CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200327

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
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Division / Office	Division of Anti-Infective and Ophthalmology Products Office of Antimicrobial Products
Reviewer Name(s)	Ariel Ramirez Porcalla, MD, MPH Neil Rellosa, MD
Review Completion Date	October 29, 2010
Established Name	Ceftaroline fosamil for injection
(Proposed) Trade Name	Teflaro
Therapeutic Class	Cephalosporin; ß-lactams
Applicant	Cerexa, Inc. Forest Laboratories, Inc.
Formulation(s)	400 mg/vial and 600 mg/vial Intravenous
Dosing Regimen	600 mg every 12 hours by IV infusion
Indication(s)	Acute Bacterial Skin and Skin Structure Infection (ABSSSI); Community-acquired Bacterial Pneumonia (CABP)
Intended Population(s)	Adults ≥ 18 years of age

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1 Recommendations/Risk Benefit Assessment

Four Phase 3 multicenter, multinational, randomized, double-blind, active-controlled clinical trials were performed to evaluate the efficacy of ceftaroline in treating two indications. Two trials (P903-08 and P903-09) were conducted for Community-Acquired Bacterial Pneumonia (CABP) and two trials (P903-06 and P903-07) were conducted for Acute Bacterial Skin and Skin Structure Infections (ABSSSI). The Phase 3 trials utilized the Applicant's suggested dose for patients with normal renal function and mild renal impairment of 600 mg given intravenously every 12 hours. As comparators, the ABSSSI trials used vancomycin plus aztreonam and the CABP trials used ceftriaxone.

The Applicant's analyses of efficacy for ceftaroline were based on a primary efficacy endpoint of clinical response rate at Test-of-Cure in the modified intent-to-treat population (MITT) and clinically evaluable (CE) populations for ABSSSI and the modified intent-to-treat efficacy (MITTE) and clinically evaluable (CE) populations for CABP. The trials were designed as noninferiority (NI) trials with a prespecified NI margin of 10%. The lower bound of the 95% confidence interval (CI) around the difference in clinical response rates (ceftaroline - comparator) for each CABP and ABSSSI trial was greater than -10. Hence, non-inferiority of ceftaroline relative to the active controls was concluded.

Based on historical evidence of a treatment effect of antibacterials relative to placebo on objective clinical factors such as fever, respiratory rate, and heart rate for CABP and fever and spread of lesion for ABSSSI, the FDA review team performed sensitivity analyses using data available from the completed trials. These primary efficacy endpoint analyses were based on an efficacy endpoint of clinical response assessed at an earlier timepoint.

For the CABP trials, using an FDA-defined microbiological intent-to-treat (mITT) population, clinical response assessed on Day 4 of therapy using clinical vital signs stability criteria and symptom improvement criteria was defined as the primary efficacy sensitivity analysis. Although the sample sizes were small and confidence intervals for the differences in the response rates were consequently wide, the results showed that ceftaroline met a 10% non-inferiority margin in both trials, with the lower bound of the 95% CI less than -7 for both trials.

For the ABSSSI trials, using the FDA modified intent-to-treat (FDA-MITT) population defined primarily by size criteria and infection type, a sensitivity analysis was performed with the efficacy endpoint of clinical response defined as cessation of spread of the lesion and absence of fever assessed at Day 3. The results of these analyses support the non-inferiority of ceftaroline compared to vancomycin/aztreonam with a lower bound of the 95% CI less than -4 for each trial.

From the safety database, ceftaroline appears to be safe and well-tolerated. The analysis of deaths that occurred during clinical trials shows that ceftaroline use does not appear to be associated with a higher risk of death. Equally important, ceftaroline appears to have a safety profile that is similar to the active comparators and existing cephalosporins. The most common adverse drug reactions observed are gastrointestinal symptoms such as diarrhea and nausea and rash. One adverse event (AE) that occurred more frequently in the ceftaroline-treated group was direct Coombs' test seroconversion following treatment with ceftaroline. Its clinical relevance is unknown since the incidence of potentially clinically significant anemia was similar in both treatment groups and no case of hemolytic anemia was diagnosed during the course of the clinical trials. As with other cephalosporins, ceftaroline could potentially cause allergic and hypersensitivity reactions and antibiotic-associated diarrhea.

Data from Clinical Pharmacology studies and the Phase 3 clinical trials provide sufficient information on directions for use, the appropriate recommended dose, and the need for dose adjustment in specific subpopulations. Because ceftaroline is primarily excreted through the kidneys, dose adjustment is recommended in patients with moderate and severe renal impairment and end-stage renal disease (ESRD), including patients on hemodialysis.

In summary, based on clinical efficacy and safety data submitted by the Applicant from the randomized, active controlled Phase 3 clinical trials, there is adequate evidence to recommend the approval of ceftaroline as a safe and efficacious treatment for CABP and ABSSSI.

1.1 Recommendation on Regulatory Action

The efficacy of ceftaroline as treatment for CABP and ABSSSI is supported by clinical data from four adequate Phase 3 randomized, active-controlled, noninferiority clinical trials. FDA sensitivity analyses of the clinical data, supported by prespecified Applicant analyses, provide adequate and robust evidence of ceftaroline's noninferiority to the active comparators. Safety analysis indicates that ceftaroline is safe and well-tolerated, with a safety profile similar to other cephalosporins. There is sufficient data to provide adequate directions for use and to recommend that dose adjustment is necessary only in patients with moderate and severe renal impairment and end-stage renal disease (ESRD).

Based on this, the Medical Officer recommends approval of ceftaroline for the treatment of CABP and ABSSSI in adult patients 18 years and older.

1.2 Risk Benefit Assessment

Ceftaroline is a semi-synthetic cephalosporin with in vitro activity against aerobic and anaerobic Gram-positive and Gram-negative bacteria implicated in skin and lower respiratory tract infections. Ceftaroline's potential use in clinical practice is underscored by its activity against methicillin-resistant *Staphylococcus aureus* (MRSA). Data from

the Phase 3 clinical trials provide sufficient and robust evidence that ceftaroline is noninferior to active comparators as treatment for CABP and ABSSSI in adult patients, with the caveat that CABP caused by MRSA was not studied in the trials. Therefore, the efficacy of ceftaroline against CABP caused by MRSA has not been established by these trials.

Safety data indicates that ceftaroline use is safe and well-tolerated, with a safety profile similar to other cephalosporins. The most common adverse reactions reported in >2% of patients receiving ceftaroline are diarrhea, nausea, and rash. Hypersensitivity reactions, including cases of anaphylactic shock and anaphylactoid reactions, *Clostridium difficile*-associated diarrhea, and seroconversion from a negative to a positive direct Coombs' test result have been reported in patients receiving ceftaroline.

In particular, direct Coombs' test seroconversion occurred more frequently in the ceftaroline-treated group than in the comparator-treated group (10.8% vs. 4.4%). Its clinical significance is unknown as there were no adverse reactions representing hemolytic anemia reported in any treatment group. Lastly, while adverse events representing renal impairment occurred rarely in both treatment groups, their incidence was slightly higher in the ceftaroline-treated group compared to the comparator-treated group (1.5% vs 0.8%), with association difficult to infer from the current safety population. Because nonclinical studies demonstrated that the renal system may potentially be a target organ system for toxicity for ceftaroline and because the relevance of the direct Coombs' test seroconversion is still unknown, the Medical Officer recommends that the incidences of AEs representing renal impairment, direct Coombs' test seroconversion, and drug-induced hemolytic anemia be monitored as part of post-marketing safety surveillance reporting.

In summary, data presented in the NDA provide sufficient information on directions for use, the appropriate recommended dose, and the dose adjustment for renal impairment. The efficacy of ceftaroline as treatment of ABSSSI and CABP in adults (except in CABP caused by MRSA) has been established by the pivotal Phase 3 trials. Safety data indicate that ceftaroline's safety profile is similar to those of other cephalosporins, with observed adverse events such as direct Coombs' test seroconversion that is of unknown clinical significance. Thus, the potential benefits associated with the use of ceftaroline as treatment for ABSSSI and CABP far outweigh the potential risks of developing associated adverse events.

1.3 Recommendations for Postmarketing Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarketing Requirements and Commitments

1.4.1. Recommendations for Postmarketing Requirements

1.4.1.1. Required Pediatric Assessments

Pediatric trials in patients aged 0 to 17 years for ABSSSI and CABP were deferred until July 2015 because the product is ready for approval for use in adults and pediatric trials have not been completed.

The deferred pediatric trials are required under section 505B(a) of the Federal Food, Drug and Cosmetic Act (FDCA) as postmarketing trials. These trials are listed below:

1. Trial 1692-001: 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:
   - ≥ 6 years – 12 years
   - ≥ 24 months – 6 years
   - ≥ 28 days to 24 months (with equal representation of patients aged 28 days to 1 year and 1-2 years)
   - Term neonates < 28 days (stratified within the group: 0 to < 14 days; ≥ 14 days to < 28 days)
   - preterm neonates (gestational age 32 - 37 weeks) < 28 days (stratified within the group: 0 to < 14 days; ≥ 14 days to < 28 days)

   There must be a minimum of 8 evaluable subjects per cohort.

   Final Protocol Submission: 11/2010
   Trial Completion Date: 01/2014
   Final Report Submission: 07/2014

2. Trial 1692-002: Pediatric CABP Trial

   Perform a randomized comparison of Teflaro (ceftaroline fosamil) and comparator in pediatric subjects with CABP utilizing an enrichment strategy for enrollment of patients with methicillin-resistant *Staphylococcus aureus* (MRSA). Pediatric patients under 17 years of age with CABP must be enrolled, with a minimum of 150 patients receiving Teflaro (ceftaroline fosamil).

Final Protocol Submission: 09/2011
Trial Completion Date: 05/2014
Final Report Submission: 11/2014

3. Trial 1692-003: Pediatric ABSSSI Trial

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).

Final Protocol Submission: 09/2011
Trial Completion Date: 05/2014
Final Report Submission: 11/2014

4. Trial 1692-004: Cerebrospinal Fluid (CSF) Concentration Trial

Perform a trial assessing the CSF concentration profile of Teflaro (ceftaroline fosamil) in infants < 2 months of age. A minimum of 12 infants receiving antibacterials for treatment of late-onset neonatal sepsis must be studied.

Final Protocol Submission: 05/2014
Trial Completion Date: 09/2016
Final Report Submission: 03/2017

5. Trial 1692-005: ABSSSI and CABP Trials in Infants < 2 months

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.

Final Protocol Submission: 05/2014
Trial Completion Date: 09/2016
Final Report Submission: 03/2017

Final trial reports and other submissions related to these required pediatric postmarketing trial should be clearly designated “Required Pediatric Assessments”.

1.4.1.2. Postmarketing Requirements under 505(o)

Trial 1692-006**:**

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.

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

1.4.2. Recommendations for Postmarketing Commitments

This commitment is listed below:

Trial 1692-007:

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

2 Introduction and Regulatory Background

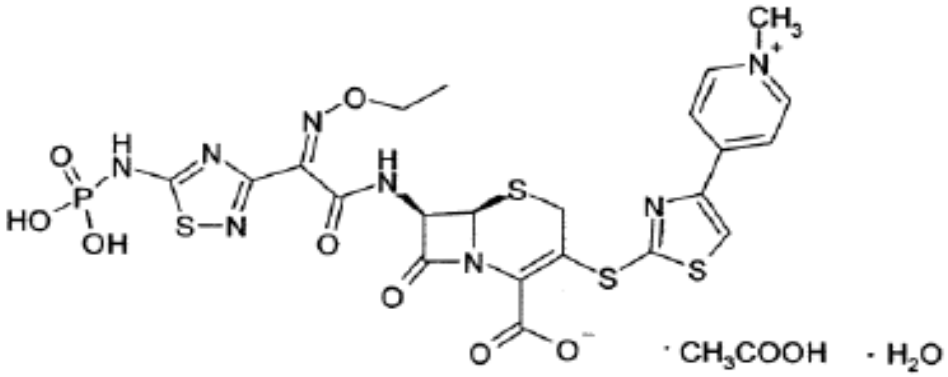
2.1 Product Information

Ceftaroline fosamil is an injectable, sterile, semi-synthetic antibacterial prodrug belonging to the cephalosporin class of beta-lactams (ß-lactams).

Its chemical name is: (6R, 7R)-7-{(2Z)-2-(ethoxyimino)-2-[5-(phosphonoamino)-1,2,4-thiadiazol-3-yl]acetamido}-3-{[4-(1-methylpyridin-1-ium-4-yl)-1,3-thiazol-2-yl]sulfanyl}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate. (b) (4)

Its empirical molecular formula is $C_{22}H_{21}N_8O_8PS_4$ and it has a molecular weight of 684.68.

Its chemical structure is:



The drug has not been marketed worldwide.

- Generic Name: Ceftaroline fosamil
- Proposed Trade Name: Teflaro®
- Chemical class: New Molecular Entity (NME)
- Pharmacological Class: Cephalosporin class of ß-lactam antibacterials
- Proposed Indications: Treatment of acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP) in adults
- Dosing regimens: 600 mg administered as a 1-hour intravenous (IV) infusion every 12 hours for 5-14 days for ABSSSI and 5 to 7 days for CABP for patients whose creatinine clearance (CrCl) is > 50 mL/min (patients with normal renal function and patients with mild renal impairment). For patients with CrCl ≥ 15 to ≤ 50 mL/min (moderate renal impairment), the Applicant has proposed a dose of 400 mg IV (over 1 hour) every 12 hours. No dosage adjustment is necessary based on age or hepatic impairment.

2.2 Tables of Currently Available Treatments for Proposed Indications

For the indication of moderate to severe CABP, the currently available treatments approved by the FDA include the following pharmacologic classes of antibacterials, along with specific drug products:

- Cephalosporins (cefepime, cefotaxime, ceftriaxone, cefuroxime)
- Penicillins with beta-lactamase inhibitors (ampicillin/sulbactam, piperacillin/ tazobactam, ticarcillin/clavulanate)
- Macrolides (azithromycin, clarithromycin)
- Quinolones (gemifloxacin, levofloxacin, moxifloxacin)
- Carbapenems (ertapenem, meropenem).

2.3 Availability of Proposed Active Ingredient in the United States

Ceftaroline fosamil is a new molecular entity (NME) that is available as an investigational agent.

2.4 Important Safety Issues With Consideration to Related Drugs

Ceftaroline fosamil is a cephalosporin in the ß-lactam class of antibacterial medications. As such, ceftaroline is anticipated to have a similar adverse event profile to other members of that class, including hypersensitivity, rash, and cross-sensitivity to other ß-lactams.

Cephalosporin-class adverse reactions and altered laboratory tests that may be observed with ceftaroline fosamil include the following: vomiting, abdominal pain, colitis, vaginitis (including vaginal candidiasis), toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage, prolonged prothrombin time, pancytopenia, and agranulocytosis. In particular, several cephalosporins have been implicated in triggering seizures, particularly in healthy patients who receive an overdose or in patients with renal impairment when the dose was not reduced.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The presubmission regulatory history and milestones related to the current NDA submission are summarized as follows:

- In December 2004, IND 71,371 was submitted by Peninsula Pharmaceuticals, Inc. to develop ceftaroline fosamil (Teflaro®) for the treatment of ABSSSI.
- In June 2005, the sponsorship of IND 71,371 was transferred to Cerexa, Inc.
- February 28, 2006: Cerexa was granted fast track designation by the Division of Anti-Infectives and Ophthalmology Products (DAIOP) for the treatment of ABSSSI. This designation was based on ceftaroline fosamil's potential to address unmet medical need for patients not responding to or unable to tolerate current treatment regimens for ABSSSI, specifically methicillin-resistant *Staphylococcus aureus* (MRSA).
- On October 24, 2006, during an End-of-Phase 2 meeting, the evaluation of ceftaroline in the treatment of ABSSSI and CABP, in the setting of non-inferiority trials with a 10% margin, was discussed. A non-inferiority clinical trial for ABSSSI was deemed acceptable on June 1, 2007.
- The two pivotal Phase 3 ABSSSI studies (P903-06 and P903-07) were initiated in February 2007 and March 2007, respectively, and enrollment was completed in November 2007 and December 2007, respectively.
- January 26, 2007: A Special Protocol Assessment (SPA) for the Phase 3 CABP protocols (Studies 903-08 and P903-09) was submitted by the Applicant. On March 15, 2007, DAIOP advised the Applicant not to include treatment with a concomitant macrolide or option for an oral switch that could potentially confound

the assessment of ceftaroline's efficacy. Cerexa responded on April 17, 2007, that due to incompatibility with the Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) guidelines (Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults),[1] enrollment in the United States (US) would be difficult. On June 1, 2007, it was agreed that adjunctive clarithromycin would be allowed for 24 hours in Trial P903-08, with no option for oral switch.

- September 11, 2007: The use of a 10% non-inferiority margin to evaluate the efficacy of ceftaroline as treatment for moderate to severe CABP, defined as Pneumonia Outcomes Research Team (PORT) Risk Class III or greater, was deemed acceptable.
- November 2, 2007: During a Type A teleconference between the DAIOP and Cerexa, inclusion of PORT II patients was deemed unacceptable by the Division. Cerexa subsequently amended the protocols for both trials, excluding PORT Risk Class II patients from enrollment. PORT Risk Class II patients previously enrolled were to be analyzed in a subgroup analysis.
- The two Phase 3 CABP trials (P903-08 and P903-09) were initiated in January 2008 and July 2007, respectively, and enrollment was completed in December 2008 and August 2008, respectively.
- The Statistical Analysis Plans (SAPs) for the ABSSSI and CABP trials were submitted to DAIOP for review. Additional analyses were recommended by DAIOP for the ABSSSI studies.
- July 7, 2009: A face-to-face Type B Pre-NDA meeting was held between DAIOP and the Applicant, with the objective of obtaining concurrence on the content and format of the NDA and the planned data analyses. During the meeting, Cerexa committed to additional analyses of data from the ABSSSI and CABP pivotal trials. Cerexa also agreed to provide the following:
    - Proposed Pediatric Study Request (submitted August 10, 2009)
    - Sample raw and derived datasets in CDISC format and transport files for preliminary review by the FDA (submitted on October 27, 2009). Comments on the datasets were emailed by DAIOP to Cerexa on December 2, 2009 and a subsequent teleconference between the Division and Cerexa occurred on December 11, 2009.
    - Original Metabolite Profiling Study Report (submitted). Division comments on August 20, 2009 requested the identification of Peak 1 metabolite and a justification for the discrepancy observed between total urinary recovery and the % of dose. With Cerexa's response, the Division replied on November 6, 2009, stating that the issues were resolved.
    - Patient ID Numbers for the Phase 3 studies. After submission, the Division provided a random list of patient numbers (5%) whose case report forms (CRFs) were requested.
- On July 22, 2009, a separate face-to-face Type B Pre-NDA Chemistry, Manufacturing, and Controls (CMC) meeting was held to obtain concurrence with the product development plans and regulatory strategy. The Division requested

that Cerexa to provide a revised proposal on the starting materials and to include a synthetic scheme for the entire process, which was submitted on October 2, 2009.

The following public discussions and FDA regulatory-related activities provided the backbone with which the FDA reviewers performed a number of sensitivity analyses for efficacy assessment in the Phase 3 ABSSSI and CABP clinical trials.

- A public workshop jointly sponsored by the FDA, the Infectious Diseases Society of America (IDSA), the American Thoracic Society (ATS), and the American College of Chest Physicians (ACCP) was held on January 17-18, 2008. Primary endpoints, historical evidence for treatment effect of antibacterials, microbiology, and possible trial designs for CABP were discussed.
- An Anti-Infective Drugs Advisory Committee (AIDAC) meeting was held on April 1-2, 2008. The committee unanimously voted that in patients with severe CABP, a non-inferiority margin could be justified based on mortality data. Issues discussed included the extrapolation of mortality to clinical endpoints, the appropriate study population and analysis, and the need for microbiologic confirmation of bacterial etiology to link to historical data.
- A draft guidance on development of antibacterial drugs to treat CABP was issued and posted for comment on March 20, 2009. Several public discussions have been held to clarify appropriate clinical trial design using non-inferiority margins.
- An Anti-Infective Drugs Advisory Committee (AIDAC) meeting was held on December 9, 2009 to discuss comments received regarding the draft CABP guidance. The majority of the AIDAC members believed that historical data could support the use of a clinical endpoint, in addition to that of all-cause mortality, as a primary endpoint. Both parameters can serve as part of a composite endpoint. Based on historical evidence where maximal treatment effect was noted 48-72 hours after initiation of therapy, the assessment of clinical response at 48-72 hours was mentioned as possible timing for endpoint assessment. The committee recommended the use of the microbiological intent-to-treat (mITT) population as the primary analysis population. The enrollment of sicker patients as assessed by pneumonia severity scoring systems such as the Pneumonia Patient Outcomes Research Team (PORT) [17] or CURB-65, or of patients older than 50 years of age was recommended because these populations are at higher risk for morbidity and mortality.

For the indication of ABSSSI, as part of a multi-day AIDAC meeting on November 8, 2008, the use of a non-inferiority trial design and justification for an NI margin in patients with severe cellulitis or wound infections was supported by adequate evidence in the historical literature. However, the treatment effect of antibacterials following primary incision and drainage in patients with abscesses could not be estimated. Hence, major abscesses lacking significant inflammatory components should be excluded in NI trials.

2.6 Other Relevant Background Information

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was relatively well-organized and based on the electronic common technical document (eCTD) format described in the ICH M2 EWG Electronic Common Technical Document Specification of 2008. The submission was straightforward to navigate with information accessible in the various modules, summaries, and clinical trial reports. Information contained in the submission was relatively complete.

A number of issues were encountered during the review. The initial NDA submission datasets contained no decode variables, so amended clinical datasets with decode variables, new study day variables, and clarifications to labels were submitted on February 2, 2010. The datasets amended included pivotal clinical study report analysis databases, CSR SDTM databases, and Integrated Summary of Efficacy and Integrated Summary of Safety analysis databases. The datasets that were submitted were comprehensive but contained redundant information.

Overall, clinical case summaries were comprehensive. However, additional information was requested for specific mortality reports and was provided by the Applicant.

A review of a 5% random sample of case report forms (CRFs) for each of the four Phase 3 trials was performed. Minor inconsistencies between information contained in the CRFs and the datasets were noted. Examples are errors in categorizing degrees of renal insufficiency and inclusion of patients in the clinically evaluable (CE) or microbiologically evaluable (ME) populations as noted in the datasets. Since central laboratory analyses were not part of the CRF but rather recorded separately in an electronic database, some of the renal function discrepancies may have been explained if central, rather than local serum creatinine was used to calculate creatinine clearance. Other inconsistencies in coding from the CRFs to the datasets appear to be minor and few, such that they would not impact the study results and analyses.

An information amendment relating to the CABP Phase 3 Trial P903-09 was received August 13, 2010. This amendment provided follow-up details of the Applicant's investigation of a clinical investigator who enrolled seven patients at Site 9001 in Trial P903-09. The Applicant had initiated an investigation after becoming aware through an internet posting of alleged fradulent activity by this investigator in another Sponsor's study. The investigator had been monitored by a contract research organization (CRO), (b) (4), who performed nine monitoring visits at the site. The site monitors had claimed 100% verification of source materials. However, during the Applicant's investigation, including a site visit on June 24-25, 2010, none of the study files or source

materials could be located at the study site. The Applicant concluded that study data from the Investigator's sites could not be supported and performed a sensitivity analysis excluding patients from that investigator's site, with no impact on the efficacy outcome of the trial noted. Although this information amendment did not affect the reviewer's ability to perform the review within the allotted timeframes, DAIOP, in consultation with the Division of Scientific Investigations (DSI), excluded data from this site in its efficacy and safety analyses. This impacted 7 patients; 2 additional patients at two sites monitored by the same CRO were also excluded from the reviewer's analyses since DSI could not ensure the integrity of data at those sites. A total of nine patients (five in the ceftaroline group and four in the ceftriaxone group) were excluded as a result.

3.2 Compliance with Good Clinical Practices

Study protocols, amendments, informed consent forms, information sheets, and advertisements were approved by the Institutional Review Board (IRB) or Independent Ethics Committee at each study center in conformance with the International Conference of Harmonisation (ICH) Guidelines E6 (1996) and E3 (1995), and 21 Code of Federal Regulations (CFR), Part 56. The Applicant further states that the clinical trials were conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and in accordance with the laws of the country in which the research was conducted, using whichever code represented the greatest protection for the patient. All clinical studies in the submission were conducted in full compliance with the US FDA regulations 21 CFR 50 and 21 CFR 312 Parts B and D.

As a requirement for inclusion, each patient was provided with a written informed consent form that complied with 21 CFR Parts 50 and 312 at baseline, before randomization. Each patient should have read, assented to, understood, and voluntarily signed an instrument of informed consent prior to the performance of any study procedure. Patients reportedly had an opportunity to discuss these documents with the Clinical Investigator before signing and were made aware that they could withdraw from the trial at any time. In the United States, patients also signed a Health Insurance Portability and Accountability Act (HIPAA) authorization form after having the study explained to them.

To ensure that trial conduct was rigorous and trials were performed with strict adherence to the protocol, activities such as pre-enrollment qualification of all sites, Investigator meetings in all regions, required protocol training, review of blinding procedures, monitoring of sites during and after active enrollment, enforcement of ICH compliance, and auditing of more than 30% of the total sites and patients, were performed.

3.3 Financial Disclosures

The financial disclosure statements of the majority of the investigators from the Phase 2 and Phase 3 clinical trials were obtained and kept on file by the Applicant.

The Applicant, however, failed to obtain financial disclosures from 17 investigators at 8 sites. Despite three attempts by the Applicant to obtain financial disclosure information for two investigators (b) (4) in two of the Phase 2 clinical trials, no response was received. Similarly, the Applicant was not able to obtain financial disclosure information for three investigators at three sites in Trial 06 for ABSSSI. After requesting the information, the three sites ((b) (4) responded that the investigators were no longer affiliated with the site and the requested information could not be obtained. The remaining 12 investigators with no financial disclosure information belonged to three sites in Trial 07 for ABSSS (b) (4) that either did not enroll patients or decided not to participate in the trial.

Hence, only three investigators from Trial 06 with no financial disclosure information obtained could potentially impact the results of the Phase 3 clinical trials for ABSSSI.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Based on the review of Dr. Andrew Yu, the submission has provided sufficient information to assure the identity, strength, purity, and quality of the drug product, with approval dependent on the determination of sterility assurance by the Product Quality Microbiology Reviewer. All manufacturing sites have been found acceptable by the CDER Office of Compliance.

Ceftaroline fosamil for injection is supplied in single-use, clear glass vials containing 600 mg and 400 mg, packaged in a carton containing 10 vials. Ceftaroline vials should be stored refrigerated at 2 to 8 degrees Centigrade (36-46 degrees Fahrenheit), with a shelf life of 24 months when stored under these conditions. The drug product should be constituted by adding 20 mL of Water for Injection, USP and the entire constituted solution should be diluted within 2 minutes in ≥ 250 mL of 0.9% Sodium Chloride Injection, USP (normal saline), 0.45% Sodium Chloride Injection, USP, 5% Dextrose Injection, USP, 2.5% Dextrose Injection USP, or Lactated Ringer's Injection, USP before infusion. Compatibility evaluation includes evaluation of appearance, turbidity, stability, and examination for particulate matter. The resulting solution should be administered over 1 hour. The constituted solution should be used within 6 hours when stored at room temperature or within 24 hours when refrigerated at 2 to 8 degrees centigrade.

(b) (4)
, ceftaroline fosamil is available as an acetate monohydrate

which is a stable solvate. Manufactured by ACS Dobfar under Drug Master File (DMF) 23167, ceftaroline fosamil has (b) (4) related impurities which have been chemically characterized and controlled by specifications in the DMA and the NDA. Concerns regarding impurity level, specifications, and other quality issues have been adequately addressed and the DMF was deemed acceptable.

The drug product (Teflaro) consists of ceftaroline fosamil formulated with (b) (4) arginine supplied by (b) (4). It was deemed that the DMFs for the container components and the sterility of the arginine were adequate. Because the drug substance (b) (4), stability upon exposure to (b) (4) in the recommended container was determined and found acceptable.

During drug development, arginine was found to form a (b) (4) with the drug in infusion solutions. The (b) (4) formation was determined to be (b) (4) in all reconstituted infusion studies, well within the NMT (b) (4) qualification limit or cutoff.

Currently, the compatibility of ceftaroline with other drugs has not been fully determined but a list of chemically incompatible drugs based on preliminary studies was provided in the NDA. The package insert states that ceftaroline should not be mixed with or physically added to solutions containing other drugs.

For more details, the reader is referred to Dr. Yu's review.

4.2 Clinical Microbiology

In Vitro Activity
Surveillance studies of *Staphylococcus aureus* isolates from Europe and the United States demonstrated that the MIC_{90} values ranged from 0.12-2 mcg/ml against all staphylococci tested. Against methicillin-resistant *Staphylococcus aureus* (MRSA), the ceftaroline MIC_{90} value was reported to be 1 mcg/ml for US isolates. Ceftaroline is also active in vitro against *Streptococcus pneumoniae*, including penicillin-intermediate and –resistant isolates. MIC_{90} values ranged from 0.004 to 0.025 mcg/ml against all *S. pneumoniae* isolates. Ceftaroline MIC_{90} values were ≤0.016 mcg/ml for some β-hemolytic streptococcal isolates. Against penicillin-resistant viridans group streptococci, ceftaroline MIC_{90} values were 1 mcg/ml. Ceftaroline activity was also assessed against bacteria belonging to the *Enterobacteriaceae* family. The Applicant's data shows that ceftaroline demonstrated activity with MICs ranging from ≤ 0.016 mcg/ml to > 32 mcg/ml against all isolates. Decreased in vitro activity was observed against AmpC and ESBL producing and ceftazidime non-susceptible *Enterobacteriaceae* isolates such as *E. coli, K. pneumoniae, K. oxytoca, Enterobacter cloacae,* and *E. aerogenes.* Ceftaroline's in vitro activity against non-fermenting Gram-negative bacteria such as *P. aeruginosa* suggests that it would not be successful in treating infections caused by these organisms.

Mechanism of Resistance
For staphylococcal organisms, mechanisms of resistance include the production of β-lactamase and modification of the PBP target by either gene acquisition of an exogenous PBP or target alteration. In particular, methicillin resistance in *S. aureus* isolates is mediated by the presence of the mecA gene and the production of PBP2a, which has low-affinity for β-lactams. Ceftaroline's activity against MRSA is secondary to ceftaroline's high affinity to PBP2a. Streptococcal resistance to β-lactams is mediated via alterations in the β-lactam-binding site of PBP1a, PBP2b and PBP2x. Mutations resulting in changes in the active binding sites correlate with decreased affinity for β-lactams and increase in MIC. In Gram-negative organisms, the predominant mode of resistance is the production of β-lactamase hydrolyzing enzymes such as extended spectrum β-lactamases (ESBLs). Ceftaroline hydrolysis by ESBLs is a major contributing factor for resistance in Gram-negative organisms. High rates of ceftaroline hydrolysis were reported for CTX-M-15, KPC-2, TEM-1 SHV-4 and P99. In addition, AmpC β-lactamases have been frequently identified in Gram-negative organisms, of which there are two types (plasmid-mediated and chromosomal or inducible AmpC). Ceftaroline is also degraded by isolates that hyper-produce AmpC β-lactamases. Thus, ESBL producing and AmpC Gram-negative bacteria are clinically resistant to ceftaroline.

Several in vitro studies described in the application indicate a low propensity for the development of ceftaroline resistance among *S. aureus*, including MRSA, *S. pneumoniae, and E. faecalis* isolates tested, following serial passage experimental studies compared with the comparator agents.

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

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

For more details, including a discussion of the FDA-proposed ceftaroline in vitro susceptibility test interpretive criteria, please refer to the review by Dr. Avery Goodwin, the Clinical Microbiology reviewer.

4.3 Preclinical Pharmacology/Toxicology

Immediately after intravenous administration, ceftaroline fosamil is rapidly dephosphorylated to its active form, ceftaroline, in the plasma and distributed to tissues. It is also metabolized into an open ß-lactam ring metabolite, ceftaroline M-1, which may also be detected in the plasma. The pharmacokinetic properties of ceftaroline fosamil, ceftaroline, and ceftaroline M-1 have been characterized in mice, rats, rabbits, and monkeys using different dose levels administered intravenously or intramuscularly. The primary excretion for ceftaroline is renal, with some fecal excretion. In rats, 67% of radiolabeled ceftaroline was recovered in the urine and 29% in the feces, while in monkeys, 65% and 19% of administered ceftaroline was excreted through the kidney and stool, respectively, mostly in the active form of ceftaroline. Table 1 shows the exposure in rats and monkeys after specific repeated doses of ceftaroline fosamil.

Table 1. Ceftaroline exposure in rats and monkeys after repeated IV administration

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

Nonclinical studies in rats, rabbits, and monkeys were performed. Toxicities observed occurred at dose equivalents greater than the maximum recommended human dose (MRHD) of 600 mg every 12 hours administered intravenously. The primary organs of toxicity were the kidney and the central nervous system (CNS), consistent with target organs of toxicity experienced with other cephalosporins. Rats and monkeys given high doses of ceftaroline (1000 mg/kg and 400 mg/kg, respectively) experienced tonic-clonic convulsions during the 4-weeks studies. This observation was confirmed by a 13-week

study in rats, with estimated ceftaroline plasma AUC level of approximately 12-20 times the human AUC at therapeutic levels.

Changes in laboratory parameters reflecting renal function and microscopic renal changes were seen in rats at ≥ 300 mg/kg and monkeys at ≥ 80 mg/kg when administered daily for a month. Pathological changes which were reversible in rats but not in monkeys, included the presence of foreign material in the renal tubules and vacuolization, hyaline droplet formation and inflammation of the renal tubular epithelium. Minimal vacuolation of renal collecting ducts that resolved spontaneously was the predominant pathologic change that was seen in rats receiving IV doses of 90 mg/kg/day, except for one rat that developed granuloma formation with foreign material.

Doses up to 450 mg/kg/day did not appear to cause impairment of fertility in adult male or female rats or toxicity to rat pups exposed in utero from Gestation Day 6 through lactation. F1 pups from dams receiving ceftaroline were comparable to control F1 pups in terms of survival and body weight gain. Pups given ceftaroline attained developmental landmarks at approximately the same rates as controls. Their behavior, motor activity, learning, and reproductive capacity did not appear to be different from controls. Developmental toxicity was not observed in a study of rats given the highest ceftaroline dose tested of 300 mg/kg/day. In rabbits, developmental toxicity studies were limited by excessive maternal toxicity, an observation typical for this type of antibacterial drug.

Toxicities occurring in other body systems are discussed further in Section 7.2.3. (Special Animal and/or In Vitro Testing) and in the review by Dr. Amy Ellis, Pharmacology/Toxicology reviewer. In general, toxicities were noted in animals given high exposures of ceftaroline, with toxicities consistent with other cephalosporin use.

4.4 Clinical Pharmacology

The proposed dosing regimen of ceftaroline fosamil is 600 mg every 12 hours given as a 1-hour intravenous infusion for 5-7 days for the treatment of CABP and for 5-14 days for the treatment of ABSSSI. For more details (including the FDA recommended dose adjustments for renal impairment), please refer to the review of Dr. Aryun Kim, the Clinical Pharmacology reviewer.

4.4.1 Mechanism of Action

Ceftaroline exerts its bactericidal action by inhibiting bacterial cell wall biosynthesis through its binding to essential penicillin-binding proteins (PBPs), similar to the mechanism of action of other ß-lactams. It has affinity for PBP2a and PBP2x, making it active against methicillin-resistant staphylococci and against *S. pneumoniae* with reduced susceptibility to penicillin, respectively.

4.4.2 Pharmacodynamics

Ceftaroline activity is primarily directed toward bacteria. Hence, except for the Thorough ECG Trial (Study P903-05), ceftaroline's pharmacodynamic properties in humans is not discussed in this review.

4.4.3 Pharmacokinetics

General Pharmacokinetics
Single and multiple dose studies demonstrate that ceftaroline fosamil is rapidly converted in plasma to its bioactive form, ceftaroline, following IV infusion. Ceftaroline exhibits linear pharmacokinetics, with dose-proportional increase in exposure (maximum plasma concentrations (C_{max}) and area under the plasma concentration-time curve (AUC) values) within the dose range of 50 to 1000 mg. No accumulation of ceftaroline fosamil or its active form was observed with either every 12 or 24 hour regimens. Ceftaroline's ß-lactam ring is subsequently hydrolyzed to form the inactive, open-ring metabolite, ceftaroline M-1.

The time of maximum plasma concentrations for ceftaroline generally occurs near the end of the infusion, and the terminal elimination half life ($T_{½}$) of ceftaroline was in the range of 2 to 3 hours over the dose range studied (mean of 2.54 ± 0.29 hours in healthy adult patients with normal renal function across studies). Other pharmacokinetic parameters of ceftaroline and ceftaroline M-1 following single and multiple 1-hour infusions of the proposed dosage are summarized in Table 2.

Table 2.Pharmacokinetic Properties of Ceftaroline

Parameter	Dose of 600 mg every 12 hours (n=6)	
	Ceftaroline (active)	Ceftaroline M-1 (open-ring metabolite)
Single Dose (Day 1)		
C_{max} (µg/mL)	18.97 ± 0.71	2.72 ± 0.77
T_{max} (h)[a]	1.00 (0.92-1.25)	1.00 (0.67-5.00)
AUC_{inf} (µg*h/mL)	56.79 ± 9.31	15.80 ± 3.21
$t_{1/2}$ (h)	1.60 ± 0.38	3.50 ± 1.36
CL (L/h)	9.58 ± 1.85	35.63 ± 6.60
V_z (L)	21.97 ± 5.43	177.1 ± 60.5
Multiple Dose (Day 14)		
C_{max} (µg/mL)	21.33 ± 4.10	3.58 ± 0.62
T_{max} (h)[a]	0.92 (0.92-1.08)	1.08 (0.92-1.53)
AUC_{tau} (µg*h/mL)	56.25 ± 8.90	18.95 ± 4.62
$t_{1/2}$ (h)	2.66 ± 0.40	6.84 ± 0.59
CL (L/h)	9.60 ± 1.40	30.05 ± 6.40
V_z (L)	35.30 ± 7.40	221.5 ± 73.1
Accumulation Ratio	1.00 ± 0.12	1.19 ± 0.08

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

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

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

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

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

Intrinsic Factors

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

Gender: Pharmacokinetics of ceftaroline and ceftaroline M-1 were evaluated in healthy elderly males and females and healthy young adult males and females following a single 1-hour IV infusion of ceftaroline fosamil 600 mg. No dose adjustment based on gender is necessary.

(b) (4)

(b) (4)

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 3 summarizes the human clinical trials for the ceftaroline development program, with their respective description, ceftaroline dosage, number of patients, and demographics of patients.

Table 3. Table Summary of Phase 1, 2, and 3 Clinical Studies

Study Number	*Study Title*	*Dosage Regimen for Comparator*	*Dosage Regimen for Ceftaroline fosamil*	*Number of Patients Enrolled/ Ceftaroline Group/No. Recommended Dose**/ Comparator Group*	*Demographics*
Completed Phase 1 Studies					
Pharmacokinetic Studies in Healthy Patients					
Study P903-01 (2004)	Randomized, Double-blind, Dose-escalation Study to Determine the Safety, Tolerability, and Pharmacokinetics of PPI-0903 for Injection in Healthy Subjects	Single 1-hour infusion of normal saline Multiple 1-hour IV infusions of normal saline q 12 h for 14 days or q24 h for 7 days	Single 1-hour IV infusion of 50, 100, 250, 500, 750, or 1000 mg Multiple 1-hour IV infusions of 300 or 600 mg q12h for 14 days or 800 mg q24h for 7 days	72 54 6 18 placebo	100% male 93% white Mean age: 26 Age range: 19-54 years
Study P903-05 (2009)	Randomized, Double-blind, Placebo-controlled, Crossover Study to Evaluate Safety, and Pharmacokinetics and Effect on the Electrocardiogram of a Supratherapeutic Dose of Ceftaroline in Healthy Subjects	Single 1-hour IV infusion of saline Single 1-hour IV infusion of 400 mg moxifloxacin	Single 1-hour IV infusion of 1500 mg	54 54 0 54 placebo 53 moxifloxacin	50% male 72% white Mean Age: 27 years Range: 18-45 years
Study P903-11 (May 15, 2009)	An Open-label Pharmacokinetic, Safety, and Tolerability Study of Single Intravenous (IV) Doses of Ceftaroline in Healthy Elderly and Healthy Young Adult Subjects	NA	Single 1-hour IV infusion of 600 mg	33 33 32 0	Group 1 (65+): 59% male 94% white Mean Age: 72 years Range: 65-81 years Group 2 (18-45 years): 38% male 94% white

Study Number	***Study Title***	***Dosage Regimen for Comparator***	***Dosage Regimen for Ceftaroline fosamil***	***Number of Patients Enrolled/ Ceftaroline Group/No. Recommended Dose**/ Comparator Group***	***Demographics***
					Mean Age: 31 years Range: 19-44 years
Study P903-13 (Mar 10, 2009)	A Single-dose, Open-label Study to Assess the Metabolism and Elimination of Ceftaroline Prodrug After IVAdministration of [^{14}C] Ceftaroline Fosamil in Healthy Subjects	NA	Single 1-hour IV infusion of 600 mg,[^{14}C] labeled	6 6 6 0	100% male 50% white Mean Age: 31 years Range: 23-45 years
Study P903-14 (2009)	A Phase 1 Single-center, Multiple-dose, Open-label Study to Assess the Effect of Ceftaroline on the Intestinal Microflora of Healthy Human Subjects	NA	1-hour IV infusion of 600 mg q12h for 6 days and a single infusion on Day 7	12 12 12 0	50% male 100% white Mean age: 25 years Range: 20-41 years
Study P903-17 (Mar 6, 2009)	A Phase 1 Randomized, Two-part, Single and Multiple Dose Study to Determine the Safety, Tolerability, and Pharmacokinetics of Ceftaroline Administered by Intramuscular (IM) Injection in Healthy Subjects	Part A: NA Part B: multiple IM injections of 1000 mg cefepime HCl q12h on Study Days 1 through4 and single dose on Study Day 5	Part A: Single IM injection of 400 mg, 600 mg, 1000 mg, or single IM injection of 600 mg on Day 1 plus 600 mg IV infusion on Day 8 Part B: Multiple IM injections of 600 mg q12h on Study Days 1 though 4 and a single dose on Study Day 5	42 36 6 6 cefepime	Part A: 73% male 75% white Mean Age: 27.4 years Range: 19-44 years Part B: 78% male 33 % white Mean Age: 27 years Range: 18-41 years
Study P903-20 (Jun 10, 2009)	A Phase 1 Randomized, Double-blind, Placebo-controlled Study to Determine the Safety and Pharmacokinetics of Single Doses and Multiple-dose Regimens of Ceftaroline in Healthy Subjects	Part A: Single 1-hour IV infusion of saline placebo Part B: 1-hour IV infusions of saline placebo once on Study Day 1, q8h on Study Days 2-9, and once on Study Day 10	Part A: Single 1-hour IV infusion of 1500 or 2000 mg Part B: 1-hour IV infusions of 600 mg on Study Days 1 and 10 and multiple doses on Study Days 2-9	30 24 0 6 placebo	Part A: 40% male 90% white Mean age: 29 years Range: 18-41 years Part B: 50% male 90% white Mean Age: 31 years Range: 18-44 years
Pharmacokinetic Studies in Subjects with Renal Impairment					
P903-02 (Jul 12, 2007)	An Open-label Pharmacokinetic, Safety, and Tolerability Study of Single IV Doses of PPI-0903 in Subjects with Normal Renal Function, Mild Renal Impairment, or Moderate Renal Impairment	NA	Single 1-hour IV infusion of 600 mg Single 30-minute IV infusion of 500 mg (in healthy patients only)	23 23 12 0	57% male 48% white Mean age: 50 years Range: 24-75 years
Study P903-04 (Apr 11, 2009)	An Open-label Pharmacokinetic,	NA	Single 1-hour IV infusion 400 mg	12	83% male 67% white

Study Number	***Study Title***	***Dosage Regimen for Comparator***	***Dosage Regimen for Ceftaroline fosamil***	***Number of Patients Enrolled/ Ceftaroline Group/No. Recommended Dose**/ Comparator Group***	***Demographics***
	Safety, and Tolerability Study of Single IV Doses of Ceftaroline in Subjects with Normal Renal Functions or Severe Renal Impairment			12 0 0	Mean Age: 64 years Range: 51-79 years
Study P903-18 (May 20, 2009)	An Open-label Pharmacokinetic, Safety, and Tolerability Study of Single IV Doses of Ceftaroline in Subjects with End-stage Renal Disease (ESRD) on Intermittent Hemodialysis and Subjects with Normal Renal Function	NA	Two single 1-hour IV infusions of 400 mg separated by ≥ 7 days for ESRD subjects Single 1-hour IV infusion of 400 mg for healthy subjects	12 12 0 0	100% male 67% white Mean Age: 48 years Range: 35-58 years
Pharmacokinetic Study in Pediatric Subjects					
Study P903-15 (2009)	Pharmacokinetics of a Single Dose of Ceftaroline in Subjects 12-17 Years of Age Receiving Antibiotic Therapy	NA	Single 1-hour IV infusion of 8 mg/kg for subjects who weighed less than 75 kg (165.4 lb) or 600 mg for subjects who weighed 75 kg (165.4 lb) or more	9 9 0 0	56% male 66.7% white Mean Age: 14 years Range: 12-16 years
Total No. of Subjects Treated with Any Dose of Ceftaroline = 275 Total No. of Subjects Treated with Recommended Dose of Ceftaroline (IV over 1 hour) = 74 Total No. of Subjects Treated with Comparator or Placebo = 84					
Completed Phase 2 Studies					
Study P903-03 (Jul 12, 2007)	A Phase 2, Multicenter, Randomized, Observer-blinded Study to Evaluate the Safety and Efficacy of PPI-0903 Versus Standard Therapy in Adult Subjects with Acute bacterial Skin and Skin Structure Infections (ABSSSI)	1 hour IV infusion of vancomycin of 1 g q12h and 30 minute IV infusion of aztreonam of 1 g q8h for 7 to14 days	1 hour IV infusion of 600 mg q12h for 7-14 days	100 67 67 32	Ceftaroline: 55 male 52% white Mean Age: 42 years Range: 18-84 years Vancomycin: 59% male 53% white Mean Age: 44 yrs Range: 21-83 years
Study P903-19 (2009)	A Phase 2, Multicenter, Randomized, Open-label, Comparative Study to Evaluate the Efficacy and Safety of IM Ceftaroline Versus IV Linezolid in Adult Subjects with ABSSSI	1 hour IV infusion of linezolid of 600 mg q12h for 5-14 days. Aztreonam 1000 mg q12h IV could be started with linezolid or added up to 72 hours after the first dose of linezolid for subjects with mixed Gram (+) and Gram (-) infection	IM injections of 600 mg q12h for 5-14 days	150 98 0 45	Ceftaroline: 69% male 77% white Mean Age: 39 years Range: 18 to 70 years Linezolid: 62% male 76% white Mean age: 40 years Range: 18-89 years
Total Number of Subjects Treated with Ceftaroline fosamil = 165					

Study Number	***Study Title***	***Dosage Regimen for Comparator***	***Dosage Regimen for Ceftaroline fosamil***	***Number of Patients Enrolled/ Ceftaroline Group/No. Recommended Dose**/ Comparator Group***	***Demographics***
Total Number of Subjects Treated with the Recommended Dose of Ceftaroline fosamil = 67 Total Number of Subjects Treated with Comparator = 77					
Completed Phase 3 Trials					
Trial P903-06 (2009)	A Phase 3, Multicenter, Randomized, Double-blind, Comparative Trial to Evaluate the Safety and Efficacy of Ceftaroline Versus Vancomycin plus Aztreonam in Adult Subjects with ABSSSI	1-hour IV infusion of vancomycin 1 g q12h plus 1 hour IV infusion of aztreonam 1 g q12h for 5-14 days	1-hour IV infusion of 600 mg q12h for 5-14 days	702 351 351 347	Ceftaroline: 63% male 74% white Mean Age: 47 years Range: 18 to 90 yrs Vancomycin: 63% male 74% white Mean Age: 49 yrs Range: 18 - 87 years
Trial P903-07 (2009)	A Phase 3, Multicenter, Randomized, Double-blind, Comparative Trial to Evaluate the Safety and Efficacy of Ceftaroline Versus Vancomycin plus Aztreonam in Adult Subjects With ABSSSI	1 hour IV infusion of vancomycin 1 g q12h plus 1 hour IV infusion aztreonam of 1 g q12h for 5-14 days	1 hour IV infusions of 600 mg q12h for 5-14 days	694 341 [341] 339	Ceftaroline: 65% male 72% white Mean Age: 48 years Range: 18 - 93 years Vancomycin: 60% male 75% white Mean Age: 48 years Range: 18 - 96 years
Trial P903-08	A Phase 3, Multicenter, Randomized, Double-blind, Comparative Trial to Evaluate the Safety and Efficacy of Ceftaroline versus Ceftriaxone, with Adjunctive Clarithromycin, in the Treatment of Adult Subjects with Community-acquired Pneumonia (CABP)	30-minute IV infusion of ceftriaxone 1 g followed by IV infusion of placebo to correspond to the q12h infusion of ceftaroline fosamil for 5-7 days	Two consecutive 30-minute IV infusions of 300 mg each q12h for 5-7 days	614 298 298 308	Ceftaroline: 64% male 89% white Mean Age: 61 years Range: 20 - 94 years Ceftriaxone: 64% male 89% white Mean Age: 61 years Range: 18 - 91 years
Trial P903-09*	A Phase 3, Multicenter, Randomized, Double-blind, Comparative Trial to Evaluate the Safety and Efficacy of Ceftaroline versus Ceftriaxone in the Treatment of Adult Subjects with CABP	30-minute IV infusion ceftriaxone of 1g followed by IV infusion of placebo to correspond to the q12h infusion of ceftaroline fosamil for	Two consecutive 30-minute IV infusions of 300 mg each q12h for 5-7 days	618 310 [310] 303	Ceftaroline: 60% male 96% white Mean Age: 59 years Range: 18 - 99 years Ceftriaxone: 66% male 97% white

Study Number	*Study Title*	*Dosage Regimen for Comparator*	*Dosage Regimen for Ceftaroline fosamil*	*Number of Patients Enrolled/ Ceftaroline Group/No. Recommended Dose**/ Comparator Group*	*Demographics*
		5-7 days			Mean Age: 60 years Range: 18 - 91 years
Total Number of Subjects Treated with Ceftaroline fosamil* = 1300 Total Number of Subjects Treated with the Recommended Dose of Ceftaroline* = 1300 Total Number of Subjects Treated with Comparator* = 1297					

Source: Integrated Summary of Safety (ABSSSI and CABP), p. 78-87.

* Nine patients were excluded from Trial 09 because of data integrity.

** The recommended dose of ceftaroline is 600 mg IV q12 hours.

5.2 Review Strategy

Four Phase 3 clinical trials were performed to evaluate the efficacy of ceftaroline in treating two indications: two trials were conducted for Community-Acquired Bacterial Pneumonia (CABP) and two trials were conducted for Acute Bacterial Skin and Skin Structure Infections (ABSSSI). The efficacy review for the ABSSSI indication was completed by Neil Rellosa, M.D. and the CABP indication by Ariel R. Porcalla, M.D., M.P.H. The Safety Review for ceftaroline was performed by Ariel R. Porcalla, M.D., M.P.H. Statistical analyses for efficacy were completed by Daniel Rubin, Ph.D. for CABP and Christopher Kadoorie, Ph.D. for ABSSSI.

For the treatment of CABP, the Applicant's primary efficacy analysis used a 10% non-inferiority margin in comparing the difference in clinical response between treatment groups (ceftaroline – ceftriaxone) in the clinically evaluable and modified intent-to-treat-efficacy populations at the Test-of-Cure (TOC) visit 8-15 days after the end of treatment.

Based on the previously mentioned public discussions on study design for CABP treatment trials, the posting of a new guidance document by FDA for development of antimicrobial agents for CABP, and work by the Foundation for the National Institutes of Health (FNIH), a public/private consortium composed of members of academia, government, and industry, the FDA conducted a number of sensitivity analyses to evaluate the efficacy of ceftaroline. These analyses were focused on assessment of clinical status (i.e. normalization of vital signs and symptom improvement) at an earlier timepoint. This endpoint and timing of assessment in a sicker population (PORT Risk Class III or IV) with microbiological or serologic evidence of a bacterial pathogen was thought to be more representative of the historical population from which the treatment effect of antibacterial therapy was estimated and justification for a non-inferiority margin provided.

