Ceftaroline Fosamil for the Treatment of Community-acquired Bacterial Pneumonia and Complicated Skin and Skin Structure Infections

FDA Briefing Document for
Anti-Infective Drugs Advisory Committee Meeting
September 7, 2010

Table of Contents

I. BACKGROUND

Cerexa, Inc, a wholly-owned subsidiary of Forest Laboratories, Inc, submitted a New Drug Application (NDA) 200327, Ceftaroline Fosamil for Injection, for review for the treatment of community-acquired bacterial pneumonia (CABP) and complicated skin and skin structure infection (cSSSI) indications on December 30, 2009.

Ceftaroline, the active metabolite of ceftaroline fosamil, is a β-lactam of the cephalosporin class of antimicrobials. It has antibacterial activity against aerobic and anaerobic gram positive and aerobic gram negative bacteria which are associated with skin and respiratory infections. The bactericidal action results from inhibition of cell wall synthesis by high affinity binding to penicillin-binding proteins (PBPs). Unlike most β-lactams, ceftaroline has activity against methicillin-resistant *Staphylococcus aureus* (MRSA) due to high affinity for PBP2a and against *Streptococcus pneumoniae* due to high affinity for PBP2x.

The proposed clinical dose of ceftaroline is 600 mg administered IV every 12 hrs, with reduction of the dose to 400 mg IV every 12 hrs for patients with moderate renal impairment. Clinical studies and trials have been performed in adults ≥ 18 years of age, with the exception of a single pharmacokinetic (PK) study performed in adolescents.

The Applicant is seeking the following indications:
Community-Acquired Bacterial Pneumonia
Ceftaroline fosamil is indicated for the treatment of community-acquired bacterial pneumonia (CABP) caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Streptococcus pneumoniae*, (including multidrug-resistant isolates [MDRSP] and cases with concurrent bacteremia, *Staphylococcus aureus*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Klebsiella pneumoniae*, and *Escherichia coli*.

Complicated Skin and Skin Structure Infections
Ceftaroline fosamil is indicated for the treatment of complicated skin and skin structure infections (cSSSI) caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus anginosus* group (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Enterococcus faecalis* (ampicillin-susceptible isolates only), *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Morganella morganii*.

This briefing document includes ceftaroline nonclinical data (pharmacology/toxicology and microbiology), clinical pharmacology data, as well as a discussion of the Phase 3 CABP and cSSSI trials submitted in support of the NDA. Topics highlighted in the document are to advance the committee's discussion, and to seek expert advice regarding

issues pertinent to the benefit/risk assessment of ceftaroline, considering the primary efficacy results, pertinent subgroup analyses and potential safety issues.

II. REGULATORY HISTORY

Plans for the Phase 3 clinical development program for ceftaroline, including clinical trial design for use in the treatment of cSSSI and CABP were initiated at the End-of-Phase 2 meeting between Cerexa, Inc. and the Agency on October 27, 2006. The cSSSI clinical trials were begun in February and March 2007 and the CABP clinical trials in 2007, prior to public discussions regarding the use of non-inferiority (NI) trials for these indications. The Applicant had received requests from the Agency to provide adequate evidence for the proposed NI margin selected for each indication and responded to these requests.

For CABP, there have been three public discussions regarding appropriate clinical trial design and a draft guidance on development of antibacterial drugs for the treatment of CABP.

- FDA and Infectious Diseases Society of America (IDSA) public workshop on January 17 and 18, 2008. This meeting included discussion of the primary endpoint(s), historical evidence of treatment effect of antibacterial agents for the treatment of bacterial pneumonia, microbiology, and possible trial designs.
- Anti-Infective Drugs Advisory Committee (AIDAC) meeting on April 1 and 2, 2008. This meeting focused on key issues such as whether a NI margin could be defined; the committee unanimously voted that in patients with severe CABP, a non-inferiority margin could be justified based on mortality data. However, whether the mortality benefit could be extrapolated to clinical endpoints was less clear. Discussion also focused on the appropriate study population and analysis; microbiologic confirmation of bacterial etiology was strongly encouraged to link to historical data.
- On March 20, 2009, FDA issued and posted for comment, a draft guidance on development of drugs for treatment of CABP.
- A second meeting of the AIDAC was held on December 9, 2009 to discuss comments received regarding the draft guidance. At the meeting, the majority of the committee felt the historical data could support use of all-cause mortality as a primary endpoint, but also thought a clinical endpoint could serve as a primary endpoint. Both of these endpoints could perhaps be bolstered or serve as part of a composite endpoint. Based on the literature, assessment of clinical status at 48-72 hours was mentioned as possible timing for endpoint assessment. The committee also supported use of the microbiological intent to treat population as the primary analysis population. Enrollment of sicker patients as assessed by the Pneumonia Patient Outcomes Research Team (PORT) or CURB-65 severity scoring systems or patients older than 50 years of age was recommended as this population is at higher risk for morbidity and mortality.

For cSSSI, during a single session of a multi-day AIDAC meeting on November 8, 2008, use of a NI trial design for clinical trials for this indication was discussed. Based on review of the historical literature, it was concluded there was adequate evidence to support using a noninferiority design and justification for an NI margin in patients with

severe cellulitis or wound infections. However, in patients with abscesses, the treatment effect of antibacterial agents following primary incision and drainage could not be estimated; therefore major abscesses lacking a significant surrounding cellulitis (inflammatory) component should not be included in NI trials.

III. PHARMACOLOGY/TOXICOLOGY

Following IV administration, the ceftaroline prodrug is quickly dephosphorylated in plasma to its active form, which is rapidly distributed to tissues. Significant levels of a metabolite (open β-lactam ring) of the active form are also detected in plasma from animals in repeat dose toxicity tests. The primary route of excretion for ceftaroline is renal, with some fecal excretion also observed. In rats, about 67% of IV-administered radiolabel was recovered in the urine over 96 hours and 29% in the feces. These recovery percentages were 65% and 19% respectively in monkeys (over 168 hours). Most urinary radioactivity appeared to be associated with the active (dephosphorylated) form of ceftaroline.

Table 3.1 Ceftaroline (Dephosphorylated Active Form) Exposure in Rats and Monkeys After Repeated IV Administration of the Prodrug

	Cmax (µg/ml)	AUC* (µg·hr/ml)
Rats 4 weeks daily dose		
100 mg/kg (NOAEL[@])	247	124
300 mg/kg	561	307
1000 mg/kg	1017	740
Monkeys 4 weeks daily dose		
16 mg/kg (NOAEL[@])	21	42
80 mg/kg	97	205
400 mg/kg	522	1146
Rats 13 weeks daily dose		
30 mg/kg (NOAEL[@])	76	45
90 mg/kg	187	108
270 mg/kg	323	267
Monkeys 13 weeks daily dose		
32 mg/kg	33	43
64 mg/kg	78	110
*AUC: 0-24 hr 4 week rat and monkey; 0-∞ 13 week rat and monkey [@] NOAEL, no observed adverse effect level		

Studies conducted in rats and monkeys showed that the primary target organs of toxicity for intravenous ceftaroline were the kidney and CNS, consistent with other cephalosporins. High doses of ceftaroline (1000 mg/kg, rat; 400 mg/kg, cynomolgus monkey) were associated with tonic/clonic convulsions during 4 week studies. Clinical chemistry changes and microscopic evaluation of the kidneys demonstrated renal toxicity in rats at $\geq$ 300 mg/kg and in monkeys at $\geq$ 80 mg/kg when these doses were administered daily for one month. At the same doses of ceftaroline, hypertrophy of the germinal centers of the spleen was observed in rats and hyperplasia of the lymphoid follicles of the spleen was seen in monkeys. In the high dose monkey group, hyperplasia of mandibular or mesenteric lymph nodes or GALT was also observed in some animals.

Reductions in several RBC parameters (RBC number, hematocrit, hemoglobin) were observed in several high dose monkeys and as this observation might have be related to immune complex formation, Coombs tests were conducted in some Phase 2 clinical trials. Splenic and lymphoid changes were not observed in 13-week studies in rats and monkeys where the highest doses administered were 270 and 64 mg/kg/day, respectively, and no signs of anemia were observed in the monkeys. There were no drug-related histopathologic findings in the monkeys at 64 mg/kg in the longer study; a single death (moribund sacrifice) at this dose was difficult to attribute to ceftaroline, although an association could not be ruled out completely. The animal's moribund condition appeared to be associated with respiratory distress and no other animals in the study demonstrated clinical signs of toxicity. The 13-week rat study confirmed the kidney and CNS to be targets of toxicity for ceftaroline. Treatment-related mortality, clonic convulsions, and kidney changes including granulomas associated with the presence of foreign material and hyperplasia of transitional renal epithelium were observed in rats that received IV doses of 270 mg/kg/day. At 90 mg/kg/day, minimal vacuolation of renal collecting ducts was the predominant microscopic observation, but a granuloma associated with foreign material was seen in the kidney of one animal at this dose level.

Ceftaroline doses up to 450 mg/kg/day did not appear to cause impairment of fertility in adult male or female rats or toxicity to rat pups exposed *in utero* from Gestation Day 6 through lactation. Survival and body weight gain of F_1 pups from dams that received ceftaroline were comparable to controls and the ceftaroline groups attained developmental landmarks at approximately the same rate as controls. Their behavior, motor activity, learning, and reproductive capacity did not appear different from controls. Developmental toxicity was not observed in a rat study at doses up to 300 mg/kg/day, the highest dose tested. Developmental toxicity studies conducted in rabbits were limited by excessive maternal toxicity, not unusual for this type of antimicrobial drug.

Ceftaroline prodrug was negative in the Ames bacterial reverse mutation assay and mouse lymphoma assay. Prodrug and dephosphorylated active form induced chromosome aberrations in Chinese hamster lung cells and Chinese hamster ovary cells, respectively, in the absence of metabolic activation, but not in the presence of hepatic microsomal enzymes derived from rats. Active form did not induce mutations at the HGPRT locus of Chinese hamster ovary cells. Ceftaroline doses of up to 2000 mg/kg (given IV) did not induce the formation of micronucleated erythrocytes in male rats or mice and it did not induce unscheduled DNA synthesis in rat hepatocytes.

IV. MICROBIOLOGY

Antimicrobial Spectrum of Activity

The Applicant has submitted data from surveillance and other studies demonstrating ceftaroline's in vitro activity against pathogens associated with cSSSI and CABP. Surveillance studies included *S. aureus* from Europe and the USA and included isolates positive for the Panton-Valentine leukocidin *(pvl*) gene, heterogeneous vancomycin-intermediate (hVISA), vancomycin-intermediate (VISA), vancomycin-resistant (VRSA),

quinupristin/dalfopristin non-susceptible, tetracycline-resistant, mupirocin-resistant, linezolid-resistant, daptomycin nonsusceptible and fluoroquinolone-resistant isolates. The MIC_{90} values ranged from 0.12 to 2 µg/ml for all staphylococci tested. Against MRSA, the ceftaroline MIC_{90} for US isolates is 1 mcg/ml. The ceftaroline MIC_{90} value for US isolates of coagulase-negative staphylococci is 0.5 mcg/ml.

Ceftaroline is active in vitro against *S. pneumoniae*, including penicillin-intermediate and –resistant isolates. MIC_{90} values ranged from 0.004 to 0.025 mcg/ml against all *S. pneumoniae* isolates. Ceftaroline MIC_{90} values were ≤0.016 mcg/ml for some β-hemolytic streptococci isolates. Against penicillin-resistant viridans group streptococci, ceftaroline MIC_{90} values were 1 mcg/ml. Ceftaroline activity was also assessed against bacteria belonging to the *Enterobacteriaceae* family. The Applicant's data shows that ceftaroline demonstrated activity with MICs ranging from ≤ 0.016 mcg/ml to >32 mcg/ml against all isolates. Decreased in vitro activity was observed against AmpC and ESBL producers and ceftazidime non-susceptible *Enterobacteriaceae* isolates such as *E. coli, K. pneumoniae, K. oxytoca, Enterobacter cloacae,* and *E. aerogenes.* Ceftaroline's in vitro activity against non-fermenting Gram-negative bacteria such as *P. aeruginosa* suggests that it would not be successful in treating infections caused by this organism.

Mechanism of Action

Investigations into the activity of ceftaroline support that it binds to penicillin binding proteins (PBPs) in bacteria. In *S. aureus*, there are four natural PBPs (PBP1-4) and ceftaroline was shown to bind to all, with the highest affinity to PBP2a. A principal factor of the broad-spectrum β-lactam resistance in MRSA isolates is the penicillin-binding protein 2a (PBP2a). PBP2a has low affinity for β-lactam and thus provides transpeptidase activity to allow cell wall synthesis at β-lactam concentrations that inhibit the β-lactam-sensitive PBPs normally produced by *S. aureus*. The binding of ceftaroline to the PBP2a in *S. aureus* is responsible for ceftaroline activity against methicillin-resistant *S. aureus*.

In *S. pneumoniae*, there are six known PBPs and the in vitro data suggest that ceftaroline binds to PBP 3, 1A, 2X, 1B and 2A/B and are considered the primary target of ceftaroline. In the *Enterobacteriaceae*, the primary target of ceftaroline is membrane PBPs that are responsible for transpeptidase or transglycosidase reaction in cell wall biosynthesis.

Mechanism of Resistance

Mechanisms of resistance in staphylococci include the production of β-lactamase and modification of the PBP target by either gene acquisition of an exogenous PBP or target alteration. Streptococcal resistance to β-lactams is mediated via alterations in the β-lactam-binding site of PBP1a, PBP2b and PBP2x. Mutations resulting in changes in the active binding sites correlate with decreased affinity for β-lactams and increase in MIC. In Gram negative organisms, the predominant mode of resistance is the production of β-lactamase hydrolyzing enzymes such as extended spectrum β-lactamases (ESBLs). Ceftaroline hydrolysis by ESBLs is a major contributing factor for resistance in Gram-

negative organisms. High rates of ceftaroline hydrolysis were reported for CTX-M-15, KPC-2, TEM-1 SHV-4 and P99. In addition, AmpC β-lactamases have been frequently identified in Gram-negative organisms, of which there are two types (plasmid-mediated and chromosomal or inducible AmpC). Ceftaroline is also degraded by isolates that hyper-produce AmpC β-lactamases. Thus, ESBL producing and AmpC Gram-negative bacteria are clinically resistant to ceftaroline.

Resistance Studies

The in vitro studies described within this review indicate a low propensity for the development of ceftaroline resistance following serial passage experimental studies compared with comparator agents. The in vitro studies show that the MIC of ceftaroline for MRSA did not change during 10 serial passages, while the MIC of rifampin increased 16 fold after 5 passages. In another study after 10 serial passages, a 2-fold change in ceftaroline MIC was observed for *S. aureus* and *S. pneumoniae* isolates, with the exception of *S. pneumoniae* isolate 884 whose MIC increased 4-fold (from 0.12 to 0.5 mcg/ml). For *E. faecalis* isolates, the ceftaroline MIC increased 4-fold (from 2 to 8 mcg/ml) after 10 serial passages. Against the comparator rifampin, the MIC increased 16-fold for *S. pneumoniae* 884; 16-fold for *E. faecalis* 847; and 16,000-fold for MRSA 2053. Against another comparator, vancomycin, the MIC increased 4-fold for *S. pneumoniae* 884; and for levofloxacin, the MIC increased 8-fold for MRSA 2202 and *S. pneumoniae* 3130 and 128-fold for MSSA 753.

The Applicant has submitted additional in vitro data that show the propensity of ceftaroline to induce AmpC. The production of AmpC has been reported in a variety of *Enterobacteriaceae* and non-fermentative Gram negatives. AmpC induction may complicate the use of β-lactams for the treatment of infections caused by members of the *Enterobacteriaceae* group of bacteria.

Post-Antibiotic Effect

Based on the data provided, ceftaroline would be expected to have a post-antibiotic effect (PAE) ranging from 0.8 to 7.2 hours for *S. aureus* and lower for *S. pneumoniae* and *E. coli*. The duration of the PAE is species specific and dependent on the drug used. The bactericidal activity was observed at greater than or equal to twice the MIC with bactericidal effects ($\geq$ 3-$\log_{10}$ killing) occurring within 8 to 24 hours.

Susceptibility Test Methods

The Applicant has evaluated the activity of ceftaroline and comparator agents in accordance with Clinical and Laboratory Standards Institute (CLSI) methods. The evaluation methods included broth microdilution; disk diffusion and agar dilution. CLSI methods were used in the development of provisional interpretive criteria and proposed quality control ranges. The Applicant conducted a disk content study using six organisms to determine optimal disk loading to achieve zones of inhibition that best correlated with the MIC from broth microdilution. Resistance phenotypes were determined by reference

broth microdilution tests followed by confirmatory techniques that included CLSI M100 methods. PCR screens with mechanism-specific primer sets were also performed on certain strains with unusual resistance patterns.

Antimicrobial Interaction Studies

The Applicant has provided data from synergy studies that evaluated the effect of ceftaroline in combination with other antimicrobial agents against a variety of bacterial isolates, using the checkerboard technique. No antagonism was observed when ceftaroline was tested and compared with other antimicrobial agents. Ceftaroline demonstrated synergy with meropenem against *S. aureus* strain 2296 (CA-MRSA) and *K. pneumoniae* strain (1468 ESBL). Synergy was also observed with amikacin against *E. coli* strain 2273 (ESBL) and *P. aeruginosa* strain 2559. Because the synergy data are very limited no final conclusion can be made from the data.

Animal Studies

The Applicant has submitted data from a variety of animal models, including the mouse neutropenic thigh (MNT) model, murine subcutaneous infection (MSI) model, endocarditis infection model, pneumonia infection model, bacteremia infection model, and meningitis infection model. Efficacy has been demonstrated in mouse lung, thigh, and peritonitis infection models against Gram-positive and –negative organism. Efficacy has also been demonstrated in rat endocarditis models against MSSA and MRSA, and *E. faecalis*; in a rabbit pneumonia model against *S. pneumoniae* including PRSP and in a rabbit model of MRSA osteomyelitis. Ceftaroline was also studied in a rabbit model of meningitis against *E. coli* and *K. pneumoniae* and the in vivo activity of ceftaroline was better than or similar to cefepime. Similar to other β-lactam antimicrobial agents, the pharmacodynamic (PD) parameter that best supports the efficacy of ceftaroline is the %T>MIC.

CEFTAROLINE IN VITRO SUSCEPTIBILITY TEST INTERPRETIVE CRITERIA

Table 4.1 Applicant's Proposed Ceftaroline In Vitro Susceptibility Test Interpretive Criteria

Pathogen	*Minimum Inhibitory Concentrations (µg/mL)*			*Disk Diffusion (zone diameter in mm)*		
	S	*I*	*R*	*S*	*I*	*R*
Staphylococcus aureus (including methicillin-resistant isolates)	≤ 2[a]	—	—	≥ 22	—	—
Streptococcus spp. (β-hemolytic)	≤ 0.12[a]	—	—	≥ 23	—	—
Streptococcus pneumoniae	≤ 0.5[a]	—	—	≥ 26	—	—
Haemophilus spp.	≤ 0.25[a]	—	—	≥ 27	—	—
Enterobacteriaceae	≤ 1	2	≥8	≥ 21	18 - 20	≤ 17

Abbreviations: S = susceptible, I = intermediate, R = resistant

a The current absence of resistant isolates precludes defining any results other than "Susceptible" Isolates yielding MIC results other than Susceptible should be submitted to a reference laboratory for further testing

FDA Proposed Ceftaroline In Vitro Susceptibility Test Interpretive Criteria

From a clinical microbiology perspective, the data provided by the Applicant does not provide adequate clinical experience to support their proposed susceptibility breakpoints or the inclusion of some organisms in the interpretive criteria tables. For instance there was very limited information on clinical efficacy for MRSA, *H. influenzae*, *S. pyogenes* and *S. agalactiae* associated with community-acquired pneumonia. For the Gram-positive bacteria in the tables there are no disc diffusion criteria because there is not a good fit between the MIC interpretive value and a disc diffusion zone size. Based on ceftaroline in vitro susceptibility data, pharmacokinetic/pharmacodynamic analysis and clinical success rates, the Agency recommends the following interpretive criteria for isolates from complicated skin and skin structure infections and community acquired bacterial pneumonia.

Table 4.2 Susceptibility Interpretive Criteria for Ceftaroline proposed by the Agency for cSSSI

Pathogen	***Minimum Inhibitory Concentrations (mcg/mL)***			***Disk Diffusion (zone diameter in mm)***		
	S[a]	**I**	**R**	**S**	**I**	**R**
Staphylococcus aureus (includes methicillin-resistant isolates)	≤0.5	-	-	──	-	-
S. pyogenes	≤0.004	-	-	-	-	-
S. agalactiae	≤0.015	-	-	-	-	-
Enterobacteriaceae[b]	≤0.5	1	≥2	≥23	20-22	≤19
[a] The current absence of resistant isolates precludes defining any results other than "Susceptible" [b] A determination of the potential clinical efficacy of ceftaroline could only be determined for *Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca, Proteus mirabilis and Morganella morganii* because of insufficient experience with other members of the *Enterobacteriaceae*.						

