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FOCUS 1: a randomized, double-blinded, multicentre, Phase III trial of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in community-acquired pneumonia

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Objectives: Ceftaroline, the active form of the prodrug ceftaroline fosamil, is a novel cephalosporin with bactericidal activity against important pathogens associated with community-acquired pneumonia (CAP), including *Streptococcus pneumoniae* and common Gram-negative pathogens. FOCUS 1 is a randomized, double-blinded, Phase III study that was conducted to evaluate the efficacy and safety of ceftaroline fosamil in treating patients with CAP. The primary objective was to determine non-inferiority [lower limit of 95% confidence interval (CI) $\geq -10\%$] in clinical cure rates achieved with ceftaroline fosamil compared with those achieved with ceftriaxone in the clinically evaluable (CE) and modified intent-to-treat efficacy (MITTE) populations.

Methods: Patients hospitalized in a non-intensive care unit setting with CAP of Pneumonia Outcomes Research Team (PORT) risk class III or IV requiring intravenous (iv) therapy were randomized (1:1) to receive 600 mg of ceftaroline fosamil iv every 12 h or 1 g of ceftriaxone iv every 24 h. Patients also received two 500 mg doses of oral clarithromycin every 12 h administered on day 1. Clinical cure, microbiological response, adverse events (AEs) and laboratory tests were assessed. FOCUS 1 registration number NCT00621504 (http://clinicaltrials.gov/ct2/show/NCT00621504).

Results: Of 613 enrolled patients, 298 received ceftaroline fosamil and 308 received ceftriaxone. Baseline characteristics between treatment groups were comparable. Clinical cure rates were as follows: CE population, 86.6% (194/224) for ceftaroline fosamil and 78.2% (183/234) for ceftriaxone [difference (95% CI), 8.4% (1.4, 15.4)]; and MITTE population, 83.8% (244/291) for ceftaroline fosamil and 77.7% (233/300) for ceftriaxone [difference (95% CI), 6.2% (−0.2, 12.6)]. Clinical cure rates for CAP caused by *S. pneumoniae* in the microbiological MITTE population were 88.9% (24/27) and 66.7% (20/30) for ceftaroline fosamil and ceftriaxone, respectively. Both agents were well tolerated, with similar rates of AEs, serious AEs, deaths and discontinuations because of an AE. The most common AEs for ceftaroline fosamil-treated patients were diarrhoea, headache, insomnia and nausea, and the most common AEs for ceftriaxone-treated patients were hypokalaemia, hypertension, nausea and diarrhoea.

Conclusions: Ceftaroline fosamil demonstrated high clinical cure and microbiological response rates in hospitalized patients with CAP of PORT risk class III or IV. Ceftaroline fosamil was well tolerated, with a safety profile similar to that of ceftriaxone and consistent with the cephalosporin class. In this study, ceftaroline fosamil was an effective and well-tolerated treatment option for CAP.

Keywords: CAP, CABP, *Streptococcus pneumoniae*, antimicrobial therapy

Introduction

Community-acquired pneumonia (CAP) is a commonly occurring serious illness, which is often associated with significant morbidity, mortality and considerable costs of care.[1–4] *Streptococcus pneumoniae* remains the most common bacterial pathogen of CAP although *Staphylococcus aureus* and Gram-negative pathogens may be involved.[5,6] The emergence of antimicrobial

resistance among *S. pneumoniae* is a significant concern. These microbiological trends are important to consider during selection of antimicrobial treatment for a patient with CAP, in addition to local susceptibility patterns and recommendations from treatment guidelines. Continued efforts to improve treatment options and outcomes for patients with CAP are needed.

Ceftaroline fosamil (herein after, 'ceftaroline') is the prodrug form of ceftaroline. Ceftaroline is a broad-spectrum cephalosporin that demonstrates bactericidal activity against pathogens associated with CAP, including Gram-positive pathogens and common Gram-negative organisms.[7–9] The efficacy and safety of ceftaroline in the treatment of patients with CAP was evaluated in the FOCUS (ceFtarOline Community-acquired pneUmonia trial vS ceftriaxone in hospitalized patients) programme. This programme consisted of two similarly designed trials that compared the efficacy and safety of ceftaroline with those of ceftriaxone in hospitalized adult patients with CAP of Pneumonia Outcomes Research Team (PORT) risk class III or IV.[10] (The PORT score is a validated prediction rule for prognosis. Patients with PORT scores of class III or IV have a mortality of 2.8% and 8.2%–8.5%, respectively.) In the integrated analysis of the FOCUS studies, ceftaroline was found to be safe and efficacious, with clinical cure rates higher than those for ceftriaxone.[11] The purpose of this report is to describe in more detail the results from the FOCUS 1 study (registration number NCT00621504; http://clinicaltrials.gov/ct2/show/NCT00621504).

Methods

Study design and treatment

The FOCUS 1 study was a Phase III, double-blinded, randomized, multinational, multicentre trial that compared the efficacy and safety of ceftaroline versus ceftriaxone administered intravenously (iv) for 5–7 days in adults hospitalized in a non-intensive care unit (ICU) setting with CAP of PORT risk class III or IV. The primary objective of this study was to determine non-inferiority [lower limit of 95% confidence interval (CI) $\geq -10\%$] in the clinical cure rates of ceftaroline compared with those of ceftriaxone observed at the test-of-cure (TOC) visit (8–15 days post-therapy), in the clinically evaluable (CE) and modified intent-to-treat efficacy (MITTE) populations (Figure 1). Secondary objectives that were evaluated included clinical cure in the microbiologically evaluable (ME) and microbiological modified intent-to-treat efficacy (mMITTE) populations at the TOC visit, clinical cure at the end-of-therapy (EOT) visit, microbiological outcome at the TOC visit, overall (clinical and radiographic) success rate at the TOC visit, clinical and microbiological response by pathogen at the TOC visit, clinical relapse at the late follow-up (LFU) visit (21–35 days after the last dose of study drug), microbiological re-infection/recurrence at the LFU visit and safety. A total of 114 study centres in Africa, Asia, Eastern Europe, Western Europe, Latin America and the USA participated in the trial. The study period was from January 2008 to December 2008. All patients or their legally authorized representatives were required to provide written informed consent, including willingness and ability to comply with all study procedures. Rigorous study conduct was confirmed throughout the study with intensive

