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APPLICATION NUMBER:

200327

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	October 28, 2010
From	Janice Pohlman, MD, MPH
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	200327
Applicant	Cerexa, Inc. , a subsidiary of Forest Laboratories, Inc.
Date of Submission	December 30, 2009
PDUFA Goal Date	October 30, 2010
Proprietary Name / Established (USAN) names	Teflaro/ceftaroline fosamil
Dosage forms / Strength	400 mg and 600 mg of ceftaroline fosamil, powder for injection
Proposed Indication(s)	1. Acute Bacterial Skin and Skin Structure Infections 2. Community-Acquired Bacterial Pneumonia
Recommended:	Approval

Cross Discipline Team Leader Review Template

1. Introduction

The New Drug Application (NDA 200327), ceftaroline fosamil for injection, was submitted by Cerexa, Inc., a subsidiary of Forest Laboratories, Inc., on December 30, 2009. Ceftaroline fosamil is a new molecular entity (NME) of the cephalosporin class of beta-lactam (β-lactam) antibacterial agents.

Ceftaroline has in vitro activity against both Gram positive and Gram negative bacteria, including activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and *Enterobacteriaceae*. Although MRSA is generally resistant to β-lactam antibacterial agents due to the presence of the mecA gene, ceftraoline retains activity through its strong binding to penicillin binding protein (PBP) PBP2a. *Enterobacteriaceae* producing AmpC β-lactamase and extended spectrum β-lacatmases (ESBLs) are resistant to ceftaroline.

The Applicant is seeking the following indications for ceftaroline fosamil:

Community-Acquired Bacterial Pneumonia
Teflaro 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 (b) (4) cases with concurrent bacteremia), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Haemophilus influenzae,* (b) (4) *Klebsiella pneumoniae,* and *Escherichia coli.*

Complicated Skin and Skin Structure Infections
Teflaro 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 -resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, (b) (4)), *Escherichia coli*, *Klebsiella pneumoniae, Klebsiella oxytoca,* and (b) (4)

The primary review issue for this application was related to the evolution of understanding of the science of clinical trial design, including the use of noninferiority (NI) trial design in CABP and acute bacterial skin and skin structure infections (ABSSSI) treatment trials. [NOTE: The term complicated skin and skin structure infections will be replaced with ABSSSI throughout the rest of the document.] Continuing evaluation of the historical evidence for treatment effect of antibacterial agents relative to placebo in the treatment of CABP and ABSSSI has led to

discussions about appropriate primary efficacy endpoints, timing of assessment of those endpoints, and NI margin which can be justified by the literature for those endpoints. These topics will be discussed more fully in the body of this review.

The clinical safety profile is similar to that of other cephalosporins. Preclinical animal studies identified the central nervous system and renal system as the primary organs of toxicity. The neurotoxicity was manifested as seizures at high exposures (greater than those in humans at the recommended dose) and vacuolization of the renal tubular epithelium. The major finding noted in clinical trials was the higher incidence of direct Coombs' test seroconversion in ceftaroline-treated patients, particularly when compared to patients receiving cetriaxone; this finding was not associated with drug-induced hemolytic anemia in these clinical trials.

Data integrity issues were identified at one site in India, enrolling seven patients. These patients were subsequently excluded from the FDA analyses at the recommendation of the Division of Scientific Investigation (DSI). Additionally, the Office of Antimicrobial Products (OAP) made the decision to exclude two additional sites in India, enrolling a single patient each, since they utilized the same contract research organization (CRO), and DSI could not assure reliability of these data.

2. Background

- Peninsula Pharmaceuticals, Inc. submitted the original IND for ceftaroline fosamil, IND 71371, on December 13, 2004.
- The FDA was notified about the change in Sponsor from Peninsula Pharmaceuticals to Cerexa, Inc. on June 30, 2005.
- Cerexa, Inc. received fast track designation for their ABSSSI indication on February 28, 2006.
- An End of Phase 2 (EOP2) meeting was held between Cerexa, Inc., and FDA on October 24, 2006. The meeting package contained the protocol for the planned Phase 3 clinical trials in ABSSSI (independent, but of identical design). Discussion at the meeting focused on the proposed use of an adjunctive macrolide in the CABP trials; Cerexa maintained that US sites would not participate in a trial which did not include a macrolide given the IDSA/ATS clinical guidelines for community-acquired pneumonia (CAP).[1] FDA recommended that the primary analysis populations for the Phase 3 trials should be the modified intent-to-treat (MITT) and clinically evaluable (CE) populations. The FDA also requested justification for the proposed NI margin for the ABSSSI trials.
- Although the basic design of the proposed ABSSSI trial was acceptable, discussion regarding justification for the proposed NI margin of 10% continued throughout the first half of 2007. On June 1, 2007, FDA acknowledged that an NI study design was acceptable to support an ABSSSI indication and a 10% NI margin was acceptable.
- Special protocol assessments (SPAs) were submitted for the CABP indication on January 26, 2007 for Trial P903-09 and January 29, 2007 for trial P903-08. A no agreement letter was issued by the Agency to Cerexa, Inc., on March 15, 2007.

- The CABP trial designs continued to be a topic of discussion between the Agency and Cerexa during the second quarter of 2007, in light of the public workshop and April 2007 AIDAC meeting (see discussion below); relevant issues discussed with Cerexa included concomitant use of a macrolide and justification for the NI margin of 10%. Cerexa was informed by the Agency on September 11, 2007, that sufficient evidence was available to support a NI margin of 10% in patients with moderate to severe CABP (i.e. Pneumonia Patient Outcomes Research Team (PORT) Risk Class III or greater).[2] This ultimately resulted in the Applicant amending the CABP protocol to enroll only patients in Port Risk Class III and IV to the trials. Cerexa was also advised to enrich the population for patients with microbiologically documented disease.
- A teleconference between the Division and Cerexa took place on November 2, 2007. Cerexa, Inc. attempted to justify continued enrollment of patients in PORT Risk Class II. The Division did not support this idea, unless sufficient clinical parameters could provide evidence of disease similar to that of the historical populations from which the margin was derived.
- A pre-NDA meeting was held between representatives of Cerexa, Inc., Forest Laboratories, Inc., and FDA on July 7, 2009.
- A separate CMC pre-NDA meeting was held between Cerexa, Inc., Forest Laboratories, Inc., and the FDA on July 22, 2009.
- The Agency received a follow-up report from Cerexa regarding an investigator from India who had participated in the CABP Trial 09 on August 13, 2010. This investigator had been reported on the internet to have allegedly committed fraud in another company's clinical trial. In a follow-up site inspection, Cerexa was unable to locate source material or documents. Data from the 7 patients enrolled at this site were excluded from FDA analyses based on recommendations from the DSI. Additionally, the OAP chose to exclude two additional sites from India (one patient enrolled per site) from the analysis since DSI could not insure reliability of the data.
- At the time of the Anti-Infective Drugs Advisory Committee (AIDAC) meeting on September 7, 2010, there was a meaningful difference between the Applicant proposed antimicrobial susceptibility breakpoints and those proposed by the FDA. Upon continued review of the data, including clinical experience, pharmacokinetic/pharmacodynamic models, and Monte Carlo simulations, the FDA proposed less stringent breakpoints, to which the Applicant agreed.

Plans for the Phase 3 clinical development program for ceftaroline, including clinical trial design for use in the treatment of ABSSSI and CABP were initiated at the EOP2 meeting between Cerexa, Inc. and the Agency on October 24, 2006. The ABSSSI clinical trials were begun in February and March 2007 and the CABP clinical trials in July 2007 and January 2008, prior to public discussions regarding the use of non-inferiority trials for these indications.

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.
- 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 NI 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 a draft guidance on development of antibacterial drugs for treatment of CABP for public comment.
- 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 (mITT) population as the primary analysis population along with recommendations for enrollment of sicker patients (PORT IV and V) or patients who were older than 50 years of age who are at higher risk for morbidity and mortality.

For ABSSSI, during a single session of a multi-day AIDAC meeting on November 8, 2008, use of a non-inferiority 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 NI 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.

3. CMC/Device

The Chemistry, Manufacturing, and Controls (CMC) review was completed by Andrew Yu, PhD. Dr. Yu concluded that the NDA contained sufficient information to assure identity, strength, purity, and quality of the drug product and recommended approval. Additional details may be found in his review.

The drug substance as manufactured is ceftaroline fosamil monoacetate monohydrate. Ceftaroline fosamil is a prodrug synthesized from the active moiety to increase water solubility. [redacted] (b) (4) the

drug substance is a stable solvate substance, ceftaroline fosamil monoacetate monohydrate.

Ceftaroline fosamil (DMF # 23167) is manufactured by ACS Dobfar. The drug substance has (b) (4) related impurities that have been chemically characterized and controlled by specifications noted in the NDA. Adequate stability data was submitted with the NDA to support a 24 month shelf life for the drug substance. The drug substance (b) (4) must be stored in its recommended container.

The drug product (Teflaro) contains ceftaroline fosamil formulated with (b) (4) arginine (b) (4) It is supplied in single use, clear glass vials, containing 400 or 600 mg of ceftaroline fosamil (calculated on (b) (4) anhydrous basis) and is manufactured by ACS Dobfar. The ceftaroline fosamil is (b) (4) and packaged by Facta Farmaceutica.

Two manufacturing issues were identified during the review cycle, but were adequately resolved by the Applicant. These issues were:

- Exposure of the drug to (b) (4) could potentially cause drug degradation, however adequate protective measures were put in place by the Applicant with no stability loss.
- (b) (4) . However, additional batch data assured tha (b) (4) was adequate, so that the product still falls within acceptable limits.

Teflaro 400 and 600 mg are adequately controlled with product specifications for appearance, potency, uniformity, individual and total impurities, moisture, pH, endotoxin, sterility, particulate matter, and other USP tests.

The drug product is to be constituted with 20 mL of Water for Injection, USP and constitution time is 2 minutes. The entire contents must be further diluted to ≥ 250 mL before infusion. Appropriate infusion solutions include 0.9% Sodium Chloride Injection, USP; 5% Dextrose Injection, USP, 2.5% Dextrose, USP; 0.45% Sodium Chloride Injection, USP; or lactated Ringer's solution. Arginine (b) (4) with the drug in solution, but is controlled within a qualified level of (b) (4). Recommended infusion time is 1 hour. The constituted drug product in the infusion bag should be used within 6 hours when stored at room temperature or within 24 hours under refrigeration at 2 to 8°C

The compatibility of Teflaro with other drugs has not been fully established, however a list of chemically incompatible dugs are included in the NDA.

Facilities inspections have been completed. The drug substance, ceftaroline fosamil and (b) (4) and the site was found to be acceptable as determined by profile (b) (4) The ceftaroline fosamil for injection is packaged into vials

by Facta Farmaceutica S.p.A. in Teramo, Italy and the site was also found to be acceptable by profile [LPV].