Table 4.3 Susceptibility Interpretive Criteria for Ceftaroline proposed by the Agency for CABP

Pathogen	***Minimum Inhibitory Concentrations (mcg/mL)***			***Disk Diffusion (zone diameter in mm)***		
	S[a]	**I**	**R**	**S**	**I**	**R**
Staphylococcus aureus (excluding methicillin-resistant isolates)	≤0.25	-	-	──	-	-
S. pneumoniae	≤0.008	-	-	-	-	-
Enterobacteriaceae[b]	≤0.5	1	≥2	≥23	20-22	≤19
[a] The current absence of resistant isolates precludes defining any results other than "Susceptible" [b] A determination of the potential clinical efficacy of ceftaroline could only be determined for *Escherichia coli, Klebsiella oxytoca and Klebsiella pneumoniae* because of insufficient experience with other members of the *Enterobacteriaceae.*						

V. CLINICAL PHARMACOLOGY

The proposed dosing regimen of ceftaroline fosamil is 600 mg Q12h as 1-hour IV infusion for 5-7 days for treatment of CABP and 5-14 days for treatment of cSSSI**.**

5.1 Summary of Pharmacokinetic Characteristics

General pharmacokinetics: Ceftaroline fosamil (prodrug) is rapidly converted during IV infusion by *in vivo* phosphatase enzymes to the microbiologically active ceftaroline. Ceftaroline is the predominant circulating compound in plasma, and exhibits linear pharmacokinetics with approximately dose-proportional increase in exposure over the studied single dose range of 50-1000 mg. The β-lactam ring of ceftaroline undergoes hydrolysis to form the inactive, open-ring metabolite, ceftaroline M-1.

Pharmacokinetic parameters of ceftaroline and ceftaroline M-1 following single and multiple 1-hour IV infusions of ceftaroline fosamil 600 mg Q12h are summarized in **Table 5.1-1**. Due to rapid biotransformation, concentrations of ceftaroline fosamil were generally measurable only during IV infusion.

Table 5.1-1 Mean ± SD pharmacokinetic parameters following single and multiple 1-h IV infusions of ceftaroline fosamil in healthy adults

Parameter	**600 mg Q12h (n=6)**	
	Ceftaroline (active)	**Ceftaroline M-1 (open-ring metabolite)**
Single Dose (Day 1)		
C_{max} (µg/mL)	18.97 ± 0.71	2.72 ± 0.77
T_{max} (h)[a]	1.00 (0.92-1.25)	1.00 (0.67-5.00)
AUC_{inf} (µg*h/mL)	56.79 ± 9.31	15.80 ± 3.21
$t_{1/2}$ (h)	1.60 ± 0.38	3.50 ± 1.36
CL (L/h)	9.58 ± 1.85	35.63 ± 6.60
V_z (L)	21.97 ± 5.43	177.1 ± 60.5
Multiple Dose (Day 14)		
C_{max} (µg/mL)	21.33 ± 4.10	3.58 ± 0.62
T_{max} (h)[a]	0.92 (0.92-1.08)	1.08 (0.92-1.53)
AUC_{tau} (µg*h/mL)	56.25 ± 8.90	18.95 ± 4.62
$t_{1/2}$ (h)	2.66 ± 0.40	6.84 ± 0.59
CL (L/h)	9.60 ± 1.40	30.05 ± 6.40
V_z (L)	35.30 ± 7.40	221.5 ± 73.1
Accumulation Ratio	1.00 ± 0.12	1.19 ± 0.08

[a] T_{max} reported as median (minimum-maximum)
Accumulation ratio, AUC_{tau} ratio of Day 14 to Day 1; **AUC_{inf},** area under concentration-time curve from time 0 to infinity (for Day 1); **AUC_{tau},** area under concentration-time curve over dosing interval (for Day 14); **C_{max},** maximum observed concentration; **CL,** plasma clearance; **$t_{1/2}$,** elimination half-life; **T_{max},** time of maximum observed concentration; **V_z,** apparent volume of distribution of terminal phase

Distribution: Plasma protein binding of ceftaroline is approximately 20% in humans and decreases minimally with increasing concentration over clinically relevant concentrations (1-50 μg/mL, 14.5-28.0% bound).

Metabolism: The CYP450 system does not appear to be a significant metabolic pathway for ceftaroline. Low metabolic turnover (<12%) was observed for ceftaroline in pooled human liver microsomes expressing major CYP450 isoenzymes.

Following single 1-hour IV infusion of [^{14}C] ceftaroline fosamil 600 mg in healthy males (n=6), ceftaroline fosamil, ceftaroline, ceftaroline M-1, and three unidentified minor metabolites were detected in plasma. Ceftaroline was the predominant compound systemically available, followed by ceftaroline M-1, which was approximately 20% of ceftaroline AUC_{inf}.

Excretion: Ceftaroline and accompanying metabolites are primarily eliminated by the kidneys. Following single 1-hour IV infusion of [^{14}C] ceftaroline fosamil 600 mg in healthy males (n=6), approximately 64.3% of the radioactive dose was excreted in urine as ceftaroline and 2.3% as ceftaroline M-1.

5.2 Intrinsic Factors

Elderly: Pharmacokinetics of ceftaroline were evaluated in healthy elderly (≥65 years of age) subjects versus healthy young adult (18-45 years of age) subjects with equal number of males and females, following single 1-hour IV infusion of ceftaroline fosamil 600 mg. Ceftaroline AUC_{inf} was 33% greater in elderly subjects (n=16) than in young adults (n=16) based on geometric mean ratios, due to decreased renal function in elderly cohort. No dose adjustment is necessary based on elderly age alone.

Gender: Pharmacokinetics of ceftaroline and ceftaroline M-1 were evaluated in healthy elderly males and females and healthy young adult males and females following a single 1-hour IV infusion of ceftaroline fosamil 600 mg. A gender effect was not apparent as systemic exposure of ceftaroline was similar between males (n=16) and females (n=16) across age groups. No dose adjustment based on gender is necessary.

Pediatric (Adolescent): Pharmacokinetics of ceftaroline were evaluated in hospitalized adolescent (12-17 years of age) subjects receiving antibiotic therapy, following single 1-hour IV infusion of ceftaroline fosamil 8 mg/kg for those <75 kg or 600 mg for those ≥75 kg. Mean CL and Vz for ceftaroline were similar between adolescent subjects (n=7) in this study and healthy adults (n=6) in a separate study following single 1-hour IV infusion of ceftaroline fosamil 600 mg. However, mean ceftaroline C_{max} and AUC_{inf} for adolescent subjects receiving ceftaroline fosamil 8 mg/kg were 10% and 23% lower, respectively, than mean estimates for healthy adults receiving ceftaroline fosamil 600 mg.

Additional pediatric studies are planned for the future.

Renal impairment: Pharmacokinetics of ceftaroline were evaluated in subjects with normal renal function versus subjects with mild, moderate, and severe renal impairment, as well as subjects with end-stage renal disease (ESRD) on intermittent hemodialysis (HD).

Pharmacokinetic results following single 1-hour IV infusion of ceftaroline fosamil 600 or 400 mg in various renal function cohorts are summarized in **Table 5.2-1**.

Table 5.2-1 Summary of Phase 1 renal impairment studies for ceftaroline fosamil

Renal Function	CrCL (mL/min)	N	Studied Dose	Mean AUC_{inf} (μg*h/mL)	Mean $t_{1/2}$ (h)	Mean CL (L/h)
Normal	>80	6	600 mg, 400 mg	75.56 48.63-52.81	2.87 2.75-3.02	7.11 6.90-7.47
Mild (Study -02)	>50 to ≤80	6	600 mg	92.27	3.67	6.12
Moderate (Study -02)	>30 to ≤50	6	600 mg	114.8	4.60	4.68
Severe (Study -04)	≤30	6	400 mg	113.3	5.05	3.22
ESRD (Study -18)	(on HD)*	6	400 mg, post-HD	128.6	6.16	2.77
* Average of 21.6% of the dose is removed by HD when doses are administered pre-HD						

Dose adjustments are proposed by the Applicant for patients with moderate and severe renal impairment, while no dosing regimen was proposed for ESRD patients on intermittent HD (**Table 5.2-2**). Renal-adjusted regimens derived by the Applicant were based on matching ceftaroline exposures (i.e., AUC and the pharmacokinetic-pharmacodynamic [PK-PD] parameter best associated with *in vivo* efficacy, free drug % time above MIC [% *f*T>MIC]) to that of subjects with normal renal function receiving the proposed therapeutic regimen of ceftaroline fosamil 600 mg Q12h as 1-hour IV infusions (data not shown).

Table 5.2-2 Proposed regimens of ceftaroline fosamil by the Applicant based on renal function

Renal Function	CrCL (mL/min)	Ceftaroline Fosamil Regimen
Normal	>80	600 mg Q12h (1-h IV infusion)
Mild	>50 to ≤80	
Moderate	>30 to ≤50	**400 mg Q12h** (1-h IV infusion)
Severe	≤30	
ESRD	(on HD)	**None**

Appropriate dosing regimens for varying degrees of renal impairment, including ESRD requiring intermittent HD, are currently being evaluated by the Agency.

5.3 Drug Interactions

In vitro studies indicate ceftaroline is not an inhibitor or inducer of major CYP450 isoenzymes, and thus, unlikely to cause clinically significant drug interactions with known CYP450 substrates. As such, no Phase 1 drug interaction studies were performed.

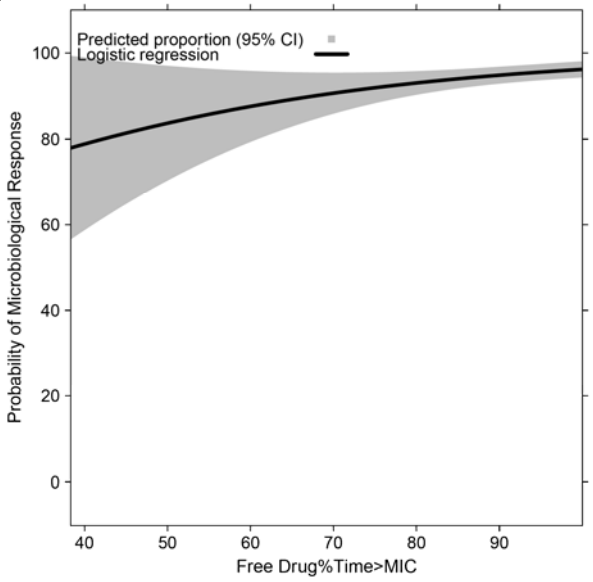
No clinically significant differences in ceftaroline C_{max} or AUC_{0-12} were observed with concomitant medication use in an exploratory population pharmacokinetic analysis of Phase 2/3 patients with CABP or cSSSI. Studied concomitant medications were categorized as substrates, inhibitors, or inducers of major CYP450 isoenzymes; anionic or cationic drugs known to undergo active renal secretion; and vasodilator or vasoconstrictor drugs that may alter renal blood flow.

5.4 Exposure-Response for Efficacy

Animal infection models: The characteristic of β-lactams of % *f*T>MIC (i.e., percentage of the dosing interval that free drug concentrations are greater than the MIC) was best associated with efficacy in a neutropenic murine thigh model against *S. pneumoniae* (n=5) and *S. aureus* (n=4, MSSA and MRSA). Median % *f*T>MIC ≥51 was correlated with 2-log kill (99% reduction) against *S. pneumoniae* and *S. aureus* strains, in accordance with historical PK-PD data of cephalosporins (optimal % *f*T>MIC, 50-70).

Population PK-PD: For cSSSI, estimated *f*T>MIC was generally greater than 40% in microbiologically evaluable (ME) patients with mono- or poly-microbial *S. aureus* or *S. pyogenes* infections (n=449). Logistic regression analysis of % *f*T>MIC versus per-patient microbiological response showed a significant positive relationship (p=0.011) (**Figure 5.4-1**).

Figure 5.4-1 Relationship between % *f*T>MIC and probability of per-patient microbiological response for ME population with mono- or poly-microbial *S. aureus* or *S. pyogenes* cSSSI (solid line = mean; shaded area = 95% confidence interval)



An exposure-response relationship was not identified for CABP as majority of Phase 3 patients had ceftaroline exposures of 91.7-100% *f*T>MIC.

5.5 Exposure-Response for Safety

Cardiovascular effects: A thorough QT study was performed in healthy adults (n=54) with a single supratherapeutic dose of IV ceftaroline fosamil (1500 mg as 1-hour infusion), a single dose of IV placebo (negative control), and a single dose of IV moxifloxacin (400 mg as 1-hour infusion, positive control) in a randomized, double-blind, three-period crossover design. Following review by the Interdisciplinary Review Team for QT Studies (IRT), no significant QT prolongation effect of ceftaroline 1500 mg was detected.

VI. CLINICAL TRIALS

A. Community-acquired Bacterial Pneumonia (CABP)

The two Phase 3 CABP clinical trials (P903-08 and P903-09) were multicenter, multinational, randomized, double-blind, active comparator-controlled trials comparing ceftaroline fosamil and ceftriaxone in adult subjects with CABP requiring treatment with an IV antimicrobial agent in a hospital or urgent care setting. Patients in both trials were treated with ceftaroline 600 mg IV q 12 hr or ceftriaxone 1 g IV q 24 hr for treatment duration of 5-7 days. The two trials were similar in design except for the addition of 24 hours of adjunctive therapy with clarithromycin (2 doses) in Study P903-08; the Applicant's rationale for including a macrolide was to allow participation by US centers who were unwilling to participate as the published Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) treatment guidelines for CAP recommend such treatment.

Ceftaroline was administered as two 300 mg infusions, each given over 30 minutes, q 12 hr, with dose adjustment for moderate renal impairment (defined as calculated CrCl 30 ≤ 50 mL/min) to two 200 mg infusions, each given over 30 minutes, q 12 hr. Patients in the ceftriaxone treatment group received a 1 g infusion over 30 minutes and a second infusion of IV saline placebo over 30 minutes q 24 hr, with two IV saline placebo infusions, each administered over 30 minutes, 12 hours later.

To be enrolled in the trial, patients were required to have:

- Radiographically-confirmed pneumonia (new or progressive pulmonary infiltrate)

AND

- Acute illness (≤ 7 days duration) with at least three of the following clinical signs or symptoms:
  - new or increased cough
  - purulent sputum or change in sputum character
  - auscultatory findings consistent with pneumonia (eg, rales, egophony, findings of consolidation)

- dyspnea, tachypnea, or hypoxemia (O_2 saturation < 90% on room air or pO_2 < 60 mmHg)
- fever > 38°C oral (> 38.5°C rectally or tympanically) or hypothermia (< 35°C)
- WBC > 10,000 cells/mm^3 or < 4500 cells/mm^3
- greater than 15% immature neutrophils (bands) irrespective of WBC

AND

- Pneumonia Patient Outcomes Research Team (PORT) score > 70 and ≤ 130 (PORT Risk Class III or IV). This criterion was added to Study P903-08 in Protocol Amendment 2, dated November 13, 2007, after 128 patients (21% of the study population) had enrolled and to Study P903-09 in Protocol Amendment 2, dated October 12, 2007 after 375 patients (60% of the study population) had enrolled.
- Patients were required to be hospitalized or treated in an urgent care center and require initial treatment with an IV antimicrobial agent.

Important exclusion criteria included:

- CABP suitable for outpatient treatment with an oral antimicrobial agent
- Infection with an atypical organism
- Previous treatment with an antimicrobial agent within 96 hours leading up to randomization EXCEPT for a single dose of a short-acting antimicrobial agent OR unequivocal clinical evidence of treatment failure following at least 48 hours of systemic antimicrobial therapy
- Severe renal impairment (CrCl ≤ 30 mL/min).

Baseline clinical and microbiological assessments were performed within the 24 hours prior to initiation of study therapy. Clinical assessment included medical history, prior and concomitant medications, and physical examination, including evaluation for signs and symptoms of pneumonia (as listed in inclusion criteria). Microbiological assessment included collection of a respiratory specimen (sputum or other appropriate respiratory specimen such as bronchoalveolar lavage or pleural fluid) for Gram stain and culture, blood for microbiological culture and serology for atypical pathogens (*Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Legionella pneumophila*) and urine for *L. pneumophila* and *S. pneumoniae* urinary antigen. An assessment of severity of illness was also made at baseline using the PORT Risk Class. Patients with a positive *L. pneumophila* urinary antigen were to be excluded from the study.

Patients had daily clinical assessments while on study therapy; these assessments included resting vital signs, maximum temperature for the preceding 24 hour period, and evaluation for signs and symptoms of CABP (as listed in the inclusion criteria). An End-of-Therapy (EOT) visit was performed following the last dose of study drug, a Test-of-Cure (TOC) visit 8-15 days after the last dose of study drug, and late follow-up (LFU) visit 21-35 days after the last dose of study drug. In addition to clinical evaluation at these visits, safety laboratories and a respiratory specimen (if indicated) were obtained. A chest radiograph was obtained at the TOC and LFU visit and blood for atypical pathogen serology was obtained at LFU.

The primary efficacy endpoint was the per-subject clinical response (cure) rate assessed by the investigator at the TOC visit.

- Clinical cure was defined as total resolution of all signs and symptoms of pneumonia or improvement to such an extent that further antimicrobial therapy was not necessary.
  - Improvement required the absence of fever (temperature ≤ 38°C oral or ≤ 38.5°C rectally or tympanically) for at least 24 continuous hours with temperature recorded twice daily, in addition to a substantial improvement in signs and symptoms of CABP. This substantial improvement required a return to pre-CABP baseline levels for subjects with decreased pulmonary function (e.g., subjects with chronic obstructive pulmonary disease (COPD)).
- Clinical failure was defined as any of the following:
  - Persistence, incomplete clinical resolution, or worsening of signs or symptoms of CABP requiring alternative antimicrobial therapy
  - Treatment limiting adverse event leading to study treatment discontinuation and an alternative antimicrobial agent is necessary
  - Death due to CABP
- Indeterminate outcome was defined as study data not available for evaluation of efficacy, for reasons including treatment change before completing 48 hrs of therapy, death where pneumonia was non-contributory, loss to follow-up, or extenuating circumstances.

The primary objective was to determine the non-inferiority of ceftaroline fosamil treatment compared to ceftriaxone treatment in adult subjects with CABP based on the difference in clinical cure rates (ceftaroline – ceftriaxone), using a non-inferiority margin of 10%. In the submission the primary efficacy endpoint assessment was performed at TOC. A similar assessment occurred at EOT and was considered to be an important secondary endpoint. Clinical failure was also carried forward from the EOT to the TOC, in that only subjects who were classified as cures at the EOT could be clinical cures at the TOC.

The Applicant defined the following analysis populations:

- ITT (Intent-to-Treat): All randomized subjects.
- MITT (Modified Intent-to-Treat): All randomized subjects who received any amount of study drug.
- MITTE (Modified Intent-to-Treat Efficacy): All MITT subjects in PORT Risk Class III or IV.
- CE (Clinically Evaluable): All subjects in the MITTE Population who met the inclusion criteria for CABP and all evaluability criteria, including subjects who received at least the prespecified minimal amount of the intended dose and duration of study drug therapy, for whom sufficient information regarding the infection was available to determine the outcome. Subjects with *M. pneumoniae* or *C. pneumoniae* as the sole causative pathogen of infection, and all subjects with *L. pneumophila* infections were excluded from the CE Population.
- mMITT (Microbiological Modified Intent-to-Treat): All subjects in the MITT Population who met the inclusion criteria for CABP, and had at least one typical

bacterial organism consistent with a CABP pathogen identified from a microbiological specimen (e.g., blood, sputum, or pleural fluid). Subjects with *M. pneumoniae* or *C. pneumoniae* as the sole causative pathogen of infection, and all subjects with *L. pneumophila* infections were excluded.

- mMITTE (Microbiological Modified Intent-to-Treat Efficacy): All subjects in the mMITT Population in PORT Risk Class III or IV.
- ME (Microbiologically Evaluable): All subjects in both the CE and mMITTE Populations.

The analysis populations focused on in this document are the MITTE and CE populations which were pre-specified as the co-primary efficacy analysis populations by the Applicant and agreed to by the FDA.

Trial Results

As noted in Section II, Regulatory History, the protocols were designed and clinical trials were initiated prior to the public discussions about CABP study design. Therefore, this section presents results of the prespecified Applicant's analysis, followed by results of additional FDA reviewer analyses that were largely based on discussions from the FDA/IDSA workshop and two AIDAC meetings.

Patient disposition

In Study P903-08, there were 305 patients randomized to the ceftaroline treatment group and 309 to the ceftriaxone treatment group; there were 299 and 307 patients in the ceftaroline and ceftriaxone treatment groups, respectively, who received any amount of study drug. Although 128/614 patients (20.8%) were randomized prior to Protocol Amendment 2 limiting patients to PORT Risk Class III and IV, only 17/614 patients (2.8%) enrolled in the study were not PORT III or PORT IV.

In Study P903-09, there were 317 patients randomized to the ceftaroline treatment group and 310 to the ceftriaxone treatment group; 315 and 307 patients in the ceftaroline and ceftriaxone treatment groups, respectively, received any amount of study drug. In Study P903-09, 375/627 patients (59.8%) were randomized prior to Protocol Amendment 2 limiting patients to PORT Risk Class III and IV and 61/627 (9.7%) were not classified as PORT Risk Class III or IV.