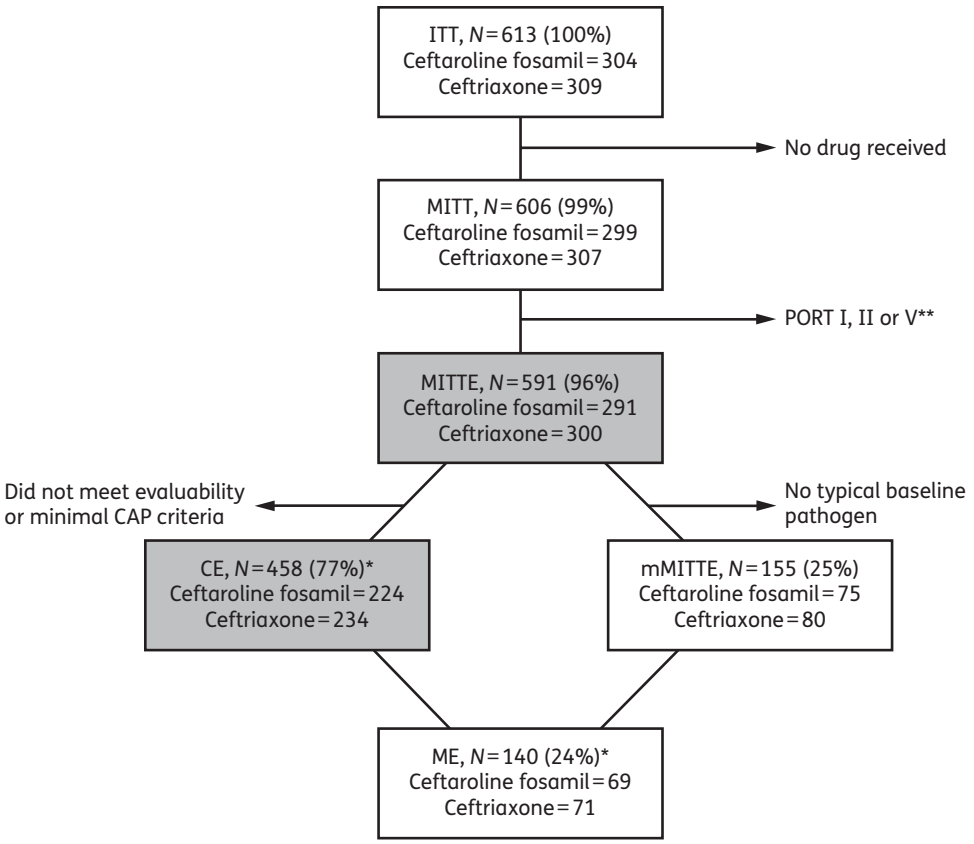

Figure 1. Disposition of patients enrolled in FOCUS 1. *Percentages of MITTE. **Patients with CAP of PORT risk class II severity were initially planned to be enrolled in the FOCUS 1 study; however, the protocol was amended to exclude these patients from the co-primary CE and MITTE populations. ITT, intent-to-treat.

site monitoring during and after active enrolment to ensure protocol adherence, enforcement of International Committee on Harmonisation (ICH) compliance[12] and extensive auditing (i.e. >30% of sites and patients). Prior to study initiation, all sites received approval for study conduct from their independent Ethics Committee or Institutional Review Board.

Block randomization using an interactive voice response system (stratified by PORT risk class) was conducted by a study-site pharmacist to assign patients to receive 600 mg of ceftaroline iv every 12 h or 1 g of ceftriaxone iv every 24 h. In patients with moderate renal impairment [creatinine clearance (CL_{CR}) 31–50 mL/min], the dose of ceftaroline was adjusted to 400 mg by an unblinded pharmacist. All patients were to also receive two 500 mg doses of oral clarithromycin as adjunctive therapy, limited to a course of 24 h (coinciding with the first two doses of study drug) to minimize any potential impact on the treatment effect of study drug. Patients remained hospitalized throughout the course of iv study drug therapy. Switch to oral therapy or to outpatient parenteral therapy was not permitted. Patients were required to receive a minimum of 48 h of treatment and at least 72 h of treatment to evaluate clinical cure and clinical failure, respectively. The maximum duration of study treatment was 7 days.

Inclusion criteria

Patients were adults at least 18 years of age with CAP requiring hospitalization and treatment with an iv antimicrobial. Patients were also required to have the presence of new or increasing pulmonary infiltrate(s) on chest radiograph or chest CT scan consistent with pneumonia, acute illness (≤7 days' duration) with three or more clinical signs or symptoms consistent with a lower respiratory tract infection [i.e. new or increased cough, purulent sputum or change in sputum character, auscultatory findings consistent with pneumonia (e.g. rales, aegophony, consolidation), dyspnoea, tachypnoea or hypoxaemia (O_2 saturation <90% on room air or pO_2 <60 mm Hg), oral temperature >38°C (>38.5°C rectally or tympanically) or hypothermia (<35°C), white blood cell (WBC) count >10 000 cells/mm^3 or <4500 cells/mm^3, >15% immature neutrophils (bands) irrespective of WBC count] and PORT score 71–130 (i.e. PORT risk class III or IV only).

Exclusion criteria

Patients were excluded if they had CAP of PORT risk class I, II or V, required admission to an ICU at baseline, had CAP suitable for outpatient therapy with an oral antimicrobial agent, had a confirmed or suspected respiratory tract infection attributed to a source other than community-acquired bacterial pathogens (e.g. hospital-acquired or healthcare-associated pneumonia pathogens),[13] had a non-infectious cause of pulmonary infiltrates or had pleural empyema. Patients with a microbiologically documented infection with a pathogen known to be resistant to study medication or an epidemiological or clinical context suggesting a high likelihood of a resistant pathogen, including ceftriaxone-resistant organisms, were also excluded. Patients with risk factors for methicillin-resistant *S. aureus* (MRSA) infection or with a predominance of Gram-positive cocci in clusters on sputum Gram's stain were also excluded in consideration of the inactivity of ceftriaxone monotherapy against this pathogen. Patients with a known or suspected infection caused solely by an atypical pathogen (i.e. *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae* and *Legionella* spp.) at baseline were also excluded from the study. All patients underwent *Legionella* urinary antigen testing at baseline, and patients with a positive test result were excluded from the study. Additional reasons for exclusion were as follows: previous therapy with a systemic antimicrobial agent for the treatment of CAP within 96 h prior to randomization [exception: a single short-acting antimicrobial was allowed within 96 h prior to randomization; long-acting antibiotics (i.e. dose ≥every 24 h, were excluded)]; receipt of chronic concomitant systemic corticosteroids >40 mg of prednisone equivalent; severe renal impairment (i.e. CL_{CR} ≤30 mL/min); and significant hepatic (i.e. known acute viral hepatitis, aspartate aminotransferase or alanine aminotransferase concentration >10-fold the upper limit of normal (ULN) or total bilirubin >3-fold the ULN or manifestations of end-stage liver disease, such as ascites or hepatic encephalopathy), haematological (i.e. current or anticipated neutropenia defined as <500 neutrophils/mm^3 or thrombocytopenia with platelet count <60 000 cells/mm^3) or immunological (i.e. known HIV infection and either a CD4 count of ≤200 cells/mm^3 at the most recent measurement or current diagnosis of another AIDS-defining illness) disease.