5.3 Discussion of Individual Studies/Clinical Trials

Community-Acquired Bacterial Pneumonia (CABP)

The Phase 3 program to evaluate the safety and efficacy of ceftaroline to treat CABP consisted of two clinical trials: Trial P903-08 (referred to as Trial 08 hereafter) and P903-09 (referred to as Trial 09 hereafter), which were both randomized, double-blind, multicenter, multinational, active-controlled noninferiority trials. Both trials were identical in design in terms of objectives, inclusion and exclusion criteria, analysis populations, and dosage regimen for ceftaroline (600 mg every 12 hours in patients with normal renal function or mild renal impairment, with adjustment to 400 mg every 12 hours in patients with moderate renal impairment), administered as two consecutive intravenous infusions over 30 minutes).

Both trials utilized ceftriaxone sodium, a third-generation cephalosporin approved for the treatment of lower respiratory tract infections caused by susceptible typical community-acquired pathogens, at a dose of 1 gram every 24 hours as an active control. Each trial enrolled slightly over 600 patients randomized 1:1 to ceftaroline and ceftriaxone for a total of 5-7 days. In order to maintain the blind, ceftaroline was administered as two 300 mg infusions over 30 minutes each and ceftriaxone as a 1 gram infusion over 30 minutes, followed by an infusion of normal saline placebo over 30 minutes.

Patient selection criteria (inclusion and exclusion criteria) are discussed in Section 6.1.1 (Methods). Since the protocol required intravenous therapy with no option for oral switch, the protocols were designed to ensure that enrolled patients have an acute illness with a new or progressive pulmonary infiltrate on chest radiography and with signs and symptoms consistent with CABP which was moderate to severe enough to warrant intravenous therapy and hospitalization. An amendment to both protocols added that patients should be ill enough to be classified as PORT Risk Class III or IV.

There were a few differences between the two clinical trials. One was the use of adjunctive clarithromycin administered as 2 oral doses of 500 mg 12 hours apart at the time of study drug initiation in Trial 08 to provide initial coverage for atypical organisms such as *Legionella pneumophila, Chlamydophyla pneumoniae, or Mycoplasma pneumoniae*. This was added to promote enrollment of patients in the United States where investigators were reluctant to participate without macrolide therapy due to published Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) guidelines for the treatment of CAP requiring the initial use of macrolides to cover for atypical bacteria and/or to provide anti-inflammatory effects[1]. With this design modification, the Applicant was only able to enroll a few patients in the United States in Trial 08 (11 patients in the ceftaroline group and 12 patients in the ceftriaxone group). There were no patients enrolled from the United States in Trial 09 where a macrolide was not permitted.

With the two trials being nearly identical, the Applicant considered pooling of the efficacy and safety results of the two trials to be acceptable for the purpose of an integrated analysis. According to the Applicant, pooling results of the trials was supported by similarities of the two trials, including similar baseline demographic characteristics of the populations, clinical markers (fever, cough, sputum production, tachypnea, dyspnea, chest pain) for CABP, clinical cure rates within treatment groups, and microbiological results.

Medical Officer Comment:
Pooling of the results of the two pivotal Phase 3 trials, despite their similarity in design and results, is generally inappropriate. Each trial should provide independent evidence of efficacy of ceftaroline in treating CABP and the Applicant is still required to demonstrate the efficacy and safety of ceftaroline using two independent, adequate and well-controlled Phase 3 clinical trials.

The schedule of evaluations and procedures, patient population, treatment duration, efficacy endpoints and statistical methods used for analysis were similar for both trials. Once randomized, patients were evaluated for baseline characteristics that included a medical history, physical examination, chest radiography, and laboratory evaluation 24 hours prior to study drug administration. Subsequent assessment for response, safety, laboratory, and radiographic evaluations were scheduled at specific timepoints (e.g. during study drug treatment, end-of-therapy [EOT], test-of-cure [TOC], and late follow-up [LFU] visits). Details of the procedures performed during these assessments can be found in Appendix 5-B.

The Applicant's prespecified analysis consisted of a comparison of clinical cure rates between the ceftaroline- and ceftriaxone- treated groups assessed by an Investigator at the TOC timepoint using a noninferiority margin of 10%. The two co-primary populations used for the analysis were the Modified Intent-to-Treat Efficacy (MITTE) and Clinically Evaluable (CE) populations.

The study design and prespecified analyses of the two Phase 3 CABP trials were based on the 1998 FDA Draft Guidance for Industry: CAP – Developing Antimicrobial Drugs for Treatment, the existing guidelines at the time the protocol was written. [2] These were modified by the Applicant based on continued public discussions and an updated draft guidance for the development of antibacterial drugs for CABP posted on the internet (March 19, 2009) [3]. After protocol revisions were made and the trials were conducted, the understanding of the science and interpretation of noninferiority trials designed to evaluate the efficacy of antibacterial treatment of CABP continued to evolve and change.

Several elements in the design and analysis of non-inferiority trials performed to support the efficacy of antibacterials to treat CABP have changed. First, enrollment of sicker patients (PORT III and above) were encouraged as historical data suggest that these

categories of patients benefit the most from antibacterials. Second, to ensure that only pneumonia patients with a bacterial etiology are included in the analysis of the noninferiority trials in CABP, the use of the microbiological intent-to-treat (MITT) population for analysis is recommended. Third, there is historical data to support the use of all-cause mortality rates between treatment groups to justify a noninferiority margin. However, its utility and practicality in the current clinical setting is unknown. Therefore, current discussions focus on comparing clinical response rates assessed at earlier timepoints (48-96 hours after initiation of therapy) to analyze data from noninferiority trials. At earlier timepoints, historical evidence suggests that the antibacterial treatment effect on CABP is large so that a noninferiority margin can be justified. It was therefore imperative for the FDA review team to explore and utilize the changing paradigm for analyzing data from noninferiority trials for CABP.

The FDA review team performed several sensitivity analyses that incorporated these changing principles. The FDA compared responder rates between the ceftaroline- and ceftriaxone-treated groups assessed earlier at Day 4 after initiation of therapy, using an FDA-defined microbiological intent-to-treat population. Clinical response was determined by a combination of stabilization of signs and improvement of symptoms at Day 4.

Acute Bacterial Skin and Skin Structure Infections

The Phase 3 program to evaluate the safety and efficacy of ceftaroline to treat ABSSSI consisted of two clinical trials. Trials P903-06 and P903-07 were multicenter, multinational, randomized, double blind, active controlled noninferiority trials. The trials were conducted independently, but were of identical design. Each trial randomized approximately 700 patients in a 1:1 fashion to receive ceftaroline plus placebo or vancomycin plus aztreonam.

Patients randomized to the ceftaroline treatment group received a 600 mg IV dose of ceftaroline infused over 1 hour (with dose adjustment to 400 mg in patients with moderate renal impairment), every 12 hours. The cefatroline infusion was followed by administration of a placebo infusion over 1 hour, every 12 hours. Patients randomized to the comparator treatment group received a 1 g IV dose of vancomycin infused over 1 hour, every 12 hours. The vancomycin infusion was followed by administration of aztreonam 1 g IV over 1 hour, every 12 hours. The duration of treatment was 5-14 days. The aztreonam (or placebo) infusion was discontinued if a Gram negative pathogen was neither identified nor suspected.

The patients were evaluated at baseline, during study drug administration, at end of therapy (EOT), test of cure (TOC) 8-15 days after the last dose of study medication, and late follow-up (LFU) 21-35 days after the last dose of study medication. Evaluations included examination of the infection site, and vital signs daily, and safety laboratories every 3-4 days. A microbiological culture was performed at baseline and performed at

follow-up visits only if clinically indicated. Study procedures are described in detail in Section 6.2.1 Methods.

The trials were evaluated independently. The Applicant's prespecified analysis was to demonstrate the noninferiority of the difference in clinical cure rates (ceftaroline – vancomycin + aztreonam) as assessed by the investigator at the TOC using a noninferiority margin of 10%.

Following design and conduct of the trials, at a meeting of the Anti-Infective Drugs Advisory Committee (AIDAC) on November 18, 2008, discussion focused on the historical evidence of treatment effect of antibacterial agents relative to placebo that could be used to define a noninferiority margin in ABSSSI trials. Justification for the 10% NI margin was based on evidence in cessation of spread of infection and absence of fever in erysipelas and more rapid healing in wound infections. There was insufficient evidence to support an NI margin for treatment of major abscesses without a significant cellulitis component beyond that of primary incision and drainage. Additionally, a new guidance document on development of antibacterial agents for treatment of ABSSSI was posted on the internet by FDA for public comment at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071185.pdf.

Therefore, in addition to presenting the Applicant's prespecified efficacy analyses, the FDA reviewers conducted a number of sensitivity analyses, with the primary analysis focused on a primary efficacy endpoint of cessation of spread of the skin lesion and absence of fever at a Day 3 endpoint. These analyses will be described in Section 6.2.10. Additional Efficacy Issues/Analyses.

6 Review of Efficacy

The efficacy of ceftaroline was assessed as a potential treatment for two indications: community-acquired bacterial pneumonia (CABP) (Discussed in Section 6.1) and acute bacterial skin and skin structure infections (ABSSSI) (Discussed in Section 6.2).

Efficacy Summary for CABP

The Applicant submitted data from two Phase 3 clinical trials (Trials P903-08 and P903-09) to support the efficacy of ceftaroline for the treatment of Community-Acquired Bacterial Pneumonia (CABP). These trials were randomized, double-blind, multicenter, multinational studies of patients diagnosed with CABP using a clinical signs and symptoms criteria in addition to a radiographic confirmation of pneumonia. The inclusion criteria required patients to be sick enough to warrant hospitalization and intravenous antibacterial treatment by requiring classification in PORT Risk Class III or IV.

The protocols for both trials were similar except for the administration of two adjunctive doses of oral clarithromycin to patients in Trial P903-08 to promote enrollment by US investigators. Both protocols allowed patients to have at most one dose of a short-acting systemic antibacterial within 96 hours prior to randomization. Enrolled subjects were randomized to either ceftaroline or ceftriaxone for treatment after baseline evaluation. Confirmation of bacterial etiology, although not required, consisted of isolation of pathogens from sputum, pleural fluid, blood, blood samples for serology testing, and urine samples for antigen testing.

The main objective of the two Phase 3 trials for CABP was to compare the difference in Investigator-assessed clinical response rates at the Test-of-Cure (TOC) visit (8-15 days after end-of-therapy) between patients treated with ceftaroline and those treated with ceftriaxone, using a noninferiority margin of 10%. The two co-primary analysis populations were the Modified-Intent-to-Treat Efficacy (MITTE) population (defined as randomized patients who received any amount of therapy and classified as PORT Risk Class III or IV) and the Clinically Evaluable (CE) population (defined as MITTE patients who were compliant with the prespecified protocol).

Both trials met the prespecified noninferiority margin of 10%. Trial 08 showed clinical response rates favoring ceftaroline in the co-primary MITTE and the CE populations, with the difference being 6.2%, with a 95% CI of (-0.2 to 12.5) and 8.4%, with a 95% CI of (1.4 to 15.4), respectively. Similarly, Trial 09 showed a difference in cure rates favoring ceftaroline in the co-primary MITTE and CE populations with the difference being 5.9%, 95% CI (-1.0, 12.8) and 5.2, 95% CI (-2.2, 12.8).

However, the Applicant did not provide sufficient historical evidence supporting the 10% noninferiority margin for the clinical response endpoint assessed at the TOC visit. The Applicant's margin justification at this timepoint relied on an antibacterial treatment effect on mortality that could not be extrapolated to the Applicant's clinical response endpoint at TOC, when spontaneous resolution of pneumonia may have occurred. Furthermore, analysis of all-cause mortality rates in the two Phase 3 trials were between 1-2%, despite enrichment of the population with more severe cases of CABP (i.e. Port Risk Class III and IV). The mortality rates were too low to draw any meaningful conclusions on ceftaroline efficacy. Therefore, despite meeting the prespecified noninferiority margin of 10%, the Applicant's noninferiority analyses of the two Phase 3 clinical trials could not support ceftaroline's efficacy.

Historical evidence for a large antibacterial treatment effect does exist for clinical response assessed at an earlier timepoint (48-72 hours after initiation of therapy). During this time, clinical stability of vital signs and improvement of symptoms may be attributable to antibacterial effect. The Agency thus performed several sensitivity analyses with data submitted in the Application. The primary efficacy endpoint used was the difference in clinical responder rates between the ceftaroline- and ceftriaxone-

*treated groups assessed on Day 4 after initiation of therapy. The FDA clinical responder endpoint was defined as achieving a combination of stability of vital signs and improvement of baseline symptoms of pneumonia as reflected in the CRFs on Day 4 following initiation of therapy. The primary analysis population used was the subgroup of randomized patients receiving any amount of study drug with microbiologic or immunologic confirmation of a typical bacterial etiology of CABP (*Streptococcus pneumoniae*, methicillin-sensitive* Staphylococcus aureus, Streptococcus pyogenes, Moraxella catarrhalis, Haemophilus influenzae, Klebsiella pneumoniae *and other Gram-negative bacteria).*

FDA analyses of the clinical responder rates show that the treatment differences (and the corresponding 95% CI) was 11.2% (-4.6, 26.5) for Trial 08 and 7.6% (-6.8, 21.8) for Trial 09, in favor of ceftaroline. These results were consistent when the endpoint definition was modified in terms of signs or symptoms considered (i.e. clinical stability versus symptoms), timing of assessment (Day 3, EOT or TOC), and choice of analysis population (Applicant's MITTE, CE, mMITT).

In particular, 85 to 90% of responders in the Day 4 FDA analysis population were clinical responders at the EOT assessment, suggesting good concordance between Day 4 and EOT assessments and persistence of antibacterial effects.

The FDA analyses were limited by the fact that the analyses were post-hoc and exploratory. Moreover, data obtained from the CRFs (vital signs and changes in symptomatology) were not captured in a standardized and optimal manner. The signs and symptoms endpoint may be affected by prior or concomitant medications such as prior antibacterial use, antipyretics, anti-inflammatory medications, and steroids. The effect of active antibacterials prior to initiation of study therapy and effect on the early efficacy assessment timepoint is not clear since the number of patients in the analysis groups (prior antibacterials versus no antibacterials) was small to make any meaningful conclusion. It remains to be seen how early responder analyses can be utilized clinically in predicting clinical response at the end of therapy. Lastly, since patients with MRSA at baseline were excluded from the trials, the current data and analyses do not establish the efficacy of ceftaroline against CABP caused by MRSA.

In conclusion, the FDA analyses of the efficacy data in the Application provide evidence of ceftaroline's efficacy as treatment for CABP (except in CABP caused by MRSA), in support of the Applicant's prespecified analysis results.

Efficacy Summary for ABSSSI

The Applicant performed two Phase 3 clinical trials (P903-06 and P903-07) to demonstrate efficacy in the treatment of complicated skin and skin structure infections (cSSSI), hereafter referred to as acute bacterial skin and skin structure infections (ABSSSI). The Phase 3 clinical trials were of non-inferiority (NI) design and were

originally designed to investigate the primary efficacy endpoint of the per-subject clinical response rate as assessed by the investigator at the Test-of-Cure (TOC) visit 8 to 15 days after completing study drug therapy. In addition, key secondary endpoints investigated were the per-subject clinical response at End-of-Therapy (EOT) visit and the per-subject microbiological response at TOC.

These trials were conducted prior to public discussions regarding appropriate trial design for evaluation of new antibacterial agents for the treatment of skin infections, including the definition of the primary efficacy endpoint, and timing of primary endpoint assessment. The Applicant's pre-specified primary and secondary analyses were performed as discussed with the FDA. Based on these pre-specified analyses the following conclusions can be made:

- *Ceftaroline demonstrated non-inferiority to the comparator, vancomycin plus aztreonam, as evidenced by the lower limit of the 95% CI around the difference in cure rates at TOC being greater than the pre-specified NI boundary of -10, thus demonstrating the non-inferiority of ceftaroline relative to vancomycin plus aztreonam.*
- *Ceftaroline demonstrated comparable cure rates at EOT, an earlier timepoint, to the cure rates of vancomycin plus aztreonam, which further supports its efficacy relative to a comparator.*
- *Ceftaroline demonstrated comparable cure rates at TOC for the microbiological populations to the cure rates of vancomycin plus aztreonam, also supporting its efficacy relative to a comparator.*

On November 8, 2008, at the Anti-Infective Drugs Advisory Committee (AIDAC) meeting, discussion focused on the use of NI trial design for the indication of ABSSSI. Based on historical data, they voted unanimously that there was adequate evidence to support use of a NI trial design for patients with significant cellulitis or wound infections. The committee suggested an earlier timepoint for endpoint assessment (i.e. 48-72 hours after the initiation of therapy) than the qtimepoint used in previous trials, based on previous studies that looked at the treatment of erysipelas with sulfonamide derivates. In addition, they concluded that clinical features such as cessation of spread of infection and resolution of fever should be included in the assessment More recent discussions with the Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium in evaluating endpoints for ABSSSI clinical trials have also suggested the use of an earlier timepoint and specific clinical features such as cessation of spread and resolution of fever.

Based on these discussions, application of a new, earlier clinical endpoint focusing on cessation of spread of the infection from baseline and absence of fever at Day 3 was explored. The relevance of this endpoint in contemporary trials has not been established and relationship between previous endpoints such as TOC and EOT are being explored. However, further sensitivity analyses using a modified analysis population definition and utilizing an endpoint of cessation of spread and absence of

fever assessed at an earlier time point were performed by the FDA review team. In addition several secondary analyses were performed to examine the performance of this endpoint in relation to pre-specified analyses conducted by the Applicant.

Conclusions drawn from these analyses are the following:

- *Ceftaroline demonstrated non-inferiority to the comparator, vancomycin plus aztreonam, as evidenced by the lower limit of the 95% CI around the difference in responder rates at Day 3 being greater than -10, the pre-specfied NI margin for the TOC endpoint. In Trial P903-06 the lower bound of the 95% CI was 0.03 and in Trial P903-07 the lower bound was -3.6,thus demonstrating that with the earlier endpoint assessment, a much smaller NI margin (i.e. 4%) would have been met.*
- *Potential investigator measurement error of lesion size did not appear to influence responder rates at Day 3. In addition, there was consistency of clinical response to ceftaroline across several time points and varying degree of lesion size reduction at both Day 3 and EOT.*
- *In key secondary sensitivity analyses, ceftaroline demonstrated non-inferiority when comparing absences rates of key symptoms at Day 3 and pathogen-specific responder rates at Day 3.*

6.1 Indication (Community-Acquired Bacterial Pneumonia)

Community-acquired pneumonia is the eighth leading cause of death in the United States, accounting for over 4 million healthcare office visits in the country. Hospitalization rates have increased to over 1600 per 100,000 persons over the last decade.[4] Mortality rates secondary to CAP have not decreased despite advances in medical treatment.[5] This observation is attributed to an increase in populations at higher risk for morbidity and mortality such as the elderly and immunocompromised and the emergence of resistant organisms such as penicillin-resistant *S. pneumoniae* (PRSP) and MRSA. Therefore, there is a need to develop new antibacterials to effectively treat CABP.

6.1.1 Methods

The Applicant performed two Phase 3 clinical trials, Trial 08 and Trial 09, to support the indication of CABP. Discussed in the succeeding subsections is the methodology utilized in both trials.

Study Objectives

Primary (Prespecified) Objective

The primary objective was to determine the noninferiority of ceftaroline compared with ceftriaxone based on the difference in clinical cure rate (ceftaroline – ceftriaxone) at the Test-of-Cure (TOC) visit in the co-primary Clinically Evaluable (CE) and Modified Intent-to-Treat Efficacy (MITTE) populations.

Secondary Objectives

- To evaluate the clinical response at the End-of-Therapy (EOT);
- To evaluate the microbiological success rate at TOC;
- To evaluate the overall (clinical and radiographic) success rate at TOC;
- To evaluate the clinical and microbiological response by pathogen at TOC;
- To evaluate clinical relapse at LFU;
- To evaluate microbiological reinfection/recurrence at LFU; and
- To evaluate safety.

Inclusion Criteria

- Adult patients aged 18 years or older who require hospitalization and treatment with intravenous antibacterials for pneumonia, or treatment in an emergency room or urgent care setting by standard of care with intravenous antibacterials are included in the trials.
- Patients must have at least 3 of the following clinical signs or symptoms consistent with a lower respiratory tract infection of acute onset (≤ 7 day duration):
  - Fever greater than 38°C oral (> 38.5°C rectally or tympanically) or hypothermia (< 35°C)
  - Purulent sputum or change in sputum character
  - Auscultatory findings consistent with pneumonia (e.g., rales, egophony, findings of consolidation)
  - Dyspnea, tachypnea, or hypoxemia (oxygen saturation < 90% on room air or pO_2 < 60 mm Hg)
  - White blood cell (WBC) count greater than 10,000 cells/mm^3 or less than 4,500 cells/mm^3
  - Greater than 15% immature neutrophils (bands) irrespective of WBC count.
- Pneumonia was confirmed radiographically by the presence of a new or progressive infiltrate on a chest radiograph or chest computerized tomography scan (CT scan) that is consistent with bacterial pneumonia.
- The patient had to be categorized as Risk Class III or IV by the Pneumonia Outcomes Research Team (PORT) score to enrich the population with patients having a moderate-to-severe risk for mortality due to pneumonia that would necessitate inpatient treatment with an intravenous antibacterial.

Key Exclusion Criteria

- Respiratory infection confirmed or suspected to be secondary to other types of pneumonia (ventilator-associated, hospital-acquired, or healthcare associated) or that required treatment in an intensive care unit (ICU) setting;
- Noninfectious causes of pulmonary infiltrates (e.g. cancer, pulmonary embolism, aspiration);
- Patients with organisms resistant to ceftaroline and/or ceftriaxone (*Pseudomonas aeruginosa*, MRSA, or atypical bacteria such as *Mycoplasma pneumoniae,*

Chlamydophila pneumoniae, Legionella spp.) based on microbiological documentation in culture positive respiratory or pulmonary specimens or epidemiologic characteristics of patients such as residence in a nursing home or assisted living facility, existence of an ongoing local MRSA infection outbreak, known skin colonization with MRSA, recent skin and skin structure infection from MRSA, IV drug use, and concomitant influenza. Patients with risk factors for MRSA infection who had Gram positive cocci in clusters in a sputum specimen were excluded;

- Patients who received a long-acting antibacterial agent for CABP (such as ceftriaxone, levofloxacin, moxifloxacin, gatifloxacin, or azithromycin), unless the patient had unequivocal clinical evidence of treatment failure following at least 48 hours of prior systemic therapy and/or isolation of an organism that was resistant to the therapy. Patients were also included if they had received only a single dose of an oral or intravenous short-acting antibiotic. Table 4 shows the antibacterials that are allowed for enrollment.

Medical Officer Comment:
This exclusion criterion arose from concerns that in trials evaluating the efficacy of antibiotics in treating CABP, the use of an antibacterial within 24 hours prior to randomization could conceal the inferiority of the study drug[6]. The 12/09/2009 AIDAC strongly recommended that CABP noninferiority trials should not allow effective prior antibacterial therapy. A subgroup analysis was done to evaluate the effect of a dose of the allowed antibacterials on the efficacy results.

Table 4. Prior Antibacterials Allowed (Patients should have been given only one dose within 96 hours of randomization).

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

- Patients with severe renal impairment (CrCl ≤ 30 mL/min);
- Patients with a past or current history of epilepsy or seizures
- Patients with immediate life-threatening illness; and
- Patients with previous participation in a ceftaroline study, pregnancy, hypersensitivity to ceftaroline.

Concomitant Medications

Concomitant systemic antibacterial agents, other than the study drug therapy, were not permitted. Probenecid was not allowed for three days prior to study drug initiation or concomitantly with study drug administration; all other medications were permitted. Antibacterials administered within four weeks prior to baseline evaluation through the late follow-up (LFU) visit and all other medications given within 4 weeks prior to baseline evaluation and through TOC were documented in the CRFs.

Schedule of Visits and Clinical Assessments

Once enrolled and randomized to a treatment group, baseline evaluation included obtaining a medical history, physical examination, chest radiography, and laboratory evaluation within 24 hours prior to study drug administration. Day 1 was defined as the first day of study drug administration.

The timepoints for evaluation were defined as follows:

- Baseline: confirmation of eligibility and randomization;
- Study Drug Administration: during treatment with the study drug;
- End-of-Therapy (EOT): last day the study drug was administered or day of withdrawal from study;
- Test-of-Cure (TOC) visit: 8-15 days after the last dose of the study drug; and
- Late Follow-Up (LFU): 21-35 days after the last dose of the study drug.

Appendix 5-B shows the schedule of clinical assessments and procedures performed during those assessments.

At each study visit, vital signs (including the maximum daily temperature, heart rate, respiratory rate, systolic and diastolic blood pressure, and pulse oxymetry) were determined and recorded in the CRFs. During study visits, signs and symptoms associated with the patient's clinical status related to the diagnosis of pneumonia were assessed and recorded in the CRFs. The signs and symptoms and grading system for those symptoms are as follows:

- Pleuritic chest pain (absent, mild, moderate, severe);
- Dyspnea (absent, mild, moderate, severe);
- Tachypnea (absent, mild, moderate, severe);
- Cyanosis (absent, mild, moderate, severe);
- Abnormal auscultatory findings (absent, mild, moderate, severe);
- Dullness to percussion (absent, mild, moderate, severe);

- Cough (absent, mild, moderate, severe);
- Confusion/disorientation (absent, present); and
- Sputum production (absence, presence, if present change in character from baseline and purulence).

Microbiological Assessments

Baseline microbiological specimens based on specimen- and organism-specific protocols were obtained at baseline from the following: sputum, pleural fluid, and blood. Additional pathogen identification included blood sampling for serologic testing for atypical pathogens (i.e. *M. Pneumoniae*, *C. pneumoniae*, and *Legionella* spp,) and urine sampling for *S. pneumoniae* and *Legionella pneumophilia* antigen testing.

The collection of adequate sputum samples for Gram stain, culture, and susceptibility testing at baseline, and during the study treatment, at EOT, TOC or LFU, if medically indicated, was attempted in all patients. Adequacy of the sputum specimens was determined using the following criteria:

- Appropriate sample: sputum with ≥ 25 WBCs per low-power field (LPF) and ≤ 10 squamous epithelial cells/LPF on Gram stain;
- Potentially appropriate sample: sputum with < 25 WBCs/LPF and ≤ squamous epithelial cells/LPF on Gram stain;
- Potentially inappropriate sample: sputum sample with missing squamous epithelial cells count;
- Inappropriate sample: sputum with squamous epithelial cells/LPF > 10.

Culture and susceptibility testing were performed at local and regional laboratories, as applicable. All isolates not considered contaminants were sent to the central laboratory for verification of identification and susceptibility. Any isolate was identified to the genus and species level at the central laboratory. Susceptibility testing of all isolates from sputum, pleural fluid, and blood were performed in the central laboratory using broth microdilution and Kirby-Bauer disk diffusion tests.

Analysis Populations

For the CABP trials, the Applicant defined seven analysis populations as shown in Table 5.

Table 5. Definitions of the Applicant's Analysis Populations

Population	
ITT	**Intent-to-Treat**: All randomized patients.
MITT	**Modified Intent-to-Treat**: All randomized patients who received any amount of study drug.
MITTE	**Modified Intent-to-Treat Efficacy** (**co-primary analysis population**): All MITT patients in PORT Risk Class III or IV.
CE	**Clinically Evaluable** (**co-primary analysis population**): All patients in the MITTE Population who met the minimal criteria for CABP and all evaluability criteria, including patients who received at least a prespecified minimal dose and duration

	of the study drug, for whom sufficient information regarding the infection was available to determine the outcome. Patients with *M. pneumoniae* or *C. pneumoniae* as the sole causative pathogen of infection, and all patients with *L. pneumophila* infections were excluded from the CE Population.
mMITT	**Microbiological Modified Intent-to-Treat**: All patients in the MITT Population who met the inclusion criteria for CABP, and had at least one typical bacterial organism consistent with a CABP pathogen identified from a microbiological specimen (e.g., blood, sputum, or pleural fluid). Patients with *M. pneumoniae* or *C. pneumoniae* as the sole causative pathogen of infection, and all patients with *L. pneumophila* infections were excluded.
mMITTE	**Microbiological Modified Intent-to-Treat Efficacy**: All patients in the mMITT Population in PORT Risk Class III or IV.
ME	**Microbiologically Evaluable**: All patients in both the CE and mMITTE Populations.

The MITTE and the CE populations were prespecified as the co-primary analysis populations by the Applicant and were modified (i.e. addition of the MITTE population as PORT Risk Class III or IV was added to the inclusion criteria) as the discussion of CABP trial design was evolving and following the recommendations by FDA.

Medical Officer Comment:
The Applicant's MITTE and CE population definitions do not require microbiological diagnosis with a bacterial pathogen as the basis for the CABP diagnosis. To ensure that patients included in the efficacy analysis for treatment of CABP did indeed have a diagnosis of CABP (community-acquired bacterial pneumonia), recent discussions and the FDA draft CABP guidance document have focused on utilization of a microbiologically defined population requiring the isolation of a typical bacterial pathogen at enrollment. Therefore, in the FDA sensitivity analysis population, the primary population of interest was the microbiological Modified-Intent-to-Treat (mMITT) population.
The Applicant mMITT population was determined by the following criteria:

Typical Pathogens
Bacterial isolates consistent with a CABP pathogen from any blood culture and pleural fluid culture were reviewed by the Sponsor Review Committee (SRC) for determination of pathogenicity.

The Applicant classified bacterial isolates into three categories:

- Typical CABP Pathogens: *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Klebsiella pneumoniae, Staphylococcus aureus, and Streptococcus pyogenes*
- Contaminants (classified as contaminants from expectorated sputum, rather than primary pathogens of CABP): fungi, *Enterococcus* spp., viridans streptococci, coagulase-negative staphylococci, *Micrococcus* spp., *Neisseria* spp. other than *N. meningitides*, *Corynebacterium* spp. and other coryneforms, *Lactobacillu*s

spp., *Vibrio* spp., *Capnocytophaga* spp., *Cardiobacterium* spp., *Flavobacterium* spp.

- Determined case-by-case via a blinded review by the Applicant: cultures that may suggest possible contamination such as isolation of ≥ 3 species, light or scant growth, and growth of organism not associated with CABP from pleural fluid and/or blood cultures, growth of organisms not commonly isolated from immunocompetent individuals, etc.

Atypical Pathogens

In addition to the Legionella urinary antigen test for the detection of *Legionella pneumophila* serotype 1, results of which had to be available prior to enrollment for exclusion, serological methods were utilized to identify atypical pathogens for identification of co-infection or exclusion from the study.

- *Mycoplasma pneumoniae*: 4-fold or greater rise in IgG titer between baseline and convalescent serology or IgM titer ≥ 1:16 at baseline;
- *Chlamydophila pneumoniae*: 4-fold or greater rise in IgG titer between baseline and convalescent serology or IgM titer ≥ 1:10 at baseline;
- *Legionella pneumophila*: 4-fold or greater rise in total antibody titer between baseline and convalescent serology or a positive *Legionella* urinary antigen test.

Outcome Measures

Clinical Outcomes

The primary outcome measure in Trial 08 and Trial 09 relied on the investigator-based assessment of clinical response. These assessments were made at both the EOT and TOC visits. Clinical response was classified by the investigator as *Clinical Cure, Clinical Failure*, *or Indeterminate*. Patients determined to be a *Clinical Failure* at the EOT were carried forward to the TOC and LFU timepoints. Patients classified as *Clinical Cure* at the TOC were also classified as *Clinical Cure* at the EOT. The definitions of Clinical Cure, Clinical Failure, and Indeterminate at the EOT and TOC visits used by the investigators for patient assessment are shown in Table 6.

Table 6. Definitions of Clinical Outcomes.

Outcome	Definition
Clinical Cure	Total resolution of all signs and symptoms of pneumonia, or improvement such that further antimicrobial therapy was not necessary. Improvement required the absence of fever (temperature ≤ 38°C orally or ≤ 38.5°C rectally or tympanically) for at least 24 hours with temperature recorded twice daily, in addition to a substantial improvement in signs and symptoms of CABP that includes a return to pre-CABP functional level for patients with decreased pulmonary function
Clinical Failure	Any of the following: • Persistence, incomplete clinical resolution, or worsening in signs and symptoms of CABP that required alternative antimicrobial therapy. • Treatment-limiting AE leading to discontinuation of the study drug, when alternative antimicrobial therapy to treat pneumonia was required.

	• Death wherein pneumonia was considered causative.
Indeterminate	Study data were not available for evaluation of efficacy, for reasons including treatment change before 48 hours of therapy; death where pneumonia was noncontributory, loss to follow-up or extenuating circumstances.

Radiographic Outcomes
Radiographic outcome assessments were made at TOC and LFU by local radiologists. Patients were classified as *Radiographic Success* if there was improvement in or resolution of pulmonary infiltrates or other baseline abnormalities, or stability without development of new radiographic abnormalities , *Radiographic Failure* if there was worsening of baseline radiographic abnormalities, or *Indeterminate* if the chest radiograph was either not done, missing, or could not be adequately interpreted.

MO Comment: Radiographic outcomes were not used in the FDA sensitivity analyses.

Microbiological Outcomes
For patients with a baseline CABP pathogen identified, a microbiological outcome at TOC was derived using electronic microbiology culture data from the central laboratory and from pathogen information determined by the Applicant for each baseline isolate. Categories were *Eradication*, *Presumed Eradication*, *Persistence*, *Presumed Persistence*, and *Indeterminate*. Favorable microbiological outcomes were *Eradication* or *Presumed Eradication*, while unfavorable outcomes were *Persistence* or *Presumed Persistence*.

Efficacy Endpoints

The prespecified primary objective of the Phase 3 CABP trials was to demonstrate non-inferiority of the clinical response in the ceftaroline treatment group compared to the ceftriaxone treatment group of CABP in the co-primary CE and MITTE populations as evaluated at the Test-of-Cure visit.

In addition, prespecified secondary efficacy endpoints assessed in these trials included the following:

- Clinical response at EOT in the CE and MITTE populations;
- Per-patient microbiological response at TOC in the mMITT and mMITTE populations;
- Overall (combined clinical and radiographic) response at TOC in MITTE and CE populations;
- Clinical and microbiological responses by baseline pathogen at TOC in the mMITTE and ME populations;
- Relapse at LFU visit in patients classified as Clinical Cure at TOC
- Reinfection or recurrence at LFU in patients with Clinical and Microbiologic Cure at TOC.

Statistical Methods

The primary objective of the two trials was to determine the non-inferiority of ceftaroline fosamil based on the difference in clinical cure rates between ceftaroline fosamil and ceftriaxone (ceftaroline – ceftriaxone) in adult patients with CABP in the MITTE and CE populations at the TOC visit. A 10% noninferiority margin was used. An important secondary endpoint was the determination of clinical cure rates at EOT.

The lower limit of the 95% confidence interval (CI) for the difference in the proportions of patients with clinical cure was obtained using the Miettinen and Nurminen method for comparing proportions. Noninferiority was demonstrated if the lower limit of the 95% confidence interval (CI) was greater than -10 using a 2-sided significance level of 0.5 for statistical significance of the test of non-inferiority.

Medical Officer Comment:
The study and prespecified analyses, when designed, were consistent with the existing guidance and discussions between the Applicant and DAIOP. The prespecified analyses of the clinical trials used investigator-assessment of clinical response at a TOC visit 7-14 days after the end of study drug treatment as the primary endpoint. Additionally, the co-primary analysis populations, the MITT and CE populations, did not require a confirmed bacterial etiology. The Applicant justified the noninferiority margin used in their analysis with historical data that was based on mortality. Historical data does not reliably provide evidence of treatment effect for antibacterial agents relative to placebo for a clinical response endpoint 7-14 days after therapy is complete and it is difficult to extrapolate the treatment effect on mortality to that clinical response endpoint.

At the 12/09/2009 AIDAC meeting, discussions focused on the historical data that might provide a basis for a primary endpoint based on clinical response assessed at an earlier timepoint was discussed. Existing evidence for antibacterial treatment effect was based on resolution of signs and symptoms of patients with pneumonia assessed at an earlier timepoint [7,8,9,10,11]. This treatment effect relative to placebo for clinical endpoints was primarily based on defervescence, decrease in pulse rate, and resolution of "toxemia" which was not well defined. The historical evidence supporting a large antibacterial treatment effect on clinical response early in the treatment course compared to a later timepoint was deemed acceptable in an analysis population with microbiologic documentation of bacterial etiology of CABP. Therefore, the Agency performed a sensitivity analysis based on clinical response at Day 4 in the microbiologically-confirmed population, as recommended by the 12/09/2009 AIDAC. The subsequent sections will present results of the Applicant's prespecified analysis, followed by the FDA sensitivity analyses presented in Section 6.1.10 (Additional Efficacy Issues/Analyses).

As discussed previously in Section 3.1, data integrity issues relating to a single investigator and monitoring contract research organization (CRO), resulted in this

investigator site being excluded from the analyses, based on DSI recommendations. Two more sites from India with the same CRO were also excluded because DSI could not insure the reliability of data from those 2 sites. A total of 9 patients were excluded from Trial 09; 5 in the ceftaroline and 4 in the ceftriaxone treatment groups.

6.1.2 Demographics

In Trial 08, there were 300 patients randomized to receive ceftaroline and 309 to receive ceftriaxone. Two hundred ninety nine and 307 patients in the ceftaroline and ceftriaxone treatment groups, respectively, received any amount of study drug.

Table 7. Baseline Characteristics of the Applicant's MITTE Population

	Trial P903-08		Trial P903-09	
	Ceftaroline	Ceftriaxone	Ceftaroline	Ceftriaxone
Total Patients	291	300	284	269
Sex				
Male	187 (64%)	191 (64%)	172 (61%)	172 (64%)
Female	104 (36%)	109 (36%)	112 (39%)	97 (36%)
Race				
White	260 (89%)	268 (89%)	278 (96%)	264 (97%)
Black	17 (6%)	15 (5%)	0 (0%)	0 (0%)
Asian	14 (5%)	16 (5%)	0 (0%)	0 (0%)
American Indian	0 (0%)	0 (0%)	5 (2%)	5 (2%)
Age				
18-49	74 (25%)	71 (24%)	58 (20%)	45 (17%)
50-<65	74 (25%)	81 (27%)	96 (34%)	92 (34%)
≥ 65	143 (49%)	148 (49%)	130 (45%)	132 (49%)
Region				
Africa	17 (6%)	18 (6%)	0 (0%)	0 (0%)
Asia	13 (4%)	15 (5%)	0 (0%)*	0 (0%)*
Eastern Europe[1]	201 (69%)	207 (69%)	223 (77%)	212 (78%)
Latin America	16 (5%)	16 (5%)	48 (17%)	44 (16%)
North America	11 (4%)	12 (4%)	0 (0%)	0 (0%)
Western Europe[1]	33 (11%)	32 (11%)	13 (4%)	13 (5%)

* Nine patients were excluded from Trial 09 because of data integrity issues.
[1] Poland and Hungary included in the Eastern European region by FDA.
[2] Temperature measured orally, rectally, tympanically.
FDA Reviewer Table and adapted Applicant Tables:
P903-08, CSR Tables: 10.3.1-1., 10.3.3-1., 10.3.4-1.
P903-09, CSR Tables: 10.3.1-1., 10.3.3-1., 10.3.4-1.

In Trial 09, there were 317 patients randomized to the ceftaroline treatment group and 310 to the ceftriaxone treatment group; 315 and 307 patients in the ceftaroline and ceftriaxone treatment groups, respectively, received any amount of study drug.. The baseline demographics of the Modified Intent-to-Treat Efficacy (MITTE) population were examined and are presented in Table 7. The baseline characteristics of the two treatment groups in each individual trial appear similar.

Most of the patients were enrolled from Eastern Europe, Western Europe, and Latin America. Enrollment from the US was limited to Trial 08, enrolling 4% of the patients in

each group. Of particular interest is the fact that the Applicant categorized Hungary and Poland as part of Western Europe.

Table 8. Relevant Medical History and Baseline Clinical Presentation of MITTE Population

	Trial P903-08		Trial P903-09	
	Ceftaroline	Ceftriaxone	Ceftaroline	Ceftriaxone
Total Patients	291	300	284	269
PORT Risk Class				
III	190 (65%)	182 (61%)	168 (59%)	169 (63%)
IV	101 (35%)	118 (39%)	116 (41%)	100 (37%)
Smoking History				
Yes	156 (54%)	141 (47%)	148 (52%)	144 (53%)
No	135 (46%)	159 (53%)	136 (48%)	125 (47%)
Lung Disease				
Yes	64 (22%)	60 (20%)	95 (33%)	87 (32%)
No	227 (78%)	240 (80%)	189 (67%)	182 (68%)
Bacteremia				
Yes	8 (3%)	9 (3%)	14 (5%)	11 (4%)
No	283 (97%)	291 (97%)	270 (95%)	258 (96%)
Renal Function				
80 < CrCl	150 (52%)	150 (50%)	122 (43%)	131 (49%)
50 < CrCl ≤ 80	86 (30%)	94 (31%)	108 (38%)	91 (34%)
30 < CrCl ≤ 50	46 (16%)	44 (15%)	39 (14%)	36 (13%)
CrCl ≤ 30	4 (1%)	5 (2%)	9 (3%)	5 (2%)
Prior Antibiotics				
Yes	137 (47%)	143 (48%)	95 (33%)	113 (42%)
No	154 (53%)	157 (52%)	189 (65%)	156 (57%)
Abnormal Signs				
Temperature > 37.8°C[2]	213 (73%)	204 (68%)	161 (56%)	166 (61%)
Heart Rate>100/minute	126 (43%)	113 (38%)	104 (36%)	102 (37%)
Respiratory Rate >24 /minute	161 (55%)	169 (56%)	152 (53%)	139 (51%)
Systolic BP < 90 mmHg	33 (11%)	36 (12%)	49 (17%)	45 (16%)
Oxygen Saturation <90%	81 (28%)	84 (28%)	100 (35%)	80 (29%)
Symptoms Present				
Cough	280 (97%)	293 (97%)	282 (98%)	265 (97%)
Dyspnea	239 (82%)	254 (84%)	252 (87%)	235 (86%)
Chest Pain	159 (55%)	165 (55%)	166 (57%)	149 (55%)
Sputum Production	223 (77%)	226 (75%)	205 (71%)	194 (71%)
Confusion	5 (2%)	11 (4%)	6 (2%)	8 (3%)

* Nine patients were excluded from Trial 09 because of data integrity issues.
[1] Poland and Hungary included in the Eastern European region by FDA.
[2] Temperature measured orally, rectally, tympanically.
FDA Reviewer Table and adapted Applicant Tables:
P903-08, CSR Tables: 10.3.1-1., 10.3.3-1., 10.3.4-1.
P903-09, CSR Tables: 10.3.1-1., 10.3.3-1., 10.3.4-1.

Variables that predict the patient's risk for morbidity and mortality from CABP, such as age, presence of bacteremia, renal function, pre-existing lung disease, and smoking history, are similar between the treatment groups. Around half (45-49%) of the enrolled

patients in each group in each trial were ≥ 65 years old and 25% in Trial 08 and 34% in Trial 09 were 50 to 65 years of age.

Around half of the enrolled patients had mild renal impairment or worse. Variables reflecting the severity of the pneumonia such as PORT Risk Class and abnormal signs and symptoms, were also similar between groups. By definition, all patients in the MITTE population were categorized as PORT Risk Class III or IV. Around 60 to 65% in each treatment group were categorized under PORT Risk Class III. 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. As a consequence, 61/627 (9.7%) were not classified as PORT Risk Class III or IV (not included in the listing in Table 8). Finally, only a small proportion, around 3-5%, of patients in each trial was bacteremic at baseline.

Nearly half of patients in Trial 08 and around 40% of patients in Trial 09 were given one dose of a short-acting antibiotic 96 hours before randomization. Most of these antibacterials were given within 24 hours of the first dose of the study drug in order to begin treatment while consent was being obtained. The most common prior antibiotics given to patients were amoxicillin/clavulanate, cefotaxime, ciprofloxacin, and ampicillin/sulbactam.

6.1.3 Patient Disposition

The number of patients in the prespecified analysis populations of the Applicant is shown in Table 9.

Table 9. Pre-Specified Analysis Populations of the Applicant

	Trial P903-08		Trial P903-09	
	Ceftaroline (%)	Ceftriaxone (%)	Ceftaroline (%)	Ceftriaxone (%)
ITT	305 (100)	309 (100)	312 (100)	306 (100)
MITT	299 (98)	307 (99)	310 (99)	303 (99)
MITTE	291 (95)	300 (97)	284 (91)	269 (88)
CE	224 (73)	234 (76)	232 (74)	214 (70)
mMITT	75 (25)	82 (27)	98 (31)	102 (33)
mMITTE	75 (25)	80 (26)	89 (29)	88 (29)
ME	69 (23)	71 (23)	84 (27)	76 (25)
Adapted from Source Tables: Trial P903-08, CSR, Table 10.1-2. Trial P903-09, CSR, Table 10.1-2.				

Of those randomized, only a small number of patients did not receive any amount of study drug so the number of dropouts from the ITT population prior to treatment was small. Similarly, only a few patients in the MITT population did not qualify for the PORT Risk Class requirement for the MITTE population. Around 75% of randomized patients met all clinical evaluability criteria. Only around 25-33% of the MITT population had microbiological pathogen confirmation (mMITT).

Tabular summaries of the disposition of enrolled patients in the two trials are shown in Table 10.

Table 10. Premature Discontinuation of Study Drug in Phase 3 CABP Trials in the MITTE Population

Disposition	Trial 08		Trial 09	
	Ceftaroline	Ceftriaxone	Ceftaroline	Ceftriaxone
Completed Study Drug	277 (95.2)	283 (94.3)	271 (93.8)	246 (90.1)
Premature Discontinuation of Study Drug	14 (4.8)	17 (5.7)	18 (6.2)	27 (9.9)
Reason for Premature Discontinuation				
Adverse Event	5 (1.7)	4 (1.3)	7 (2.4)	8 (2.9)
Pregnancy/Nursing	0	0	0	0
Significant Laboratory Abnormality	0	0	0	0
Insufficient therapeutic Effect	2 (0.7)	6 (2.0)	8 (2.8)	12 (4.4)
Clinical Worsening, Lack of Clinical Progress	2 (0.7)	6 (2.0)	7 (2.4)	10 (3.7)
Resistant Pathogen	0	0	1 (0.3)	2 (0.7)
Consent Withdrawn	5 (1.7)	6 (2.0)	2 (0.7)	4 (1.5)
Lost to Follow-Up	0	0	0	2 (0.7)
Other	2 (0.7)	1 (0.3)	1 (0.3)	1 (0.4)

Source: Table 1.1.1.1. Integrated Summary of Safety and Efficacy. P. 3780.

Overall, 93% of the patients in each treatment group completed study drug administration. Only a small proportion of patients prematurely discontinued the study drug, with the rate slightly higher in the group treated with the comparator. As will be discussed in the Safety Review in Section 7.3.4 (Significant Adverse Events), the most common reasons for premature discontinuation of study drug were insufficient therapeutic effect, treatment-limiting AE, and withdrawal of consent. Insufficient therapeutic effect was due to clinical worsening, lack of clinical progress, or isolation of a resistant organism.

Table 11 summarizes the rate of withdrawal in the treatment groups of the two CABP trials.

Table 11. Withdrawal from the Phase 3 CABP Trials in the MITTE Population.

Disposition	Trial 08		Trial 09	
	Ceftaroline	Ceftriaxone	Ceftaroline	Ceftriaxone
Completed Trial	272 (91.3)	283 (91.9)	284 (90.2)	278 (90.6)
Reason for Withdrawal from the Trial				
Noncompliance	0	0	0	1 (0.3)
Request of Applicant/Investigator	1 (0.3)	0	1 (0.3)	2 (0.7)
Consent Withdrawal	9 (3.0)	6 (1.9)	4 (1.3)	8 (2.6)
Loss to Follow-up	8 (2.7)	10 (3.2)	16 (5.1)	10 (3.3)
Death	6 (2.0)	6 (1.9)	6 (1.9)	6 (2.0)
Adverse Event	1 (0.3)	3 (1.0)	3 (1.0)	2 (0.7)
Other	1 (0.3)	0	1 (0.3)	0

Source: Table 1.2.2.1. Integrated Summary of Safety and Efficacy. P. 10746.

Around 8 to 9% of the patients withdrew from the trials, with the most common reason for withdrawal as “Lost to Follow-up”.

Table 12. Baseline Pathogens in the Applicant's mMITT Population

Bacteria	Trial P903-08		Trial P903-09	
	Ceftaroline (%)	Ceftriaxone (%)	Ceftaroline (%)	Ceftriaxone (%)
Total Patients	75	82	98	102
Chlamydophila pneumoniae	2 (3)	3 (4)	3 (3)	4 (4)
Citrobacter freundii complex	0	0	0	2 (2)
Citrobacter koseri	1 (1)	1 (1)	1 (1)	0
Enterobacter aerogenes	0	0	2 (1)	2 (2)
Enterobacter cloacae	6 (8)	8 (10)	2 (2)	6 (6)
Escherichia coli	8 (11)	7 (9)	4 (4)	6 (6)
Haemophilus influenzae	5 (7)	12 (15)	15 (15)	16 (16)
Haemophilus parainfluenzae	8 (11)	10 (12)	10 (10)	9 (9)
Klebsiella oxytoca	3 (4)	6 (7)	3 (3)	3 (3)
Klebsiella pneumoniae	8 (11)	5 (6)	8 (8)	10 (10)
Legionella pneumophila	0	0	0	0
Moraxella catarrhalis	1 (1)	1 (1)	3 (3)	2 (2)
Mycoplasma pneumoniae	4 (5)	7 (9)	11 (11)	11 (11)
Proteus mirabilis	1 (1)	0	2 (2)	0
Pseudomonas aeruginosa	1 (1)	0	3 (3)	2 (2)
Serratia liquefaciens	0	1 (1)	1 (1)	1 (1)
Serratia marcescens	3 (4)	2 (2)	0	1 (1)
Staphylococcus aureus [+]	10 (13)	13 (16)	16 (16)	18 (18)
Streptococcus pneumoniae	27 (36)	30 (37)	47 (48)	44 (43%)
Streptococcus pyogenes	0 (0%)	0 (0%)	0 (0%)	1 (1)

Data Source: FDA Statistical Reviewer. Nine patients were excluded from Trial 09 because of data integrity issues.
[+] MSSA only. MRSA isolates were excluded

The most common bacteria isolated in the mMITT population in the two trials were *Streptococcus pneumoniae* and *Staphylococcus aureus* among Gram-positive bacteria and *Klebsiella pneumoniae* and *Escherichia coli* among Gram-negative bacteria (Table 12). Among the causes of atypical pneumonia, *Legionella pneumophila* was the most frequently documented pathogen, followed by *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*.

6.1.4 Analysis of Primary Endpoint(s)

The objective of the primary analysis was to demonstrate noninferiority of the difference in clinical cure rate at TOC for ceftaroline compared to ceftriaxone (ceftaroline-ceftriaxone), using a noninferiority margin of 10%. The co-primary analysis populations were the MITTE population and the CE population.

Table 13 shows the clinical response rates at TOC of Trial 08 and Trial 09 for the two co-primary analysis populations.

Table 13. Clinical Cure Rates for MITTE and CE Populations at TOC Visit

Trial 08	Ceftaroline	Ceftriaxone	Difference (95% CI)
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)
Trial 09			
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)

Data Source: FDA Statistical Reviewer. Nine patients were excluded from Trial 09 because of data integrity issues.

The results shown in Table 13 demonstrate that the 10% noninferiority margin was met in both trials for each of the two co-primary analysis populations, with the lower bound of the 95% CI >-10 in each of the analyses.

6.1.5 Analysis of Secondary Endpoints(s)

6.1.5.1. Clinical Cure Rates at EOT Visit

An important secondary endpoint was to evaluate the clinical cure rate at the end-of-therapy timepoint. Results are shown in Table 14.

Table 14. Clinical Cure Rates for MITTE and CE Populations at EOT Visit

Trial 08	Ceftaroline	Ceftriaxone	Difference (95% CI)
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)
Trial 09			
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)

Data Source: FDA Statistical Reviewer. Nine patients were excluded from Trial 09 because of data integrity issues.

All prespecified objectives were met in both trials at both timepoints. Numerical trends for treatment differences between ceftaroline and ceftriaxone, as well as the lower bound of the 95% confidence limit, were greater than zero in some of the primary and secondary analyses.