Table 6A.1 shows the baseline demographic characteristics for patients included in the co-primary analysis population, the modified intent to treat efficacy (MITTE) population.

Table 6A.1 Baseline Characteristics of the Applicant's MITTE Population

	Study P903-08		Study P903-09	
	Ceftaroline	Ceftriaxone	Ceftaroline	Ceftriaxone
Total Subjects	291	300	289	273
Sex				
Male	187 (64%)	191 (64%)	175 (61%)	175 (64%)
Female	104 (36%)	109 (36%)	114 (39%)	98 (36%)
Race				
White	260 (89%)	268 (89%)	278 (96%)	264 (97%)
Black	17 (6%)	15 (5%)	0 (0%)	0 (0%)
Asian	14 (5%)	16 (5%)	5 (2%)	4 (1%)
American Indian	0 (0%)	0 (0%)	5 (2%)	5 (2%)
Age				
18-49	74 (25%)	71 (24%)	62 (21%)	48 (18%)
50-<65	74 (25%)	81 (27%)	97 (34%)	92 (34%)
≥ 65	143 (49%)	148 (49%)	130 (45%)	133 (49%)
PORT Risk Class				
III	190 (65%)	182 (61%)	170 (59%)	171 (63%)
IV	101 (35%)	118 (39%)	119 (41%)	102 (37%)
Bacteremia				
Yes	8 (3%)	9 (3%)	15 (5%)	11 (4%)
No	283 (97%)	291 (97%)	274 (95%)	262 (96%)
Region				
Africa	17 (6%)	18 (6%)	0 (0%)	0 (0%)
Asia	13 (4%)	15 (5%)	5 (2%)	4 (1%)
Eastern Europe[1]	201 (69%)	207 (69%)	223 (77%)	212 (78%)
Latin America	16 (5%)	16 (5%)	48 (17%)	44 (16%)
North America	11 (4%)	12 (4%)	0 (0%)	0 (0%)
Western Europe[1]	33 (11%)	32 (11%)	13 (4%)	13 (5%)
Prior Antibiotics				
Yes	137 (47%)	143 (48%)	100 (35%)	117 (43%)
No	154 (53%)	157 (52%)	189 (65%)	156 (57%)
Renal Function				
80 < CrCl	150 (52%)	150 (50%)	124 (43%)	133 (49%)
50 < CrCl ≤ 80	86 (30%)	94 (31%)	109 (38%)	93 (34%)
30 < CrCl ≤ 50	46 (16%)	44 (15%)	40 (14%)	36 (13%)
CrCl ≤ 30	4 (1%)	5 (2%)	9 (3%)	5 (2%)
Lung Disease				
Yes	64 (22%)	60 (20%)	96 (33%)	87 (32%)
No	227 (78%)	240 (80%)	193 (67%)	186 (68%)
Smoking History				
Yes	156 (54%)	141 (47%)	150 (52%)	145 (53%)
No	135 (46%)	159 (53%)	139 (48%)	128 (47%)
Abnormal Signs				
Temperature > 37.8°C[2]	213 (73%)	204 (68%)	161 (56%)	166 (61%)
Heart Rate >100 beats/minute	126 (43%)	113 (38%)	104 (36%)	102 (37%)
Respiratory Rate > 24 breaths/minute	161 (55%)	169 (56%)	152 (53%)	139 (51%)
Systolic BP < 90 mmHg	33 (11%)	36 (12%)	49 (17%)	45 (16%)
Oxygen Saturation <90%	81 (28%)	84 (28%)	100 (35%)	80 (29%)

	Study P903-08		Study P903-09	
	Ceftaroline	Ceftriaxone	Ceftaroline	Ceftriaxone
Symptoms Present				
Cough	280 (97%)	293 (97%)	282 (98%)	265 (97%)
Dyspnea	239 (82%)	254 (84%)	252 (87%)	235 (86%)
Chest Pain	159 (55%)	165 (55%)	166 (57%)	149 (55%)
Sputum Production	223 (77%)	226 (75%)	205 (71%)	194 (71%)
Confusion	5 (2%)	11 (4%)	6 (2%)	8 (3%)

[1] Poland and Hungary included in the Eastern European region by FDA.
[2] Temperature measured orally, rectally, tympanically.
FDA Reviewer Table and adapted Applicant Tables:
P903-08, CSR Tables: 10.3.1-1., 10.3.3-1., 10.3.4-1.
P903-09, CSR Tables: 10.3.1-1., 10.3.3-1., 10.3.4-1.

The Applicant's MITTE populations, co-primary analysis populations, for each trial included 45-49% of patients who were ≥ 65 years of age, with another 25% in Study P903-08 and 34% in Study P903-09 of patients 50-65 years of age. Only a small percent (3-5%) of patients in either trial were bacteremic at baseline. By definition, all patients in this MITTE analysis population were categorized as PORT Risk Class III or IV. The majority of patients were enrolled in Eastern Europe (69-78%). Only 4% of patients in Study P903-08 were from the US; there were no US patients enrolled in Study P903-09.

The MITTE population was selected as the co-primary population of interest based upon previous discussions at the FDA/IDSA workshop and the two meetings of the AIDAC and at the recommendation of the FDA. The rationale for selecting this population was that the justification for a 10% non-inferiority margin was provided by historical data based on a mortality endpoint and this population was thought to include patients with higher risk of mortality. Inclusion of patients in these populations did not require isolation of a bacterial pathogen, although this criterion had been raised in discussions.

Table 6A.2 shows the number of subjects in selected prespecified Applicant analysis populations, as well as the proportion of randomized subjects represented in these populations.

Table 6A.2: Applicant Subject Populations

	Study P903-08		Study P903-09	
	Ceftaroline	Ceftriaxone	Ceftaroline	Ceftriaxone
ITT	305 (100%)	309 (100%)	317 (100%)	310 (100%)
MITTE	291 (95%)	300 (97%)	289 (91%)	273 (88%)
CE	224 (73%)	234 (76%)	235 (74%)	215 (69%)
mMITT	75 (25%)	82 (27%)	99 (31%)	102 (33%)

Source Tables:
Study P903-08, CSR, Table 10.1-2.
Study P903-09, CSR, Table 10.1-2.

To demonstrate noninferiority, a two-sided 95% confidence interval (CI) for the observed difference in the clinical cure rates (ceftaroline - ceftriaxone) was constructed using the method of Miettinen and Nurminen with noninferiority concluded if the lower limit of the

95% CI was greater than –10%. An important secondary endpoint was to evaluate the clinical cure rate at the end of therapy endpoint.

Table 6A.3 shows the results of the analyses for Study P903-08 at TOC and EOT in the Applicant's co-primary MITTE and CE populations.

Table 6A.3: Study P903-08 Cerexa Primary and Secondary Analysis, MITTE and CE Populations

Population	Ceftaroline	Ceftriaxone	Difference	95% CI
Clinical Cure Rates at the TOC Visit				
MITTE	244/291 (83.8%)	233/300 (77.7%)	6.2%	(-0.2%, 12.5%)
CE	194/224 (86.6%)	183/234 (78.2%)	8.4%	(1.4%, 15.4%)
Clinical Cure Rates at the EOT Visit				
MITTE	253/291 (86.9%)	242/300 (80.7%)	6.3%	(0.3%, 12.2%)
CE	197/224 (87.9%)	188/234 (80.3%)	7.6%	(0.9%, 14.3%)
Source: Study P903-08, CSR, Table 11.1.1.1-1., 11.1.1.2.1-1.				

The 30-day all-cause mortality rate in the MITT population was low, with 6 deaths (about 2%) reported in each treatment group.

Table 6A.4 shows the clinical response rates in the mMITT at both TOC and EOT visits.

Table 6A.4: Study P903-08 Clinical Response at TOC in the mMITT Population

Clinical Response mMITT	Ceftaroline N (%)	Ceftriaxone N (%)	Difference (ceftaroline – ceftriaxone) (95% CI)
N	75	82	
TOC	66/75 (88.0)	62/82 (75.6)	12.4 (0.2, 24.4)
EOT	66/75 (88.0)	64/82 (77.5)	10.0 (-2.0, 21.8)
Source: Study P903-08, CSR, Table 14.4.1.2E, FDA Reviewer.			

The results in the mMITT population also favored treatment with ceftaroline, however because the size of the population had decreased considerably, the 95% confidence intervals were much wider, but still met the non-inferiority margin specified at both the TOC and EOT.

Table 6A.5 shows the results of the analyses for study P903-09 at TOC and EOT in the co-primary MITTE and CE populations.

Table 6A.5: Study P903-09 Clinical Response at TOC in the mMITT Population

Population	Ceftaroline	Ceftriaxone	Difference	95% CI
Clinical Cure Rates at the TOC Visit				
MITTE	235/289 (81.3%)	206/273 (75.5%)	5.9%	(-0.9%, 12.7%)
CE	193/235 (82.1%)	166/215 (77.2%)	4.9%	(-2.5%, 12.4%)
Clinical Cure Rates at the EOT Visit				
MITTE	249/289 (86.2%)	215/273 (78.8%)	7.4%	(1.1%, 13.8%)
CE	202/235 (86.0%)	172/215 (80.0%)	6.0%	(-1.0%, 13.0%)
Source: Study P903-09, Table 11.1.1.1-1., 11.1.1.2.1-1.				

All numerical trends favored ceftaroline and the 10% non-inferiority margin was met for the co-primary analysis populations. Results at the EOT timepoint were similar. The 30-day all cause mortality rate in the MITT population was low, with 9 deaths (3%) in the ceftaroline treatment group and 6 in the ceftriaxone treatment group (2%) reported for each of the treatment groups.

Table 6A.6 shows the clinical response rates in the mMITT at both the TOC and EOT.

.

Table 6A.6: Study P903-09 Clinical Response at TOC in the mMITT Population

Clinical Response mMITT	Ceftaroline N (%)	Ceftriaxone N (%)	Difference (ceftaroline – ceftriaxone) (95% CI)
N	99	102	
TOC	79/99 (79.8)	78/102 (76.5)	3.3 (-8.2, 14.8)
EOT	82/99 (82.8)	82/102 (80.4)	2.4 (-8.4, 13.3)
Source: Study P903-09, CSR, Table 14.4.1.2E, FDA Reviewer.			

Results in this mMITT population also favored treatment with ceftaroline, however because the size of the population had decreased considerably, the 95% confidence intervals were wider, but still met the non-inferiority margin specified.

Table 6A.7 below shows the clinical response rate by pathogen in the microbiological evaluable (ME) population.

Table 6A.7: Clinical Cure Rates at TOC (by baseline pathogen) Applicant ME population

	P903-08		P903-09		Pooled Studies 08 and 09	
Baseline Pathogen	Ceftaroline n/N (%)	Ceftriaxone n/N (%)	Ceftaroline n/N (%)	Ceftriaxone n/N (%)	Ceftaroline n/N (%)	Ceftriaxone n/N (%)
S. pneumoniae[1]	21/24 (87.5)	18/27 (66.7)	33/39 (84.6)	23/32 (71.9)	54/63 (85.7)	41/59 (69.5)
S, aureus (MSSA)	8/10 (80.0)	7/11 (63.6)	10/15 (66.7)	7/14 (50.0)	18/25 (72.0)	14/25 (56.0)
H. influenzae	2/3 (66.7)	6/8 (75.0)	13/15 (86.7)	11/12 (91.7)	15/18 (83.3)	17/20 (85.0)
M. catarrhalis	1/1 (100.0)	0	1/2 (50.0)	2/2 (100.0)	2/3 (66.7)	2/2 (100.0)
E. coli	8/8 (100.0)	5/6 (83.3)	2/4 (50.0)	4/6 (66.7)	10/12 (83.3)	9/12 (75.0)
E. cloacae	6/6 (100.0)	6/8 (75.0)	1/1 (100.0)	3/4 (75.0)	7/7 (100.0)	9/12 (75.0)
K. oxytoca	2/3 (66.7)	5/6 (83.3)	3/3 (100.0)	2/2 (100.0)	5/6 (83.3)	7/8 (87.5)
K. pneumoniae	7/7 (100.0)	3/4 (75.0)	6/6 (100.0)	7/8 (87.5)	13/13 (100)	10/12 (83.3)

[1] Pathogen number includes patients with *S. pneumoniae* infection identified by urinary antigen testing.
Source P903-08: Table 11.1.1.3.11-1 CSR pg 169-170
Source P903-09: Table 11.1.1.3.11-1 CSR pg, 170-172

The clinical response rates by pathogen at TOC indicate that the response rates were higher for ceftaroline for both *S. pneumoniae* and MSSA. Ceftriaxone response rates were slightly better than ceftaroline for *H. influenzae*. The remaining pathogens isolated were of small numbers and it is difficult to see much of a difference.

The 12/09/2009 AIDAC strongly recommended that CABP non-inferiority trials should not allow effective prior antibacterial therapy, and the restriction to one dose of a short-acting drug in the 96 hours before randomization was employed for the purpose of these analyses. Results in the subgroup of subjects given no prior therapy were of interest as they did not depend on the definition of "effective prior antibiotics" or "short-acting" as shown in Table 6A.8

Table 6A.8 Clinical Cure Rates at TOC by Prior Therapy in the MITTE Population

Study P903-08	Ceftaroline	Ceftriaxone	Difference	95% CI
Prior Antibiotics	105/137 (76.6%)	112/143 (78.3%)	-1.7%	(-11.5%, 8.1%)
No Prior Antibiotics	139/154 (90.3%)	121/157 (77.1%)	13.2%	(5.1%, 21.4%)
Study P903-09	Ceftaroline	Ceftriaxone	Difference	95% CI
Prior Antibiotics	84/100 (84%)	94/117 (80.3%)	3.7%	(-6.8%, 13.8%)
No Prior Antibiotics	151/189 (79.9%)	112/156 (71.8%)	8.1%	(-0.9%, 17.3%)

In non-inferiority trials, a high degree of noncompliance or unevaluable data can make treatment arms appear similar and mask potential inferiority of the investigational product. The Applicant reported the results based on the CE Population (i.e., a per-protocol population), as it only included subjects who met all evaluability criteria. However, the results based on the CE population are also limited due to the post-randomization selection and lack of randomization protection. The reasons for exclusion from the CE Population are given in Table 6A.9. The exclusion rates were similar between the ceftaroline and ceftriaxone arms. Exclusions due to post-baseline factors were often due to incomplete assessments at the TOC visit (e.g., window violations), so results for the secondary EOT endpoint may have been more robust to problems related to unevaluable data than MITTE non-inferiority results at TOC.

Table 6A.9 Number of Subjects with Different Reasons for Exclusion from the CE Population

	Study P903-08		Study P903-09	
	Ceftaroline	Ceftriaxone	Ceftaroline	Ceftriaxone
Not in MITTE	14	9	37	66
Did not meet disease criteria	6	5	1	2
Exclusion criterion violation	2	2	1	2
Atypical as sole pathogen or *L. pneumophila*	39	34	39	77
Prior antibiotic violation	2	4	1	3
Unblinding	0	1	0	0
> 24 h of systemic antibiotic, not given for treatment failure	6	5	9	15
Less than 80% compliance	0	0	1	1
Indeterminate TOC response, not failure at EOT	15	9	12	20
Missing TOC assessment, not failure at EOT	4	2	1	3
TOC window violation	11	13	6	9
Dose not met[1]	20	11	16	25
Wrong study drug	1	0	0	0

[1] At least 48 hours of study drug to be an evaluable failure or at least 72 hours of study drug to be evaluable success.
Source:
P903-08, CSR, Table 10.1-2.
P903-09, CSR, Table 10.1-2.

Non-Inferiority Margin and Efficacy Review Issues

Studies P903-08 and P903-09 use a traditional investigator-assessed clinical response primary endpoint at a test-of-cure visit in a population without a confirmed bacterial etiology. Agency reviewers have not identified historical data which reliably demonstrates a large treatment effect for antibacterial therapy relative to placebo for such an endpoint. The Applicant's margin justification relied on data concerning an antibacterial treatment effect for mortality, but even if such a margin was justified, this would not imply that a margin could be extrapolated for clinical response at TOC.

Historical data may provide evidence for improvement in patient signs and symptoms at a time earlier than the test-of-cure following therapy. Evidence for and against an early clinical response endpoint was discussed at the 12/09/2009 meeting of AIDAC (Bullowa, 1937; Flippin et al., 1939; Meakins and Hanson, 1939; Wilson et al., 1939; Finland et al., 1940). We refer to this evidence when the terms "historical data" or "historical studies" are mentioned subsequently in this document. Even if the justification is valid for an early clinical response margin, the Agency reviewers considered it problematic to

extrapolate a margin for clinical response at an early time to one much later in the treatment course.

To address this issue, and examine whether the seemingly favorable results in the application could support efficacy in light of reservations about the endpoint, Agency reviewers conducted two additional analyses. First, because historical evidence of a treatment effect was in terms of clinical improvement early in the treatment course, the Agency reviewers considered results at an earlier time than the TOC or EOT. Based on recommendations of the 12/09/2009 AIDAC, this analysis was performed in a microbiologically-confirmed population.

In the second analysis, two CABP trials of daptomycin were reexamined to see if they could support a small non-inferiority margin for clinical response among subjects similar to those enrolled in the ceftaroline studies. The two clinical trials had shown daptomycin to be inferior to ceftriaxone, and it was later discovered that the drug could be partially deactivated by interaction with lung surfactant. A treatment effect for ceftriaxone relative to daptomycin could be considered conservative for the treatment effect of ceftriaxone relative to placebo, and such a treatment effect would provide indirect evidence for the efficacy of ceftaroline in the current submission.

FDA Sensitivity Analyses

Based on historical evidence of a treatment effect on objective clinical factors (such as fever, respiratory rate, and heart rate) at an earlier timepoint, FDA reviewers examined the evidence gathered in the completed trials that could be used to define an early clinical response efficacy endpoint. The population utilized for analysis was the microbiological ITT (FDA-mITT). However, use of a microbiologically-defined population for primary analysis markedly decreased the size of the population.

The inclusion criteria for enrollment in the trial required signs and symptoms consistent with pneumonia, chest radiograph confirmation of an infiltrate, and pneumonia of specified severity based on PORT Risk Class. Therefore the FDA-mITT population included randomized patients who received any amount of study therapy and had demonstration of a baseline pathogen as stated below:

- Patients with sputum specimens as the respiratory specimen for culture were required to have at least > 10 WBC/LPF and < 10 squamous epithelial cells (Applicant required only presence of WBCs and < 10 squamous cells).
- Patients with adequate sputum specimens as defined above or blood culture positive for the following organisms or positive urinary antigen for *S. pneumoniae* were included:

- *Streptococcus pneumoniae*
- *Haemophilus influenzae*
- *Moraxella catarrhalis*
- *Streptococus pyogenes*
- *Staphylococcus aureus*
- *Klebsiella pneumoniae*

Note: *Haemophilus parainfluenzae* was not considered to be a pathogen in the FDA population

- Patients with the following Gram-negative enteric organisms were included if the patient was classified as PORT III or greater, the sputum specimen was adequate as described above, or isolate was from another appropriate sample, such as brocheolar lavage or pleural fluid:

- *Citrobacter freundii* complex
- *Citrobacter koseri*
- *Enterobacter aerogenes*
- *Escherichia coli*
- *Klebsiella oxytoca*
- *Proteus mirabilis*
- *Serratia liquefaciens*
- *Serratia marcescens*

- FDA also included patients from whom *Legionella* spp. was identified in addition to a typical pathogen, while the Applicant excluded all subjects with *Legionella* from microbiological populations.

Table 6A.10 shows the baseline demographics for the FDA-mITT population.

Table 6A.10: Baseline demographics for the FDA microbiologic (FDA-mITT) population

	Study P903-08		Study P903-09	
	Ceftaroline	Ceftriaxone	Ceftaroline	Ceftriaxone
Total Subjects	69	72	85	83
Age				
< 65	30 (43)	39 (54)	54 (64)	50 (60)
≥ 65	39 (57)	33 (46)	31 (36)	33 (40)
< 75	50 (72)	52 (72)	68 (80)	71 (86)
≥ 75	19 (28)	20 (28)	17 (20)	12 (14)
PORT Risk Class				
I	0 (0)	0 (0)	1 (1)	0 (0)
II	0 (0)	1 (1)	8 (9)	10 (12)
III	46 (67)	39 (54)	38 (45)	43 (52)
IV	23 (33)	31 (43)	38 (45)	30 (36)
V	0 (0)	1 (1)	0 (0)	0 (0)
Bacteremia				
Yes	8 (12)	10 (14)	15 (18)	11 (13)
No	61 (88)	62 (86)	70 (82)	72 (87)
Region				
Africa	3 (4)	4 (6)	0 (0)	0 (0)
Asia	2 (3)	4 (6)	1 (1)	0 (0)
Eastern Europe	51 (74)	45 (62)	63 (74)	58 (70)
Latin America	3 (4)	4 (6)	20 (24)	23 (28)
North America	2 (3)	3 (4)	0 (0)	0 (0)
Western Europe	8 (12)	12 (17)	1 (1)	2 (2)
Lung Disease				
Yes	17 (25)	14 (19)	26 (31)	27 (33)
No	52 (75)	58 (81)	59 (69)	56 (67)
Smoking History				
Yes	42 (61)	39 (54)	44 (52)	55 (66)
No	27 (39)	33 (46)	41 (48)	28 (34)
Abnormal Signs				
Temperature	57 (83)	58 (81)	51 (60)	60 (72)
Heart Rate	32 (46)	32 (44)	40 (47)	37 (44)
Respiratory Rate	41 (59)	41 (57)	48 (57)	51 (62)
Systolic BP	4 (6)	11 (15)	12 (14)	14 (17)
Oxygen Saturation	16 (23)	19 (26)	30 (35)	19 (23)
Symptoms Present				
Cough	68 (99)	72 (100)	84 (99)	81 (98)
Dyspnea	53 (77)	57 (79)	73 (86)	69 (83)
Chest Pain	44 (64)	44 (61)	65 (76)	48 (58)
Sputum Production	64 (93)	63 (88)	71 (83)	76 (92)
Confusion	0 (0)	5 (7)	4 (5)	2 (2)
Source: FDA reviewer.				

