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Ceftaroline fosamil for the treatment of patients with cSSTI or CAP and concurrent bacteraemia: analysis of six Phase III trials

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Background

- Complicated skin and soft tissue infections (cSSTI) and community-acquired pneumonia (CAP) are among the most common bacterial infections requiring intravenous antimicrobial therapy in hospitalised patients.[1,2] Bacteraemia in such patients is associated with increased mortality and healthcare resource utilisation/length of hospital stay.[3,4]
- *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA) and *Streptococcus pneumoniae* are among the predominant pathogens responsible for cSSTI and CAP, respectively.[1,2] Ceftaroline, the active metabolite of the pro-drug ceftaroline fosamil, is a cephalosporin antibiotic with *in vitro* activity against common Gram-negative and Gram-positive pathogens associated with cSSTI and CAP, including MRSA and *S. pneumoniae*.[5]
- Based on the results of four Phase III trials, FOCUS 1 and 2 (NCT00424190 and NCT00423657) and CANVAS 1 and 2 (NCT00621504 and NCT00509106),[6–9] ceftaroline fosamil was approved (in the US in 2010 and in the EU in 2012) for the treatment of adult patients with cSSTI or CAP. Since then, two additional Phase III trials of ceftaroline fosamil in patients with cSSTI (COVERS; NCT01499277) and CAP (Asia CAP; NCT01371838) have been completed.[10,11]
- Here, we present a comparative analysis of efficacy and safety data among patients with cSSTI or CAP and bacteraemia across all six Phase III trials of ceftaroline fosamil.

Methods

- The six trials (see Table 1 for an overview of trial design) randomised a total of 4055 adult patients with cSSTI or CAP.
- Across the six trials, 1.0–4.6% patients had concurrent bacteraemia at baseline.
  - Patients in the cSSTI trials received ceftaroline fosamil 600 mg every 12 h (every 8 h in COVERS) or vancomycin plus aztreonam for 5–14 days.
  - Patients in the CAP trials received ceftaroline fosamil 600 mg every 12 h or ceftriaxone for 5–7 days.
- Clinical cure was assessed in all six trials at the test-of-cure (TOC) visit (8–15 days after end of treatment) in the microbiological modified intention-to-treat (mMITT) population (equivalent to the mMITT-Efficacy population in FOCUS 1 and 2) and microbiologically evaluable (ME) population.

Table 1. Trial design

	CANVAS 1 and 2	COVERS	FOCUS 1 and 2	Asia CAP
Geography	Europe, Latin America, USA	Asia, Europe, Latin America, RoW†	Africa, Asia, Europe, Latin America, USA	Asia‡
Key entry criteria	cSSSI requiring ≥5 days of IV antibiotics§	cSSTI requiring ≥5 days of IV antibioticsII	CAP requiring hospitalisation and IV antibiotics	CAP requiring hospitalisation and IV antibiotics
	≥3 clinical signs/symptoms of infection¶	≥1 sign of SIRS and/or underlying comorbidities#	PORT risk class II–IV††	PORT risk class III–IV††
Key exclusion criteria	No minimum lesion size	Minimum lesion size ≤75 cm^2	Patients requiring ICU admission at baseline	Patients requiring ICU admission at baseline
	>24 h antimicrobial therapy in the previous 96 h	>24 h antimicrobial therapy in the previous 96 h	CAP suitable for outpatient treatment	CAP suitable for outpatient treatment
Treatments administered and randomisation ratio	Ceftaroline fosamil 600 mg q12h	Ceftaroline fosamil 600 mg q8h	Ceftaroline fosamil 600 mg q12h	Ceftaroline fosamil 600 mg q12h
	OR	OR	OR	OR
	Vancomycin 1 g q12h + aztreonam 1 g q12h 1:1	Vancomycin 15 mg/kg q12h + aztreonam 1 g q8h 2:1	Ceftriaxone 1 g q24h 1:1‡‡	Ceftriaxone 2 g q24h 1:1
Duration of treatment, days	5–14	5–14	5–7	5–7

cSSSI, complicated skin and skin structure infection; DFI, diabetic foot infection; ICU, intensive care unit; IV, intravenous; PORT, Pneumonia Outcomes Research Team; q8h, every 8 h; q12h, every 12 h; q24h, every 24 h; SIRS, systemic inflammatory response syndrome.

†RoW countries in COVERS were Australia, South Africa, Israel and Turkey.

‡Asia data were limited to 30 patients from Malaysia and Thailand in FOCUS 1 and nine patients from India in FOCUS 2; hence the Asia CAP study was performed in South East Asian countries (China, South Korea, Taiwan and Vietnam) and India.