Study populations

The modified intent-to-treat (MITT) population included randomized patients who received any amount of study drug (Figure 1). The MITTE population included only MITT patients with CAP of PORT risk class III or IV. The mMITTE population included MITT patients with CAP of PORT risk class III or IV from whom one or more typical bacterial pathogens was isolated. The CE population included MITTE patients who met all evaluability criteria. The ME population included patients who met the criteria for both the CE and mMITTE populations.

Efficacy assessments

Per-patient clinical cure was defined as total resolution of all signs and symptoms of pneumonia or improvement of signs and symptoms to such an extent that no further antimicrobial therapy was necessary. Patients were also required to have absence of fever (temperature ≤38°C orally or ≤38.5°C rectally or tympanically) for 24 consecutive hours with signs and symptoms of CAP returning to baseline levels. Per-pathogen clinical cure was defined as the number and proportion of patients cured of a given pathogen isolated at baseline. Relapse was determined if a patient who was considered a clinical cure at the TOC visit had a return of symptoms and required additional antimicrobial therapy at the LFU visit.

Per-patient microbiological eradication was determined for each baseline pathogen and was defined as having a favourable response (eradicated or presumed eradicated for all baseline pathogens). Eradication was presumed if an appropriate source specimen was not available for culture, but the patient was assessed as a clinical cure. Recurrence (defined as isolation of the baseline pathogen) and reinfection (defined as isolation of a new pathogen) were determined from blood, sputum or pleural fluid cultures at the LFU visit in patients who had favourable clinical and microbiological responses at the TOC visit.

Safety assessments

Safety was evaluated in the MITT population. The one patient who was randomized to receive ceftaroline, but instead received ceftriaxone, was included in the safety analyses for ceftriaxone. Safety assessments included physical examinations, vital signs, metabolic panel tests, haematology parameters, urinalysis and urine microscopy, electrocardiograms and adverse events (AEs) and serious AEs (SAEs). An AE was defined as an untoward medical occurrence experienced by a patient from receipt of the first dose of study drug through the TOC visit. SAEs (defined as per ICH guidelines)[12] were captured up to the LFU visit or 30 days after the last dose of study drug.

Specimen analyses and laboratory assessments

Gram's stain, culture and susceptibility testing were performed on appropriate respiratory tract (i.e. induced or expectorated sputum and

bronchoalveolar lavage), pleural fluid or blood samples. Isolates from sputum samples were cultured if WBCs were present and if there were ≤10 squamous epithelial cells/low-power field on Gram's staining. Analyses were performed at a local or regional laboratory, as applicable, and all isolates that were not considered a contaminant were sent to the central laboratory for identification and susceptibility testing. Susceptibility testing was performed by broth microdilution tests and Kirby–Bauer disc diffusion tests (CLSI M7-A7 for the MIC test methods[14] and CLSI M100-S18 for susceptibility interpretive criteria[15]). Multidrug-resistant *S. pneumoniae* (MDRSP) was defined in this study as strains resistant to two or more antimicrobial classes of drugs, including penicillins, macrolides, tetracycline, fluoroquinolones, chloramphenicol, trimethoprim/sulfamethoxazole and cephalosporins.

To identify infection with *Legionella pneumophila* serogroup 1, a urine sample was collected from all patients at baseline for antigen detection. Patients could not be enrolled until results for the *Legionella* antigen test (BinaxNOW®; Inverness Medical International, Princeton, NJ, USA) were available and patients with a positive test at baseline were not enrolled in the study. Acute and convalescent blood samples for serology testing for *M. pneumoniae*, *C. pneumoniae* and *L. pneumophila* were collected at baseline and at the LFU visit (MP IFA Test System® and *Legionella* IFA Test System®; Zeus Scientific, Inc., Branchburg, NJ, USA; and *Chlamydia* Focus MIF®; Focus Diagnostics, Inc., Cypress, CA, USA). The following criteria were used to confirm evidence of acute infection: ≥4-fold rise in immunoglobulin G (IgG) titre between a negative acute (i.e. at baseline) serology and convalescent (i.e. at LFU) serology (IgG titre <1:128 and <1:16 for *M. pneumoniae* and *C. pneumoniae*, respectively); or single IgM titre of ≥1:16 and ≥1:10 at baseline for *M. pneumoniae* and *C. pneumoniae*, respectively. Acute infection with *L. pneumophila* was based on a ≥4-fold rise in *L. pneumophila* total antibody titre between a negative acute serology and the convalescent serology, a total antibody titre of ≥1:256 at baseline or a positive *Legionella* urinary antigen test. Patients found to have infection caused solely by an atypical pathogen were excluded from the CE, mMITTE and ME populations.

Statistical methods

The sample size for the study was calculated using the method of Farrington and Manning.[16] Assuming a point estimate for the clinical cure rate of 90% in the CE population in both treatment groups, a non-inferiority margin of 10% and a 25% non-evaluable rate, a total sample size of 610 patients (305 patients in each treatment group) was required for >90% power. A two-sided 95% CI for the observed difference in the primary outcome measure between ceftaroline and ceftriaxone was calculated for the co-primary populations using the method of Miettinen and Nurminen.[17] Non-inferiority was concluded if the lower limit of the 95% CI was greater than or equal to the non-inferiority margin of −10%. The difference between treatment groups in secondary efficacy outcomes and corresponding CI were estimated in the same manner.