The product quality microbiology review was completed by Vinayak Pawar, PhD. Based on his review, the product is recommended for approval. DMF Type V (b) (4) (b) (4)" held by (b) (4) was reviewed by Marla Stevens-Riley, OGD Microbiology and found adequate on November 20, 2007. Stability data for drug substance and L-arginine were reported in DMF #s 23167 and (b) (4) respectively. Each met sterility and endotoxin acceptance criteria. Stability data are within the proposed drug product specification limits for sterility (sterile) and endotoxin (<0.24 EU/mg per USP < 85 >) under the proposed storage conditions of up to 24 months when stored in refrigerated conditions (2-8°C). In addition to sterility and bacterial endotoxin, there were no observable changes in terms of appearance or clarity, nor were there any trends identified with respect to constitution time, pH, assay, related substances, (b) (4) .

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology review was completed by Dr. Amy Ellis, PhD. Additional details may be found in her review.

Ceftaroline fosamil has a nonclinical toxicity profile similar to other cephalosporins. Target organs of toxicity identified in rats and monkeys include the kidneys, central nervous system, and lymphatic tissues (spleen).

Four-week IV repeat dose toxicity studies in rats were noted to cause crystalluria and crystal nephropathy at doses of 300 and 100 mg/kg/day and were associated with histologic changes in the bladder and kidney; recovery was not complete after 28 days. Minimal to mild hypertrophy of the germinal center of the spleen was noted at 300 and 100 mg/kg after the 4 week treatment period but was reversible after discontinuation of drug. The no observed adverse effect level (NOAEL) in the rat was 100 mg/kg/day when administered IV daily for 4 weeks. Treatment related mortality occurred at doses of 1000 mg/kg apparently related to nephrotoxicity. Tonic /clonic convulsions were also noted at higher doses (1000 and 2000 mg/kg).

In a 4-week repeat dose toxicity study in monkeys, renal toxicity was observed at 80 and 400 mg/kg. Signs included increased BUN, fluid retention, and proteinuria, as well as numerous histopathologic changes in the kidney. Animals also showed evidence of lymphoid hyperplasia (spleen, lymph nodes, and gastrointestinal tissue), possibly indicating a hypersensitivity to drug or stimulation of the immune system. Reduction in red blood cell number, hemoglobin, and hematocrit was observed in several high dose animals and may be related to immune complex formation. Tonic/clonic convulsions were also noted in some high dose animals. The NOAEL in monkeys was 16 mg/kg when administered daily for 1 month.

In the Irwin test used to detect potential CNS adverse events, tonic/clonic seizures were observed in rats administered a 2000 mg dose. The estimated C_{max} for the 2000 mg dose is approximately 100 times higher than human C_{max} at therapeutic doses. Additionally, ceftaroline fosamil demonstrated proconvulsant activity by reducing seizure latency time in rats following pentylenetetrazol administration at C_{max} levels approximately 20 X the C_{max} level in humans.

In vitro cardiovascular safety pharmacology showed that ceftaroline fosamil did not inhibit the hERG channel maximal tail current in HEK293 cells at concentrations as high as 1200 mcg/mL. In isolated canine Purkinje fibers, it did not impact action potential duration APD_{60} or APD_{90} at frequencies ranging from 0.5 to 3 Hz at concentrations up to100 µmol/L. In a dose-escalation study in monkeys, systolic, diastolic, and mean arterial pressures were comparable to vehicle control at doses up to 400 mg/kg (estimated 25 times human C_{max}). There were no drug-induced changes in heart rate, PR or QT intervals, QTcQ, and QRS duration. The electrocardiogram (ECG) waveform was not affected in 2/4 monkeys, however the remaining 2 monkeys developed ventricular tachycardia 2-3 hours following administration of ceftaroline. These two animals had exhibited premature ventricular contractions with vehicle control.

The safety pharmacology studies exploring respiratory and water and electrolyte balance demonstrated no significant change.

Genetic toxicity of the M-1 metabolite of ceftaroline fosamil was not addressed adequately in vitro in the rat, because it is not converted to the metabolite by rat hepatic microsomes. Ceftaroline fosamil was negative in the Ames bacterial reverse mutation assay and mouse lymphoma assay. It induced chromosomal aberrations in Chinese hamster lung cells in the absence of metabolic activation, but not in the presence of hepatic microsomal enzymes derived from rats. Doses of ceftaroline fosamil up to 2000 mg/kg in rats or mice did not induce formation of micronucleated erythrocytes in bone marrow of rats or mice and did not induce unscheduled DNA syntheisis in rat hepatocytes.

Due to excessive maternal toxicity in rabbits, including mortality, the rabbit may not be appropriate model for reproductive toxicity. Rats appeared to be acceptable and did not demonstrate evidence of teratogenicity.

Ceftaroline fosamil does not appear to be highly antigenic when administered IV.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology review was completed by Aryun Kim, Pharm.D. The Pharmacometric review was done by Yongheng Zhang, Ph.D. Additional clinical pharmacology information can be found in their reviews. The clinical pharmacology reviewer recommended approval of ceftaroline fosamil.

Ceftaroline fosamil (prodrug) is rapidly converted during infusion by in vivo phosphatase enzymes to active ceftaroline. Ceftaroline is the primary circulating compound and exhibits linear pharmacokinetics with approximately dose-proportional increase in exposure over the single dose range studied (50-1000 mg). The β-lactam ring of ceftaroline undergoes hydrolysis to form the inactive open-ring metabolite (ceftaroline M-1). The half-life is short at approximately 1-1/2 hours. Due to rapid biotransformation, concentrations of ceftaroline were generally measurable only during IV infusion.

Plasma protein binding is low at about 20% in humans. The cytochrome P450 system does not appear to be a significant metabolic pathway for ceftaroline as assessed by an in vitro study of human liver microsomes. Ceftaroline and metabolites are eliminated primarily through renal excretion.

In vitro, ceftaroline is not an inhibitor or inducer of the CYP450 isoenzymes and is therefore unlikely to have in vivo drug interactions with CYP450 substrates. In a population PK study, no major differences in exposure were observed with concomitant medications including CYP450 substrates, inhibitor, or inducers, anionic or cationic drugs known to undergo active renal secretion, and vasodilator or vasoconstrictor drugs that may alter blood flow.

Pharmacokinetic analysis of ceftaroline in healthy elderly subjects (≥ 65 years) compared to young adult subjects (18-45 years) showed that mean plasma clearance was decreased 25% in the elderly and correspondingly, exposure was 33% greater in the elderly. The higher exposure is likely to be related to age-related decline in renal function. No dose adjustment is necessary based on age.

The pharmacokinetics of ceftaroline were studied in adolescent patients 12-17 years of age, receiving concomitant antibiotic therapy. Based on the single dose PK, the 600 mg IV every12 hours appears to be appropriate for adolescents.

There was a slight trend (15%) toward higher exposures in females, however no adjustment is necessary based on gender.

Since the primary means of elimination is through the renal system, it is anticipated that exposure would vary (decrease) with increasing levels of renal impairment. Ceftaroline was studied in patients with mild (creatinine clearance (CrCL) >50 to ≤80 mL/min), moderate (CrCL >30 to ≤50 mL/min), and severe renal impairment (CrCL ≤30 mL/min) and in patients with end-stage renal disease (ESRD) dosed prior to and following hemodialysis. Ceftaroline clearance, renal clearance, and amount of drug in the urine decreased with declining renal function. Half-life in patients with ESRD was approximately 3 hours compared to 1-1/2 hours in those without renal impairment. Approximately 22% of a dose was removed by hemodialysis. Dose adjustments are recommended for patients with moderate and severe renal impairment and in patients on hemodialysis. For patients with moderate renal impairment (CrCL > 30 to ≤50 mL/min) a decrease in dose to 400 mg IV every 12 hrs is recommended. For patients

with severe renal impairment (CrCL ≥ 15 to ≤ 30 mL/min) a decrease in dose to 300 mg IV every 12 hrs is recommended and in patients with end-stage renal disease (ESRD) on hemodialysis, a decrease in dose to 200 mg IV every12 hrs is recommended.

No hepatic impairment studies were performed.

A thorough QT study was performed. There was no significant QT prolongation noted in this study. The study performed was a blinded, single dose, three-period cross-over study in which 54 healthy adult subjects (50% each gender) were administered a single supratherapeutic dose of 1500 mg of ceftaroline IV, moxifloxacin 400 mg IV, and placebo with a 5 day wash out between doses. The largest difference for the two-sided 90% CI for mean difference between ceftaroline and placebo was < 10 msec, the threshold of regulatory concern. The largest lower bound of the two sided 90% CI for ΔΔQTcIb was greater than 5 msec indicating that assay sensitivity was established.

Exposure-Response (Pharmacodynamics)
In a neutropenic mouse thigh model against methhicillin-susceptible *S. aureus* (MSSA) and MRSA and *S. pneumoniae*, percent time above minimum inhibitory concentration (%T>MIC) (i.e. percent of the dosing interval that free drug concentrations are greater than MIC) was associated with in vivo efficacy, as for other β-lactams. Exposure-response analysis with population PK analysis indicated a significant positive relationship between %T>MIC and per-patient microbiological response with monomicrobial or polymicrobial *S. aureus* or *S. pyogenes* in ABSSSI. For CABP, an exposure response relationship was not identified, as a majority of patients had a high and limited range of ceftaroline exposures.

Based on PK-PD target attainment analyses by Monte Carlo simulation, ceftaroline exposures associated with bacteriostasis were predicted to be at a MIC of ≤ 2 mcg/mL against *S. aureus* and MIC of ≤ 1 mcg/mL against *S. pneumoniae* for the proposed regimen of ceftaroline fosamil 600 mg every 12 hr.

6. Clinical Microbiology

The Clinical Microbiology review was completed by Avery Goodwin, Ph.D., who recommended approval of the application with changes to the microbiology subsection of the proposed label.

Ceftaroline is a new molecular entity in the cephalosporin class of antibacterial agents. It inhibits cell wall synthesis by binding to PBP of bacteria and inhibits peptidoglycan synthesis. Unlike most other β-lactams, ceftaroline has activity against MRSA due to high affinity for PBP2a and against *S. pneumoniae* with reduced susceptibility to penicillin due to high affinity for PBP2x.

Ceftaroline has activity against pathogens related to ABSSSI and CABP including MSSA, MRSA,*S. pyogenes*, *S. agalactiae*, *S. pneumoniae, H. influenzae, Moraxella catarrahlis,* and a variety of *Enterobacteriaceae*. Decreased in vitro activity is noted in Gram negative bacterial isolates with AmpC and ESBL producers and ceftazidime non-susceptible *Enterobacteriaceae*. Activity is minimal against *Pseudomonas aeruginosa* and therefore ceftaroline would be unlikely to adequately treat infections caused by this bacterium.

Based on surveillance data, the ceftaroline MIC_{90} for United States (US) isolates of MRSA is 1 mcg/mL. Ceftaroline MIC_{90} values for *S. pneumoniae* including penicillin-intermediate and penicillin-resistant isolates ranged from 0.004 to 0.025 mcg/mL. The ceftaroline MIC_{90} values for some β-hemolytic streptococci were ≤0.016 mcg/mL and 1 mcg/mL against penicillin resistant viridans streptococci. MIC_{90} values for *Enterobacteriaceae* ranged from ≤ 0.016 mcg/mL to > 32 mcg/mL.

