and 8.31 (3.3) days for vancomycin plus aztreonam, and exposures were generally consistent within and between age comorbidity subgroups. AEs and serious AEs up to the late follow-up visit are summarized in Table 4. Overall, treatment-emergent AEs were reported in 541/1198 (45.2%) patients treated with ceftaroline fosamil and 442/941 (47.0%) patients treated with vancomycin plus aztreonam (Table 4). The most frequently reported AEs were nausea (occurring in 61/1198 [5.1%] patients treated with ceftaroline fosamil and 46/941 [4.9%] patients treated with

vancomycin plus aztreonam) and pruritis (occurring in 24/1199 [2.0%] and 61/940 [6.5%] patients, respectively).

Results from evaluation of vital signs, physical examinations, and clinical chemistry/laboratory tests were generally similar between treatment groups and within age and comorbidity subgroups.

DISCUSSION

This exploratory analysis evaluated the impact of a range of comorbidities on clinical outcomes in patients with cSSTI pooled from three phase III randomized controlled studies. The high proportions of patients with comorbidities, such as diabetes mellitus, PVD, and obesity, are considered representative of patients typically seen in clinical practice [3, 4].

Overall clinical cure rates at TOC (CE population) were similar for ceftaroline fosamil monotherapy (89.7%) and for vancomycin plus aztreonam combination therapy (90.8%), and were similar regardless of comorbidity status, and consistent with results in the CE and MITT