The baseline characteristics of the FDA-mITT population were similar to those of the MITTE population used as the primary efficacy analysis population by the Applicant. Bacteremia was more common in the FDA-mITT population, although positive blood culture could be the reason for inclusion.

Primary Efficacy Endpoint Determination

The historical data concerning treatment effects for antibiotics supported the conclusion that patient signs and symptoms improved dramatically after a few days if antibiotic therapy was given. Finland et al. (1940) provided estimates of treatment effect for symptom resolution at 48-72 hours after therapy. Bullowa (1939), Flippin et al. (1939), and Meakins and Hanson (1939) gave estimates of a treatment effect for clinical recovery at Day 3 of therapy. Wilson et al. (1939) provided estimates of a treatment effect for mean days to clinical improvement, fall in temperature, and clinical recovery, which respectively were 2.5, 3.4, and 4.2 days.

In its sensitivity analysis, the Agency reviewers used an endpoint defined at Day 4, which was 72-96 hours after the first dose of the study drug. For most subjects, this was halfway through their duration of therapy. The Agency reviewers considered Day 4 to be in line with where the historical evidence showed the existence of a treatment effect.

In defining the Day 4 endpoint, the Agency reviewers used a definition that combined sign and symptom measurements taken at this time. However, Study P903-08 and Study P903-09 had no overall clinician assessment of patient well-being until the EOT, which for most subjects occurred on Day 7. Therefore, the Agency reviewers defined the sensitivity analysis endpoint directly in terms of the sign and symptom measurements available at Day 4 from the patient case report forms (CRFs). The Agency reviewers were not considering the endpoint to be a surrogate for the unavailable early clinician assessment, but rather a direct measure of patient well-being.

The Agency reviewers' primary sensitivity analysis was to examine the Day 4 signs and symptoms endpoint in the FDA-mITT population. Similar to the Applicant's primary analyses, a two-sided 95% CI for the observed difference in response rates (ceftaroline - ceftriaxone) was constructed using the method of Miettinen and Nurminen with noninferiority concluded if the lower limit of the 95% CI was greater than –10%.

The Agency reviewers' endpoint required subjects to fulfill two criteria:

1. Clinical stability as defined by the Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS) Consensus Guidelines for the Management of Community-Acquired Pneumonia in Adults. The IDSA/ATS criteria for clinical stability, primarily determined by vital signs, were as follows:
   - Temperature $\leq$ 37.8°C, measured orally, rectally, or tympanically
   - Heart rate $\leq$ 100 beats/min
   - Respiratory rate $\leq$ 24 breaths/min
   - Systolic blood pressure $\geq$ 90 mm Hg
   - Oxygen saturation $\geq$ 90%
   - Normal mental status

   The IDSA/ATS definition also required the ability to maintain oral intake, and involved oxygen partial pressure in addition to oxygen saturation, but these were not captured on CRFs at Day 4. The Agency defined normal mental status as

confusion/disorientation being recorded as absent. These clinical stability criteria were originally proposed as a guide for determining whether discharge or a switch to oral therapy were acceptable for CABP patients, and were based on time-to-stability studies of Halm et al. (1998). Ninety five percent of mITT subjects in each study were abnormal at baseline according to the IDSA/ATS criteria.

2. Symptom improvement criteria involving four components:
   - Cough
   - Dyspnea
   - Pleuritic chest pain
   - Sputum production

   All mITT subjects had at least one of the four symptoms present at baseline. To be classified as a responder at Day 4, a subject had to have improved from baseline on at least one of the four components, and could not have worsened on any of the four components. For cough, dyspnea, and chest pain, this was determined through the recordings of whether these symptoms were absent, mild, moderate, or severe at baseline and on Day 4. For sputum, worsening or improvement was determined first by examining from recorded investigator assessments whether sputum was present or absent at baseline and at Day 4, and if present on both days, then whether its character was recorded as being worsened, unchanged, or improving from baseline. Additionally, all subjects who had their EOT visit on Day 4 or earlier were classified as failures in the Agency reviewers' endpoint; these subjects were also classified by the investigator as clinical failures.

Table 6A.11 shows results for the FDA reviewers' analysis using the Day 4 signs and symptoms endpoint in the mITT Population. Although sample sizes were small, and confidence intervals for differences in response rates were consequently wide, the sensitivity analysis results provided evidence of efficacy, as ceftaroline met the 10% non-inferiority margin in both studies.

Table 6A.11 Responder Rates for Day 4 Signs and Symptoms Endpoint, mITT Population

Day 4 Endpoint	Ceftaroline	Ceftriaxone	Difference	95% CI
Study P903-08	48/69 (71.0%)	42/72 (58.3%)	11.2%	(-4.6%, 26.5%)
Study P903-09	58/85 (68.2%)	51/83 (61.4%)	6.8%	(-7.6%, 21.0%)
Source: FDA Reviewer.				

The Agency reviewers recognize that defining an endpoint in terms of these signs and symptoms is problematic for several reasons. First, the recording of the sign and symptom information by investigators was not standardized, in terms of how many times per day they were measured, or when the information was recorded. Also, the investigators' evaluations of whether symptoms were absent, mild, moderate, or severe were subjective. Thus, differences between patients in the sign and symptom measurements could have been due to differences between investigators rather than differences in patient well-being. This subjectivity and variation in measurement is

considered more problematic in non-inferiority trials than in superiority trials as it can artificially make the treatment effect appear similar between the two groups. Also, while the historical data concerned resolution of fever, and fall in pulse and respiratory rates, no algorithmic combination of the Day 4 signs and symptoms would have precisely corresponded to measures discussed in these historical studies. Another concern with vital signs was that they did not necessarily directly capture patient feeling, function, or survival. Finally, a concern with these signs and symptoms in non-inferiority studies was that many of them could have been influenced by concomitant therapy. For instance, temperature could have been affected by antipyretic use, or oxygen saturation by supplemental oxygen. This was true for symptoms as well as vital signs, because drugs like codeine could have suppressed cough or chest pain, while mucolytics could have been given for sputum production, or nebulizers for dyspnea.

The FDA-mITT analysis population was also assessed with the Applicant-defined primary efficacy endpoint (clinical response at TOC) and secondary efficacy endpoint (clinical response at EOT). The results are shown in Table 6A.12.

Table 6A.12: Investigator-Assessed Clinical Response in the FDA-mITT Population

Study P903-08	Ceftaroline	Ceftriaxone	Difference	95% CI
EOT	60/69 (87.0%)	53/72 (73.6%)	13.3%	(0.2%, 26.4%)
TOC	60/69 (87.0%)	51/72 (70.8%)	16.1%	(2.7%, 29.3%)
Study P903-09	Ceftaroline	Ceftriaxone	Difference	95% CI
EOT	70/85 (82.4%)	66/83 (79.5%)	2.8%	(-9.2%, 14.9%)
TOC	67/85 (78.8%)	64/83 (77.1%)	1.7%	(-10.9%, 14.4%)
Source: FDA Reviewer.				

Clinical response rates assessed by the investigator were higher than those assessed at the early endpoint for the FDA-mITT analysis population. Clinical response at TOC in Study P903-08, in which patients received 24 hours of adjunctive macrolide therapy, continued to be higher in the ceftaroline treatment group versus the comparator treatment group. Although the clinical response rate at TOC continued to favor the ceftaroline treatment group in Study P903-09, the magnitude of the treatment difference has considerably decreased.

Table 6A.13 below shows results by pathogen in the FDA-mITT population using the Day 4 signs and symptoms endpoint. Ceftaroline success rates were higher than ceftriaxone rates for *S. pneumoniae*, and the numbers were too small for other pathogens to notice any differences.

Table 6A.13: Day 4 Sign and Symptom Response Rates by Pathogen, FDA mITT Population

	Study P903-08		Study P903-09	
	Ceftaroline	Ceftriaxone	Ceftaroline	Ceftriaxone
C. freundii complex	0/0	0/0	0/0	2/2 (100)
C. koseri	0/1 (0)	0/1 (0)	1/1 (100)	0/0
E.aerogenes	0/0	0/0	1/1 (100)	1/1 (100)
E. cloacae	6/6 (100)	4/7 (57)	2/2 (100)	3/4 (75)
E.coli	3/8 (38)	5/6 (83)	1/4 (25)	4/7 (57)
H. influenzae	5/6 (83)	10/13 (77)	11/14 (79)	10/15 (67)
K. oxytoca	3/3 (100)	4/4 (100)	3/3 (100)	2/2 (100)
K. pneumoniae	8/9 (89)	1/3 (33)	6/9 (67)	5/8 (62)
M. catarrhalis	0/1 (0)	1/1 (100)	1/3 (33)	1/2 (50)
P. mirabilis	1/1 (100)	0/0	1/2 (50)	0/0
S. liquefaciens	0/0	1/1 (100)	0/0	0/0
S. marcescens	2/3 (67)	1/2 (50)	0/0	1/1 (100)
S. aureus	4/9 (44)	5/15 (33)	10/15 (67)	11/16 (69)
S.pneumoniae	19/27 (70)	17/32 (53)	34/47 (72)	25/43 (58)
S. pyogenes	0/0	0/0	0/0	1/1 (100)
Source: FDA Reviewer.				

The Day 4 FDA-mITT analysis was also performed by prior antibiotic use. However, the FDA-mITT population was already small enough so that subgroup analysis had too much uncertainty to be meaningful.

Table 6A.14: Day 4 Signs and Symptoms Results by Prior Therapy, FDA-mITT Population

Study P903-08	Ceftaroline	Ceftriaxone	Difference	95% CI
Prior Antibiotics	21/30 (70%)	21/37 (56.8%)	13.2%	(-10.1%, 34.8%)
No Prior Antibiotics	27/39 (69.2%)	21/35 (60%)	9.2%	(-12.4%, 30.3%)
Study P903-09	Ceftaroline	Ceftriaxone	Difference	95% CI
Prior Antibiotics	20/27 (74.1%)	17/31 (54.8%)	19.2%	(-5.6%, 41.6%)
No Prior Antibiotics	38/58 (65.5%)	34/52 (65.4%)	0.1%	(-17.4%, 17.8%)
Source: FDA Reviewer.				

Robustness of Efficacy Results

Although the Agency reviewers' main sensitivity analysis result supported the efficacy of ceftaroline, the analysis was not conclusive, because the choice of an analysis population and endpoint was not straightforward. Several committee members of the 12/09/2009 AIDAC voiced concerns about whether historical data supported an early clinical response endpoint based on signs and symptoms, and these concerns would also have applied to the Agency reviewers' sensitivity analysis. Even if it could have been agreed that the data supported a margin for clinical response, the Agency reviewers' signs and symptoms endpoint involved several arbitrary choices and cutoffs. To examine the robustness of the evidence using sensitivity analysis, the Agency reviewers considered results when modifications were made to the following:

- The definition of the endpoint in terms of different signs and symptoms. Results were examined when using the IDSA/ATS clinical stability definition and symptom resolution definition separately for the responder analysis.

Table 6A.15: Day 4 FDA-mITT Results, Separately for Clinical Stability and Symptom Resolution

Study P903-08	Ceftaroline	Ceftriaxone	Difference	95% CI
Clinical Stability	49/69 (71.0%)	44/72 (61.1%)	9.9%	(-5.8%, 25.1%)
Symptoms	66/69 (95.7%)	63/72 (87.5%)	8.2%	(-1.2%, 18.4%)
Study P903-09	Ceftaroline	Ceftriaxone	Difference	95% CI
Clinical Stability	62/85 (72.9%)	56/83 (67.5%)	5.5%	(-8.4%, 19.2%)
Symptoms	75/85 (88.2%)	69/83 (83.1%)	5.1%	(-5.7%, 16.1%)
Source: FDA Reviewer.				

- The timing of the early assessment. Results for the signs and symptoms endpoint were examined at Day 3 and at the EOT.

Table 6A.16: Day 3 and EOT Results for FDA-mITT Signs and Symptoms Endpoint

Study P903-08	Ceftaroline	Ceftriaxone	Difference	95% CI
Day 3	35/69 (50.7%)	30/72 (41.7%)	9.1%	(-7.4%, 25.0%)
EOT	59/69 (85.5%)	55/72 (76.4%)	9.1%	(-4.0%, 22.1%)
Study P903-09	Ceftaroline	Ceftriaxone	Difference	95% CI
Day 3	48/85 (56.5%)	47/83 (56.6%)	-0.2%	(-15.0%, 14.7%)
EOT	66/85 (77.6%)	65/83 (78.3%)	-0.7%	(-13.3%, 12.0%)
Source: FDA Reviewer.				

- The definition of the analysis population. Results for the Day 4 responder analysis were examined using the Applicant's co-primary MITTE and CE and the Applicant's microbiological population (mMITT) were used, instead of the reviewer-defined FDA-mITT population.

Table 6A.17: Day 4 Signs and Symptoms for MITTE, CE, and mMITT Populations

Study P903-08	Ceftaroline	Ceftriaxone	Diff	95% CI
MITTE	194/291 (66.7%)	184/300 (61.3%)	5.3%	(-2.4%, 13.0%)
CE	150/224 (67.0%)	145/234 (62.0%)	5.0%	(-3.8%, 13.7%)
mMITT	54/75 (72.0%)	53/82 (64.6%)	7.4%	(-7.3%, 21.6%)
Study P903-09	Ceftaroline	Ceftriaxone	Diff	95% CI
MITTE	194/289 (67.1%)	165/273 (60.4%)	6.7%	(-1.3%, 14.6%)
CE	165/235 (70.2%)	137/215 (63.7%)	6.5%	(-2.2%, 15.1%)
mMITT	66/99 (66.7%)	64/102 (62.7%)	3.9%	(-9.3%, 17.0%)
Source: FDA Reviewer.				

These analyses showed that non-inferiority results were relatively robust to the choice of endpoint, timing of the assessment, and analysis population, although a 10% non-

inferiority margin would not have been met in Study P903-09 if the assessment had been at Day 3 or the EOT rather than Day 4.

Non-Inferiority Margin Examination Using Daptomycin Studies

Although historical evidence suppporting a 10% non-inferiority margin for a clinical response endpoint at test-of-cure has not been identified, the Agency reviewers conducted a posthoc assessment of whether a small margin could be empirically justified. Placebo-controlled trials are considered unethical for CABP, but two recent trials compared ceftriaxone to daptomycin, which was later shown to be deactivated by interaction with lung surfactant (Pertel et al., 2008). As daptomycin may have had some activity, the Agency reviewers considered it as a substitute for a placebo arm that would be conservative in determining an effect size.

The daptomycin trials (DAP-00-05 and DAP-CAP-00-08) had similar protocols to the ceftaroline trials. They were conducted from 2000-2001, so were more recent than the observational studies from before 1940 that have previously been cited in the discussion of CABP non-inferiority margins. The daptomycin trials were randomized, double-blind, multinational studies of subjects aged 18 years or older, with pneumonia requiring at least five days of intravenous therapy. Subjects were required to have pneumonia confirmed radiographically, and the required symptoms for inclusion were similar to those in the ceftaroline trials. Subjects with PORT Risk Class V at baseline were excluded. The primary endpoint was an assessment of clinical cure at a test-of-cure 7-14 days after completing treatment, with cure defined as the absence of clinically significant symptoms or improvement such that no additional therapy was required. The ITT Population was defined as all subjects who received any study drug. The daptomycin trials were therefore similar to the ceftaroline trials in terms of analysis populations and endpoints. The main differences were that more PORT Risk Class I and II subjects were enrolled in the daptomycin trials (around 40% of ITT subjects), there were fewer restrictions on long-acting prior antibiotics, and aztreonam was often given as adjunctive therapy.

The primary analysis in the ceftaroline trials was based upon subjects in Risk Class III-IV who were only allowed one dose of a short-acting prior antimicrobial in the 96 hours prior to study drug administration. This was the subgroup of patients in whom the daptomycin data was analyzed. Table 6A.18 shows the antibiotics allowed and disallowed in the ceftaroline trials.

Table 6A.18: Allowed Prior Antibiotics in Ceftaroline Studies (One Dose in Prior 96 Hours)

Antibiotics Allowed	Antibiotics Disallowed
Cephalosporins	
Cefaclor, Cefadroxil, Cefdinir, Cefepime, Cefixime (200 mg), Cefotaxime, Cefpodoxime, Cefprozil, Ceftazidime, Ceftibuten, Cefditoren, Cefruoxime, Cephalexin, Loracarbef	Cefixime (400 mg), Ceftriaxone
Fluoroquinolones	
Ciprofloxacin, Norfloxacin	Gatifloxacin, Gemifloxacin, Grepafloxacin, Levofloxacin, Moxifloxacin, Sparfloxacin
Macrolides and Ketolides	
Clarithromycin, Erythromycin, Roxithromycin	Azithromycin, Clarithromycin XL (extended release), Dirithromycin, Telithromycin
Penicillins and Carbapenems	
Amoxicillin, Amoxicillin-Clavulanate, Amoxicillin-Sulbactam, Ampicillin, Ampicillin-Sulbactam, Dicloxacillin, Imipenem, Meropenem, Nafcillin, Oxacillin, Penicillin-G, Penicillin-V, Piperacillin, Piperacillin-Tazobactam, Ticarcillin-Clavulanate	Ertapenem, Penicillin-G, Benzathine/Procaine
Tetracyclines	
Doxycycline (100 mg), Minocycline, Tetracycline	Doxycycline (200 mg), Minocycline Extended Release
Other Antibiotics	
Clindamycin, Co-trimoxazole	

For the analyses performed using daptomycin data, any drug that would be allowed for ceftaroline subjects (e.g., clarithromycin) was not considered long-acting, while drugs that were disallowed (e.g., azithromycin, levofloxacin, ceftriaxone) were considered long-acting. Some drugs administered in the daptomycin trials that can treat CABP were not explicitly identified as being allowed or disallowed in the ceftaroline studies. Of these, the Agency reviewers only considered lincomycin to be a long-acting drug. Drugs not explicitly allowed or disallowed in the ceftaroline trials that were considered short-acting included cephalexin, cefazolin, ceftizoxime, and ofloxacin, because these would not be considered longer-acting than drugs allowed in the ceftaroline studies. The following tables show results in the two daptomycin studies by PORT Risk Class and prior antibiotic use.

Table 6A.19: Clinical Cure Rates in DAP-00-05, ITT Population

	Daptomycin	Ceftriaxone	Diff	95% CI
All Risk Classes				
All subjects	231/326 (70.9%)	258/335 (77.0%)	-6.2%	(-12.8%, 0.5%)
No long-acting prior therapy	179/248 (72.2%)	212/261 (81.2%)	-9.0%	(-16.4%, -1.7%)
No prior therapy	111/155 (71.6%)	142/173 (82.1%)	-10.5%	(-19.6%, -1.4%)
Risk Class III-IV				
All subjects	131/192 (68.2%)	128/175 (73.1%)	-4.9%	(-14.1%, 4.4%)
No long-acting prior therapy	**101/145 (69.7%)**	**103/130 (79.2%)**	**-9.6%**	**(-19.7%, 0.8%)**
No prior therapy	67/95 (70.5%)	68/84 (81.0%)	-10.4%	(-22.7%, 2.3%)
Source: FDA Reviewer.				

Table 6A.20: Clinical Cure Rates in DAP-00-08, ITT Population

	Daptomycin	Ceftriaxone	Diff	95% CI
All Risk Classes				
All subjects	62/87 (71.3%)	68/86 (79.1%)	-7.8%	(-20.6%, 5.1%)
No long-acting prior therapy	57/80 (71.2%)	58/76 (76.3%)	-5.1%	(-18.7%, 8.8%)
No prior therapy	43/66 (65.2%)	48/61 (78.7%)	-13.5%	(-28.6%, 2.2%)
Risk Class III-IV				
All subjects	33/55 (60.0%)	50/61 (82.0%)	-22.0%	(-37.7%, -5.6%)
No long-acting prior therapy	**30/50 (60.0%)**	**42/53 (79.2%)**	**-19.2%**	**(-36.1%, -1.5%)**
No prior therapy	21/41 (51.2%)	33/40 (82.5%)	-31.3%	(-49.3%, -11.1%)
Source: FDA Reviewer.				