Resistance to ceftaroline can occur due to production of β-lactamase or alteration of the PBP target site. Based on in vitro studies, there was a low propensity for development of ceftaroline resistance with serial passage experiments compared with other agents.

Ceftaroline displays short post-antibiotic effect (PAE) ranging from 0.8 to 7.2 hours for *S. aureus* and less for *S. pneumoniae.* The ceftaroline PAE against *Enterobacteriaceae* was not observed.

Animal Infection models:
A PK-PD relationship was established in the neutropenic and non-neutropenic murine thigh and lung infection models. The %T>MIC was identified as the pharmacodynamic parameter best predictive of ceftaroline efficacy.

Based on PK-PD target attainment data alone, (where desired targets were %*f*T>MIC associated with maximal efficacy or bacterial stasis from neutropenic thigh models or higher probabilities of per-patient microbiological success from clinical exposure response analysis), a susceptible MIC breakpoint of 0.5-2 mcg/mL for *S. aureus* and 1 mcg/mL for *S. pneumoniae* could be established based on PK-PD target attainment.

The Applicant evaluated the activity of ceftaroline and comparator agents in accordance with Clinical and Laboratory Standards Institute (CLSI) methods including broth microdilution, disk diffusion, and agar diffusion testing. The Applicant proposed interpretive criteria based on these studies which are noted in Table 1 below.

CEFTAROLINE IN VITRO SUSCEPTIBILITY TEST INTERPRETIVE CRITERIA

Table 1 Applicant's Proposed Ceftaroline In Vitro Susceptibility Test Interpretive Criteria

(b) (4)

[redacted]

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. (b) (4)

[redacted] Based on ceftaroline in vitro susceptibility data, pharmacokinetic/pharmacodynamic analysis and clinical success rates, the Agency recommends the susceptibility interpretive criteria for isolates from ABSSSI and CABP shown in Table 2.

Table 2: Susceptibility Interpretive Criteria for Ceftaroline proposed by the Agency

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 – skin isolates only)	≤1	-	-	≥ 24	-	-
S. agalactiae[a] (skin isolates only)	≤0.03	-	-	≥ 26	-	-
S. pyogenes[a] (skin isolates only)	≤0.015	-	-	≥ 24	-	-
S. pneumoniae[a] (CABP Isolates only)	≤0.25	-	-	≥ 27	-	-
Haemophilus influenzae (CABP isolates only)	≤0.12			≥ 33		
Enterobacteriaceae[b] (CABP and skin isolates)	≤0.5	1	≥2	≥23	20-22	≤19
S = susceptible, I = intermediate, R= resistant [a]The current absence of resistant isolates precludes defining any results other than "Susceptible" [b] Clinical efficacy was shown for the following *Enterobacteriaceae: Escherichia coli, Klebsiella pneumoniae, and Klebsiella oxytoca.*						

During subsequent discussions regarding product labeling, the Applicant agreed with the susceptibility interpretive criteria proposed by the Agency for ceftaroline.

7. Clinical/Statistical- Efficacy

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 control trials comparing ceftaroline fosamil and ceftriaxone in adult subjects with CABP, with illness severe enough to require treatment with an IV antimicrobial agent in a hospital or urgent care setting. Patients in both trials were treated with ceftaroline 600 mg IV every 12 hr [with decrease in dose to 400 mg IV every 12 hr for patients with moderate renal impairment (CrCL > 30 to ≤ 50 mL/min)] or ceftriaxone 1 g IV every 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.

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

- 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.

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 or suspected atypical pathogen were to be excluded from the trial.

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 Applicant's primary prespecified efficacy endpoint, as discussed with FDA, 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.
- Clinical failure was defined as :
  - Treatment with an alternative antibacterial agent due to progression or incomplete resolution of infection or treatment-limiting adverse event
  - 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 prespecified 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) at the TOC visit, using a non-inferiority margin of 10%. A similar assessment occurred at EOT and was considered to be an important secondary endpoint. The primary pre-specified analysis populations were the MITTE (Modified Intent-to-Treat Efficacy) population defined as patients in PORT Risk Class III or IV who received any amount of study treatment and the CE (Clinically Evaluable) population defined as patients in the MITTE population who met evaluability criteria including receipt of at least the minimal amount of intended dose and duration of study medication and for whom sufficient information regarding the infection was available to determine outcome. Patients with atypical pathogens (*M. pneumoniae* or *C. pneumoniae* as the sole causative pathogen of infection) or *L. pnuemophila* were not included in this population.

Trial results

In Trial 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 Trial P903-09, there were 317 patients randomized to the ceftaroline treatment group and 310 to the ceftriaxone treatment group; 310 and 303 patients in the ceftaroline and ceftriaxone treatment groups, respectively, received any amount of study drug. In Trial 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 3 shows the results of the analyses for Trial P903-08 at TOC and EOT in the Applicant's co-primary MITTE and CE populations.

Table 3: Trial P903-08 Cerexa Primary and Secondary Analysis

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 4 shows the results of the analyses for Trial P903-09 at TOC and EOT in the co-primary MITTE and CE populations.

Table 4: Trial P903-09 Cerexa Primary and Secondary Analysis

Population	Ceftaroline	Ceftriaxone	Difference	(95% CI)
Clinical Cure Rates at the TOC Visit				
MITTE	231/284 (81.3%)	203/269 (75.5%)	5.9	(-1.0, 12.8)
CE	191/232 (82.3%)	165/214 (77.1%)	5.2	(-2.2, 12.8)
Clinical Cure Rates at the EOT Visit				
MITTE	245/284 (86.3)	212/269 (78.8)	7.5	(1.1, 13.9)
CE	200/232 (86.2)	171/214 (79.9)	6.3	(-0.7, 13.4)
Source: Study P903-09, 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 9 deaths (3%) in the ceftaroline treatment group and 6 (2%) in the ceftriaxone treatment group reported for each of the treatment groups.

All numerical trends favored ceftaroline and the 10% non-inferiority margin was met for the co-primary analysis populations for both Trials P903-08 and P903-09

.Non-Inferiority Margin and Efficacy Review Issues

Trials P903-08 and P903-09 used a traditional investigator-assessed clinical response primary endpoint at TOC 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 December 9, 2009 meeting of

the AIDAC (Bullowa, 1937[3], Flippin et al., 1939[4]; Meakins and Hanson, 1939[5]; Wilson et al., 1939[6]; Finland et al., 1940[7]).

Since there is historical evidence of a treatment effect related to clinical improvement early in the treatment course, the Agency reviewers conducted a key sensitivity analysis based on clinical response assessed in terms of stabilization of vital signs and resolution of symptoms of pneumonia on Day 4. Based on recommendations of the December 9, 2009 AIDAC, this analysis was performed in a microbiologically-confirmed population.

The FDA microbiological Intent-to-Treat (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
- Patients with positive urinary antigen for *S. pneumoniae* and/or adequate sputum specimens as defined above and/or blood culture positive for the following organisms were included: *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *S. pyogenes*, *S. aureus*, *K. pneumoniae*
- 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, or isolate was from another appropriate sample, such as bronchoalveolar lavage or pleural fluid: *Citrobacter freundii* complex, *Citrobacter koseri*, *Enterobacter aerogenes*, *E. 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.

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 ≤ 37.8°C, measured orally, rectally, or tympanically
    - Heart rate ≤ 100 beats/min
    - Respiratory rate ≤ 24 breaths/min
    - Systolic blood pressure ≥ 90 mm Hg
    - Oxygen saturation ≥ 90%

- Normal mental status

  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 FDA-mITT subjects in each trial were abnormal at baseline according to the IDSA/ATS criteria.

2. Symptom improvement criteria involving four components: cough, dyspnea, pleuritic chest pain, sputum production.

Table 5 shows results for the FDA reviewers' analysis using the Day 4 signs and symptoms endpoint in the FDA-mITT population.

Table 5 Responder Rates for Day 4 Signs and Symptoms Endpoint, mITT Population

Day 4 Endpoint	Ceftaroline	Ceftriaxone	Difference	95% CI
Trial P903-08	48/69 (71.0%)	42/72 (58.3%)	11.2%	(-4.6%, 26.5%)
Trial P903-09	58/84 (68.2%)	51/83 (61.4%)	6.8%	(-7.6%, 21.0%)
Source: FDA Reviewer.				

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.

Results were examined when using the IDSA/ATS clinical stability definition and symptom resolution definition separately for the responder analysis.

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

Trial 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%)
Trial P903-09	Ceftaroline	Ceftriaxone	Difference	95% CI
Clinical Stability	62/84 (73.8%)	56/83 (67.5%)	6.3%	(-7.5%, 20.0%)
Symptoms	75/84 (89.3%)	70/83 (83.1%)	5.1%	(-5.5%, 15.7%)
Source: FDA Reviewer.				

Results, when analyzed by either the sign or symptom component of the clinical response endpoint continued to demonstrate the efficacy of ceftaroline, with the lower bound of the 95% CI > -10.

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 7.

Table 7: Investigator-Assessed Clinical Response in the FDA-mITT Population

Trial 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%)
Trial P903-09	Ceftaroline	Ceftriaxone	Difference	95% CI
EOT	69/84 (82.1%)	66/83 (79.5%)	2.8%	(-9.5%, 14.7%)
TOC	66/84 (78.6%)	64/83 (77.1%)	1.5%	(-11.2%, 14.7%)
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 Trial 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 Trial P903-09, the magnitude of the treatment difference decreased considerably.

Table 8 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 draw any specific conclusions.

Table 8: Day 4 Sign and Symptom Response Rates by Pathogen, FDA mITT Population

	Trial P903-08		Trial P903-09	
	Ceftaroline	Ceftriaxone	Ceftaroline	Ceftriaxone
S. pneumoniae	19/27 (70)	17/32 (53)	34/47 (72)	25/43 (58)
S. aureus (MSSA)	4/9 (44)	5/15 (33)	10/15 (67)	11/16 (69)
H. influenzae	5/6 (83)	10/13 (77)	11/14 (79)	10/15 (67)
K. pneumoniae	8/9 (89)	1/3 (33)	6/9 (67)	5/8 (62)
K. oxytoca	3/3 (100)	4/4 (100)	3/3 (100)	2/2 (100)
E. coli	3/8 (38)	5/6 (83)	1/4 (25)	4/7 (57)
Source: FDA Reviewer.				

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

Table 9: Day 4 Signs and Symptoms Results by Prior Antibacterial Therapy, FDA-mITT Population

Trial 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%)
Trial P903-09	Ceftaroline	Ceftriaxone	Difference	95% CI
Prior Antibiotics	19/26 (73.1%)	17/31 (54.8%)	18.2%	(-7.0%, 40.9%)
No Prior Antibiotics	39/58 (67.2%)	34/52 (65.4%)	1.9%	(-15.6%, 19.4%)
Source: FDA Reviewer.				

The size of the population is further decreased for patients who had received either no antibacterials or a single dose of a short acting antibacterial agent. Subgroup analysis for clinical response at Day 4 in those who received "prior" and those who received "no prior" antibacterial populations were too small to draw meaningful conclusions.