Results

Patient disposition and analysis populations

Of the 613 enrolled patients, 606 received study drug, constituting the MITT population [299/304 (98.4%) in the ceftaroline group and 307/309 (99.4%) in the ceftriaxone group] (Figure 1). A total of 591 patients were included in the MITTE population [291/304 (95.7%) in the ceftaroline group and 300/309 (97.1%) in the ceftriaxone group]. A total of 458 patients with CAP of PORT risk class III or IV met clinical evaluability criteria, constituting the CE population [224/291 (77.0%) in the ceftaroline group and 234/300 (78.0%) in the ceftriaxone group]. The most common reasons for exclusion from the CE population are shown in Table 1. A total of 155 patients met criteria for inclusion in the mMITTE population [75/304 (24.7%) in the ceftaroline group and 80/309 (25.9%) in the ceftriaxone group]. Both microbiological and clinical evaluability criteria were met in 140 patients [69/291 (23.7%) in the ceftaroline group and 71/300 (23.7%) in the ceftriaxone group], constituting the ME population.

Table 1. Patient disposition (ITT population)

Characteristic	*n* (%)	
	ceftaroline fosamil (*N*=304)	ceftriaxone (*N*=309)
Patients excluded from CE population	80 (26.3)	75 (24.3)
Reasons for exclusion[a]		
atypical sole pathogen[b]	39 (12.8)	34 (11.0)
inadequate duration of therapy	19 (6.3)	11 (3.6)
indeterminate response at TOC[c]	15 (4.9)	9 (2.9)
PORT risk class I, II or V	13 (4.3)	9 (2.9)
TOC visit outside the specified window	11 (3.6)	13 (4.2)

ITT, intent-to-treat.
[a]Patients could have more than one reason for exclusion.
[b]Or any serological evidence of *L. pneumophila* infection despite a negative urinary antigen test at baseline required for enrolment. Data from ITT population. Atypical pathogens included *C. pneumoniae* (4 and 10 patients in the ceftaroline and ceftriaxone groups, respectively), *L. pneumophila* (11 and 4 patients) and *M. pneumoniae* (22 and 19 patients).
[c]And not assessed as a clinical failure at EOT.

Patient demographics and baseline characteristics

The majority of the patients enrolled in this study were white and male (Table 2). The mean age ± SD was 61.1 ± 16.5 years, and 49.2% of patients were aged ≥65 years across both treatment groups. Enrolment was highest in Eastern and Western Europe among the geographical regions. Patients in both treatment groups had similar demographic characteristics and relevant comorbid conditions. Overall, 62.9% and 37.1% of the patients had pneumonia of PORT risk class III and IV, respectively. In addition, 31.0% and 16.1% of the patients had mild or moderate renal impairment, respectively. The mean ± SD duration of treatment was 6.4 ± 1.1 and 6.5 ± 1.1 days in the MITTE population for patients who received ceftaroline and ceftriaxone, respectively (range, 5–8 days for >95% of patients). One patient received 15 doses of study drug in 8 days, and all other patients received no more than 7 days of therapy. No patient had a positive *Legionella* antigen test, and all tests were confirmed as being negative prior to randomization. In the ME population, 90.7% (127/140) of patients had CAP caused by a typical pathogen only, whereas the remaining 9.3% (13/140) had CAP caused by a mixed infection with a typical and an atypical pathogen. The two most commonly isolated pathogens were *S. pneumoniae* [36.4% (51/140)] and *S. aureus* [15.7% (22/140)]. Ceftaroline and ceftriaxone baseline MIC values were, respectively, 0.015–0.03 mg/L and 0.015–0.25 mg/L for *S. pneumoniae* and 0.12–0.25 mg/L and

Table 2. Demographic and baseline characteristics of the MITTE population

Characteristic	Ceftaroline fosamil (*N*=291)	Ceftriaxone (*N*=300)
Age (years), mean ± SD	61.0 ± 16.6	61.2 ± 16.4
≥65 years, *n* (%)	143 (49.1)	148 (49.3)
Male, *n* (%)	187 (64.3)	191 (63.7)
Race, *n* (%)		
white	260 (89.3)	268 (89.3)
Asian	14 (4.8)	16 (5.3)
Black or African American	17 (5.8)	15 (5.0)
Region of enrolment, *n* (%)		
Africa	17 (5.8)	18 (6.0)
Asia	13 (4.5)	15 (5.0)
Eastern Europe	128 (44.0)	134 (44.7)
Latin America	16 (5.5)	16 (5.3)
USA	11 (3.8)	12 (4.0)
Western Europe	106 (36.4)	105 (35.0)
Most common co-morbid conditions, *n* (%)		
structural lung disease[a]	64 (22.0)	60 (20.0)
any prior pneumonia	61 (21.0)	51 (17.0)
asthma	25 (8.6)	25 (8.3)
PORT risk class III or IV, *n* (%)		
III	190 (65.3)	182 (60.7)
IV	101 (34.7)	118 (39.3)
Bacteraemia, *n* (%)	8 (2.7)	9 (3.0)
Modified ATS severe CAP criteria met,[b] *n* (%)	82 (28.2)	89 (29.7)
SIRS criteria met,[c] *n* (%)	231 (79.4)	232 (77.3)
Renal impairment, *n* (%)		
mild (CL_{CR} 51–80 mL/min)	88 (30.2)	95 (31.7)
moderate (CL_{CR} 31–50 mL/min)	47 (16.2)	48 (16.0)
Prior antibiotic use,[d] *n* (%)	137 (47.1)	143 (47.7)

[a]Defined as any chronic parenchymal or airway disease [e.g. chronic obstructive pulmonary disease (emphysema, chronic bronchitis), bronchiectasis or interstitial fibrosis].
[b]Modified ATS severe CAP criteria[18] include the presence of three or more of the following at baseline: respiratory rate ≥30 breaths/min; O_2 <90% or PaO_2 <60 mm Hg; multilobar infiltrates; confusion/disorientation; blood urea nitrogen level ≥20 mg/dL; leucopenia (WBC count <4000 cells/mm^3); thrombocytopenia (platelet count <100 000 cells/mm^3); hypothermia (core temperature <36°C); systolic blood pressure <90 mm Hg; or diastolic blood pressure ≤60 mm Hg.
[c]SIRS criteria include the presence of at least two of the following at baseline: temperature <36°C or >38°C; heart rate >90 beats/min; respiratory rate >20 breaths/min; WBC count <4000 or >12 000; or immature neutrophils >10%.
[d]Prior antibiotic usage within 96 h prior to first dose of study drug.