6.1.5.2. Clinical Response at TOC in the mMITT Population

Clinical Response in the Applicant's mMITT population was explored as shown in the following table (Table 15)

Table 15. Clinical Cure Rates at TOC and EOT in the mMITT Population

Trial 08	Ceftaroline	Ceftriaxone	Difference (95% CI)
TOC	66/75 (88.0)	62/82 (75.6)	12.4 (0.2, 24.4)
EOT	66/75 (88.0)	64/82 (77.5)	10.0 (-2.0, 21.8)
Trial 09			
TOC	78/98 (79.6)	78/102 (76.5)	3.1 (-8.5, 14.6)
EOT	81/98 (82.7)	82/102 (80.4)	2.3 (-8.7, 13.1)
Source: Trial P903-08, CSR, Table 14.4.1.2E, FDA Statistical Reviewer. Nine patients were excluded from Trial 09 because of data integrity issues.			

These results support the efficacy of ceftaroline in the treatment of patients with pathogen-documented CABP compared to ceftriaxone. Because the number of patients in the mMITT population is smaller than the MITTE and CE population, the width of the confidence interval has increased in size.

Table 16 shows the clinical cure by pathogen for each of the two trials.

Table 16. Clinical Cure Rates at TOC by Pathogen in the Applicant's mMITT Population

	P903-08		P903-09	
Baseline Pathogen	Ceftaroline (%)	Ceftriaxone (%)	Ceftaroline (%)	Ceftriaxone (%)
S. pneumoniae	24/27 (88.9)	20/30 (66.7)	39/47 (83.0)	32/44 (72.7)
S. aureus[+]	8/10 (80.0)	8/13 (61.5)	10/16 (62.5)	11/18 (61.1)
H. influenzae	4/5 (80.0)	9/12 (75.0)	13/15 (86.7)	14/16 (87.5)
M. catarrhalis	1/1 (100)	1/1 (100)	1/3 (33.3)	2/2 (100)
E. coli	8/8 (100)	5/7 (71.4)	2/4 (50.0)	4/6 (66.7)
E. cloacae	6/6 (100)	6/8 (75.0)	2/2 (100)	5/6 (83.3)
K. oxytoca	2/3 (66.7)	5/6 (83.3)	3/3 (100)	2/3 (66.7)
K. pneumoniae	7/8 (87.5)	3/5 (60.0)	8/8 (100)	9/10 (90.0)

Data Source: FDA Statistical Reviewer. Nine patients were excluded from Trial 09 because of data integrity issues.
[+] MSSA only. MRSA isolates were excluded.

6.1.5.3. Clinical Cure Rates in the MITTE Population by Prior Antibacterial Use
Because of the concern about the effect of the prior use of antibacterials on clinical response rates, a subgroup analysis was performed and results are shown in Table 17.

Table 17. Clinical Cure Rates in MITTE Population at TOC by Prior Antibacterial Use

Trial 08	Ceftaroline	Ceftriaxone	Difference (95% CI)
Prior Antibacterials	105/137 (76.6)	112/143 (78.3)	-1.7 (-11.5, 8.1)
No Prior Antibacterials	139/154 (90.3)	121/157 (77.1)	13.2 (5.1, 21.4)
Trial 09			
Prior Antibacterials	80/95 (84.2)	91.113 (80.5)	3.7 (-7.0, 14.0)
No Prior Antibacterials	151/189 (79.9)	112/156 (71.8)	8.1 (-0.9, 17.3)

Data Source: FDA Statistical Reviewer. Nine patients were excluded from Trial 09 because of data integrity issues.

Among patients who did not receive prior active therapy, clinical cure rates were greater for patients treated with ceftaroline than patients treated with ceftriaxone. Cure rates were more similar between the treatment groups given prior antibacterials.

6.1.6 Other Endpoints

6.1.6.1. Mortality
The all-cause mortality rate between treatment groups was compared. Historical evidence provides an estimate of an antibiotic treatment effect relative to placebo on mortality rates in the mMITT population that may be used as a basis for determining a noninferiority margin for CABP trials. However, despite enrolling patients in Port Risk Class III and IV, mortality rates were low in the ceftaroline trials.

Table 18 show pooled mortality rates for both trials in these subgroups.

In both CABP trials, all-cause mortality rates were low.

Table 18. 30 Day All-Cause Mortality for the MITTE Population

	Ceftaroline	Ceftriaxone	Odds Ratio (95% CI)
Trial 08	4/291 (1.4)	5/300 (1.7)	0.82 (0.16, 3.86)
Trial 09	7/284 (2.5)	5/269 (1.9)	1.33 (0.36,5.40)

Data Source: FDA Statistical Reviewer. Nine patients were excluded from Trial 09 because of data integrity issues.

Using a non-inferiority margin of 1.67 on the odds ratio scale on a mortality endpoint recommended by Fleming and Powers[12] for CABP, ceftaroline was unable to meet this margin in either trial.

No deaths were observed among patients with bacteremia at baseline.

Medical Officer Comment:
The observation that the mortality rates were lower than what was expected for the pooled MITTE population and the subgroups at higher risk for mortality may indicate that using a mortality endpoint in the ceftaroline CABP trials may not be feasible.

6.1.7 Subpopulations

The efficacy of ceftaroline was examined in various subpopulations to ensure that the treatment effects are consistent across all relevant subpopulations (categorized according to demographic characteristics such as age, sex, and race, and prior treatment). The MITTE population was analyzed as it was one of the prespecified co-primary analysis populations. Table 19 shows differences in pooled clinical cure rates for subgroups with at least 20 patients in both ceftaroline and ceftriaxone treatment groups for both Trials 08 and 09.

Table 19. Clinical Cure Rates in Subpopulations of the MITTE Population of Pooled Phase 3 Trials

Subgroup	Ceftaroline	Ceftriaxone	Difference (95% CI)
All Patients	475/575 (82.6)	436/569 (76.6)	6.0 (1.3, 10.7)
Sex			
Male	292/359 (81.3)	262/363 (72.2)	9.2 (3.0, 15.3)
Female	183/216 (84.7)	174/206 (84.5)	0.3 (-6.7, 7.3)
Race			
White	443/538 (82.3)	408/532 (76.7)	5.7 (0.8, 10.5)
Black	15/17 (88.2)	12/15 (80.0)	X
Asian	12/14 (85.7)	11/16 (68.8)	X
American Indian	4/5 (80.0)	4/5 (80.0)	X
Age			
18-49	108/132 (81.8)	82/116 (70.7)	11.1 (0.6, 21.8)
50-64	142/170 (83.5)	129/173 (74.6)	9.0 (0.3, 17.5)
≥ 65	225/273 (82.4)	225/280 (80.4)	2.1 (-4.5, 8.6)

Data Source: FDA Statistical Reviewer. Nine patients were excluded from Trial 09 because of data integrity issues.

Analysis of the pooled results from both trials shows that differences in clinical cure rates between ceftaroline and ceftriaxone demonstrate the efficacy of ceftaroline in these subpopulations.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

All patients in the Phase 3 clinical trials for CABP received the recommended dosage for ceftaroline.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Studies that explore the persistence of efficacy and/or tolerance effects were not performed in the Phase 3 clinical trials as cephalosporins do not demonstrate these drug effects.

6.1.10 Additional Efficacy Issues/Analyses

The use of an investigator-assessed clinical response at the TOC visit as a primary endpoint in a population without a confirmed bacterial etiology is problematic. The historical data that reliably demonstrate an antibacterial treatment effect relative to placebo exist for either a mortality endpoint or clinical endpoints assessed earlier than the TOC visit, and come primarily from studies in pneumonia due to *S. pneumoniae*. Even if a justification based on early clinical endpoints is valid, extrapolation to a clinical response assessed at TOC may still be considered problematic. The Applicant's justification for the noninferiority margin was based on antibacterial treatment effect on mortality. Observations from the completed trials indicate that the mortality rates of the pooled population in both treatment groups were lower than the rates expected from historical data, even when subgroups with a higher risk of mortality (e.g. elderly, PORT Risk Class IV, bacteremic patients) are considered. Therefore, the validity of a mortality endpoint in these trials may not be helpful.

Historical data suggest that a large antibacterial treatment effect may be demonstrated in terms of clinical improvement of baseline signs and symptoms assessed at an earlier time than the TOC visit. If therapy is effective, patients typically experience a dramatic improvement in the signs and symptoms of pneumonia after the first few days of treatment.

A number of sensitivity analyses were therefore performed with the primary endpoint of clinical improvement at an earlier timepoint than the TOC or EOT visits, in patients with a microbiologically-confirmed diagnosis of CABP.

6.1.10.1. FDA Sensitivity Analyses

The following analyses examine the evidence for efficacy of ceftaroline as treatment for CABP based on historical data of a treatment effect of antibacterials relative to placebo based on objective parameters of response (e.g. fever, respiratory rate, and heart rate) at an earlier timepoint.

The primary analysis population used for these FDA reviewer analyses was the microbiological ITT (termed FDA-mITT), the population with a bacterial pathogen isolated at baseline as defined by the FDA.

6.1.10.1. A. Inclusion Criteria for the FDA-mITT Population

Patients were to have the required clinical and radiologic features (e.g. signs and symptoms consistent with pneumonia and an infiltrate on chest X-ray) for enrollment in the trials and should have received any amount of study drug. In addition, patients should have microbiological culture documentation of a baseline bacterial pathogen consistent with CABP and based on the following criteria:

- Patients with the following organisms identified from the blood, from appropriate lower respiratory specimens (adequate sputum specimen as defined, pleural fluid, and bronchoalveolar lavage), and from urine (identified by urinary antigen testing) should be included in the FDA-mITT population:
    - *Streptococcus pneumoniae*
    - *Haemophilus influenzae*
    - *Moraxella catarrhalis*
    - *Streptococcus pyogenes*
    - *Staphylococcus aureus* (MSSA only)
    - *Klebsiella pneumoniae*.
- Adequate sputum specimens were defined as specimens with at least > 10 WBC/LPF and < 10 squamous epithelial cells.
- Patients with the following Gram-negative enteric organisms were included if the patient was classified as PORT III or greater, the sputum specimen was adequate as described above, or the isolate was from another appropriate sample, such as broncho-alveolar lavage or pleural fluid:
    - *Citrobacter freundii* complex
    - *Citrobacter koseri*
    - *Enterobacter aerogenes*
    - *Escherichia coli*
    - *Klebsiella oxytoca*
    - *Proteus mirabilis*
    - *Serratia liquefaciens*
    - *Serratia marcescens*
- Patients from whom coinfection with a typical pathogen and *Legionella* spp., *Mycoplasma pneumoniae*, or *Chlamydophila pneumoniae* were identified were included in the FDA-mITT population.

6.1.10.1. B. Primary Efficacy Endpoint of the FDA Sensitivity Analysis

Estimates of earlier timepoints than the EOT or TOC visits in assessing the treatment effect of antibacterials on signs and symptoms of pneumonia in patients with CABP (e.g. absence of fever, clinical improvement, clinical recovery) have been found in historical studies[13,14,15,16,17]. These studies estimate treatment effect between 48 to 96 hours after initiation of treatment. In accordance with this historical evidence, the FDA used an endpoint assessed at Day 4 (72 to 96 hours) after the initiation of therapy.

There was no overall clinician assessment of clinical response at Day 4. Hence, the FDA defined an endpoint consisting of combined sign and symptom measurements that were directly available from the CRFs.

The FDA's primary efficacy endpoint consists of the following criteria:

1. Clinical stability as defined by the Infectious Diseases Society of America (IDSA) and the 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, are 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 IDSA/ATS definition also requires the ability to maintain oral intake, and involves oxygen partial pressure in addition to oxygen saturation, but these were not captured on the CRFs. The Agency defined normal mental status as confusion/disorientation being reported as absent. These criteria are used by clinicians to determine whether a patient can be discharged or switched to oral therapy.[18]

   Using the IDSA/ATS criteria, ninety-five percent of mITT patients had clinical instability at baseline.

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

   To be classified as a responder at Day 4, a patient had to improve from baseline on at least one of the four components, and could not have worsened on any of the other four components. For cough, dyspnea, and chest pain, this was determined by assessment of their severity on the CRFs, whether symptoms were absent, mild,

moderate, or severe at baseline and on Day 4. For sputum, worsening or improvement was determined first by examining for the presence or absence of sputum at baseline and at Day 4. If present on both days, then severity was assessed as worsened, stable, or improving.

Patients were classified as failures if there was insufficient data on Day 4 to compare patient status from baseline. All patients who had their EOT visit on Day 4 or earlier were classified as failures in the Agency's analyses; these patients were also classified by the investigator as clinical failures.

6.1.10.1. C. Baseline Demographic Information of the FDA-mITT Population

The following table (Table 20) summarizes the baseline demographic information for the FDA-mITT population. Overall, the FDA-mITT population was similar to the Applicant's co-primary MITTE population. Demographic characteristics were similar between the group treated with ceftaroline and the group treated with ceftriaxone in both trials.

Table 20. Demographics of the FDA-mITT Population

	Trial P903-08		Trial P903-09*	
	Ceftaroline	Ceftriaxone	Ceftaroline	Ceftriaxone
Total Patients	69	72	85	83
Age				
18-49	12 (17)	16 (22)	26 (31)	20 (24)
50-64	18 (26)	23 (32)	27 (32)	30 (36)
≥ 65	39 (57)	33 (46)	31 (37)	33 (40)
Region				
Africa	3 (4)	4 (6)	0 (0)	0 (0)
Asia	2 (3)	4 (6)	0 (0)	0 (0)
Eastern Europe	51 (74)	45 (62)	63 (75)	58 (70)
Latin America	3 (4)	4 (6)	20 (24)	23 (28)
North America	2 (3)	3 (4)	0 (0)	0 (0)
Western Europe	8 (12)	12 (17)	1 (1)	2 (2)
Bacteremia				
Yes	8 (12)	10 (14)	14 (17)	11 (13)
No	61 (88)	62 (86)	70 (83)	72 (87)
PORT Risk Class				
I	0 (0)	0 (0)	1 (1)	0 (0)
II	0 (0)	1 (1)	8 (10)	10 (12)
III	46 (67)	39 (54)	37 (44)	43 (52)
IV	23 (33)	31 (43)	38 (45)	30 (36)
V	0 (0)	1 (1)	0 (0)	0 (0)
Lung Disease				
Yes	17 (25)	14 (19)	26 (31)	27 (33)
No	52 (75)	58 (81)	59 (69)	56 (67)
Smoking History				
Yes	42 (61)	39 (54)	44 (52)	55 (66)
No	27 (39)	33 (46)	40 (48)	28 (34)
Abnormal Signs				
Temperature	57 (83)	58 (81)	50 (60)	60 (72)
Heart Rate	32 (46)	32 (44)	39 (46)	37 (45)
Respiratory Rate	41 (59)	41 (57)	48 (57)	51 (61)
Systolic BP	4 (6)	11 (15)	12 (14)	14 (17)
Oxygen Saturation	16 (23)	19 (26)	30 (36)	19 (23)
Symptoms Present				
Cough	68 (99)	72 (100)	83 (99)	81 (98)
Dyspnea	53 (77)	57 (79)	73 (87)	70 (84)
Chest Pain	44 (64)	44 (61)	64 (76)	48 (58)
Sputum Production	64 (93)	63 (88)	69 (82)	76 (92)
Confusion	0 (0)	5 (7)	4 (5)	2 (2)

Source: FDA Statistical Reviewer.
*One patient was excluded from Trial 09 because of data integrity issues.

6.1.10.1. C. Sensitivity Analysis on Day 4 in the FDA-mITT population.

Using the primary efficacy endpoint of clinical response determined by evaluation of signs and symptoms on Day 4 in the FDA-mITT population, responder rates were analyzed and are shown on Table 21. Sample sizes were small so confidence intervals for response rate differences were large.

Table 21. Clinical Response Rates on Signs and Symptoms Endpoint on Day 4

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%)	7.6% (-6.8%, 21.0%)

Source: FDA Statistical Reviewer. One patient was excluded from Trial 09 because of data integrity issues.

Despite the small sample sizes, in both trials, the FDA's sensitivity analyses provide evidence for the efficacy of ceftaroline. The antibacterial met the 10% noninferiority margin in both studies, with the lower limit of the 95% CI for the difference in responder rates for ceftaroline-ceftriaxone exceeding -10 in both trials.

6.1.10. D. Sensitivity Analysis of FDA-mITT Population at EOT and TOC

Using the Applicant-defined primary and secondary efficacy endpoints (e.g. clinical response at TOC and EOT, respectively), the FDA-mITT population was analyzed for congruence with the prior sensitivity analysis for the FDA primary endpoint. The following table shows that the Investigator-assessed clinical response rates for ceftaroline were higher than for ceftriaxone in Trial 08, therefore favoring the ceftaroline-treated group. Results were similar in Trial 09 but the magnitude of the treatment difference was smaller. The results are shown in Table 22.

Table 22. Investigator-Assessed Clinical Response Rates 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%)	2.6%	(-9.5, 14.7)
TOC	66/84 (78.6%)	64/83 (77.1%)	1.5%	(-11.2, 14.7)
Source: FDA Statistical Reviewer. One Patient was excluded from Trial 09 because of data integrity issues.				

From the previous analyses, results using the early signs and symptoms endpoint defined by the FDA are similar to results when the later endpoint of clinical response at the EOT or TOC visits was used. Among the FDA-mITT population who were Day 4 responders using the FDA criteria, 90% and 85% were clinical responders at the EOT visit in Trial 08 and Trial 09, respectively, suggesting that the early signs and symptoms endpoint is predictive of later clinical response.

6.1.10. E. Sensitivity Analysis of FDA-defined Early Endpoint by Pathogen

The by pathogen response rates were analyzed using the signs and symptoms endpoint assessed at Day 4. Results are shown in Table 23.

Table 23. Response Rates Using Early FDA Endpoint by Pathogen

Organism	Trial P903-08		Trial P903-09	
	Ceftaroline	Ceftriaxone	Ceftaroline	Ceftriaxone
S. pneumoniae	19/27 (70)	17/32 (53)	35/47 (74)	25/43 (58)
S. aureus[+]	4/9 (44)	4/14 (29)	10/15 (67)	10/15 (67)
H. influenzae	5/6 (83)	10/13 (77)	11/14 (79)	10/15 (67)
M. catarrhalis	0/1 (0)	1/1 (100)	1/3 (33)	1/2 (50)
K. pneumoniae	8/9 (89)	1/3 (33)	5/8 (62.5)	5/8 (62)
E.coli	3/8 (38)	5/6 (83)	1/4 (25)	4/7 (57)
K. oxytoca	3/3 (100)	4/4 (100)	3/3 (100)	2/2 (100)
E. cloacae	6/6 (100)	4/7 (57)	2/2 (100)	3/4 (75)

Source: FDA Statistical Reviewer. One patient was excluded from Trial 09 because of data integrity issues.
[+]MSSA only. MRSA isolates were excluded.

In congruence with the Applicant's results for response rates by pathogen assessed at the TOC visit, ceftaroline cure rates were higher than ceftriaxone cure rates for *S. pneumoniae*. For the rest, the number of patients from whom pathogens were isolated was too small to infer meaningful observations.

Medical Officer Comment:
The observed microbiologic cure rates were higher for S. pneumoniae *and* H. influenzae *in the ceftaroline group compared to the ceftriaxone group. For* S. aureus*, meaningful observations could not be made.*

6.1.10. F. Sensitivity Analysis of FDA-defined Early Endpoint by Prior Antibacterial Use

Due to the concern that prior antibacterial use may confound the interpretation of the Day 4 responder rates in the FDA-mITT population, analyses were conducted based upon use and non-use of prior antibacterials. The results are shown in Table 24.

Table 24. Response Rates Using Early FDA Endpoint by Prior Antibacterial Use

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 Statistical Reviewer. One patient was excluded from Trial 09 because of data integrity issues.

Patients who had not received prior antibiotics (except for possibly one dose of a short-acting agent) continued to demonstrate the efficacy of ceftaroline relative to ceftriaxone, although the small number of patients that were included in the analysis groups precludes meaningful observations and conclusions to be made.

6.1.10.2. Evaluation of Robustness of FDA Sensitivity Analyses

The FDA endpoint assessed on Day 4 was based on historical evidence for antibacterial treatment effect in CABP based on an early clinical response endpoint. Even if based

on historical data, the choice of population to examine, time of assessment, and parameters used to define clinical stability and improvement can vary. These modifications may affect the analysis of responder rates. Therefore, to examine the robustness of the FDA sensitivity analysis, several parameters were modified and analyzed.

6.1.10.2. A. Modification of Endpoint

In this analysis, the endpoint was modified to clinical response based on achievement of clinical stability using the IDSA/ATS guidelines or symptom resolution alone. Table 25 summarizes the analysis.

Table 25. Clinical Response Rates for FDA-mITT Population when Endpoint is Modified

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 (84.3%)	5.1%	(-5.5%, 15.7%)

Source: FDA Statistical Reviewer. One patient was excluded from Trial 09 because of data integrity issues.

Medical Officer Comment:
In both trials, when the endpoint was modified using clinical stability of vital signs alone or improvement of symptoms alone, the differences in the response rates between ceftaroline and ceftriaxone favored ceftaroline, with the lower limit of the 95% CI greater than -10. These findings support the results using the primary endpoints of the FDA sensitivity analysis.

6.1.10.2. B. Modification of Timing of Assessment

As shown in Table 26, results were examined when assessment was performed on Day 3, Day 4, or the EOT.

Table 26. Clinical Response Rates when Timing of Assessment is Modified

Trial P903-08	Ceftaroline	Ceftriaxone	Difference	95% CI
Day 3	35/69 (50.7%)	30/72 (41.7%)	9.1%	(-7.4%, 25.0%)
EOT	59/69 (85.5%)	55/72 (76.4%)	9.1%	(-4.0%, 22.1%)
Trial P903-09	Ceftaroline	Ceftriaxone	Difference	95% CI
Day 3	48/84 (57.1%)	47/83 (56.6%)	0.5%	(-14.4%, 15.4%)
EOT	66/84 (78.6%)	65/83 (78.3%)	0.3%	(-12.3%, 12.9%)

Source: FDA Statistical Reviewer. One patient was excluded from Trial 09 because of data integrity issues.

Medical Officer Comment:
Analysis of the comparison of responder rates with the timing of assessment at an earlier timepoint (Day 3) or at later timepoint (EOT) showed inconsistent findings. Trial 08 favored ceftaroline with a point estimate of the difference being 9.1% while Trial 09 showed no difference between treatments. However, because of the low number of

patients included in the analysis, meaningful observations could not be made with this analysis.

6.1.10.2. C. Modification of Analysis Population

Results were examined when the endpoint was applied to the Applicant's MITTE, CE, and mMITT populations. Results of these analyses are shown in Table 27.

Table 27. Clinical Response Rate Using Day 4 Endpoint when Population is Modified

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

Source: FDA Statistical Reviewer. One patient was excluded from Trial 09 because of data integrity issues.

These analyses showed that the results using Day 4 assessment of clinical stability in the FDA-mITT population were robust.

Medical Officer Comment:
Based on the prespecified 10% noninferiority margin used to compare investigator-assessed clinical response rates between the ceftaroline- and ceftriaxone-treated groups at the TOC visit 8 to 15 days after the end of therapy, both trials established the noninferiority of ceftaroline compared to ceftriaxone as treatment for CABP.

6.2 Indication (Acute Bacterial Skin and Skin Structure Infections)

The Applicant seeks the following proposed indication:

Teflaro (ceftaroline) is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) 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*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*.

6.2.1 Methods

The Applicant performed two Phase 3 clinical trials to support the ABSSSI indication. Both trials (P903-06 and P903-07) were multicenter, multinational, randomized, double-blinded, well-controlled trials in adults (≥18 years of age) with a total of 1396 patients enrolled.

6.2.1.1 Inclusion and Exclusion Criteria

Inclusion Criteria:
For enrollment into either trial, patients were required to have the following:

1. Age greater or equal to 18 years
2. 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
     - o "Deeper soft tissue" is defined as subdermal tissue, including subcutaneous fat; for example, extension of infection to muscle or fascia constitutes evidence of deeper soft tissue involvement
     - o "Significant surgical intervention" is defined as a major operative procedure, not including commonly performed minor procedures such as incision and drainage of minor abscesses performed at the bedside, suture removal, needle aspiration, superficial debridement of devitalized tissue, or routine wound care
     - o "Wound infection" is defined by the presence of either purulent/seropurulent discharge from the surgical/traumatic wound or greater than or equal to 5 cm of erythema (i.e. cellulitis) surrounding the wound margin. Onset must have occurred within 7 days prior to randomization and no later than 30 days following the trauma or surgical procedure.
     - o "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
     - o "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 the lower extremity which occurs in patients with diabetes mellitus or well-documented peripheral vascular disease (PVD). NOTE: Patients with a history of diabetes mellitus must be taking insulin, insulin analogues, or oral hypoglycemic agents to be eligible for the study. "Well documented PVD" is defined as arterial or venous vascular disease resulting in ischemia of the lower extremity as manifest by ulceration, poor wound healing, or the absence of readily palpable dorsalis pedis and posterior tibial pulses.

3. 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
   - Greater than 10% immature neutrophils (bands) irrespective of WBC count.
4. Patients must require initial hospitalization, or treatment in an emergency room or urgent care setting
5. Patient's infection is expected to require at least 5 days of intravenous therapy

Exclusion Criteria

The following are the major exclusion criteria:

1. More than 24 hrs of treatment with an antimicrobial agent (other than a topical) within 96 hours leading up to randomization
   - EXCEPTION: Patients 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-positive 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 study drug therapy
2. Skin and skin structure infection with ANY of the following characteristics (partial list):
   - Diabetic foot ulcer or ulcer associated with PVD that has the following characteristics: accompanied by osteomyelitis, likely to require amputation within 60 days, likely to require revascularization within 60 days
   - Human or animal bites
   - Rapidly necrotizing process
   - Gangrene
   - Infection site complicated by presence of prosthetic materials
   - Known or suspected osteomyelitis
3. Severe renal impairment (CrCl ≤ 30 mL/min)
4. Required significant surgical intervention that could not be performed within 48 hours after initiation of study drug therapy.

6.2.1.2 Study Drug Administration

Patients randomly assigned to the ceftaroline group received IV ceftaroline fosamil (600 mg) infused over 60 (±10) minutes (Infusion A1), followed by an IV line flush, and then IV normal saline placebo infused over 60 (±10) minutes (Infusion B), every 12 hours for 5 to 14 days (up to a maximum of 21 days, with the approval of the Applicant's Medical Monitor). Normal saline placebo (Infusion B) was discontinued if a Gram-negative pathogen was neither identified nor suspected.

Patients randomly assigned to the vancomycin plus aztreonam group received IV vancomycin (1g) over 60 (±10) minutes (Infusion A1), followed by line flush, and then IV aztreonam (1g) infused over 60 (±10) minutes (Infusion B), every 12 hours for 5 to 14 days (up to a maximum of 21 days, with the approval of the Applicant's Medical Monitor). Aztreonam was discontinued if a Gram-negative pathogen infection was neither identified nor suspected.

6.2.1.3 Study Evaluations

Baseline clinical and microbiological assessments were performed within 24 hours prior to the initiation of therapy. Clinical assessments included medical history, prior and concomitant medications, complete physical exam including vital signs and inspection of the ABSSSI. Measurements of the length and width in centimeters of the site were obtained. In addition, signs and symptoms at the ABSSSI site were assessed including depth of involvement, erythema, swelling, tenderness, warmth, fluctuance and discharge. Further clinical assessments (Day 2, Day 3, Day 4-14, and Day 15-21) were taken between Day 1 of therapy up to and including the EOT visit and at the TOC visit which occurred 8 to 15 days after the administration of the last dose of therapy. A Late Follow-Up (LFU) assessment was conducted 21 to 35 days after the last dose of therapy.

6.2.1.4 Analysis Population Definitions

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 group, respectively.

The Applicant defined the following analysis populations:

- ITT (Intent-to-Treat): All randomized patients.

- MITT (Modified Intent-to-Treat): All randomized patients who received any amount of study drug.
- cMITT (Clinical Modified Intent-to-Treat Efficacy): All MITT patients who met minimal disease criteria.
- mMITT (Microbiological Modified Intent-to-Treat): All patients in the cMITT population who had at least one bacterial organism consistent with a ABSSSI pathogen identified from a baseline microbiological specimen.
- CE (Clinically Evaluable): All patients in the cMITT population who met the inclusion criteria for ABSSSI and all evaluability criteria, including patients who received at least the pre-specified minimal amount of the intended dose and duration of study drug therapy, for whom sufficient information regarding the infection was available to determine the outcome. These criteria included the following:
    - Between 80% and 120% of the intended doses of study drug therapy received
    - At least 48 hours of therapy received in order to be considered an evaluable failure, unless deemed a clinical failure based on a treatment-limiting adverse event
    - At least 96 hours of therapy received in order to be considered an evaluable success
    - Outcome assessment performed at the TOC visit, unless previously determined to be a clinical failure
    - Did not receive potentially effective alternative systemic antimicrobial therapy prior to the TOC visit
- ME (Microbiologically Evaluable): All patients in both the mMITT and CE populations.

Based on FDA evidentiary standards in 21 CFR 314.126, the Applicant was required to perform two independent trials as evidence for efficacy, however the two trials had virtually identical study designs and similar study populations in terms of baseline characteristics. Therefore, although data from each Trial was independently analyzed, the data were also pooled for the purpose of an integrated summary.

The primary clinical data from both trials was reviewed individually and as integrated data. The case report forms (CRFs), datasets and Applicant's study reports were also reviewed for each trial. The Applicant submitted a random sample of CRFs from each trial. These CRFs were reviewed by the FDA reviewer for the purpose of establishing consistency among the investigators in their conduct of the study, interpretation of protocol, and accuracy in reporting of results. Seventy CRFs were evaluated for each study.

Medical Officer's Comments:
Results from both trials were examined independently. However, because there was no significant difference in the design of P903-06 and P903-07 and trial populations were similar, this review will also pool results for the purpose of an integrated summary.

There was general agreement between the Applicant's assessment of outcomes and that of the FDA reviewer based on the 70 CRFs reviewed and there were no major discrepancies noted.

6.2.1.5 Efficacy Endpoints

The primary pre-specified efficacy endpoint was the per-patient clinical response (cure) rate in MITT and CE populations 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:
  - Persistence, incomplete clinical resolution, or worsening of the infection that required alternative antimicrobial therapy.
  - A surgical intervention that was performed as an adjunct or follow-up therapy due to failure of the study drug to adequately treat the infections. Minor surgical interventions conducted at the bedside and considered standard adjunctive therapy to appropriate antimicrobial therapy, surgical interventions on SSSI lesions other than the index lesion, surgeries not related to ABSSSI, or execution of planned surgical interventions did not constitute evidence of study drug failure.
  - New signs and symptoms associated with the original ABSSSI or a new ABSSSI at the same anatomical site.
  - Patient required alternative antimicrobial therapy to treat the ABSSSI, including oral step-down therapy.
  - Treatment limiting adverse event leading to study treatment discontinuation when alternative antimicrobial agent to treat the ABSSSI is necessary.
  - 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.

The primary objective was to determine the non-inferiority of ceftaroline fosamil treatment compared to vancomycin + aztreonam treatment in adult patients 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 from when antibiotics became available but were in limited supply.

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%.

To further evaluate the efficacy of ceftaroline a number of secondary endpoints were analyzed. These secondary endpoints included: clinical response at EOT in the MITT and CE populations, clinical response at TOC in the mMITT and ME population, and clinical response by pathogen at TOC.

Medical Officer's Comments:
Data collected in the CRF was adequate for the pre-specified analyses, but this data limited the FDA review team's ability to apply sensitivity analyses consistent with current thoughts on clinical endpoints and timing of assessment addressed in recent and ongoing public discussions regarding the use of non-inferiority clinical trial design and establishment of an NI margin for ABSSSI trials. These recent discussions have focused on primary efficacy endpoints assessed at earlier time points, based on evidence from the historical literature used to demonstrate antibacterial treatment effect relative to placebo in skin infections (Snodgrass and Anderson, 1937). The endpoints suggested by the literature for which an NI margin may be justified include time to cessation of spread of the lesion and defervescence in those with fever at baseline in a population of patients with extensive cellulitis and wound infections. Therefore, FDA reviewers carried out sensitivity analyses utilizing an endpoint assessed at an earlier time point which will be discussed in further detail in Section 6.2.10.

6.2.2 Demographics

For the two Phase 3 ABSSSI trials, the modified intent-to-treat (MITT) analysis population was comprised of all randomized patients who received any amount of study therapy. The pooled MITT group consisted of 1378 patients; 693 received ceftaroline and 685 received comparator drug. The following tables are adapted from tables presented in the Applicant's Integrated Summary of Efficacy and highlight demographics and baseline characteristics of the MITT population.

Table 28. Demographic and Baseline Characteristics of Applicant MITT Population

Parameter	P903-06			P903-07		
	Ceftaroline (n=351)	Vancomycin + Aztreonam (n=347)	Total (n=698)	Ceftaroline (n=342)	Vancomycin + Aztreonam (n=338)	Total (n=680)
Gender, n (%)						
Female	220	218	438 (62.8)	224	201	425

	(62.7)	(62.8)		(65.5)	(59.5)	(62.5)
Male	131 (37.3)	129 (37.2)	260 (37.2)	118 (34.5)	137 (40.5)	255 (37.5)
Race, n (%)						
White	263 (74.9)	261 (75.2)	524 (75.1)	246 (71.9)	254 (75.1)	500 (73.5)
Black	15 (4.3)	22 (6.3)	37 (5.3)	33 (9.6)	21 (6.2)	54 (7.9)
Asian	6 (1.7)	4 (1.2)	10 (1.4)	3 (0.9)	1 (0.3)	4 (0.6)
Other	70 (19.9)	64 (18.4)	134 (19.2)	60 (17.5)	62 (18.3)	122 (17.9)
Ethnicity, n (%)						
Hispanic	83 (23.6)	77 (22.2)	160 (22.9)	63 (18.4)	59 (17.5)	122 (17.9)
Non-Hispanic	268 (76.4)	270 (77.8)	538 (77.1)	279 (81.6)	279 (82.5)	558 (82.1)
Age, n (%)						
Mean ± SD	47.2 ± 17.01	49.2 ± 17.17	48.2 ± 17.10	47.8 ± 16.98	47.5 ± 16.07	47.7 ± 16.52
Median(range)	48.0 (18, 90)	48.0 (18, 87)	48.0 (18, 90)	47.0 (18, 93)	48.0 (18, 96)	48.0 (18, 96)

Source: Adapted from Applicant Table 3.1.3.1-1 in the Summary of Clinical Efficacy-ABSSSI

Medical Officer's Comments:
The two treatment groups for both trials were relatively well matched within each trial and between trials P903-06 and P903-07 with respect to age and race. In P903-06, approximately two-thirds of the patients in each treatment group were female, but gender was more closely matched between treatment groups in P903-07 with females constituting approximately 63% of the study population.

Table 29. Enrollment by Region Groups, MITT Population

Region Group	P903-06		P903-07		Pooled Data	
	Ceftaroline (n=351) n(%)	Vancomycin + Aztreonam (n=347) n(%)	Ceftaroline (n=342) n(%)	Vancomycin + Aztreonam (n=338) n(%)	Ceftaroline (n=693) n(%)	Vancomycin + Aztreonam (n=685) n(%)
Region						
Eastern Europe	145 (41.3)	147 (42.4)	106 (31.0)	104 (30.8)	251 (36.2)	251 (36.6)
Latin America	31 (8.8)	28 (8.1)	25 (7.3)	25 (7.4)	56 (8.1)	53 (7.7)
Western Europe	42 (12.0)	41 (11.8)	41 (12.0)	41 (12.0)	83 (12.0)	82 (12.0)
United States	133 (37.9)	131 (37.8)	170 (49.7)	168 (49.7)	303 (43.7)	299 (43.6)
US and Non-US						
US	133 (37.9)	131 (37.8)	170 (49.7)	168 (49.7)	303 (43.7)	299 (43.6)
Non-US	218 (62.1)	216 (62.2)	172 (50.3)	170 (50.3)	390 (56.3)	386 (56.4)

Source: Adapted from Applicant Table 3.1.2.1-2 in the Summary of Clinical Efficacy-ABSSSI

Medical Officer's Comments:

Slightly less than half of the patients were from the United States in the pooled trials. In Trial P903-06, approximately two-thirds of the patients were non-US patients with the majority of patients coming from Eastern Europe. Trial P903-07 was more closely matched with approximately half of the patients being from the United States.

The next table (Table 30) shows an overview of comorbid medical conditions and signs and symptoms of baseline skin infections.

Table 30. Comorbidities and Disease Severity at Baseline, Trials P903-06 and P903-07, MITT Population

Disease Severity Patients with:	P903-06			P903-07		
	Ceftaroline (n=351)	Vancomycin +Aztreonam (n=347)	Total (n=698)	Ceftaroline (n=342)	Vancomycin +Aztreonam (n=338)	Total (n=680)
Medical history, n (%)						
> 75 years of age	22 (6.3)	26 (7.5)	48 (6.9)	24 (7.0)	19 (5.6)	43 (6.3)
Diabetes	62 (17.7)	68 (19.6)	130 (18.6)	60 (17.5)	52 (15.4)	112 (16.5)
PVD	47 (13.4)	53 (15.3)	100 (14.3)	46 (13.5)	40 (11.8)	86 (12.6)
Moderate renal dysfunction*	14 (4.0)	17 (4.9)	31 (4.4)	13 (3.8)	13 (3.8)	26 (3.8)
Prior failures [a]	28 (8.0)	32 (9.2)	60 (8.6)	31 (9.1)	26 (7.7)	57 (8.4)
Signs and symptoms (s/s), n (%) or n/N (%)						
Fever	121/350 (34.5)	110/347 (31.7)	231/697 (33.1)	90/342 (26.3)	91/338 (26.9)	181/680 (26.6)
Elevated WBC count (> $10^3/mm^3$)	120/314 (34.2)	126/313 (36.3)	246/627 (35.2)	126/306 (41.2)	127/305 (41.6)	253/611 (41.4)
≥ 1 systemic sign[b]	199 (56.7)	193 (55.6)	392 (56.2)	179 (52.3)	169 (50.0)	348 (51.2)
≥ 2 severe[c] signs & symptoms	191 (54.4)	203 (58.5)	394 (56.4)	181 (52.9)	176 (52.1)	357 (52.5)
Erythema, n (%)						
Absent	2 (0.6)	2 (0.6)	4 (0.6)	1 (0.3)	0	1 (0.1)
Mild	15 (4.3)	8 (2.3)	23 (3.3)	14 (4.1)	11 (3.3)	25 (3.7)
Moderate	130 (37.0)	125 (36.0)	255 (36.5)	138 (40.4)	147 (43.5)	285 (41.9)
Severe	204 (58.1)	212 (61.1)	416 (59.6)	189 (55.3)	180 (53.3)	369 (54.3)
Swelling, n (%)						
Absent	1 (0.3)	0	1 (0.1)	2 (0.6)	1 (0.3)	3 (0.4)
Mild	28 (8.0)	23 (6.6)	51 (7.3)	23 (6.7)	31 (9.2)	54 (7.9)
Moderate	186 (53.0)	174 (50.1)	360 (51.6)	160 (46.8)	152 (45.0)	312 (45.9)
Severe	136 (38.7)	150 (43.2)	286 (41.0)	157 (45.9)	154 (45.6)	311 (45.7)
Tenderness, n (%)						
Absent	5 (1.4)	2 (0.6)	7 (1.0)	2 (0.6)	2 (0.6)	4 (0.6)
Mild	14 (4.0)	12 (3.5)	26 (3.7)	26 (7.6)	26 (7.7)	52 (7.6)
Moderate	132 (37.6)	133 (38.3)	265 (38.0)	139 (40.6)	132 (39.1)	271 (39.9)
Severe	200 (57.0)	200 (57.6)	400 (57.3)	175 (51.2)	178 (52.7)	353 (51.9)
Other signs, n (%) or n/N (%)						
Bacteremia	20 (5.7)	10 (2.9)	30 (4.3)	9 (2.6)	14 (4.1)	23 (3.4)

Abscess , 1 dimension >5cm	83/99 (83.8)	88/101 (87.1)	171/200 (85.5)	124/139 (89.2)	120/133 (90.2)	244/272 (89.7)
Infection area median, range (cm^2)	173.9 (1, 3150)	180 (2.3, 3015)	180 (1, 3150)	151(1.4, 2860)	120 (0, 4950)	136 (0, 4950)

Source: Adapted from Applicant Table 10.3.10-1 of Protocol and Applicant Table 7.1.3.4-1 of the Integrated Summary of Efficacy-ABSSSI
a Patients who received > 48 hours of systemic antibiotic therapy with evidence of prior failure (positive Gram's stain or isolation of resistant organism) before administration of study drug.
b Fever greater than 38ºC oral (> 38.5ºC rectally or tympanically) or hypothermia (< 35ºC), WBC count greater than 10,000/mm3, greater than 10% immature neutrophils (bands) irrespective of WBC count.
c Erythema, swelling, tenderness, or warmth.
d Denominator is the number of patients with major abscess.
*Moderate renal impairment is defined as CrCl > 30 to ≤ 50 mL/min.

Medical Officer's Comments:
In terms of medical history, within each trial treatment groups were well matched. Overall, diabetes mellitus was present in 15-20% of the population and PVD in 12-15%. Baseline renal function was similar between trial populations.

In terms of baseline signs and symptoms and their severity, within each individual trial patients were relatively well matched. Overall, only 3-6% of patients had bacteremia at baseline. Fever was present in 26-32% of patients, elevated WBC in 35-41%, and 50-57% of the study patients had >1 systemic sign (i.e. fever, elevated WBC, or bandemia).

Table 31. Types of Infection at Baseline, Trials P903-06 and P903-07, MITT Population

	P903-06			P903-07		
Description of Infection	**Ceftaroline (n=351)** (%)	**Vancomycin +Aztreonam (n=347)** (%)	**Total (n=698)**	**Ceftaroline (n=342)** (%)	**Vancomycin + Aztreonam (n=338)** (%)	**Total (n=680)**
Type of infection n (%)						
Major abscess	99 (28.2)	101 (29.1)	200 (28.7)	139 (40.6)	133 (39.3)	272 (40.0)
Deep/extensive cellulitis	121 (34.5)	120 (34.6)	241 (34.5)	103 (30.1)	123 (36.4)	226 (33.2)
Infected wound	54 (15.4)	43 (12.4)	97 (13.9)	48 (14.0)	39 (11.5)	87 (12.8)
Infected ulcer	23 (6.6)	31 (8.9)	54 (7.7)	31 (9.1)	21 (6.2)	52 (7.6)
Lower extremity ABSSSI in patient w/ diabetes or PVD	21 (6.0)	20 (5.8)	41 (5.9)	9 (2.6)	12 (3.6)	21 (3.1)
Cellulitis	17 (4.8)	19 (5.5)	36 (5.2)	8 (2.3)	11 (3.3)	19 (2.8)
Abscess	4 (1.1)	1 (0.3)	5 (0.7)	1 (0.3)	1 (0.3)	2 (0.3)
Infected bite	7 (2.0)	7 (2.0)	14 (2.0)	6 (1.8)	4 (1.2)	10 (1.5)
Infected burn	25 (7.1)	20 (5.8)	45 (6.4)	1 (0.3)	2(0.6)	3 (0.4)
Other	1 (0.3)	5 (1.4)	6 (0.9)	5 (1.5)	4 (1.2)	9 (1.3)

Source: Adapted from Applicant Table 7.1.3.3-2 in the Integrated Summary of Clinical Efficacy-ABSSSI

Medical Officer's Comments:
Within each trial, patients were well matched in terms of infection type (Table 31). However, in Trial P903-07 there were slightly more patients with deep/extensive cellulitis (36.4%) in the comparator group as compared to the ceftaroline group (30.1%).

Overall, 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 patients. One to 2% of the population had infection type classified as "bites". However, patients with human and animal bites had been excluded from the trials.

Table 32 shows the dimensions of the area of the primary infection site by trial and pooled data.

Table 32. Primary Infection Site Measurement at Baseline, MITT Population

	P903-06			P903-07		
Measure	**Ceftaroline (n=351)**	**Vancomycin +Aztreonam (n=347)**	**Total (n=698)**	**Ceftaroline (n=342)**	**Vancomycin + Aztreonam (n=338)**	**Total (n=680)**
Infection length (cm)						
Mean ± SD	16.6 ± 10.2	18.3 ± 12.1	17.4 ± 11.2	17.2 ± 10.9	16.5 ± 12.1	16.8 ± 11.5
Median (range)	15 (0.4, 65.0)	15 (1.5, 68.6)	15 (0.4, 68.6)	15 (1.3, 65.0)	14 (0.2, 99.0)	14 (0.2, 99.0)
Infection width (cm)						
Mean ± SD	13.5 ± 9.4	14.4 ± 10.2	13.9 ± 9.8	12.5 ± 9.6	12.1 ± 9.7	12.3 ± 9.6
Median (range)	11 (0.5, 55.0)	12 (1.5, 61.3)	11.6 (0.5, 61.3)	10 (0.5, 54.0)	9 (0.2, 54.0)	10 (0.2, 54.0)
Infection area (cm^2)						
Mean ± SD	290.9 ± 393.0	340.4± 432.0	315.5 ± 413.3	283.8 ± 402.3	278.7 ± 490.2	281.3 ± 447.8
Median (range)	173.9 (1, 3150)	180 (2.3, 3015)	180 (1.0, 3150)	151 (1.4, 2860)	120 (0, 4950)	136 (0, 4950)

Source: Adapted from Applicant Table 7.1.3.4-2 of the Integrated Summary of Efficacy

Medical Officer's Comments:
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.

Between the two trials, P903-06 had mean and median infection area greater than the mean and median area seen in Trial P903-07. However, the two trials were relatively well matched in terms of dimensions of length and width.

Overall, the two treatment groups for both P903-06 and P903-07 were relatively well matched with respect to underlying medical condition, baseline signs and symptoms, severity of disease, and size of lesion.

6.2.3. Subject Disposition

The table below shows the number of patients contained within each of the Applicant's analysis populations.

Table 33. Subject Populations Table

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

The following tables provide an accounting of the reasons for exclusion from the both the Clinical Evaluable (CE) and Microbiologically Evaluable (ME) populations.

Table 34. Subject Populations and Reasons for Exclusion from Study Populations, CE Population

Population	P903-06		P903-07		Pooled Data	
	Ceftaroline (n=353) n (%)	Vancomycin + Aztreonam (n=349) n (%)	Ceftaroline (n=348) n (%)	Vancomycin + Aztreonam (n=346) n (%)	Ceftaroline (n=701) n (%)	Vancomycin + Aztreonam (n=695) n (%)
Subjects in CE population	316 (89.5)	300 (86.0)	294 (84.5)	292 (84.4)	610 (87.0)	592 (85.2)
Subjects excluded from CE	37 (10.5)	49 (14.0)	54 (15.5)	54 (15.6)	91 (13.0)	103 (14.8)
Reasons for Exclusion						
Not in MITT	2 (0.6)	2 (0.6)	6 (1.7)	8 (2.3)	8 (1.1)	10 (1.4)
Not in cMITT	8 (2.3)	5 (1.4)	7 (2.0)	9 (2.6)	15 (2.1)	14 (2.0)
Exclusion Criteria Violation	6 (1.7)	5 (1.4)	6 (1.7)	6 (1.7)	12 (1.7)	11 (1.6)
Inclusion Criteria Violation	6 (1.7)	3 (0.9)	1 (0.3)	1 (0.3)	7 (1.0)	4 (0.6)
Received Both Study Drugs	2 (0.6)	0	2 (0.6)	0	4 (0.6)	0
Study Personal Unblinded	1 (0.3)	1 (0.3)	9 (2.6)	9 (2.6)	10 (1.4)	10 (1.4)
Received >1 Dose of a Potentially Effective Antibiotic not for Treatment Failure	2 (0.6)	6 (1.7)	0	6 (1.7)	2 (0.3)	12 (1.7)

<80% or >120% Compliance	0	0	1 (0.3)	0	1 (0.1)	0
Indeterminate at TOC and not Failure at EOT	20 (5.7)	31 (8.9)	32 (9.2)	29 (8.4)	52 (7.4)	60 (8.6)
TOC >7 Days or >20 Days after EOT and not Failure at EOT	5 (1.4)	3 (0.9)	3 (0.9)	5 (1.4)	8 (1.1)	8 (1.2)
Received Incorrect Drug	0	0	1 (0.3)	0	1 (0.1)	0
<48 Hours of Therapy, a Failure not Due to Treatment Limited AE	0	0	0	0	0	0
<96 Hours of Therapy for a Success	0	0	1 (0.3)	0	1 (0.1)	0
Received Prior Antibiotics and cannot Verify Enrolled as Failure	0	1(0.3)	1 (0.3)	0	1 (0.1)	1 (0.1)

Source: Adapted from Applicant Table 7.1.1-3 from the Integrated Summary of Efficacy-ABSSSI

Medical Officer's Comments:
The major reason for exclusion from the CE population from both trials was that the patient's clinical assessment at TOC was indeterminate and the patient was not assessed as treatment failure at EOT. Between treatment groups in both Trial P903-06 and Trial P903-07, there is a difference in the number of patients excluded for the reason of having an indeterminate clinical assessment at TOC and not assessed as treatment failure at EOT. For Trial P903-06, the ceftaroline group had 5.7% of patients excluded for this reason as opposed to the comparator group's rate of 8.9%. However, in Trial P903-07, the comparator group's rate of exclusion for this reason was slight lower (8.4%) as compared to the ceftaroline group's rate (9.2%). Overall, the pooled data shows that the two treatment groups' rates were relatively closely matched (7.4% versus 8.6%)

According to the Applicant, for the 112 patients assessed as indeterminate at TOC in Table 34, the primary reason for both trials was "lost to follow up" accounting for approximately 61% of this group. Other reasons for being assessed as" indeterminate" were deemed as "extenuating circumstances" which accounted for approximately 36-38% in this group of 20 patients. Extenuating circumstances included withdrawal of consent, diagnosis of osteomyelitis 7 or fewer days following randomization, and antibacterial treatment change before completing at least 48 hours of study drug therapy.

Overall, reasons for exclusion from the CE population were well matched within treatment arms of each trial and between trials.

Table 35. Subject Populations and Reasons for Exclusion from Study Populations, ME Population

	P903-06	P903-07	Pooled Data

Population	Ceftaroline (n=353) n (%)	Vancomycin + Aztreonam (n=349) n (%)	Ceftaroline (n=348) n (%)	Vancomycin + Aztreonam (n=346) n (%)	Ceftaroline (n=701) n (%)	Vancomycin + Aztreonam (n=695) n (%)
Subjects in ME population	244 (69.1)	227 (65.0)	224 (64.4)	219 (63.3)	468 (66.8)	466 (64.2)
Subjects excluded from ME	109 (30.9)	122 (35.0)	124 (35.6)	127 (36.7)	233 (33.2)	249 (35.8)
Reasons for Exclusion						
Not in CE	37 (10.5)	49 (14.0)	54 (15.5)	54 (15.6)	91 (13.0)	103 (14.8)
Not in mMITT	82 (23.3)	86 (24.6)	79 (22.7)	87 (25.1)	161 (23.0)	173 (24.9)
Pathogen Identified but Not Tested for Susceptibility	1 (0.3)	2 (0.6)	5 (1.4)	4 (1.2)	6 (0.9)	6 (0.9)
Monomicrobial Infection of anaerobe or *Pseudomonas aeruginosa*	4 (1.1)	3 (0.9)	6 (1.7)	5 (1.4)	10 (1.4)	8 (1.2)

Source: Adapted from Applicant Table 7.1.1-3 from the Integrated Summary of Efficacy-ABSSSI

Medical Officer's Comments:
The majority of the patients excluded from the ME population were those patients who were not included in the mMITT (no pathogen at baseline). The second most common reason for exclusion from the ME population were non-inclusion in the CE population. Overall, reasons for exclusion from the ME population were well matched within treatment arms of each trial and between trials.

The following tables summarize the premature discontinuations from the study drug and withdrawals from the trials for the MITT populations.