In summary, Trial P903-08 and Trial P903-09 each met prespecified efficacy endpoints, and showed trends favoring ceftaroline over ceftriaxone for the treatment of CABP. Historical evidence suppoprting a 10% NI margin for a clinical response endpoint at TOC has not been identified to date. Agency reviewers consequently performed a key 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. Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

The two Phase 3 ABSSSI 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 ABSSSI 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 every 12 hr [with decrease in dose to 400 mg IV every 12 hr for patients with moderate renal impairment (CrCL > 30 to ≤ 50 mL/min)] or vancomycin 1 g IV every 12 hr plus aztreonam 1 g IV every 12 hr for treatment duration of 5-14 days.

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
    - "Significant surgical intervention" is defined as a major operative procedure
    - "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.
    - "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).
- 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

An important exclusion criterion was:
Receipt of 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 ABSSSI 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

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 ABSSSI 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. 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 ABSSSI (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 EOT visit was performed following the last dose of study drug (up to Day 14), a TOC visit 8-15 days after the last dose of study drug, and 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 Applicant's 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 ABSSSI or improvement to such an extent that further antimicrobial therapy was not necessary.
- Clinical failure was defined as any of the following:
  - Alternative antibacterial therapy for persistence, incomplete clinical resolution, or worsening of signs or symptoms or treatment limiting adverse event
  - A surgical intervention that was performed as an adjunct or followup therapy due to failure of the study drug to adequately treat the infections.
  - Diagnosis of osteomyelitis 8 or more days after randomization
  - Death due to ABSSSI
- 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 ABSSSI 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 ABSSSI 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.

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.

Patient Disposition

Trial P903-06 was conducted from February 2007 to November 2007. In Trial 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. Trial P903-07 was conducted from March 2007 to December 2007. In Trial 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.

Table 10 shows baseline infection characteristics for the two trials.

Table 10: Baseline Infections Characteristics, Applicant's MITT Population

	Trial P903-06		Trial 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 Trial P903-06, the median infection size area was similar in the two treatment groups. In Trial 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 Trial P903-06 and 40% in Trial P903-07. Cellulitis was present in about 35% of patients in both trials 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.

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 11 shows the results of these analyses in Trial P903-06.

Table 11: Applicant Analysis: Study P903-06 Clinical Cure Rates at TOC and EOT

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 Trial 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 12 shows the results of the Applicant's co-primary analyses for Trial P903-07, as well as the results for the secondary endpoint of clinical response at EOT.

Table 12: Applicant Primary Analysis: Study P903-07 Clinical Cure Ratesat TOC and EOT

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 Trial 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. The clinical cure rates in the ME population, one of the criteria used to establish antimicrobial susceptibility breakpoints, are shown in Table 13.

Table 13: Clinical Cure Rates at TOC by Baseline Pathogen from the Primary Infection Site or Blood

	Trial P03-06		Trial P903-07	
Population *Pathogen*	**Ceftaroline** n/N (%)	**Vancomycin + Aztreonam** n/N (%)	**Ceftaroline** n/N (%)	**Vancomycin + Aztreonam** n/N (%)
Gram + bacteria				
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)
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)
Adapted from 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				

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 in each

trial. Although the Applicant is seeking the ABSSSI indication for *E. coli*, *K. pneumoniae*, *K. oxytoca*, (b) (4) the number of isolates was too small to make any meaningful conclusions regarding comparative activity of treatments for any specific bacteria.

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, 1938[8,9]). The endpoints suggested by the literature for which an NI margin may be justified include time to cessation of spread of the lesion and absence of fever in those with fever at baseline in patients with cellulitis or wound infections. Therefore, FDA reviewers carried out a key sensitivity analysis 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 key 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’
- ‘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 14: Baseline Infection Characteristics, FDA-MITT Population

	Trial P903-06		Trial 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.

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 15 below shows the results of this analysis in the FDA-MITT population for Trial P903-06 and Trial P903-07.

Table 15: 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 Trial 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

Trial P903-07, treatment comparisons 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.

Table 16 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 16: Sensitivity Analysis of Responder Rates in FDA-MITT Subjects Varying the Required % Reduction in Lesion Size from Baseline to Day 3

	Trial P903-06 (n=409)		**Trial 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 16 above, for both Trial P903-06 and Trial 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.

Since the historical literature provides information regarding endpoints at an earlier timepoint, the investigator assessment of clinical response (from the Applicant's analyses) at EOT was assessed in the FDA-MITT population. Results of the analyses are shown in Table 17.

Table 17: 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 Trial P903-06 but slightly favored vancomycin + aztreonam in Trial 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 18: FDA Secondary Endpoints, Absence Rates of Key Signs and Symptoms in FDA-MITT Subjects at EOT

	Trial P903-06 (n=409)		Trial 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 Trial P903-06 versus P903-07 as well as higher in ceftaroline versus vancomycin + aztreonam. These findings were consistent with the key sensitivity analyses and further supported the non-inferiority of ceftaroline.

Table 19 below shows the by-pathogen clinical cure rates at Day 3.

Table 19: Responder Rates at Day 3 by Baseline Pathogen from the Primary Infection Site or Blood, FDA-MITT Population

	Trial P903-06		Trial P903-07	
Pathogen	**Ceftaroline** n/N (%)	**Vancomycin + Aztreonam** n/N (%)	**Ceftaroline** n/N (%)	**Vancomycin + Aztreonam** n/N (%)
Gram + bacteria				
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)
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)
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.

Subgroup Analyses

Subgroup analyses were conducted to investigate the heterogeneity of treatment differences across patient groups meeting specific characteristics of interest. Table 20 shows the clinical response rates at Day 3 by baseline infection type.

Table 20: Responder Rates at Day 3 in Key Sensitivity Analyses by Infection Type (FDA-MITT)

	Trial P903-06		Trial 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 Trial 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.

One concern with use of an earlier endpoint, is a history of any antibacterial therapy administered in the period immediately prior to study treatment and potential effect on response rates. Table 21 shows the responder rates at Day 3 in patients who had or had not received antibacterial therapy in the 24 hours prior to study drug initiation. 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 21: Responder Rates at Day 3 in FDA Reviewer Analyses by Prior Systemic Antimicrobial Use for Any Reason within 24 hours of Study Drug Initiation

	Trial P903-06		Trial 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 Trial P903-07. However, in patients with prior use of antibiotics, treatment differences were inconsistent across trials, favoring ceftaroline in Trial P903-06 but favoring vancomycin + aztreonam in Trial 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 Trial P903-07, however, this trend was reversed in Trial P903-06.

In FDA reviewer sensitivity analyses, responder rates at Day 3 supported the non-inferiority of ceftaroline to vancomycin + aztreonam in ABSSSI 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 Trials P903-06 and P903-07, analyses based on an earlier timepoint such as Day 3 versus EOT tended to show a larger treatment difference in favor of ceftaroline versus vancomycin + aztreonam.

8. Safety

The safety database included 1740 subjects/patients of whom 1441 had received the recommended therapeutic dose of ceftaroline. There were 1300 patients treated with ceftaroline and 1297 treated with comparator in the four Phase 3 trials combined.

The extent of exposure to the study drug by treatment group for the four Phase 3 trials can be seen in Table 22.

Table 22. Calendar Days on Study Drug for Phase 3 ABSSSI and CABP Safety Population

	ABSSI		CABP		Pooled Phase 3 trials	
	Ceftaroline (N=692)	Vancomycin plus Aztreonam (N=686)	Ceftaroline (N=613)	Ceftriaxone (N=615)	Ceftaroline (N=1305)	Comparator (N=1301)
Days on Study Drug						
Distribution n (%)						
1-4	35 (5.1)	46 (6.3)	26 (4.2)	35 (5.2)	61 (4.7)	75 (5.8)
5-7	315 (45.5)	293 (42.7)	564 (92.0)	566 (92.0)	879 (67.4)	859 (66)
8-10	213 (30.8)	219 (31.9)	23 (3.8)	17 (2.8)	236 (18.1)	236 (18.1)
11-14	112 (16.2)	111 (16.2)	0	0	112 (8.6)	111 (8.5)
> 14	17 (2.5)	20 (2.9)	0	0	17 (1.3)	20 (1.5)
Mean	8.4	8.4	6.5	6.5	7.5	7.5
SD	3.1	3.3	1.1	1.1	2.6	2.7
Median	7.0	8.0	7.0	7.0	7.0	7.0
Min, max	1, 22	1, 21	1,8	1, 8	1, 22	1, 21

Source: Integrated Summary of Safety (ABSSSI and CABP), p. 120.

Most patients in the ceftaroline and comparator treatment groups (67.4% or 879/1305) and 66% or 859/1301, respectively) received 5 to 7 calendar days of the study drug. Approximately 28% of patients received either ceftaroline or comparators (28% or 365/1305) and 28.1% or 367/1301), respectively) for more than 7 days. The median duration of ceftaroline or comparator therapy was 7.0 days.

Demographics of the Target Population

Across the pooled Phase 3 ABSSSI and CABP trials, patients were predominantly male, white, and had normal renal function. Approximately 31% (397/1305 for the ceftaroline group and 414/1301 for comparator group) of patients were 65 years or older and approximately 14% (186/1305 for ceftriaxone and 180/1305 for comparator) were 75 years or older. Table 23 shows some demographic and baseline characteristics of the Phase 3 Trial safety population.

Table 23. Demographic and Baseline Characteristics of the Phase 3 Trials Safety Population

	ABSSSI		CABP		Pooled Phase 3 Trials	
	Ceftaroline (N=692) n (%)	Vancomycin plus Aztreonam (N=686) N (%)	Ceftaroline (N=608) n (%)	Ceftriaxone (N=611) n(%)	Ceftaroline (N=1300) n(%)	Pooled Comparators (N=1297) n(%)
Age Group I – n (%)						
< 65	572 (82.7)	556 (81.0)	331 (54.4)	328 (53.7)	903 (69.5)	884 (68.1)
≥ 65	120 (17.3)	130 (19.0)	277 (45.6)	283 (46.3)	397 (30.5)	413 (31.8)
Age Group II – n (%)						
< 75	638 (92.2)	636 (92.7)	476 (78.3)	481 (78.7)	1114 (85.7)	1117 (86.1)
≥ 75	54 (7.8)	50 (7.3)	132 (21.7)	130 (21.3)	186 (14.3)	180 (13.9)
Sex – n (%)						
Male	443 (64.0)	420 (61.2)	376 (61.8)	395 (64.7)	819 (63.0)	815 (62.8)
Female	249 (36.0)	266 (38.8)	232 (38.2)	216 (35.3)	481 (37.0)	482 (37.2)
Race – n (%)						
White	505 (73.0)	513 (74.8)	567 (93.2)	573 (93.8)	1072 (82.5)	1086 (83.7)
American Indian or Alaskan Native	6 (0.9)	4 (0.6)	7 (1.1)	5 (0.8)	13 (1.00)	9 (0.7)
Asian	6 (0.9)	5 (0.7)	15 (2.5)	16 (2.6)	21 (1.6)	21 (1.6)
Black or African-American	48 (6.9)	41 (6.0)	13 (2.9)	16 (2.6)	66 (5.1)	57 (4.4)
Native Hawaiian or Other Pacific Islander	2 (0.3)	2 (0.3)	0	0	2 (0.2)	2 (0.2)
Multi-race/Other	6 (0.9)	7 (1.0)	1 (0.2)	1 (0.2)	7 (0.5)	8 (0.6)
Unknown	119 (17.2)	114 (16.6)	0	0	119 (9.1)	114 (8.8)
Creatinine Clearance (mL/min)						
> 80	563 (81.4)	551 (80.3)	297 (48.8)	310 (50.7)	860 (66.1)	861 (66.4)
> 50 and ≤ 80	95 (13.7)	96 (14.0)	197 (32.4)	194 (31.7)	292 (22.5)	290 (22.3)
> 30 and ≤ 50	22 (3.2)	26 (3.8)	89 (14.6)	83 (13.6)	111 (8.5)	109 (8.4)
≤ 30	2 (0.3)	2 (0.3)	13 (2.1)	10 (1.6)	15 (1.1)	12 (0.9)
Missing	10 (1.4)	11 (1.6)	12 (2.0)	14 (2.3)	22 (1.7)	25 (1.9)

Source: Integrated Summary of Safety, Table 7.1.1-1. p 134-6. Nine patients were excluded from Trial P903-09 in the CABP trials because of data integrity.