In order to justify a non-inferiority margin, the Agency reviewers combined the trials using meta-analysis methods to estimate the treatment effect of ceftriaxone. Table 6A.21 shows estimated treatment effects and confidence intervals when using the Dersimonian and Laird random effects model.

Table 6A.21: Meta-Analysis of Clinical Cure Rates in DAP-00-05 and DAP-00-08

	Daptomycin - Ceftriaxone	95% CI
All Risk Classes		
All subjects	-6.5%	(-12.4%, -0.6%)
No long-acting prior therapy	-8.1%	(-14.6%, -1.7%)
No prior therapy	-11.3%	(-19.1%, -3.4%)
Risk Class III-IV		
All subjects	-12.1%	(-28.6%, 4.4%)
No long-acting prior therapy	**-12.1%**	**(-20.1%, -3.2%)**
No prior therapy	-19.5%	(-39.8%, 0.8%)

For subjects in PORT Risk Class III-IV given no long-acting prior antibiotics, the estimated difference in clinical cure rates between daptomycin and ceftriaxone was -12.1%, with a 95% confidence interval of (-20.1%, -3.2%). Based on the upper limit of

this confidence interval, the Agency reviewers concluded that the daptomycin trials may provide evidence of a treatment effect (M1) of ~3% for the clinical response endpoint. A fraction of M1 would need to be preserved based on clinical judgment to derive the NI margin, e.g. 50% preservation would result in an NI margin of 1.5%. While this M1 estimate is relatively small, one could justify an NI margin with up to 66% preservation of the treatment effect and still provide enough of a buffer for the prespecified MITTE and CE ceftaroline analysis to demonstrate efficacy.

However, there were serious concerns in trying to use the daptomycin data to justify a margin. First, this was an attempted posthoc justification performed by the Agency reviewers, and non-inferiority trials traditionally require an appropriate margin justification as part of the protocol. Further, the idea to examine daptomycin subjects without long-acting prior therapy was based on the posthoc subgroup analysis in Pertel et al. (2008), and such analyses are best considered exploratory. Also, the 3% margin that resulted was small, and large NI margins are considered more robust to uncertainties in the justification process. Given the concerns with this analysis, the Agency reviewers considered the daptomycin trials to be weak but supportive evidence for the efficacy of ceftaroline.

In summary, Study P903-08 and Study P903-09 each met prespecified efficacy endpoints, and showed trends favoring ceftaroline over ceftriaxone for the treatment of CABP. The prespecified primary endpoint was clinical response at TOC. Historical evidence which supports a 10% NI margin for a clinical response endpoint at TOC has not been identified to date. Agency reviewers consequently performed a sensitivity analysis examining a Day 4 endpoint defined by signs and symptoms in a population that included only subjects with confirmed baseline CABP pathogens. This analysis supported the efficacy conclusions of the Applicant's prespecified analyses, in spite of the fact that sample sizes suggested the sensitivity analysis may be underpowered. The Agency reviewers also conducted a posthoc examination of whether daptomycin trials can empirically justify a (small) clinical response non-inferiority margin for PORT Risk Class III-IV subjects given no long-acting prior antibiotics; this analysis provided supportive evidence for the clinical response endpoint at TOC.

B. Complicated Skin and Skin Structure Infections (cSSSI)

The two Phase 3 cSSSI clinical trials (P903-06 and P903-07) were multicenter, multinational, randomized, double-blind, active comparator controlled trials comparing ceftaroline fosamil and vancomycin + aztreonam in adult subjects with cSSSI requiring initial treatment with an IV antimicrobial agent in a hospital or urgent care setting. The two trials were of the same design. Patients in both trials were treated with ceftaroline 600 mg IV q 12 hr or vancomycin 1 g IV q 12 hr plus aztreonam 1 g IV q12 hr for treatment duration of 5-14 days.

Ceftaroline was administered as a 600 mg infusion over one hour, followed by a saline placebo infusion over one hour on a q 12 hr schedule, with dose adjustment for moderate renal impairment (defined as calculated CrCl > 30 and ≤ 50 mL/min) to a 400 mg

infusion of ceftaroline over one hour, followed by the IV saline placebo over 1 hr on a q 12 hr schedule. Patients in the vancomycin + aztreonam treatment group received a 1 g infusion of vancomycin over 60 minutes and a 1 g infusion of aztreonam over 60 minutes on a q 12 hr schedule, with a dose of adjustment of vancomycin for moderate renal impairment to ≤ 1 g IV q 24 hr per local guidelines. Vancomycin dosing adjustment was also made for high body weight.

To be enrolled in the trial, patients were required to have:

- Skin and skin structure infection that met EITHER of the following criteria:
  - Involves deeper soft tissue or requires significant surgical intervention, such as a wound infection (surgical or traumatic), a major abscess, an infected ulcer, or deep and extensive cellulitis
    - "Deeper soft tissue" is defined as subdermal tissue, including subcutaneous fat; for example, extension of infection to muscle or fascia constitutes evidence of deeper soft tissue involvement
    - "Significant surgical intervention" is defined as a major operative procedure, not including commonly performed minor procedures such as incision and drainage of minor abscesses performed at the bedside, suture removal, needle aspiration, superficial debridement of devitalized tissue, or routine wound care
    - "Wound infection" is defined by the presence of either purulent/seropurulent discharge from the surgical/traumatic wound or greater than or equal to 5 cm of erythema (i.e. cellulitis) surrounding the wound margin. Onset must have occurred within 7 days prior to randomization and no later than 30 days following the trauma or surgical procedure.
    - "Abscess" is defined by the presence of a loculated fluid collection with greater than or equal to 2 cm of erythema (i.e. cellulitis) extending from the abscess margin and onset within 7 days prior to randomization. A "major abscess" either extends to deeper soft tissue or requires significant surgical intervention
    - "Cellulitis" is defined by the presence of advancing erythema, edema, and heat with onset within 7 days prior to randomization. "Deep and extensive cellulitis" involves deeper soft tissue and has a surface area of greater than or equal to 10 cm^2.

  OR

  - Cellulitis or abscess on lower extremity which occurs in subjects with diabetes mellitus or well-documented peripheral vascular disease (PVD). NOTE: Subjects with a history of diabetes mellitus must be taking insulin, insulin analogues, or oral hypoglycemic agents to be eligible for the study. "Well documented PVD" is defined as arterial or venous vascular disease resulting in ischemia of the lower extremity as manifest by ulceration, poor wound healing, or the absence of readily palpable dorsalis pedis and posterior tibial pulses.
- Three or more of the following clinical signs:
  - Purulent or seropurulent drainage or discharge
  - Erythema
  - Fluctuance
  - Heat or localized warmth

- Pain or tenderness to palpation
- Fever greater than 38°C oral (>38.5°C rectally or tympanically) or hypothermia (<35°C)
- White blood cell count greater than 10,000/mm^3
- Geater than 10% immature neutrophils (bands) irrespective of WBC count

- Patients were required to be hospitalized or treated in an urgent care center and require initial treatment with an IV antimicrobial agent for a minimum of 5 days.

Important exclusion criteria included:

- More than 24 hrs of treatment with an antimicrobial agent (other than a topical) within 96 hours leading up to randomization
  - EXCEPTION: Subjects may be eligible if they meet BOTH of the following conditions:
    - Clinical evidence of treatment failure following at least 48 hrs of prior systemic antimicrobial therapy

    AND
    - Microbiological evidence of failure including either:
      - Gram stain of purulent discharge, revealing white blood cells, and at least one potential pathogen (e.g. gram-postivie cocci in clusters) from the cSSSI site obtained at least 48 hr after the first dose of a prior systemic, antimicrobial (i.e. therapy administered prior to randomization

      OR
      - Isolation of an organism resistant in vitro to the prior systemic antimicrobial therapy at any time after initiation of such drug therapy
- Skin and skin structure infection with ANY of the following characteristics (partial list):
  - Diabetic foot ulcer or ulcer associated with PVD that has the following characteristics: accompanied by osteomyelitis, likely to require amputation with 60 days, likely to require revascularization within 60 days
  - Human or animal bites
  - Rapidly necrotizing process
  - Gangrene
  - Infection site complicated by presence of prosthetic materials
- Severe renal impairment (CrCl ≤ 30 mL/min).

Baseline clinical and microbiological assessments were performed within the 24 hours prior to initiation of study therapy. Clinical assessment included medical history, prior and concomitant medications, and physical examination, including evaluation of the cSSSI site, measurement of the width and length of the skin infection in centimeters with a ruler, and all signs and symptoms of infection. Microbiological assessment included collection of an appropriate specimen for gram stain and culture and blood for microbiological culture. The types of specimen varied depending on type of infection; for cellulitis, a leading edge needle aspirate or punch biopsy and other cSSSI, deep specimen biopsy or needle aspiration or surgically obtained tissue, fluid, or pus physically contiguous with ulcer or wound. Superficial swabs were specified as unacceptable.

Patients had daily clinical assessments while on study therapy; information recorded at these assessments included resting vital signs (heart rate, blood pressure, and respiratory temperature), maximum temperature for the preceding 24 hour period, measurement of infection site width and length, and assessment of clinical signs and symptoms of cSSSI (i.e. depth of involvement, swelling, tenderness, warmth, fluctuance, discharge, and associated pathological signs like bullae, ulceration, and necrosis). Overall characteristics of the lesion (e.g. improved, worsened, unchanged) as assessed by the investigator were captured on Days 3, 7, 10. An End-of-Therapy (EOT) visit was performed following the last dose of study drug (up to Day 14), a Test-of-Cure (TOC) visit 8-15 days after the last dose of study drug, and late follow-up (LFU) visit 21-35 days after the last dose of study drug. In addition to clinical evaluation at these visits, safety laboratories and a skin infection site specimen (if indicated) were obtained.

The primary efficacy endpoint was the per-subject clinical response (cure) rate assessed by the investigator at the TOC visit.

- Clinical cure was defined as total resolution of all signs and symptoms of cSSSI or improvement to such an extent that further antimicrobial therapy was not necessary.
- Clinical failure was defined as any of the following:
  - Persistence, incomplete clinical resolution, or worsening of signs or symptoms of CAP requiring alternative antimicrobial therapy
  - A surgical intervention that was performed as an adjunct or followup therapy due to failure of the study drug to adequately treat the infections. Minor surgical interventions conducted at the bedside and considered standard adjunctive therapy to appropriate antimicrobial therapy, surgical interventions on SSSI lesions other than the index lesion, surgeries not related to cSSSI, or execution of planned surgical interventions did not constitute evidence of study drug failure.
  - New signs and symptoms associated with the original cSSSI or a new cSSSI at the same anatomical site
  - Subject required alternative antimicrobial therapy to treat the cSSSI, including oral step-down therapy
  - Treatment limiting adverse event leading to study treatment discontinuation when alternative antimicrobial agent to treat the cSSSI is necessary
  - Diagnosis of osteomyelitis 8 or more days after randomization
  - Death due to cSSSI
- Indeterminate outcome was defined as study data not available for evaluation of efficacy, for reasons including treatment change before completing 48 hrs of therapy, death where cSSSI was clearly non-contributory, loss to follow-up, or extenuating circumstances.

Although the primary efficacy endpoint assessment was performed at TOC, a similar assessment occurred at EOT and was considered to be an important secondary endpoint.

The primary objective was to determine the non-inferiority of ceftaroline fosamil treatment compared to vancomycin + aztreonam treatment in adult subjects with cSSSI based on the difference in clinical cure rates (ceftaroline – vancomycin + aztreonam) at TOC, using a non-inferiority margin of 10%. The Agency had requested that the Applicant provide justification for this margin at the End of Phase 2 meeting, October 24,

2006; Cerexa responded to this request with a submission to IND 71,371 (November 30, 2006), providing a review of historical evidence of sensitivity of skin infections to antimicrobial effect, outlining design elements to ensure that only patients with complicated skin and skin structure infections are enrolled, and defined a margin based on a "putative placebo effect." Justification for this NI margin was primarily based upon natural history descriptions from the pre-antibiotic era, as well as when antibiotics became available but were in limited supply.

The Applicant defined the following analysis populations:

- ITT (Intent-to-Treat): All randomized subjects.
- MITT (Modified Intent-to-Treat): All randomized subjects who received any amount of study drug.
- cMITT (Clinical Modified Intent-to-Treat Efficacy): All MITT subjects who met minimal disease criteria.
- mMITT (Microbiological Modified Intent-to-Treat): All subjects in the cMITT Population who had at least one bacterial organism consistent with a cSSSI pathogen identified from a baseline microbiological specimen.
- CE (Clinically Evaluable): All subjects in the cMITT Population who met the inclusion criteria for cSSSI and all evaluability criteria, including subjects who received at least the prespecified minimal amount of the intended dose and duration of study drug therapy, for whom sufficient information regarding the infection was available to determine the outcome.
- ME (Microbiologically Evaluable): All subjects in both the mMITT and CE Populations.

The analysis populations focused on in this document are the MITT and CE populations which were pre-specified as the co-primary efficacy analysis populations by the Applicant and agreed to by the FDA.

Trial Results

Since these clinical trials were designed and conducted prior to the 2008 AIDAC discussion about the use of a non-inferiority study design for this indication, the Applicant provided results based on their pre-specified analysis plan. This section includes results of the Applicant's analyses, as well as additional FDA reviewer analyses based on ongoing review and interpretation of the scientific literature.

Patient Disposition

Study P903-06 was conducted from February 2007 to November 2007. In Study P903-06, there were 353 patients randomized to the ceftaroline treatment group and 349 patients to the vancomycin + aztreonam groups; 351 and 347 patients in the ceftaroline and vancomycin + aztreonam group, respectively, received any study treatment. Study P903-07 was conducted from March 2007 to December 2007. In Study P903-07, there were 348 patients randomized to the ceftaroline treatment group and 346 to the vancomycin +

aztreonam group; 342 and 338 patients received any study drug in the ceftaroline and vancomycin treatment groups, respectively.

Baseline Characteristics

Table 6B.1 below shows baseline demographic and medical characteristics of the Applicant's MITT populations for Studies P903-06 and P903-07.

Table 6B.1: Baseline Characteristics, Applicant's MITT Population

	Study P903-06		Study P903-07	
	Ceftaroline N=351	Vancomycin + Aztreonam N=347	Ceftaroline N=342	Vancomycin + Aztreonam N=338
Gender				
Male	220 (62.7)	218 (62.8)	224 (65.5)	201 (59.5)
Female	131 (37.3)	129 (37.2)	118 (34.5)	137 (40.5)
Race				
White	263 (74.9)	261 (75.2)	246 (71.9)	254 (75.1)
Black	15 (4.3)	22 (6.3)	33 (9.6)	21 (6.2)
Asian	6 (1.7)	4 (1.2)	3 (0.9)	1 (0.3)
Other	70 (19.9)	64 (18.4)	60 (17.5)	62 (18.3)
Age				
Age ≤ 65 years	294 (83.8)	275 (79.3)	281 (82.2)	291 (86.1)
Age > 65 years	57 (16.2)	72 (20.7)	61 (17.8)	47 (13.9)
Age ≤ 75 years	329 (93.7)	321 (92.5)	318 (93.0)	319 (94.4)
Age > 75 years	22 (6.3)	26 (7.5)	24 (7.0)	19 (5.6)
Region				
Eastern Europe[1]	170 (48.4)	171 (49.3)	136 (39.8)	134 (39.6)
Latin America	31 (8.8)	28 (8.1)	25 (7.3)	25 (7.4)
US	133 (37.9)	131 (37.8)	170 (49.7)	168 (49.7)
Western Europe	17 (4.8)	17 (4.9)	11 (3.2)	11 (3.3)
Diabetes				
Yes	62 (17.7)	68 (19.6)	60 (17.5)	52 (15.4)
PVD				
Yes	47 (13.4)	53 (15.3)	46 (13.5)	40 (11.8)
Renal Function				
CrCl > 80 mL/min	276 (78.6)	267 (76.9)	273 (79.8)	257 (76.0)
CrCl >50 and ≤80 mL/min	60 (17.1)	61 (17.6)	56 (16.4)	68 (20.1)
CrCl >30 and ≤50 mL/min	14 (4.0)	17 (4.9)	13 (3.8)	13 (3.8)
CrCL <30 mL/min[2]	0	0	0	0

1 Poland included with Eastern Europe
2 CrCl < 30 mL/min was an exclusion criteria for the studies
Source:
P903-06: CSR Table 10.3.1-1, Pg 109, Table 10.3.5-1, Pgs 115-116, Table 14.2.41, Pgs 552-554, Table 14.4.1.3, pg 802-804
P903-07: CSR Table 10.3.1-1, Pg 110, Table 10.3.5-1, Pgs 115, Table 10.3.10-1, Pg 122

The trial populations were relatively balanced in regard to gender, age, and race. Approximately 2/3 of the study populations were male, 75% were Caucasian, and 93-

95% of patients were < 75 years of age. Study P903-06 enrolled more subjects from Eastern Europe, while P903-07 enrolled more subjects from the US. Diabetes mellitus was present in 15-20% of the population and PVD in 12-15%. Baseline renal function was similar between trial populations.

Table 6B.2 shows baseline infection characteristics for the two trials.

Table 6B.2: Baseline Infections Characteristics, Applicant's MITT Population

	Study P903-06		Study P903-07	
	Ceftaroline N=351	Vancomycin + Aztreonam N=347	Ceftaroline N=342	Vancomycin + Aztreonam N=338
Bacteremia				
Yes	20 (5.7)	10 (2.9)	9 (2.6)	14 (4.1)
Signs and Symptoms				
Fever	121/350 (34.5)	110/347 (31.7)	90/342 (26.3)	91/338 (26.9)
Elevated WBC	120/314 (34.2)	126/313 (36.3)	126/306 (41.2)	127/305 (41.6)
≥1 systemic sign[1]	199 (56.7)	193 (55.6)	179 (52.3)	169 (50.0)
Abscess, >5 cm erythema	83/99 (83.8)	88/101 (87.1)	124/139 (89.2)	120/133 (90.2)
Infection area median, range (cm^2)	173.9 (1, 3150)	180 (2.3, 3015)	151(1.4, 2860)	120 (0, 4950)
Types of Infection				
Major abscess	99 (28.2)	101 (29.1)	139 (40.6)	133 (39.3)
Deep/extensive cellulitis	121 (34.5)	120 (34.6)	103 (30.1)	123 (36.4)
Infected wound	54 (15.4)	43 (12.4)	48 (14.0)	39 (11.5)
Infected ulcer	23 (6.6)	31 (8.9)	31 (9.1)	21 (6.2)
LE cSSSI with DM or PVD	21 (6.0)	29 (5.8)	9 (2.6)	12 (3.6)
Cellulitis	17 (4.8)	19 (5.5)	8 (2.3)	11 (3.3)
Abscess	4 (1.1)	1 (0.3)	1 (0.3)	1 (0.3)
Infected bite	7 (2.0)	7 (2.0)	6 (1.8)	4 (1.2)
Infected burn	25 (7.1)	20 (5.8)	1 (0.3)	2 (0.6)
Other	1 (0.3)	5 (1.4)	5 (1.5)	4 (1.2)

[1] A systemic sign was defined as fever >38°C oral (>38.5°C rectal or tympanic) or hypothermia (temperature <35°C), WBC >10,000/mm^3, or >10% immature neutrophils irrespective of WBCs.
Source:
P903-06: CSR Table 10.3.1-1, Pg 109, Table 10.3.4-1,Table 10.3.5-1, Pgs 115-116, Table 14.2.41, Pgs 552-554, Table 14.2.39, pg 550.
P903-07: CSR Table 10.3.1-1, Pg 110, Table 10.3.4-1, pg 114,Table 10.3.5-1, Pg 115, Table 10.3.10-1, Pg 122

Only 3-6% of subjects had bacteremia at baseline. Fever was present in 26-32% of patients, elevated WBC in 35-41%, and 50-57% of the study subjects had >1 systemic sign (i.e. fever, elevated WBC, or bandemia). The area of infection size varied widely among patients within a single treatment group. In Study P903-06, the median infection size area was similar in the two treatment groups. In Study P903-07, the median size of the infection site area in the ceftaroline treatment group was greater than that in the comparator treatment group. Major abscesses accounted for approximately 30% of infections in Study P903-06 and 40% in Study P903-07. Cellulitis was present in about

35% of patients in both studies and infected wounds in 11-15% of subjects. One to 2% of the population had infection type classified as "bites", however patients with human and animal bites had been excluded from the trials.

Table 6B.3 below shows the number of subjects contained within each of the Applicant's analysis populations. The designated co-primary populations for the primary efficacy analysis were the MITT and CE populations.

Table 6B.3: Subject Populations Table

	Study P903-06			**Study P903-07**		
Study Populations	Ceftaroline	Vancomycin + Aztreonam	Total	Ceftaroline	Vancomycin + aztreonam	Total
ITT	353 (100)	349 (100)	702 (100)	348 (100)	346 (100)	694 (100)
MITT	351 (99.4)	347 (99.4)	698 (99.4)	342 (98.3)	338 (97.7)	680 (98.0)
cMITT	345 (97.7)	344 (98.6)	689 (98.1)	341 (98.0)	337 (97.4)	678 (97.7)
mMITT	271 (76.8)	263 (75.4)	534 (76.1)	269 (77.3)	259 (74.9)	528 (76.1)
CE	316 (89.5)	300 (86.0)	616 (87.7)	294 (84.5)	292 (84.4)	586 (84.4)
ME	244 (69.1)	227 (65.0)	471 (67.1)	224 (64.4)	219 (63.3)	443 (63.8)
Source: P903-06: CSR, Table 10.1-2., pg 106. P903-07: CSR, Table 10.1-2, pg 106.						