2–8 mg/L for *S. aureus*. For *Haemophilus influenzae*, the baseline MIC values of ceftaroline and ceftriaxone were 0.008–0.015 mg/L and 0.008–0.008 mg/L, respectively, and for *Klebsiella pneumoniae*, they were 0.06–0.5 mg/L and 0.06–0.06 mg/L.

Clinical outcomes

The study met its primary objective of confirming the non-inferiority of ceftaroline with respect to ceftriaxone. Clinical cure rates in the co-primary populations were as follows: CE population, 86.6% (194/224) and 78.2% (183/234) for ceftaroline and ceftriaxone, respectively [difference (95% CI), 8.4% (1.4, 15.4)] (Table 3 and Figure 2); and MITTE population, 83.8% (244/291) and 77.7% (233/300) for ceftaroline and ceftriaxone, respectively [difference (95% CI), 6.2% (−0.2, 12.6)] (Table 3 and Figure 2). Clinical cure rates at the EOT were consistent with the primary results of this study (Table 3), as were the clinical cure rates in the microbiological populations. Clinical

Table 3. Clinical cure rates by study population

	% (*n*/*N*)			
Assessment visit	CE	MITTE	ME	mMITTE
TOC				
ceftaroline fosamil	86.6 (194/224)	83.8 (244/291)	89.9 (62/69)	88.0 (66/75)
ceftriaxone	78.2 (183/234)	77.7 (233/300)	76.1 (54/71)	75.0 (60/80)
difference, % (95% CI)	8.4 (1.4, 15.4)	6.2 (−0.2, 12.6)	13.8 (1.3, 26.4)	13.0 (0.7, 25.2)
EOT				
ceftaroline fosamil	87.9 (197/224)	86.9 (253/291)	NA	NA
ceftriaxone	80.3 (188/234)	80.7 (242/300)	NA	NA
difference, % (95% CI)	7.6 (0.9, 14.3)	6.3 (0.3, 12.3)	NA	NA

NA, not applicable.

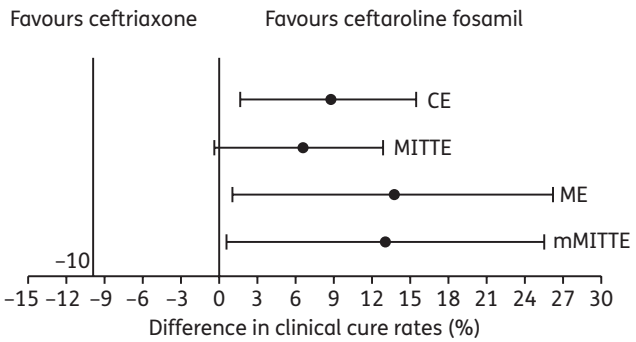

Figure 2. CIs for the difference in clinical cure rates at TOC (CE, MITTE, ME and mMITTE populations).

cure was observed in 89.9% (62/69) and 76.1% (54/71) of patients in the ceftaroline and ceftriaxone groups, respectively, in the ME population [difference (95% CI), 13.8% (1.3, 26.4)] (Table 3 and Figure 2). In the mMITTE population, clinical cure was observed in 88.0% (66/75) and 75.0% (60/80) of patients in the ceftaroline and ceftriaxone arms, respectively [difference (95% CI), 13.0% (0.7, 25.2)] (Table 3 and Figure 2). Among patients in the mMITTE population with CAP caused by *S. pneumoniae*, clinical cure rates were 88.9% (24/27) and 66.7% (20/30) for ceftaroline and ceftriaxone, respectively (Table 4). Clinical response at TOC and EOT in the MITT population is provided as Supplementary data at *JAC* Online. There was no apparent difference in MICs for *S. aureus* in successes or failures for the ceftaroline group (MICs 0.12–0.25 mg/L). For the ceftriaxone group, the MICs for successes were 2–4 mg/L and for failures were 4–8 mg/L. For the Enterobacteriaceae isolates, there was no apparent correlation of MICs of either agent for the Enterobacteriaceae isolates with clinical success.The MICs of ceftaroline for isolates associated with clinical success and failure were 0.03–1.0 mg/L and 0.03–0.06 mg/L, respectively, and the MICs of ceftriaxone for isolates associated with clinical success and failure were 0.03–0.5 mg/L and 0.06–0.12 mg/L, respectively.

Although clinical cure rates varied by geographical region, they were numerically higher for ceftaroline than for ceftriaxone in each region except Africa [ranging between 77.8% and 90.9% and 69.2% and 81.0% for ceftaroline and ceftriaxone, respectively; in Africa, the clinical cure rate was 92.3% (12/13) for ceftaroline and 100.0% (6/6) for ceftriaxone]. Clinical cure rates by patient subgroup in the CE population (including age, sex, PORT risk class III or IV, prior antibiotic use, mild or moderate renal impairment and presence of bacteraemia), and clinical cure rates in patients with mixed typical and atypical pathogen infection are displayed in Table 5. Rates of clinical cure in these subgroups were generally higher for ceftaroline than for ceftriaxone. There was a 1.1% difference (95% CI, −11.8, 9.5) in the clinical cure rate between the ceftaroline [81.0% (85/105)] and ceftriaxone [82.1% (87/106)] groups for patients who had received prior systemic antibiotic treatment (a single dose of short-acting antibiotic ≤96 h before the first dose of study drug; see footnote in Table 5 for list of excluded antibiotics). Among patients who did not receive prior antibiotic therapy, clinical cure rates were 91.6% (109/119) for ceftaroline and 75.0% (96/128) [difference (95% CI), 16.6% (7.5, 25.8)]. Most patients in whom prior antibiotics had been used received them within 24 h before the first dose of study drug; the majority of these antibiotics were penicillins or combinations of a penicillin with a β-lactamase inhibitor (Table 6).