Acute Bacterial Skin and Skin Structure Infection Studies

Table 24 shows the incidence of various categories of AEs in the pooled Phase 3 ABSSSI trials.

Table 24. Incidence of TEAEs, SAEs, Discontinuations, and Deaths in Individual and Pooled Phase 3 ABSSSI Trials

	P903-06		P903-07		Pooled Phase 3 ABSSSI Trials	
	Ceftaroline (N=351) n (%)	Vancomycin plus Aztreonam (N=347) N (%)	Ceftaroline (N=341) n (%)	Vancomycin plus Aztreonam (N=339) n(%)	Ceftaroline (N=692) n(%)	Vancomycin plus Aztreonam (N=686) n(%)
Number of Patients with:						
Any TEAE	165 (47)	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)
Discontinuations due to TEAE	13 (3.7)	16 (4.6)	8 (2.3)	17 (5.0)	21 (3.0)	33 (4.8)
Deaths	3 (0.9)	0	0	0	3 (0.4)	0

Source: Integrated Summary of Safety (ABSSSI and CABP), p. 144.

The overall incidence of TEAEs, SAEs, and discontinuations due to TEAEs is similar between the ceftaroline group and the vancomycin plus aztreonam group.

Community Acquired Bacterial Pneumonia

Table 25 shows the incidence of various categories of AEs in the pooled Phase 3 CABP trials.

Table 25. Incidence of TEAEs, SAEs, Discontinuations, and Deaths in Individual and Pooled Phase 3 CABP Trials

	P903-08		P903-09		Pooled Phase 3 CABP Trials	
	Ceftaroline (N=298) n (%)	Ceftriaxone (N=308) N (%)	Ceftaroline (N=310) n (%)	Ceftriaxone (N=303) n(%)	Ceftaroline (N=608) n(%)	Ceftriaxone (N=611) n(%)
Number of Patients with:						
Any TEAE	119 (39.9)	136 (44.2)	164 (52.9)*	142 (46.9)*	283 (46.5)*	278 (45.5)*
Any SAE	28 (9.4)	33 (10.7)	39 (12.6)*	39 (12.8)*	67 (11.0)*	72 (11.7)*
Discontinuations due to TEAE	11 (3.7)	12 (3.9)	15 (4.8)*	13 (4.3)*	26 (4.3)*	25 (4.1)*
Deaths	6 (2.0)	6 (1.9)	9 (2.9)**	6 (2.0)**	15 (2.4)**	12 (2.0)**

Source: Integrated Summary of Safety (ABSSSI and CABP), p. 144.
* Nine patients were excluded in Trial P903-09 in the CABP trials because of data integrity.
** One death was reported at an India site with data integrity issues.

The overall incidence of TEAEs, SAEs, deaths, and discontinuation of study drug or withdrawal from study drug due to TEAEs were similar for both the ceftaroline group and the ceftriaxone group.

Deaths

ABSSSI

In the ABSSSI Phase 3 trials, there were three deaths. All the deaths occurred in Trial P903-06 in the ceftaroline treatment group; there were no deaths in the vancomycin plus aztreonam group in either trial. The SAEs associated with outcomes of death included cardiopulmonary insufficiency, malignant neoplasm progression

(undifferentiated carcinoma of the neck), and respiratory failure (congestive heart failure). All of the deaths occurred while the patient was no longer receiving study drug and were thought to be unrelated by the investigator. Based upon review of the narratives, the FDA reviewer agrees with this assessment.

An additional four patients in the ABSSSI trials died after LFU or 30 days after EOT if there was no LFU. Two of the patients had received ceftaroline and two received vancomycin plus aztreonam.

CABP

In the CABP Phase 3 trials, twenty seven patients died during the trial reporting period (before LFU or within 30 days after EOT if no LFU was done); there were 15 deaths in the ceftaroline treatment group and 12 in the ceftriaxone treatment group.

In Trial P903-08 (trial included 24 hours of macrolide therapy) there were six deaths in patients treated with ceftaroline and 6 deaths in patients treated with ceftriaxone. One patient in each treatment group died while on study therapy (Days 3 and 2 for ceftaroline and ceftriaxone, respectively).

Two of these twelve deaths were assessed by the investigator as related to study medication; one patient had been treated with ceftaroline and the other with ceftriaxone. The patient who was treated with ceftaroline was found unresponsive and \the SAE leading to death was classified as “sudden death”. She was a 73 year old female with a history of smoking, admitted as a PORT Risk Class III patient and had a right middle lobe pneumonia. On Study Day 3, the patient was found unresponsive and was intubated without difficulty, with no airway swelling noted on intubation. Resuscitation was unsuccessful. The patient treated with ceftriaxone was a 60 year old male who died on Study Day 14 due to hepatic failure and multi-organ disorder. He had a history of smoking, hypertension, and alcohol abuse. He was categorized in PORT Risk Class IV. He received 6 days of ceftriaxone for bilateral CABP. Hepatic transaminsaes were noted to be >10 times the patient’s baseline on Study Day 6 and on Study Day 7, the patient was reported to have hepatic failure. This was followed by multi-organ failure on Study Day 11. The remaining 10 deaths in the ceftaroline and ceftriaxone group (5 and 5, respectively) were thought to possibly be related to underlying comorbidities

Four deaths, one in the ceftaroline treatment group and three in the ceftriaxone group, were determined by the investigator to be secondary to CABP, including the ceftriaxone-treated patient described above who experienced hepatic and multi-organ failure. All four of these patients had multilobar and/or bilateral lung involvement with no pathogen isolated at baseline.

The remaining four deaths in the ceftaroline treatment group in Trial 903-08 are as follows

- 1004-08340: 71 year old male with a history of smoking and cardiac failure was treated for 5 days with ceftaroline for PORT Risk Class IV, bilateral lower lobe

pneumonia. At baseline, the patient's hepatic transaminases were mildly elevated, along with prothrombin time and INR. He was also noted to have inverted T-waves at baseline, which persisted on Day 3 and Day 5. On Study Day 15 (10 days after discontinuing study medication) he was noted to have a positive direct Coombs' test (seroconversion from negative baseline), with stable to slightly increased hemoglobin from baseline. On Day 32 (27 days after study medication discontinuation), he died suddenly and the investigator reported the cause as sudden death.

- 6635-08316: 74 year old white male with a history of smoking, structural lung disease, atrial fibrillation, heart failure, and coronary artery disease who was treated with 7 days of ceftaroline for PORT Risk Class III, right upper and middle lobe pneumonia. On Study Day 8, the patient experienced a SAE of suspected gastrointestinal perforation and was treated medically with ceftixome plus gentamicin and achieved resolution with medical management on Study Day 20. Radiologic evaluation revealed several liver metastases; a primary pulmonary neoplasm was suspected. He died on Study Day 24 with associated SAE of disseminated neoplasm.
- 6642-08567: 87 year old female with a history of hypertension, cardiac failure, cardiomyopathy, angina pectoris, and renal failure received 7 days of ceftaroline for PORT Risk Class IV, right lower lobe pneumonia with no pathogen identified at baseline. The chest X-ray also showed bilateral pleural effusions. At EOT (Day 8), the patient was assessed as a **treatment failure** and was treated with clarithromycin and ceftriaxone. The patient's ejection fraction that day was estimated to be 15-20% and on Study Day 9 the patient experienced an SAE of cardiac failure. On study day 14, the patient developed cardiogenic shock and died, with an investigator assessment of worsening heart failure as unrelated to study drug.
- 6827-08190: 82 year old female with a history of ischemic stroke, ischemic cardiomyopathy, congestive heart failure, atherosclerosis, hypertension, diabetes mellitus, osteoporosis, and chronic renal insufficiency was treated with 4 days of ceftaroline for PORT Risk Class V bilateral lower lobe pneumonia with no identified baseline pathogen. On Study Day 4, the patient experience severe dyspnea, acrocyanosis, hypoxia, hypercapnia, and acidosis and required intubation. The patient was diagnosed with a SAE of left ventricular failure. The patient developed a fever on Study Day 6 and was treated with amoxicillin-clavulanate and moxifloxacin, On Study Day 22, the patient developed blood cultures positive for coagulase negative staphylococci and received treatment with amoxicillin-clavulanate and gentamicin until Day 30. The patient's respiratory status deteriorated despite medical intervention and she died on Study Day 32 with cause of death listed as sepsis, The SAEs of left ventricular failure and sepsis were not attributed to the durg, Based on respiratory decompensation while on study therapy, this patient could also be categorized as a **treatment failure**.

The remaining 3 deaths in the ceftriaxone treatment group were due to cardiac causes.

Four additional patients died outside the reporting window; one patient had received ceftaroline and three had received ceftriaxone. The ceftaroline-treated patient had a pancreatic neoplasm with duodenal infiltration and died secondary to the pancreatic adenocarcinoma. One of the three ceftriaxone patients, with HIV and bilateral *S. pnumoniae* pneumonia, may have been a treatment failure but was subsequently diagnosed with hospital acquired pneumonia and died on Study Day 43.

In CABP Trial P903-09 there were 15 deaths; nine in the ceftaroline treatment group and six in the ceftriaxone treatment group. None of the deaths were attributed to study drug by the investigator. There was one death in a ceftraixone patient that occurred outside the reporting period.

One death in the ceftaroline group was assessed by the investigator to be **due to underlying CABP**.