Table 36. Premature Discontinuation from Study Drug, , MITT Population

Population	P903-06		P903-07		Pooled Data	
	Ceftaroline (n=351) n (%)	Vancomycin + Aztreonam (n=347) n (%)	Ceftaroline (n=342) n (%)	Vancomycin + Aztreonam (n=338) n (%)	Ceftaroline (n=693) n (%)	Vancomycin + Aztreonam (n=685) n (%)
Completed Study Drug	325 (92.6)	315 (90.8)	316 (92.4)	304 (89.9)	641 (92.5)	619 (90.4)
Prematurely Discontinued	26 (7.4)	32 (9.2)	26 (7.6)	34 (10.1)	52 (7.5)	66 (9.6)
Reasons for Premature Discontinuation of Study Drug						
Adverse Event	13 (3.7)	15 (4.3)	7 (2.0)	17 (5.0)	20 (2.9)	32 (4.7)
Insufficient Therapeutic Effect	3 (0.9)	5 (1.4)	9 (2.6)	9 (2.7)	12 (1.7)	14 (2.0)
Clinical worsening, lack of progress	0	3 (0.9)	4 (1.2)	8 (2.4)	4 (0.6)	11 (1.6)
Significant surgical Intervention	2 (0.6)	0	4 (1.2)	8 (2.4)	4 (0.6)	11 (1.6)

Due to Resistant Pathogen	1 (0.3)	2 (0.6)	3 (0.9)	0	4 (0.6)	2 (0.3)
Withdrew Consent	1 (0.3)	2 (0.6)	3 (0.9)	0	4 (0.6)	2 (0.3)
Lost to Follow Up	5 (1.4)	7 (2.0)	4 (1.2)	2 (0.6)	9 (1.3)	9 (1.3)
Other	4 (1.1)	5 (1.4)	5 (1.5)	5 (1.5)	9 (1.3)	10 (1.5)

Source: Adapted from Applicant Table 7.1.2.2.1-1 from the Integrated Summary of Efficacy-ABSSSI

Medical Officer's Comments:
More than 90% of patients in each treatment group completed their designated study drug. The most common reasons for premature discontinuation were adverse events, insufficient therapeutic effect and loss to follow up.

The percentage of patients who prematurely discontinued the study medication due to AEs was lower in the ceftaroline group compared to the comparator group overall. This difference was greater in Trial P903-06 than in the Trial P903-07. Otherwise, the frequencies and reasons for premature discontinuation were relatively matched overall between the two trials.

Table 37. Withdrawal From Study, Studies P903-06 and P903-07, MITT Population

Population	P903-06		P903-07		Pooled Data	
	Ceftaroline (n=351) n (%)	Vancomycin + Aztreonam (n=347) n (%)	Ceftaroline (n=342) n (%)	Vancomycin + Aztreonam (n=338) n (%)	Ceftaroline (n=693) n (%)	Vancomycin + Aztreonam (n=685) n (%)
Completed Study	329 (93.7)	317 (91.4)	316 (92.4)	313 (92.6)	645 (93.1)	630 (92.0)
Withdrew from Study	22 (6.3)	30 (8.6)	26 (7.6)	25 (7.4)	48 (6.9)	55 (8.0)
Reasons for Withdrawal from Trial						
Noncompliance with regimen	1 (0.3)	2 (0.6)	0	1 (0.3)	1 (0.1)	3 (0.4)
Withdrew Consent	3 (0.9)	4 (1.2)	10 (2.9)	8 (2.4)	13 (1.9)	12 (1.8)
At Request of Subject, Investigator or Applicant	0	2 (0.6)	1 (0.3)	0	1 (0.1)	2 (0.3)
Lost to Follow Up	15 (4.3)	19 (5.5)	14 (4.1)	11 (3.3)	29 (4.2)	30 (4.4)
Death	3 (0.9)	0	0	0	3 (0.4)	0
Adverse Event	0	0	0	1 (0.3)	0	1 (0.1)
Other	0	3 (0.9)	1 (0.3)	4 (1.2)	1 (0.1)	7 (1.0)

Source: Adapted from Applicant Table 7.1.2.2.2-1 from the Integrated Summary of Efficacy-ABSSSI

Medical Officer's Comments:
More than 90% of patients in each treatment group completed the trials. The most common reason for not completing the trial was loss to follow up. The frequencies and reasons for premature withdrawal from the trial were relatively well matched overall, within each individual trial, and between trials.

6.2.4 Analysis of Primary Endpoints

The primary objective was to determine the non-inferiority of ceftaroline fosamil treatment compared to vancomycin + aztreonam treatment in adult patients 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.

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%. Table 38 shows the results of these analyses in trials P903-06 and P903-07.

Table 38. Applicant Primary Analysis: Clinical Cure Rates at TOC (MITT and CE)

	P903-06			P903-07		
Analysis Population	**Ceftaroline** n/N (%)	**Vancomycin + Aztreonam** n/N (%)	**Difference (95% CI)**	**Ceftaroline** n/N (%)	**Vancomycin + Aztreonam** n/N (%)	**Difference (95% CI)**
MITT	304/351 (86.6)	297/347 (85.6)	1.0 (-4.2, 6.2)	271/294 (92.2)	269/292 (92.1)	0.1 (-4.4, 4.5)
CE	288/316 (91.1)	297/347 (93.3)	-2.2 (-6.6, 2.1)	291/342 (85.1)	208/219 (85.5)	-0.4 (-5.8, 5.0)

Source: Partially Adapted from Applicant Table 7.7.2.2.1-1 from the Integrated Summary of Efficacy-ABSSSI

Medical Officer's Comments:
Cure rates for ceftaroline and the comparator were relatively well matched for each trial. In P903-06, the cure rate for ceftaroline was approximately 86.6% as compared to the comparator cure rate of 85.6%. In P903-07, the cure rate for ceftaroline was 92.2% and approximately equal to that of the comparator rate at 92.1%. Based on these data, ceftaroline demonstrated non-inferiority to the comparator, vancomycin plus aztreonam as evidenced by the lower limit of the 95% CI around the difference in cure rates being greater than the pre-specified NI boundary of -10 thus demonstrating the non-inferiority of ceftaroline relative to vancomycin plus aztreonam.

6.2.5 Analysis of Secondary Endpoints

To further evaluate the efficacy of ceftaroline a number of secondary endpoints were analyzed. These secondary endpoints included: clinical response at EOT in the MITT and CE populations, clinical response at TOC in the mMITT and ME population, and clinical response by pathogen at TOC. The following table shows clinical cure rates at the EOT.

Table 39. Applicant's Secondary Analysis Clinical Cure Rates at EOT, MITT and CE Populations

	P903-06			P903-07		
Analysis Population	**Ceftaroline** n/N (%)	**Vancomycin + Aztreonam** n/N (%)	**Ceftaroline - Vancomycin + Aztreonam (95% CI)**	**Ceftaroline** n/N (%)	**Vancomycin + Aztreonam** n/N (%)	**Ceftaroline - Vancomycin + Aztreonam (95% CI)**
MITT	322/351 (91.7)	313/347 (90.2)	1.5 (-2.8, 5.9)	304/342 (88.9)	302/338 (89.3)	-0.5 (-5.2, 4.3)
CE	298/316 (94.3)	282/300 (94.0)	0.3 (-3.5, 4.2)	274/294 (93.2)	271/292 (92.8)	0.4 (-3.9, 4)

Source: Adapted from Applicant Table 7.2.3.2-1 from the Integrated Summary of Efficacy-ABSSSI

Medical Officer's Comments:
In Trial P903-06, the clinical cure rates for ceftaroline were 91.7% and 94.3% for both the MITT and CE populations, respectively at the earlier time point, EOT, and were comparable to the cure rates of 90.2% and 94.0% for both the MITT and CE populations, respectively, seen for the comparator.

In Trial P903-07, for the MITT population the clinical cure rate at EOT was slightly lower than that of that of the comparator (88.9% vs. 89.3%). Cure rates in the CE population were slightly higher than those in the MITT population and in the CE population the cure rate was slightly higher with ceftaroline than with the comparator (93.2% vs. 92.8%). The lower bound of the 95% CI was greater than -10 for each population in both trials satisfying the non-inferiority margin pre-specified for the primary endpoint. Overall, this data helps to support the efficacy of ceftaroline at an earlier endpoint.

The following table shows the clinical response at TOC of the mMITT and ME populations. These populations are based on patients having a pathogen isolated from baseline microbiological culture and satisfying clinical requirements.

Table 40. Applicant's Secondary Analysis: Clinical Cure Rates at TOC, mMITT and ME Populations

Analysis Population	P903-06			P903-07		
	Ceftaroline n/N (%)	**Vancomycin + Aztreonam** n/N (%)	**Ceftaroline - Vancomycin + Aztreonam (95% CI)**	**Ceftaroline** n/N (%)	**Vancomycin + Aztreonam** n/N (%)	**Ceftaroline - Vancomycin + Aztreonam (95% CI)**

mMITT	235/271 (86.7)	226/263 (85.9)	0.8 (-5.1, 6.7)	234/269 (87.0)	227/259 (87.6)	-0.7 (-6.4, 5.1)
ME	225/224 (92.2)	215/227 (94.7)	-2.5 (-7.2, 2.1)	209/224 (93.3)	206/219 (94.1)	-0.8 (-5.5, 4.0)

Source: Adapted from Applicant Table 7.2.3.3-1 from the Integrated Summary of Efficacy-ABSSSI

Medical Officer's Comments: Except for the mMITT population in the P903-06 trial, the clinical cure rates for ceftaroline were slightly lower than the cure rates seen for the comparator in the mMITT and ME populations at TOC. However, for all populations in both trials the lower bound of the 95% CI was still greater than -10, thus demonstrating non-inferiority of ceftaroline to vancomycin plus aztreonam.

The following table shows clinical response rate by pathogen for the bacterial isolates from appropriate baseline microbiological specimens (infection site or blood culture) in the mMITT and ME populations.

Table 41. Clinical Cure Rates at TOC by Baseline Pathogen from the Primary Infection Site or Blood

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

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

Medical Officer's Comments:
For methicillin-sensitive S. aureus *(MSSA), in both the mMITT and ME populations, the clinical response rate by-pathogen was similar when comparing treatment groups and when comparing both trials.*
For methicillin-resistant S. aureus *(MRSA), in ME populations, the clinical response rate was similar when comparing treatment groups and when comparing both trials. However, for the mMITT population, the cure rate for the vancomycin plus aztreonam group (77.5%) was lower as compared to the ceftaroline group (88.2%) in Trial P903-06. These rates were more comparable in Trial P903-07 where the rate for the comparator was 87.3% and for ceftaroline was 84.9%.*

For S. pyogenes*, in the mMITT population, the cure rates in Trial P903-06 were comparable but were slightly lower for the ceftaroline group (84.2%) as compared to the comparator group rates of 84.2% and 89.3%, respectively, in Trial P903-07. In addition, the cure rates for both treatment groups were lower than those rates seen in Trial P903-06. In the ME populations, the cure rates were equal in the P903-06 trial showing a 100% clinical cure rate. In P903-07, ceftaroline again had a 100% cure rate but vancomycin plus aztreonam had a lower cure rate of 92.3%.*

For S. agalactiae*, in the mMITT population, the cure rates were more variable although this is likely due to the lower number of patients. In P903-06, the comparator had a higher cure rate of 93.3% as compared to ceftaroline's rate of 88.2%. However, in P903-07, ceftaroline had the higher cure rate of 100% as compared to the comparator's rate of 85.7% In the ME population, again in Trial P903-06, ceftaroline had a cure rate lower than that of vancomycin plus aztreonam (93.8% versus 100%). However, in Trial P903-07 the two treatments had equal cure rates of 100%.*

For other beta-hemolytic streptococci and Gram-negative bacteria, the number of isolates was too small to make any meaningful conclusions regarding comparative activity of treatments.

6.2.6 Other Endpoints

The Applicant evaluated several other exploratory efficacy endpoints including superinfection or colonization at EOT and TOC, decreased susceptibility, and other sensitivity analyses. Because these analyses were overall not significantly pertinent to the FDA review, they will not be discussed in detail. Section 6.1.10 will discuss further sensitivity analyses conducted by the FDA and Applicant that are more pertinent to current thinking on the evaluation of efficacy in the treatment of ABSSSI at an earlier time point.

6.2.7 Subgroups

To explore the homogeneity of ceftaroline efficacy, treatment group differences were examined for a variety of subgroups defined by baseline characteristics. Because the baseline characteristics of the population are similar, the results from each trial were pooled.

The following table shows clinical cure rates at TOC by demographic baseline characteristics from the pooled populations.

Table 42. Clinical Cure Rates at TOC by Demographics and Baseline Characteristics, CE Population

Demographic or Baseline Parameters		Pooled Phase Trials (P903-06 & P903-07)	
		Ceftaroline (N=610)	Vancomycin plus Aztreonam (N=592)
Age Group-I			
<65	n/N (%)	461/499 (92.4)	438/474 (92.4)
	Crude Difference (95% CI)	0.0 (-3.4,3.4)	
	Weighted Difference (95% CI)	-0.1 (-3.5,3.4)	
≥ 65	n/N (%)	98/111 (88.3)	111/118 (94.1)
	Crude Difference (95% CI)	-5.8 (-13.8,1.7)	
	Weighted Difference (95% CI)	-6.3 9-14.5,1.1)	
Age Group-II			
<75	n/N (%)	517/562 (92.0)	509/547 (93.1)
	Crude Difference (95% CI)	-1.1 (-4.2,2.1)	
	Weighted Difference (95% CI)	-1.1 (-4.2,2.1)	
≥ 75	n/N (%)	42/48 (87.5)	40/45 (88.9)
	Crude Difference (95% CI)	-1.4 (-15.5,12.9)	
	Weighted Difference (95% CI)	-1.9 (-16.2,12.3)	
Sex			
Male	n/N (%)	366/395 (92.7)	337/363 (92.8)
	Crude Difference (95% CI)	-0.2 (-3.9,3.6)	
	Weighted Difference (95% CI)	-0.2 (-3.9,3.7)	
Female	n/N (%)	193/215 (89.8)	212/229 (92.6)
	Crude Difference (95% CI)	-2.8 (-8.4,2.5)	
	Weighted Difference (95% CI)	-2.8 (-8.4,2.5)	
Ethnicity			
Hispanic	n/N (%)	107/123 (87.0)	99/111 (89.2)
	Crude Difference (95% CI)	-2.2 (-10.7, 6.5)	
	Weighted Difference (95% CI)	-2.4 (-11.0,6.2)	
Non-Hispanic	n/N (%)	452/487 (92.8)	450/481 (93.6)
	Crude Difference (95% CI)	-0.7 (-4.0, 2.5)	
	Weighted Difference (95% CI)	-0.7 (-4.0, 2.5)	
Race			
White	n/N (%)	419/457 (91.7)	431/458 (94.1)
	Crude Difference (95% CI)	-2.4 (-5.9, 0.9)	
	Weighted Difference (95% CI)	-2.4 (-5.8,1.0)	
Black or African-	n/N (%)	35/36 (97.2)	21/26 (80.8)
	Crude Difference (95% CI)	16.5 (1.6, 35.7)	

Demographic or Baseline Parameters		Pooled Phase Trials (P903-06 & P903-07)	
		Ceftaroline (N=610)	Vancomycin plus Aztreonam (N=592)
American	Weighted Difference (95% CI)	16.3 (0.9, 35.8)	
Asian	n/N (%)	6/6 (100.0)	4/4 (100.0)
	Crude Difference (95% CI)	0.0	
	Weighted Difference (95% CI)		
Other	n/N (%)	5/6 (83.3)	5/6 (83.3)
	Crude Difference (95% CI)	0.0	
	Weighted Difference (95% CI)		
Unknown	n/N (%)	88/99 (88.9)	83/93 (89.2)
	Crude Difference (95% CI)	-0.4 (-9.6,9.0)	
	Weighted Difference (95% CI)	-0.9 (-10.1,8.5)	

Source: Adapted from Applicant Table 7.2.5.2-1 from the Integrated Summary of Efficacy-ABSSSI

Medical Officer's Comments:
Overall the pooled population showed relatively comparable clinical cure rates between the two treatment groups when evaluated by age, sex, ethnicity and race. There was a difference seen in Black or African American patients, however the number of patients in this group was relatively small.

In addition, within each treatment group, there were no significant differences within a given demographic or baseline characteristic.

The next table displays the clinical cure rates at TOC by baseline signs and symptoms associated with ABSSSIs and baseline clinical features such as prior antibiotic use at baseline for the pooled population.

Table 43. Clinical Cure Rates at TOC by Markers of ABSSSI at Baseline, CE Population

Marker		Pooled Phase 3 Trials (P903-06 & P903-07)	
		Ceftaroline (N=610)	Vancomycin plus Aztreonam (N=592)
Systemic Signs			
Subjects with at least One Systemic Sign	n/N (%)	308/338 (91.1)	294/314 (93.6)
	Crude Difference (95% CI)	-2.5 (-6.7,1.7)	
	Weighted Difference (95% CI)	-2.5 (-6.7,1.7)	
Subjects with No Systemic Signs	n/N (%)	251/272 (92.3)	255/278 (91.7)
	Crude Difference (95% CI)	0.6 (-4.1,5.2)	
	Weighted Difference (95% CI)	0.6 (-4.1,5.3)	

Fever			
No (Temp ≤ 38 C)	n/N (%)	381/417 (91.4)	373/409 (91.2)
	Crude Difference (95% CI)	0.2 (-3.7,4.1)	
	Weighted Difference (95% CI)	0.2 (-3.7,4.1)	
Yes (Temp >38 C)	n/N (%)	178/192 (92.7)	176/183 (96.2)
	Crude Difference (95% CI)	-3.5 (-8.5,1.3)	
	Weighted Difference (95% CI)	-3.5 (-8.6,1.2)	
Elevated WBC			
No	n/N (%)	304/326 (93.3)	294/319 (92.2)
	Crude Difference (95% CI)	1.1 (-3.0,5.3)	
	Weighted Difference (95% CI)	1.1 (-3.0,5.3)	
Yes	n/N (%)	192/217 (89.4)	196/212 (92.5)
	Crude Difference (95% CI)	-3.1 (-8.7,2.5)	
	Weighted Difference (95% CI)	-3.1 (-8.7,2.5)	
Presence of Abscess			
No	n/N (%)	372/405 (91.9)	370/402 (92.0)
	Crude Difference (95% CI)	-0.2 (-4.0,3.7)	
	Weighted Difference (95% CI)	-0.2 (-4.0,3.6)	
Yes	n/N (%)	187/205 (91.2)	179/190 (94.2)
	Crude Difference (95% CI)	-3.0 (-8.4,2.3)	
	Weighted Difference (95% CI)	-3.0 (-8.4,2.3)	
At Least One Dimension >5cm	n/N (%)	164/180 (91.1)	160/169 (94.7)
	Crude Difference (95% CI)	-3.6 (-9.3,2.0)	
	Weighted Difference (95% CI)	-3.5 (-8.4, 2.3)	
No Dimension >5cm	n/N (%)	23/25 (92.0)	19/21 (90.5)
	Crude Difference (95% CI)	1.5 (-17.5,22.5)	
	Weighted Difference (95% CI)	1.5 (-17.8,22.7)	
Presence of Bacteremia			
No	n/N (%)	532/578 (92.0)	521/564 (92.4)
	Crude Difference (95% CI)	-0.3 (-3.5,2.8)	
	Weighted Difference (95% CI)	-0.3 (-3.5,2.8)	
Yes	n/N (%)	22/26 (84.6)	21/21 (100.0)
	Crude Difference (95% CI)	-15.4 (-33.8,1.5)	

	Weighted Difference (95% CI)		
Subjects Enrolled as Prior Treatment Failure			
No	n/N (%)	511/557 (91.7)	502/542 (92.6)
	Crude Difference (95% CI)	-0.9 (-4.1,2.3)	
	Weighted Difference (95% CI)	-0.9 (-4.1,2.4)	
Yes	n/N (%)	48/53 (90.6)	47/50 (94.0)
	Crude Difference (95% CI)	-3.4 (-15.3,8.2)	
	Weighted Difference (95% CI)	-2.5(-14.5,9.3)	
Previous Antibiotic Use			
No	n/N (%)	356/377 (94.4)	353/374 (94.4)
	Crude Difference (95% CI)	0.0 (-3.4,3.5)	
	Weighted Difference (95% CI)	0.0 (-3.4,3.4)	
Yes	n/N (%)	203/233 (87.1)	196/218 (89.9)
	Crude Difference (95% CI)	-2.8 (-8.8,3.2)	
	Weighted Difference (95% CI)	-2.8 (-8.8,3.2)	

Source: Adapted from Applicant Table 7.2.5.3-1 from the Integrated Summary of Efficacy-ABSSSI

Medical Officer's Comments:
Overall, in terms of baseline characteristics, signs and symptoms, the two treatment arms had similar rates of cure.

A difference was seen in the cure rates for patients with bacteremia; ceftaroline had lower cure rates as compared to vancomycin plus aztreonam (84.6% vs. 100.0%). As per the Applicant's report, of the four bacteremic patients who were clinical failures in the ceftaroline treatment group, two patients were failures due to treatment-limiting adverse events, one patient was deemed a treatment failure secondary to the need for surgical intervention, so three were failures not directly due to bacteremia. The last patient had a ceftaroline non-susceptible pathogen.

The following table shows clinical cure rates at TOC by type of infection and anatomical site of the primary infection for the pooled population.

Table 44. Clinical Cure Rates at TOC by Type of Infection and by Anatomical Site of Primary Infection, CE Population

	Pooled Phase Trials (P903-06 & P903-07)	
Marker	**Ceftaroline (N=610)**	**Vancomycin plus Aztreonam (N=592)**

Type of Infection			
Infected Wound	n/N (%)	73/84 (86.9)	65/73 (89.0)
	Crude Difference (95% CI)	-2.1 (-12.7,8.7)	
	Weighted Difference (95% CI)	-2.2 (-12.8,8.7)	
Abscess	n/N (%)	187/205 (91.2)	179/190 (94.2)
	Crude Difference (95% CI)	-3.0 (-8.4,2.3)	
	Weighted Difference (95% CI)	-3.0 (-8.4,2.3)	
Infected Ulcer	n/N (%)	48/53 (90.6)	47/50 (94.0)
	Crude Difference (95% CI)	-3.4 (-15.3,8.2)	
	Weighted Difference (95% CI)	-3.5 (-15.7,8.3)	
Infected Burn	n/N (%)	25/25 (100.0)	18/18 (100.0)
	Crude Difference (95% CI)	0.0 (-13.6,17.9)	
	Weighted Difference (95% CI)		
Cellulitis	n/N (%)	213/229 (93.0)	222/243 (91.4)
	Crude Difference (95% CI)	1.7 (-3.4, 6.7)	
	Weighted Difference (95% CI)	1.7 (-3.4, 6.7)	

Source: Adapted from Applicant Table 7.2.5.3-1 from the Integrated Summary of Efficacy-ABSSSI

Medical Officer's Comments:
Overall, the clinical cure rates were relatively well matched between the two treatment groups in terms of type of infections.

The next table shows clinical cure rates at TOC with respect to co-morbid conditions at baseline for the pooled population.

Table 45. Clinical Cure Rates at TOC by Baseline Co-morbid Conditions, CE Population

Condition		**Pooled Phase Trials (P903-06 & P903-07)**	
		Ceftaroline (N=610)	**Vancomycin plus Aztreonam (N=592)**
Diabetes Mellitus (DM)			
Subjects with DM	n/N (%)	96/110 (87.3)	100/110 (90.9)
	Crude Difference (95% CI)	-3.6 (-12.3, 4.9)	
	Weighted Difference (95% CI)	-3.5 (-12.2,5.0)	
Subjects without DM	n/N (%)	463/500 (92.6)	449/482 (93.2)
	Crude Difference (95% CI)	-0.6 (-3.8,2.7)	

	Weighted Difference (95% CI)	-0.5 (-3.8,2.8)	
Peripheral Vascular Disease (PVD)			
Subjects with PVD	n/N (%)	80/90 (88.9)	75/84 (89.3)
	Crude Difference (95% CI)	-0.4 (-10.1,9.5)	
	Weighted Difference (95% CI)	-0.2 (-10.0,9.7)	
Subjects without PVD	n/N (%)	479/520 (92.1)	474/508 (93.3)
	Crude Difference (95% CI)	-1.2 (-4.4,2.0)	
	Weighted Difference (95% CI)	-1.2 (-4.4,2.1)	
Creatinine Clearance (mL/min)			
>80	n/N (%)	458/496 (92.3)	442/476 (92.9)
	Crude Difference (95% CI)	-0.5 (-3.9,2.8)	
	Weighted Difference (95% CI)	-0.5 (-3.9,2.8)	
>50 and ≤ 80	n/N (%)	83/92 (90.2)	85/90 (94.4)
	Crude Difference (95% CI)	-4.2 (-12.8,3.9)	
	Weighted Difference (95% CI)	-4.0 (-12.6,4.1)	
>30 and ≤ 50	n/N (%)	17/20 (85.0)	20/24 (83.3)
	Crude Difference (95% CI)	1.7 (-22.6,24.3)	
	Weighted Difference (95% CI)		
≤ 30	n/N (%)	1/2 (50.0)	2/2 (100.0)
	Crude Difference (95% CI)	-50.0	
	Weighted Difference (95% CI)		

Source: Adapted from Applicant Table 7.2.5.5-1 from the Integrated Summary of Efficacy-ABSSSI

Medical Officer's Comments:
Overall, the treatment groups' clinical cure rates were relatively well matched between the two treatment groups in terms of type of co-morbid conditions and there does not appear to be any condition that shows inconsistency of treatment effect for ceftaroline. In general, higher cure rates were seen in both treatment groups in patient without a history of diabetes mellitus or peripheral vascular disease.

The Applicant also analyzed patients having surgical procedures performed on the primary infection site during the trial. They defined "relevant" surgical procedures as any procedure that occurred during the (as opposed to relevant surgical history) that may have affected the outcome of the primary infection. Surgical relevance was determined for all procedures recorded before TOC or until an outcome of clinical failure was recorded. Relevant surgical procedures included procedures such as amputation,

debridement, fasciotomy and incision and drainage. This final table shows the clinical cure rates at TOC of patients in the CE population having surgical procedures.

Table 46. Clinical Cure Rates at TOC of Subjects Having Surgical Procedures, CE Population

Surgical Procedure (SP)		Pooled Phase 3 Trials (P903-06 & P903-07)	
		Ceftaroline (N=610)	Vancomycin plus Aztreonam (N=592)
Subjects with No Relevant SP During Trial	n/N (%)	457/498 (91.8)	448/484 (92.6)
	Crude Difference (95% CI)	-0.8 (-4.2,2.6)	
	Weighted Difference (95% CI)	-0.8 (-4.2,2.6)	
Subjects with Any Relevant SP	n/N (%)	102/112 (91.1)	101/108 (93.5)
	Crude Difference (95% CI)	-2.4 (-10.1,5.0)	
	Weighted Difference (95% CI)	-2.4 (-10.1,5.1)	
Subjects with Any Relevant SP ≤ 48 Hrs Post Enrollment	n/N (%)	68/71 (95.8)	75/79 (94.9)
	Crude Difference (95% CI)	0.8 (-7.3,8.7)	
	Weighted Difference (95% CI)	1.2 (-6.9,9.4)	
Subjects with Any Relevant SP > 48 Hrs Post Enrollment	n/N (%)	35/43 (81.4)	28/32 (87.5)
	Crude Difference (95% CI)	-6.1 (-22.7,12.1)	
	Weighted Difference (95% CI)	-6.3 (-22.9,12.0)	

Source: Adapted from Applicant Table 7.2.5.6-1 from the Integrated Summary of Efficacy-ABSSSI

Medical Officer's Comments:
It is unclear why patients who received a relevant surgical procedure post enrollment were not deemed clinical failures in this analysis. Any patient who received procedures such as non-bedside incision and drainage, debridement, amputation or fasciotomy should have been considered to be clinical failures.

However, in considering this analysis performed by the Applicant, the clinical cure rates at TOC were well relatively well matched when comparing the two treatment groups. There was a drop-off in cure rates for the ceftaroline-treated group for patients with any relevant surgical procedure greater than 48 hours post-enrollment,, however the number of patients is small. Overall, ceftaroline maintained its treatment effect regardless of whether or not a patient received any surgical procedure any relevant surgical procedure as defined by the Applicant.

Clinical response at TOC was examined by the Applicant in a variety of subgroups. Based on the results submitted, overall ceftaroline has demonstrated consistency and homogeneity of treatment effect across regions, demographic and baseline

characteristics, clinical markers, infection types, baseline co-morbid conditions, and surgical procedures. Any observed treatment difference in cure rates was likely due to the smaller number of patients in that individual subgroup, however generally the treatment differences were also greater than -10%.

6.2.8 Analysis of Clinical Information Relevant to Dosing Recommendations

As previously discussed, the recommended dose of ceftaroline for adult patients with normal renal function or mild renal impairment is 600 mg of ceftaroline administered intravenously every 12 hours as a one hour infusion. As per the Applicant, the duration of therapy should be guided by the severity and site of infection and the patient's clinical and microbiological progress. Doses above 600 mg every 12 hours have not been studied in Phase 3 controlled clinical trials.

Based primarily on the clinical experience from Phase 1 clinical pharmacology studies, controlled Phase 3 efficacy trials in ABSSSI, and population pharmacokinetic (PK) and pharmacokinetics/pharmacodynamics (PK/PD) modeling, the Applicant has recommended modified dosing regimens for varying degrees of renal impairment, including end-stage renal disease (ESRD) requiring intermittent hemodialysis (HD). The following table summarizes the PK results following a single 1-hour IV infusion of ceftaroline fosamil 600 mg or 400 mg in various renal function cohorts.

Table 47. Summary of Phase 1 Renal Impairment Studies for Ceftaroline fosamil

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

The Applicant's proposed regimens based on renal function are summarized in the following table:

Table 48. Applicant's Proposed Dose Adjustments for Renal Impairment

(b) (4)

(b) (4)

No formal individual dose-response clinical studies or blood level-response relationship studies were performed. However, the dose rationale for ceftaroline in the Phase 3 ABSSSI trials was based on data from in vitro microbiological studies, in vivo animal infection models, population PK analyses from Phase 1 and Phase 2 human studies/trials including patients with mild and moderate renal impairment and Monte Carlo simulations for predicting the appropriate percent of time during the dosing interval that ceftaroline free drug plasma concentrations exceed MIC values for the target pathogens of interest.

Medical Officer's Comments:
Although no formal individual dose-response clinical trials or blood level-response relationship trials were performed, the Applicant has presented adequate data for their overall dosing rationale.

In addition, please see Dr. Aryun Kim's Clinical Pharmacology Review for further discussioin on the justification for renal dosing for patients with moderate and severe renal impairment. Dr Kim's recommendations for regimens for ceftaroline are represented in the table below:

Table 49. FDA Proposed Regimens of Ceftaroline Fosamil Based on Renal Function

Renal Function	CrCL (mL/min)	Ceftaroline Fosamil Regimen
Normal	>80	600 mg Q12h (1-h IV infusion)
Mild	>50 to ≤80	
Moderate	>30 to ≤50	300 mg Q12h (1-h IV infusion)
Severe	≥10 to 30	
ESRD	(on HD)	200 mg Q12h (1-h IV infusion)

6.2.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Late Follow-Up (LFU) visits were conducted 21-45 days after the last dose of the study drug to evaluate the evidence for sustained clinical response (cure) or relapse of symptoms (failure).

Analyses of at LFU were performed for the Phase 3 trials including evaluation for sustained clinical response and clinical relapse in the CE population and by-patient re-infection or recurrence in the ME population. The following table summarizes those results.

Table 50. Clinical Relapse at LFU, Trials P903-06 and P903-7, CE Population

Clinical Relapse	P903-06		P903-07		Pooled Data	
	Ceftaroline n (%)	Vancomycin + Aztreonam	Ceftaroline n (%)	Vancomycin + Aztreonam	Ceftaroline n (%)	Vancomycin + Aztreonam

		n (%)		n (%)		n (%)
Subjects with a Clinical Cure at TOC						
N	288	280	271	269	559	549
Relapse	3 (1.0)	3 (1.1)	3 (1.1)	2 (0.7)	6 (1.1)	5 (0.9)
Indeterminate	6 (2.1)	0	5 (1.8)	1 (0.4)	11 (2.0)	1 (0.2)
Crude Difference (95% CI)	-0.0 (-2.2, 2.1)		0.4 (-1.7, 2.6)		0.2	
Weighted Difference (95% CI)					0.2 (-1.2,1.5)	

Source: Adapted from Applicant Table 7.2.6.1-1 from the Integrated Summary of Efficacy-ABSSSI

Medical Officer's Comments:
Approximately 1% of patients with an assessment of clinical cure at TOC had a clinical relapse at LFU in both treatment groups. Of the 11 patients classified as indeterminate in the ceftaroline group, 8 did not have a LFU and 3 were assessed by the investigator to be "indeterminate" at LFU.

Microbiological re-infection or recurrence analyses were performed looking at all patients who had a favorable microbiological outcome (eradication and presumed eradication) at TOC including patients who did not return for LFU. The following table summarizes those results.

Table 51. By-Subject Microbiological Re-infection or Recurrence at LFU, ME Population

Clinical Relapse	P903-06		P903-07		Pooled Data	
	Ceftaroline n(%)	Vancomycin + Aztreonam n(%)	Ceftaroline n(%)	Vancomycin + Aztreonam n(%)	Ceftaroline n(%)	Vancomycin + Aztreonam n(%)
Subjects who Had a Favorable Outcome at TOC regardless if they had LFU						
N	224	210	208	208	432	418
Reinfection/ Recurrence	2 (0.9)	0	0	0	2 (0.5)	0
Sustained Eradication	215 (96.0)	210 (100.0)	200 (96.2)	202 (97.1)	415 (96.1)	412 (98.6)
Indeterminate	7 (3.1)	0	8 (3.8)	6 (2.9)	15 (3.5)	6 (1.4)

Source: Adapted from Applicant Table 7.2.6.2-1 from the Integrated Summary of Efficacy-ABSSSI

Medical Officer's Comments:
In terms of microbiological re-infection or recurrence at LFU, there were no re-infections or recurrences seen in either treatment group in P903-07. Two patients in the ceftaroline group experienced re-infection associated with clinical relapse in Trial P903-06. There were no relapses seen in the comparator group in Trial P903-06.

Overall, ceftaroline demonstrated persistence of efficacy with only approximately 1% clinical relapse rate and 0.5% re-infection or recurrence rate.

6.2.10 Additional Efficacy Issues/Analyses

Recent public discussions have focused on primary efficacy endpoint assessment at earlier timepoints, based on evidence from the historical literature which can be used to demonstrate antibacterial treatment effect in skin infections (Snodgrass and Anderson, 1937). The endpoints suggested by the literature for which an NI margin may be justified include time to cessation of spread of the lesion and defervescence in those with fever at baseline in patients with cellulitis and wound infections. Therefore, sensitivity analyses utilizing an endpoint(s) of cessation of spread assessed at earlier time point(s) were performed by the FDA review team. In addition, several secondary analyses were performed for comparison to the pre-specified secondary analyses conducted by the Applicant.

6.2.10.1. Sensitivity Analysis Population

For the FDA review sensitivity analyses, the primary analysis population, the FDA-Modified Intent-to-Treat (FDA-MITT) population. This population was defined as any randomized patient who received any amount of study treatment with a 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 peripheral vascular disease (PVD)
- nineteen patients with infection type “bite” that met size criteria, were not of human or animal origin, and were consistent with literature reports of MRSA infection

Medical Officer’s Comments:
The treatment effect of antibacterial therapies following primary incision and drainage has not been well defined and therefore for patients with abscesses to be included in the FDA-MITT population required that there be a significant cellulitis surrounding the abscess (i.e. surrounding erythema >5 cm) to be included in the FDA sensitivity analysis population.

The table below shows the relative size of the FDA-MITT population in relation to the Applicant’s pre-specified MITT and CE co-primary analysis populations.

Table 52. Subject Analysis Populations

	Trial P903-06			Trial P903-07		
Study Populations	Ceftaroline	Vancomycin + Aztreonam	Total	Ceftaroline	Vancomycin + aztreonam	Total
Applicant						
MITT	351 (99.4)	347 (99.4)	698 (99.4)	342 (98.3)	338 (97.7)	680 (98.0)
CE	316 (89.5)	300 (86.0)	616 (87.7)	294 (84.5)	292 (84.4)	586 (84.4)
FDA-MITT	**200 (56.7)**	**209 (59.9)**	**409 (58.3)**	**200 (57.5)**	**188 (54.3)**	**388 (55.9)**
Source: P903-06: CSR, Table 10.1-2., pg 106. P903-07: CSR, Table 10.1-2, pg 106.						

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

The table below shows the baseline characteristics of the FDA defined primary analysis population.

Table 53. Baseline Characteristics of the FDA-MITT Population

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

Medical Officer Comment:

The FDA-MITT population was predominately male with approximately 61.7 to 71.5% men in each treatment group and in each trial. The majority of patients were less than or equal to 65 years of age with approximately 11.7 to 17.2% of patients in each treatment group and each trial being greater than 65 years of age. Most patients in this population came from either Eastern Europe or the United States. There was a larger proportion of patients with diabetes and PVD in the comparator group (22.5% and 12.0%, respectively) in Trial P903-06 as compared to the ceftaroline group (14.5% and 9.5%, respectively) but they were relatively evenly matched in the P903-07 trial. Renal function was generally well matched between treatment groups and when compared across trials.

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

Table 54 shows the baseline infection characteristics in the FDA-MITT population.

Table 54. 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 ABSSSI, subject with diabetes or PVD	13 (6.5)	18 (8.6)	8 (4.0)	8 (4.3)
Infected bite	3 (1.5)	7 (3.3)	6 (3.0)	3 (1.6)

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

6.2.10.2 FDA Primary Sensitivity Analyses

The FDA primary sensitivity endpoint of clinical responder 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 at or on Day 3 and assessed by the investigator as a clinical failure, could not be classified as a clinical responder.

Table 55 below shows the results of this analysis along with a secondary analysis at EOT in the FDA-MITT population for Trial P903-06 and Trial P903-07.

Table 55. Clinical Responders at Day 3, FDA-MITT Population

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)

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. In Trial P903-07, the treatment effect also favored ceftaroline. The lower bound of the 95% CI for both analyses was >-4.

These findings supported the non-inferiority of ceftaroline to vancomycin + aztreonam for a NI margin of less than 4% for both trials.

The following table is provided to help compare and contrast with the investigator assessment at EOT using the FDA-MITT population where “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.

Table 56. Investigator Assessment, Clinical Cure Rates at EOT, FDA-MITT Population

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)

In this 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 with a 10% NI margin

based on the lower bound of the 95% CI for the treatment difference which was at or below -7.4% in both trials.

To further support these findings, related sensitivity analyses were examined in order to rule out the potential influence of investigator measurement error of lesions at Day 3. Other additional sensitivity analyses were also examined to confirm that treatment comparisons in clinical response would remain consistent across later time points such as at the end-of-therapy. Findings from these additional sensitivity analyses are provided in the two tables below.

Table 57. Responder Rates in FDA-MITT Subjects Varying the Required Percent 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)

In Table 57, for both Trial P903-06 and Trial P903-07, responder rates favored ceftaroline regardless of the percent reduction required in defining a responder. These findings show that key sensitivity analysis findings were robust in supporting the non-inferiority of ceftaroline to vancomycin + aztreonam at the Day 3 endpoint and that potential systematic measurement error in the measurement of lesion size was unlikely to affect findings of non-inferiority.

Table 58 considers a similar analysis at the EOT time point by varying the required % reduction in lesion size in defining a responder.

Requiring a larger percent reduction for responders would better ensure against responders who could have achieved cessation only through investigator error (i.e. overestimation) of lesion size.

Table 58. Sensitivity Analysis of Responder Rates in FDA-MITT Subjects Varying the Required Percent Reduction in Lesion Size at EOT from Baseline

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

This table suggests that differences between treatment groups in responder rates at the EOT time point were reduced in comparison to differences at Day 3. However, consistent with the Day 3 analysis, the EOT analysis still supported the non-inferiority of ceftaroline over comparator. Across both trials, treatment differences at EOT tended to be similar between treatment groups regardless of the % reduction of lesion size required for a responder.

Overall, these sensitivity analyses also provided insight into the amount of reduction in the size of the lesion (i.e. resolution) that could be used as an objective measure of response at EOT. This analysis indicates that in 72.0-77.5% of patients, there was a 75% reduction in lesion size at EOT determined by the investigator when a sufficient amount of resolution of the infection had occurred and antibacterial therapy was discontinued.

6.2.10.3 FDA Key Secondary Sensitivity Analyses

Key secondary outcomes in the FDA-MITT population included rates of absence of erythema, swelling and tenderness at EOT, absolute and percentage changes in lesion dimensions at Day 3 and EOT and clinical cure rates by pathogen at Day 3 and EOT for FDA-MITT patients included in the Applicant's ME and mMITT populations.

Table 59 shows absence rates of key signs and symptoms including erythema, swelling and tenderness at EOT.

Table 59. FDA Secondary Endpoints, Absence Rates of Key Signs and Symptoms at EOT, FDA-MITT Population

	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)

Rates for absence of erythema were similar between treatment groups across the 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 across trials. These findings were consistent with the key sensitivity analyses and further supported the non-inferiority of ceftaroline to vancomycin plus aztreonam.

Table 60 below show the by-pathogen clinical cure rates at Day 3 in the FDA microbiological-MITT (FDA mMITT).

Table 60. Responder Rates at Day 3 by Baseline Pathogen from the Primary Infection Site or Blood, FDA mMITT Population

	Trial 06		Trial 07	
Pathogen	**Ceftaroline** n/N (%)	**Vancomycin + Aztreonam** n/N (%)	**Ceftaroline** n/N (%)	**Vancomycin + Aztreonam** n/N (%)
Gram-positive bacteria				
S.aureus				
MRSA	34/45 (75.6)	30/41 (73.2)	50/57 (87.7)	35/43 (81.4)
MSSA	44/61 (72.1)	42/73 (57.5)	58/81 (71.6)	50/79 (63.3)
S. pyogenes	9/18 (50.0)	13/26 (50.0)	16/28 (57.1)	15/23 (65.2)
S. agalactiae	4/7 (57.1)	5/6 (83.3)	5/6 (83.3)	1/1 (100)
S. dysgalactiae	2/2 (100)	2/3 (66.7)	4/6 (66.7)	2/5 (40)
S. anginosus	4/4 (100)	0/2 (0)	2/2 (100)	4/4 (100)
S. anginosus group	6/6 (100)	2/5 (40)	2/4 (50)	4/5 (80)
Gram-negative 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)

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.

6.2.10.4 FDA Subgroup Sensitivity Analyses

Subgroup analyses were conducted to investigate the heterogeneity of treatment differences across patient groups meeting specific characteristics of interest for the FDA-MITT population.

Table 61 shows the clinical response rates at Day 3 by baseline infection type.

Table 61. Responder Rates at Day 3 by Infection Type, FDA-MITT Population

	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)
Infected Bite	3/3 (100)	5/7 (71.4)	5/6 (83.3)	1/3 (33.3)

Medical Officer's Comments:
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.

Table 62 shows the responder rates at Day 3 in patients who have or have not received antibacterial therapy in the 24 hours prior to study drug initiation. This issue is considered to be especially important when exploring the use of earlier endpoints which may be especially sensitive to prior antibiotic therapy

The effect is shown on both the primary measure (cessation of spread and absence of fever) as well as a sensitivity measure which includes the percent reduction in the size of the lesion.

Table 62. Responder Rates at Day 3 by Prior Systemic Antimicrobial Use for Any Reason within 24 hours of Study Drug Initiation, FDA-MITT Population

	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)

Medical Officer's Comments:
In patients with no prior use of antibiotics within the 24 hour period before study drug initiation, treatment differences favored ceftaroline over comparator, 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 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.

Due to limited numbers of patients included in the FDA-MITT population of each trial, integrated analyses were also explored for various subgroups of interest at Day 3 and EOT. However, statistical inferences are limited in these analyses due to trial differences and lack of randomization protection. Table 63 provides integrated analyses of responder rates of various subgroups across Trial P903-06 and Trial P903-07.

Medical Officer's Comments:
Based on integrated findings in Table 63, responder rates at Day 3 were substantially higher for the following subgroups: US and Latin America versus Eastern and Western Europe, patients with no fever versus fever at baseline and patients with major abscesses versus other infection types.

Treatment differences appeared to be generally similar across categories within most subgroups, but were observed to be less favorable towards ceftaroline for patients with diabetes compared to those without diabetes. The treatment differences between the ceftaroline and comparator groups were smaller in patients with prior antibiotics versus without prior antibiotics, and patients with major abscesses compared to other infection types. (Tables 61, 62, and 63)

This latter finding may help explain the smaller overall treatment difference favoring ceftaroline in Trial P903-07 versus Trial P903-06 since in Trial P903-07, in comparison to Trial P903-06, included substantially more patients with major abscesses than other infection types in the FDA-MITT analysis.

Table 63. Integrated Analyses of Responder Rates at Day 3 by Subgroup, FDA-MITT Population

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

[1] 95% CI computed using an Exact Test

6.2.10.5 Other Efficacy Issues

These 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 when the response was measured. Consideration 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 comparator. However, there are several limitations to the sensitivity analyses performed.

These clinical trials were designed to investigate the initial pre-specified endpoints and thus not designed to investigate the FDA sensitivity analysis endpoints. The case report forms were not designed to capture all data needed to make an assessment at the earlier timepoint at Day 3. Working retrospectively with the data captured from these case reports may have limited the ability to obtain an accurate account of information needed to perform these types of analyses.

Another example was the lack of a standardized approach to accurately measure lesion size which would be key in establishing the FDA analysis population and examining for accurate percent reduction. Precise measurement of lesion size was not as essential for the pre-specified endpoints.

Lastly, prior antimicrobial use and prior or concomitant antipyretic use may have confounded the findings of the sensitivity analysis using an earlier endpoint. If these types of medications were used closer to the start of a patient's illness and thus closer to time of enrollment, they may have confounded clinical findings seen at Day 3.

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

7 Review of Safety

Safety Summary

The data submitted in the Application support the safety of ceftaroline as treatment for the following indications: Acute Bacterial Skin and Skin Structure Infections (ABSSSI) and Community-Acquired Bacterial Pneumonia (CABP).

Prior to clinical trials, animal studies indicated that when given high exposures of ceftaroline, animals manifest toxicities of the central nervous system and the renal system similar to those experienced by animals given high doses of other cephalosporins.

The safety database of the Application consists of 1740 patients given ceftaroline from ten Clinical Pharmacology studies, two Phase 2 ABSSSI trials, two Phase 3 ABSSSI trials, and two Phase 3 CABP trials. Of these, 1441 received the proposed dose of ceftaroline (600 mg intravenously every 12 hours for 5 to 14 days). In the pooled Phase 3 trials, 95.3% (1239/1300) of the safety population received the proposed dose with 7 days as the median duration of ceftaroline therapy. The pooled safety population has had adequate exposure to ceftaroline to detect AEs expected to occur at a frequency of 1 in 500 in the general population.

Patients in the pooled Phase 3 safety population were predominantly male, white, non-Hispanic, with a mean body mass index (BMI) of 27 kg/m^2, a mean age of 54 years, and normal renal function. Demographic characteristics (e.g. age, gender, height, weight, BMI, ethnicity, race, and creatinine clearance [CrCl]) were similar between the ceftaroline- and comparator-treated groups. In particular, the elderly, overweight, and patients with mild and moderate renal impairment were well-represented in the safety population.

Safety monitoring was performed daily. Laboratory evaluation included hematology and chemistry profiles performed at baseline, Days 3, 4-14, 21, end-of-therapy (EOT), and test-of-cure (TOC); Coombs' test at baseline, EOT and TOC; urinalysis with microscopy at baseline, Day 3, EOT and TOC; and pregnancy test and CrCl at baseline. Treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and potentially clinically significant laboratory changes were monitored until the late follow-up (LFU) visit or 30 days after the end of therapy. All deaths were reported through the LFU visit or 30 days after EOT if there was no LFU visit. Additional deaths were also reported after the trial reporting period..

In both the ABSSSI Phase 3 trials, the incidence of TEAEs (44.7% [309/692] vs 47.5% [326/686]), SAEs (4.3% [30/692] vs 4.1% [28/686]), premature discontinuations because of TEAEs (3.0% [21/692] vs 4.8% [33/686]), and deaths (0.4% [3/692] vs 0) were similar between the ceftaroline-treated groups compared to the vancomycin plus aztreonam-treated group, respectively. For both CABP trials, the incidence of TEAEs (46.5% [283/608] vs 45.5% [278/611]), SAEs (11.0% [67/608] vs 11.7% [72/611]), premature discontinuations because of TEAEs (4.3% [26/608] vs 4.1% [25/611]), and deaths (2.4% [15/608] vs 2.0% [12/611]) were similar between the ceftaroline-treated groups compared to the ceftriaxone-treated group, respectively.

A total of 30 deaths were reported before the LFU visit, 18 (1.4%) of whom were treated with ceftaroline and 12 (0.9%) were treated with the comparators. After the LFU visit, 3 more deaths in the ceftaroline group and 6 more deaths in the comparator group were reported. One patient's sudden death from an unknown etiology may potentially be related to ceftaroline. One death caused by hepatic failure and subsequent multi-organ dysfunction syndrome was potentially related to ceftriaxone. Lastly, insufficient therapeutic effect by ceftaroline may have caused a patient to die of septic shock.

Overall, the incidence of death was low and similar between the two treatment groups. Deaths were from cardiac, respiratory, neoplastic, and infectious etiologies. It is therefore unlikely that ceftaroline use was associated with an increased risk of death.

The incidences of SAEs were low and similar between the two treatment groups. Most SAEs were categorized under the System Organ Class (SOC) Infections (pneumonia, pyothorax, and cellulitis), Respiratory Disorders (pulmonary embolism, pleural effusion, respiratory failure), and Cardiac disorders (cardiac failure congestive, cardiopulmonary failure). Most SAEs appeared to be either from complications of the primary indications of the trials or from chronic underlying comorbidities of the patients.

In the pooled Phase 3 clinical trials, the incidences of TEAEs that caused either premature discontinuation of the study medication or premature study withdrawal were low and similar between the ceftaroline and comparator-treated group (3.7% and 4.5%, respectively). Most TEAEs were classified under Skin and Subcutaneous Tissue Disorders (rash, rash generalized, rash maculopapular). Hypersensitivity was the most common TEAE reported causing study drug discontinuation or study withdrawal in the ceftaroline group.

The most frequently reported adverse drug reactions (ADRs) experienced by the ceftaroline-treated group in the Phase 3 trials for both indications were: diarrhea (5%), nausea (4%), rash (3%), and constipation, vomiting, increased transaminases, hypokalemia, and phlebitis (2%). ADRs reported in the pooled safety population were consistent with ADRs expected in the cephalosporin class of antibacterials.

Potentially clinically significant changes (PCS) in laboratory parameters such as hematology, coagulation, clinical chemistry, and urinalysis occurred infrequently and similarly between the two treatment groups in the pooled Phase 3 trial population. The only exception is the higher incidence of Coombs' test seroconversion in the ceftaroline group compared to the comparator group (10.7% vs 4.4%). Its clinical relevance is unknown since the incidence of anemia was low and similar between the two groups (1.2% and 1.3%) and no case of drug-induced hemolytic anemia was reported.

The incidence of AEs in organ systems relevant to the cephalosporin class of antibacterials were analyzed for the pooled Phase 3 population. TEAEs that represent potential renal impairment and PCS changes in renal chemistry values were infrequent but were reported at higher frequencies in the ceftaroline treated group compared to the comparator-treated group (1.5% vs 0.8%, respectively). Association between the renal events and ceftaroline was difficult to ascertain because of patients' confounding medical conditions and concomitant medications.

AEs that represent potential hepatic injury occurred infrequently and at similar rates between the two treatment groups. Allergic reactions (anaphylactic shock and hypersensitivity reactions) occurred infrequently but with lower frequency in the

ceftaroline-treated group than the comparator-treated group (5.4 % vs 8.5%, respectively). The incidence of antibiotic-associated diarrhea was similar in both groups (4.5% vs 3.2%, respectively), with 2 documented cases of Clostridium difficile colitis reported in the ceftaroline group compared to 1 case in the comparator-treated group. Lastly, three cases of seizures (two ceftaroline-treated and one ceftriaxone-treated patient) were assessed to be unrelated to the study medications.

In summary, clinical experience from the pooled safety population indicates that ceftaroline is safe when used to treat ABSSSI and CABP. Ceftaroline use was not associated with a higher risk of mortality. The similar incidence of allergic reactions, antibiotic-associated diarrhea, and ADRs such as diarrhea, nausea, and rash between ceftaroline- and comparator-treated groups further indicate a safety profile similar to existing cephalosporins.

However, the higher incidence of Coombs test seroconversion without a reported case of drug-induced hemolytic anemia and the rare but higher incidence of potential renal events in the ceftaroline group both warrant further monitoring in postmarketing safety reports to understand their relevance in clinical practice.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The clinical Safety Population consisted of all patients receiving any amount of study drug (ceftaroline fosamil or comparator). Patients were analyzed in the safety population with the treatment group corresponding to the study drug received for the majority of the dosing period. All AEs, premature discontinuations of study drug, withdrawals from study, concomitant medications received, laboratory results (including baseline and postbaseline chemistry, hematology, and coagulation profiles), electrocardiogram (ECG) results, and vital signs were recorded.