At the TOC visit, overall (clinical and radiographic) success was observed in 86.6% (194/224) of patients in the ceftaroline group and 78.2% (183/234) of patients in the ceftriaxone group in the CE population [difference (95% CI), 8.4% (1.4, 15.4)]. In the MITTE population, 83.5% (243/291) of ceftaroline patients and 77.7% (233/300) of ceftriaxone patients experienced overall success [difference (95% CI), 5.8% (−0.6, 12.2)]. At the LFU visit, clinical relapse was noted in 2 (1.1%) of 180 patients in the ceftaroline group and 3 (1.8%) of 165 patients in the ceftriaxone group [difference (95% CI), −0.7% (−4.2, 2.4)] of the CE population. These patients were all ≥65 years, four were male and one was female, all but two had at least one risk factor for pneumonia and the PORT scores were III for the patients in the ceftriaxone group and IV for the patients in the ceftaroline group. In the MITTE population, 3 (1.2%) of 244 patients in the ceftaroline group and 3 (1.3%) of 233 patients in the ceftriaxone group [difference (95% CI), −0.1% (−2.6, 2.4)] were considered a clinical relapse.

Table 4. Clinical cure rates by baseline pathogens at the TOC visit (mMITTE population)

Baseline pathogen	Ceftaroline fosamil, *n*/*N* (%)	Ceftriaxone, *n*/*N* (%)	Crude difference, % (95% CI)
Gram-positive[a]	32/36 (88.9)	28/43 (65.1)	23.8 (5.1, 41.0)
Streptococcus pneumoniae	24/27 (88.9)	20/30 (66.7)	22.2 (0.2, 42.6)
MDRSP	2/2 (100)	0/1 (0)	100
Staphylococcus aureus[b]	8/10 (80.0)	9/14 (64.3)	15.7 (−23.0, 48.0)
Gram-negative[a]	39/44 (88.6)	37/44 (84.1)	4.5 (−10.6, 19.9)
Escherichia coli	8/8 (100)	5/7 (71.4)	28.6
Haemophilus parainfluenzae	7/8 (87.5)	9/10 (90.0)	−2.5
Klebsiella pneumoniae	7/8 (87.5)	3/5 (60.0)	27.5
Enterobacter cloacae	6/6 (100)	6/8 (75.0)	25.0
Haemophilus influenzae	4/5 (80.0)	7/10 (70.0)	10.0

[a]Denominators for Gram-positive and -negative rows are reflective of the number of patients with a Gram-positive and/or -negative infection. Patients with infection caused by more than one pathogen are counted once per pathogen.
[b]One patient in the ceftriaxone arm had infection with Panton–Valentine leucocidin-negative MRSA and was assessed as a clinical failure. All other *S. aureus* isolates were methicillin susceptible.

Table 5. Clinical cure rates in select patient subgroups (CE population)

	n/*N* (%)		
Patient subgroup	ceftaroline fosamil	ceftriaxone	Difference, % (95% CI)
Age, years			
<65	89/105 (84.8)	86/118 (72.9)	11.9 (1.1, 22.4)
≥65	105/119 (88.2)	97/116 (83.6)	4.6 (−4.4, 13.8)
Sex			
male	122/141 (86.5)	115/153 (75.2)	11.4 (2.3, 20.3)
female	72/83 (86.7)	68/81 (84.0)	2.8 (−8.3, 14.1)
PORT risk class			
III	136/150 (90.7)	113/142 (79.6)	11.1 (3.0, 19.5)
IV	58/74 (78.4)	70/92 (76.1)	2.3 (−10.9, 15.0)
Receipt of prior antibiotic treatment			
yes[a]	85/105 (81.0)	87/106 (82.1)	−1.1 (−11.8, 9.5)
no	109/119 (91.6)	96/128 (75.0)	16.6 (7.5, 25.8)
Renal impairment			
mild (CL_{CR}=51–80 mL/min)	58/69 (84.1)	57/73 (78.1)	6.0 (−7.2, 19.0)
moderate (CL_{CR}=31–50 mL/min)	36/41 (87.8)	27/35 (77.1)	10.7 (−6.7, 28.9)
Bacteraemia	6/8 (75.0)	4/7 (57.1)	NA
Mixed typical pathogen and atypical pathogen infection[b]	5/5 (100)	5/8 (62.5)	NA
Typical pathogen infection	57/64 (89.1)	49/63 (77.8)	11.3 (−1.8, 24.6)

NA, not applicable.
[a]Prior antibiotic treatment defined as receipt of systemic antibacterials ≤96 h before the first dose of study drug. Patients were permitted to receive a single dose of short-acting antibiotics. Patients were not permitted to receive long-acting antibiotics, such as cefixime (400 mg), ceftriaxone, gatifloxacin, gemifloxacin, grepafloxacin, levofloxacin, moxifloxacin, sparfloxacin, azithromycin, clarithromycin extended-release, dirithromycin, telithromycin, ertapenem, penicillin G benzathine/procaine, doxycycline (200 mg) and minocycline extended-release. Ciprofloxacin and norfloxacin were allowed, if single dose.
[b]Data from ME population. In total, three versus six patients had co-infection with *M. pneumoniae* in the ceftaroline group and ceftriaxone group, respectively, one patient versus two patients had co-infection with *C. pneumoniae*, respectively, and one patient in the ceftaroline group had co-infection with both of these atypical pathogens. Of the three failures in the ceftriaxone group, the typical pathogen was *S. pneumoniae* in one patient and *S. aureus* in two patients.

Table 6. Single doses of prior systemic antibiotics received within 24 h and from 25 to 96 h prior to receipt of the first dose of study drug (CE population)

	Prior antibiotics received within 24 h (*n*)		Prior antibiotics received from 25 to 96 h (*n*)	
Antibiotic class[a]	ceftaroline fosamil (*N*=224)	ceftriaxone (*N*=234)	ceftaroline fosamil (*N*=224)	ceftriaxone (*N*=234)
Penicillins	14	17	1	2
Penicillin+β-lactamase inhibitor	38	33	7	4
Cephalosporins				
first generation	0	1	0	0
second generation	10	15	1	0
third generation	10	13	0	0
fourth generation	3	6	0	0
Carbapenems	0	1	0	0
Aminoglycosides	1	1	0	2
Fluoroquinolones	14	8	1	0
Macrolides	4	1	0	1
Tetracyclines	0	0	0	0
Other[b]	1	1	0	0

[a]Patients were not permitted to receive prior long-acting antibiotics (i.e. antibiotics dosed ≥24 h). The following antibiotics were excluded per protocol: cefixime (400 mg); ceftriaxone; gatifloxacin; gemifloxacin; grepafloxacin; levofloxacin; moxifloxacin; sparfloxacin; azithromycin; clarithromycin extended-release; dirithromycin; telithromycin; ertapenem; penicillin G benzathine/procaine; doxycycline (200 mg); and minocycline extended-release.
[b]Includes clindamycin, trimethoprim/sulfamethoxazole and rifampicin.