- 9008-09619: 57 year old male with a history of smoking, structural lung disease, old pulmonary tuberculosis, and diabetes who received 5 days of ceftaroline for treatment of a PORT Risk Class IV bilateral pneumonia, with no pathogen isolated at baseline. On Study Day 6, the patient developed high grade fever and chills and respiratory demise that required admission to the ICU. He was treated with non-invasive ventilation. He experienced SAEs of anoxic encephalopathy, toxic encephalopathy, sepsis, and septic shock. He then had cardiac arrest and was resuscitated. He wss treated with meropenem, vancomycin, hydrocortisone, and high-dose inotropic support, but died on Study Day 13.

The remaining 14 deaths were attributed to underlying comorbidities. Deaths in the 8 remaining ceftaroline patients included:

- 5012-09074: 78 year old male with a history of smoking, structural lung disease, chronic bronchitis, pulmonary embolism, atrial fibrillation, atherosclerosis, chronic pyelonephritis and prostate adenoma who was treated with 6 days of ceftaroline for a PORT Risk Class IV, bilobar pneumonia, with no pathogen identified at baseline. The patient developed acute pancreatitis on Day 5 and on Day 6 experienced a pulmonary embolism, renal failure, and hepatic failure and study drug was discontinued. He died on study day 12. An autopsy showed ischemic heart disease, chronic circulatory failure, congestive hyperemia of the lungs, kidneys, and spleen, and hepatic cirrhosis with ascites.
- 2015-09618: 69 year old male with a history of smoking, structural lung disease, asthma, diabetes, and chronic renal insufficiency who received ceftaroline for 7 days for treatment of PORT Risk Class IV right lower lobe pneumonia, with no identified pathogens at baseline. The patient was assessed as a clinical cure on Day 7. On Day 8 he suffered a SAE of exacerbation of COPD and required mechanical assistance for ventilation. He was subsequently diagnosed on Study Day 14 with nosocomial pneumonia and was treated with piperacillin-tazobactam and dopamine. He ultimately developed renal failure and died on Study Day 16. The investigator assessed his death as attributable to nosocomial pneumonia, although it is possible he may have been a **treatment failure** since the COPD exacerbation occurred right after study medication discontinuation.

- 5101-09115: 67 year old male with a history of smoking and hypertension treated with ceftaroline for 7 days for PORT Risk Class III, left lower lobe pneumonia, with no baseline pathogen identified. On Study Day 12, the patient experienced increased chest and back pain, cough, and weight loss and was subsequently diagnosed with a malignant lung neoplasm with metastases. The patient was lost to follow-up and died about 1 month after receiving study treatment.
- 5203-09541: 70 year old male with a history of hypertension, congestive heart failure, brain contusion, and cerebral hematoma who was treated with ceftaroline for 7 days for PORT Risk Class III left lower lobe pneumonia, with no baseline pathogen identified. He was deemed a clinical cure on Study Day 8. On study day 14, the patient had an elective MRI as follow-up for the brain contusion and this revealed evidence of a hematogenously disseminated lung tumor. His condition worsened the same day and he developed right hemiparesis. The patient died on Study Day 31.
- 6602-09365:57 year old male with a history of smoking, hyperuricemia, pneumothorax, and structural lung disease who received 6 days of treatment with ceftaroline for PORT Risk Class III right lower lobe pneumonia and no idenitifed pathogen, He was assessed as a **clinical failure** on day 6, and treated with ciprofloxacin to Day 11; additional antimicrobial treatment included amikacin and ceftazidime, On Day 15 he experienced worsening of his COPD and was admitted to the ICU. He experienced respiratory failure on Day 28 and was admitted again to the ICU and mechanically ventilated. He died on Day 28 due to respiratory failure from COPD.
- 6608-09621: 80 year old male with a history of smoking, pulmonary interstitial fibrosis, pulmonary tuberculosis, hypertension, and hyperthyroidism, who received ceftaroline for 6 days for PORT Risk Class IV, CABP with no identified pathogens. On day 4 he experienced a pulmonary embolism and died on Study Day 10.
- 6613-09346: 84 year old male with a history of smoking, tricuspid and mitral valve insufficiency, deep vein thrombosis, chronic respiratory failure, hypertension, and congestive heart failure was treated with 7 days of ceftaroline for PORT Risk Class V left bilobar pneumonia due to *S. aureus* and *M catarrhalis*. He was assessed as a clinical cure on Day 7. On study day 10, cancer cells were found in the sputum and he died on Study Day 11 due to progression of the neoplasm.
- 6804-09374: 87 year old male with a history of smoking, arteriosclerosis obliterans, myocardial ischemia, hypertension, cardiac failure, and prostatitis,.who was treated with 7 days of ceftaroline for PORT Risk Class IV bilateral CABP due to *E. coli* and *Haemophilus parahemolyticus*. Baseline ECGs showed evidence of ischemia. He was assessed as a clinical cure on Study Day 8 but was found later that day, dead from cardiac arrest. Autopsy revealed cardiac arrest secondary to right ventricular failure as a result of COPD and pneumonia.

Cause of death in 4 of the 6 remaining ceftriaxone treatment group could have been secondary of failure of the drug to adequately treat the pneumonia.

Nonfatal Serious Adverse Events

Overall, across the pooled Clinical Pharmacology studies, Phase 2, and Phase 3 clinical trials, 106/1701 (6.2%) of ceftaroline-treated patients compared to 102/1452 (7.0%) of placebo or comparator-treated patients experienced at least one SAE.

The incidence of SAEs (including those with outcomes of death) for patients in the Phase 3 trials for both indications is summarized by system organ class (SOC) in Table 26.

Table 26. Incidence of SAEs by System Organ Class (SOC) for Phase 3 Trials (ABSSSI and CABP)

System Organ Class	ABSSSI (Trial 06, 07)		CABP (Trial 08, 09)		Pooled Phase 3 Trials (Trials 06, 07, 08, 09)	
	Ceftaroline (N=692) n (%)	Vancomycin plus Aztreonam (N=686) n (%)	Ceftaroline (N=608) n (%)	Ceftriaxone (N=611) n (%)	Ceftaroline (N=1300) n (%)	Pooled Comparators (N=1297) n (%)
Patients with at Least One SAE	30 (4.3)	28 (4.1)	67 (11.0)	72 (11.7)	99 (7.6)	100 (7.7)
Blood and Lymphatic System Disorders	0	2 (0.3)	3 (0.5)	0	3 (0.2)	2 (0.2)
Cardiac Disorders	4 (0.6)	5 (0.7)	7 (1.1)	11 (1.8)	11 (0.8)	16 (1.2)
Endocrine Disorders	0	0	1 (0.2)	0	1 (0.1)	0
Gastrointestinal Disorders	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 Disorders	0	1 (0.1)	1 (0.2)	4 (0.7)	1 (0.1)	5 (0.4)
Immune System Disorders	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)	22 (3.6)*	25 (4.1)*	30 (2.3)*	31 (2.4)*
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 and Nutrition Disorders	1 (0.1)	1 (0.1)	3 (0.5)	4 (0.7)	4 (0.3)	5 (0.4)
Musculoskeletal and Connective Tissue Disorders	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 Disorders	2 (0.3)	3 (0.4)	2 (0.3)*	1 (0.2)	4 (0.3)*	4 (0.3)
Renal and Urinary Disorders	2 (0.3)	1 (0.1)	2 (0.3)	2 (0.3)	4 (0.3)	3 (0.2)
Reproductive System and Breast Disorders	0	0	0	1 (0.2)	0	1 (0.1)
Respiratory, Thoracic, and Mediastinal Disorders	4 (0.6)	1 (0.1)	20 (3.3)	25 (4.1)	24 (1.8)	26 (2.0)
Vascular Disorders	1 (0.1)	2 (0.3)	4 (0.7)	2 (0.3)	5 (0.4)	4 (0.3)

Source: Integrated Summary of Safety (ABSSSI and CABP), p. 166.
Nine patients were excluded from Trial P903-09 in the CABP trials because of data integrity.
* One subject from India excluded.

The incidence of SAEs was similar in the ceftaroline and comparator treatment groups for the pooled Phase 3 trials (7.6% vs 7.7%, respectively). The most commonly reported SAE system organ class (SOC) was Infections and Infestations (31 patients

versus 32 patients in the ceftaroline and comparator-treated groups, respectively), followed by Respiratory, Thoracic and Mediastinal Disorders (24 patients in the ceftaroline group and 26 in the comparator group), and Cardiac Disorders (11 patients in the ceftaroline group and 16 in the comparator group). Generally, the incidence of SAEs classified according to SOC is similar between the ceftaroline and comparator groups.

Table 27 shows the most common preferred terms (PT) within SOCs accounting for the SAEs

Table 27. Most Common SAE SOCs and PTs Experienced by the Pooled Phase 3 Trials Population

System Organ Class/Preferred Term	ABSSSI (Trial 06, 07)		CABP (Trial 08, 09)		Pooled Phase 3 Trials (Trials 06, 07, 08, 09)	
	Ceftaroline (N=692) n (%)	Vancomycin plus Aztreonam (N=686) n (%)	Ceftaroline (N=608) n (%)	Ceftriaxone (N=611) n (%)	Ceftaroline (N=1305) n (%)	Pooled Comparators (N=1301) n (%)
Infections and Infestations	8 (1.2)	6 (0.9)	22 (3.6)*	25 (4.1)*	30 (2.3)*	31 (2.4)*
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)
Immune System Disorders	3 (0.4)	1 (0.1)	0	1 (0.2)	3 (0.2)	2 (0.2)
Anaphylactic Shock	1 (0.1)	0	0	0	1 (0.1)	0
Anaphylactoid reaction	1 (0.1)	0	0	0	1 (0.1)	0
Hypersensitivity	1 (0.1)	1 (0.1)	0	1 (0.2)	1 (0.1)	2 (0.2)
Nervous System Disorders	2 (0.3)	3 (0.4)	2 (0.3)*	1 (0.2)	4 (0.3)*	4 (0.3)
Convulsion	1 (0.1)	0	1 (0.2)	0	2 (0.2)	0
Anoxic encephalopathy	0	0	1 (0.2)	0	1 (0.1)	0
Renal and Urinary Disorders	2 (0.3)	1 (0.1)	2 (0.3)	2 (0.3)	4 (0.3)	3 (0.2)
Renal failure	1 (0.1)	0	2 (0.3)	0	3 (0.2)	0
Acute prerenal failure	1 (0.1)	0	0	0	1 (0.1)	0
Renal failure acute	0	1 (0.1)	0	0	0	1 (0.1)

Source: Table 4.2.3.3.1. Integrated Summary of Safety. pp. 868-74.
Nine patients were excluded from Trial P903-09 in the CABP trials because of data integrity.
* One subject from India excluded.

Overall, the SAEs listed by specific PT were evenly balanced across treatment groups. Within the Infections and Infestation SOCs, the SAEs reported (i.e. pneumonia, pyothorax, and lung abscess for the CABP trials and cellulitis for the ABSSSI trials) likely represent treatment failures rather than adverse events. SAEs

within the Respiratory SOC are indicative of underlying disease (COPD), immobility (pulmonary embolism), and possible events related to the primary infection (i.e. pleural effusion, respiratory failure) or cardiac disease. Anaphylactic reactions occurred rarely and were seen only in ceftaroline treated patients.