The primary sources of clinical data for this review consisted of datasets and case report forms of patients enrolled in four Phase 3 trials for treatment of acute bacterial skin and skin structure infections (ABSSSI) or community-acquired bacterial pneumonia (CABP). These were supported by data from 12 of the 13 clinical trials included in the pooled safety analyses: two Phase 2 ABSSSI trials and the ten Clinical Pharmacology studies (P903-01, P903-02, P903-04, P903-05, P903-11, P903-13, P903-14, P903-17, P903-18, and P903-20) conducted in adults.

All patients completing the study or prematurely withdrawing from the study, with the corresponding reasons for withdrawal and reasons for discontinuation, were summarized for the overall safety population and by region (Africa, Asia, Eastern Europe, Latin America, Western Europe, and the United States).

Table 3 provides a summary of Phase 1, 2, and 3 studies/clinical trials in the ceftaroline development program.

7.1.2 Categorization of Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence, such as any unfavorable and unintended sign, symptom, or disease experienced by a patient given a medicinal product in a clinical investigation. Although usually temporally associated with the use of a medicinal product, an AE may not necessarily have a causal relationship with the treatment. AEs may include post-treatment complications from protocol-mandated procedures such as venipunctures and biopsies. Pre-existing events that increased in severity or changed in nature during or after the use of a drug product can be considered AEs.

AEs do not include the following:

- Medical or surgical procedures; the condition that necessitates the procedure is the AE;
- Any pre-existing disease or condition or laboratory abnormality present at baseline, that did not worsen;
- Laboratory abnormalities without clinical manifestations, which did not require intervention, or which did not result in termination or delay of study drug administration;
- Situations where an untoward medical occurrence has not occurred;
- Overdose of any study drug or concomitant medication without signs or symptoms, unless the patient was hospitalized;
- Insufficient therapeutic effect, which was captured as an efficacy outcome, unless it caused prolonged hospitalization or death.

Serious adverse events (SAEs) were monitored through 30 days after the last dose of the study drug for Clinical Pharmacology studies and through the LFU for all other trials (Phase 2 and 3 trials). SAEs include any AE at any dose of the study drug that resulted in any of the following outcomes:

- Death;
- Life-threatening situation;
- In-patient hospitalization or prolongation of existing hospitalization;
- Persistent or significant disability/incapacity;
- Congenital anomaly/birth defect in the offspring of a patient who received the study drug; and
- Events that jeopardized the patient sufficiently that medical or surgical intervention may have been required to prevent one of the above outcomes. (e.g. intensive treatment in the ER or at home for allergic bronchospasm, blood dyscrasias not resulting in hospitalization, seizures that did not result in hospitalization, etc.)

Treatment-emergent adverse events (TEAEs) were defined as events that began or worsened in severity during or after the first dose of study drug administration through the end of the last study visit or follow-up evaluation for Clinical Pharmacology studies and through the TOC for all other trials (Phase 2 and 3 trials). Patients who did not return for a TOC visit had an imputed TOC date of EOT plus 20 days. AEs with no onset time available, but with an onset date equal to the first study medication dose date, were counted as treatment emergent.

While pregnancy was not considered a TEAE, any pregnancy complication or elective termination of a pregnancy for medical reasons was considered a TEAE or an SAE. A spontaneous abortion was always considered an SAE. Any SAE that occurred as an adverse pregnancy outcome post-trial was to be reported to the Applicant.

To standardize the presentation of data across all trials, AEs, SAEs, and TEAEs were coded to a system organ class (SOC) and preferred term (PT) using a consistent version 11.1 of the Medical Dictionary for Regulatory Activities (MedDRA) and World Health Organization (WHO) Drug Dictionary (March 2008) coding. Because of this standardization, the presentation and numeric results of individual data will differ slightly from those reported in the individual clinical study report (CSR). All summaries were generated using version 9.1.3 of SAS running on a VMS operating system Categorical summaries included counts and percents of patients in each category. Descriptive summaries included the n, mean, standard deviation, median, minimum, and maximum.

To categorize AE severity and relationship to the study drug, the incidence of all TEAEs by SOC, PT, and severity were presented. TEAEs were classified by severity as:

- Mild – if symptoms were barely noticeable or did not make the patient uncomfortable and the AE did not influence performance of functions. No medications were needed to relieve symptoms;
- Moderate – if symptoms made the patient uncomfortable and performance of daily activities were affected so that treatment of symptoms may have been required;
- Severe – if symptoms caused the patient severe discomfort to cause cessation of treatment with the drug and necessitated treatment of symptoms.

An additional severity category of “life-threatening” was used in some trials and was classified as severe in the tables. If multiple classifications were reported for the same TEAE, the highest degree of severity was used for the analysis.

The TEAE’s relationship to the study medication was classified as either unrelated or related. Any TEAE reported as related, probably related, or possibly related was considered related. Any AE recorded as unrelated, unlikely to be related, or not related was considered unrelated. If multiple assessments of relationship were reported for the same TEAE, the occurrence assessed by the Investigator as the most related to the study drug exposure was used for the analysis.

TEAEs classified with an action with respect to study drug of “Discontinued” or with respect to study conduct of “Withdrawn” are reported under TEAEs leading to premature study drug discontinuation and study withdrawal. Patients whose study drug was prematurely discontinued and who were withdrawn from the trial were counted once. AEs leading to premature study drug discontinuation that represented worsening of disease (i.e. SAEs due to hospitalization) were included.

To clarify and avoid confusion over the terms “serious” and “severe”, the following explanation was excerpted from ICH E2A:

> “The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as “serious”, which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a patient’s life or functioning. Seriousness (not severity) serves as a guide for determining regulatory reporting obligations.”

Death was defined as any death that occurred on or before LFU, or within 30 days of EOT for patients who did not return for LFU. The incidence of SAEs leading to death was summarized by SOC and PT.

Clinical laboratory tests for hematology, coagulation parameters, serum chemistry, and urinalysis were monitored during the ceftaroline drug development program. The analytes tested for each laboratory category were enumerated and the criteria for potentially clinically significant (PCS) changes were discussed in the Integrated Summary of Safety (ABSSSI and CABP). Incidence of patients with PCS postbaseline value changes for the laboratory parameters were analyzed and compared between the ceftaroline and comparator/placebo groups. Shift tables in the overall pooled ceftaroline and comparator groups were used to compare the proportion of patients below, within, or above normal limits at baseline versus EOT for all hematology, chemistry, and coagulation analytes. Box plots of overall pooled ceftaroline and pooled comparator at baseline, EOT, and TOC were provided for hemoglobin (Hgb), leukocytes, eosinophils, platelets, prothrombin time (PT), activated partial thromboplastin time (aPTT), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gammaglutamyl transpeptidase (GGT), creatine kinase (CK), total bilirubin, and creatinine were provided. Scatter plots were used to compare baseline to minimum postbaseline hematology and creatinine clearance (CrCl) values or baseline to maximum postbaseline ALT, AST, and total bilirubin values.

PCS changes from baseline in vital signs, including supine pulse rate and systolic and diastolic blood pressure, together with body temperature from the Clinical Pharmacology studies were presented. Lastly, PCS criteria and results of measured electrocardiogram parameters that include heart rate (HR), PR interval, QRS interval,

and QT interval (specifically corrected for heart rate by Fridericia's formula [QTcF] and by Bazett's formula [QTcB]) were summarized and analyzed in incidence tables.

Medical Officer Comment:
Definitions of AEs, SAEs, TEAEs, and PCS values and changes from baseline of laboratory parameters and analytes, vital signs, and ECG parameters appear appropriate, in addition to the timepoints at which these variables were evaluated (EOT, TOC, etc.). The Medical Reviewer reviewed and analyzed datasets enumerating the ADR and TEAE terms used by Investigators and the corresponding PTs and SOCS to which the ADRs and TEAEs were coded using version 11.1 of the MedDRA dictionary and World Health Organization (WHO) Drug Dictionary (March 2008) coding. It appears that the ADR and TEAE terms were appropriately coded to corresponding PTs and SOCs.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

In the pooled analyses and presentations of data, the 16 completed studies/trials in adults are organized into five groups of studies, each represented by separate sets of tables and figures for purposes of analyses:

<u>The Phase 3 ABSSSI and CABP trials</u>
This group consists of the two Phase 3 ABSSSI trials (Trials P903-06 and P903-07) and two Phase 3 CABP trials (Trials P903-08 and P903-09). These trials evaluated adult patients who received ceftaroline fosamil 600 mg IV q 12 hours or 400 mg IV q 12 hours (for patients with moderate renal impairment). All trials were multinational, multicenter, randomized, double-blind, well-controlled trials using comparator regimens. The safety information is summarized for the pooled Phase 3 ABSSSI trials (ceftaroline vs. vancomycin plus aztreonam), pooled Phase 3 CABP trials (ceftaroline vs ceftriaxone), and the pooled Phase 3 ABSSSI and CABP trials combined (ceftaroline vs pooled comparators). Given the same routes of administration and dosages of ceftaroline fosamil, overlapping durations of treatment, similar active comparator trial designs and safety assessments for each trial, pooling of the safety data from the these four trials was considered appropriate.

<u>The Phase 3 ABSSSI trials</u>
This group consisting of the two Phase 3 ABSSSI studies also known as CANVAS (**C**eft**a**roli**n**e **V**ersus V**a**ncomycin in **S**kin and Skin Structure Infections) were conducted simultaneously under identical protocols. Duration of treatment was between 5 to 14 days. Pooling of the safety data was considered appropriate.

<u>The Phase 2 and Phase 3 ABSSSI trials</u>
This group consists of the two Phase 2 and two Phase 3 ABSSSI trials. Considering design similarities, use of vancomycin + aztreonam as an active comparator, and same

route of administration (intravenous), pooling was considered reasonable. The two Phase 3 ABSSSI trials were conducted simultaneously under identical protocols. Safety data from Trial P903-19 were excluded because of differences in route of administration (intramuscular), active comparator and trial design (open-label study).

The Phase 3 CABP trials
This consists of the two Phase 3 CABP trials (Trials P903-08 and P903-09), also known as FOCUS (Ce**f**tar**o**line **C**ommunity-acquired Pne**u**monia Trial v**S** Ceftriaxone in Hospitalized Patients). These two trials were conducted simultaneously under nearly identical protocols for 5 to 7 days of study drug treatment. Given the similarities, pooling was considered appropriate.

The Clinical Pharmacology Studies
Safety information from the ten completed studies (P903-01, P903-02, P903-04, P903-05, P903-11, P903-13, P903-14, P903-17, P903-18, and P903-20) was pooled because the same route of administration of ceftaroline fosamil was used. Data from the IM dosing periods in Study P903-17 (because of the different route of administration) and the moxifloxacin exposure data from Study P903-05 were not included. The pool was further subdivided into:

- The Special Populations which include the elderly patients in Study P903-11 and patients with renal impairment in Study P903-02, P903-04, and P903-18;
- The Healthy Population that included all Phase 1 patients not belonging to the Special Populations;
- Patients in the pooled Clinical Pharmacology studies.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Overall Exposure at Appropriate Doses/Duration

Overall, the ceftaroline development program consisted of a total of 3144 patients, 1740 of whom were treated with ceftaroline (1603 adult patients received IV ceftaroline fosamil, 98 adult patients received IM ceftaroline fosamil in a Phase 2 trial, 30 adult patients received only IM ceftaroline in a Phase 2 trial, and 9 adolescent patients received IV ceftaroline fosamil) while 1458 of whom were treated with a comparator. Of the 1740 patients treated with ceftaroline, 1441 patients were assigned to receive the proposed recommended dose. (Table 64)

The pooled Clinical Pharmacology, the Phase 2 and Phase 3 ABSSSI trials, and the Phase 3 CABP studies included a total of 1701 patients who received ceftaroline fosamil (1603 patients received IV ceftaroline fosamil and 98 patients received IM ceftaroline fosamil in a Phase 2 trial) and 1451 patients who received the comparator.

The Phase 3 ABSSSI and CABP studies included a total of 2597 patients, 1300 of whom received ceftaroline fosamil and 1297 received the comparators.

Table 64. Number of Patients for Ceftaroline Drug Development

Study Grouping Study Subgrouping Study	Ceftaroline (Recommended Dose)	Comparator	Total
Clinical Pharmacology	275 (74)	84	305
Pooled Clinical Pharmacology studies	236 (74)	78	260
Single-dose studies (dose 50 mg to 2000 mg IV)	192 (56)	70	208
Multiple-dose studies	44 (18)	8	52
Study P903-17 (IM study)*	36 (0)	6	42
Study P903-15 (pediatric study)	9 (0)	0	9
Phase 2 and 3 ABSSSI studies			
Phase 2 ABSSSI studies	165 (67)	77	242
Trial P903-03	67 (67)	32	99
Trial P903-19	98 (0)	45	143
Pooled Phase 3 ABSSSI trials	692 (692)	686	1378
Pooled Phase 3 CABP trials			
Trial P903-08	298 (298)	308	606
Trial P903-09	310 (310)	303	613
Total Phase 3 CABP trials	608 (608)	611	1219
Total Phase 3 ABSSSI and CABP trials	1300 (1300)	1297	2597
Total pooled Clinical Pharmacology studies, Phase 2 and 3 trials	1701 (1441)	1452	3099
Total for all studies/trials	1740 (1441)	1458	3144

Adapted from Integrated Summary of Safety (ABSSSI and CABP), p. 118-9.
Nine patients were excluded from Trial 09 because of data integrity.
* Six subjects were given both IV and IM ceftaroline.

The extent of exposure to the study drug by treatment group for the four Phase 3 trials can be seen in Table 65. 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 and a small proportion of patients received the study drug for 1 to 4 calendar days (4.7% or 61/1305) and 5.8% or 75/1301), respectively). 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.

For the Phase 3 ABSSSI trials, a total of 1378 patients received ceftaroline fosamil (692/1378 or 50.2%) or vancomycin plus aztreonam (686/1378 or 49.8%). The majority of patients received 5 to 14 calendar days of the study drug (92.5% or 640/692) and 90.8% or 623/686, respectively) and only small minorities of patients received 1 to 4 calendar days of therapy or 15 or more calendar days of therapy. The median duration of ceftaroline fosamil and vancomycin/aztreonam therapy was 7.0 and 8.0 days, respectively. The extent of exposure to the study drug was similar between the treatment groups, as can be seen in Appendix 1.

For Trial P903-06, the majority of patients received the study drug for 5-14 days (94.9% or 333/351 for ceftaroline and 91.6% or 318/347 for vancomycin/aztreonam), with a mean treatment calendar days of 8.5 days and 8.6 days, respectively, and median treatment days of 8.0 days for both. For Trial P903-07, the majority of patients received the study drug for 5-14 days (90% or 307/341 for ceftaroline and 305/339 for vancomycin/aztreonam), with a mean treatment duration of 8.2 calendar days and a median duration of treatment of 7.0 days. (Appendix 1)

For the pooled Phase 3 CABP trials, a total of 1228 patients received ceftaroline fosamil (613/1228 patients or 49.9%) and ceftriaxone (615/1228 or 50.1%). Most of the patients received 5 to 8 calendar days of either ceftaroline or ceftriaxone (95.8% or 587/613 and 94.8% or 583/615, respectively) while a small percentage received ceftaroline or ceftriaxone for 1-4 calendar days (4.2% or 26/613 and 5.2% or 32/615,respectively). None of the patients received therapy for more than 8 calendar days. The median duration of ceftaroline or ceftriaxone therapy was 7.0 days. (Table 65) The extent of exposure to the study drug was similar between treatment groups in the pooled Phase 3 CABP trials. (Appendix 2)

Table 65. Calendar Days on Study Drug for Phase 3 ABSSSI and CABP Safety Population

	ABSSI		CABP		Pooled Phase 3 Studies	
	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.

For Trial P903-08, the majority of patients received the study medication for 5-7 days (91.6% (273/298) for ceftaroline fosamil and 93.2% (287/308) for ceftriaxone), with similar mean treatment days (6.4 days and 6.5 days, respectively) and the same median treatment days (7.0 calendar days) for both. For Trial P903-09, the majority of the patients received the study medication for 5 -7 days (92.4% (291/315) for ceftaroline fosamil and 90.9% (279/307) for ceftriaxone), with the same mean treatment days (6.5 calendar days for both treatment groups) and the same median treatment days (7.0 calendar days). (Appendix 2)

Demographics of the Target Population

Patients given ceftaroline in the pooled Clinical Pharmacology studies were predominantly male (67.2% or 131/195), white (82.1% or 160/195), non-Hispanic, and healthy, with a mean age of 36 years.

Across the pooled Phase 3 ABSSSI and CABP trials, patients were predominantly male, white, and non-Hispanic, with a mean body mass index (BMI) of approximately 27 kg/m^2, mean age of around 54 years, and 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. The demographic and baseline characteristics were similar between the ABSSSI and CABP trials in terms of gender, height, weight, body mass index (BMI) and BMI distribution but differed in terms of age, ethnicity, race, and CrCl. The most clinically significant differences between the two indications were age and CrCl. Patients in the CABP trials are older and had lower CrCl compared to patients in the ABSSSI trials. (Table 4) The Applicant suggested that the higher ages and the lower CrCl values of Phase 3 CABP patients were likely driven by the PORT Score inclusion criteria for the CABP studies which are heavily weighted by age and renal function.

Table 66. 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 (years)						
Mean	47.5	48.4	60	60.5	53.4	54.1
St. Dev.	17.0	16.6	16.9	16.1	18.0	17.4
Median	47.5	48.0	62.0	62.0	54.0	54.0
Min, Max	18, 93	18, 96	18, 99	18, 91	18, 99	18, 96
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	2 (0.3)	2 (0.3)	0	0	2 (0.2)	2 (0.2)

	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(%)
Other Pacific Islander						
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)
BMI Distribution – n (%)						
Underweight (<18.5)	15 (2.2)	7 (1.0)	40 (6.6)	20 (3.3)	55 (4.2)	27 (2.1)
Normal Weight (18.5 to 25.0)	237 (34.2)	224 (32.7)	257 (42.3)	238 (38.9)	494 (38.0)	462 (35.6)
Overweight (30 to 40)	178 (25.7)	180 (26.2)	110 (18.1)	131 (21.4)	288 (22.2)	311 (24.0)
Morbidly Obese (≥ 40)	44 (6.4)	47 (6.9)	12 (2.0)	12 (2.0)	56 (4.3)	59 (4.5)
Missing	2 (0.3)	1 (0.1)	0	0	2 (0.2)	1 (0.1)
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.

In the pooled Phase 3 ABSSSI trials, patients were predominantly male, white, and non-Hispanic, with a BMI of around 28 kg/m^2, a mean age of 48 years, and normal renal function. The demographic and baseline characteristics of the safety population of the pooled ABSSSI trials were similar between the treatment groups (Appendix 3). In the pooled Phase 3 CABP trials, patients were predominantly male, white, and non-Hispanic, with a mean BMI of around 26 kg/m^2. The demographic and baseline characteristics of patients in the ceftaroline and ceftriaxone groups were similar (Appendix 4).

The Phase 3 trials enrolled patients from specific populations: the elderly, the overweight and obese, and those with renal insufficiency. As previously stated, around 31% of patients from the pooled trials were ≥ 65 years old, mostly enrolled in the CABP trials. Around 23% of patients were overweight and approximately 4% were morbidly obese. Patients with mild (22%) and moderate (9%) renal insufficiency were enrolled.

Relevant medical and surgical histories were also examined for the safety population by indication. Because enrollment was limited to predominantly healthy patients, medical conditions were not summarized for Clinical Pharmacology studies. For the Phase 2 and Phase 3 IV ABSSSI trials, the following conditions were considered: any relevant

medical or surgical history, relevant surgical procedures, recent trauma, diabetes mellitus, peripheral vascular disease (PVD), current or recent IV drug use, current or recent alcohol abuse, and prior skin infection. Around 90% of patients in each treatment group had relevant medical conditions, the most common of which were recent trauma, diabetes, PVD, prior skin infection, and relevant surgical procedures. The incidences of these conditions were similar between the two treatment groups.

For Phase 3 CABP trials, the following conditions were considered: any relevant medical history, structural lung disease, gastro-esophageal reflux, asthma, chronic sinusitis, alcohol abuse, and prior pneumonia. Approximately 43% of patients in each treatment group had relevant medical conditions, the most common of which were structural lung disease, prior pneumonia, and asthma. The incidences of these conditions were similar between the two treatment groups. In order to enroll patients with similar degrees of risk for death and other adverse outcomes of CABP, the PORT Scoring System[19] was utilized. Heavily driven by age and renal function, the PORT Score is also determined by ongoing medical conditions. As can be seen in Table 67, in both CABP trials, most patients were classified as PORT Risk Class III or IV, reflecting protocol specification. The distribution of patients in each risk class was similar between the ceftaroline and ceftriaxone groups in both trials.

Table 67. Distribution of PORT Risk Class for Phase 3 CABP Trials

PORT Risk Class n (%)	P903-08		P903-09		Pooled Phase 3 Trials	
	Ceftaroline (N=298)	Ceftriaxone (N=308)	Ceftaroline (N=310)	Ceftriaxone (N=303)	Ceftaroline (N=608)	Ceftriaxone (N=611)
I (Score 0-50)	0	1 (0.3)	2 (0.6)	0	2 (0.3)	1 (0.2)
II (Score 51-70)	6 (2.0)	4 (1.3)	24 (7.6)	33 (10.7)	30 (4.9)	37 (6.0)
III (Score 71-90)	190 (63.8)	182 (59.1)	168 (54.0)	169 (55.7)	358 (58.9)	351 (57.4)
IV (Score 91-130)	100 (33.6)	119 (38.6)	116 (37.8)	1020(33.2)	216 (35.5)	219 (35.8)
V (Score ≥ 131)	2 (0.7)	2 (0.6)	0	1 (0.3)	2 (0.3)	3 (0.5)

Source: Adapted from Table 2.2.2.1. Demographics and Baseline Characteristics Phase 3 Studies for CAP. Integrated Summary of Safety. P. 10762.
Nine subjects were excluded in Trial 09 because of data integrity.

The regional distribution of patients enrolled for the overall and pooled Phase 3 trials, indicates that a total of 612 (35.9%) patients who received ceftaroline were enrolled in the US (182 in the Clinical Pharmacology studies, 114 in the Phase 2 ABSSSI trials, 303 in the Phase 3 ABSSSI trials, and 13 in the Phase 3 CABP trials) while 424 (29.1%) patients who received the comparator drug were enrolled in the US for the corresponding studies (60 in Clinical Pharmacology studies, 52 in Phase 2 ABSSSI trials, 299 in Phase 3 ABSSSI trials, and 13 in Phase 3 CABP trials. In the pooled Phase 3 ABSSSI trials, the highest number of patients was enrolled from Eastern Europe, followed by the US and Western Europe. By indication, the majority of patients was enrolled from the US in the ABSSSI trials (43.8% (303/692) in the ceftaroline group vs 43.6% (299/686) in the vancomycin group) while majority of patients were enrolled from Eastern Europe in the CABP trials (284/613 (46.3%) in the ceftaroline group vs 289/615 (47%) in the ceftriaxone group). As previously indicated, only 13 of the

patients in the CABP trials were enrolled in the US (2.1% or 13/613 in the ceftaroline group and 2.1% or 13/615 in the ceftriaxone group). (Table 68)

Table 68. Enrollment by Region Groups for Phase 3 Trials

	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(%)
Region n (%)						
Africa	0	0	18 (2.9)	19 (3.1)	18 (1.4)	19 (1.5)
Asia	0	0	13 (2.1)	15 (2.5)	13 (1.0)	15 (1.2)
Eastern Europe	250 (36.1)	252 (36.7)	284 (46.7)	289 (47.3)	534 (41.1)	541 (41.7)
Latin America	56 (8.1)	53 (7.7)	68 (11.1)	66 (10.8)	124 (9.5)	119 (9.1)
US	303 (43.8)	299 (43.6)	13 (2.1)	13 (2.1)	316 (24.3)	312 (24.0)
Western Europe	83 (12.0)	82 (12.0)	212 (34.9)	209 (34.2)	295 (22.7)	291 (22.4)
US and Non-Us n (%)						
US	303 (43.8)	299 (43.6)	13 (2.1)	13 (2.1)	316 (24.3)	312 (24.1)
Non-US	389 (56.2)	387 (56.4)	595 (97.9)	598 (97.9)	989 (76.1)	989 (76.2)

Source: Integrated Summary of Safety (ABSSSI and CABP. Table 6.1.1-1, p 125.

Medical Officer Comment:
A total of 1740 patients received ceftaroline during its development program, with 1441 patients receiving the recommended to-be-marketed dose. Using the rule of 3's [20, 21], the number of patient exposures (1740) is adequate to reliably detect adverse events with a frequency of around 1 in 500. This means that with the number of patients exposed, it can be confidently stated that, if not observed, adverse events with a frequency of more than 1 in 500 can be ruled out.

In addition, 95.3% of patients received the recommended dose and duration of ceftaroline (600 mg IV every 12 hours for ≥ 5-14 days) for both indications pooled, similar to the proportion of patients (94.2%) who received the recommended duration of the comparator drugs (vancomycin/aztreonam and ceftriaxone). The median duration of treatment was 7.0 days for both the ceftaroline and comparator groups in the pooled Phase 3 trials. Based on this, it appears that the overall exposure of the safety population to ceftaroline was adequate.

Comparing baseline characteristics between populations for each indication, patients in the CABP trials were older and had lower CrCl values. In agreement with the Applicant, a plausible reason for this was the need to enroll patients with PORT Scores between 70 and 130 (PORT Risk Class III and IV), driven primarily by age and renal function. Moreover, admitted patients with CABP tend to be older with greater morbidities compared to admitted patients with ABSSSI. Another difference between the ABSSSI and CABP populations is that while US patients comprised the greatest proportion of ABSSSI patients (around 44% for both treatment groups) compared to other regions, only 13 US patients (around 4%) were enrolled in CABP Trial 08 and none were

enrolled in Trial 09. This may potentially limit the applicability of these studies to the US CABP patient population.

The demographic and baseline characteristics of patients who received ceftaroline were similar compared to patients given the comparator drug, in terms of gender, race and ethnic background, height, weight, BMI, and BMI distribution, age distribution, and CrCl distribution, indicating that the two populations were comparable. The incidence of relevant ongoing medical conditions, while indication-specific, was similar in the ceftaroline- and comparator-treated groups for each indication. Similar proportions of patients in both treatment groups have relevant ongoing medical conditions. For the CABP trials, this is verified by the similar proportion of patients classified in each PORT Risk Class, indicating that these two populations had comparable risks for death and adverse outcomes from CABP.

In summary, the safety population appears to have had adequate ceftaroline exposure of an appropriate dose and duration to confidently rule out AEs occurring with a frequency of 1 in 500 if an event has not occurred. Specific populations such as the elderly (≥ 65 and ≥ 75 years of age) and those with mild and moderate renal insufficiency were well represented. Patients given ceftaroline were comparable to patients given the comparator drugs for both indications. However, patients enrolled in the CABP trials were mostly non-US patients, were disproportionately older, and had lower CrCl values.

7.2.2 Explorations for Dose Response

The ceftaroline drug development program consisted of several Phase 1 dose-ranging Clinical Pharmacology studies which also assessed the safety and tolerability of ceftaroline at these doses (Table 69).

Table 69. Clinical Pharmacology Studies with Different Ceftaroline Dosing Regimens

Study Number	***Study Title***	***Dosage Regimen for Comparator***	***Dosage Regimen for Ceftaroline fosamil***	***Number of Patients Enrolled/ Ceftaroline Group/ No. Recommended Dose/ Comparator Group***	***Demographics***
Study P903-01 (2004)	Randomized, Double-blind, Dose-escalation Study to Determine the Safety, Tolerability, and Pharmacokinetics of PPI-0903 for Injection in Healthy Subjects	Single 1-hour infusion of normal saline Multiple 1-hour IV infusions of normal saline q 12 h for 14 days or q 24 h for 7 days	Single 1-hour IV infusion of 50, 100, 250, 500, 750, or 1000 mg Multiple 1-hour IV infusions of 300 or 600 mg q 12h for 14 days or 800 mg q 24h for 7 days	72 54 6 18 placebo	100% male 93% white Mean age: 26 Age range: 19-54 years
Study P903-05 (2009)	Randomized, Double-blind, Placebo-controlled, Crossover	Single 1-hour IV infusion of saline	Single 1-hour IV infusion of 1500 mg	54 54	50% male 72% white Mean Age: 27

Study Number	*Study Title*	*Dosage Regimen for Comparator*	*Dosage Regimen for Ceftaroline fosamil*	*Number of Patients Enrolled/ Ceftaroline Group/ No. Recommended Dose/ Comparator Group*	*Demographics*
	Study to Evaluate Safety, and Pharmacokinetics and Effect on the Electrocardiogram of a Supratherapeutic Dose of Ceftaroline in Healthy Subjects	Single 1-hour IV infusion of 400 mg moxifloxacin		0 54 placebo 53 moxifloxacin	years Range: 18-45 years
Study P903-17 (Mar 6, 2009)	A Phase 1 Randomized, Two-part, Single and Multiple Dose Study to Determine the Safety, Tolerability, and Pharmacokinetics of Ceftaroline Administered by Intramuscular Injection in Healthy Subjects	Part A: NA Part B: multiple IM injections of 1000 mg cefepime HCl q 12h on Study Days 1 through 4 and single dose on Study Day 5	Part A: Single IM injection of 400 mg, 600 mg, 1000 mg, or single IM injection of 600 mg on Day 1 plus 600 mg IV infusion on Day 8 Part B: Multiple IM injections of 600 mg q 12h on Study Days 1 though 4 and a single dose on Study Day 5	42 36 6 6 cefepime	Part A: 73% male 75% white Mean Age: 27.4 years Range: 19-44 years Part B: 78% male 33 % white Mean Age: 27 years Range: 18-41 years
Study P903-20 (Jun 10, 2009)	A Phase 1 Randomized, Double-blind, Placebo-controlled Study to Determine the Safety and Pharmacokinetics of Single Doses and Multiple-dose Regimens of Ceftaroline in Healthy Subjects	Part A: Single 1-hour IV infusion of saline placebo Part B: 1-hour IV infusions of saline placebo once on Study Day 1, q 8h on Study Days 2-9, and once on Study Day 10	Part A: Single 1-hour IV infusion of 1500 or 2000 mg Part B: 1-hour IV infusions of 600 mg on Study Days 1 and 10 and multiple doses on Study Days 2-9	30 24 0 6 placebo	Part A: 40% male 90% white Mean age: 29 years Range: 18-41 years Part B: 50% male 90% white Mean Age: 31 years Range: 18-44 years

Source: Integrated Summary of Safety. Table 4.1.1-3, p. 83-87.

Study P903-01 was a randomized double-blind dose-escalating study in which 72 healthy male patients were enrolled. Forty-eight patients were enrolled in Part 1, with 36 receiving single doses of ceftaroline ranging from 50 to 1000 mg. In the second part, six patients received placebo, six received 300 mg ceftaroline every 12 hours for 14 days, six received 600 mg of ceftaroline every 12 hours for 14 days and six received 800 mg of ceftaroline every 24 hours for 7 days. No discontinuations or withdrawals were reported. The highest safe and tolerated doses tested over multiple days were 800 mg every 24 hours for 7 days and 600 mg every 12 hours for 14 days and the highest safe and tolerated total daily dose administered over multiple days was 1200 mg (600 mg every 12 hours). No dose limiting toxicity was seen. No clinically significant change in biochemistry, hematology, coagulation or urinalysis parameters was noted.

In this study, the overall frequency of AEs reported was similar between all doses of ceftaroline and the control groups. However, urine discoloration, change in urine odor, change in body odor, rash, thrombophlebitis, and injection site inflammation occurred more frequently in patients receiving ceftaroline. Most of the reported AEs were mild in severity and self-limiting, with the exception of injection site inflammation and rash. Urine discoloration (reported by all patients receiving 600 mg every 12 hours for 14 days) and changes in urine odor (67%) and body odor (50%) were considered related to ceftaroline and may stem from the excretion of the drug and/or its metabolites via sweat or urine. Thrombophlebitis and injection site inflammation (17% in ceftaroline-treated vs 6% in the placebo group) may be related to study drug administration. Lastly, self-limiting rash was reported in three patients receiving ceftaroline, with association to ceftaroline difficult to rule out. All in all, in this dose-escalating study, ceftaroline was found to be safe and well-tolerated in all patients given different doses and dosing regimens.

Study P903-05 was a 54-patient randomized, double-blind, placebo-controlled, three-period crossover study of a single supratherapeutic dose of IV ceftaroline, a single dose of IV placebo, and a single dose of IV moxifloxacin, to determine the effect of ceftaroline on the ECG, particularly the QTc interval. Twenty-seven male and 27 female patients were enrolled and completed dosing with ceftaroline and placebo. Overall age was 18-45 years, with a median age of 24 years. Patients were mostly white and non-Hispanic, with a BMI range of 18 to 29 kg/m^2.

A single supratherapeutic dose of 1500 mg IV of ceftaroline did not result an increase in QTcIb (QT interval corrected with an individual patient correction formula based on the baseline QT-RR slope) compared with placebo. Safety evaluation showed that 37% (20/54) of patients receiving ceftaroline and 36% (19/53) of patients receiving moxifloxacin experienced TEAEs, compared to 20% (11/54) of patients receiving placebo. Thirty-two (32%) of the TEAEs experienced by patients with ceftaroline administration were assessed as drug-related, compared to 23% of TEAEs by patients with moxifloxacin administration and 11% of TEAEs by patients receiving placebo. In the ceftaroline group, the most common SOC involved is the Gastrointestinal System, with nausea being the most common TEAE (11 patients), followed by diarrhea (3 patients) and abdominal pain (3 patients). Nervous system disorders (6 patients) and Skin and Subcutaneous Tissue disorders (6 patients) were the next most common SOCs involved, with headache (3 patients) and dermatitis (4 patients) being the TEAEs most commonly experienced, respectively. No severe TEAEs, SAEs, or deaths occurred during the study.

Comment:
Studies evaluating dose-response utilizing multiple doses of ceftaroline exhibit that ceftaroline, even when given in supratherapeutic doses, has a good safety and tolerability profile with TEAEs being generally mild. No SAEs, severe TEAEs, and deaths occurred during dose-exploration studies.

7.2.3 Special Animal and/or In Vitro Testing

Nonclinical studies were performed in rats, rabbits, and monkeys. Toxicities observed with ceftaroline fosamil occurred at dose equivalents greater than the maximum recommended human dose (MRHD) of 600 mg q 12h. The toxicities observed are known to occur with IV cephalosporins and have been described in nonclinical animal models as class effects. The primary toxicities observed are as follows:

Central Nervous System
At doses greater than or equal to 200 mg/kg or an estimated ceftaroline maximum plasma concentration (C_{max}) level of approximately 12 times human levels at therapeutic doses, ceftaroline demonstrated proconvulsant activity by significantly reducing seizure latency time in rats following pentylenetetrazol administration. In a rat 4-week repeat dose toxicity study, tonic/clonic convulsions were noted at an area under the time concentration curve (AUC) level of five times the human AUC level at therapeutic doses. These findings were confirmed in the 13-week rat study. In a monkey 4-week IV repeat dose toxicity study, tonic/clonic convulsions occurred at an estimated ceftaroline plasma AUC level of approximately 20 times the human AUC at therapeutic levels. In summary, these results demonstrate that at human therapeutic doses, ceftaroline fosamil is unlikely to cause seizure activity.

Cardiovascular System
Ceftaroline fosamil did not inhibit the human ether-a-go-go-related gene (hERG/Kcnh2 gene) K^+ channel maximal tail current amplitude in vitro, in human embryonic kidney-293 cells stably expressing the hERG channel, at any of the concentrations tested (up to 1200 mcg/ml). At doses greater than or equal to 800 mcg/mL (greater than the human C_{max} levels at therapeutic doses), ceftaroline inhibited the hERG channel maximal tail current amplitude relative to vehicle controls. To assess the effect of increasing concentrations of ceftaroline (up to 100 mcmol/L) or vehicle on cardiac action potential, isolated canine ventricular Purkinje fiber preparations from 5 male Beagle dogs were studied. No effects were observed when concentrations of ceftaroline were increased to 300 mcM on the action potentials of dog Purkinje fibers in vitro, using normal stimulation rates of 0.5 to 13 Hz and a pacing frequency of 3 Hz. No effects on cardiovascular parameters were noted in conscious male cynomolgus monkeys given ceftaroline (40, 120, and 400 mg/kg) up to 25 times human C_{max} levels at therapeutic levels. Systolic and diastolic blood pressure, and mean arterial blood pressure were comparable to vehicle controls at all doses and there were no drug-induced changes in the pulse rate, PR interval, QT interval and QRS duration.

Renal System
A single dose of ceftaroline fosamil of up to 600 mg/kg given to rats had no effect on cumulative urine volume or urinary excretion of Na+, K+, and Cl- relative to vehicle controls.

In rat 4- and 13-week IV and in monkey 4- and 13-week IV repeat dose toxicity studies, the kidney was considered the primary target organ in both species. Renal findings included cloudy urine, changes in urinalysis and chemistry parameters, and increased kidney weights. Pathological changes observed, which were reversible in rats but not in monkeys, included foreign material, vacuolization, hyaline droplet formation, and inflammation of the renal tubular epithelium. In rats that received IV doses of 270 mg/kg/day, granulomas associated with foreign material and hyperplasia of the transitional renal epithelium were observed, while in rats receiving IV doses of 90 mg/kg/day, minimal vacuolation of renal collecting ducts was noted. These changes occurred at estimated ceftaroline plasma AUC levels greater than 1 times the human AUC at therapeutic doses for each species.

Hepatic System
During the 4 week recovery period of the 4 week repeat dose study in rats treated with 1000 mg/kg/day (estimated ceftaroline plasma AUC level of approximately 20 times the human AUC at therapeutic doses), an increase in the aspartate aminotransferase (AST) was noted. The no adverse effect level (NOAEL) for the study was 100 mg/kg/day. No transaminase abnormalities were noted during the dosing period. Furthermore, no transaminase abnormalities were observed in a 13-week repeat dose study in rats or in the 4- and 13-week studies in monkeys.

Gastrointestinal System
Clinically significant gastrointestinal manifestations were not observed in the majority of animal studies performed with ceftaroline. Rats given 1000 mg/kg/day in a 4 week study (an estimated ceftaroline plasma AUC level of approximately 20 times human AUC at therapeutic doses) and rabbits in a rabbit Segment II study developed loose stools. Furthermore, the rats also developed abdominal distention and enlarged ceca, both of which were attributed to antibiotic effects on the intestinal flora. These effects were not observed in the 13-week study.

Immune System and Sensitization
Antigenicity studies examining the potential induction of passive cutaneous anaphylaxis (PCA) and active systemic anaphylaxis (ASA) of ceftaroline fosamil were negative. However, when combined with adjuvant, a positive response was noted in the PCA assay, suggesting that ceftaroline fosamil can potentially cause sensitization under conditions of immunostimulation. As a consequence, the study suggests that ceftaroline can potentially cause allergic reactions under conditions of immunostimulation.

Local Effects of Intravenous or Intramuscular Administration
Following daily intramuscular injection for 10 days, rabbits appeared to tolerate administration of ceftaroline fosamil, despite the presence of red/blue discoloration and swelling at the injection sites of both vehicle control and ceftaroline-treated animals. Rabbits administered ceftaroline appeared to have more severe lesions, in the absence of histopathological findings. Rabbits given ceftaroline with a stabilizer, L-arginine, in a

single dose IV study and a repeat dose IV study tolerated the preparation with no local irritation noted.

Reproductive System
Rats in reproductive studies performed during early pregnancy receiving IV doses equivalent to 8 times the exposure in humans, at a dose of 600 mg every 12 hours by AUC, did not demonstrate any evidence of maternal and fetal toxicity. Doses as high as 450 mg/kg/day did not appear to impair fertility in adult male or female rats. Reproductive studies performed in rabbits given IV doses similar to the exposure in humans given the recommended dose by AUC demonstrated spontaneous abortion and an increased incidence of angulated hyoid alae, a common skeletal variant in rabbits. These effects were surmised to be from the rabbit's sensitivity to broad-spectrum antibiotics. Maternal toxicity noted in the rabbit studies included a reduction of body weight and food consumption, discoloration of urine, decrease in fecal volume, and moribundity/mortality at high doses.

Growth and Development
Survival and body weight gain of F1 pups that received ceftaroline were similar to controls. Developmental landmarks were attained by F1 pups receiving ceftaroline at approximately comparable timing as control pups. Behavior, learning, motor activity, and reproductive capacity did not appear to be affected by ceftaroline exposure. No developmental toxicity was noted in rats given up to 300 mg/kg/day of ceftaroline. In rabbits, however, developmental toxicity studies were limited by excessive maternal toxicity.

Carcinogenicity and Mutagenesis
Ceftaroline fosamil tested negative in the Ames bacterial reverse mutation assay and mouse lymphoma assay. Ceftaroline fosamil and its active form induced chromosomal aberrations in Chinese hamster lung cells and ovary cells, respectively, in the absence of metabolic activation but not in the presence of hepatic microsomal enzymes derived from rats. The active form did not induce mutations at the HGPRT locus of Chinese hamster ovary cells. Lastly, the micronucleus test was negative for ceftaroline doses up to 2000 mg/kg as they did not induce the formation of micronucleated RBCs in male rats or mice. Ceftaroline likewise did not induce unscheduled DNA synthesis in rat hepatocytes.

Medical Officer Comment:
Nonclinical studies utilizing animal models showed that potential toxicities may be seen in the central nervous system (CNS), the renal system, and the immune system. CNS toxicity was manifested as tonic-clonic convulsions in rats and monkeys at an AUC level 5-20 times the human AUC at therapeutic levels. Renal toxicity was manifested by changes in urine characteristics, urinalysis and chemistry laboratory values, and renal parenchymal changes in rats, at an AUC level greater than 1 times the human AUC at therapeutic levels. Lastly, as expected, antigenicity studies indicate that ceftaroline can

potentially cause allergic reactions. These body systems were closely monitored for possible toxicities during the clinical trials.

7.2.4 Routine Clinical Testing

Safety assessment and procedures were scheduled to comprehensively capture evidence of safety findings in the trial populations, in the context of administration of antibacterial agents. Data for the both the Clinical Pharmacology and clinical trials safety population included information from any patient who received any amount of ceftaroline fosamil or comparator.

All AEs, premature discontinuations of the study drug, withdrawals from the study, concomitant medications, laboratory results that include baseline, on-treatment, and postbaseline hematology (including complete blood count (CBC) with differential and Coombs' testing) comprehensive metabolic panel (with CrCl), coagulation panels, C-reactive protein (CRP), urinalysis, pregnancy test, 12-lead electrocardiogram (ECG) results and vital signs were collected at specific timepoints.

The Schedule of Assessments and Procedures for the ABSSSI and CABP indications can be seen in Appendix 5-A and Appendix 5-B, respectively.

Medical Officer Comment:
Based on the schedule of assessment and procedures, the routine clinical testing of clinical trial patients appear adequate to elicit adverse event data and monitor changes in physical examination findings, laboratory parameters, vital signs, and ECGs. Daily assessments of concomitant medications, vital signs including temperature, daily clinical assessment of the disease-specific signs or symptoms, and daily monitoring and recording of SAEs and AEs were performed. Intermittent monitoring of laboratory parameters, ECG, and intermittent physical examination appear to be sufficient to obtain adequate safety signals during the trials.

7.2.5 Metabolic, Clearance, and Interaction Workup

Drug-Food Interactions
Cephalosporins are typically not associated with drug-food interactions with the exception of cephalosporins with an N-methyl-tetrazole-thiol side chain such as cefoperazone, cefamandole, and cefotetan which can interact with alcohol or alcohol-containing medications to cause a disulfiram-type of reaction. More importantly, ceftaroline was administered intravenously so drug-food interactions were not expected. Hence, studies to evaluate drug-food interactions were not done.

Drug-Drug Interactions
Ceftaroline-drug interactions were thought to be unlikely due to a number of factors. First, in vitro studies demonstrated that ceftaroline is not an inhibitor or inducer of major

cytochrome P450 enzymes. Consequently, in vivo drug interactions through hepatic mechanisms are unlikely. Secondly, the plasma protein binding of ceftaroline in vitro is generally low (20%) and concentration-independent in human plasma over the clinically relevant concentration range. Interaction of ceftaroline with drugs that are highly protein-bound is unlikely. Lastly, ceftaroline renal clearance is generally less than or similar to the glomerular filtration rate (GFR), suggesting that active secretion of ceftaroline in the kidneys is not a significant mode of excretion. Interactions with drugs that inhibit active renal secretion are therefore not expected. Because of these factors, drug-drug interactions were not expected with ceftaroline and formal clinical pharmacokinetic (PK) studies were not performed to investigate potential drug interactions.

However, exploratory PK analysis was done in enrolled patients with ABSSSI and CABP taking concomitant medications that are known inhibitors, inducers, and substrates of the cytochrome P450 system.

Lastly, TEAEs of patients from the pooled Phase 3 trials who were taking specific concomitant medications, namely probenecid, warfarin, furosemide, acetylsalicylic acid (ASA), paracetamol, and metamizole were analyzed for potential safety concerns that may develop with concomitant administration of ceftaroline and these medications. The incidences of the 10 most common TEAEs were analyzed as supportive information. Interactions between ceftaroline and these medications are not expected based on their known pharmacodynamic properties.

Medical Officer Comment:
The potential for ceftaroline to interact with other medications appears to be minimal based on its pharmacodynamic properties.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The incidence of TEAEs and laboratory parameters classified under organ systems or syndromes relevant to the cephalosporin class of antibacterials were summarized and analyzed to assess for potential AEs. The following categories were included:

- TEAEs indicating potential renal impairment;
- TEAEs indicating potential drug-induced anemia;
- TEAEs indicating potential liver injury;
- TEAEs indicating potential antibiotic-associated diarrhea;
- TEAEs indicating potential allergic reaction.

7.3 Major Safety Results

Overall Incidence

Pooled Phase 3 Trials

The overall incidence of TEAEs, SAEs, discontinuation of study drug due to TEAEs, and deaths in the pooled Phase 3 ABSSSI and CABP trials is summarized in Table 70. The overall incidence appears to be similar between the ceftaroline and comparator groups.

Table 70. Overall Incidence of TEAEs, SAEs, Discontinuations, Deaths in ABSSSI, CABP, and Pooled 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(%)
Number of Patients with:						
Any TEAE	309 (44.7)	326 (47.5)	283 (46.5)*	278 (45.5)*	592 (45.5)	604 (46.6)
Any SAE	30 (4.3)	28 (4.1)	67 (11.0)*	72 (11.7)*	97 (7.5)	100 (7.7)
Discontinuations due to TEAE	21 (3.0)	33 (4.8)	26 (4.3)*	25 (4.1)*	47 (3.6)	58 (4.5)
Deaths	3 (0.4)	0	15 (2.4)**	12 (2.0)**	18 (1.4)	12 (0.4)

Source: Integrated Summary of Safety (ABSSSI and CABP), p. 142.
* 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.

Clinical Pharmacology Studies

For the pooled Clinical Pharmacology studies, the profile and incidence of TEAEs and discontinuations due to TEAEs were similar in both the ceftaroline and placebo groups. No SAEs or deaths were reported in these studies.

The incidence of TEAEs was 38.6% (91/236) in the ceftaroline group compared with 32.1% (25/78) in the placebo group. The number of discontinuations due to TEAEs was 4 (1.7%) for the ceftaroline group and 1 (1.3%) for the placebo group. The most common TEAE SOC for the ceftaroline and placebo treatment groups was Gastrointestinal Disorders (12.7% vs 11.5%). The most common TEAEs in the ceftaroline group were nausea (24 patients, 10.2%), headache (20, 8.5%), vomiting (8, 3.4%), dizziness, abnormal urine colour, and abnormal urine odour (7 patients each, 3.0% each) while the most common in the placebo group were contact dermatitis (5 patients, 6.4%), nausea (4, 5.1%), headache (3, 3.8%), and diarrhea, contusion, and abdominal pain (2 patients each, 1.3% each).

Table 71. Overall Incidence of TEAEs, SAEs, Discontinuations, Deaths in Clinical Pharmacology Studies

	Healthy Population (Studies 01, 02, 04, 05, 11, 13, 14, 17, 18, 20)		Special Populations (Studies 02, 04, 11, 18)		Pooled Clinical Pharmacology Studies (01, 02, 04, 05, 11, 13, 14, 17, 18, 20)	
	Ceftaroline (N=195) n (%)	Placebo (N=78) N (%)	Ceftaroline (N=41) n (%)	Placebo (N=0) n(%)	Ceftaroline (N=236) n(%)	Pooled Comparators (N=78) n(%)
Number of Patients with:						
Any TEAE	76 (39)	25 (32.1)	15 (36.6)	NA	91 (38.6)	25 (32.1)
Any SAE	0	0	0	NA	0	0
Discontinuations due to TEAE	4 (2.1)	1 (1.3)	0	NA	4 (1.7)	1 (1.3)

	Healthy Population (Studies 01, 02, 04, 05, 11, 13, 14, 17, 18, 20)		Special Populations (Studies 02, 04, 11, 18)		Pooled Clinical Pharmacology Studies (01, 02, 04, 05, 11, 13, 14, 17, 18, 20)	
	Ceftaroline (N=195) n (%)	Placebo (N=78) N (%)	Ceftaroline (N=41) n (%)	Placebo (N=0) n(%)	Ceftaroline (N=236) n(%)	Pooled Comparators (N=78) n(%)
Deaths	0	0	0	NA	0	0

Source: Integrated Summary of Safety (ABSSSI and CABP), p, 143.

Medical Officer Comment:
The Applicant indicates that the profile and incidence of TEAEs and discontinuations in the Clinical Pharmacology studies were similar between ceftaroline- and placebo-treated patients. However, as expected in placebo-controlled pharmacokinetic/pharmacodynamic studies including dose-ranging studies, it appears that the frequency of TEAEs and discontinuations from TEAEs are greater in the group of patients given ceftaroline compared to the group of patients receiving placebo.

Acute Bacterial Skin and Skin Structure Infection Studies

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

Table 72. Incidence of TEAEs, SAEs, Discontinuations, and Deaths in Individual and Pooled Phase 3 ABSSSI Trials

	P903-06		P903-07		Pooled Phase 3 ABSSSI rials	
	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.

Medical Officer Comment:
Overall, although the incidence rates of TEAEs, SAEs, and discontinuations appear to be similar between the two treatment groups, it is apparent that there are more TEAEs and discontinuations due to TEAEs in the vancomycin plus aztreonam group compared to the ceftaroline group. With SAEs, there appears to be no specific pattern that can be observed. Lastly, the three mortalities in the ceftaroline group in one of the two trials is concerning and need to be further investigated.

Community Acquired Bacterial Pneumonia

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.

Table 73. 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.

7.3.1 Deaths

The Safety Population was monitored for 30 days following the last dose of study drug for Clinical Pharmacology studies and through the LFU assessment for all other trials (Phase 2 and 3 trials). Furthermore, patients in the Phase 3 trials were monitored for all-cause mortality after LFU or more than 30 days after EOT when there was no LFU. All patients with at least one SAE with an outcome of death were included in the analysis.

Overall, thirty patients had SAEs with outcomes of death in the ceftaroline and comparator groups in the pooled safety population. No deaths occurred in any Clinical Pharmacology study or in any Phase 2 clinical trial. In the pooled Phase 3 ABSSSI and CABP trials, eighteen (1.4%) patients in the ceftaroline treatment group and twelve (0.9%) in the comparator treatment group had SAEs with outcomes of death during the reporting period.

All but one of the deaths in each treatment group was assessed by an Investigator as unrelated to the study drug. One death in the ceftaroline group, a case of sudden death, may possibly be attributed to ceftaroline while another death from multi-organ failure in the comparator group may possibly be attributed to ceftriaxone and to the underlying infection. These cases will be discussed in detail later in this review.

Of the 28 remaining deaths, four (2 in each treatment group in the CABP trials) fatalities were determined to be caused by the underlying primary infection. The remaining 24 deaths, 15 in the ceftaroline group and 9 in the comparator group, were assessed by the Applicant as unlikely to be study-related and could be attributed to the underlying disease (e.g. cardiomyopathy, chronic pulmonary disease, myopathy, or malignancy) or to acute cardiac or respiratory events that occurred after the study drug treatment period (myocardial infarction, pulmonary emboli, or carcinoma).

Nine patients in the ceftaroline and comparator treatment groups (3 vs 6, respectively) died after LFU or greater than 30 days after EOT when no LFU was performed. Four of these fatalities were in the ABSSSI trials (2 ceftaroline-treated patients vs 2 comparator-treated patients, respectively) and five (1 ceftaroline-treated patient vs 4 comparator-

treated patients, respectively) were in the CABP trials. These patients will be discussed after the deaths occurring within the reporting period.