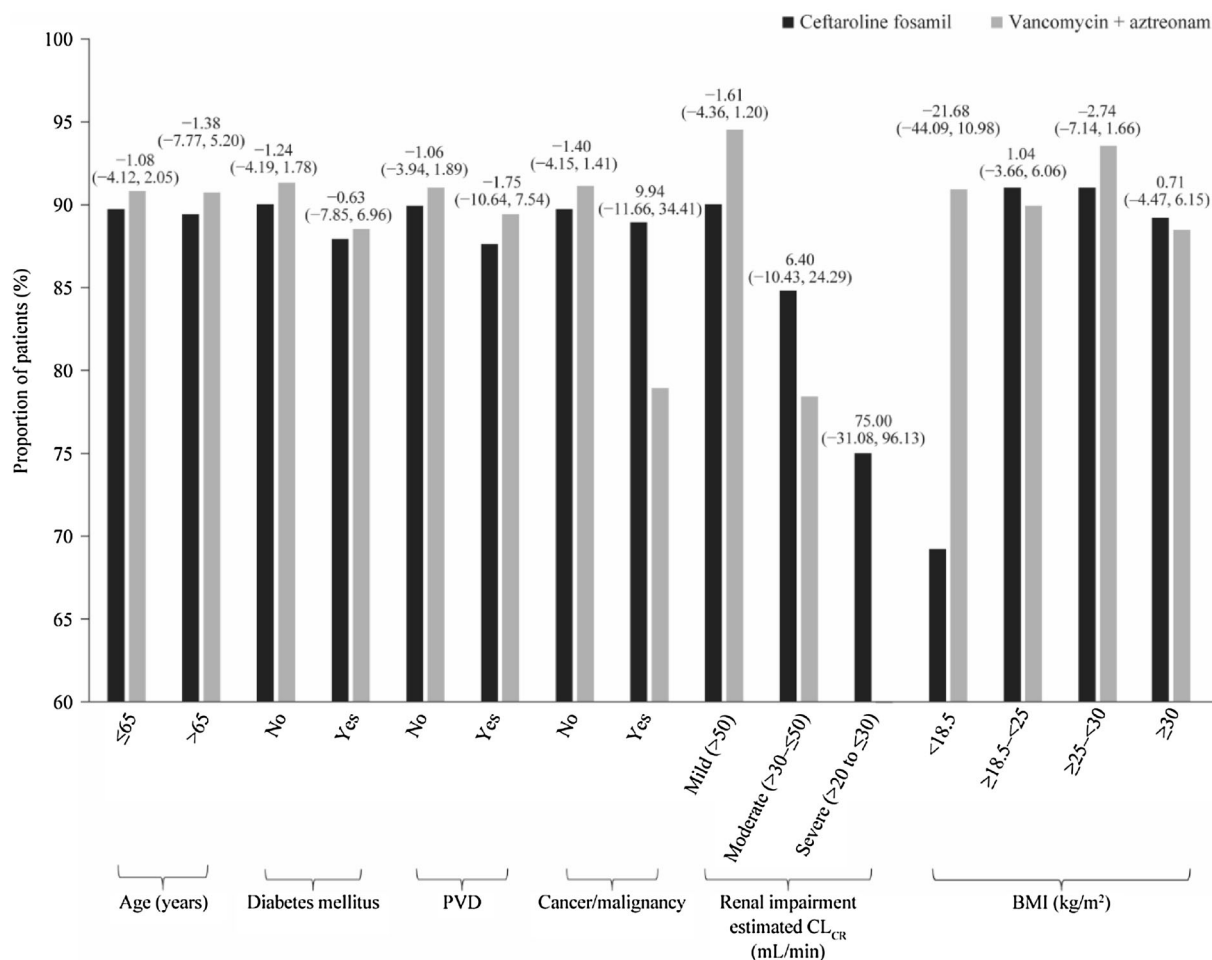


Fig. 1 Clinical cure rates at TOC by baseline age, BMI, and comorbidity subgroups in patients with cSSTI (CE population)^a. *BMI* body mass index, *CE* clinically evaluable, *CL_{CR}* creatinine clearance, *cSSTI* complicated skin

and soft tissue infection, *PVD* peripheral vascular disease, *TOC* test of cure. ^aValues above bars represent treatment differences (95% CI)

populations in the individual trials [1, 8, 9]. Moreover, favorable microbiological response rates were generally comparable across comorbidity subtypes for key cSSTI pathogens, including *S. aureus*.

Presence of comorbidities may increase the likelihood of acquiring a cSSTI and have an impact on the progression and course of the condition as well as its response to treatment [5]. Comorbidities associated with impaired immune response include critical illness, elderly age, immunocompromised state, hepatic and renal disease, vascular insufficiency, and malignancy [5, 9, 13, 14]. Such comorbidities

represent risk factors for potentiation of cSSTI and poor wound healing. Moreover, severe systemic inflammation can affect antibiotic pharmacokinetics, potentially negatively affecting efficacy [15].

In patients with diabetes mellitus or PVD, the ability of some antibiotics to penetrate soft tissues may be compromised, resulting in a lower drug concentration reaching the site of infection. It has previously been hypothesized that poor soft tissue distribution of vancomycin in patients with diabetes mellitus has been responsible for treatment failure in some patients [16–18]. Clinical cure response rates at

Table 3 Per-pathogen favorable microbiological response rates at TOC for the most commonly isolated pathogens overall, by baseline age, and comorbidity subgroups in patients with cSSTI (mMITT population)