AEs Leading to Premature Discontinuation of Study Drug or Withdrawal from Study

Broken down, the following table (Table 27) summarizes the number of patients who prematurely discontinued the study drug or withdrew from the study due to at least one SAE:

Table 27: Number of Patients with at Least One AE Leading to Premature Discontinuation of Study Drug or Withdrawal from Study

Study	Number of Patients with at Least One SAE (%)	
	Ceftaroline	Comparator Drug/Placebo
Pooled Clinical Pharmacology Studies	4/236 (1.7%)	1/78 (1.3%)
Phase 2 ABSSSI Trials	7/165 (4.2%)	1/77 (1.3%)
Phase 3 ABSSSI Trials	21/692 (3.0%)	33/686 (4.8%)
Phase 3 CABP Trials	27/608 (4.4%)	25/611 (4.1%)
P903-17 (IM Ceftaroline)	0/36	0
P903-15 (Phase 1 pediatric study)	1/9 (11.1%)	No patients

Source: Integrated Summary of Safety (ABSSSI and CABP)
Nine patients were excluded from Trial P903-09 in the CABP trials because of data integrity.

Table 28 provides a summary of the incidence of AEs by SOC that led to the discontinuation of the study medications or withdrawal from the study in the pooled Phase 3 safety population.

Table 28. Incidence of AEs by SOC Leading to Discontinuation of Study Drug or Withdrawal of Study Drug or Withdrawal from Study

System Organ Class	ABSSSI (Trial 06, 07)		CABP (Trial 08, 09)		Pooled Phase 3 Trials (Trials 06, 07, 08, 09)	
	Ceftaroline (N=692) n (%)	Vancomycin plus Aztreonam (N=686) n (%)	Ceftaroline (N=608) n (%)	Ceftriaxone (N=611) n (%)	Ceftaroline (N=1300) n (%)	Pooled Comparators (N=1297) n (%)
Patients with at Least one AE	21 (3.0)	33 (4.8)	26 (4.3)	25 (4.1)	47 (3.6)	58 (4.5)
Cardiac Disorders	0	2 (0.3)	2 (0.3)	7 (1.1)	2 (0.2)	9 (0.7)
Eye Disorders	0	1 (0.1)	0	0	0	1 (0.1)
Gastrointestinal Disorders	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 Disorders	0	0	2 (0.3)	2 (0.3)	2 (0.2)	2 (0.2)
Immune System Disorders	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)	5 (0.8)	7 (1.1)	8 (0.6)	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 Disorders	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 Disorders	0	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Renal and Urinary Disorders	0	1 (0.1)	1 (0.2)	0	1 (0.1)	1 (0.1)
Respiratory, Thoracic, and Mediastinal Disorders	1 (0.1)	1 (0.1)	6 (1.0)	4 (0.7)	7 (0.5)	5 (0.4)
Skin and subcutaneous tissue disorders	8 (1.2)	17 (2.5)	0	1 (0.2)	8 (0.6)	18 (1.4)
Vascular Disorders	0	2 (0.3)	3 (0.5)	1 (0.2)	3 (0.2)	3 (0.2)

Source: Integrated Summary of Safety (ABSSSI and CABP), p. 180.
Nine patients were excluded from Trial P903-09 in the CABP trials because of data integrity.

The incidence of AEs resulting in premature discontinuation of study drug or withdrawal from the clinic trial was generally similar between the ceftaroline and comparator treatment groups (3.7% vs 4.5%, respectively). However, patients experiencing Skin and Subcutaneous Tissue Disorders were more frequently in the comparator treatment group; this finding was most marked in the ABSSSI trials where skin rashes and pruritis were more frequent in the vancomycin (plus aztreonam) comparator group. This was followed by Infections and Infestations (9 ceftaroline- and 12 comparator-treated patients, respectively), Immune System Disorders (7 ceftaroline- and 6 comparator-treated patients, respectively), and Respiratory, Thoracic, and Mediastinal Disorders (7 ceftaroline- and 5 comparator-treated patients,

respectively) SOCs were relatively well-balanced. Excluding Respiratory Disorders and Immune System Disorders, the only SOC in which the incidence of discontinuation due to AEs was greater in the ceftaroline group than the comparator group was the Neoplasms SOC (4 ceftaroline-treated patients and 1 comparator-treated patient, respectively).

Immune system reactions in the ceftaroline treated group included anaphylactic reaction, anaphylactic shock, and anaphylactoid reaction. None of these reactions resulted in discontinuation or withdrawal from the trial in comparator-treated patients.

Adverse Drug Reactions

Adverse drug reactions (ADRs), a subset of treatment-emergent adverse events (TEAEs), were summarized according to preferred terms (PTs) to identify important adverse drug reactions experienced by patients receiving ceftaroline fosamil, excluding events that would commonly be observed in the absence of ceftaroline therapy. The ADRs occurring in ≥2 percent of patients receiving ceftaroline fosamil are shown in Table 29.

Table 29. ADRs occurring in ≥ 2% of Patients Receiving Ceftaroline fosamil in Phase 3 Trials

System Organ Class/Preferred Term	Pooled Phase 3 Trials	
	Ceftaroline fosamil (N=1300) (%)	Pooled Comparators (N=1297) (%)
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%
Skin and subcutaneous tissue disorders		
Rash	3%	2%
Vascular disorders		
Phlebitis	2%	1%

Source: Integrated Summary of Safety (ABSSSI and CABP), p. 146-7.
Nine patients were excluded from Trial P903-09 in the CABP trials because of data integrity.

ADRs in the Gastrointestinal Disorders category appear to be most frequent. The incidence of ADRs in the ceftaroline-treated group appears to be low and comparable to those in the comparator-treated group. No ADR occurred in greater than 5% of patients who received ceftaroline.

Electrocardiograms (ECGs) – Study P903-05 Thorough ECG Trial

The Thorough ECG Trial (Study P903-05) was a randomized, double-blind, placebo controlled, three-period crossover study. The study enrolled 54 healthy patients who received a single supratherapeutic dose of 1500 mg of ceftaroline fosamil, 400 mg of

moxifloxacin, and placebo. The study demonstrated that a supratherapeutic dose of ceftaroline did not result in a clinically meaningful increase in QTcIb (QT interval corrected with an individual patient correction formula based on the baseline QT-RR slope) and in the QTcFridericia (QTcF) and QTcBazett (QTcB) corrections.

The Interdisciplinary Review Team (IRT) for QT Studies consult corroborated the Applicant's findings. Overall ECG acquisition and interpretation in the study appeared to be acceptable. Assay sensitivity was established with the active control, moxifloxacin, with an unadjusted 90% lower confidence interval of 16.8 msec. No significant QT prolongation from ceftaroline was detected in the study. The largest upper bound of the 2-sided 90% confidence interval (CI) for the mean difference between ceftaroline and placebo was less than 10 msec, the threshold for regulatory concern as stated in the ICH E14 guidelines. The overall summary is presented in Table 30.

Table 30. IRT Analysis of Point Estimate and 90% CI of QTcIB Changes in Thorough QT Study

Treatment and dose	Time (hour)	ΔΔQTcIb* (ms)	90% CI (ms)
Ceftaroline 1500 mg	1.5	1.6	-0.8, 4.0
Moxifloxacin 400 mg	1	19.2	16.8, 21.5

Source: Interdisciplinary Review Team for QT Studies Consultation:Thorough QT Study Review. p. 2.
* QT interval corrected with an individual patient correction formula based on the baseline QT-RR slope

The supratherapeutic dose of 1500 mg of ceftaroline produced mean ceftaroline C_{max} values 3.9 fold higher than those observed after the therapeutic dose, simulating levels seen with exposure increases due to intrinsic and extrinsic factors (e.g. severe renal impairment). At this dose, the mean ceftaroline concentration was approximately 4.6 times that observed in patients with severe renal insufficiency receiving a dose of 400 mg of ceftaroline.

In the study, none of the events identified to be of clinical importance in the ICH E 14 guideline such as syncope, seizure, significant ventricular arrhythmias, or sudden cardiac death, occurred in the study. There were no clinically significant effects of the supratherapeutic ceftaroline dose on the PR and the QRS intervals.

TEAEs Indicating Potential Drug-Induced Anemia

Hematological effects, such as decreased red blood cell counts, were observed in monkeys at supratherapeutic doses representing approximately 20 times the human equivalent exposure at therapeutic doses. Overall, the clinical trial results suggest that the effect of ceftaroline on hematological parameters is small and similar to the comparators studied. However, the incidence of patients with direct Coombs' test seroconversion was higher in the ceftaroline-treated group compared with the comparator-treated groups. None of the patients developed hemolytic anemia. The potentially clinically significant (PCS) decreases in hematocrit (Hct), hemoglobin (Hgb), and red blood cell (RBC) counts occurred at similar frequencies in the ceftaroline and comparator groups, and in the pooled Phase 3 ABSSSI and CABP trials.

Across the pooled safety population (Clinical Pharmacology studies, Phase 2 and Phase 3 clinical trials), nineteen patients (1.1% or 19/1701) in the ceftaroline group and eighteen patients (1.2% or 18/1452) in the comparator/placebo groups developed treatment-emergent adverse events (TEAEs) representing potential drug-induced anemia (e.g. anemia, hemoglobin decreased). Table 31 summarizes the incidence data when broken down.

Table 31. Incidence of patients with TEAEs of potential drug-induced anemia broken down by study

Study	Number of Patients with TEAEs representing potential drug-induced anemia(%)	
	Ceftaroline	Comparator Drug/Placebo
Phase 2 ABSSSI Trials	3/165 (1.8%)	1/77 (1.3%)
Phase 3 ABSSSI Trials	13/692 (1.9%)	14/686 (2.0%)
Phase 3 CABP Trials	3/608 (0.5%)	3/61 (0.5%)
P903-17 (IM Ceftaroline)	0/36	0
P903-15 (Phase 1 pediatric PK study)	0/9	No patients

Source: Summarized from the Integrated Summary of Safety (ABSSSI and CABP), p. 206.
Nine patients were excluded from Trial P903-09 in the CABP trials because of data integrity.

In the pooled Phase 3 ABSSSI and CABP trials, TEAEs representing potential drug-induced anemia were uncommon and their frequencies were similar between the ceftaroline and comparator groups (1.2% versus 1.3%, respectively). No patients had an outcome of death, prematurely discontinued the study drug, or withdrew from the study as a result of a TEAE representing potential drug-induced anemia. One patient in each treatment group experienced a potentially drug-induced anemia SAE, both unassociated with a PCS decrease in Hct and Hgb values, or RBC counts, and both were assessed as not related to the study drug. The patient from the ceftaroline group had baseline anemia and a TEAE of hemorrhagic gastritis and the patient from the comparator group was diagnosed with anemia based on an unconfirmed local laboratory result.

Ceftaroline fosamil is not marketed anywhere in the world.

9. Advisory Committee Meeting

An AIDAC meeting was held on September 7, 2010 to discuss the NME, ceftaroline, as required by the Food and Drug Administration Amendments Act (FDAAA) 2007. In the absence of such a requirement, this application would likely have been presented to the AIDAC because of the changes made to the key efficacy analyses by the FDA review team, focusing on earlier rather than TOC endpoints for clinical response, for which the scientific literature (historical evidence) can provide adequate justification for an NI margin.