Baseline pathogens were present in approximately 75% of patients in each trial. Clinical evaluability rates were relatively high at 85-90%.

The pre-specified primary efficacy endpoint was clinical response at the TOC visit. To demonstrate noninferiority, a two-sided 95% confidence interval (CI) for the observed difference in the clinical cure rates (ceftaroline – vancomycin+aztreonam) was constructed using normal approximation to the binomial with a continuity correction with noninferiority concluded if the lower limit of the 95% CI was greater than –10%. An important secondary endpoint was clinical response at EOT. Table 6B.4 shows the results of these analyses in Study P903-06.

Table 6B.4: Applicant Analysis: Study P903-06 Clinical Cure Rates at TOC and EOT (MITT and CE)

Analysis Population	**Ceftaroline** n/N (%)	**Vancomycin + Aztreonam** n/N (%)	**Difference (95% CI)**
TOC			
MITT	304/351 (86.6)	297/347 (85.6)	1.0 (-4.2, 6.2)
CE	288/316 (91.1)	280/300 (93.3)	-2.2 (-6.6, 2.1)
EOT			
MITT	322/351 (91.7)	313/347 (90.2)	1.5 (-2.8, 5.9)
CE	298/316 (94.3)	282/300 (94.0)	0.3 (-3.5, 4.2)
Source: Partially Adapted from Applicant Table of Study Synopsis			

For Study P903-06, at the TOC visit, based on the difference in cure rates (ceftaroline – vancomycin+aztreonam), the NI margin of 10% was met for both of the pre-specified co-

primary populations. Results observed at the EOT visit also supported non-inferiority and would have met a NI margin of 5% for both co-primary populations.

Table 6B.5 shows the results of the Applicant's co-primary analyses for Study P903-07, as well as the results for the secondary endpoint of clinical response at EOT.

Table 6B.5: Applicant Primary Analysis: Study P903-07 Clinical Cure Ratesat TOC and EOT (MITT and CE)

Analysis Population	**Ceftaroline** n/N (%)	**Vancomycin + Aztreonam** n/N (%)	**Difference (95% CI)**
TOC			
MITT	291/342 (85.1)	289/338 (85.5)	-0.4 (-5.8, 5.0)
CE	271/294 (92.2)	269/292 (92.1)	0.1 (-4.4, 4.5)
EOT			
MITT	304/342 (88.9)	302/338 (89.3)	-0.5 (-5.2, 4.3)
CE	274/294 (93.2)	271/292 (92.8)	0.4 (-3.9, 4.7)
Source: Partially Adapted from Applicant Table of Study Synopsis			

Similarly for Study P903-07, non-inferiority of ceftaroline to vancomycin + aztreonam was demonstrated at the TOC visit in both the MITT and CE co-primary analysis populations, with the lower bound of the 95% CI for the treatment difference > -10%. Similar findings supporting non-inferiority were also observed when performing the analysis using an EOT time point.

Another important secondary efficacy analysis was to examine the clinical response rate by pathogen for the bacterial isolates from appropriate baseline microbiological specimens (infection site or blood culture) in the microbiological modified intent to treat (mMITT) and microbiologically evaluable (ME) populations.

Table 6B.6: (Applicant) Clinical Cure Rates at TOC by Baseline Pathogen from the Primary Infection Site or Blood

	Study P03-06		Study P903-07	
Population *Pathogen*	**Ceftaroline** n/N (%)	**Vancomycin + Aztreonam** n/N (%)	**Ceftaroline** n/N (%)	**Vancomycin + Aztreonam** n/N (%)
mMITT				
Gram + bacteria				
S. aureus	177/199 (88.9)	170/200 (85.0)	200/226 (88.5)	186/209 (89.0)
MRSA	82/93 (88.2)	62/80 (77.5)	73/86 (84.9)	62/71 (87.3)
MSSA	97/108 (89.8)	109/120 (90.8)	124/137 (90.5)	124/138 (89.9)
S. pyogenes	24/25 (96.0)	32/34 (94.1)	32/38 (84.2)	25/28 (89.3)
S. agalactiae	15/17 (88.2)	14/15 (93.3)	10/10 (100)	12/14 (85.7)
S. dysgalactiae	6/6 (100)	8/10 (80)	8/8 (100)	8/8 (100)
S. anginosus group	7/9 (77.8)	4/6 (66.7)	6/7 (85.7)	9/9 (100)*
E. faecalis	13/17 (76.5)	11/14 (78.6)	7/11 (63.6)	12/14 (85.7)
Gram - bacteria				
E. coli	9/10 (90)	13/15 (86.7)	12/13 (92.3)	6/6 (100)
K. oxytoca	3/5 (60)	3/4 (75)	7/7 (100)	4/4 (100)
K. pnuemoniae	10/11 (90.9)	10/11 (90.9)	7/7 (100)	4/8 (50)
M. morganii	6/6 (100)	3/4 (75)	5/6 (83.3)	2/3 (66.7)
ME				
Gram + bacteria				
S. aureus	170/183 (92.9)	164/173 (94.8)	182/195 (93.3)	172/183 (94.0)
MRSA	78/82 (95.1)	59/62 (95.2)	64/70 (91.4)	56/60 (93.3)
MSSA	94/103 (91.3)	106/112 (94.6)	118/125 (94.4)	119/126 (94.4)
S. pyogenes	24/24 (100.0)	32/32 (100.0)	32/32 (100.0)	24/26 (92.3)
S. agalactiae	15/16 (93.8)	13/13 (100)	6/6 (100)	5/5 (100)
S. dysgalactiae	5/5 (100)	8/9 (88.9)	8/8 (100)	7/7 (100)
S.anginosus group[1]	7/8 (87.5)	7/8 (87.5)	6/6 (100)	8/8 (100)
E. faecalis	13/14 (92.9)	11/12 (91.7)	7/11 (63.6)	11/12 (91.7)
Gram - bacteria				
E. coli	9/10 (90)	13/15 (86.7)	11/11 (100)	6/6 (100)
K. oxytoca	3/5 (60.0)	3/3 (100)	7/7 (100)	3/3 (100)
K. pneumoniae	10/11 (90.9)	10/10 (100)	7/7 (100)	3/4 (75.0)
M. morganii	6/6 (100)	3/3 (100)	5/6 (83.3)	2/3 (66.7)

Source:
P903-06, CSR Table 11.2.2.2.4-1, pg 134, Table 14.4.2.16, pgs 908-913
P903-07, CSR Table 11.2.2.2.4-1, pg 134, Table 14.4.2.16, pgs 914-917
1 *Streptococcus anginosus* group includes: *S. anginosus*, *S. intermedius*, *S. constellatus*

In the ME population, the clinical response rate by-pathogen was similar for *S. aureus* (both MRSA and MSSA), *S. pyogenes*, and other beta-hemolytic streptococci. Activity

against *E.faecalis* was slightly lower in the ceftaroline arm. Although the Applicant is seeking the cSSSI indication for *E. coli*, *K. pneumoniae*, *K. oxytoca*, and *M. morganii*, the number of isolates was too small to make any meaningful conclusions regarding comparative activity of treatments.

FDA Analyses

Recent public discussions have focused on primary efficacy endpoints assessed at earlier timepoints, based on evidence from the historical literature which can be used to demonstrate antibacterial treatment effect in skin infections (Snodgrass and Anderson, 1937). The endpoints suggested by the literature for which an NI margin may be justified include time to cessation of spread of the lesion and defervescence in those with fever in patients with cellulitis and wound infections. Therefore, FDA reviewers carried out sensitivity analyses utilizing an endpoint assessed at an earlier time point. The treatment effect of antibacterial therapies following primary incision and drainage has not been defined and therefore inclusion of patients with abscesses required that there be a significant cellulitic component (i.e. surrounding erythema > 5 cm) to be included in the FDA sensitivity analysis population.

For the FDA reviewer sensitivity analysis, the primary analysis population, the FDA-Modified Intent-to-Treat (FDA-MITT), was defined as follows:
Randomized patients who received any amount of treatment with lesion size ≥ 75 cm^2 having one of the following infection types: 'major abscess' with ≥ 5 cm of surrounding erythema, 'wound infection', deep/extensive cellulitis' or 'lower extremity SSSI in patients with diabetes mellitus or PVD'. The Applicant also presented information on 19 patients with infection type defined as "bite" that met size criteria and were not of human or animal origin and were consistent with literature reports of MRSA infection; these patients were also included in the FDA-MITT population.

Table 6B.7 below shows the baseline characteristics of the FDA defined primary analysis population.

Table 6B.7: Baseline Characteristics of the FDA MITT Population

	Study P903-06		Study P903-07	
	Ceftaroline N=200	Vancomycin + Aztreonam N=209	Ceftaroline N=200	Vancomycin + Aztreonam N=188
Gender				
Female	75 (37.5)	80 (38.3)	57 (28.5)	68 (36.2)
Male	125 (62.5)	129 (61.7)	143 (71.5)	120 (63.8)
Age				
≤ 65 years	168 (84.0)	173 (82.8)	170 (85.0)	166 (88.3)
> 65 years	32 (16.0)	36 (17.2)	30 (15.0)	22 (11.7)
> 75 years	13 (6.5)	14 (6.7)	13 (6.5)	10 (5.3)
Region				
Eastern Europe[1]	85 (42.5)	89 (42.6)	75 (37.5)	79 (42.0)
Latin America	21 (10.5)	23 (11.0)	20 (10.0)	17 (9.0)
US	81 (40.5)	85 (40.7)	100 (50.0)	85 (45.2)
Western Europe	13 (6.5)	12 (5.7)	5 (2.5)	7 (3.7)
Diabetes				
Yes	29 (14.5)	47 (22.5)	33 (16.5)	29 (15.4)
PVD				
Yes	19 (9.5)	25 (12.0)	17 (8.5)	14 (7.4)
Renal Function	N=199	N=208	N=200	N=188
CrCl > 80 mL/min	163 (81.9)	162 (77.9)	163 (81.5)	139 (73.9)
CrCl > 50-80 mL/min	28 (14.1)	38 (18.3)	28 (14.0)	43 (22.9)
CrCl > 30-50 mL/min	8 (4.0)	8 (3.8)	9 (4.5)	6 (3.2)
CrCL ≤ 30 mL/min	0 (0)	0 (0)	0 (0)	0 (0)
Source: Reviewer Table				

The baseline characteristics of the FDA-MITT population appear to be similar to those of the Applicant's MITT population, with some variation in numbers likely due to smaller sample size.

Table 6B.8 shows the baseline infection characteristics in the FDA-MITT population.

Table 6B.8: Baseline Infection Characteristics, FDA-MITT Population

	Study P903-06		Study P903-07	
	Ceftaroline N=200	Vancomycin + Aztreonam N=209	Ceftaroline N=200	Vancomycin + Aztreonam N=188
Bacteremia				
Yes	14 (7.0)	5 (2.4)	7 (3.5)	11 (5.9)
Signs and Symptoms				
Fever	88 (44.0)	91 (43.5)	82 (41.0)	88 (46.8)
Elevated WBC	76/181 (42.0)	88/189 (46.6)	87/175 (49.7)	80/164 (48.8)
Infection area median, range (cm^2)	247 (75, 3150)	255 (75, 2451)	224 (76, 2860)	237 (80, 4950)
Infection Type				
Major abscess	43 (21.5)	46 (22.0)	69 (34.5)	50 (26.6)
Deep/extensive cellulitis	111(55.5)	111 (53.1)	88 (44.0)	103 (54.8)
Infected wound	30 (15.0)	27 (12.9)	29 (14.5)	24 (12.8)
Lower extremity cSSSI, subject with diabetes or PVD	13 (6.5)	18 (8.6)	8 (4.0)	8 (4.3)
Infected bite[a]	3 (1.5)	7 (3.3)	6 (3.0)	3 (1.6)
Source: Reviewer Table				

In comparison to the Applicant's MITT population, the FDA-MITT population in both trials included a higher percentage of cellulitis patients and a lower percentage of patients with major abscesses.

Table 6B.9 shows the relative size of the FDA-MITT population in relation to the various analysis populations of the Applicant.

Table 6B.9: Subject Analysis Populations

	Study P903-06			**Study P903-07**		
Study Populations	Ceftaroline	Vancomycin + Aztreonam	Total	Ceftaroline	Vancomycin + aztreonam	Total
Applicant						
ITT	353 (100)	349 (100)	702 (100)	348 (100)	346 (100)	694 (100)
MITT	351 (99.4)	347 (99.4)	698 (99.4)	342 (98.3)	338 (97.7)	680 (98.0)
CE	316 (89.5)	300 (86.0)	616 (87.7)	294 (84.5)	292 (84.4)	586 (84.4)
mMITT	271 (76.8)	263 (75.4)	534 (76.1)	269 (77.3)	259 (74.9)	528 (76.1)
ME	244 (69.1)	227 (65.0)	471 (67.1)	224 (64.4)	219 (63.3)	443 (63.8)
FDA-MITT	**200 (56.7)**	**209 (59.9)**	**409 (58.3)**	**200 (57.5)**	**188 (54.3)**	**388 (55.9)**
Source: P903-06: CSR, Table 10.1-2., pg 106. P903-07: CSR, Table 10.1-2, pg 106.						

The FDA population represents only about 56-58% of the originally randomized trial populations. As a result of smaller sample sizes, the width of the 95% CI for the treatment difference widens and statistical power in demonstrating non-inferiority is substantially reduced.

FDA Reviewers' Key Sensitivity Analysis

The FDA reviewers' key sensitivity endpoint of 'clinical response' was defined as those patients with cessation of spread of the lesion from baseline along with absence of fever at the Day 3 assessment. In addition to the defined population, patients having an EOT assessment on Day 3 and assessed by the investigator as a clinical failure, could not be classified as a clinical responder.

Table 6B.10 below shows the results of this analysis in the FDA-MITT population for Study P903-06 and Study P903-07.

Table 6B.10: FDA Reviewer Key Sensitivity Analysis: Clinical Responders at Day 3

Analysis Population	**Ceftaroline** n/N (%)	**Vancomycin + Aztreonam** n/N (%)	**Ceftaroline – (Vancomycin + Aztreonam) (95% CI)**
FDA-MITT (P903-06)	148/200 (74.0)	135/209 (64.6)	9.4 (0.03, 18.8)
FDA-MITT (P903-07)	148/200 (74.0)	128/188 (68.1)	5.9 (-3.6, 15.5)
Source: Reviewer Table			

In Study P903-06, the key sensitivity analysis shows that the responder rate at Day 3 is significantly higher in the ceftaroline treatment group than that in the vancomycin + aztreonam treatment group for the FDA primary analysis population (FDA-MITT). In Study P903-07, treatment comparisons in this analysis also favored ceftaroline but were less pronounced with a lower bound of -3.6%.

These findings supported the non-inferiority of ceftaroline to vancomycin + aztreonam for a NI margin of less than 4% for both trials. However, to support this finding, further related sensitivity analyses were examined in order to rule out the potential influence of investigator measurement error of lesions at Day 3. Other additional sensitivity analyses were also examined to confirm that treatment comparisons in clinical response would remain consistent across later time points such as at the end-of-therapy. Findings from these additional sensitivity analyses are provided in the two tables below.

Table 6B.12 shows the responder rates with varying % reduction in lesion sizes required to be defined a responder. Requiring a larger % reduction for responders would better ensure against responders who could have achieved cessation only through investigator error (i.e. overestimation) of lesion size.

Table 6B.11: Sensitivity Analysis of Responder Rates in FDA-MITT Subjects Varying the Required % Reduction in Lesion Size from Baseline to Day 3

	Study P903-06 (n=409)		Study P903-07 (n=388)	
% Reduction Required for Responder	**Ceftaroline N=200** n/N (%)	**Vancomycin + Aztreonam N=209** n/N (%)	**Ceftaroline N=200** n/N (%)	**Vancomycin + Aztreonam N=188** n/N (%)
0% (Cessation)	**148/200 (74.0)**	**135/209 (64.6)**	**148/200 (74.0)**	**128/188 (68.1)**
10%	127/200 (63.5)	121/209 (57.9)	133/200 (66.5)	115/188 (61.2)
20%	115/200 (57.5)	106/209 (50.7)	120/200 (60.0)	105/188 (55.9)
30%	94/200 (47.0)	93/209 (44.5)	106/200 (53.0)	92/188 (48.9)
Source: Reviewer Table				

As noted in Table 6B.11 above, for both Study P903-06 and Study P903-07, responder rates favored ceftaroline regardless of the % reduction required in defining a responder. These findings show that key sensitivity analysis findings were robust in supporting the non-inferiority of ceftaroline to vancomycin + aztreonam at the Day 3 endpoint and that potential systematic measurement error in the measurement of lesion size was unlikely to affect findings of non-inferiority.

Table 6B.12: Sensitivity Analysis of Responder Rates in FDA-MITT Subjects Varying the Required % Reduction in Lesion Size at EOT from Baseline

	Study 06 (n=409)		Study 07 (n=388)	
% Reduction Required for Responder	**Ceftaroline N=200** n/N (%)	**Vancomycin + Aztreonam N=209** n/N (%)	**Ceftaroline N=200** n/N (%)	**Vancomycin + Aztreonam N=188** n/N (%)
75%	155 (77.5)	158 (75.6)	144 (72.0)	137 (72.9)
80%	149 (74.5)	152 (72.7)	137(68.5)	129 (68.6)
85%	139 (69.5)	146 (69.9)	132 (66.0)	122 (64.9)
90%	134 (67.0)	137 (65.6)	122 (61.0)	111 (59.0)
95%	119 (59.5)	114 (54.5)	108 (54.5)	98 (52.1)
Source: Reviewer Table **Responders were those with reduction of lesion size area of 75%, 80%, 85%, 90% 95% and absence of fever at EOT. Responders also could not be classified as a clinical failure at EOT.**				

Table 6B.12 above considers a similar analysis at the EOT time point by varying the required % reduction in lesion size in defining a responder. This table suggests that treatment differences in responder rates at the EOT time point were reduced in comparison to differences at Day 3. However, consistent with the Day 3 analysis, the EOT analysis still supported the non-inferiority of ceftaroline over vancomycin + aztreonam. Across both trials, treatment differences at EOT tended to slightly favor ceftaroline regardless of the % reduction of lesion size required for a responder.

The sensitivity analysis above also provided insight into the amount of reduction in the size of the lesion (i.e. resolution) that could be used as an objective measure of response

at EOT. This analysis indicates that in 72.0-77.5% of subjects, there was a 75% reduction in lesion size at EOT determined by the investigator when sufficient resolution of the infection had occurred.

Key Secondary Outcomes Analyzed in the FDA-MITT Population

Key secondary outcomes in the FDA-MITT population included investigator assessment at EOT, rates of absence of erythema, swelling and tenderness at EOT, absolute and percentage changes in lesion dimensions at Day 3 and EOT and clinical cure rates by pathogen at Day 3 and EOT for FDA-MITT subjects included in the Applicant's ME and mMITT populations. Results from these endpoints were generally consistent with findings of non-inferiority in the FDA Reviewer key sensitivity analysis.

Table 6B.13: Investigator Assessment, Cure Rates at EOT (FDA-MITT)

Analysis Population	**Ceftaroline** n/N (%)	**Vancomycin + Aztreonam** n/N (%)	**Ceftaroline - Vancomycin + Aztreonam (95% CI)**
FDA-MITT (P903-06)	188/200 (94.0)	187/209 (89.5)	4.5 (-1.3, 10.3)
FDA-MITT (P903-07)	179/200 (89.5)	170/188 (90.4)	-0.9 (-7.4, 5.6)
Source: Reviewer Table			

In the secondary analysis of investigator assessment at EOT in the FDA-MITT population, cure rates favored ceftaroline in Study P903-06 but slightly favored vancomycin+aztreonam in Study P903-07. Analyses were consistent with non-inferiority within a 10% margin based on the lower bound of the 95% CI for the treatment difference which was at or below -7.4% in both trials.

Table 6B.14: FDA Secondary Endpoints, Absence Rates of Key Signs and Symptoms in FDA-MITT Subjects at EOT

	Study P903-06 (n=409)		**Study P903-07 (n=388)**	
Sign/Symptom	**Ceftaroline N=200** n/N (%)	**Vancomycin + Aztreonam N=209** n/N (%)	**Ceftaroline N=200** n/N (%)	**Vancomycin + Aztreonam N=188** n/N (%)
Erythema	127/200 (63.5)	134/209 (64.1)	131/200 (65.5)	123/188 (65.4)
Swelling	138/200 (69.0)	127/209 (60.8)	113/200 (56.5)	99/188 (52.7)
Tenderness	146/200 (73.0)	146/209 (69.9)	120/200 (60.0)	106/188 (56.4)
Source: Reviewer Table				

Rates for absence of erythema were similar between treatment groups across trials whereas rates for absence of swelling and tenderness tended to be higher in Study P903-06 vs. P903-07 as well as higher in ceftaroline vs. vancomycin+aztreonam. These findings were consistent with the key sensitivity analyses and further supported the non-inferiority of ceftaroline.