§CANVAS 1 and 2: cSSSI was defined as deep extensive cellulitis, major abscess (loculated fluid with ≥2 cm of surrounding erythema) requiring surgical drainage, infected wound or ulcer, or infected burn (no minimum surface area) and included DFI.

‖COVERS: cSSTI was defined as deep extensive cellulitis, major cutaneous abscess (limited to 30% of the population), burn infection, or traumatic/surgical wound infection with purulent drainage (minimum surface area of 75 cm^2) and excluded DFI.

¶Clinical signs/symptoms of infection: purulent or seropurulent drainage or discharge, erythema, fluctuance, heat or localised warmth, pain or tenderness to palpation, temperature >38°C or hypothermia, white blood cell count >10,000 cells/mL, or 110% immature neutrophils irrespective of white blood cell count.

#Underlying comorbidities included: diabetes mellitus requiring drug therapy; stage 2 or 3 HIV infection; chronic renal impairment (estimated creatinine creatinine clearance ≥20 to <50 mL/min calculated by the Cockcroft-Gault formula; cirrhosis with Child-Pugh Stage A or B; cSSTI below the knee associated with peripheral vascular disease; albumin <2.5 g/dL or pre-albumin <11 mg/dL in the absence of liver disease; use of immunosuppressive agents, including a glucocorticoid (excluding >40 mg per day of prednisone or equivalent for > 1 week in the 2 weeks prior to enrolment); malignancy, other than non-melanoma skin cancers, with a life expectancy of >3 months.

††PORT risk class II patients were excluded from all efficacy analyses so the populations used for the primary analysis were consistent across FOCUS and Asia CAP.

‡‡Patients also received two doses of oral clarithromycin on Day 1 in FOCUS 1.

Results

- Baseline characteristics of patients with bacteraemia across the six trials are shown in Table 2.
- The most frequently isolated pathogens from the blood of bacteraemic patients were *S. aureus* (majority from cSSTI patients [ceftaroline MIC range 0.25–2 mg/L for MRSA and 0.12–0.5 mg/L for methicillin-susceptible *S. aureus*]) and *S. pneumoniae* (all from CAP patients [ceftaroline MIC range ≤0.015–0.06 mg/L]).
- Clinical cure rates at TOC in patients with bacteraemia are summarised in Tables 3 and 4. The overall clinical cure rates for bacteraemic patients at TOC were high. The pooled results of ceftaroline fosamil versus comparator in cSSTI and CAP bacteraemic patients were in line with the general population.
- Population pharmacokinetic modelling was used to predict individual patient exposure in COVERS and showed that plasma exposure of ceftaroline in patients with cSSTI was similar irrespective of the presence of bacteraemia (Figure 1) or various other patient comorbidities.[12]
- Safety and tolerability of ceftaroline fosamil among patients with bacteraemia were generally consistent with the overall populations in each trial.

Table 2. Baseline characteristics of patients with bacteraemia across the six Phase III trials (mMITT populations)

	cSSTI trials				CAP trials			
	CANVAS 1 and 2		COVERS†		FOCUS 1 and 2		Asia CAP	
	Ceftaroline fosamil	Comparator	Ceftaroline fosamil	Comparator	Ceftaroline fosamil	Comparator	Ceftaroline fosamil	Comparator
Number of patients	29	24	18	16	23	20	3	5
Mean (SD) age, years	47.7 (19.4)	52.3 (20.2)	59.0 (12.5)	62.4 (13.8)	60.6 (16.1)	63.5 (15.7)	79.7 (10.1)	63.8 (14.7)
Sex, n (%)								
Male	17 (58.6)	12 (50.0)	8 (44.4)	11 (68.8)	15 (65.2)	16 (80.0)	2 (66.7)	3 (60.0)
Female	12 (41.4)	12 (50.0)	10 (55.6)	5 (31.3)	8 (34.8)	4 (20.0)	1 (33.3)	2 (40.0)
Mean (SD) BMI, kg/m^2	28.1 (10.0)	28.3 (9.6)	26.8 (6.5)	27.1 (5.4)	27.5 (7.6)	23.2 (2.4)	25.0 (5.6)	22.9 (4.3)
SIRS, n (%)	11 (37.9)	11 (45.8)	11 (61.1)	8 (50.0)	21 (91.3)	19 (95.0)	2 (66.7)	3 (60.0)

BMI, body mass index †The COVERS mMITT analysis includes two patients (one in each group) who did not meet minimal disease criteria for the mMITT population because they had DFI; they are included here because DFI was not a reason for exclusion from the mMITT population in CANVAS 1 and 2.