Microbiological outcomes

Per-patient favourable microbiological response rates in the ME population were 89.9% (62/69) in the ceftaroline group compared with 78.9% (56/71) in the ceftriaxone group [difference (95% CI), 11.0% (−1.2, 23.3)]. Consistent results were observed in the mMITTE population; 88.0% (66/75) in the ceftaroline group and 78.8% (63/80) in the ceftriaxone group [difference (95% CI), 9.3% (−2.7, 21.1)]. No patient in either treatment group met criteria for microbiological reinfection or recurrence at the LFU visit.

Safety and tolerability

The incidence rates of treatment-emergent AEs are shown in Table 7. The most common AEs for ceftaroline-treated patients were diarrhoea, headache, insomnia and nausea, compared with hypokalaemia, hypertension, nausea and diarrhoea for ceftriaxone-treated patients. The most common study drug-related treatment-emergent AEs were diarrhoea (4.4% for ceftaroline and 1.0% for ceftriaxone), sinus bradycardia (1.0% for ceftaroline and 1.0% for ceftriaxone), nausea (1.3% for ceftaroline and 0.6% for ceftriaxone) and phlebitis (1.3% for ceftaroline and 0.6% for ceftriaxone). Discontinuation of study drug as a result of a treatment-emergent AE occurred in 3.7% and 3.9% of patients who received ceftaroline and ceftriaxone, respectively. The incidence of SAEs was 9.4% for ceftaroline and 10.7% for ceftriaxone. Of all the SAEs, eight were considered by the investigator related to study treatment [two for ceftaroline (one sudden death and one liver function test abnormal) and six for ceftriaxone (one multiorgan disorder, two hepatic failures, one acute cholecystitis, one hypersensitivity and one gastroenteritis)]. Potentially clinically significant haematology, coagulation, hepatic and renal laboratory abnormalities occurred at low rates (hepatic and renal parameters are shown in Table 8). In patients with a negative baseline direct Coombs' test result, 11.8% (28/238) of patients in the ceftaroline group and 5.2% (14/271) of patients in the ceftriaxone group had a positive direct Coombs' test result at EOT, TOC or both visits; however, no patient was found to have evidence of haemolytic anaemia, and no significant changes in haemoglobin from baseline to the end of study were reported. A similar percentage of patients (1.4% of ceftaroline patients and 1.0% of ceftriaxone patients) developed a QTcB interval (QT interval corrected using the Bazett correction formula) that was both >500 ms and ≥60 ms change from baseline. No patient experienced torsade de pointes.

Six patients in each treatment group (2.0% of ceftaroline-treated patients and 1.9% of ceftriaxone-treated patients) died, and one death in each group was considered possibly related to study treatment. A 73-year-old ceftaroline-treated female patient died on study day 3. The investigator-reported cause was sudden death with an alternative aetiology of myocardial infarction. A 60-year-old ceftriaxone-treated male patient died on study day 14 as a result of multiorgan disorder.

Of the 10 deaths considered unlikely to be related to study drug, 3 were attributed to underlying CAP and 7 were attributed

Table 7. AEs in the safety (MITT) population

AE	Ceftaroline fosamil, *n* (%) (*N*=298)	Ceftriaxone, *n* (%) (*N*=308)
Any treatment-emergent AE	119 (39.9)	136 (44.2)
Severity of AE		
mild	59 (19.8)	62 (20.1)
moderate	41 (13.8)	52 (16.9)
severe or life-threatening	19 (6.4)	22 (7.1)
Discontinuation because of an AE	11 (3.7)	12 (3.9)
Treatment-emergent AEs occurring in ≥2% of patients		
diarrhoea[a]	14 (4.7)	7 (2.3)
headache	10 (3.4)	4 (1.3)
insomnia	9 (3.0)	6 (1.9)
nausea	8 (2.7)	8 (2.6)
constipation	7 (2.3)	5 (1.6)
phlebitis	7 (2.3)	5 (1.6)
hypertension	6 (2.0)	8 (2.6)
hypokalaemia	4 (1.3)	10 (3.2)
Any SAE	28 (9.4)	33 (10.7)
Most common SAEs		
worsening of pneumonia	2 (0.7)	5 (1.6)
respiratory failure	2 (0.7)	1 (0.3)
sudden death	2 (0.7)	0
empyema	1 (0.3)	2 (0.6)
asthma	0	2 (0.6)
gastroenteritis	0	2 (0.6)

[a]No *Clostridium difficile* infection was confirmed in either treatment group.

Table 8. Potentially clinically significant (PCS) hepatic and renal laboratory parameters

Clinical laboratory parameter (PCS criterion)	*n*/*N* (%)[a] ceftaroline fosamil	ceftriaxone
Serum creatinine (>2.0× ULN and >100% increase)	0/296	3/306 (1.0)
Alkaline phosphatase (>2.0× ULN and >100% increase)	3/291 (1.0)	5/299 (1.7)
Alanine aminotransferase (>3.0× ULN and >200% increase)	6/277 (2.2)	10/283 (3.5)
Aspartate aminotransferase (>3.0× ULN and >200% increase)	2/272 (0.7)	8/276 (2.9)
Total bilirubin (>2.5× ULN and >150% increase)	0/278	1/284 (0.4)
Bilirubin, direct conjugated (>2.5× ULN and >150% increase)	0/244	2/242 (0.8)
γ-Glutamyl transferase (>3.0× ULN and >200% increase)	5/291 (1.7)	7/299 (2.3)

[a]Patients with at least one post-baseline assessment of the laboratory parameter were included in the denominator (*N*) and patients who met the PCS criterion at least once based on all post-baseline assessments of the laboratory parameter were included in the numerator (*n*).

to underlying disease (such as cardiomyopathy, chronic obstructive pulmonary disease, myopathy or malignancy) or acute myocardial infarction and pulmonary emboli that occurred after the study treatment period.

Discussion

Consistently ranked as a leading cause of death, CAP continues to be associated with high morbidity and economic burden.[1–4] In this randomized, multinational, double-blinded, Phase III study, 600 mg of ceftaroline iv every 12 h was demonstrated to be non-inferior to 1 g of ceftriaxone iv every 24 h, achieving higher cure rates in hospitalized patients with CAP of PORT risk class III or IV across all predefined populations.