Table 6B.15 and 6B.16 below show the by-pathogen clinical cure rates at Day 3 and EOT respectively, in the FDA microbiological-MITT.

Table 6B.15: Responder Rates at Day 3 by Baseline Pathogen from the Primary Infection Site or Blood (FDA mMITT Reviewer Subset)

	Study 06		Study 07	
Pathogen	**Ceftaroline** n/N (%)	**Vancomycin + Aztreonam** n/N (%)	**Ceftaroline** n/N (%)	**Vancomycin + Aztreonam** n/N (%)
Gram + bacteria				
S.aureus	77/104 (74.0)	72/114 (63.2)	110/140 (78.6)	84/121 (69.4)
MRSA	34/45 (75.6)	30/41 (73.2)	50/57 (87.7)	35/43 (81.4)
MSSA	44/61 (72.1)	42/73 (57.5)	58/81 (71.6)	50/79 (63.3)
S. pyogenes	9/18 (50.0)	13/26 (50.0)	16/28 (57.1)	15/23 (65.2)
S. agalactiae	4/7 (57.1)	5/6 (83.3)	5/6 (83.3)	1/1 (100)
S. dysgalactiae	2/2 (100)	2/3 (66.7)	4/6 (66.7)	2/5 (40)
S. anginosus	4/4 (100)	0/2 (0)	2/2 (100)	4/4 (100)
S. anginosus group[1]	6/6 (100)	2/5 (40)	2/4 (50)	4/5 (80)
E. faecalis	2/4 (50)	3/5 (60)	5/8 (62.5)	3/5 (60)
Gram - bacteria				
E. coli	2/3 (66.7)	7/12 (58.3)	3/5 (60)	0/1 (0)
K. oxytoca	2/3 (66.7)	1/2 (50)	3/4 (75)	2/4 (50)
K. pneumoniae	3/4 (75)	1/5 (20)	2/5 (40)	0/2 (0)
M. morganii	1/2 (50)	-	2/2 (100)	0/1 (0)
Source: Reviewer Table				

Responder rates in patients with baseline *S. aureus* isolates, both MRSA and MSSA, were higher in the ceftaroline treatment group. Responder rates in patients with *S. pyogenes* isolated at baseline were similar in both treatment groups. The number of additional baseline pathogens was too few to draw specific conclusions regarding comparison of efficacy of the treatments for a particular genus and species of bacteria.

Table 6B.16: Clinical Cure Rates at EOT by Baseline Pathogen from the Primary Infection Site or Blood (FDA mMITT Reviewer Subset)

	Study 06		Study 07	
Pathogen	**Ceftaroline n/N (%)**	**Vancomycin + Aztreonam n/N (%)**	**Ceftaroline n/N (%)**	**Vancomycin + Aztreonam n/N (%)**
S. aureus	**98/104 (94.2)**	**104/114 (91.2)**	**131/140 (93.6)**	**112/121 (92.6)**
MRSA	**43/45 (95.6)**	**35/41 (85.4)**	**49/57 (86.0)**	**40/43 (93.0)**
MSSA	**57/61(93.4)**	**69/73(94.5)**	**80/81 (98.8)**	**73/79 (92.4)**
S. pyogenes	**18/18 (100)**	**24/26 (92.3)**	**25/28 (89.3)**	**21/23 (91.3)**
S. agalactiae	**6/7 (85.7)**	**5/6 (83.3)**	**6/6 (100)**	**1/1 (100)**
S. dysgalactiae	**2/2 (100)**	**3/3 (100)**	**6/6 (100)**	**5/5 (100)**
***S. anginosus* group**[1]	**6/6 (100)**	**5/5 (100)**	**4/4 (100)**	**5/5 (100)**
E. faecalis	**4/4 (100)**	**5/5 (100)**	**4/8 (50)**	**4/5 (80)**
Gram - bacteria				
E. coli	**3/3 (100)**	**11/12 (91.7)**	**4/5 (80)**	**1/1 (100)**
K. oxytoca	**3/3 (100)**	**2/2 (100)**	**4/4 (100)**	**4/4 (100)**
K. pneumoniae	**4/4 (100)**	**4/5 (80)**	**5/5 (100)**	**1/2 (50)**
M. morganii	**2/2 (100)**	**-**	**2/2 (100)**	**0/1 (0)**
Source: Reviewer Table				

Cure rates for all baseline pathogens appear similar at EOT in both treatment arms.

Subgroup Analyses

Subgroup analyses were conducted to investigate the heterogeneity of treatment differences across patient groups meeting specific characteristics of interest. Table 6B.17 shows the clinical response rates at Day 3 by baseline infection type.

Table 6B.17: Responder Rates at Day 3 in Key Sensitivity Analyses by Infection Type (FDA-MITT)

	Study P903-06		Study P903-07	
	Ceftaroline (N=200) n/N (%)	**Vancomycin + Aztreonam (N=209)** n/N (%)	**Ceftaroline (N=200)** n/N (%)	**Vancomycin + Aztreonam (N=188)** n/N (%)
Deep/Extensive Cellulitis	81/111 (73.0)	72/111 (64.9)	60/88 (68.2)	67/103 (65.0)
Major Abscess	36/43 (83.7)	35/46 (76.1)	56/69 (81.2)	41/50 (82.0)
Wound Infection	20/30 (66.7)	16/27 (59.3)	21/29 (72.4)	14/24 (58.3)
Lower extremity cSSSI, subject w/ diabetes or PVD	8/13 (61.5)	7/18 (38.9)	6/8 (75.0)	5/8 (62.5)
Infected Bite	3/3 (100)	5/7 (71.4)	5/6 (83.3)	1/3 (33.3)
Source: Reviewer Table				

Responder rates at Day 3 favored treatment with ceftaroline for all types of infections except for major abscesses in Study P903-07 where differences were modest. The highest response rates were observed in patients with major abscesses which may be related to the effect of incision and drainage of the abscess.

The next table explores whether antibiotic therapy administered in the period immediately prior to study treatment has an effect on response rates. This issue is considered to be especially important when exploring the use of earlier endpoints which may be especially sensitive to prior antibiotic therapy

Table 6B.18 shows the responder rates at Day 3 in patients who have or have not received antibacterial therapy in the 24 hours prior to study drug initiation. The effect is shown on both the primary measure (cessation of spread and absence of fever) as well as a sensitivity measure which includes the % reduction in the size of the lesion.

Table 6B.18: Responder Rates at Day 3 in FDA Reviewer Analyses by Prior Systemic Antimicrobial Use for Any Reason within 24 hours of Study Drug Initiation

	Study P903-06		Study P903-07	
Prior Antimicrobial Use?	**Ceftaroline (N=200)** n/N (%)	**Vancomycin + Aztreonam (N=209)** n/N (%)	**Ceftaroline (N=200)** n/N (%)	**Vancomycin + Aztreonam (N=188)** n/N (%)
Responder Rate at Day 3 (Absence of Fever and Cessation of Lesion Spread)				
Prior Use	72/99 (72.7)	58/99 (58.6)	66/92 (71.7)	63/82 (76.8)
No Prior Use	76/101 (75.2)	77/110 (70.0)	82/108 (75.9)	65/106 (61.3)
Responder Rate at Day 3 (Absence of Fever and ≥ 10% Reduction of Lesion Spread)				
Prior Use	62/99 (62.6)	54/99 (54.5)	60/92 (65.2)	61/82 (74.4)
No Prior Use	65/101 (64.4)	67/110 (60.9)	73/108 (67.6)	54/106 (50.9)
Source: Reviewer Table				

In patients with no prior use of antibiotics within 24 hours, treatment differences favored ceftaroline over vancomycin + aztreonam, especially in Study P903-07. However, in patients with prior use of antibiotics, treatment differences were inconsistent across trials, favoring ceftaroline in Study P903-06 but favoring vancomycin + aztreonam in Study P903-07.

These findings suggest that administration of antimicrobial agents prior to study drug treatment do not appear to increase (enhance) the ceftaroline treatment effect over vancomycin + aztreonam Prior use of antibiotics appeared to lead to higher responder rates in patients treated with vancomycin + aztreonam in Study P903-07, however, this trend was reversed in Study P903-06.

Due to limited numbers of subjects included in the FDA-MITT population of each trial, integrated analyses were also explored for various subgroups of interest at Day 3 and EOT. However, statistical inferences are limited in these analyses due to trial differences and lack of randomization protection. Table 6B.19 provides integrated analyses of responder rates of various subgroups across Study P903-06 and Study P903-07.

Table 6B.19: Integrated Analyses of Responder Rates at Day 3 by Subgroup (FDA Reviewer Subset of MITT)

	Combined Studies (N=797)		
Subgroup	**Ceftaroline (N=400)** n/N (%)	**Vancomycin + Aztreonam (N=397)** n/N (%)	**Ceftaroline – Vancomycin + Aztreonam (95% CI)**
Age			
> 65	50/62 (80.6)	39/58 (67.2)	13.4 (-3.8, 30.7)
≤ 65	246/338 (72.9)	224/339 (66.1)	6.7 (-0.5, 13.9)
Region			
US	150/181 (82.9)	127/170 (74.7)	8.2 (-0.9, 17.3)
Latin America	33/41 (80.6)	31/40 (77.5)	3.0 (-17.2, 23.2)
Eastern Europe	101/160 (63.1)	92/168 (54.8)	8.4 (-2.9, 19.6)
Western Europe	12/18 (66.7)	13/19 (68.4)	-1.8 (-37.4, 33.8)
Prior Antibiotics (within 24 hours of study drug)			
Prior antibiotics	138/191 (72.3)	121/181 (66.9)	5.4 (-4.5, 15.3)
No prior antibiotics	158/209 (75.6)	142/216 (65.7)	9.9 (0.8, 18.9)
Fever			
Fever	97/170 (57.1)	90/179 (50.3)	6.8 (-4.2, 17.8)
No Fever	199/230 (86.5)	173/218 (79.4)	7.2 (-0.2, 14.6)
Diabetes			
Diabetes	40/62 (64.5)	56/76 (73.7)	-9.2 (-26.1, 7.8)
No Diabetes	256/338 (75.7)	207/321 (64.5)	11.3 (4.0, 18.5)
Renal function (CrCl in mL/min)			
> 80	241/326 (73.9)	200/301 (66.4)	7.5 (0.1, 15.0)
> 50 to 80	40/56 (71.4)	52/81 (64.2)	7.2 (-10.1, 24.5)
> 30 to 50	14/17 (82.4)	10/14 (71.4)	10.9 (-20.3, 43.4)[1]
Infection Type			
Deep/Extensive Cellulitis	141/199 (70.9)	139/214 (65.0)	5.9 (-3.6, 15.4)
Major Abscess	92/112 (82.1)	76/96 (79.2)	3.0 (-8.8, 14.7)
Wound Infection	41/59 (69.5)	30/51 (58.8)	10.7 (-9.1, 30.4)
Lower extremity cSSSI, subject w/ diabetes or PVD	14/21 (66.7)	12/26 (46.2)	20.5 (-11.6, 52.6)
Infected Bite	8/9 (88.9)	6/10 (60.0)	28.9 (-14.1, 65.6)[1]

[1] 95% CI computed using an Exact Test
Source: Reviewer Table

Based on integrated findings in Table 6B.19, responder rates at Day 3 were substantially higher for the following subgroups: US and Latin America vs. Eastern and Western Europe, patients with no fever vs. fever at baseline and patients with major abscesses vs.

other infection types. Treatment differences appeared to be generally similar across categories within most subgroups, but were observed to be less favorable towards ceftaroline vs. vancomycin + aztreonam for patients with diabetes vs. without diabetes, patients with prior antibiotics vs. without prior antibiotics, and patients with major abscesses vs. other infection types. This later finding may help to explain the smaller overall treatment difference favoring ceftaroline in Study P903-07 vs. Study P903-06 since Study P903-07, in comparison to Study P903-06, included substantially fewer patients with major abscesses vs. other infection types in the FDA-MITT analysis.

Table 6B.20: Integrated Analyses of Clinical Cure Rates Based on Investigator Assessment at EOT by Subgroup (FDA Reviewer Subset of MITT)

	Combined Studies (N=797)		
Subgroup	**Ceftaroline (N=400)** n/N (%)	**Vancomycin + Aztreonam (N=397)** n/N (%)	**Ceftaroline – Vancomycin + Aztreonam (95% CI)**
Age			
> 65	58/62 (93.5)	53/58 (91.4)	2.2 (-8.4, 13.2)[1]
≤ 65	309/338 (91.4)	304/339 (89.7)	1.7 (-3.0, 6.5)
Region			
US	159/181 (87.8)	144/170 (84.7)	3.1 (-4.6, 10.9)
Latin America	37/41 (90.2)	32/40 (80.0)	10.2 (-7.6, 28.1)
Eastern Europe	156/160 (97.5)	165/168 (98.2)	-0.7 (-4.5, 3.0)
Western Europe	15/18 (83.3)	16/19 (84.2)	-0.9 (-27.4, 26.3)[1]
Prior Antibiotics (within 24 hours of study drug)			
Prior antibiotics	173/191 (90.6)	161/181 (89.0)	1.6 (-5.1, 8.3)
No prior antibiotics	194/209 (92.8)	196/216 (90.7)	2.1 (-3.6, 7.8)
Fever			
Fever	157/170 (92.4)	167/179 (93.3)	-0.9 (-6.9, 5.1)
No Fever	210/230 (91.3)	190/218 (87.2)	4.1 (-2.0, 10.3)
Diabetes			
Diabetes	56/62 (90.3)	67/76 (88.2)	2.2 (-9.6,14.0)
No Diabetes	311/338 (92.0)	290/321 (90.3)	1.7 (-3.0, 6.3)
Renal function (CrCl in mL/min)	N=399	N=396	
> 80	301/326 (92.3)	269/301 (89.4)	3.0 (-1.9, 7.8)
> 50 to 80	49/56 (87.5)	76/81 (93.8)	-6.3 (-18.0, 5.3)
> 30 to 50	16/17 (94.1)	11/14 (78.6)	15.5 (-10.7, 46.5)[1]
Infection Type			
Deep/Extensive Cellulitis	186/199 (93.5)	192/214 (89.7)	3.7 (-2.1, 9.6)
Major Abscess	99/112 (88.4)	88/96 (91.7)	-3.3 (-12.4, 5.8)
Wound Infection	54/59 (91.5)	44/51 (86.3)	5.3 (-8.4, 18.9)
Lower extremity cSSSI, subject w/ diabetes or PVD	20/21 (95.2)	24/26 (92.3)	2.9 (-16.8, 21.6)[1]
Infected Bite	8/9 (88.9)	9/10 (90.0)	-1.1 (-38.5, 34.1)[1]

[1] 95% CI computed using an exact test
Source: Reviewer Table

Integrated findings in Table 6B.20, clinical cure rates based on investigator assessment at EOT were similar across most subgroups but were substantially higher for Eastern Europe vs. other regions. Treatment differences also appeared to be generally similar across subgroups but were observed to be less favorable towards ceftaroline vs. vancomycin + aztreonam for patients from Eastern and Western Europe vs. US and Latin

America, patients with vs. without fever, and patients with major abscesses vs. other infection types.

In FDA reviewer sensitivity analyses, responder rates at Day 3 supported the non-inferiority of ceftaroline to vancomycin + aztreonam in cSSSI patients included in the FDA-MITT analysis population. This finding was found to be robust to varying the size of the required reduction of lesion size as well as to varying the time in which response was measured (i.e. Day 3 timepoint vs. an EOT timepoint). Considerations of other endpoints such as investigator assessment and changes in key signs and symptoms at EOT also supported non-inferiority. In both Study P903-06 and P903-07, analyses based on an earlier timepoint such as Day 3 vs. EOT tended to show a larger treatment difference in favor of ceftaroline vs. vancomycin + aztreonam.

However, there are limitations with strength of evidence observed from the FDA reviewer sensitivity analyses which arise from Studies P903-06 and P903-07 not having been designed appropriately for showing treatment differences based on a Day 3 responder rate in FDA-MITT patients. One limitation was that the requirements for prior antibiotic therapy using a TOC primary endpoint would not be adequate for a Day 3 endpoint which could be more sensitive to use of prior antibiotic therapy. However, this limitation was less of a concern given that ceftaroline patients had actually fared less favorably when taking vs. when not taking prior antibiotic therapy. Another limitation was that use of antipyretic medication could have influenced responder rates at Day 3. Since the exact timing of the highest temperature measurement was not recorded on the patient CRF, the timing and relationship between the prior antipyretic use and absence of fever was unclear. However, given the magnitude of the treatment difference in responder rates at Day 3, it is unlikely that demonstration of non-inferiority would have been affected when adjusting patient responses based on use of antipyretics. Another limitation was lack of a standardized approach to measuring lesion size which may have led to imprecise measurements that could vary from investigator to investigator. This limitation was examined in further sensitivity analyses which defined responders according to varying % reductions in lesion size. Regardless of the % reduction required to be considered a responder, comparisons of ceftaroline to vancomycin + aztreonam remained favorable.

Overall, findings of non-inferiority of ceftaroline to vancomycin + aztreonam based on key sensitivity analyses of Day 3 responder rates in FDA-MITT subjects appeared to be robust.

VII. SAFETY

The ceftaroline safety database through August 9, 2009 contains data from 17 studies and includes information on 3153 subjects, including 1305 patients treated with the proposed to-be marketed dose of ceftaroline, 600 mg IV q 12 hr (or 400 mg IV q 12 with moderate renal impairment) in Phase 3 clinical trials. Table 7.1 shows the types of studies and number of subjects/patients enrolled.

Table 7.1: Ceftaroline Safety Database

Study Type/Group	Ceftaroline (Recommended Dose)[1]	Comparator[2]	Total
Clinical Pharmacology Studies	236 (74)	78	260[3]
• Single dose	192 (56)	70	208[3]
• Multiple dose	44 (18)	8	52
IM study	36 (0)	6	42
Pediatric (adolescent) PK study	9 (0)	0	0
Phase 2 IV cSSSI study	67 (67)	32	99
Phase 2 IM cSSSI study	98 (0)	45	143
Pooled Phase 3 IV cSSSI studies (P903-06 and P903-07)	692 (692)	686	1378
Pooled Phase 3 CABP studies (P903-08 and P903-09)	613 (613)	615	1228
Total Phase 3 studies	1305 (1305)	1301	2606
Total All Studies	1745 (1446)	1462	3153

Source: Adapted from ISS, Table 5.1-1, pg119
1 Proposed recommended dose: 600 mg IV q 12 hr, with decrease dose of 400 mg IV q 12 hr for patients with moderate renal impairment (CrCl > 30 and ≤ 50 mL/min)
2 Comparator was placebo for the Clinical Pharmacology Studies, vancomycin + aztreonam for IV cSSSI studies, linezolid + aztreonam for IM cSSSI study, and ceftriaxone for CABP (with 24 hrs of clarithromycin in P903-08)
3 Subjects who received ceftaroline fosamil, placebo, and moxifloxacin in croosover study for "thorough QT" are counted once in the total column

In the Phase 3 cSSSI clinical trials, 315/692 (45.5%) of ceftaroline-treated patients received 5-7 days of therapy and in the Phase 3 CABP clinical trials 564/613 (92.0%) of ceftaroline-treated patients received 5-7 days of treatment.

Tables 7.2 and 7.3 below contain a summary of adverse events (AEs) which occurred in each of the two Phase 3 cSSSI clinical trials (P903-06 and P903-07) and two Phase 3 CABP clinical trials (P903-08 and P903-09).

Table 7.2: Summary of Adverse Events in the Phase 3 cSSSI Clinical Trials

	Study P903-06		P903-07		Total Phase 3 cSSSI	
	Ceftaroline (N=351) n (%)	Comparator (N=347) n (%)	Ceftaroline (N=341) n (%)	Comparator (N=339) n (%)	Ceftaroline (N=692) n (%)	Comparator (N=686) n (%)
Number of Subjects with:						
Any TEAE	165 (47.0)	167 (48.1)	144 (42.2)	159 (46.9)	309 (44.7)	326 (47.5)
Any SAE	16 (4.6)	12 (3.5)	14 (4.1)	16 (4.7)	30 (4.3)	28 (4.1)
Discontinuation due to TEAE	13 (3.7)	16 (4.6)	8 (2.3)	17 (5.0)	21 (3.0)	33 (4.8)
Death	3 (0.9)	0	0	0	3 (0.4)	0

Source: ISS, Table 8.1.3-1, pg 144.

The number of patients discontinuing treatment in the comparator group is slightly greater than in the ceftaroline group, but overall, the number of treatment emergent

adverse events (TEAEs) and serious adverse events (SAEs) appear to be similar between the treatment groups. The number of deaths in the cSSSI studies was low as expected.