Subgroup	Pathogen	Patients, <i>n/N</i> (%)	
		Ceftaroline fosamil (<i>n</i> = 787)	Vancomycin + aztreonam (<i>n</i> = 659)
Age ≤ 65 years	MSSA	261/292 (89.4)	222/253 (87.7)
	MRSA	161/192 (83.9)	123/159 (77.4)
	<i>S. pyogenes</i>	66/75 (88.0)	57/61 (93.4)
Age > 65 years	MSSA	57/60 (95.0)	61/66 (92.4)
	MRSA	17/18 (94.4)	12/15 (80.0)
	<i>S. pyogenes</i>	6/6 (100)	7/8 (87.5)
Diabetes mellitus: no	MSSA	271/303 (89.4)	240/273 (87.9)
	MRSA	164/193 (85.0)	124/158 (78.5)
	<i>S. pyogenes</i>	67/76 (88.2)	62/66 (93.9)
Diabetes mellitus: yes	MSSA	47/49 (95.9)	43/46 (93.5)
	MRSA	14/17 (82.4)	11/16 (68.8)
	<i>S. pyogenes</i>	5/5 (100)	2/3 (66.7)
Peripheral vascular disease: no	MSSA	271/303 (89.4)	240/273 (87.9)
	MRSA	164/193 (85.0)	124/158 (78.5)
	<i>S. pyogenes</i>	67/76 (88.2)	62/66 (93.9)
Peripheral vascular disease: yes	MSSA	47/49 (95.9)	43/46 (93.5)
	MRSA	14/17 (82.4)	11/16 (68.8)
	<i>S. pyogenes</i>	5/5 (100)	2/3 (66.7)
Cancer/malignancy: no	MSSA	308/342 (90.1)	279/315 (88.6)
	MRSA	174/206 (84.5)	130/168 (77.4)
	<i>S. pyogenes</i>	72/81 (88.9)	64/69 (92.8)
Cancer/malignancy: yes	MSSA	10/10 (100)	4/4 (100)
	MRSA	4/4 (100)	5/6 (83.3)
	<i>S. pyogenes</i>	0	0
Severe renal impairment (CL _{CR} > 20 to ≤ 30 ml/min)	MSSA	0	0
	MRSA	0	0
	<i>S. pyogenes</i>	0/1 (0)	0
Moderate renal impairment (CL _{CR} > 30 to ≤ 50 ml/min)	MSSA	13/13 (100)	10/12 (83.3)
	MRSA	4/5 (80.0)	4/6 (66.7)
	<i>S. pyogenes</i>	3/3 (100)	2/2 (100)

Table 3 continued

Subgroup	Pathogen	Patients, <i>n/N</i> (%)	
		Ceftaroline fosamil (<i>n</i> = 787)	Vancomycin + aztreonam (<i>n</i> = 659)
Mild renal impairment or normal ($CL_{CR} > 50$ ml/min)	MSSA	302/336 (89.9)	271/304 (89.1)
	MRSA	173/203 (85.2)	129/165 (78.2)
	<i>S. pyogenes</i>	68/77 (88.3)	62/67 (92.5)
BMI < 18.5 kg/m ²	MSSA	11/13 (84.6)	2/3 (66.7)
	MRSA	0/2 (0)	2/3 (66.7)
	<i>S. pyogenes</i>	5/5 (100)	1/1 (100)
BMI ≥ 18.5 to < 25 kg/m ²	MSSA	131/146 (89.7)	199/116 (85.3)
	MRSA	61/72 (84.7)	38/54 (70.4)
	<i>S. pyogenes</i>	33/39 (84.6)	36/39 (92.3)
BMI ≥ 25 to < 30 kg/m ²	MSSA	91/101 (90.1)	107/113 (94.7)
	MRSA	54/61 (88.5)	49/58 (84.5)
	<i>S. pyogenes</i>	24/26 (92.3)	18/19 (94.7)
BMI ≥ 30 kg/m ²	MSSA	85/92 (92.4)	75/87 (86.2)
	MRSA	62/73 (84.9)	46/59 (78.0)
	<i>S. pyogenes</i>	10/11 (90.9)	9/10 (90.0)

BMI body mass index, *CL_{CR}* creatinine clearance, *cSSTI* complicated skin and soft tissue infection, *mMITT* microbiological modified intention to treat, *MRSA* methicillin-resistant *Staphylococcus aureus*, *MSSA* methicillin-sensitive *Staphylococcus aureus*, *S. pyogenes* *Streptococcus pyogenes*, *TOC* test of cure

TOC were similar for ceftaroline fosamil and vancomycin plus aztreonam in patients with and without diabetes mellitus and in those with and without PVD.

Renal impairment is associated with impairment of host defenses [19]. Furthermore, drug pharmacokinetics are often affected by impaired renal clearance [14]. Of the small proportions of patients with moderate renal impairment ($CL_{CR} > 30$ to ≤ 50 ml/min), clinical cure rates for patients treated with ceftaroline fosamil were 84.8% ($n = 39/46$) and for patients treated with vancomycin plus aztreonam were 78.4% ($n = 29/37$).