The FOCUS 1 trial was designed to include patients with commonly implicated typical bacterial CAP pathogens (i.e. *S. pneumoniae*, *H. influenzae* and *S. aureus*). Infections of patients in the mMITTE population included in this trial are consistent with the intention of the reclassification for community-acquired bacterial pneumonia (CABP), a description of CAP established in 2009 to identify patients most likely to have CAP caused by a bacterial pathogen and for whom antimicrobial treatment would be appropriate.[19] Ceftaroline showed consistent efficacy against the broad range of CABP pathogens, including *S. pneumoniae*, the most common pathogen identified in this trial. The clinical cure rate for ceftaroline (88.9%; 24/27) was ∼22 percentage points higher than that for ceftriaxone (66.7%; 20/30) in this subgroup. This treatment difference can potentially be explained by the relative affinity of each agent for penicillin-binding proteins (PBPs) of *S. pneumoniae* and *S. aureus*. It is hypothesized that the activity of β-lactams against *S. pneumoniae* is a result of their affinity for PBP 1A, 2A, 2B and 2X, with genetic alterations in these proteins leading to β-lactam resistance. By inhibiting PBPs, β-lactams weaken the cell wall, resulting in lysis and cell death. In a recent *in vitro* study conducted by Kosowska-Shick *et al.*,[20] ceftaroline demonstrated similar affinity for PBP 1A and higher affinity for PBPs 2A and 2B when compared with ceftriaxone, and both agents demonstrated similar affinity for PBP 2X, with the exception of one penicillin-resistant strain for which ceftaroline affinity was 16-fold higher. Moisan *et al.*[21] also found that ceftaroline had stronger affinity (2-fold higher) for PBP 2X than did ceftriaxone for *S. pneumoniae* and PBP 2 for *S. aureus*. This is supported by the observation that the MICs of ceftaroline were lower for *S. pneumoniae* (0.015–0.03 mg/L) and *S. aureus* (0.015–0.25 mg/L) than the MICs of ceftriaxone for *S. pneumoniae* (0.12–0.25 mg/L) and *S. aureus* (2–8 mg/L).

The characteristics of the study population with pneumonia enrolled in FOCUS 1 were consistent with moderate to severe disease (PORT risk class III or IV), and, in general, this severity of disease was higher than that studied in previous registration trials. For example, ∼23%–30% of subjects enrolled in recent tigecycline, ertapenem and daptomycin Phase III CAP studies had PORT risk class III disease and ∼19%–27% had PORT risk class IV disease, compared with 63% PORT risk class III and 37% PORT risk class IV in this trial.[22–24] At least 30% of the subjects enrolled in these recent Phase III CAP studies had PORT risk class I and/or II disease, whereas no subjects in the co-primary populations of the FOCUS 1 trial had PORT risk class I or II disease. Furthermore, tigecycline was approved for CAP based on a US FDA *post hoc* analysis of 69.2% of enrolled subjects with a 'higher risk for mortality', defined by the FDA as age ≥50 years, PORT risk class ≥III or *S. pneumoniae* bacteraemia.[22,25] All subjects in the co-primary populations of the FOCUS 1 trial met these criteria for higher risk of mortality. These data, in addition to the enrolment of ∼29% of subjects meeting modified American Thoracic Society (ATS)[18] criteria for severe CAP and ∼78% with systemic inflammatory response syndrome (SIRS) (Table 2), support the fact that the subjects with CABP in the FOCUS 1 trial had moderate to severe disease requiring hospitalization and iv therapy.

Clinical cure rates were similar among patients who received prior short-acting antibiotic therapy within the 96 h preceding study initiation; however, among patients who did not receive prior short-acting antibiotic therapy, a 16.6 percentage point higher cure rate was observed in the ceftaroline group compared with the ceftriaxone group. These exploratory results not only indicate that a single dose of short-acting antibiotic may confound evaluation of the efficacy of an antimicrobial agent in CAP, as has been previously observed,[24] they also reinforce the observed benefit of ceftaroline versus ceftriaxone seen in the primary and secondary analyses.

It is interesting to note that despite a 24 h course of clarithromycin for initial coverage of infection caused by atypical pathogens, the clinical cure rates observed in patients with mixed typical and atypical pathogen infection did not differ from those with infection caused by typical pathogens alone.

The safety profile of ceftaroline observed in this study is consistent with that reported in other Phase III studies of ceftaroline.[26–28] In the FOCUS 1 study, ceftaroline was as well tolerated as ceftriaxone, consistent with the favourable benefit–risk balance seen in the cephalosporin class. There were no significant differences between treatment groups in the incidence of treatment-emergent AEs or severity of AEs, SAEs, discontinuations or deaths. Cephalosporins are known to be associated with direct Coombs' test seroconversion, and the rates of seroconversion were higher in the ceftaroline group than in the ceftriaxone group (11.8% versus 5.2%, respectively). However, these figures lie within the expected range of Coombs' test seroconversion associated with cephalosporins (e.g. as high as 16.2% reported for cefepime[29]), and no subject with clinical findings or laboratory results that were consistent with haemolytic anaemia was identified.

The majority of the small number of deaths that occurred during the course of this study were attributed to underlying causes and were considered by the investigators unlikely to be related to the study drug.

This trial, being a registration trial, has restrictions that exclude a number of patient populations that would be encountered in clinical practice, such as those who received prior treatment for CAP within 96 h (excluding short-acting antimicrobials), were immunocompromised, required treatment in an ICU or were at high risk for MRSA pneumonia, which precludes making conclusions on efficacy in these populations. In addition, a limited number of subjects were enrolled from North America, which probably reflects the restrictions on prior antibiotic use and lack of a full course of adjunctive macrolide therapy as recommended by the Infectious Diseases Society of America (IDSA)/ATS CAP guidelines.[6] These limitations contributed to the robustness of the study, in allowing for the comparison of two cephalosporin monotherapies in a well-defined population of patients hospitalized with moderate to severe CAP of PORT risk class III or IV, without the confounding effects of prior or adjunctive antimicrobial therapy.

In conclusion, the results from the FOCUS 1 trial support the efficacy and safety of ceftaroline as a potential new antimicrobial treatment option for CAP in hospitalized non-ICU patients.

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T. M. F. was involved in study design, interpretation of data for publication and was an investigator. D. E. L. was involved in study design and

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Supplementary data

A list of the number of patients enrolled at each study site and the outcomes in the MITT population are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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