Table 7.3: Summary of Adverse Events in the CABP Clinical Trials

	Study P903-08		P903-09		Total Phase 3 CABP	
	Ceftaroline (N=298) n (%)	Comparator (N=308) n (%)	Ceftaroline (N=315) n (%)	Comparator (N=307) n (%)	Ceftaroline (N=613) n (%)	Comparator (N=615) n (%)
Number of Subjects with:						
Any TEAE	119 (39.9)	136 (44.2)	169 (53.7)	145 (47.2)	288 (47.0)	281 (45.7)
Any SAE	28 (9.4)	33 (10.7)	41 (13.0)	39 (12.7)	69 (11.3)	72 (11.7)
Discontinuation due to TEAE	11 (3.7)	12 (3.9)	16 (5.1)	13 (4.2)	27 (4.4)	25 (4.1)
Death	6 (2.0)	6 (1.9)	9 (2.9)	6 (2.0)	15 (2.4)	12 (2.0)
Source: ISS, Table 8.1.4-1, pg 144.						

The overall number of TEAEs appears similar across the pooled CABP population treatment groups, as do SAEs and TEAEs leading to discontinuations. The mortality rate was 2-2.5% despite enrollment of patients in PORT III and PORT IV Risk Classes and is balanced across treatment groups.

Deaths

There were three SAEs leading to death reported in ceftaroline-treated patients in Study P903-06. The SAEs leading to death, by preferred term, included respiratory failure (1), progression of low differentiated carcinoma of the neck (1), and cardiopulmonary insufficiency (1); none of the deaths was considered to be related to study medication. There were four additional deaths reported to the Applicant after the reporting period (through long-term follow-up or 30 days after EOT), with two deaths in ceftaroline-treated patients and two deaths in comparator-treated patients. The causes of death for the ceftaroline-treated patients were multi-organ failure and myocardial infarction and occurred 45 days after study drug initiation.

In the CABP trials, there were 15 SAEs leading to death in the ceftaroline-treated patients; there were six and nine deaths in Study P903-08 and P903-09, respectively. The SAEs leading to death in Study P903-08 included: sudden death (2), cardiac failure (1), sepsis (1), respiratory failure (1), and liver metastases (1). The SAEs leading to death in P903-09 included: cardiac arrest (1), nosocomial pneumonia (1), pulmonary embolism (1), malignant lung neoplasm (1), interstitial lung disease (1), respiratory failure (1), septic shock (1), metastatic neoplasm (1), and malignant neoplasm progression (1). Only one of the SAE's was considered by the investigator to be possibly related to ceftaroline. Five additional deaths were reported to the Applicant after the study recording period; one occurred in a ceftaroline-treated patient on Day 68 after initiation of study treatment due to pancreatic neoplasm. The other four deaths occurred in comparator-treated patients.

A relationship between ceftaroline and events leading to death in one ceftaroline-treated patient in Study P903-08 occurred on Study Day 3. The patient was a 73 year old Hispanic female with a remote 20-pack year history of smoking who was admitted with

right middle lobe pneumonia with no identified pathogen and was classified as PORT III. Upon admission, the patient was febrile with tympanic temperature of 105.4°C, HR 118, RR 19, and BP 110/70. ECG showed premature atrial complexes. Creatinine was normal at 0.8 mg/dl and WBC of 12.36 $X10^3/\mu L$. At 2:10 AM on the morning of Day 3, the subject was found unresponsive and was intubated (with no reported swelling of the airway or other signs of hypersensitivity). Resuscitation was not successful. The Investigator reported the death to be possibly related to study medication, but a consulting cardiologist suspected acute myocardial infarction. No autopsy was performed.

Table 7.4 shows the number of SAEs by System Organ Class (SOC) for the Phase 3 studies, separated by indication and pooled.

Table 7.4: Incidence of SAEs by System Organ Class (SOC) for Phase 3 Studies (cSSSI and CABP)

System Organ Class	cSSSI (Study 06, 07)		CABP (Study 08, 09)		Pooled Phase 3 Studies (Studies 06, 07, 08, 09)	
	Ceftaroline (N=692) n (%)	Vanc + Aztreonam (N=686) n (%)	Ceftaroline (N=613) n (%)	Ceftriaxone (N=615) n (%)	Ceftaroline (N=1305) n (%)	Pooled Comparators (N=1301) n (%)
Subjects with at Least One SAE	30 (4.3)	28 (4.1)	69 (11.3)	72 (11.7)	99 (7.6)	100 (7.7)
Blood/ Lymphatic	0	2(0.3)	3 (0.5)	0	3 (0.2)	2 (0.2)
Cardiac	4 (0.6)	5 (0.7)	7 (1.1)	11 (1.8)	11 (0.8)	16 (1.2)
Endocrine	0	0	1 (0.2)	0	1 (0.1)	0
Gastrointestinal	4 (0.6)	2 (0.3)	3 (0.5)	2 (0.3)	7 (0.5)	4 (0.3)
General Disorders and Administration Site Conditions	1 (0.1)	2 (0.3)	2 (0.3)	1 (0.2)	3 (0.2)	3 (0.2)
Hepatobiliary	0	1 (0.1)	1 (0.2)	4 (0.7)	1 (0.1)	5 (0.4)
Immune System	3 (0.4)	1 (0.1)	0	1 (0.2)	3 (0.2)	2 (0.2)
Infections and Infestations	8 (1.2)	6 (0.9)	23 (3.8)	26 (4.2)	31 (2.4)	32 (2.5)
Injury, Poisoning, and Procedural Complications	2 (0.3)	1 (0.1)	0	0	2 (0.2)	1 (0.1)
Investigations	1 (0.1)	0	1 (0.2)	1 (0.2)	2 (0.2)	1 (0.1)
Metabolism/ Nutrition	1 (0.1)	1 (0.1)	3 (0.5)	4 (0.7)	4 (0.3)	5 (0.4)
Musculoskeletal and Connective Tissue	2 (0.3)	0	0	1 (0.2)	2 (0.2)	1 (0.1)
Neoplasms Benign, Malignant, and Unspecified (incl cysts and polyps)	1 (0.1)	2 (0.3)	11 (1.8)	3 (0.5)	12 (0.9)	5 (0.4)
Nervous System	2 (0.3)	3 (0.4)	3 (0.5)	1 (0.2)	5 (0.4)	4 (0.3)
Renal and Urinary	2 (0.3)	1 (0.1)	2 (0.3)	2 (0.3)	4 (0.3)	3 (0.2)
Reproductive System and Breast	0	0	0	1 (0.2)	0	1 (0.1)
Respiratory, Thoracic, and Mediastinal	4 (0.6)	1 (0.1)	20 (3.3)	25 (4.1)	24 (1.8)	26 (2.0)
Vascular	1 (0.1)	2 (0.3)	4 (0.7)	2 (0.3)	5 (0.4)	4 (0.3)
Source: Integrated Summary of Safety (cSSSI and CABP), Table 8.5.1.1-1, Pg 166.						

Serious AEs occurring in greater than 1% of patients within a SOC for either treatment group are outlined in Table 7.5.

Table 7.5: Most Common SAE SOCs and PTs Experienced by Phase 3 Trials Population

System Organ Class/Preferred Term	cSSSI (Study 06, 07)		CABP (Study 08, 09)		Pooled Phase 3 Studies (Studies 06, 07, 08, 09)	
	Ceftaroline (N=692) n (%)	Vancomycin plus Aztreonam (N=686) n (%)	Ceftaroline (N=613) n (%)	Ceftriaxone (N=615) n(%)	Ceftaroline (N=1305) n(%)	Pooled Comparators (N=1301) n(%)
Infections and Infestations	8 (1.2)	6 (0.9)	23 (3.8)	26 (4.2)	31 (2.4)	32 (2.5)
Pneumonia	0	1 (0.1)	9 (1.5)	9 (1.5)	9 (0.7)	10 (0.8)
Pyothorax	0	0	4 (0.7)	0	4 (0.3)	0
Cellulitis	2 (0.3)	1 (0.1)	1 (0.2)	1 (0.2)	3 (0.2)	2 (0.2)
Lung abscess	0	0	2 (0.3)	4 (0.7)	2 (0.2)	4 (0.3)
Respiratory, Thoracic, and Mediastinal Disorders	4 (0.6)	1 (0.1)	20 (3.3)	25 (4.1)	24 (1.8)	26 (2.0)
Pulmonary embolism	1 (0.1)	0	5 (0.8)	4 (0.7)	6 (0.5)	4 (0.3)
Pleural effusion	0	0	5 (0.8)	6 (1.0)	5 (0.4)	6 (0.l5)
Respiratory failure	1 (0.1)	0	4 (0.7)	1 (0.2)	5 (0.4)	1 (0.1)
COPD	0	0	4 (0.7)	6 (1.0)	4 (0.3)	6 (0.5)
Cardiac Disorders	4 (0.6)	5 (0.7)	7 (1.1)	11 (1.8)	11 (0.8)	16 (1.2)
Cardiac failure congestive	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.2)	2 (0.2)	2 (0.2)
Cardiopulmonary failure	1 (0.1)	0	1 (0.2)	1 (0.2)	2 (0.2)	1 (0.1)
Bradycardia	1 (0.1)	1 (0.1)	0	0	1 (0.1)	1 (0.1)
Source, ISS, Supporting Table 4.2.3.3.1, Pg 868.						

Event in the Infections and Infestations SOC were primarily related to the underlying infection, as were those in the Respiratory, Thoracic, and Mediastinal SOC, with the exception of pulmonary embolism. SAEs related to hypersensitivity were rare and included one event each of anaphylactic shock, anaphylactoid reaction, and hypersensitivity in the ceftaroline treatment group and two events of hypersensitivity noted in the comparator treatment group. Two patients treated with ceftaroline had convulsions, one of which was assessed by the investigator, but not the FDA clinical reviewer, as possibly related to study medication. Gastrointestinal and renal SAEs were rare.

TEAEs leading to discontinuation of study medication

Table 7.6 shows the incidence of AE by SOC leading to discontinuation of study drug or withdrawal from the clinical trial.

Table 7.6: Incidence by SOC of AE Leading to Discontinuation of Study Drug or Withdrawal from the Clinical Trial

System Organ Class	cSSSI (Study 06, 07)		CABP (Study 08, 09)		Pooled Phase 3 Studies (Studies 06, 07, 08, 09)	
	Ceftaroline (N=692) n (%)	Vancomycin plus Aztreonam (N=686) n (%)	Ceftaroline (N=613) n (%)	Ceftriaxone (N=615) n(%)	Ceftaroline (N=1305) n(%)	Pooled Comparators (N=1301) n(%)
Subjects with at Least AE	21 (3.0)	33 (4.8)	27 (4.4)	25 (4.1)	48 (3.7)	58 (4.5)
Cardiac	0	2 (0.3)	2 (0.3)	7 (1.1)	2 (0.2)	9 (0.7)
Eye	0	1 (0.1)	0	0	0	1 (0.1)
Gastrointestinal	0	1 (0.1)	3 (0.5)	2 (0.3)	3 (0.2)	3 (0.2)
General Disorders and Administration Site Conditions	1 (0.1)	3 (0.4)	3 (0.5)	1 (0.2)	4 (0.3)	4 (0.3)
Hepatobiliary	0	0	2 (0.3)	2 (0.3)	2 (0.2)	2 (0.2)
Immune System	6 (0.9)	6 (0.9)	1 (0.2)	0	7 (0.5)	6 (0.5)
Infections and Infestations	3 (0.4)	5 (0.7)	6 (1.0)	7 (1.1)	9 (0.7)	12 (0.9)
Investigations	2 (0.3)	2 (0.3)	1 (0.2)	1 (0.2)	3 (0.2)	3 (0.2)
Metabolism and Nutrition	0	1 (0.1)	0	1 (0.2)	0	2 (0.2)
Neoplasms Benign, Malignant, and Unspecified (incl cysts and polyps)	0	0	4 (0.7)	1 (0.2)	4 (0.3)	1 (0.1)
Nervous System	0	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Renal and Urinary	0	1 (0.1)	1 (0.2)	0	1 (0.1)	1 (0.1)
Respiratory, Thoracic, and Mediastinal	1 (0.1)	1 (0.1)	6 (1.0)	4 (0.7)	7 (0.5)	5 (0.4)
Skin and subcutaneous tissue	8 (1.2)	17 (2.5)	0	1 (0.2)	8 (0.6)	18 (1.4)
Vascular	0	2 (0.3)	3 (0.5)	1 (0.2)	3 (0.2)	3 (0.2)
Source: Integrated Summary of Safety (cSSSI and CABP), Table 8.6.1.1-1, pg 180.						

Overall, the number of patients discontinuing study medication or withdrawing from the clinical trial because of an AE is < 5% of the pooled study populations. The only SOC in which >1% of the trial population discontinued study drug or withdrew from the study is the Skin and Subcutaneous Tissue Disorders SOC. These events occurred primarily in the cSSSI studies and were more common (twice as high) in the comparator treatment group with vancomycin + aztreonam.

In the Clinical Pharmacology studies, there were no deaths or SAEs. Four/195 (2.1%) healthy subjects in the ceftaroline treatment groups discontinued from study medication compared to 1/78 (1.3%) subject in the placebo treated group; the AEs leading to discontinuation in the ceftaroline treatment group included pruritis, rash maculopapular, urticaria, and phlebitis. There were no discontinuations from the special population studies.

Adverse Drug Reactions

Adverse drug reactions, a subset of TEAEs, were summarized in an effort to try to identify important adverse reactions in subjects receiving ceftaroline fosamil and to avoid including events that would commonly be observed in the absence of ceftaroline or would not be plausibly associated with ceftaroline. For the Phase 3 trials, these adverse drug reactions were chosen as follows:

- Any preferred term occurring in the ceftaroline treatment group with an incidence greater than or equal to 1% greater than observed in the comparator group within a pooled indication (CABP or cSSSI) or all pooled Phase 3 studies.
- Any preferred term occurring in the ceftaroline group with an incidence greater than or equal to 5% in either pooled indication or in all Phase 3 studies pooled.
- The three most recently revised cephalosporin labels for cefditoren (2007), cefotaxime (2007), and ceftriaxone (2004) were reviewed for all terms mentioned in the adverse drug reaction section, with like or related preferred terms from these drugs included in the list for ceftaroline.

Adverse drug reactions which occurred in greater than or equal to 2% of patients receiving ceftaroline fosamil in the pooled Phase 3 clinical trials are shown in Table 7.7 below.

Table 7.7: Adverse Drug Reactions Occurring in ≥ 2% of Ceftaroline Treated Patients

System Organ Class Preferred Term	Pooled Phase 3 Clinical Trials	
	Ceftaroline (N=1305)	Pooled Comparators (N=1301)
Gastrointestinal Disorders		
Diarrhea	5%	3%
Nausea	4%	4%
Constipation	2%	2%
Vomiting	2%	2%
Investigations		
Increased transaminases	2%	3%
Metabolism and nutrition disorders		
Hypokalemia	2%	3%
Nervous system disorders		
Headache	4%	3%
Psychiatric disorders		
Insomnia	3%	2%
Skin and subcutaneous tissue disorders		
Rash	3%	2%
Pruritus	2%	5%
Vascular disorders		
Phlebitis	2%	1%
Source: ISS, Table 8.2-1, pgs 146-147.		

In addition to the previous summary of adverse events, the Applicant also looked at TEAEs and safety laboratory studies by organ system or syndromes relevant to the cephalosporin class. Included in this analysis were TEAEs indicating potential renal impairment, drug-induced anemia, liver injury, antibiotic-associated diarrhea, and allergic reactions.

- In preclinical animal studies there had been some evidence of renal toxicity as manifested by inflammatory changes in the renal tubular epithelium of rats and monkeys. Monkeys who received supratherapeutic doses in relation to human doses had evidence of decreased red blood cell counts. A decrease in seizure latency time was noted in rats following pentylenetaetrazol administration at ceftaroline doses resulting in plasma levels ≥ 12 times those of the human Cmax. Seizures were also noted in rats and monkeys in 4 and 13-week repeat dose toxicity studies at estimated plasma AUC levels of 5 and 20 times human AUCs, respectively.
- In the pooled Phase 3 clinical trials, the incidence of TEAEs representing potential renal impairment were low and similar between ceftaroline and comparator-treated groups at 1.5% and 0.8% respectively. Potentially clinically significant renal chemistry creatinine and creatinine clearance values occurred in 1.4 and 0.7% of ceftaroline treated patients, respectively and 1.9 and 1.3% of comparator-treated patients respectively.
- In clinical trials, the incidence of Coomb's test seroconversion was higher in the ceftaroline-treated group compared to the comparator-treated group, with 10.7% of ceftaroline-treated patients and 4.4% of comparator-treated patients noted to have seroconversion. However, in the pooled Phase 3 clinical trials, TEAEs representing potential drug-induced hemolytic anemia were low at 1.2% and 1.3% in the

ceftaroline and comparator-treated groups, respectively. Potentially clinically significant decrease in hemoglobin and hematocrit (both defined as < 0.8 x LLN and decrease from baseline > 20%) occurred in 1.5% and 1.2% of ceftaroline-treated patients, respectively, compared to 1.9% and 1.7% in the comparator-treated group.

- In the Phase 3 clinical trials, two ceftaroline-treated patients and one comparator-treated patient had seizures. Although the seizure experienced by one patient treated with ceftaroline was assessed by the investigator as being related to study drug, the seizure occurred 2 days after the last dose of ceftaroline and was likely not related, The second ceftaroline-treated patient had a seizure 23 days after study medication was discontinued and the seizure was assessed by the investigator as unrelated.
- In the Phase 3 clinical trials, the incidence of TEAEs representing potential allergic reactions occurred in 5.4% of ceftaroline-treated patients and 8.5% of comparator-treated groups. Three TEAEs indicative of potential anaphylaxis were noted; all occurred in ceftaroline-treated patients.
- In the pooled Phase 3 clinical trials potential antibiotic-associated diarrhea was observed in ceftaroline treatment groups with similar incidence to that of comparator (4.5% vs. 3.2%, respectively). Three patients with *C. difficile*-associated diarrhea were confirmed; two patients were treated with ceftaroline and one with comparator.
- In the clinical trials, there did not appear to be any evidence of cardiac toxicity as determined by TEAEs or ECG testing in clinical trials. The FDA review of the "thorough QT" study found that a single supratherapeutic dose of ceftaroline (1500 mg) had no significant QT prolongation effect.
- In the Phase 3 clinical trials, the incidence of TEAEs representing potential liver injury or elevations of ALT or AST to 3X, 5X, and 10X the upper limit of normal did not differ between treatment groups. No subject/patient treated with ceftaroline met Hy's Law laboratory criteria.

VIII: ISSUES FOR DISCUSSION

I. Community-acquired Pneumonia (CABP)

Has the applicant demonstrated the safety and efficacy of ceftaroline for the requested indication of community-acquired bacterial pneumonia (CABP)? (VOTE)

- If yes, are there any specific issues that should be addressed in labeling?
- If not, please discuss what additional data are needed.

II. Complicated Skin and Skin Structure Infections (cSSSI)

Has the applicant demonstrated the safety and efficacy of ceftaroline for the requested indication of complicated skin and skin structure infections (cSSSI)? (VOTE)

- If yes, are there any specific issues that should be addressed in labeling?
- If not, please discuss what additional data are needed.

X. REFERENCES

Bullowa, J.G.M. *The Management of Pneumonias*. 1937; Oxford University Press, New York.

Finland, M., Spring, W.C., Lowell, F.C. Clinical and laboratory studies on the use of serum and sulfapyridine in the treatment of the pneumococcal pneumonias. *N Engl J Med.* 1940; 222:739–47.

Flippin, H.F., Lockwood, J.S., Pepper, D.S., Schwartz, L. (1939). The treatment of pneumococcic pneumonia with sulfapyridine. *JAMA*. 1939; 112:529-34.

Halm., E., Fine, M.J., Marrie, T.J., Coley, C.M., Kapoor, W.N., Obrosky, D.S., Singer, D.E. (1998). Time to clinical stability in patients hospitalized with community-acquired pneumonia. JAMA. 1998; 279:1452-1457.

Mandell, L.A., Wunderink, R.G., Anzueto, A., Bartlett, J.G., Campbell, G.D., Dean, N.C., Dowell, S.F., File, T.M., Musher, D.M., Niederman, M.S., Torres, A., Whitney, C.G. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clinical Infectious Diseases*. 2007; 44:S27-72.

Meakins J.C. and Hanson, F.R. The treatment of pneumococcic pneumonia with sulfapyridine. *Can Med Assoc J*. 1939; 40(4):333-336.

Pertel, P.E., Bernardo, P., Fogarty, C., Matthews, P., Northland, R., Benvenuto, M., Thorne, G.M., Luperchio, S.A., Arbeit, R.D., Alder, J. Effects of prior effective therapy on the efficacy of daptomycin and ceftriaxone for the treatment of community-acquired pneumonia. *Clinical Infectious Diseases*. 2008; 46(8):1142-51.

Snodgrass, W.R. and Anderson T. Prontosil in the Treatment of Erysipelas, A Controlled Series of 312 Cases. *British Medical Journal*. July 17, 1937:101-104.

Snodgrass, W.R. and Anderson T. Sulphanilamide in the Treatment of Erysipelas, A Controlled Series of 270 Cases. *British Medical Journal*. December 11, 1937:1156-1159.

Wilson A.T., Spreen, A.H., Cooper, M.L., Stevenson, M.D., Cullen, G.E., Mitchell, A.G. Sulfapyridine in the treatment of pneumonia in infancy and childhood. *JAMA*. 1939; 112(15):1435-1439.

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought this issue to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.