Patients with malignancy are highly susceptible to infection [13], and both hematological

and solid tumors have been shown to influence the cSSTI disease course [20]. Among patients with malignancy, 24 of 27 (88.9%) patients treated with ceftaroline fosamil and 15 of 19 (78.9%) patients treated with vancomycin plus aztreonam were cured, although the small patient numbers limit the interpretation of these results. Previous studies have suggested that patients with certain malignancies may require much higher dosages of vancomycin than those with no known malignancy to achieve therapeutic drug plasma concentrations [21–23]. However, these studies, and other literature on treatment of infections in patients with malignancy, included patients with varying levels of neutropenia. As patients with

Table 4 Overview of AEs (safety population)

AE category	Number (%) of patients	
	Ceftaroline fosamil (<i>n</i> = 1198)	Vancomycin + aztreonam (<i>n</i> = 941)
Patients with ≥ 1 AE	541 (45.2)	442 (47.0)
Any AE related to study drug	244 (20.4)	223 (23.7)
Any AE with outcome of death	8 (0.7)	3 (0.3)
Any SAE	56 (4.7)	41 (4.4)
Any AE leading to discontinuation of study drug	53 (4.4)	44 (4.7)
Any AE of severe intensity	40 (3.3)	37 (3.9)

AE adverse event, *SAE* serious adverse event

neutropenia (< 500 neutrophils/mm³) were excluded from the CANVAS and COVERS trials, comparisons with results from the literature should be made with caution.

Obesity and low antibiotic dosage at discharge are associated with cSSTI onset and clinical failure at hospital discharge [24, 25]. In addition, higher BMI may result in lower relative doses of an antibiotic that are not adjusted for body weight [17], potentially leading to less optimal clinical outcomes [26, 27]. However, model-based predictions of multiple ceftaroline fosamil doses have indicated adequate target attainment achievement with time-dependent pharmacodynamics [28]. Currently, there is no evidence for worse clinical outcomes in obese vs. non-obese patients with cSSTI using standard doses of ceftaroline fosamil [28]. In the present analysis, favorable clinical response rates at TOC were similar for ceftaroline and vancomycin plus aztreonam in patients with and without obesity.

Regardless of comorbidity status, some patients with cSSTI initially require empirical antibiotic treatment providing polymicrobial coverage [29]. Ceftaroline fosamil has a broad spectrum of activity against clinically relevant gram-positive strains, including MRSA, as well as some gram-negative pathogens involved in cSSTI [30, 31]. In the current pooled analysis, patients with comorbidities that put them at risk of treatment failure demonstrated similar

success rates in the ceftaroline fosamil and the vancomycin plus aztreonam treatment groups, with response rates generally consistent with those of the overall cSSTI population of the individual studies.

The lack of stratification for comorbidity at randomization represents a limitation of this analysis. Another limitation is the low numbers of patients in the BMI < 18.5 kg/m², moderate/severe renal impairment, and malignancy subgroups, which make it difficult to draw conclusions from these results. Additionally, information regarding stability of the comorbidity, which may potentially impact response to therapy, was not collected as part of the current analysis.

Ceftaroline fosamil has been shown to have a favorable safety profile [32]. Observations from the CANVAS studies indicated that when AEs did occur with ceftaroline fosamil they were generally of mild intensity [1, 8]. No new safety signals were reported for ceftaroline fosamil in the CANVAS or COVERS studies [1, 8, 9]. In the present analysis, the frequency of patients with any AE within each comorbidity subgroup was generally similar between those treated with ceftaroline fosamil and vancomycin plus aztreonam.

CONCLUSIONS

In conclusion, this pooled analysis of three randomized controlled trials provides supportive evidence of the efficacy of ceftaroline fosamil in patients with cSSTI with underlying comorbidities.

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Compliance with Ethics Guidelines. This pooled analysis was based on three previously reported phase III ceftaroline fosamil clinical trials. Ethics approval of the study protocols and any amendments from the relevant IRB/IECs and written informed consent were obtained for each trial [1, 8, 9], and all trials were conducted in accordance with the Helsinki Declaration of 1964 and its later amendments.

Data Availability. Upon request, and subject to certain criteria, conditions and exceptions, see (<https://www.pfizer.com/science/clinical-trials/trial-data-and-results> for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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