A list of patients who died within and after the LFU period can be found in Table 74, with the purported cause of death, the study day on which death occurred, and the Medical Officer's assessment of association between the study drug and the mortality outcome.

Table 74. Medical Officer's Summary of Patients with Outcome of Death with Assessment of Association

Patient ID	Cause of Death	Study Day of Death	Association with Study Drug
Patients who died prior to LFU or within 30 days after EOT			
ABSSSI, Ceftaroline			
0002-06674	Respiratory Failure	7	None
5007-06358	Malignant neoplasm progression	17	None
6609-06196	Cardio-pulmonary failure	38	None
CABP, ceftaroline			
1004-08340	Sudden death	31	None
2034-08238	Sudden death	3	Potential
6635-08316	Metastases to liver	24	None
6642-08567	Cardiac failure	14	None
6827-08190	Sepsis	32	None*
6829-08528	Respiratory failure	16	None*
2015-09618	Nosocomial pneumonia	16	None
5012-09074	Pulmonary embolism	12	None
5101-09115	Malignant lung neoplasm	24	None
5203-09541	Metastatic neoplasm	31	None
6602-09365	Respiratory failure	28	None*
6608-09621	Interstitial lung disease	10	None
6613-09346	Malignant neoplasm progression	11	None
6804-09374	Cardiac arrest	8	None
9008-09619	Septic shock	13	Treatment Failure
CABP, ceftriaxone			
0044-08030	Cardiorespiratory arrest	2	None
2031-08249	Pneumonia	23	None*
6531-08393	Cardiopulmonary failure	14	None
6626-08148	Multi-organ disorder	14	Potential
6828-08570	Acute cardiac failure	13	None
8206-08236	Cardiomyopathy	12	None
5011-09250	Cardio-respiratory arrest	5	None
5011-09540	Pulmonary embolism	27	None
6511-09215	Myocardial infarction	19	None
6612-09481	Acute respiratory failure	6	None*
7004-09012	Coronary artery disease	22	None
7004-09332	Pulmonary embolism	3	None
Patients who died after LFU or more than 30 days after EOT if with no LFU			
ABSSSI, ceftaroline			
2016-07561	Multi-organ failure	45	None
5017-07652	Myocardial infarction	45	None
ABSSSI, vancomycin plus aztreonam			
2106-07694	Unknown (cardiovascular disease, arrhythmia, infarct, or pulmonary embolism)	66	None
6511-07312	Recurrent chronic lymphocytic leukemia	43	None
CABP, ceftaroline			
5528-08119	Pancreatic neoplasm	68	None
CABP, ceftriaxone			
5027-08585	Myopathy	50	None
6204-08575	Pneumonia	43	None*

Patient ID	Cause of Death	Study Day of Death	Association with Study Drug
6634-08108	COPD	47	None
6506-09105	Pseudomonal lung infection	70	None

*Cases of treatment failure but deaths assessed as unrelated to study medication.

Discussion of Mortalities

I. Mortalities Potentially Associated with the Study Medication

A. Ceftaroline (CABP, Trial P903-08):

Patient ID: 2034-08238
SAE: Unknown Sudden Death
Outcome and Date: Fatal. Study Day 3
This was a 73 year old Hispanic female with a medical history significant for a 20 year smoking history. Concomitant medications included ranitidine, salbutamol, ibuprofen, and ampicillin with sulbactam. The patient was treated with ceftaroline for CAP (PORT Risk Class III) in the right middle lobe with no identified pathogen isolated, after presenting with fever and chest radiograph with consolidation and infiltrate with no pleural effusion. At baseline, laboratory evaluation was unremarkable except for mild leukocytosis. She received ceftaroline for a total of 2 days.

On Study Day 2, the patient experienced an AE of mild anxiety which spontaneously resolved. Vital signs during the day were normal except for a low-grade temperature of 100.8 deg Fahrenheit. Laboratory results were also unremarkable.

On Study Day 3, the patient was found unresponsive. The patient was intubated with no difficulty, without any throat swelling noted. The patient did not have any rash, hives, or other adverse events during resuscitation. The patient was pronounced dead after 45 minutes of resuscitation. Upon review, the patient reportedly did not have any previous exposure to cephalosporin drug therapy nor any allergies or sensitivity to penicillin, cephalosporins, or other ß-lactam medications. The cardiologist reportedly believed that the patient died from suspected myocardial infarction. No autopsy was performed.

The Investigator assessed the sudden death as possibly related to the study medication, since a relationship could not be ruled out and no alternative etiology could be found. No specific SAE directly leading to the sudden death was identified. The Applicant agrees with the Investigator's assessment but makes note that there was no evidence of laryngeal edema. The Applicant further states that the sudden death may have been caused by an acute event such as myocardial infarction as suspected by the cardiologist.

Medical Officer Comment:

The patient had no underlying medical conditions (including cardiovascular disease) that predisposed her to sudden death. She did have a 20 year history of smoking as a potential risk factor for coronary artery disease. In addition to the CRF and case narrative submitted in the application, the Applicant was requested to provide more information including ECG tracings, vital signs and physician assessments preceding, during, and after resuscitation, in order to clarify the circumstances surrounding the patient's death.

From Study Days 1 to 2, the patient was noted to have normal and stable vital signs except for temperatures of 38.9 to 40.6. The last set of vital signs included a BP of 120/70, heart rate of 82 beats/minute, respiratory rate of 20 breaths/minute, and temperature of 37.6 degrees C. The study medication, together with clarithromycin, was given as scheduled with no adverse event noted during infusions. Except for mild leukocytosis, laboratory parameters performed a day before were within normal limits. ECG tracings submitted as requested showed sinus rhythm with premature systoles and accelerated AV conduction at baseline. During resuscitation, regular rhythm, wide complex tachycardia, with a rate of around 150 beats per minute, was noted on the rhythm strip. Findings suggestive of ischemia were not noted on a rhythm strip.

In the absence of plausible, documented alternative etiologies such as clinical deterioration from the underlying infection and myocardial infarction as suggested by the Investigator and in the absence of underlying medical conditions, the possibility that the patient's death is related to the study medication is difficult to rule out. Without a documented history of hypersensitivity to ß-lactams, or laryngospasm/bronchospasm and rash at the time of death, and a reported AE during ceftaroline infusion, anaphylaxis is unlikely as the cause of death. Without an autopsy to determine the primary cause of death, the possibility of an association between the patient's sudden death and ceftaroline exists and can not be ruled out.

B. Ceftriaxone (CABP, Trial P903-08)

Patient ID: 6626-08148
SAE 1: Hepatic Failure
Outcome: Ongoing at Time of Death
SAE 2: Multi-organ Dysfunction Syndrome
Outcome and Date: Fatal. Study Day 14
This was a 60 year old white male with a medical history significant for a 30 year smoking history and hypertension, with no reported history of prior cephalosporin exposure, liver disease, liver infection, acetaminophen exposure, or hypersensitivity to ß-lactam antibiotics. He was classified as PORT Risk Class IV. Although the patient did not admit to alcoholism, the Investigator, based on the patient's daughter's account, reported that the patient abused alcohol until hospitalization. There was no family history of liver disease or G6PD deficiency. Concomitant medications included enalapril, enoxaparin, theophylline, promethazine, ambroxol, furosemide, verapamil, clorazepate,

and heparin. He was treated with ceftriaxone for 6 days for CAP in the right and left lower lobes and bilateral small pleural effusions with an unknown etiology. He received ceftriaxone for 6 days. Baseline laboratory evaluation showed normal liver function tests and renal function tests, with a normal liver size and structure on ultrasound performed "as part of regular practice for patients who did not have an ultrasound in the past year".

On Study Day 5, the patient experienced a moderate AE of increased fibrin D-dimer. On Study Day 6, liver enzymes were moderately increased with alkaline phosphatase 72 U/L, ALT > 3x the ULN (214 U/L), AST > 5x the ULN (231 U/L), GGT 65 U/L, LDH 521 U/L. Renal function tests were increased, with BUN 27 mg/dL, creatinine 1.6 mg/dL, and creatinine clearance decreased at 52.8 mL/min. Hepatitis A and B serologies and HIV serology were negative. On the same day, the patient experienced sensorial changes, dyspnea, tachycardia, and sweating, with overall clinical deterioration. On Study Day 7, the patient developed a life-threatening SAE of hepatic failure, presenting with hypotension, tachycardia, and severely elevated liver function tests. The patient was transferred to the ICU unconscious. No eosinophilia, fever, rash, or evidence of hemolysis was noted. On Study Day 11, the patient developed severe multi-organ disorder that reportedly caused the patient's death on Study Day 14. No autopsy was performed.

The Investigator reported that the SAEs of hepatic failure and multi-organ disorder are possibly related to the study treatment. However, the Investigator suggested that hypotension with possible shock may be considered as an alternative etiology of the multi-organ dysfunction manifested by hepatic and renal failure. The Applicant assessed the patient's SAEs as a possible case of antimicrobial-induced hepatotoxicity given the temporal sequence and the extent of transaminase elevation in the absence of alkaline phosphatase elevation.

Medical Officer Comment:
The Medical Officer agrees that this case of hepatic failure with resultant multi-organ disorder is possibly related to the study medication. There were no underlying conditions that predisposed the patient to hepatic failure except for the Investigator-reported history of alcoholism. In the absence of any other alternative etiology, the temporal association between the development of hepatotoxicity and administration of study medication is evident. No rechallenge test was performed so that at the time of completion of therapy, the hepatotoxicity was severe enough to have caused the patient's sensorium changes.

Hypersensitivity and immune-mediated reactions to the study medication were highly unlikely in the absence of eosinophilia, hemolysis, and systemic signs and symptoms. Moreover, the alternative etiology of hypotension with shock as the etiology for the hepatic and subsequent multi-organ failure as suggested by the Investigator is unlikely since the development of hepatotoxicity preceded the patient's clinical deterioration.

Information requested from the Applicant partly clarified the documentation of the alcohol abuse history. The patient's daughter reported apparent alcohol abuse by the patient, with no further information about the duration and quantity of alcohol used. Attributing the multi-organ failure and subsequent demise to alcohol abuse should be done cautiously based on the minimal information obtained from the daughter, especially with normal baseline liver sonogram and liver function tests. Without a plausible alternative etiology for the hepatic and multi-organ failure, association with the study drug can not be ruled out.

II. Mortalities Deemed Not Associated with the Study Medication

A. Deaths during Reporting Period (Prior to LFU or within 30 days after EOT)

1. ABSSSI Trials

A. Ceftaroline

P903-06

Patient ID: 0002-06674:
SAE Verbatim: Respiratory Failure-Multifactorial
Outcome and Date: Fatal, Study Day 7
This was a 90 year old white female with a acute bacterial medical history significant for diabetes mellitus, depression, cardiovascular diseases, right (R) foot infection, and chronic excoriation of the intergluteal cleft, among others, on multiple concomitant medications.

She presented with an ulceration of the R second toe and was treated with ceftaroline for 3 days. Urinalysis showed the presence of nitrates and +2 leukocytes and urine culture grew *Escherichia coli*, indicating a diagnosis of concomitant UTI with possible urosepsis.The infected ulcer grew methicillin-sensitive *Staphylococcus aureus* (MSSA).

On Study Day 3, the patient developed the SAE of respiratory failure, with hypotension, hypoxia despite oxygen supplementation, and tachypnea with poor skin perfusion. She was intubated and mechanically ventilated after becoming unresponsive. A chest X-ray (CXR) showed pulmonary edema. Gangrene of the primary site was also diagnosed.

On Study Day 4 (EOT assessment), the patient developed worsening acidosis, hyperglycemia, leukocytosis, renal insufficiency, congestive heart failure and ischemic cardiomyopathy with a poor ejection fraction, as suggested by a 2D-echocardiogram. Antibacterial treatment was changed from ceftaroline to meropenem and vancomycin

through Study Day 6. The patient was then extubated and provided comfort care. On Study Day 7, the patient died.

The Investigator assessed the SAE of respiratory failure as unrelated to the study drug and assessed the cause of death to be respiratory failure-multifactorial that was complicated by the patient's multiple comorbidities and age. The Applicant agreed with the Investigator's assessment.

Medical Officer Comment:
The patient's medical history significant for hypertension, diabetes mellitus, and severe arterial insufficiency, among others, predisposed this patient to the progression of the infected ulcer to gangrene. The Medical Officer agrees with the Investigator that the cause of death is multifactorial, namely ischemic cardiomyopathy, arterial insufficiency, hypertension, diabetes mellitus, renal insufficiency, and the infection itself. It is highly unlikely that this death is associated with the study medication.

Patient ID: 5007-06358
SAE Verbatim: Progression Low Differentiated Carcinoma of the Neck (Neoplasm Malignant)
Outcome and Date: Fatal, Study Day 17
This was a 68 year old white female with medical history significant for essential hypertension, previous neck cellulitis, and diffuse pulmonary fibrosis. Concomitant medications were diphenhydramine and metamizole. The patient was treated with ceftaroline for 4 days after debridement of the right neck on Study Day -1. The patient also was noted to have renal insufficiency, mild anemia with anisocytosis and polychromatophilia, a positive direct Coombs' test, and elevated LDH.

Surgical revision of the right neck wound was done on Study Day 8. On Study Day 13, at TOC, sonography showed the descending colonic walls to be abruptly thickened and deformed, suggesting colonic cancer. On Study Day 15, colonoscopy showed sigmoid colon diverticulum and chronic internal hemorrhoids. She underwent biopsy and further debridement of the right neck on Study Day 15. On Study Day 17, the patient experienced advanced weakness, dyspnea, and "arterial hypotonia" (possibly hypotension). Chest X-ray showed pulmonary congestion. On the same day, the patient suffered cardiac arrest and died, with the cause of death assessed to be low differentiated lymphosarcoma of the neck.

The Investigator and Applicant assessed the event to be severe and unrelated to the study drug. With the neck biopsy result showing low-differentiated carcinoma, the Investigator assessed the patient's death to be related to the neoplastic process.

Medical Officer Comment:
In addition to an unspecified primary site of malignancy (colon vs. neck), the narrative and the CRF lack details specifying the patient's immediate cause of cardiac arrest and

how the patient's neck carcinoma could have caused the acute events that led to the patient's demise. Additional information received from the Applicant revealed that the Applicant sought additional clarification on the direct cause of death, querying about the mechanism whereby the neck cancer caused the patient's death, and suggesting a different etiology such as pulmonary embolism for the patient's death. The Investigator, however, rejected the suggestion and persisted in attributing her death to disease progression from the low-differentiated carcinoma of the neck. Considering this information, the Medical Reviewer is still not convinced that the carcinoma is the patient's cause of death, with the radiographic finding of pulmonary congestion prior to the patient's demise. However, whether death was caused by the carcinoma or other acute processes such as pulmonary embolism, worsening of her pulmonary fibrosis, or heart failure, it is unlikely that her death was related to the study medication because of lack of temporal relationship and the presence of confounding medical conditions.

Patient ID: 6609-06196
SAE 1: Bowel Ischemia (Intestinal Ischemia)
Outcome and Date: Recovered. (b) (6) (Study Day 18)
SAE 2: Cerebral Stroke (CVA)
Outcome and Date: Recovered. (b) (6) (Study Day 36)
SAE 3: Cardio-Pulmonary Insufficiency (Cardiopulmonary Failure)
Outcome and Date: Fatal. (b) (6) (Study Day 38)
This was a 58 year old white female with a medical history significant for hypertension, and duodenal ulcer, among others. Concomitant medications included ranitidine, anti-hypertensives, and thrombolytic agents. She received ceftaroline for 15 days.

On Study Day 16, the patient experienced life-threatening intestinal ischemia, with laparotomy revealing torsion of the small intestine with necrosis and perforation of the intestinal wall, and resultant fecal peritonitis. The patient was treated with metronidazole and amoxicillin and underwent a partial bowel resection. She recovered from this event but remained in the hospital. On Study Day 35, the patient suffered a cerebrovascular accident (CVA) and was treated with piracetam. On Study Day 38, the patient experienced life-threatening cardiopulmonary failure which progressed to asystolic apnea, hypotension, cardiac arrest, and death. No autopsy was performed.

The Investigator did not attribute the three SAEs to the study medication. The intestinal ischemia and CVA was thought to be related to the patient's underlying chronic diseases such as atherosclerosis and the cardiopulmonary failure that resulted in the patient's demise was thought to be secondary to the CVA. The Applicant agreed with the Investigator.

Medical Officer Comment:
The Medical Officer agrees with the Investigator and the Applicant that the patient's demise was primarily a consequence of the CVA and her underlying medical conditions, rather than related to the study medication.

2. CABP Trials

A. Ceftaroline

P903-08

Patient ID: 1004-08340
SAE: Sudden Death
Outcome and Date: Fatal, Study Day 32
This was a 71 year old black male with a medical history significant for a 20 year history of cigarette-smoking, and cardiac failure. Concomitant medications included potassium chloride and furosemide. The patient was treated with ceftaroline for CABP (PORT Risk Class IV) in the right and left lower lobes with no identified pathogen. ECG tracings were abnormal with prolonged QTcB intervals, premature atrial complexes, and depressed inverted T waves that possibly represented ischemia.

On Study Day 3, an ECG showed persistence of inverted T waves, prolonged QTcB interval, and atrial premature complexes, thought to represent ischemia. On Study Day 5, at EOT and TOC, the patient was deemed a cure but had persistence of ECG abnormalities. Vital signs and relevant laboratory test results (CBC, LFTs, metabolic profile and lipid profile) were normal except for a positive direct Coombs' test. ECG still had previously documented abnormalities. On Study Day 32, the patient suddenly died. An autopsy was not performed and the death certificate listed "natural causes" as the cause of death.

The Investigator reported that the SAE of sudden death was not related to the treatment with the study medication but due to the patient's advanced age. The Applicant agrees with the Investigator stating that without an autopsy, it is difficult to determine this patient's cause of death.

Medical Officer Comment:
The Medical Officer agrees with the Investigator and the Applicant that the SAE is unlikely to be related to the study medication but is possibly related to the patient's history of cardiac failure and the ECG findings consistent with myocardial ischemia.

Patient ID: 6635-08316
SAE 1: Gastrointestinal Perforation
Outcome and Date: Complete Recovery, Study Day 20
SAE 2: Disseminated Neoplasia and Liver Metastases, Death
Outcome and Date: Fatal, Study Day 24
The patient was a 74 year old white male with a medical history significant for a 45 year smoking history, atrial fibrillation, structural lung disease (COPD), cardiac failure, and

coronary artery disease. Concomitant medications included aspirin, enoxaparin, and carvediol. He received ceftaroline for 7 days for treatment of CAP (PORT Risk Class III) in the right upper and middle lobes of the lung with no etiology isolated.

Baseline laboratory evaluation showed elevated LDH levels of 920 IU/L (normal range: 105-333 IU/L) and BUN of 23 mg/dL (normal range: 7-20 mg/dL). Liver enzyme levels were not reported. Abdominal sonography on Study Day 1 showed no hepatic enlargement, no focal liver lesions, no intrahepatic and common bile duct dilation, no portal vein dilation, numerous small deposits in the gallbladder, and poor visualization of the pancreas with no visible pancreatic focal lesions. Subsequent laboratory results on Study Day 3 showed normal liver enzymes and increasing LDH levels (1249 U/L). On Study Day 7 (EOT), the patient was noted to have abdominal pain, varices cruris, and arrhythmia. On Study Day 8, the patient developed an SAE of moderate gastrointestinal perforation treated with IV hydration, papaverine, and IV cefuroxime and gentamicin from Study Day 9-13. The suspected perforation completely resolved without surgical intervention on Study Day 20.

On Study Day 19, an abdominal ultrasound revealed severe disseminated hepatic metastases which were categorized as an SAE. An abdominal CT confirmed the presence of numerous hepatic metastases and suspected metastatic bony lesions. The liver was enlarged with hypovascular lesions and enlarged lymph nodes in the retroperitoneal space. Small foci of discrete osteolysis were noted in the vertebral bodies of the lumbar spine. The primary tumor was suspected in the right lung infiltrates. No treatment was given for the disseminated neoplasia except for pain management. At TOC, on Study Day 22, laboratory evaluation revealed elevated liver enzymes, GGT, BUN, and creatine kinase (CK). On Study Day 24, the patient died of metastatic cancer of unknown origin. An autopsy was not performed.

The Applicant agrees with the Investigator's assessment of non-relationship between the study drug and the cancer, stating that it is temporally implausible to have developed extensive metastatic disease in response to the short exposure time to the study medication.

Medical Officer Comment:
The Medical Officer concurs with the Investigator and the Applicant that the SAEs the patient experienced and his death were not related to the study medication. No temporal sequence between the development of a neoplasm with metastasis and the study drug administration appears to exist.

Patient ID: 6642-08567
SAE: Worsening Heart Failure
Outcome and Date: Fatal, Study Day 14
This was an 87 year old white female with a medical history significant for hypertension, cardiovascular disease, and renal failure. Concomitant medications included aspirin,

enoxaparin, antihypertensives, carvediol, omeprazole, perindopril, and atorvastatin. She received ceftaroline for 7 days for treatment of CAP (PORT Risk Class IV) in the right lower lobe of the lung and bilateral pleural effusions, with no organism isolated. Baseline ECGs were significant for inverted T waves and initial laboratory results showed moderate renal insufficiency.

On Study Day 8 (EOT), the patient was deemed a clinical failure so treatment was changed to clarithromycin and ceftriaxone. At this time, the patient had a positive direct Coombs' test and hyponatremia. An echocardiogram revealed an ejection fraction of 15-20% with dilated cardiomyopathy. On Study Day 9, the patient experienced worsening dyspnea. A chest X-ray was performed, showing bilateral pleural effusions, stable right lower lobe infiltrate, and pulmonary hemostasis, confirming worsening of her cardiac failure. On Study Day 14, the patient developed cardiogenic shock and cardiac arrest, leading to death. An autopsy was not performed.

The Investigator, with the Applicant's concurrence, assessed that the SAE of worsening heart failure is not related to the study medication, but rather due to preexisting cardiac disease.

Medical Officer Comment:
The Medical Officer agrees with the Investigator and the Applicant's assessment that the patient's worsening heart failure most probably caused her death and is unrelated to the study medication. Given the patient's preexisting medical conditions such as cardiac failure, hypertension, cardiomyopathy, among others, the patient's death most probably is related to decompensation of these underlying conditions, precipitated by the stress of infection from CAP.

Patient ID: 6827-08190
SAE: Sepsis, Left Sided Cardiac Failure
Outcome and Date: Fatal, Study Day 32
The patient was an 82 year old white female with a medical history significant for multiple cardiovascular diseases, diabetes, and chronic renal insufficiency. Concomitant medications included furosemide, anti-hypertensives, glibenclamide, and glyceryl nitrate, among others. She was treated with ceftaroline for 4 days to treat CAP (PORT Risk Class V) in the left and right lower lobes of the lungs, with no microbiologically identified pathogen. Baseline ECGs showed atrial fibrillation, prolonged QRS intervals, and prolonged QTc intervals.

On Study Day 4, the patient developed an SAE of left ventricular failure with respiratory failure, acidosis, and hypoxemia and was treated with diuresis and mechanical ventilation. A subsequent chest X-ray showed "stasis" and bilateral infiltrates, prompting the addition of Augmentin for two days and moxifloxacin for 10 days. This worsening in her clinical status was accompanied by leukocytosis, acidosis, and hypoxemia. Cardiac

echocardiography at this time showed biventricular hypertrophy and diastolic dysfunction.

She initially improved but on Study Day 22, she developed an SAE of severe sepsis from a sacral decubitus secondary to *Staphylococcus epidermidis*, *Staphylococcus cohnii*, and *Pseudomonas aeruginosa*, for which she was treated with amoxicillin/ clavulanate and cefuroxime. Her respiratory status deteriorated on Study Day 32 and she subsequently died, with the cause of death reported as sepsis. An autopsy was not performed.

The Investigator, with Applicant concurrence, assessed the SAEs of left ventricular failure and sepsis to be unrelated to the study medication and related to the patient's underlying ischemic cardiomyopathy.

Medical Officer Comment:
The Medical Officer agrees with both the Investigator and the Applicant that the patient's death was unrelated to the study medication, but secondary to the patient's age, extensive cardiovascular disease, diabetes, and renal insufficiency.

Patient ID: 6829-08528
SAE: Respiratory Failure
Outcome and Date: Fatal, Study Day 17
The patient was a 49 year old white male with no reported medical history. He was treated with ceftaroline for CAP (PORT Risk Class III) in the left upper and right upper, middle, and lower lobes of the lungs, with no identified pathogen. Laboratory evaluation at baseline revealed elevated liver enzymes attributed to "infectious hepatotoxicity" and a positive direct Coombs' test. On admission, the patient developed atrial fibrillation and tachycardia for which he received IV propafenone which restored normal sinus rhythm.

On Study Day 4, the patient experienced an SAE of severe respiratory failure due to progression of pneumonia with a chest radiograph revealing significant progression of bilateral pulmonary infiltrates. The patient was deemed a clinical failure. The patient required mechanical ventilation On Study Day 6, a bronchoscopy showed continuous bleeding in the airways. Thoracentesis did not reveal malignancy on cytological assessment of the fluid. At this time, the patient was treated with clarithromycin, moxifloxacin, piperacillin, levofloxacin, theophylline, methylprednisolone, prednisone, metoprolol, propafenone, and nadroparin.

On Study Day 15, the patient developed rapidly progressive renal failure and hematuria for which high dose steroids and dialysis were initiated. On Study Day 16, the patient developed bradycardia, followed by asystole and death. An autopsy revealed acute pulmonary microembolization, myocardial infarction, arteriosclerosis, acute respiratory distress syndrome (ARDS), and pulmonary hemorrhage. The primary cause of death was reported as respiratory insufficiency.

The Investigator assessed the SAE of respiratory failure to be unrelated to the study drug and due to disease progression. The Applicant agrees with the Investigator stating that despite the absence of comorbid disease at baseline, autopsy results indicated existing arteriosclerosis, myocardial infarction, and pulmonary microembolization.

Medical Officer Comment:
While the SAE of severe respiratory failure can be attributed to the progression of pneumonia documented by clinical and radiologic worsening and with drainage of pleural fluid, the patient's death can probably be attributed to the myocardial infarction and pulmonary microembolization seen on pathology or possibly caused by ARDS from the progression of pneumonia. The Medical Officer, however, agrees with the Investigator and the Applicant that it is unlikely that the patient's SAE and death is related to the study medication.

P903-09

Patient ID: 2015-09618
SAE 1: COPD Exacerbation
Outcome and Date: Ongoing at Time of Death
SAE 2: Renal Failure
Outcome and Date: Ongoing at Time of Death
SAE 3: Nosocomial Pneumonia
Outcome and Date: Fatal, Study Day 16
The patient was a 69 year old white male with medical history significant for a 51-year smoking history, cholelithiasis, hydronephrosis with chronic renal insufficiency, prostatic adenoma, diabetes, asthma, structural lung disease, and gastroesophageal reflux. Concomitant medications included insulin, H2 blockers, beta-agonists, hydrocortisone, budesonide, and insulin NPH. The patient was treated with ceftaroline for 7 days for CAP (PORT Risk Class IV) of the right lower lobe of the lung, with no isolated pathogen.

At baseline, vital signs were remarkable for systolic hypertension, tachycardia and tachypnea with abnormal ECGs. Initially deemed a clinical cure, he experienced an SAE of COPD exacerbation that prolonged his hospitalization. Chest X-ray showed resolution of the infiltrate in the right basal lung field but leukocytosis developed on Study Day 12 and a sputum culture grew *Neisseria* species that was considered a contaminant. The patient subsequently was mechanically ventilated and treated with ipratropium, salbutamol, theophylline, hydrocortisone, fentanyl, midazolam, and budesonide.

On Study Day 14, the patient developed a severe SAE of nosocomial pneumonia. The patient then developed hypotension and shock. He was treated with piperacillin/tazobactam and dopamine. His renal function deteriorated and on Day 15, a chest X-ray revealed worsening of the persistent bilateral infiltrates and no pathogen

was isolated. The patient died on Study Day 16 secondary to nosocomial pneumonia with concomitant SAEs of COPD exacerbation and renal failure.

The Investigator assessed the SAEs of COPD exacerbation, renal failure, and nosocomial pneumonia to be unrelated to the study medication but due to the underlying disease and intercurrent illness. The Applicant concurred with the Investigator stating that the underlying medical conditions contributed to complications of infection, leading to the progression of pulmonary and renal dysfunction, and death.

Medical Officer Comment:
The Medical Officer agrees with both the Investigator and Applicant in assessing the SAEs of COPD exacerbation, renal failure, and nosocomial pneumonia to be unrelated to the study medication but rather to the underlying illness acute bacterial by the patient's chronic medical conditions.

Patient ID: 5012-09074
SAE 1: Pulmonary Embolism
Outcome and Date: Fatal, Study Day 12
SAE 2 and 3: Renal Failure and Hepatic Failure
Outcome and Date: Ongoing at Time of Death
SAE 4: Disseminated Intravascular Coagulation (DIC)
Outcome and Date: Ongoing at Time of Death
The patient was a 78 year old white male with a medical history significant for a 60 year smoking history, recurrent MIs, chronic pyelonephritis, non-infective cystitis, prostatic adenoma, structural lung disease, cardiovascular diseases, and pulmonary embolism. Concomitant medications included antihypertensives, aspirin, dexamethasone, aminophylline, digoxin, and isosorbide. He received ceftaroline for 6 days to treat CAP (PORT Risk Class IV) in the right middle and lower lobes and small right pleural effusion with no identified microbiological etiology.

On Study Day 2, the patient developed atrial fibrillation which resolved with treatment with digoxin on Day 6. The patient however, developed nausea with bilious vomiting and epigastric pain, later diagnosed as a moderate AE of acute pancreatitis. On the same day, he developed increasing dyspnea, cyanosis, and acute chest pain, diagnosed as an SAE of pulmonary embolism, renal failure, and hepatic failure. Ceftaroline was replaced with cefazolin and penicillin. Relevant laboratory evaluation showed elevated liver enzymes that exceeded 10x ULN with hyperbilirubinemia and the presence of fibrin monomer-fibrinogen complex. The patient was treated with heparin and pentoxifylline for the pulmonary embolism and lactulose, ornithine, phospholipids and ademetionine for the hepatic failure.

On study Day 9, he experienced hematamesis and pulmonary hemorrhage secondary to disseminated intravascular coagulation (DIC). On Study Day 12, the patient experienced sudden increased dyspnea and subsequently died. An autopsy showed

ischemic heart disease, postinfarction, with grade 4 coronary artery disease, cardiosclerosis of the left ventricle, nephrosclerosis, atherosclerosis of the aorta, circulatory failure, congestive hyperemia of the lungs, kidneys and spleen, liver cirrhosis, ascites, pulmonary artery embolism, and pulmonary edema. The cause of death was reported as being pulmonary embolism and chronic circulatory failure.

The Investigator reported that the SAEs of pulmonary embolism, renal and hepatic failure, DIC and death were not related to the study medication. The Applicant agrees with this assessment stating that the patient's chronic severe liver disease predisposed the patient with a severe infection to thromboembolic events, hepatorenal failure, and cardiopulmonary failure.

Medical Officer Comment:
The Medical Officer concurs with the Investigator and the Applicant that the three SAEs and subsequent death were not related to study medication but related to his chronic underlying hepatorenal and cardiopulmonary illnesses, exacerbated by severe infection.

Patient: 5101-09115
SAE: Lung Cancer (Lung Neoplasm Malignant)
Outcome and Date: Fatal, Date Unknown
The patient was a 67 year old white male with medical history significant for a 50 year smoking history and hypertension. Concomitant medications included captopril. He was treated with 7 days of ceftaroline for CAP (PORT Risk Class III) in the left lower lobe with no microbiologically identified pathogen. At EOT, he was deemed a clinical cure.

On Study Day 12, the patient was diagnosed with an SAE of malignant lung neoplasm of the left pulmonary hilum partially obstructing the left intermediate bronchus and the apical segmental bronchus after he experienced increasing chest and lumbar pains, dry cough, loss of appetite, and progressive weight loss. A peribronchovascular density in the left pulmonary lobe, mediastinal and hilar lymphadenopathy with calcifications and bone structure abnormalities were also noted. Biopsy showed microcytic carcinoma with rice grain-shaped cells. Abdominal sonogram showed multiple hepatic nodules with dissemination to both kidneys, to the distal ureters, and a nonhomogenous prostate. He was discharged on Study Day 21 with a diagnosis of left pulmonary neoplasm with mediastinal adenopathy and bone and liver metastases. The patient did not finish study participation as he was lost to follow-up. He died on an unknown date.

The Investigator assessed the SAE of lung malignant neoplasm as not related to the study medication but due to underlying disease. The Applicant agrees with the assessment, stating that the patient's metastatic cancer predated the initiation of study drug.

Medical Officer Comment:

The Medical Officer concurs with both the Investigator and Applicant that the malignant neoplasm is not related to the study medication but due to the development of malignancy that predated the study medication.

Patient ID: 5203-09541
SAE: Suspected Metastatic Cancer
Outcome and Date: Fatal, Study Day 31
This was a 70 year old white male with medical history significant for hypertension, congestive heart failure (CHF), brain contusion, cerebral hematoma, and benign prostatic hyperplasia. Concomitant medications included bisoprolol, enalapril, and isosorbide dinitrate. He received ceftaroline for 7 days for CAP (PORT Risk Class III) in the left lower lobe of the lung with no microbiologically identified pathogen. He was assessed as a clinical cure on Study Day 8.

On Study Day 14, an elective MRI done as a follow-up of a cerebral contusion and intracerebral hematoma in 2009 revealed lesions of hematogenously disseminated tumor, with an unknown primary source, and systemic atrophy of the brain parenchyma. The patient was diagnosed with an SAE of metastasis to the CNS. Brain biopsy was not performed. The primary source of the neoplasm was not identified. On Study Day 14, the patient's overall condition worsened and hemiparesis of the right side occurred. On Study Day 18 (TOC), moderate right-sided central hemiparesis with Babinski reflex and slightly impaired speech were noted. No clinical evidence of meningoradicular irritation was seen. Despite treatment with mannitol and dexamethasone, the patient died on Study Day 31. An autopsy was not performed.

The Investigator reported that the SAE of metastatic neoplasm was not related to the study medication but due to the newly diagnosed metastatic cancer. The Applicant agreed with the Investigator stating that the metastasized cancer preceded the study drug administration.

Medical Officer Comment:
The Medical Officer agrees with the Investigator and the Applicant that the metastatic nature of the neoplastic lesions supports that the primary focus of malignancy was present before the administration of the study medication. There is no association between the study drug and the neoplastic process which led to the patient's death.

Patient 6602-09365
SAE: Respiratory Failure
Outcome and Date: Fatal, Study Day 28
This was a 57 year old white male with medical history significant for a 20 year smoking history, benign prostatic hyperplasia, hyperuricemia, pneumothorax, and structural lung disease. Concomitant medications included diuretics, beta-agonists, steroids, verapamil, etamsylate, enoxaparin, hydroxyzine, theophylline, omeprazole, itraconazole, and piperacillin/tazobactam. He received ceftaroline for 6 days to treat

CAP (PORT Risk Class III) in the right lower lobe of the lung, with no identified bacterial etiology.

On Study Day 6 (EOT), he was assessed as a clinical failure and ceftaroline was replaced with ciprofloxacin. On Study Day 12, an echocardiogram revealed an enlarged right heart, consistent with right ventricular overload. A chest X-ray showed regression of inflammatory changes. The patient received amikacin and ceftazidime. On Study Day 15, the patient developed an exacerbation of COPD, manifested as severe dyspnea, fatigue, hypoxia, and tachycardia. The patient also had right leg edema for which a six-point venous ultrasound showed no signs of thrombosis. Chest CT angiography showed post-inflammatory lesions and advanced emphysema. On Study Day 28, the patient worsened and he developed an SAE of severe respiratory failure. He was tachypneic and a vesicular murmur was bilaterally heard. Despite mechanical ventilation, he developed continued ventricular tachycardia and fibrillation. Despite inotropic support, he developed wide pulseless QRS complexes and died. An autopsy was not performed.

The Investigator, with the Applicant's agreement, assessed the SAE to be unrelated to the study medication but due to the patient's underlying severe pulmonary (COPD) and cardiac disease.

Medical Officer Comment:
The Medical Officer agrees with the Investigator and Applicant that the SAE was related to the patient's underlying cardiopulmonary condition and exacerbated by the patient's infection and not to the study medication since the SAE started 9 days after the end of therapy with the study drug.

Patient ID: 6608-09621
SAE 1: Progression of Interstitial Pulmonary Fibrosis
Outcome and Date: Fatal, Study Day 10
SAE 2: Pulmonary Embolism
Outcome and Date: Ongoing at the Time of Death
The patient was an 80 year old white male with medical history significant for a 10 year smoking history, pulmonary interstitial fibrosis, pulmonary tuberculosis, leg amputation, hypertension, hyperthyroidism, and structural lung disease. Concomitant medications included indapamide, enoxaparin, and metoprolol. He received ceftaroline for 6 days to treat CAP (PORT Risk Class IV) in the right lung and the left lower and upper lobes with no identified bacterial etiologic pathogen.

On Study Day 3, the patient experienced dyspnea and cyanosis with an increase in the D-dimer level. The next day, he was diagnosed with an SAE of severe progression of interstitial pulmonary fibrosis and pulmonary embolism. A chest CT confirmed the diagnoses of diffuse pulmonary fibrosis, mediastinal lymphadenopathy, and thrombi in the right pulmonary arteries. The patient was treated with steroids, enoxaparin, furosemide, omeprazole, ornithine, and aspirin. On Study Day 8, the patient was

mechanically ventilated. On Study Day 10, the patient died of respiratory insufficiency caused by pulmonary insufficiency from progression of pulmonary interstitial fibrosis. The pulmonary embolism at the time of death was ongoing.

The Investigator assessed the SAE to be unrelated to the study medication but related to the patient's underlying pulmonary disease. Although the investigator did not consider pulmonary embolism as the cause of death, he could not exclude pulmonary embolism, right-sided heart failure, or cor pulmonale as etiologies. The Applicant agreed with the assessment, indicating that the patient's advanced age, pre-existing pulmonary fibrosis, and infection placed the patient at higher risk for thromboembolic events.

Medical Officer Comments:
The Medical Officer agrees with the Investigator and the Applicant, that the patient's death and the SAEs which caused his death were unrelated to the study medication. The patient's pre-existing condition of pulmonary interstitial fibrosis with his hypertension and pulmonary embolism, as the Investigator assessed, was associated with his death.

Patient ID: 6613-09346
SAE 1: Lung Neoplasm Malignant
Outcome and Date: Ongoing at the Time of Death
SAE 2: Cancer Progression
Outcome and Study: Fatal, Study Day 11
SAE 3, 4, 5: Cardiovascular Insufficiency, Pulmonary Edema, Respiratory Failure
Outcome and Date: Ongoing at the Time of Death
This was an 84 year old white male with medical history significant for a 57 year smoking history, tricuspid and mitral valve incompetence, deep venous thrombosis, chronic respiratory failure, hypertension, congestive heart failure, and structural lung disease. Concomitant medications included ipratropium/fenoterol, fluticasone, metildigoxin, salmeterol, moduretic, and amlodipine. He received ceftaroline for 7 days to treat CAP (PORT Risk Class IV) in the left upper and lower lobes due to *Staphylococcus aureus* and *Moraxella catarrhalis*. At EOT, he was deemed a clinical cure.

On Study Day 10, an SAE of pulmonary malignancy was reported when cancer cells were found in the patient's sputum and infiltration was noted in the left lung by CT. On Study Day 11, he developed cardiovascular insufficiency, pulmonary edema, and respiratory failure, and was treated with furosemide, spironolactone, megestrol, perindopril, bisoprolol, and verapamil. Circulatory insufficiency and rapid cardiac failure were attributed to metastasis with cardiac involvement. He died on Study Day 11 due to malignant neoplasm progression and complications. It is unknown if an autopsy was performed.

The Investigator assessed the SAEs of malignant neoplasm, its progression, cardiovascular insufficiency, pulmonary edema, respiratory failure, and death as not related to the study medication. The Applicant agrees with this assessment, stating that the lung cancer predated the study medication.

Medical Officer Comment:
The Medical Officer agrees with the Investigator and the Applicant that the malignant neoplasm, possible metastases, and resultant death, is not related to the study medication.

Patient ID: 6804-09374
SAE: Cardiac Arrest
Outcome and Date: Fatal, Study Day 8
The patient was an 87 year old white male with medical history significant for a 50 year smoking history, significant cardiovascular disease, prostatitis, and structural lung disease (emphysema). Concomitant medications were aminophylline, enoxaparin, methylprednisolone, furosemide, and nifedipine. He received ceftaroline for 7 days to treat CAP (PORT Risk Class IV) in the left upper and lower lobes and the right upper lobe due to *Haemophilus parahaemolyticus* and *Escherichia coli*. ECGs were abnormal with tachyarrhythmia and atrial fibrillation. On Study Day 1, laboratory evaluation revealed hypoxemia and acidosis, elevated BUN, creatinine, and LDH. On Study Day 7 (EOT), he developed thrombocytopenia, elevated liver enzymes, acidosis, and atrial fibrillation. On Study Day 8, the patient was deemed a clinical cure with no abnormal findings noted on exam. On the same day, he was found dead. No resuscitative measures were performed. The patient had no evidence of deep vein thrombosis or pulmonary embolus and did not receive any treatments the night prior to his death as he was in stable condition. An autopsy revealed the primary cause of death was cardiac arrest from right ventricular cardiac failure from COPD and pneumonia.

The Investigator assessed the SAE of cardiac arrest and death to be unrelated to the study medication but due to underlying disease. The Applicant agreed with this assessment, given the autopsy findings and the presence of preexisting cardiac and pulmonary disease. The Applicant also points out that the liver enzymes had decreased prior to the EOT visit.

Medical Officer Comment:
The Medical Officer agrees with the Investigator and the Applicant that the cardiac arrest is unlikely to be related to the study medication, given the patient's atrial fibrillation and history of myocardial ischemia, hypertension, and atherosclerosis. These, exacerbated by the infection, likely caused his death. The elevation of LFTs and LDH, was mild and asymptomatic and may possibly be related to the study medication or underlying infectious illness.

Patient ID: 9008-09619

SAE 1: Septic Shock
Outcome and Date: Fatal, Study Day 13
SAE 2, 3, 4: Anoxic Encephalopathy, Toxic Encephalopathy, Severe Sepsis
Outcome and Date: Ongoing at the Time of Death
The patient was a 57 year old Asian male with medical history significant for a 15 year smoking history, diabetes, pulmonary tuberculosis, and structural lung disease. Concomitant medications included inhaled steroids, beta-agonists, anticholinergics, and pantoprazole. He received ceftaroline for 5 days to treat CAP (PORT Risk Class IV) in the left upper and lower lobes and right upper lobe with no isolated bacterial pathogen. At EOT, he was assessed as a clinical failure. He was moved to the ICU for high-flow oxygen, nebulization, and noninvasive ventilation with BIPAP. He was diagnosed with severe SAEs of anoxic encephalopathy, toxic encephalopathy, and septic shock. His condition rapidly deteriorated to cardiac arrest. He was mechanically ventilated, treated with inotropes, and the antibacterial coverage was changed to meropenem and vancomycin.

On Study Day 8-9, thrombocytopenia, abnormal clotting parameters, and worsening renal insufficiency developed. He was treated with hydrocortisone, budesonide, ipratropium bromide, levosalbutamol, piracetam, and amikacin. However, he developed refractory septic shock. Despite mechanical ventilation and high-dose inotropic support, he died on Study Day 13 with the cause of death reported to be refractory shock. An autopsy was not performed.

The Investigator, with the Applicant's concurrence, assessed the SAEs and death of the patient as unrelated to the study medication but due to the patient's underlying disease.

Medical Officer Comment:
The Medical Officer agrees with the Investigator and the Applicant that the patient's chronic illnesses such as diabetes and structural lung disease increased the patient's risk for a poor outcome from the infection and development of infectious complications such as sepsis and septic shock. However, this patient's SAEs that ultimately resulted to his death are a direct consequence of ceftaroline's failure to treat his infection.

This subject was among the nine patients excluded from efficacy and safety analyses, except in sections discussing Deaths and SAEs, because of issues with data integrity.

2. CABP Trials

B. Ceftriaxone

P903-08

Patient ID: 0044-08030
SAE: Cardiopulmonary Arrest

Outcome and Date: Fatal, Study Day 2
This was a 91 year old white male with a medical history significant for a 3 year smoking history, coronary artery disease, coronary artery bypass graft surgery in 2003, myocardial infarction (MI), pulmonary hypertension, atrial fibrillation, renal failure, ischemic cardiomyopathy, and moderate mitral insufficiency. Concomitant medications included oxygen, aspirin, and cefotaxime (prior to randomization). He was classified to be PORT Risk Class V. Two weeks prior to enrollment, he experienced acute onset of chest symptoms and shortness of breath with no ECG evidence of an acute MI.

He was treated with ceftriaxone for two days for community-acquired pneumonia (CAP) in the right upper lobe with no identified pathogen. Initial ECG showed ST depression with no T waves. A transthoracic echocardiogram showed a dilated left atrium, a moderately dilated right atrium and left ventricle, right ventricular pressure of 58 mm Hg and an ejection fraction of 33%, with diffuse hypokinesis and lateral akinesis.

On Study Day 2, he experienced an SAE of severe cardiorespiratory arrest while trying to ambulate from bed. Despite treatment with atropine, calcium chloride, dopamine, epinephrine, and cardiopulmonary resuscitation, the patient died.

The Investigator and Applicant both concur that the SAE of cardiorespiratory arrest was related to the infection in an elderly patient with underlying extensive cardiovascular disease such as ischemic cardiomyopathy and coronary artery disease.

Medical Officer Comment:
The Medical Officer agrees with both the Investigator and the Applicant's assessment, that the SAE is related to the patient's advanced age and severe cardiovascular disease. Based on the ECG findings suggestive of ischemia and dilated cardiomyopathy, death is probably from MI, rather than from the study medication/s.

Patient ID: 2031-08249
SAE: CAP Worsened, Septic Shock
Outcome and Date: Fatal, Study Day 23
The patient was a 50 year old white male with a medical history significant for a 32 year smoking history, MI, hypothyroidism, structural lung disease (COPD), and obesity. Concomitant medications included levothyroxine, metamizole, glucose, salbutamol, and saline.

He was treated for CABP (PORT Risk Class III) in the left lower and upper lobes and the right lower lobe and no isolated pathogen, with ceftriaxone for 2 days. On Study Day 2, the patient experienced worsening of the pneumonia with new infiltrates of the right lung and required mechanical ventilation and inotropic support. The antibacterial regimen was changed from ceftriaxone to piperacillin/tazobactam and levofloxacin. Another chest X-ray performed on Study Day 6 showed persistence of the right lung infiltrate and opacification of two thirds of the left lung, so antibacterial coverage was

changed to imipenem and vancomycin (Study Day 9-21). On Study Day 10 (TOC), the patient developed leukocytosis and severe renal insufficiency for which dialysis was started. On Study Day 15, a chest radiograph showed mild improvement.

However, on Study Day 17, the patient became confused. On Study Day 21, the patient required mechanical ventilation again and inotropic support. He subsequently experienced multiple organ failure and an SAE of septic shock. He died on Study Day 23. An autopsy was not performed.

The Investigator reported that the SAE of worsening CAP and septic shock was not related to the study medication but due to intercurrent illness. The Applicant agrees with this assessment, stating that the event and subsequent death were complications of bilateral CAP in a patient with longstanding smoking history, worsening renal function, and cardiopulmonary disease.

Medical Officer Comment:
From the narrative and case report form, it appears that antibacterial therapy was changed from ceftriaxone to piperacillin/tazobactam and levofloxacin because of insufficient therapeutic effect of the study medication. It also appears that the patient clinically improved on Study Day 15, a few days prior to the patient's episode of confusion. The arterial blood gas results at this time showed a normal pCO2 and a high HCO3, both inconsistent with the acidosis expected in septic shock and multi-organ failure. Hence, there was insufficient information about the patient's clinical course to support a diagnosis of septic shock.

Given that the patient was given only 2 days of the study medication, there is a lack of temporality between the SAE and death of the patient on Study Day 23. The patient's death is most probably unrelated to the study medication. However, with the information provided, it is unclear if septic shock may have caused the multiple organ failure that subsequently caused the demise of this patient.

Patient ID: 6531-08393
SAE: Cardiopulmonary Failure
Outcome and Date: Fatal, Study Day 14
This was an 81 year old white male with a medical history significant for a 33 year smoking history, cardiovascular disease, pancreatic insufficiency, dehydration, hyperglycemia, increased blood lactate dehydrogenase (LDH), and increased hepatic enzymes. Concomitant medications included atenolol, phenprocoumon, hydrochlorothiazide, pancreatin, quinapril, and oxazepam, among others. He was classified as PORT Risk Class IV. The patient was treated with ceftriaxone for 3 days for CAP in the right upper and lower lobes with no identified pathogen.

The patient developed cardiopulmonary failure necessitating cardiopulmonary resuscitation after becoming profoundly cyanotic. He was given inotropic support,

furosemide, heparin, sodium bicarbonate, sedatives, and paralytics. At EOT on Study Day 3, the patient was deemed a clinical failure and ceftriaxone was replaced with imipenem and fluconazole. A repeat chest X-ray done on Study Day 4 showed acute respiratory distress syndrome (ARDS) and signs of cardiac decompensation. On Study Day 14, the patient died from cardiopulmonary failure from extensive pneumonia and consequent cardiac decompensation with circulatory and renal failure. An autopsy was not performed.

The Investigator, with the agreement of the Applicant, assessed the SAE of cardiopulmonary failure as not related to the study medication, but rather due to the patient's extensive right bronchial pneumonia and consequent cardiac decompensation.

Medical Officer Comment:
The Medical Officer agrees with the Investigator and the Applicant's assessment that the patient's cardiopulmonary failure and subsequent death were not related to the study medication but rather a consequence of the patient's extensive infection, in the setting of acute respiratory distress syndrome (ARDS) and poor cardiac function.

Patient ID: 6828-08570
SAE: Cardiac Failure Acute
Outcome and Date: Fatal, Study Day 13
The patient was an 80 year old white female with a medical history significant for congestive heart failure (CHF), structural lung disease (emphysema), and recent exacerbation of CHF and emphysema 2 ½ weeks prior to study entry. Concomitant medications included enoxaparin and furosemide, among others. She received ceftriaxone for treatment for 7 days for CAP (PORT Risk Class IV) in the left lower lobe of the lung, with no identified pathogen.

Initial laboratory evaluation showed anemia, hyponatremia, and hypoalbuminemia. ECGs revealed atrial fibrillation. She was deemed a clinical cure on Study Day 7 (EOT). On the same day, the patient developed dyspnea with symptoms of cardiac and circulatory decompensation. Despite treatment with furosemide, her condition worsened so that on Study Day 13, she was diagnosed with an SAE of severe acute cardiac failure from CHF, leading to her death on the same day. No autopsy was performed.

The Investigator assessed that the SAE of cardiac failure was unrelated to the study medication but due to the patient's underlying disease. The Applicant agrees with this assessment, noting that the cause of death was acute cardiac failure alone unrelated to the 2 episodes of pneumonia.

Medical Officer Comment:
The Medical Officer agrees with the assessment of both the Investigator and the Applicant. The patient has chronic underlying cardiac and pulmonary disease that predisposed her to acute cardiac failure. Furthermore, as the Applicant stated, the

patient's clinical and radiologic improvement during the time the patient developed severe acute cardiac failure probably indicate that the pneumonia is not related to this SAE.

Patient: 8206-08236
SAE 1: Cardiomyopathy
Outcome and Date: Fatal, Study Day 12
SAE 2: Acute Urinary Retention
Outcome and Date: Ongoing at Time of Death
The patient was a 68 year old Asian male with medical history significant for asthma and diabetes. Concomitant medications included inhaled steroids, beta-agonists, anti-cholinergics, glibenclamide, and metformin. He received ceftriaxone for 7 days to treat CAP (PORT Risk Class III) of the left upper and lower lobe and right lung, caused by *Klebsiella pneumoniae*.

On Study Day 6, the patient developed shortness of breath attributed to a mild asthma attack. At EOT, Study Day 7, the patient was deemed a clinical cure and discharged. On Study Day 8, the patient experienced an SAE of moderate urinary retention due to the prior urethral catheterization and an SAE of severe cardiomyopathy, for which the patient was readmitted. ECG showed sinus tachycardia and left ventricular (LV) hypertrophy, while the echocardiogram showed poor ejection fraction (22%), poor LV function, mild tricuspid regurgitation, dilated heart chambers, dilated pulmonary artery, and global dyskinesis of the septum. A chest X-ray revealed resolving pneumonia along with cardiomegaly and bronchiectatic changes. Cardiac failure progressed and on Study Day 11 he developed hypotension treated with dopamine and spironolactone. On Study Day 12, he was found unresponsive. Despite resuscitation, the patient died with the immediate cause reported as heart failure. An autopsy was not performed.