The CABP discussion in the morning session centered primarily on use of an efficacy endpoint of clinical stability (i.e. normalization of vital signs) and symptom improvement at Day 4 in a microbiological ITT population. The committee voted

unanimously, 21-0, for approval stating that the efficacy and safety of ceftaroline in the treatment of CABP had been demonstrated. Concerns noted by the committee members included absence of data on MRSA pneumonia, concern about off-label use for this indication, and establishing appropriate susceptibility breakpoints using all available data. The committee found the FDA analyses focusing on the earlier, Day 4 endpoint to be helpful in reaching a decision.

The ABSSSI discussion in the afternoon session centered primarily on the use of the efficacy endpoint of cessation of spread of the lesion and absence of fever as assessed at Day 3 in the MITT population. The committee voted unanimously, 18-0, for approval stating that the efficacy and safety of ceftaroline in the treatment of ABSSSI had been demonstrated. Concerns voiced by the AC included the possibility of measurement error, reliability of irregularly shape lesions, whether the vancomycin comparator levels were therapeutic, and need for additional data on MRSA with higher MICs to vancomycin.

10. Pediatrics

A pediatric plan and deferral request was submitted to NDA 200-327 on February 2, 2010. The deferral request was for all pediatric age ranges birth to age <18 years, as pediatric studies had not been completed and the ceftaroline application for use in adults was under review by the FDA.

(b) (4)

The pediatric program was presented to the Pediatric Review Committee (PeRC) on October 20, 2010. A deferral of pediatric studies/trials for all age groups was acceptable. Discussion focused primarily on the Division of Anti-Infective and Ophthalmology Products (DAIOP) proposal to include neonates in the safety and efficacy trial of ceftaroline treatment in acute bacterial skin infections. Because the trial would include all age groups, the need for information regarding CSF penetration of ceftaroline was thought to be important. There was also a discussion of an appropriate age cut-off for a waiver of CABP trials in infants < 2 months of age.

Based on the DAIOP's previous proposal, discussion with the Applicant, and feedback from PeRC, the DAIOP has proposed the following pediatric post-marketing requirements.

- Study 1: Single dose pharmacokinetic trial
  Perform a trial in pediatric patients being treated concomitantly with antibacterial agent(s) to evaluate single dose pharmacokinetic parameters and assess safety of Teflaro (ceftaroline fosamil) in all pediatric age groups. Five age cohorts must be studied as follows:

(b) (4)

- Study 2: Perform a randomized comparison of Teflaro (ceftaroline fosamil) and comparator in pediatric subjects with CABP utilizing an enrichment strategy for enrollment of patients with MRSA. Pediatric patients under 17 years of age with CABP must be enrolled, with a minimum of 150 patients receiving Teflaro (ceftaroline fosamil).
- Study 3: Perform a randomized comparison of Teflaro (ceftaroline fosamil) and comparator in pediatric subjects with ABSSSI including patients with infection suspected or demonstrated to be caused by MRSA. Pediatric patients under 17 years of age with ABSSSI must be enrolled, with a minimum of 150 patients receiving Teflaro (ceftaroline fosamil).
- Study 4: Perform a trial assessing the CSF concentration profile of Teflaro (ceftaroline fosamil) in infants < 2 months of age. A minimum of 12 infants < 2 months of age receiving antibacterials for treatment of late-onset neonatal sepsis must be studied.

- Study 5: Perform a randomized comparison of Teflaro (ceftaroline fosamil) and comparator in infants < 2 months of age with ABSSSI and CABP including patients with infection suspected or demonstrated to be caused by MRSA.

Discussions are underway regarding studies/trials which could be performed as part of a Written Request.

11. Other Relevant Regulatory Issues

Financial disclosures were not obtained from three investigators participating in the Phase 3 ABSSSI trial (P903-06); Cerexa requested data from the sites and was told that the investigators were no longer affiliated with the site and the information could not be obtained. There were an additional 12 investigators from whom financial disclosure information was missing; these investigators did not enroll patients in the clinical trials.

The Division of Scientific Investigations was consulted for inspection of the Applicant and eight of the participating investigator sites. The inspection of the Applicant, Cerexa, did not reveal any violations of GCP. The eight sites inspected by DSI are shown in Table 32 below. Final reports for six of the eight inspections are still outstanding, but no major issues have been identified to date and no Form 483 “Inspectional Observations” have been issued.

Table 32: Sites Inspected Along with Field Classifications

Name of CI, IRB, or Sponsor Location	Protocol #Site#
Sergey Goryunov Filatov Municipal Hospital #15 23, Veshnyakovskaya str. Moscow, Russia 111539	P903-06/ Site #5007/
Alexander Konychev V Municipal Hospital #14 19, Kosinova St. St. Petersburg, Russia	P903-07/Site #5014
Veronika B. Popova Saint George Municipal Hospital, Therapy Department #1 1 Severny pr. St. Petersburg, Russia 194354	P903-09/ Site # 5011
Oleg Kraydashenko Zaporizhzhya State Medical University, City Clinical Hospital #6 26 Mayakovskoho Pr. AND34, Stalevariv vul. Zaporizhzhya, Ukraine, 69035	P903-09/ Site # 7004
Lyudmyla Yashyna F H Yanovskyi Phthisiology and Pulmonology Institute 10 Amosova Vul Kyiz, Ukraine 03680	P903-08/ **Site # 7030**
Joseph Surber Southeast Regional Research Group 5210 Armour Rd, Suite 400 Columbus, GA 31904	P903-07/ Site # 0037
Purvi Mahra eStudy Site 752 Medical Center Ct #105 Chula Vista, CA 91911 pmehra@estudysite.com	P903-06/ Site #0002/
Revas Tabukashvili 9 Tsinandall Str. Internal Medicine Clinic of Georgian Patriarchate Tbilisi, Georgia 0144	P903-08/Site # 5428

As previously discussed, there was a problem noted at one site in India by the Applicant. The Applicant has followed up on this issue appropriately. The FDA review team has removed 9 patients from 3 sites in India (monitored by the same CRO) from its analyses.

12. Labeling

On January 8, 2010, Cerexa proposed (b) (4) as the proprietary name for ceftaroline fosamil. This name was found to be unacceptable by the Division of Medication Error Prevention and Analysis (DMEPA) in a consult review dated April 7, 2010. There was concern regarding potential confusion with another cephalosporin, (b) (4)

On July 14, 2010, Cerexa proposed Teflaro as an alternative. This name was found to be acceptable as reported in the consult from DMEPA on October 8, 2010.

There were no major DDMAC or OSE issues to discuss with this application.

The major areas of discussion regarding the product label were the information to be presented in the clinical trials section of the label and antimicrobial susceptibility breakpoints.

Efficacy determination for ceftaroline fosamil was based on endpoints that were different from those which were prespecified. These analyses were the key analyses used by the FDA in determining the clinical efficacy of ceftaroline in the treatment of ABSSSI and CABP and therefore are presented in the product label. However, the prespecified endpoint of sustained clinical response at test of cure (i.e. for a period off of study therapy) is information which is important to healthcare providers, and it was agreed upon that this information could appear in the label with no comparative claims made about ceftaroline versus comparator based on this endpoint.

The labeling discussion regarding antimicrobial susceptibility breakpoints between FDA and the Applicant was uneventful. The Agency carefully reviewed the available clinical data, the PK/PD information, information from Monte Carlo simulations, and data regarding bacterial susceptibility reported from large surveillance studies and arrived at breakpoints which were acceptable to the Applicant.

On September 14, 2010, DMEPA recommended changes to the Applicant's proposed carton and container labeling. After revision, the carton label submitted by the Applicant on October 13, 2010 was found to be acceptable by DMEPA. The container label was revised a second time and was found to be acceptable by DMEPA on October 20, 2010.

No medication guide is necessary for this product at the present time.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

  APPROVAL

- Risk Benefit Assessment

  Ceftaroline fosamil is a NME. It is a cephalosporin antibacterial agent with in vitro activity against MRSA. The efficacy of this antibacterial against MRSA is important from a public health standpoint, in light of the increasing number of MRSA infections developing in the community in addition to those occurring in healthcare facilities. There are limited treatment options available for this bacteria and ceftaroline as a new molecular entity represents a new class of antimicrobial agents active against MRSA. Ceftaroline has demonstrated clinical efficacy in the treatment of ABSSSI caused by Gram positive bacteria, including MRSA and some *Enterobacteriaceae*. Ceftaroline has also demonstrated clinical efficacy in the treatment of CABP caused by *S. pneumoniae*, MSSA, *H. influenzae*, and some *Enterobacteriaceae*.

  The safety database did not reveal any major toxicities associated with this drug and it has a profile similar to other ceophalosporins, It did demonstrate a higher rate of serconversion from a negative to positive direct Coombs' test than comparators, including ceftriaxone, another cephalosporin with a similar profile. It was not associated with drug induced hemolytic anemia in the Phase 3 clinical trials.

  Therefore, the benefit:risk ratio for ceftaroline is positive.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

  There is no formal post-marketing Risk Evaluation and Mitigation Strategy (REMS) necessary for this product. Surveillance for adverse events based on post-marketing events reported to Medwatch and by the Applicant through periodic safety update reports will be monitored.

- Recommendation for other Postmarketing Requirements and Commitments

We are deferring submission of pediatric trials in patients aged 0 to 17 years for Acute Bacterial Skin and Skin Structure Infections (ABSSSI) and Community-Acquired Bacterial Pneumonia (CABP) until July 2015, because this product is ready for approval for use in adults and pediatric trials have not been completed. In addition to the PMRs for pediatrics, an additional PMR and PMC will be required of the Applicant.

POSTMARKETING REQUIREMENTS UNDER 505(o)

1692-005: Conduct a prospective study over a five-year period after introduction of Teflaro (ceftaroline fosamil) to the market to determine if decreased susceptibility to Teflaro (ceftaroline fosamil) is occurring in the target bacteria included in the Indications section of the approved Teflaro (ceftaroline fosamil) package insert. Provide a detailed study protocol describing the study to the Agency for review and comment before commencing the study.

The timetable you submitted on October 14, 2010 states that you will conduct this study according to the following schedule:

Final protocol Submission: 01/2011
First Interim Report: One year after introduction of Teflaro to the market and then annually
Study Completion: 04/2016
Final Report Submission: 10/2016

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

1692-006: Conduct a prospective, randomized trial evaluating the efficacy and safety of Teflaro (ceftaroline fosamil) versus comparator in the treatment of patients with CABP at high risk for infection caused by MRSA.

Final Protocol Submission: 10/2011
Trial Completion Date: 09/2016
Final Report Submission: 04/2017

- Recommended Comments to Applicant

There are no comments to be communicated at this time.

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8. Snodgrass WR, Anderson T. Sulphanilamide in the treatment of erysipelas. British Medical Journal 1937;2(4014):1156-1159.
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/s/

JANICE K POHLMAN
10/28/2010