Table 3. Patients with clinical cure at TOC across cSSTI Phase III trials[6,7,13]

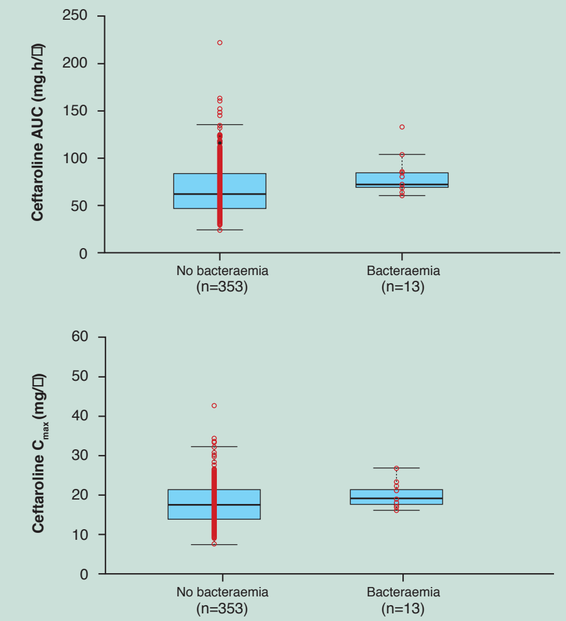
	cSSTI overall			Bacteraemia associated with cSSTI		
	CANVAS 1 and 2	COVERS	Overall	CANVAS 1 and 2	COVERS†	Overall
Patients clinically cured, n/N (%)						
mMITT population						
Ceftaroline fosamil	469/540 (86.9)	199/248 (80.2)	668/788 (84.8)	24/29 (82.8)	14/18 (77.8)	38/47 (80.9)
Vancomycin + aztreonam	453/522 (86.8)	108/136 (79.4)	561/658 (85.3)	24/24 (100.0)	10/16 (62.5)	34/40 (85.5)
ME population						
Ceftaroline fosamil	434/468 (92.7)	163/181 (90.1)	597/649 (92.0)	22/26 (84.6)	11/14 (78.6)	33/40 (82.5)
Vancomycin + aztreonam	421/446 (94.4)	97/112 (86.6)	518/558 (92.8)	21/21 (100.0)	8/12 (66.7)	29/33 (87.9)

†The COVERS mMITT analysis includes two patients (one in each group) who did not meet minimal disease criteria for the mMITT population because they had DFI; they are included here because DFI was not a reason for exclusion from the mMITT population in CANVAS 1 and 2.

Table 4. Patients with clinical cure at TOC across CAP Phase III trials [8,9,14]

	CAP overall			Bacteraemia associated with CAP		
	FOCUS 1 and 2	Asia CAP	Overall	FOCUS 1 and 2	Asia CAP	Overall
Patients clinically cured, n/N (%)						
mMITT population						
Ceftaroline fosamil	138/165 (83.6)	68/80 (85.0)	206/245 (84.0)	16/23 (69.6)	2/3 (66.7)	18/26 (69.2)
Ceftriaxone	126/168 (75.0)	67/96 (69.8)	193/264 (73.1)	13/20 (65.0)	3/5 (60.0)	16/25 (64.0)
ME population						
Ceftaroline fosamil	131/154 (85.1)	50/57 (87.7)	181/211 (85.7)	15/21 (71.4)	2/3 (66.7)	17/24 (70.8)
Ceftriaxone	111/147 (75.5)	47/62 (75.8)	158/209 (75.5)	10/17 (58.8)	1/1 (100.0)	11/18 (61.1)

Figure 1. Comparison of simulated steady state ceftaroline exposure in cSSTI patients with and without bacteraemia in the COVERS trial (PK population)



AUC, area under the curve; C_{max}, maximum plasma concentration

Conclusions

- Ceftaroline fosamil was effective and generally well tolerated in the treatment of patients with cSSTI or CAP and concurrent bacteraemia.
- These clinical outcomes are in line with expectations based on pharmacokinetic and microbiological considerations, specifically similar plasma ceftaroline exposure regardless of the presence of bacteraemia, and MIC distributions of isolates from bacteraemic patients that were broadly within ranges considered susceptible according to EUCAST and the CLSI.

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Disclosures

DW, JI and SD are employees of AstraZeneca. DM, HDF and IC are employees of Allergan Inc. (formerly Actavis).

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