The Investigator, with the Applicant's agreement, reported that the SAEs of cardiomyopathy and urinary retention were not related to the study medication but to underlying illnesses. The Applicant further states that the cardiomyopathy diagnosed resulted in acute heart failure which was the immediate cause of the patient's death.

Medical Officer Comment:
The Medical Officer agrees with the Investigator and the Applicant that the patient's SAE and the resultant death is not related to the study medication but to the underlying cardiomyopathy that resulted in acute heart failure. However, in the absence of an underlying cardiac condition and the temporal sequence between the development of cardiomyopathy and the administration of the study medication, it is plausible that the study medication may be related to the cardiomyopathy. Viral cardiomyopathy may be considered as etiology. While information provided in addition to the CRF and the case narrative verifies that cardiomyopathy was newly diagnosed 3 days after end of therapy with ceftriaxone, information such as concurrent symptoms was not provided. The etiology of the patient's cardiomyopathy was not definitively identified prior to his

demise. It is highly unlikely, however, that a severe, acute-onset, fatal case of cardiomyopathy could have resulted from a very recent ceftriaxone exposure, especially since no cases of ceftriaxone-associated cardiomyopathy have previously been reported. This patient most likely had pre-existing undiagnosed cardiomyopathy with decompensation during the current illness.

P903-09

Patient ID: 5011-09250
SAE: COPD Acute Heart-Respiratory Failure (Cardiopulmonary Failure)
Outcome and Date: Fatal, Study Day 5
This was a case of a 68 year old white male with medical history significant for a 58 year smoking history, chronic pancreatitis, cardiovascular disease, MI, toxic shock ischemia, respiratory failure, Grade II CHF, COPD with chronic bronchitis and emphysema, pulmonary hypertension, cerebrovascular disease, encephalopathy (secondary to hypertension and arteriosclerosis), urolithiasis, history of duodenal ulcer, and toxic hepatitis and hepatic steatosis from alcohol abuse. Concomitant medications included aminophylline, ipratropium bromide/fenoterol, prednisolone, enoxaparin, and omeprazole. He received 4 days of ceftriaxone to treat CAP (PORT Risk Class V) in the right and left lower lobes of the lungs, with no pathogen isolated.

ECGs were abnormal with atrial fibrillation and low T waves. Laboratory evaluation showed elevated liver enzymes which were attributed to alcohol abuse. Renal function tests show moderate renal insufficiency. On Study Day 5, the patient experienced a severe SAE of cardiopulmonary failure with change in sensorium. Despite resuscitation with inotropes, he died. An autopsy revealed no evidence of lung embolism or signs of pneumonia.

The Investigator assessed his death to be from acute circulatory failure caused by decompensation of the patient's cor pulmonale, pulmonary hypertension, and emphysema, aggravated by his coronary artery disease. The Applicant agrees with this assessment, stating that the cardiopulmonary failure was due to the stress of an acute lung infection in conjunction with significant preexisting cardiac and pulmonary disease.

Medical Officer Comment:
The Medical Officer concurs with the Investigator and Applicant. The SAE of cardiopulmonary failure probably resulted from the patient's multiple chronic cardiopulmonary conditions exacerbated by overwhelming infection. His death is probably not related to the study medication.

Patient ID: 5011-09540
SAE: Thromboembolism of Pulmonary Artery
Outcome and Date: Fatal, Study Day 27

The patient was a 75 year old white female with a medical history significant for obesity, impaired glucose tolerance, cardiovascular disease, cholecystitis, cerebrovascular disease, varicosity of deep veins of the lower extremities, multiple kidney disease, and prior episode of pneumonia. Concomitant medications included anti-hypertensives, diuretics, and digoxin, among others. She received 7 days of ceftriaxone for treatment of CAP (PORT Risk Class III) in the right lower lobe of the lung with a pleural effusion and no isolated pathogen. Baseline ECG showed atrial fibrillation which restored to sinus rhythm on Day 2. The patient was noted to have lower extremity deep venous thrombosis. Repeat chest X-ray on Study Day 7 showed worsening of the pleural effusion, with pleural fluid analysis showing Gram positive cocci on Gram stain. At EOT, on Study Day 8, the patient was deemed a clinical failure and antibacterial treatment was changed to ampicillin 1 gram IM QID from Day 8 to Day 14.

On Study Day 14, the right pleural effusion increased up to the level of the 4th rib. Thoracentesis was performed with negative pleural fluid culture result. A chest X-ray revealed an encapsulated large right pleural effusion. ECG done a few days later showed ST depression and negative T waves. On Study Day 22, pulmonary scintigraphy showed evidence of thromboembolism of the small branch of the right pulmonary artery. She was treated with warfarin. Her condition worsened on Study Day 24 with hypotension, tachycardia and dyspnea. At this time, she had soluble fibrin monomeric complexes. She developed multi-organ failure and encephalopathy and died on Study Day 27 from an SAE of pulmonary embolism. An autopsy done showed malignant mesothelioma of the parietal and visceral pleura of the right pleural cavity with lymph node metastases, acute myocardial infarction, coronary artery disease with old transmural post-infarction scarring, diffuse microfocal atherosclerotic cardiosclerosis, and recurrent thromboembolism. Cause of death was reported as pulmonary embolism combined with heart failure.

The Investigator, with concurrence from the Applicant, assessed the SAE of pulmonary embolism and death as unrelated to the study medication and due to the patient's underlying condition.

Medical Officer Comment:
The Medical Officer agrees with the assessment of the Investigator and Applicant that the SAE is unrelated to the study medication. The patient's undiagnosed malignancy in the pleural cavity, along with her obesity and deep venous thrombosis, predisposed her to a thrombotic state and subsequent pulmonary embolism and death.

Patient ID: 6511-09215
SAE 1: Pleural Effusion
Outcome and Date: Complete Recovery, Study Day 17
SAE 2 and 3: Hemiplegia, Cerebrovascular Accident
Outcome and Date: Ongoing at the Time of Death
SAE 4: Myocardial Infarction

Outcome and Date: Fatal, Study Day 19
This was an 88 year old white female with medical history significant for coronary artery disease, cerebrovascular accident (CVA), cardiac pacemaker insertion, DM, atrial fibrillation, and hypertension. Concomitant medications included aspirin, glimepiride, bisoprolol, and amlodipine. She was treated with ceftriaxone for 7 days for CAP (PORT Risk Class IV) in the right lower lobe of the lung with a small pleural effusion with no bacterial etiologic organism identified. At EOT, the patient was deemed a clinical failure because of persistent abnormal auscultatory findings and the antibacterial was changed to cefuroxime. She was discharged from the hospital on Study Day 9.

On Study Day 14, the patient developed cough, pain on respiration, and loss of appetite and was diagnosed with an SAE of severe pleural effusion. She was treated with torsemide and completely recovered by Study Day 17. At TOC, ECG showed atrial fibrillation. On Study Day 19, the patient developed SAEs of hemiplegia and CVA. Head CT done showed no intracranial bleeding and signs of cerebral ischemia but showed a perfusion defect in the right hemisphere in the posterior and mid-media branch group consistent with a thrombotic stroke. She was treated with lysis therapy. The patient also developed tachycardia and hypotension, and MI with ST elevation and ventricular tachycardia noted on ECG. Despite treatment with amiodarone, the patient died from myocardial infarction. No autopsy was performed.

The Investigator assessed the SAEs of pleural effusion, hemiplegia, CVA, myocardial infarction and death as unrelated to the study medication but due to the underlying medical disease including atrial fibrillation, hypertension and coronary artery disease. The Applicant agrees with this assessment.

Medical Officer Comment:
The Medical Officer concurs with the assessment that the SAEs of pleural effusion, hemiplegia, CVA, myocardial infarction, and death are unrelated to the study medication. The patient had severe chronic underlying cardiovascular disease which predisposed her to the thrombotic stroke, myocardial infarction, and her subsequent death.

Patient ID: 6612-09481
SAE 1: COPD Exacerbation
Outcome and Date: Ongoing at the Time of Death
SAE 2: Acute Respiratory Failure
Outcome and Date: Fatal, Study Day 6
This was a 78 year old white male with medical history significant for a 40 year smoking history, structural lung disease, peripheral vascular disease, diabetes, chronic cardiac failure, and supraventricular extrasystoles. Concomitant medications included salbutamol, metformin, fluticasone, formoterol, gliclazide, ipratropium, and theophylline. He received ceftriaxone for 5 days to treat CAP (PORT Risk Class IV) in the right middle and lower lobes of the lung with no isolated bacterial pathogen.

On Study Day 5, he was deemed a clinical failure and experienced an SAE of severe COPD exacerbation with radiologic confirmation. He developed severe bronchospasm, circulatory failure, and hypotension and treatment with mechanical ventilation, high-dose steroids, bronchodilators, digoxin, furosemide, glyceryl trinitreate, and morphine were initiated. On Study Day 6, the patient became asystolic and died. Cause of death was reported to be acute respiratory failure. It is unknown if an autopsy was performed.

The Investigator assessed the SAEs of acute respiratory failure, COPD, and subsequent death as unrelated to the study medication but rather due to the new acute infection. The Applicant agreed with this assessment.

Medical Officer Comment:
The Medical Officer agrees with the Investigator and Applicant that the SAEs and the death of the patient are unrelated to the study medication. The progressive infection, aggravated by his chronic cardiopulmonary conditions, predisposed him to develop a COPD exacerbation, acute respiratory failure, and subsequently, death.

Patient ID: 7004-09012
SAE: Coronary Artery Disease
Outcome and Date: Fatal, Study Day 22
The patient was an 82 year old white male with medical history significant for a 30 year smoking history, hypertension, myocardial fibrosis, CHF, atrial fibrillation, cerebral arteriosclerosis, benign prostatic hyperplasia, and ischemic stroke. Concomitant medications included aspirin, anti-hypertensives, drotaverine, furosemide, digoxin, and pentoxifylline. He received ceftriaxone for 7 days to treat CAP (PORT Risk Class IV) in the right lower lobe due to *S. aureus* and *K. pneumoniae*. At EOT and TOC, the patient was assessed as a clinical cure.

On Study Day 17, the patient developed worsening of CHF with pallor, enlarged abdomen, hepatomegaly, abdominal pain, arrhythmia, decreased heart sounds, bilateral lower extremity edema, and confusion. The ECG showed atrial fibrillation and a prolonged QTcB interval. On Study Day 22, the patient experienced an SAE of worsening coronary artery disease and died on the same day. The cause of death was reported to be from chronic coronary artery disease. No further information was provided and an autopsy was not performed.

The Investigator reported that the SAE of worsening coronary artery disease and death was unrelated to the study medication, but rather to the patient's underlying medical disease. The Applicant agrees with this assessment, noting that the worsening of the CHF occurred days after the last dose of study medication.

Medical Officer Comment:

Despite the paucity of information in the report regarding details surrounding the patient's death (symptoms and manifestations of worsening coronary artery disease that led to patient's death), the patient's worsening CHF and cardiovascular status, as noted by his abnormal ECG and symptomatology, may have contributed directly to the patient's death. Furthermore, the lack of temporal relationship between the administration of ceftriaxone and death makes association highly unlikely.

Patient ID: 7004-09332
SAE: Pulmonary Embolism
Outcome and Date: Fatal, Study Day 3
The patient was an 84 year old white female with a medical history significant for essential hypertension. Concomitant medications included glucose and acetylcysteine. She received ceftriaxone for 2 days for treatment of CAP (PORT Risk Class IV) in the left lower lobe with no isolated pathogen. On Study Day 3, the patient experienced an SAE of severe pulmonary embolism and was found unresponsive with hypotension and bradycardia. Despite treatment with intravenous fluids, sulfocamphocain, prednisolone, adrenaline and mechanical ventilation, she died on the same day.

An autopsy revealed massive thromboembolism of main trunks, lobular, and segmental branches of the pulmonary arteries, deep venous thrombophlebitis of the lower extremities, left lower lobe acinar pneumonia with severe peribronchial and focal pulmonary fibrosis, cor pulmonale, chronic coronary heart disease, and bilateral ventricular myocardial insufficiency. The cause of death was reported to be pulmonary embolism with acute circulatory failure.

The Investigator assessed the SAEs of pulmonary embolism and death to be unrelated to the study medication but due to intercurrent illness. The Applicant agrees with the Investigator's assessment, noting that the autopsy reported preexisting thrombophlebitis of the lower extremities and pulmonary embolism.

Medical Officer Comment:
The Medical Officer concurs with the Investigator and the Applicant that the pulmonary embolism and death was not related to the study medication but to the patient's chronic underlying cardiac and circulatory problems.

B. Deaths After Reporting Period (After LFU or more than 30 Days after EOT)

1. ABSSSI

A. Ceftaroline

P903-07

Patient ID: 2016-07561
SAE 1: Acute Pulmonary Edema
Outcome and Date: Complete Recovery, Study Day 17
SAE 2: Central Venous Catheter Related Infection
Outcome and Date: Complete Recovery, Study Day 28
SAE 3: Worsening of Renal Failure
Outcome and Date: Ongoing at the Time of Death
SAE 4: Dialysis Catheter-related Infection
Outcome and Date: Complete Recovery, Study Day 39
SAE 5: Multi-organ Failure
Outcome and Date: Fatal, Study Day 45
This was a case of a 61 year old white male with past medical history significant for ischemic cardiomyopathy, congestive heart failure (CHF), DM, hypertension, brain ischemia, renal failure, left hemiplegia, left leg lymphedema, paresthesia, and cellulitis. Concomitant medications include antihypertensives, ranitidine, insulin, tramadol, and cefalotin (prior to randomization).

He was treated with ceftaroline for 2 days. Baseline ECGs showed slight QTcB prolongation. Laboratory evaluation showed acidosis and moderate renal insufficiency. On Study Day 2, the patient experienced a life threatening SAE of acute pulmonary edema and a moderate AE of renal impairment. Ceftaroline was discontinued on Study Day 2. Vasopressors, bronchodilators, sedatives and paralytics were started, along with mechanical ventilation. The patient completely recovered on Study Day 17. However, the patient developed a life-threatening SAE of central line infection (central venous catheter-related) due to methicillin-resistant *Staphylococcus aureus* (MRSA) for which he was treated with vancomycin and imipenem. He recovered from this infection on Study Day 28. However, on the same day, the patient developed an *Enterobacter amnigenus* dialysis catheter infection and was treated with imipenem, vancomycin and removal of the catheter.

On Day 41, the patient developed multi-organ failure, with hypotension and anuria and was mechanically ventilated. On Day 45, he developed bradycardia and asystole with no response to cardiopulmonary resuscitation. He died on the same day due to multi-organ failure. No autopsy was performed.

The Investigator assessed the SAEs of acute pulmonary edema, central line infections, renal failure, and multi-organ failure which caused the patient's demise, were not related to ceftaroline but related to the patient's underlying disease or procedure. The Applicant agreed with the Investigator that the SAEs were related to the patient's preexisting cardiac disease, heart failure, and renal disease, all of which were exacerbated by underlying infections.

Medical Officer Comment:

The Medical Officer agrees with the Investigator and the Applicant that the multi-organ failure which may have caused the patient's death was unrelated to the study drug, but to the patient's ischemic cardiomyopathy, CHF, diabetes, arterial hypertension, brain ischemia, and renal failure, exacerbated by his underlying infections. Temporal association between ceftaroline treatment and the development of life-threatening SAEs leading to his death (Day 41) is not present. Moreover, septic shock from the MRSA central line infection and the Enterobacter amnigenus *dialysis catheter infection may have also been related to his demise despite his reported recovery from these infections on Study Day 39.*

Patient ID: 5017-07652
SAE: Myocardial Infarction
Outcome and Date: Fatal, Study Day 45
The patient was a 74-year old white female with a medical history significant for diabetes, cardiovascular disease, anemia, and trophic ulcer. Concomitant medications included metformin and glibenclamide, ASA, metoprolol, isosorbide dinitrate (ISDN), papaverine, nifedipine, bendazol, hydrochlorothiazide, and ketorolac.

The patient was treated with ceftaroline for 5 days for an infected right leg ulcer secondary to *Staphylococcus aureus* and *Streptococcus agalactiae* isolated from tissue culture. She also had moderate renal insufficiency, mild anemia and 2 baseline ECGs suggestive of ischemia.

On Study Day 19, the patient developed a life-threatening SAE of myocardial infarction with severe chest pain and with ECG changes. She was transferred to the cardiology unit where atrial fibrillation was diagnosed and where she was treated with heparin, insulin, propranolol, and captopril, among other medications. However, her condition deteriorated with repeated myocardial infarction and paroxysmal atrial fibrillation. She died on Study Day 45 from myocardial infarction. An autopsy was not performed.

The Investigator reported that the SAE of myocardial infarction and subsequent death was not related to the treatment with ceftaroline but due to the patient's underlying conditions of ischemic heart disease and diabetes mellitus. The Applicant agreed with the Investigator, further stating that the medication was completed approximately 2 weeks prior to the event.

Medical Officer Comment:
The Medical Officer agrees with the Investigator and the Applicant that the patient's myocardial infarction, complicated by paroxysmal atrial fibrillation and death, was unrelated to the study medication. The SAE and outcome are most possibly related to the patient's chronic condition of ischemic heart disease, atherosclerosis, hypertension, angina pectoris, and history of myocardial infarction.

B. Vancomycin plus Aztreonam

P903-07

Patient ID: 2106-07694
SAE: Bleeding of Surgically Debrided Skin Ulcer
Outcome and Date: Complete Recovery, Study Day 32
The patient was a 54 year old white male with a medical history of peripheral vascular disease, hypertension, and bilateral leg ulcers. Concomitant medications include antihypertensives, acetylsalicylic acid (ASA), enoxaparin, tigecycline, among others.

He was treated with vancomycin plus aztreonam for 14 days for an infected leg ulcer due to *Enterobacter cloacae*. AEs reported were anemia, pyrexia, wound necrosis with peripheral edema and pain, hypotension, constipation, deep vein thrombosis, anorexia, and myiasis in the left foot lesion. At EOT and TOC, the patient was deemed a clinical cure. However, on Study Day 25, the patient was treated with tigecycline for recurrence of infection of the ulcers of both legs. On Study Day 31, he underwent surgical debridement of the ulcers and developed an SAE of post-procedural hemorrhage with hypotension and anemia. Treatment with compression, blood transfusions, and discontinuation of enoxaparin and ASA were done. The patient recovered on Study Day 32.

On Study Day 64 (29 days after the LFU visit), the patient reportedly was started on cefepime for treatment of recurrent skin ulcers. He was also diagnosed with severe peripheral vascular disease and bilateral leg amputation was planned. However, on the surgical date, the patient was found unconscious and unresponsive. The patient was pronounced dead on Study Day 66. No autopsy was performed and the cause of death was unknown.

The Investigator reported that the SAE (post-procedural hemorrhage) was unrelated to the study medication (vancomycin and aztreonam) and attributed the SAE to the patient's embolism prophylaxis with enoxaparin and ASA. The Applicant agreed with the Investigator that the post-procedural hemorrhage was secondary to anticoagulants and not to the study medication.

Medical Officer Comment:
The Medical Officer agrees with the Investigator and the Applicant that the SAE of post-procedural hemorrhage was related to the use of prophylactic anticoagulants and not the study medications. Death occurred outside the SAE reporting window. Because an autopsy was not performed and the circumstances surrounding the patient's death were unknown, more information was requested. The Investigator responded to a Query Resolution from the Applicant by stating that the night prior to his death, the patient was conscious and awake with normal vital signs and no complaints and that he was found unconscious the next morning. The Investigator, with no pathological diagnosis from an

autopsy, suspects that the cause of death was unconfirmed cardiovascular disease (arrhythmia or infarct) or pulmonary embolism.

With death occurring 52 days after the last dose of vancomycin/aztreonam, there is a lack of temporal association between the study drugs and the patient's death. Furthermore, other antibacterials such as tigecycline and cefepime confound the case and make association between the patient's death and study medications highly unlikely.

Patient ID: 6511-07312
SAE 1: Clinical Worsening of General Conditions
Outcome and Date: Ongoing at the Time of Death
SAE 2: Chronic Lymphocytic Leukemia Recurrent
Outcome and Date: Fatal, Study Day 43
The patient was a 72 year old white female with a medical history significant for chronic lymphocytic leukemia (CLL), diabetes, cardiovascular disease, osteoporosis, and bilateral leg ulcers, among others. Concomitant medications included insulin, nadroparin calcium, bisoprolol, and allopurinol, among others. She was treated with vancomycin/aztreonam for deep/extensive leg cellulitis with no identified pathogen for 2 days.

On treatment, the patient had persistent fever (38.8-40 degrees C) and leukocytosis (WBC count of 57.8 x 10^3) on Study Day 2. Her blood cultures grew *Achromobacter xylosoxidans* on Study Day 3, therefore the study medication was replaced with tazobactam. On Study Day 4, a chest X-ray revealed an endothoracic goiter with left calcification, and increased expansion of the right upper mediastinum and the hilum. Because of the increasing size of the lesions without inflammatory infiltrates, recurrent chronic lymphocytic leukemia (CLL) was suspected and treated with a dose of immunoglobulin. She also received another cycle of bendamustine chemotherapy, having previously received this medication on Study Day -22, and was placed on prednisolone and moxifloxacin. She was then discharged on Study Day 20.

On Study Day 39, she was readmitted for a moderate SAE of recurrent chronic lymphocytic leukemia for planned chemotherapy. Unconfirmed reports stated that chemotherapy was not initiated because of her poor general condition. Instead, parenteral nutrition and symptomatic therapy were started. The patient died on Study Day 43 due to recurrent chronic lymphocytic leukemia. An autopsy was not performed.

The Investigator assessed that her aggravated condition and recurrent CLL was unrelated to the patient's treatment with vancomycin and aztreonam but was related to the CLL blast crisis and sepsis from the *Achromobacter xylosoxidans* infection. The Applicant agreed with the Investigator stating that the SAEs and death were related to the progressive, intermittent natural history of her underlying disease.

Medical Officer Comment:
The Medical Officer concurs with the assessment of both the Investigator and the Applicant.

2. CABP

A. Ceftaroline

P903-08

Patient ID: 5528-08119
SAE: Pancreatic Neoplasm
Outcome and Date: Fatal, Study Day 68
The patient was a 91 year old white female with a medical history significant for atrial fibrillation, paresthesia, chronic renal failure, hypertension, hypokalemia, Parkinson's disease, and reflux. Concomitant medications included anti-hypertensives, pantoprazole, digoxin, domperidone, metoclopramide, ondansetron, and paracetamol. She was treated with ceftaroline for 7 days for CAP (PORT Risk Class IV) of the right and left lower lobes with no identified etiology at baseline.

She developed progressive prolongation of coagulation parameters for which she received vitamin K to reverse anticoagulation on Study Day 4. On the same day, because of abdominal pain and difficulty eating, an ultrasound and an abdominal CT were done. The ultrasound revealed a retroperitoneal mass. The CT scan characterized the mass as a hypodense pancreatic tumor with duodenal infiltration that was probably responsible for the patient's gastric stasis. In addition, small peripancreatic and inter-aorticocaval nodes about 1 cm in diameter were noted. The remaining pancreas was atrophied. No bony lesions suggestive of metastasis were observed. She underwent gastroscopy and insertion of a duodenal stent. No treatment for the pancreatic cancer was planned because of her poor prognosis. The patient finished study participation. She died from pancreatic adenocarcinoma on Study Day 68. An autopsy was not performed.

The Investigator, with agreement from the Applicant, reported that the pancreatic neoplasm was not related to the study medication.

Medical Officer Comment:
The Medical Officer concurs with the assessment of the Investigator and the Applicant.

B. Ceftriaxone

P903-08

Patient ID: 5027-08585
SAE: Worsened Myopathy
Outcome and Date: Fatal, Study Day 50
This was a 62 year old white male with a medical history significant for muscular dystrophy/oculopharyngeal dystrophy, prior episodes of pneumonia, myocardial ischemia, hypertension, gastric ulcer, and chronic pyelonephritis. He was classified as PORT Risk Class III. Concomitant medications included enalapril, verapamil, and gentamicin (prior to randomization). He was treated with ceftriaxone for 2 days for CAP of the right lower lobe due to *Klebsiella pneumoniae* and *Escherichia coli*. Laboratory evaluation was normal. He discontinued treatment when consent was withdrawn.

He experienced an AE of moderate asthenia on Study Day 3 and a life-threatening SAE of severe worsened myopathy after going into cardiac arrest after asphyxiating on food. The Investigator assessed the cardiac arrest as directly associated with worsening of the underlying oculopharyngeal myopathy. He was admitted to the ICU for mechanical ventilation. A chest X-ray performed on Study Day 7 showed passive congestion and infiltrates in the lower lungs. A bronchoscopy revealed a large-volume gastric content aspiration, consistent with a diagnosis of aspiration pneumonia. The patient was treated with cefotaxime, metronidazole, amikacin, pentoxifylline, Dexon, proserin, ranitidine, subcutaneous heparin, and ciprofloxacin. He died on Study Day 50 from complications of oculopharyngeal myopathy-associated aspiration. An autopsy was not performed.

The Investigator assessed the SAE of worsened myopathy and death as not related to the study medication but due to the patient's progression of myopathy and associated aspiration. The Applicant agrees with this assessment, given the patient's chronic history of oropharyngeal dystrophy and other medical conditions.

Medical Officer Comment:
While it appears from the narrative and the case report form that the patient's SAE and death were caused by complications from aspiration pneumonia related to the worsening myopathic condition, details from Study Day 7 when aspiration pneumonia was radiologically diagnosed and bronchoscopically verified to Study Day 50 when the patient died, are lacking. Information submitted by the Applicant shows that Query Resolutions were requested from the Investigator concerning aspiration pneumonia that failed to improve during a five-week period. The Investigator stated that as previously stated, the patient died from myopathy-associated aspiration that had not improved from the date of diagnosis on (b) (6) *to the patient's demise on* (b) (6) *and that the patient remained in the ICU throughout the duration of his hospital stay. Although it is difficult to discount a potential role of the study medication or concomitant medications such as gentamicin in contributing to the exacerbation of the patient's myopathy, the Medical Officer agrees that the SAE of myopathy-associated aspiration was related to his chronic history of oropharyngeal dystrophy and worsening myopathy, rather than ceftriaxone which was administered for only 2 days.*

Patient ID: 6204-08575
SAE: Hospital-Acquired Pneumonia
Outcome and Date: Fatal, Study Day 43
The patient was a 70 year old white male with a medical history significant for a 40 year smoking history, HIV infection, diabetes, spinal osteoarthritis, hypercholesterolemia, and recent *Pneumocystis carinii* infection. Concomitant medications included gliclazide, metformin, insulin, and antiretroviral therapy (emtricitabine with tenofovir), among others. He was treated with ceftriaxone for treatment for 7 days for CABP (PORT Risk Class IV) of the left lower lobe and right lobes caused by *Streptococcus pneumoniae* isolated from bronchoalveolar lavage (BAL).

On Study Day 4, a CD4 count was 426/mm^3 and the patient developed increasing purulent secretions and decreasing $Pa0_2/Fi0_2$ ratio with persistent *Streptococcus pneumoniae* bacteremia. On Study Day 7 (EOT), the patient was diagnosed with an SAE of severe hospital-acquired pneumonia (HAP) with *Pseudomonas aeruginosa* isolated from a BAL sample after continued fever, leukocytosis and a chest X-ray showing worsening pneumonia. Deemed a clinical failure, ceftriaxone was discontinued and replaced with amikacin, colistin, piperacillin, ticarcillin and clavulanic acid, vancomycin, erythromycin, ciprofloxacin, and ceftazidime, after another BAL on Study Day 14 grew *P. aeruginosa* and *Stenotrophomonas maltophilia*. Because of worsening respiratory status, he was mechanically ventilated, sedated with fentanyl, midazolam, and pancuronium, and treated with inotropes. The patient died on Study Day 43 from prolonged multiorgan failure associated with HAP. An autopsy was not performed.

The Investigator assessed the HAP as not related to the study medication, but rather due to *Pseudomonas aeruginosa* infection. The Applicant agrees with this assessment and notes that the patient's chronic conditions contribute to immune suppression with increased risk for infection and poor outcome.

Medical Officer Comment:
The Medical Officer concurs with the Investigator and the Applicant that HAP, which ultimately caused the patient's death, can not be attributed to the study medication. The patient's multi-organ failure, was consistent with sepsis and/or septic shock, and was a complication of the overwhelming nosocomial infection that the patient, which due to chronic underlying immunosuppression from HIV infection and diabetes, he was predisposed to.

Patient: 6634-08108
SAE 1: COPD Exacerbation
Outcome and Date: Resolved to Stability, Study Day 34
SAE 2: COPD Exacerbation
Outcome and Date: Fatal, Study Day 47
The patient was a 65 year old white male with a medical history significant for a 30 year smoking history, hypertension, diabetes, structural lung disease (moderate COPD),

previous pneumonia, and alcohol abuse. Concomitant medications included steroids, anticholinergics, beta-agonists, and antihypertensives, among others. The patient received ceftriaxone for 7 days to treat a right middle lobe pneumonia (PORT Risk Class III) with no identified etiology. Laboratory evaluation was unremarkable from baseline to TOC evaluation except for initial hypoxia. At TOC, a chest X-ray showed improvement of the right middle lung infiltrates with residual symptoms of mild cough and abnormal auscultatory findings.

On Study Day 24, the patient experienced an exacerbation of chronic obstructive pulmonary disease (COPD) that required admission to the ICU for mechanical ventilation. A chest X-ray showed the absence of focal and infiltrative lesions. He was treated with amoxicillin/clavulanate and metronidazole from Study Day 23-24 along with inhaled beta-agonists and steroids. He was discharged from the hospital in stable condition on Study Day 34.

However, on Study Day 37, the patient developed another exacerbation of COPD for which he was readmitted to the ICU. He was treated with amoxicillin/clavulanate and ciprofloxacin, along with midazolam, promethazine, enoxaparin, hydrocortisone, insulin, beta-agonists, steroids, and mechanical ventilation. He was stabilized after 6 days (Study Day 43) and moved to the regular floor. However, he refused to take any inhalation therapy and within 3 days, he deteriorated with respiratory distress and hypoxia. ECG revealed sinus tachycardia and atrioventricular overload. On the same day (Study Day 47), the patient developed respiratory and circulatory failure and died. An autopsy was not performed.

The Investigator assessed the SAEs of COPD exacerbation and death as not related to the study medication but related to the patient's COPD. The Investigator did not consider the respiratory failure, which caused the death of the patient, as a separate adverse event. The Applicant agreed with the Investigator's assessment that the exacerbations and death were related to the patient's COPD, continued smoking, and poor compliance.

Medical Officer Comment:
The Medical Officer agrees with the Investigator and the Applicant that the patient's underlying COPD, in addition to his poor compliance, is directly related to the patient's SAEs and subsequent death.

P903-09

Patient 6506-09105
SAE: Lung Infection Pseudomonal
Outcome and Date: Fatal, Study Day 70

The patient was a 58 year old white male with a medical history significant for a 45 year smoking history, structural lung disease, hyperthyroidism, hypertension, left lung abscess, and tracheobronchomegaly. Concomitant medications include hydrochlorothiazide, losartan, budesonide, amlodipine, Decortin, theophylline, tiotropium, and prednisolone. He received ceftriaxone for a total of 7 days for treatment of CABP (PORT Risk Class III) in the left upper and right middle lobes caused by *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Despite clinical and radiographic improvement, he was deemed a clinical failure after 7 days of treatment with ceftriaxone so coverage was changed to levofloxacin. On Study Day 12, he was discharged clinically improved from the hospital.

On Study Day 20, at TOC, the subject was rehospitalized because of productive cough and leukocytosis. Chest X-ray showed a new infiltrate in the R mid field of the lung with no pleural effusion and a Sputum culture grew *Pseudomonas aeruginosa*. He was treated with levofloxacin, imipenem, and piperacillin/sulbactam. His condition deteriorated and a CT scan of the chest on Study Day 28 revealed the formation of an abscess in the posterior upper lobe segment and bilateral cupula calluses indicative of reactive tuberculosis. A T-Spot TB test was negative. Despite treatment, by Study Day 40, new infiltrates appeared in the left middle and superior pulmonary fields. Sputum culture isolated moderate *Candida albicans, Pseudomonas putida, and Enterococcus faecalis* on Study Day 67. On Study Day 70, due to an enlarging, extensive, and confluent infiltrate occupying his whole left lung, the patient died of respiratory failure and ventilation insufficiency. No resuscitation was performed and no autopsy was done.

The Investigator and the Applicant reported the SAE of persistent Pseudomonas lung infection as unrelated to the study medication. Because of his prolonged smoking history, prior history of lung abscess, prior hospitalization for treatment of pneumonia, and underlying structural lung disease, he was at higher risk to develop infections from Gram-negative and resistant organisms.

Medical Officer Comment:
The Medical Officer concurs with the Applicant that the patient's underlying pulmonary condition, prior history of a pulmonary pathology, and previous hospitalization increase his risk of infection with a Gram-negative or resistant pathogen that may be difficult to treat.

Overall Mortality Analysis:

Deaths from any etiology were included in the analysis of the safety population comprised of patients in the Clinical Pharmacology studies and the Phase 2 and Phase 3 pivotal trials. For the Clinical Pharmacology studies, mortalities occurring up to 30 days from the last dose of the study drug were included while for the Phase 3 trials, mortalities occurring within the LFU date (or 30 days after EOT if there was no LFU visit) were included. In addition, patients in the four Phase 3 trials were followed for

deaths occurring after the LFU date (or 30 days after the EOT). The inclusion of all-cause mortality during participation in the Clinical Pharmacology, Phase 2, and Phase 3 studies/trials and deaths occurring after completion of participation in the study or after a patient left a study (either because of premature withdrawal or premature discontinuation of the study drug) is reasonable since the study medication is an new molecular entity (NME) and information on safety is limited. Because ceftaroline has a prompt onset of action and a relatively short elimination half-life, four weeks after completion or discontinuation of the drug is a reasonable time to monitor for mortality that might reflect drug toxicity.[22]

Narrative summaries were primarily based on the Investigator's completed case report forms (CRFs), inpatient admission chart reviews, consultant reports, and if performed, autopsy reports. From the narratives of the mortality cases and the assessments of both the Investigator and the Applicant, it appears that the method of analyzing overall mortality and cause-specific mortality is both appropriate and generally adequate to assess association and/or causation. There were 6 deaths, however, whose narratives and CRFs did not contain sufficient information to determine association (Table 75) because the narrative lacked information on cause of death (unknown vs. sudden death) or need for further information as to how the reported SAE could have caused the patient's death. The Applicant provided more information regarding these deaths when queried.

Table 75. Medical Officer's List of Deaths with Insufficient Information to Assess Causation of Death

Patient ID	Cause of Death	Study Day of Death	Information Needed from Source Documents
ABSSSI			
5007-06358	Malignant neoplasm progression	17	Circumstances surrounding death, immediate cause of death, and explanation of how neoplasm caused death
2106-07694	Unknown (cardiovascular disease, arrhythmia, infarct, or pulmonary embolism)	66	Circumstances surrounding death, immediate cause of death
CABP			
2034-08238	Sudden death	3	ECG results, VS, and assessments done preceding death, during, and after resuscitation
5027-08585	Myopathy	50	Circumstances surrounding death
6626-08148	Multi-organ disorder	14	Clinical status, physician assessments, documentation of alcohol dependence
8206-08236	Cardiomyopathy	12	ECG results and laboratory evaluation done for diagnosis of cardiomyopathy as cause of death of a patient with no history of cardiomyopathy.

The Investigator and the Applicant's assessment of association between the SAEs reported as the cause of death appeared to be sound and logical. The Medical Officer agrees with the assessment of association of the study drug and medication in all the mortality cases, based on the information contained in the narrative summaries, with one death potentially associated with ceftaroline and another death potentially associated with ceftriaxone. (Table 74)

In particular, the Medical Officer concurs with Applicant regarding the potential association of the sudden death of Patient 2034-08238 with ceftaroline and of the multi-organ disorder that led to the demise of Patient 6626-08148. For Patient 2034-08238 who was found unresponsive on Day 3, the absence of a plausible alternative cause of death from the history and physical examination at the time of resuscitation and the lack of autopsy findings make this unexpected death potentially related to ceftaroline.

For Patient 6626-08148 who expired on Study Day 14 after initially having an increased fibrin D-dimer and deteriorating hepatic failure culminating in an SAE of multi-organ dysfunction syndrome, the patient's death and administration of ceftriaxone is potentially related. With conflicting reports of a history of alcoholism and the absence of findings consistent with hypersensitivity and immune-related reactions, the temporal association between ceftriaxone and hepatotoxicity with multi-organ dysfunction points to a possible association between ceftriaxone and this unexpected death.

When the etiologies of the deaths are classified using Preferred Terms (PTs) and by System Organ Class (SOC), the causes of death appear to be varied and distributed among different SOCs. Deaths in the pooled Phase 3 CABP trials for both treatment groups (ceftaroline versus comparator groups) tended to be caused by respiratory, thoracic, and mediastinal disorders (5 in ceftaroline-treated patients versus 3 in comparator-treated patients), neoplastic disorders (5 in the ceftaroline group versus none in the comparator group), and cardiac disorders (3 in the ceftaroline group versus 7 in the comparator group). In the ABSSSI studies, three deaths were reported for the ceftaroline treatment group (one from cardiopulmonary failure and two from malignant neoplasms).

Overall, it appears that ceftaroline is not associated with the SAEs that have an outcome of death, except for possibly for one case of sudden death.

Table 76. Incidence of SAES with an Outcome of Death in Pooled Phase 3 Trials

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=613) n (%)	Ceftriaxone (N=615) n(%)	Ceftaroline (N=1305) n(%)	Pooled Comparators (N=1301) n(%)
Patients with at Least Once SAE with an Outcome of Death	3 (0.4)	0	15 (2.4)	12 (2.0)	18 (1.4)	12 (0.9)
Cardiac Disorders	1 (0.1)	0	2 (0.3)	7 (1.1)	3 (0.2)	7 (0.5)
Cardiac arrest	0	0	1 (0.2)	0	1 (0.1)	0
Cardiac failure	0	0	1 (0.2)	0	1 (0.1)	0
Cardiopulmonary failure	1 (0.1)	0	0	1 (0.2)	1 (0.1)	1 (0.1)
Cardiac failure acute	0	0	0	1 (0.2)	0	1 (0.1)
Cardio-respiratory arrest	0	0	0	2 (0.3)	0	2 (0.2)
Cardiomyopathy	0	0	0	1 (0.2)	0	1 (0.1)
Coronary artery disease	0	0	0	1 (0.2)	0	1 (0.1)
Myocardial Infarction	0	0	0	1 (0.2)	0	1 (0.1)
General disorders and	0	0	2 (0.3)	1 (0.2)	2 (0.2)	1 (0.1)

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=613) n (%)	Ceftriaxone (N=615) n(%)	Ceftaroline (N=1305) n(%)	Pooled Comparators (N=1301) n(%)
administration site conditions						
Sudden death	0	0	2 (0.3)	0	2 (0.2)	0
Multi-organ disorder	0	0	0	1 (0.2)	0	1 (0.1)
Infections and infestations	0	0	3 (0.5)	1 (0.2)	3 (0.2)	1 (0.1)
Pneumonia	0	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Sepsis	0	0	1 (0.2)	0	1 (0.1)	0
Septic Shock	0	0	1 (0.2)**	0	1 (0.1)**	0
Neoplasms benign, malignant, and unspecified	1 (0.1)	0	4 (0.7)	0	5 (0.4)	0
Malignant neoplasm progression	1 (0.1)	0	1 (0.2)	0	2 (0.2)	0
Lung neoplasm malignant	0	0	1 (0.2)	0	1 (0.1)	0
Metastases to liver	0	0	1 (0.2)	0	1 (0.1)	0
Metastatic neoplasm	0	0	1 (0.2)	0	1 (0.1)	0
Respiratory, thoracic, and mediastinal disorders	1 (0.1)	0	4 (0.7)	3 (0.5)	5 (0.4)	3 (0.2)
Respiratory failure	1 (0.1)	0	2 (0.3)	0	3 (0.2)	0
Interstitial lung disease	0	0	1 (0.2)	0	1 (0.1)	0
Pulmonary embolism	0	0	1 (0.2)	2 (0.3)	1 (0.1)	2 (0.2)
Acute respiratory failure	0	0	0	1 (0.2)	0	1 (0.1)

Source: Adapted from Table 8.4.1.1-1. Integrated Summary of Safety (cSSSI and CABP). P. 155-6..
** One death was reported at an India site with data integrity issues.

7.3.2 Nonfatal Serious Adverse Events

Overall, across the pooled Clinical Pharmacology, Phase 2, and Phase 3 studies/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. Comparing the ceftaroline group and the comparator/placebo group for the different indications in the Safety Population, the number of patients who experienced at least one SAE is as follows:

Table 77. Number of patients experiencing at least one SAE by indication

Indication	Study/Trial	Ceftaroline Group n (%)	Comparator or Placebo Group n(%)
ABSSSI	P903-17 (IM Ceftaroline vs cefepime)	0	0
	Phase 2	7/165 (4.2%)	2/77 (2.6%)
	Phase 3	30/692 (4.3%)	28/686 (4.1%)
CABP	Phase 3	67/608 (11.0%)*	72/611 (11.8%)*
Total	Pooled Pharmacology, Phase 2 and 3 Trials	106/1701 (6.2%)	102/1452 (7.0%)

Source: Adapted from the Integrated Summary of Safety, p. 164..
*Nine patients were excluded from Trial P903-09 in the CABP trials because of data integrity.

Of the patients from the overall Safety Population who experienced SAEs, eighteen SAEs in 17 patients were assessed by an Investigator as related to the study drug, with

two patients having an outcome of death as discussed in the section on mortality. (Table 78)

Table 78. Patients with SAEs from Pooled Safety Population (Clin. Pharm, Phase 2, and Phase 3 Trials) With Investigator and Medical Officer Assessment of Association

Patient ID	Serious Adverse Event	Body System	Study Drug Discontinuation or Study Withdrawal	Severity	Investigator Assessment of Association	Medical Officer Assessment of Association
ABSSSI, ceftaroline group						
2012-06611	Hypersensitivity	Potential allergic reaction	Yes	Severe	Yes	Yes
3004-06679	*Clostridium difficile* colitis	Potential antibiotic-associated diarrhea	Yes	Severe	Yes	Yes
0003-07006	Anaphylactoid reaction	Potential allergic reaction	Yes	Severe	Yes	Yes
6515-07368	Anaphylactic shock	Potential allergic reaction	Yes	Severe	Yes	Yes
ABSSSI, vancomycin/aztreonam group						
2006-06444	Hypersensitivity	Potential allergic reaction	Yes	Moderate	Yes	Yes
0026-07208	Hypocoagulable state		No	Severe	Yes	Yes
5014-07586	Acute renal failure	Renal Organ System	Yes	Moderate	Yes	Yes
CABP, ceftaroline group						
2034-08238	Sudden death		Yes	Severe (outcome of death)	Yes	Yes
8203-08218	Liver function test abnormal	Hepatic organ system	No	Severe	Yes	Yes
6509-09273	Convulsion	Potential drug-induced seizure	No	Severe	Yes	Unlikely
CABP, ceftriaxone group						
2029-08223	Acute cholecystitis		No	Severe	Yes	Yes
2029-08266	Hypersensitivity	Potential allergic reaction	No	Severe	Yes	Yes
6531-08083	Gastroenteritis		No	Severe	Yes	Unlikely
6626-08148	Hepatic failure	Hepatic organ system	Yes	Severe (outcome of death)	Yes	Yes
	Multi-organ disorder		Yes	Severe	Yes	Yes
6641-08578	Acute hepatic failure	Hepatic organ system	Yes	Severe	Yes	Yes
3005-09131	Hepatic enzyme increased	Hepatic organ system	Yes	Severe	Yes	Yes
Phase 2 IV Study, vancomycin/aztreonam group						
2002-00001	Interstitial nephritis	Renal organ system	No	Severe	Yes	Yes

*Considered Not Related by Investigator but classified as Potentially Drug-Related in the Integrated Summary of Safety
Source: Summarized from Integrated Summary of Safety (ABSSSI and CABP), p 165-175.

In the pooled Phase 3 trials, 16/197 (8.1%) of patients experiencing at least one SAE (7 patients (3.5%) in the ceftaroline group versus 9 patients (4.6%), in the comparator treatment group, respectively) experienced SAEs assessed as related to the study drug. Of these 16 patients, ten patients (5 ceftaroline-treated versus 5 comparator-treated)

experienced SAEs that led to the premature discontinuation of the study drug or to the withdrawal from the study. Table 78 also lists the SAEs leading to either discontinuation of study drug or withdrawal from the study.

SAEs were uncommon in the pooled safety population of the four Phase 3 trials and were assessed as unrelated to ceftaroline or the comparator drug in the majority of the patients. The most common SAE SOC in both treatment groups was in the Infections and Infestations SOC (2.3% or 30/1300 in the ceftaroline group vs 2.4% or 32/1302 in the comparator group), with pneumonia being the most frequent preferred term.The incidence of the SAEs assessed as related to the study drug was similar between the ceftaroline and the comparator treatment groups.

A brief narrative of the patients in the Safety Population who experienced SAEs assessed to be related to the study medication follows:

- Patient 2012-06611: Hypersensitivity (Recovered)
  This is a 49 year old Hispanic white male with a medical history relevant for hypertension with no documented history of hypersensitivity to ß-lactam antibacterials. He was enrolled in Trial P903-06 for treatment of a *Staphylococcus aureus* hand wound with ceftaroline. On Study Day 11, 12 hours after receiving the study drug, the patient developed fever and a maculopapular rash on the thorax, abdomen, and limbs, with no evidence of laryngospasm, perioral and tongue swelling, and anaphylactic shock. Ceftaroline was discontinued.
- Patient 3004-06679: *Clostridium difficile* colitis (Recovered)
  This is an 81 year old Hispanic white female with hypertension, atrial fibrillation, subdural hematoma, and pulmonary embolism, who was treated for a subcutaneous MRSA abscess at a hip replacement surgical site with ceftaroline for 11 days. On Study Day 6, the patient had diarrhea assessed to be moderate in severity. On Study Day 10, analysis of stool sample revealed *Clostridium difficile* toxin. Ceftaroline was discontinued and the patient was treated with oral metronidazole.
- Patient 0003-07006: Anaphylactoid Reaction (Recovered)
  This is a 25 year old white male with a medical history that included headaches, back pain, IV drug use, recreational Percocet use, alcohol abuse, borderline personality disorder, and anxiety. He had no known allergies. He was treated for an MRSA abscess of the left groin with ceftaroline for 11 days. On Study Day 9, he developed severe labial paresthesia and labial swelling with labial angioedema and a maculopapular rash on his torso, neck, and extremities. The rash was associated with severe, generalized itching, tingling sensation in and around the mouth, and a sensation of mild throat closure. Laryngeal swelling was not confirmed. Prednisone, diphenhydramine, paracetamol, and epinephrine were given. Ceftaroline was discontinued on Study Day 11 and the patient's symptoms improved.

- Patient 6515-07368: Anaphylactic Shock (Recovered)
  This is a 21 year old white female with a history of nose abscess, left upper leg abscess, pollinosis, and asymptomatic UTI who was treated with ceftaroline for 1 day for a leg abscess due to *Staphylococcus aureus*. Fifteen minutes after the start of infusion, the patient developed swelling of the eyelids, redness of the face, bronchospasm, cyanosis, paleness, severe rhinitis, urticaria on the trunk, and difficulty breathing. She was diagnosed with anaphylactic shock and treated with clemastine, prednisolone, oxygen, and "shock position". The patient recovered from the SAE on Study Day 2.
- Patient 2006-06444: Hypersensitivity Reaction (Recovered)
  This is a 19 year old Hispanic white female with a history of constipation and pregnancy-induced hypertension with no history of allergic reactions. She was enrolled for treatment of extensive cellulitis of the leg and foot with vancomycin and aztreonam. She developed headache and cranial paresthesia ten minutes after the start of infusion of vancomycin on Day 1; subsequently she developed a maculopapular rash on the neck, thorax, and abdomen along with dyspnea, bronchospasm, and laryngeal spasm. She was treated with dexamethasone, hydrocortisone, and diphenhydramine. She completely recovered.
- Patient 0026-07208: Hypocoagulation (Recovered)
  This is an 82 year old white male with hyperbilirubinemia, leukocytosis, prolonged clotting times, anemia, and chronic renal insufficiency, among others, who was treated for a major abscess of the left buttock with vancomycin for 6 days and aztreonam for 3 days. Starting on Study Day 3, the patient experienced prolongation of her coagulation profile. Her warfarin dosage was adjusted and she recovered on Study Day 19. She completed the study medication on Study Day 6.
- Patient 5014-07467: Acute Renal Failure (Recovered)
  This is a 23 year old white male with a medical history that includes hypertension, hyperproteinemia, and microhematuria who was treated for a wound infection with vancomycin and aztreonam. On Study Day 2, the patient experienced back pain and on Study Day 3 developed acute renal failure. The study medication was discontinued on Study Day 3 and the patient recovered.
- Patient 2034-08238: Unknown Sudden Death (Death)
  (Discussed in the Deaths Section)
- Patient 8203-08218: Abnormal Liver Function Test (Recovered)
  This is an 80 year old Asian male with a medical history of cigarette smoking and renal failure who was treated with ceftaroline for CABP for 7 days. At EOT visit, on Study Day 8, laboratory evaluation revealed that both hepatic transaminases exceeded ten times the upper limit of normal and were reported to be possibly related to the study medication. Laboratory results of his liver function tests include alkaline phosphatase 90 U/L, ALT 1152 U/L, AST 365 U/L, total bilirubin 0.4 to 1.34 mg/dL and indirect bilirubin 0.5 mg/dL The patient was asymptomatic. By Study Day 11, the liver enzymes started improving until they returned back to normal levels.

- Patient 6509-09273: Seizures (Resolved to Stability)
  This is a 75 year old white male with a medical history of cigarette smoking, pulmonary hypertension, thrombophlebitis, benign prostatic hyperplasia, and structural lung disease who was treated with ceftaroline for 7 days for treatment of CABP in the left lower lobe of the lung. On Study Day 8, the patient was deemed a clinical cure. On Study Day 10, the patient experienced two generalized tonic-clonic seizures, lasting from one to several minutes. Head CT showed no bleeding or tumor. He was treated with diazepam and etomidate and was intubated due to hypoxia. Electroencephalogram (EEG) did not show any clinically significant changes. By Study Day 38, the frequency and severity of the convulsions stabilized. The Investigator assessed the SAE to be possibly related to the patient's treatment, with alternative etiology of idiopathic seizures and possible interaction of co-administered drugs, including beta-agonists. The Applicant however thought that the relationship of the study medication to the seizures was highly unlikely because the last dose of study medication was administered 3 days before seizure onset.
  See Comment below.
- Patient 2009-08223: Acute Cholecystitis (Recovered)
  This is a 76 year old white female with a medical history of cigarette smoking, hypertension, bronchospasm, and cholelithiasis who was treated for CABP of the right lobe of the lung with ceftriaxone for 7 days. On Study Day 15, the patient developed right upper quadrant abdominal pain with nausea and vomiting , diagnosed as acute cholecystitis. An abdominal sonogram confirmed the diagnosis of cholecystitis with cholelithiasis and choledocholithiasis. She was treated with hyoscine and ampicillin/sulbactam and a laparoscopic cholecystectomy was done. The Investigator assessed the SAE as possibly related to the study medication.
- Patient 2029-08266: Hypersensitivity Reaction (Recovered)
  This is an 80 year old white female with a medical history of cigarette smoking, osteoarthritis, hypertension, hemiparesis, CVA, and pneumonia. She was treated with ceftriaxone for 7 days for CABP in the right lower lobe of the lung. After the last planned evening dose of the study medication, the patient developed morbilliform facial erythema. She was switched to ceftriaxone after she was deemed to be a clinical failure. After her "first dose" of ceftriaxone, she developed severe hypersensitivity manifested by worsening rash, severe bronchospasm, hypoxemia, tachypnea, dyspnea, tachycardia, and fever. She was treated with hydrocortisone and dexamethasone and recovered.
- Patient 6531-08083: Gastroenteritis (Recovered)
  This is an 81 year old white male with a medical history of cigarette smoking, hypertension, cardiac failure, coronary artery disease (CAD), sleep disorder, transient ischemic attack (TIA), and DM, among others, who was treated with ceftriaxone for 7 days for CABP in the right middle lobe of the lung. On Study Day 16, the patient developed a moderate SAE of gastroenteritis with nausea and diarrhea and was admitted to the hospital. Stool culture and *C. difficile* toxin

test were negative. He recovered on Study Day 20. The Investigator and the Applicant assessed this SAE as related to the study medication.
Medical Officer Comment: The Medical Officer disagrees with the Investigator and Applicant assessment of association between the SAE and the study medication. Considering that nausea and diarrhea began 9 days after EOT with ceftriaxone and that the stool culture and C. difficile *toxin test yielded negative results, the association is unlikely.*

- Patient 6626-08148: Liver Failure and Multi-Organ Dysfunction Syndrome (Death)
  (Discussed in the Deaths Section)
- Patient ID 6641-08578: Acute Liver Failure (Resolved to Stability)
  This is a 68 year old white male with a medical history of cigarette smoking, asthma, COPD, osteoarthritis, chronic respiratory failure, and arrhythmia, who was treated with ceftriaxone for 5 days CABP with a left lower lobe lung infiltrate. On Study Day 5, the patient was diagnosed with acute liver failure with elevated liver enzymes and prolonged coagulation profile. Ceftriaxone and other medications were discontinued on Study Day 5. On Study Day 14, his liver enzymes and coagulation profile started improving. On Study day 28, the patient's acute liver failure resolved to stability with the slightly elevated liver enzymes persisting.
- Patient ID 3005-09131: Liver Enzymes Elevation (Resolved to Stability)
  This is a 61 year old white male with a medical history of osteoarthritis who was treated with ceftriaxone for 4 days for left lower lobe CABP. On Study Day 3, the patient developed elevation of hepatic enzymes that led to the discontinuation of the study medication. Serologic testing for viral etiologies and liver ultrasound were negative. On Study Day 39, at the LFU visit, her liver enzymes were normal.
- Patient ID 2002-0001: Interstitial nephritis (Improved)
  This is a 54 year white female with a medical history of Type II DM, varices in both legs, alcoholism, obesity, pyelonephritis, and Chagas disease, who was treated for facial cellulitis with vancomycin in the IV Phase 2 Trial P903-03. She received vancomycin for 10 days. On Study Day 9, she developed a skin rash and fever. Starting Study Day 10, her serum creatinine level increased and vancomycin was discontinued. She was diagnosed with interstitial nephritis by a nephrologist. On Study Day 21, the patient was discharged with improved renal function

The incidence of SAEs (including those with outcomes of death) for patients in the Phase 3 trials for both indications is summarized by SOC in Table 79. The incidences of SAEs were similar in the ceftaroline and comparator groups (7.6% vs 7.7%, respectively). The most commonly reported SAE 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 SOCs is similar between the ceftaroline and comparator groups.

Table 79. 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.

Medical Officer Comment:
The number of patients across the pooled Safety Population who experienced at least one SAE was comparable between the ceftaroline and the comparator group (6.2% and 7%). Similarly, across the Phase 3 trials for each indication, a comparable number of patients experienced at least one SAE.

Table 80 provides a summary of the most common and most relevant SAE SOCs, which were experienced by the pooled population of the Phase 3 studies. As expected,

SAEs belonging to the SOCs Infections and Infestations and Respiratory Disorders were the most common given the infection indications for the study medication. As far as the SOCs relevant to a cephalosporin, the overall incidences of Immune System Disorders and Renal Disorders were similar between the ceftaroline and comparator groups. However, in the ceftaroline treatment group, one patient each experienced anaphylactic shock and anaphylactoid reaction. Considering the low incidence of these SAEs, this difference may not be significant.

With Nervous System Disorders, while the incidence between the ceftaroline and comparator groups was similar, it is interesting to note that 2 patients in the ceftaroline group experienced convulsions compared to none in the comparator and 1 patient in the ceftaroline group compared to none in the comparator experienced anoxic encephalopathy.

One SAE of convulsion was discussed in the preceding section as being related to ceftaroline. The medical reviewer disagrees with the Investigator on the association. Typically seen in the elderly and in persons with renal insufficiency and/or prior neurologic disease, cephalosporin-induced neurotoxicity presents as convulsions and/or encephalopathy while the patient is on the antibacterial, with a latency period of around 1 to 5 days.[23] Moreover, with its purported mechanism of inhibition of gamma-amino-butyric acid (GABA) through cephalosporin-binding to GABA receptors, treatment is usually discontinuation or dose adjustment of the offending agent.[24] The patient developed seizures 3 days after EOT with ceftaroline. It is likely that, as the Investigator and Applicant suggested, the patient had idiopathic seizures.

The other SAE of convulsion involved a 64 year old white male with hypothyroidism, diabetes, cerebral infarct, recent CVA, hypertension, coronary artery disease (CAD), heart disease, hepatitis C infection, HIV infection, and chronic renal failure, among others. He developed seizures on Study Day 14 (TOC assessment) after 5 days off of ceftaroline therapy. Association was ruled out because the patient had a history of syncopal episodes prior to the study that were later diagnosed as seizures. In agreement with the Investigator and the Applicant, the Medical Reviewer notes that several underlying neurologic conditions (cerebral infarcts, recent CVA) exist that may have caused the seizures. Therefore, both cases of seizure reported as SAEs appear to be unrelated to ceftaroline.

Table 80. 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.

Appendix 7 lists SAEs by decreasing frequency. The seven most common SAEs belong to either the Infections and Infestations and Respiratory Disorder SOC. It is interesting to note that there are more cases of malignant neoplasms of the lung (3 vs 0) and renal failure (3 vs 0) in the ceftaroline group compared to the comparator group.

There were three cases of malignant pulmonary neoplasms classified as SAEs in the ceftaroline-treated group, two of which had outcomes of death. The first case was Patient No. 5101-09115 with a 50-year smoking history and hypertension who was treated successfully for CABP with ceftaroline. Five days after discharge from the hospital, he was diagnosed with lung cancer with metastases. Association between ceftaroline and pulmonary carcinoma with metastases is unlikely because the development of pulmonary cancer with metastases must have preceded ceftaroline administration, in addition to the patient's prolonged smoking history,

The second case, Patient 6608-09421, had a 28 year smoking history with recurrent lung pneumonia and structural disease. He was deemed a clinical responder after 7 days of ceftaroline therapy for R-sided pneumonia. Biopsies performed on Study Day 5 of enlarged obstructive mediastinal and hilar lymph nodes seen on bronchoscopy showed squamous cell lung cancer. With the patient's prolonged smoking history, the development of cancer must have preceded ceftaroline administration. There is therefore lack of association between the lung malignancy and ceftaroline.

The last case was Patient No. 6613-09346 who had a 57 year smoking history and treated. He was deemed a clinical responder after he received 7 days of ceftaroline for CABP despite the development of small bilateral pleural effusions. Three days after EOT, he was diagnosed with lung cancer after malignant cells were found in his sputum and a CT scan of his chest revealed a L lung mass. Again, there is lack of temporal association between ceftaroline that was recently administered and the development of lung cancer. In summary, none of the cases of newly-diagnosed malignancies appears to be associated with ceftaroline.

Three cases of renal failure in the ceftaroline group were reported as SAEs. Patient 2016-07561 had pre-existing renal failure with concurrent medical conditions that included diabetes mellitus, ischemic cardiomyopathy, congestive heart failure, and hypertension with multiple medications such as insulin, ranitidine, enalapril, atenolol, tramadol, and amlodipine. Baseline CrCl were 23.2 mL/min and 34.5 mL/min. He was treated with ceftaroline for 2 days for L leg cellulitis. He experienced an SAE of acute pulmonary edema and a moderate AE of renal impairment on Study Day 2 and subsequently developed SAEs of central line infection and worsening renal failure. On Study Day 21, he experienced an SAE of multi-organ failure that resulted to his death on Study Day 45. Demonstration of association of ceftaroline and worsening renal failure is difficult because of pre-existing renal failure, concomitant medications, concurrent illnesses that may cause exacerbation of the patient's renal failure such as diabetes, cellulitis, and the multi-organ failure.

The second case of renal failure in the ceftaroline group is Patient 2015-09618 who had a 51-year smoking history, hydronephrosis with chronic renal insufficiency, diabetes, hematuria, asthma, structural lung disease, among others, with medications such as insulin, ranitidine, hydrocortisone, salbutamol, and budesonide. Baseline CrCl was 101 mL/min. He was successfully treated with 7 days of ceftaroline for CABP. He developed SAEs of exacerbation of COPD on Study Day 8 and renal failure (CrCl of 32.9 mL/min) and nosocomial pneumonia on Study Day 14 that caused his demise on Study Day 16. With a history of pre-treatment renal insufficiency, diabetes, and hypertension, in addition to his pulmonary illnesses (CABP and exacerbation of COPD), the patient's renal failure is unlikely to be associated with ceftaroline therapy.

The last case of renal failure in the ceftaroline group is Patient 5012-09074 with a 60 year smoking history, history of myocardial infarctions and pulmonary embolism,

structural lung disease, chronic pyelonephritis, chronic bronchitis, atherosclerosis of aorta, cerebral and renal arteries, with concomitant medications of ASA, enalapril, furosemide, dexamethasone, aminophylline, isosorbide, among others. He was treated for CABP with 6 days of ceftaroline, discontinued because of clinical failure. He developed multiple AEs such as acute pancreatitis, pulmonary embolism, renal failure and hepatic failure on Study Day 6. His overall condition worsened so that on Day 10, he developed an SAE of disseminated intravascular coagulation (DIC) that subsequently caused his demise on Study Day 12. With multiple pre-existing multiple conditions and medications that may exacerbate renal failure, it is unlikely that the SAE of renal failure is associated with ceftaroline therapy.

In summary, the association between cases of renal failure reported as SAEs with ceftaroline therapy is difficult to demonstrate because of the patients' confounding pre-existing medical conditions, medications, and overall state of health.

Because nonclinical studies suggested potential toxicities in both the Nervous and Renal Systems at high exposures, monitoring for the incidence of AEs within these organ systems should continue in postmarketing safety surveillance.

Dropouts and/or Discontinuations

Premature Discontinuation from Study Drug

Patients who completed the study or prematurely discontinued from the study drug are summarized in Table 81 with the corresponding reason/s for discontinuation. Patients who prematurely discontinued from the study drug could potentially remain in the Trial for further assessments. The standardized set of reasons for premature discontinuation includes the following categories:

- Adverse Event (AE);
- Pregnancy/Nursing;
- Significant Laboratory Abnormality;
- Insufficient Therapeutic Effect
    - Clinical Worsening or Lack of Clinical Progress
    - Significant Surgical Intervention (ABSSSI only);
- Withdrawal of Consent; and
- Lost to Follow-up.

Overall and Pooled Phase 3 Trials

Across all Phase 2 and Phase 3 clinical trials, 1470 patients received ceftaroline fosamil. The breakdown of patients treated with ceftaroline is as follows: 165 patients in Phase 2 ABSSSI trials, 692 patients in Phase 3 ABSSSI trials, and 613 patients in Phase 3 CABP trials. A total of 1362 patients (92.7%) of these patients completed the study drug (145 in the Phase 2 ABSSSI trials, 640 in Phase 3 ABSSSI trials, and 577 in Phase 3 CABP trials). A comparable number of patients (1378) received the comparator

drug (77 in Phase 2 ABSSSI trials, 686 in Phase 3 ABSSI trials, and 615 in Phase 3 CABP trials). Table 81 shows the premature discontinuation rate from study drug and the reasons for premature discontinuation in patients in the Phase II and Phase III ABSSSI and CABP trials.

Table 81. Rate of Premature Discontinuation from Study Drug in Phase 3 Trials

	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 (%)
Completed Study Drug	640 (92.5)	620 (90.4)	577 (94.9)	567 (92.8)	1217 (93.6)	1187 (91.5)
Prematurely Discontinued from Study Drug	52 (7.5)	66 (9.6)	36 (5.9)	48 (7.8)	88 (6.8)	114 (8.8)
Reason for Premature Discontinuation of Study Drug						
Adverse Event	20 (2.9)	32 (4.7)	14 (2.3)	14 (2.3)	34 (2.6)	46 (3.5)
Insufficient therapeutic Effect	12 (1.7)	14 (2.0)	12 (2.0)	20 (3.3)	24 (1.8)	34 (2.6)
Clinical Worsening, Lack of Clinical Progress	4 (0.6)	11 (1.6)	11 (1.8)	18 (2.9)	15 (1.1)	29 (2.2)
Significant Surgical Intervention	4 (0.6)	1 (0.1)	NA	NA	4 (0.3)	1 (0.1)
Resistant Pathogen	4 (0.6)	2 (0.3)	1 (0.2)	2 (0.3)	5 (0.4)	4 (0.3)
Consent Withdrawn	2 (0.3)	1 (0.1)	7 (1.1)	10 (1.6)	9 (0.7)	11 (0.8)
Lost to Follow-Up	9 (1.3)	9 (1.3)	0	2 (0.3)	9 (0.7)	11 (0.8)
Other	9 (1.3)	10 (1.5)	3 (0.5)	2 (0.3)	12 (0.9)	12 (0.9)

Source: Integrated Summary of Safety (ABSSSI and CABP), p. 128.

Clinical Pharmacology Studies and Studies by Indications

The incidence of patients in the ceftaroline group (1.7%) who prematurely discontinued from the study drug or withdrew from the study due to a treatment-emergent adverse event (TEAE) was similar to those who received placebo (1.3%).

For the pooled Phase 3 ABSSSI trials, around 8% of patients who received ceftaroline and 10% of patients who received vancomycin plus aztreonam prematurely discontinued the study drug, most commonly due to TEAEs and insufficient therapeutic effect. The reasons for discontinuation of treatment for these groups were similar.

For the pooled CABP trials, similar rates of premature discontinuation (6% for the ceftaroline group and 8% for the ceftriaxone group) were observed, with the most common reasons being insufficient therapeutic effect, TEAE, and consent withdrawal. Reasons for discontinuation of study drug were similar between treatment groups.

Medical Officer Comment:
Based on the data presented in Table 81, the overall incidence rates of premature discontinuation in the four pivotal Phase 3 clinical trials appear to be similar between the

ceftaroline and comparator groups. Moreover, there is a trend toward a higher rate of premature discontinuation in patients receiving comparator treatments (vancomycin plus aztreonam and ceftriaxone) for both indications due to adverse events and insufficient therapeutic effect.

As with SAEs, the most frequent AEs leading to discontinuation or withdrawal belong to the following SOCs: Immune Disorders, Respiratory Disorders, and Infections and Infestations.

Withdrawal from the Study

Patients withdrawing from the study were summarized with the corresponding reasons for withdrawal in Table 82. The standard reasons for withdrawal from the study across all pooled Phase 3 trials include the following categories:

- Noncompliance with the Study Treatment Regimen;
- Request of Applicant or Investigator;
- Withdrawal of Consent;
- Lost to Follow-up;
- Adverse Event;
- Death; and
- Other.

Overall and Pooled Phase 3 Trials

A total of 1470 patients received ceftaroline across all Phase 2 and Phase 3 trials. A total of 1350 patients (91.8%) treated with ceftaroline fosamil completed the trials. Of 1378 patients who received the comparator drug, 1261 (91.5%) patients completed the trial. In the pooled Phase 3 ABSSSI and CABP trials, the incidence rates of withdrawal from the study were similar for both treatment groups for the ABSSSI and CABP indications and the pooled ABSSSI and CABP trials (around 8%), with the most frequent reasons cited as withdrawal of consent and loss to follow-up. The study data were reviewed by the Applicant for unidentified safety concerns and no other adverse events were identified. (Table 82)

Table 82. Withdrawal from Phase 3 Trials - ABSSSI and CABP Safety Populations

	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 (%)
Completed Study Drug	644 (93.1)	631 (92.0)	556 (90.7)	561 (91.2)	1200 (92)	1192 (91.6)
Withdrawal from Study	48 (6.9)	55 (8.0)	57 (9.3)	54 (8.8)	105 (8.0)	109 (8.4)
Reason for Withdrawal from the Study						
Noncompliance with Study Treatment Regimen	1 (0.1)	3 (0.4)	0	1 (0.2)	1 (0.1)	4 (0.3)
Request of Applicant or Investigator	1 (0.1)	2 (0.3)	2 (0.3)	2 (0.3)	3 (0.2)	4 (0.3)
Withdrawal of Consent	13 (1.9)	12 (1.7)	13 (2.1)	14 (2.3)	26 (2.0)	26 (2.0)
Loss to Follow-up	29 (4.2)	30 (4.4)	24 (3.9)	20 (3.3)	53 (4.1)	50 (3.8)

	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 (%)
Death	3 (0.4)	0	12 (2.0)**	12 (2.0)**	15 (1.1)**	12 (0.9)**
Adverse Event	0	1 (0.1)	4 (0.7)	5 (0.8)	4 (0.3)	6 (0.5)
Other	1 (0.1)	7 (1.0)	2 (0.3)	0	3 (0.2)	7 (0.9)

Source: Integrated Summary of Safety (ABSSSI and CABP), p. 130-1.
Nine patients were excluded from Trial P903-09 in the CABP trials because of data integrity.
** One death from India site included.

Trials by Indication

Around 7% of patients in the ceftaroline group and 8% of patients in the vancomycin plus aztreonam group withdrew from the Phase 3 ABSSSI trials, with the most common reasons for withdrawal reported to be loss to follow-up, withdrawal of consent, and other. There were three patients in the ceftaroline group who did not complete the trial because of death.

For the pooled Phase 3 CABP trials, 57 patients (9.3%) in the ceftaroline group withdrew from the trial, compared to 54 patients (8.8%) who received ceftriaxone, with the most common reasons for withdrawal cited in descending order, loss to follow-up, withdrawal of consent, and death. Reasons for withdrawal were similar between the two groups.

Medical Officer Comment:
The overall pooled data for both indications indicate that the withdrawal rates between the ceftaroline and comparator groups and the reasons for withdrawal for both groups are similar. The most frequent reason cited for withdrawal is loss to follow-up which is driving the greater incidence of withdrawal in the ceftaroline group.

7.3.4 Significant Adverse Events

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

Across the pooled Clinical Pharmacology studies, Phase 2, and Phase 3 trials, 59/1701 patients (3.5%) in the ceftaroline group and 60/1452 patients (4.1%) in the comparator or placebo groups experienced at least one AE leading to the premature discontinuation of the study drug or withdrawal from the study.

Broken down, the following table (Table 83) summarizes the number of patients who prematurely discontinued the study drug or withdrew from the trial due to at least one SAE:

Table 83. Number of Patients with at Least One AE Leading to Premature Discontinuation of Study Drug or Withdrawal from Study

Trial/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 84 provides a summary of the incidence of AEs that led to the discontinuation of the study medications, withdrawal of study medication or from the study in the pooled Phase 3 safety population. The incidences of AEs resulting in premature discontinuation of study drug or withdrawal from the trial were similar between the ceftaroline and comparator groups (3.7% vs 4.5%, respectively). The Skin and Subcutaneous Tissue Disorders SOC was the most frequent for AEs leading to discontinuation (8 in the ceftaroline groups vs 18 in the pooled 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. Excluding Respiratory Disorders and Immune System Disorders, the only SOC in which the incidence of discontinuations from AEs were greater in the ceftaroline group than the comparator group was the Neoplasms SOC (4 ceftaroline- and 1 comparator-treated patients, respectively).

Table 84. 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 Trial (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	0	0	4 (0.7)	1 (0.2)	4 (0.3)	1 (0.1)

System Organ Class	ABSSSI (Trial 06, 07)		CABP (Trial 08, 09)		Pooled Phase 3 Trial (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 (%)
Unspecified (incl cysts and polyps)						
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 Preferred Terms (PTs) of AEs leading to discontinuation of the study medication or withdrawal from the study are tabulated in Table 85. Hypersensitivity is the most common reason for discontinuation or withdrawal in the ceftaroline group. The other AEs, except for the increased blood creatinine, typically belong to the Respiratory Disorders, Infections and Infestations, and Immune Disorders SOCs.

The second most common reason for premature study drug discontinuation or study withdrawal is an increase in blood creatinine that occurred rarely (2/1300 in the ceftaroline treated group compared to none in the comparator group). One case (Patient 0010-06389) was a 37 year old male with concurrent hypertension and baseline renal insufficiency and taking antihypertensives (nifedipine, amlodipine, atenolol, captopril and clonidine)who was treated with ceftaroline for cellulitis. Baseline BUN was 22 mg/dL and baseline creatinine was 1.5 mg/dL. On Study Day 4, when BUN and creatinine levels were noted to be 23 mg/dL and 1.7 mg/dL, ceftaroline was discontinued.

The other case, Patient 7008-09290, was an 80-year old male with medical history relevant for myocardial ischemia, cardiac failure, angina, hypertension, urinary calculus, renal cyst, cholecystitis, among others, and concomitant medications of atorvastatin, carvediol, enalapril, hydrochlorothiazide, isosorbide, among others. Baseline relevant laboratory results include an elevated BUN of 142 mg/dL and elevated creatinine of 3.9 mg/dL. On Study Day 4, ceftaroline was discontinued because of a “mild serum creatinine increase” with BUN of 142 mg/dL and creatinine of 4.0 mg/dL. Both cases were confounded by concurrent pre-existing renal disease and either a baseline renal insufficiency or baseline elevated creatinine level. In addition, the rise in creatinine levels was minimal for both cases. Hence, attributing these rare cases of elevated creatinine to ceftaroline use is difficult.

Table 85. Most Common Adverse Events Leading to Discontinuation of Study Drug or Withdrawal from Study by Decreasing Incidence in the Pooled Ceftaroline Group

	cSSSI (06, 07)				CAP (08, 09)				Pooled Phase 3 Studies (06, 07, 08, 09)			
Preferred Term	Ceftaroline (N=692) n(%)		Vancomycin plus Aztreonam (N=686) n(%)		Ceftaroline (N=613) n(%)		Ceftriaxone (N=615) n(%)		Ceftaroline (N=1305) n(%)		Pooled Comparators (N=1301) n(%)	
Subjects with at Least One AE Leading to Discontinuation of Study Drug or Withdrawal from Study	21	(3.0)	33	(4.8)	27	(4.4)	25	(4.1)	48	(3.7)	58	(4.5)
Hypersensitivity	3	(0.4)	6	(0.9)	1	(0.2)	0		4	(0.3)	6	(0.5)
Blood creatinine increased	1	(0.1)	0		1	(0.2)	0		2	(0.2)	0	
Pneumonia	0		0		2	(0.3)	3	(0.5)	2	(0.2)	3	(0.2)
Pruritus generalised	2	(0.3)	3	(0.4)	0		0		2	(0.2)	3	(0.2)
Pulmonary embolism	0		0		2	(0.3)	2	(0.3)	2	(0.2)	2	(0.2)
Rash	2	(0.3)	4	(0.6)	0		0		2	(0.2)	4	(0.3)
Rash generalised	2	(0.3)	1	(0.1)	0		0		2	(0.2)	1	(0.1)
Rash maculo-papular	2	(0.3)	0		0		0		2	(0.2)	0	
Respiratory failure	0		0		2	(0.3)	0		2	(0.2)	0	
Septic shock	0		0		2	(0.3)	0		2	(0.2)	0	
Sudden death	0		0		2	(0.3)	0		2	(0.2)	0	
Abdominal pain	0		0		1	(0.2)	1	(0.2)	1	(0.1)	1	(0.1)
Acute pulmonary oedema	1	(0.1)	0		0		0		1	(0.1)	0	
Anaphylactic reaction	1	(0.1)	0		0		0		1	(0.1)	0	
Anaphylactic shock	1	(0.1)	0		0		0		1	(0.1)	0	
Anaphylactoid reaction	1	(0.1)	0		0		0		1	(0.1)	0	
Aortic dissection	0		0		1	(0.2)	0		1	(0.1)	0	
Blood urea increased	1	(0.1)	0		0		0		1	(0.1)	0	
Cardiac failure	0		0		1	(0.2)	0		1	(0.1)	0	
Cardiovascular insufficiency	0		0		1	(0.2)	1	(0.2)	1	(0.1)	1	(0.1)
Cellulitis	1	(0.1)	0		0		0		1	(0.1)	0	
Chest pain	1	(0.1)	0		0		0		1	(0.1)	0	
Clostridium difficile colitis	1	(0.1)	1	(0.1)	0		0		1	(0.1)	1	(0.1)
Cytolytic hepatitis	0		0		1	(0.2)	0		1	(0.1)	0	

Source: Integrated Summary of Safety (ABSSSI and CABP), p. 890.

The incidence of AEs leading to premature discontinuation of study drug or withdrawal from study that were assessed as related to the study drug was 1.7% (22/X patients) in the ceftaroline group and 2.3% (30/X patients) in the comparator group. Twelve of these AEs were classified as severe (6 in each treatment group). In the group given ceftaroline, the only severe AE that has not been previously discussed was fatigue. In the group given the comparator drug, the severe related AEs not previously discussed were Abnormal Laboratory Test (abnormal vancomycin level), Hypersensitivity, and Erythema.

Considering the pooled safety population for ceftaroline, premature discontinuations from study drug and withdrawals from study were uncommon, and the incidences of the AEs causing premature discontinuation of the study drug or withdrawal were similar between the two treatment groups.

For the Phase 3 ABSSSI trials, the incidences of patients who prematurely discontinued the study drug or withdrew from the study due to AEs were similar in both treatment groups (3.0% in the ceftaroline group and 4.8% in the vancomycin plus aztreonam group). The most common SOC for AEs in this category was Skin and Subcutaneous

Tissue Disorders, with the most common preferred term AEs in the ceftaroline group of hypersensitivity (0.4%), generalized pruritus (0.3%), and rash (0.3%) and in the comparator group of hypersensitivity (0.9%), erythema (0.7%), and rash (0.6%). Forty-one or 3.0% of patients experienced AEs resulting in premature discontinuation of study medication or withdrawal from study assessed as related to the study medication by the Investigator; 17 (1.2%) were in the ceftaroline group and 24 (1.7%) were in the comparator group .

In the Phase 3 CABP trials, the incidences of patients who prematurely discontinued the study drug or withdrew from the study were similar in the ceftaroline and ceftriaxone groups (4.4% vs 4.1%, respectively). The most common SOC for the AEs in this category was Infections and Infestations, while the most common preferred term AEs were pneumonia, pulmonary embolism, respiratory failure, septic shock, and sudden death. Eleven patients or 0.9% of patients experienced AEs assessed as related; 5 (0.4%) were in the ceftaroline group and 6 (0.5%) were in the ceftriaxone group.

In the Phase 3 trials for both indications, premature discontinuations from the study drug and withdrawals from the study were uncommon. The incidences of AEs leading to these events were comparable between the two treatment groups.

Medical Officer Comment:
The AEs and associated SOCs leading to premature discontinuation of the study drug or withdrawal from the study occurred infrequently. Their incidences are comparable between the group receiving ceftaroline and the group receiving either placebo or the comparator drug. This finding applies across the pooled safety population and sub-populations (pooled Phase 3 trials, ABSSSI Phase 3 trials, and CABP Phase 3 trials). The AEs leading to drug discontinuation or study withdrawal (hypersensitivity, rash, urticaria, pruritus, pneumonia, increased blood creatinine, acute renal failure, erythema, anaphylactic reaction, Clostridium difficile *colitis, diarrhea/gastroenteritis, hepatic failure/hepatic enzyme increased, etc.) appear consistent with the expected AEs associated with cephalosporin use. In agreement with the Investigator, the 3 cases of pulmonary neoplasms diagnosed were unlikely to be related to the drug. Two Cardiac System AEs, one case each of prolonged QRS complex and prolonged QT interval, were assessed to be related to ceftaroline. This finding being related to drug was not supported by the results of the thorough QT study described elsewhere in this review. Lastly, the cases where modest increases of creatinine levels were observed were unlikely to be associated with ceftaroline because cases were highly confounded by concurrent disease (e.g. hypertension) and concomitant nephrotoxic medications.*

In all, AEs resulting in drug discontinuation or study withdrawal are uncommon and are consistent with AEs expected with cephalosporin use.

7.3.5 Submission Specific Safety Concerns

None.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

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. PTs selected for the ADR list in the ceftaroline groups were selected based on the following:

- PTs with an incidence of ≥ 1% than that observed in the placebo group in the pooled Clinical Pharmacology studies;
- PTs demonstrating a clear dose response in any Clinical Pharmacology studies;
- PTs with an incidence of ≥ 3% than that observed in the comparator group in the individual Phase 2 ABSSSI trials;
- PTs with an incidence of ≥ 1% than that observed in the comparator group in either pooled indication (Phase 3 ABSSSI or Phase 3 CABP) or in the pooled Phase 3 trials (Phase 3 ABSSSI and CABP trials);
- PTs with an incidence of ≥ 5% than that observed in either pooled indication or in the pooled Phase 3 trials.

A summary of all TEAE PTs satisfying one or more of the above criteria for Adverse Drug Reactions can be seen in Table 86.

Table 86. AE PTs Identified for ADR Summary in Different Safety Populations

Pooled Clinical Pharmacology Studies with ≥ 1% Difference	Pooled Clinical Pharmacology Dose Response	Phase 2 ABSSSI ≥3% Difference	Pooled Phase 3 with ≥ 1% Difference	Pooled Phase 3 with ≥ 5% Difference Overall
Dizziness	Nausea	Anxiety	Diarrhea	Headache
Headache		Bradycardia	Headache	Nausea
Infusion Site Pain		Constipation	Renal Failure	
Nausea		Dermatitis contact		
Pruritus		Dysgeusia		
Rash		GGT increased		
Skin odor abnormal		Headache		
Urine color abnormal		Hypokalemia		
Urine odor abnormal		Infusion site pain		
Vomiting		Injection site irritation		
		Injection site pain		
		Nasopharyngitis		
		Nausea		
		Pain in Extremity		
		Pollakiuria		
		Pruritus		
		Rash		
		RBC urine		

		Urine color abnormal		

The most common ADRs occurring at a frequency greater than or equal to 2% of patients receiving ceftaroline fosamil in the pooled Phase 3 trials are also summarized in Table 87. 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.

Table 87. 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%
Nervous system disorders		
Headache	4%	3%
Psychiatric disorders		
Insomnia	3%	2%
Skin and subcutaneous tissue disorders		
Rash	3%	2%
Pruritus	2%	5%
Vascular disorders		
Phlebitis	2%	1%

Source: 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.

Common Adverse Events (Treatment-Emergent Adverse Events)

Clinical Pharmacology Studies
The incidences of TEAEs were numerator/denominator (38.6%) in the ceftaroline-treated group compared to numerator/denominator (32.1%) in the placebo group. The most common SOC in the ceftaroline and placebo groups associated with TEAEs was the Gastrointestinal Disorders (12.7% in ceftaroline-treated and 11.5% in comparator-treated patients, respectively) SOC. In the ceftaroline group, the most common TEAEs were nausea (10.2%) and headache (8.5%). In the placebo group, the most common TEAEs were contact dermatitis and nausea (6.4% and 5.1%, respectively). (See Appendix 8.)

Pooled Phase 3 Trials
Table 88 summarizes the incidence of TEAEs with at least 1% incidence in either treatment group in the pooled Phase 3 trials for ABSSSI and CABP. The percentages of patients are shown by SOCs and preferred term.

The incidences of TEAEs for the ceftaroline and comparator groups were comparable (45.7% vs 46.7%, respectively). For both treatment groups, the most common TEAE SOC was Gastrointestinal Disorders (13.3% in ceftaroline-treated and 11.1% in comparator-treated patients, respectively). None of the TEAEs occurred in 5% or more of patients in the pooled Phase 3 trials population. The most common TEAEs experienced in the ceftaroline group were diarrhea, headache, nausea, insomnia, constipation, and vomiting. The most common TEAEs in the comparator group were pruritus, nausea, diarrhea, headache, insomnia, and hypokalemia. The incidences of TEAEs were similar in both groups.

Table 88. Incidence of Common (>1%) TEAEs in Pooled Phase 3 Trials

System Organ Class Preferred Term	*cSSSI (06, 07)*		*CABP (08, 09)*		*Pooled Phase 3 Studies (06, 07, 08, 09)*	
	Ceftaroline (N = 692) n(%)	*Vancomycin plus Aztreonam (N = 686) n(%)*	*Ceftaroline (N = 613) n(%)*	*Ceftriaxone (N = 615) n(%)*	*Ceftaroline (N = 1305) n(%)*	*Pooled Comparators (N = 1301) n(%)*
Subjects with at Least One TEAE	309 (44.7)	326 (47.5)	288 (47.0)	281 (45.7)	597 (45.7)	607 (46.7)
Gastrointestinal disorders	99 (14.3)	88 (12.8)	74 (12.1)	57 (9.3)	173 (13.3)	145 (11.1)
Diarrhoea	34 (4.9)	26 (3.8)	26 (4.2)	16 (2.6)	60 (4.6)	42 (3.2)
Nausea	41 (5.9)	35 (5.1)	14 (2.3)	14 (2.3)	55 (4.2)	49 (3.8)
Constipation	18 (2.6)	18 (2.6)	9 (1.5)	6 (1.0)	27 (2.1)	24 (1.8)
Vomiting	20 (2.9)	18 (2.6)	7 (1.1)	2 (0.3)	27 (2.1)	20 (1.5)
Abdominal pain	9 (1.3)	7 (1.0)	5 (0.8)	3 (0.5)	14 (1.1)	10 (0.8)
General disorders and administration site conditions	66 (9.5)	69 (10.1)	25 (4.1)	24 (3.9)	91 (7.0)	93 (7.1)
Pyrexia	9 (1.3)	16 (2.3)	4 (0.7)	5 (0.8)	13 (1.0)	21 (1.6)
Investigations	62 (9.0)	60 (8.7)	34 (5.5)	35 (5.7)	96 (7.4)	95 (7.3)
Blood pressure increased	9 (1.3)	9 (1.3)	5 (0.8)	4 (0.7)	14 (1.1)	13 (1.0)
Alanine aminotransferase increased	8 (1.2)	12 (1.7)	5 (0.8)	6 (1.0)	13 (1.0)	18 (1.4)
Metabolism and nutrition disorders	40 (5.8)	43 (6.3)	33 (5.4)	39 (6.3)	73 (5.6)	82 (6.3)
Hypokalaemia	10 (1.4)	15 (2.2)	14 (2.3)	15 (2.4)	24 (1.8)	30 (2.3)
Nervous system disorders	64 (9.2)	56 (8.2)	31 (5.1)	24 (3.9)	95 (7.3)	80 (6.1)
Headache	36 (5.2)	31 (4.5)	21 (3.4)	9 (1.5)	57 (4.4)	40 (3.1)
Dizziness	14 (2.0)	8 (1.2)	3 (0.5)	2 (0.3)	17 (1.3)	10 (0.8)
Psychiatric disorders	32 (4.6)	31 (4.5)	26 (4.2)	26 (4.2)	58 (4.4)	57 (4.4)
Insomnia	17 (2.5)	17 (2.5)	19 (3.1)	14 (2.3)	36 (2.8)	31 (2.4)
Skin and subcutaneous tissue disorders	75 (10.8)	110 (16.0)	13 (2.1)	13 (2.1)	88 (6.7)	123 (9.5)
Pruritus	24 (3.5)	56 (8.2)	1 (0.2)	3 (0.5)	25 (1.9)	59 (4.5)
Rash	22 (3.2)	17 (2.5)	2 (0.3)	2 (0.3)	24 (1.8)	19 (1.5)
Pruritus generalised	15 (2.2)	19 (2.8)	0	0	15 (1.1)	19 (1.5)

Vascular disorders	28 (4.0)	30 (4.4)	43 (7.0)	37 (6.0)	71 (5.4)	67 (5.1)
Hypertension	9 (1.3)	10 (1.5)	14 (2.3)	16 (2.6)	23 (1.8)	26 (2.0)
Phlebitis	3 (0.4)	5 (0.7)	17 (2.8)	13 (2.1)	20 (1.5)	18 (1.4)

Source: Integrated Summary of Safety (ABSSSI and CABP). P. 148-9.

In the pooled Clinical Pharmacology studies, most TEAEs were mild or moderate in severity. Moderate TEAEs occurred more frequently in the ceftaroline group than in the placebo group (7.2% in ceftaroline-treated and 1.3% in comparator-treated patients, respectively). The only severe TEAE reported was vomiting in a patient with ESRD in the ceftaroline group. In the pooled Phase 3 ABSSSI and CABP trials, most TEAEs in the ceftaroline and comparator treatment groups were mild or moderate in severity, with the comparable incidences between the ceftaroline and comparator groups (mild: 24% vs 23%; moderate: 16.6% vs 17.8%; severe: 5.0% vs 5.8%, in ceftaroline- and comparator-treated groups, respectively). Severe TEAEs in the pooled and individual Phase 3 trials by indication were reportedly rare and their incidences were similar between the two treatment groups. None of the severe TEAEs occurred in more than 1% of the patients.

The incidences of TEAEs assessed as related to the study drug were similar between the ceftaroline and the comparator groups (19.4% vs 20.1%, respectively) in the pooled Phase 3 ABSSSI and CABP trials. The most common related TEAEs in the two groups were diarrhea (3.2% vs 2.1%, for ceftaroline and comparator, respectively), nausea (2.3% vs 2.2% for ceftaroline and comparator, respectively), and pruritus (1.3% vs 3.6% for ceftaroline and comparator, respectively). For the ABSSSI trials, related TEAEs occurred in 23.6% of patients in the ceftaroline group (with the most common TEAEs reported: nausea, diarrhea, and headache) and 26.4% in the comparator group (with the most common TEAEs reported: pruritus, nausea, and generalized pruritus). For the CABP trials, related TEAEs occurred in 14.7% of patients in the ceftaroline group compared to 13.2% in the comparator group. The most common related TEAEs in both groups were diarrhea, phlebitis, and nausea.

Medical Officer Comment:
Gastrointestinal complaints (nausea, diarrhea, constipation, and vomiting) were the most common AEs experienced by patients receiving ceftaroline, followed by neurologic complaints such as headache and insomnia, and by dermatologic complaints such as pruritus and rash. These TEAEs appear to be consistent with the experience from other cephalosporins and beta-lactams. While the incidences of most of the TEAEs are similar between the ceftaroline and comparator groups, some TEAEs (gastrointestinal disorders and nervous system disorders) have a slightly higher incidence in the ceftaroline group.

The incidence of severity and relatedness of the TEAEs are similar between the ceftaroline and comparator-treated groups, with TEAEs consistent with previous cephalosporin experience.

7.4.2 Laboratory Findings

Hematology

The incidences of Potentially Clinically Significant (PCS) hematology values were low and similar in both treatment groups. Mean hematology values and shifts over time were similar in both ceftaroline and comparator/placebo groups, indicating that ceftaroline has no observable effect on hematology parameters compared to the comparators utilized. However, a higher incidence of positive direct Coombs' seroconversion, the clinical significance of which is not known, was noted in the ceftaroline treatment group, with no reports of hemolytic anemia developing in any of the patients who seroconverted to a positive direct Coombs' test.

In the Clinical Pharmacology studies, only one PCS hematology value, decrease in platelet count, developed in one patient in the placebo group. Mean hematology values, box plots, scatter plots, and shift tables were not produced.

In the pooled Phase 3 trials, the most common PCS hematology findings occurring in 1% or more of patients were decreases in hematocrit (Hct), hemoglobin (Hgb), and red blood cell (RBC) count; increase in platelet count, and direct Coombs' seroconversion. The frequencies of patients who developed these aforementioned findings were low and similar between treatment groups except for seroconversion of the direct Coombs' test to positive. Hematology laboratory results (including mean hematology values), box plots, scatter plots, and shift tables revealed similar results between treatment groups. Therefore, except for the seroconversion of direct Coombs' test, aggregated study results show that no findings, trends, or safety concerns were observed in either treatment group.

Coagulation

Because the coagulation studies for the Phase 3 ABSSSI trials were tested using two different assay methodologies before and after July 29, 2007, analyses excluded patients whose coagulation profiles were evaluated by earlier assays. As a result, 8.7% of patients (60/692) treated with ceftaroline and 7.7% of patients (53/686) treated with vancomycin/aztreonam were excluded. In the pooled Phase 3 trials, the exclusion affected 4.6% (numerator/denominator) of patients treated with ceftaroline and 4.1% (numerator/denominator) of patients treated with the comparator.

In the pooled Phase 3 trials, the frequencies of patients with PCS elevations in postbaseline coagulation parameter values were comparable between the ceftaroline and comparator groups. The frequencies of PCS elevations for PT were 2.0% versus 1.8%, for INR 1.7% versus 1.3%, and for PTT were 1.7% vs 1.9%, for the ceftaroline and comparator treatment groups, respectively. (Appendix 9).

The frequencies of PCS coagulation parameters were low and comparable in both treatment groups. Mean coagulation parameters and shifts over time were similar between treatment groups. Coagulation laboratory result summaries, box plots, and shift tables for each parameter revealed comparable results. No trends indicative of safety concerns in both treatment groups were apparent, with the Applicant concluding that ceftaroline has no observable effect on coagulation parameters.

Clinical Chemistry Values

The PCS chemistry value changes (including PCS renal and hepatic parameters discussed separately in Section 7.4.5) occurred infrequently and were similar between the two treatment groups. In addition, mean chemistry values and shifts over time were comparable between the ceftaroline and comparator treatment groups. Analyses did not show any trends or safety concerns between the two treatment groups, indicating that ceftaroline has no observable effect on blood chemistry parameters more pronounced than the comparators.

In the pooled Phase 3 trials, non-renal and non-hepatic chemistry laboratory test results summaries, box plots, scatter plots, and shift tables for each parameter and time point revealed comparable results between the ceftaroline and comparator treatment groups. (Appendix 10)

In the Clinical Pharmacology studies, with the exception of one patient from whom a PCS chemistry value was obtained, none of the patients in the healthy population studies or in the special population studies, developed any PCS chemistry value. Only one patient with a mildly elevated CK at baseline developed a PCS creatine kinase (CK) value that was > 4.0 x ULN and increased from baseline > 300%. This occurred on Study Day 8 after administration of a single dose of ceftaroline on Study Day 1 and the elevated CK value returned to baseline by Study Day 15.

Urinalysis

For both the Clinical Pharmacology studies and the pooled Phased 3 trials, no patients in either the ceftaroline and comparator/placebo groups developed any PCS urine pH or PCS urine specific gravity values. This indicates that ceftaroline did not appear to have an effect on the urine chemistry parameters studied.

Medical Officer Comment:
The PCS changes in the laboratory parameters investigated appeared to occur infrequently in the pooled safety population. The comparable frequencies of PCS changes in the hematologic, coagulation, chemistry, and urinalysis profiles between the ceftaroline and the comparator/placebo treatment groups indicate that ceftaroline may not have minimal to no effects on these laboratory parameters.

7.4.3 Vital Signs

Vital signs, including temperature, supine pulse rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were monitored for PCS changes. Values meeting both the observed value criteria and the change from baseline criteria were classified as low or high PCS.

In the pooled Phase 3 ABSSSI and CABP trials, shown in Table 89, the incidence of PCS SBP, DBP, and pulse rate changes were low and comparable between the ceftaroline and comparator treatment groups.

Table 89. PCS Postbaseline Vital Sign Values in Pooled Phase 3 Trials

Vital Sign PCS Criteria	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 (%)
Systolic BP (mmHg)						
≥ 180 and Increase ≥ 20	11/ 690 (1.6)	11/ 681 (1.6)	13/ 613 (2.1)	18/ 614 (2.9)	24/1303 (1.8)	29/1295 (2.2)
≤ 90 and Decrease ≥ 20	18/ 690 (2.6)	16/ 681 (2.3)	20/ 613 (3.3)	11/ 614 (1.8)	38/1303 (2.9)	27/1295 (2.1)
Diastolic BP (mmHg)						
≥ 105 and Increase ≥ 15	13/ 690 (1.9)	15/ 681 (2.2)	7/ 613 (1.1)	7/ 614 (1.1)	20/1303 (1.5)	22/1295 (1.7)
≤ 50 and Decrease ≥ 15	37/ 690 (5.4)	33/ 681 (4.8)	15/ 613 (2.4)	14/ 614 (2.3)	52/1303 (4.0)	47/1295 (3.6)
Pulse Rate (bpm)						
≥ 120 and Increase ≥ 15	7/ 690 (1.0)	7/ 681 (1.0)	12/ 613 2.0)	6/ 614 (1.0)	19/1303 (1.5)	13/1295 (1.0)
≤ 50 and Decrease ≥ 15	14/ 690 (2.0)	8/ 681 (1.2)	8/ 613 (1.3)	7/ 614 (1.1)	22/1303 (1.7)	15/1295 (1.2)

Source: Integrated Summary of Safety (ABSSSI and CABP), pp. 243-4.
Nine patients were excluded from Trial P903-09 in the CABP trials because of data integrity.

In the pooled Clinical Pharmacology studies, the incidence of patients with PCS vital sign changes was similar between the ceftaroline and placebo treatment groups.

However, a number of patients met PCS criteria for decreased BP in Study P903-01 and in Study P903-02. These PCS changes were attributed to the large number of BP determinations in the former study and to the determination of supine BPs followed by a standing BP for each time point in the later study. As shown in Table 90, for both the healthy and special populations studied in the Clinical Pharmacology studies, PCS BP changes fulfilled the orthostatic criteria for systolic BP (SBP) and diastolic BP (DBP). After reviewing these PCS changes, these changes were assessed to have no clinically significant evidence of orthostatic decreases in BP.

Table 90. PCS Changes in Systolic and Diastolic BP Meeting Orthostatic Criteria.

Vital Sign PCS/Orthostatic Criteria	Healthy Population (Studies 01, 02, 04, 05, 11, 13, 14, 17, 18, 20)		Special Populations (Studies 02, 04, 11, 18)		Pooled Clinical Pharmacology Studies (01, 02, 04, 05, 11, 13, 14, 17, 18, 20)	
	Ceftaroline (N=195) n (%)	Placebo (N=78) n (%)	Ceftaroline (N=41) n (%)	Placebo (N=0) n (%)	Ceftaroline (N=236) n (%)	Pooled Comparators (N=78) n (%)
Systolic BP						
PCS Low (Supine ≤ 90 and Decrease ≥ 15 from Baseline)	5/195 (2.6)	5/78 (6.4)	1/41 (2.4)	NA	6/236 (2.5)	5/78 (6.4)
Orthostatic Criteria (Decrease of > 20 from Supine to Standing at Any Post-Dose Timepoint	22/65 (33.8)	11/18 (61.1)	7/12 (58.3)	NA	29/77 (37.7)	11/18 (61.1)
Met Both PCS Low and Orthostatic Criteria	0/65	0/18	0/12	NA	0/77	0/18
Diastolic BP						
PCS Low (Supine ≤ 90 and Decrease ≥ 15 from Baseline)	25/195 (12.8)	9/78 (11.5)	0/41	NA	256/236 (10.6)	9/78 (11.5)
Orthostatic Criteria (Decrease of > 20 from Supine to Standing at Any Post-Dose Timepoint	35/65 (53.8)	14/18 (77.8)	2/12 (16.7)	NA	37/77 (48.1)	14/18 (77.8)
Met Both PCS Low and Orthostatic Criteria	1/65 (1.5)	1/18 (5.6)	0/12	NA	1/77 (1.3)	1/18 (5.6)

Source: Supporting Table 6.3.3.2. Orthostatic Analysis of Systolic and Diastolic Blood Pressure in Clinical Pharmacology Studies. Integrated Summary of Safety (ABSSSI and CABP), p. 530.
Nine patients were excluded from Trial P903-09 in the CABP trials because of data integrity.

Medical Officer Comment:
It appears that the frequency of PCS vital sign changes in pulse rate and systolic and diastolic blood pressure were low and comparable between the ceftaroline and the comparator/placebo treatment groups. It appears that ceftaroline did not have any evident effect on vital sign parameters in the clinical pharmacology studies. However, certain trends can be observed in the pooled Phase 3 trials where the ceftaroline group had greater incidences of PCS decreases in SBP, DBP, and both increases and decreases in pulse rate that were clinically not significant.

For the Clinical Pharmacology studies, the increased incidence of orthostatic changes in the placebo group compared to the ceftaroline group may indicate that other factors beside the study drug may account for this observation and that this trend may not be clinically significant and unrelated to the study drug.

7.4.4 Electrocardiograms (ECGs)

Cardiac Organ System in the Pooled Safety Population

Across the pooled Clinical Pharmacology studies and all Phase 2 and Phase 3 clinical trials, similar percentages of patients in the ceftaroline and comparator/placebo

treatment groups experienced TEAEs in the Cardiac Disorders SOC (4.2% vs 4.6%, respectively). In the pooled safety population, the frequencies of patients with PCS non-QT and QTc values meeting PCS criteria and with changes from baseline in QTcF and QTcB values, were low and similar between the ceftaroline and comparator/placebo groups.

In the pooled Phase 3 ABSSSI and CABP trials, the incidences of TEAEs in the Cardiac Disorders SOC were low and similar between the ceftaroline and comparator treatment groups (5.1% vs 5.1%, respectively). The SAEs within the Cardiac Disorders SOC with outcomes of death occurred in 3 patients in the ceftaroline group and in 7 patients in the comparator group (0.8% vs 1.2%, respectively). None was assessed as related to the study drug. Cardiac TEAEs that resulted in premature drug discontinuation or study withdrawal were rare and similar in the two treatment groups (0.2% vs 0.7%, for ceftaroline and comparator respectively). None was assessed as related to the study drug.

Three patients in the ceftaroline group in the Phase 3 trials experienced cardiac-related SAEs. One patient (Patient 0002-06539) experienced an unrelated SAE of ECG ST segment elevation, another (Patient 6613-09346) experienced an unrelated SAE of cardiovascular insufficiency, and Patient 0042-07307 experienced an asymptomatic prolongation of the QRS interval from 86 msec to 106 msec which resolved after discontinuation of ceftaroline.

In the Phase 2 IV ABSSSI trial, Patient 2004-00003 experienced a nonserious TEAE of QT prolongation with a QTc duration of 501 msec, assessed by the Investigator as related to study drug. In the adolescent PK study, two patients experienced cardiac-related TEAE. Patient 0001-15004 experienced a related TEAE of “extrasystoles” and Patient 0001-15007 experienced a related TEAE of “ECG prolonged QT interval”, with QTcB and QTcF both less than 450 msec.

Overall, no safety concerns related to the Cardiac Disorders SOC were identified, specifically on outlying ECG values including the QT interval and mean changes in ECG parameters. Cardiac TEAEs, cardiac SAEs with outcomes of death, and cardiac TEAEs resulting in premature discontinuation of study drug or study withdrawal, were all low in incidence and comparable between the two treatment groups.

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 QTcF and QTcB.

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 91.

Table 91. 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.

Medical Office Comment:
Analyses of data from the pooled safety population from the Clinical Pharmacology, Phase 2, and Phase 3 trials, and Thorough QT Study, did not demonstrate evidence that ceftaroline has an effect on the QTc interval and did not have any clinically significant effect on the cardiac system in general, consistent with the nonclinical studies.

7.4.5 Special Safety Studies/Clinical Trials

The following organ systems and syndromes relevant to the cephalosporin class of antibacterials were analyzed for medically important categories of TEAEs associated with ceftaroline as follows:

- TEAEs indicating potential renal impairment
- TEAEs indicating potential drug-induced anemia

- TEAEs indicating potential liver injury
- TEAEs indicating potential antibiotic-associated diarrhea
- TEAEs indicating potential allergic reaction.

Renal Organ System/Potential Renal Impairment

Nonclinical studies in rats and monkeys indicated that the renal system may be a primary site of toxicity, with changes such as inflammation of the renal tubular epithelium observed in both species at doses greater than the human equivalent exposure at therapeutic doses. In the pooled Phase 3 ABSSSI and CABP trials, the incidence of TEAEs representing potential renal impairment (acute renal failure, renal failure, renal impairment, increased creatinine, decreased CrCl) was 1.5% in the ceftaroline treatment group and 0.8% in the comparator treatment groups (Table 93). The Potentially Clinically Significant (PCS) renal chemistry creatinine (> 1.5 mg/dL increase and increase > 50% from baseline) and creatinine clearance (CrCl) values (decreased > 50% from baseline) were noted in 1.4% and 0.7%, respectively, in the ceftaroline group, and 1.9% and 1.3%, respectively, in the comparator groups. The Applicant concluded that these rates were low and similar between the ceftaroline and comparator groups. Furthermore, for the majority of SAEs, TEAEs that resulted in premature drug discontinuation or study withdrawal, and PCS increases in creatinine, the relationship to the study drug (ceftaroline and comparators) was assessed to be unlikely.

Across the safety population (pooled Clinical Pharmacology studies, Phase 2, and Phase 3 trials), only 19 (1.1%) patients who received ceftaroline and 11 (0.8%) patients who received the comparator drug or placebo experienced TEAEs representing potential renal impairment. Table 92 shows the incidence rates of TEAEs representing potential renal impairment broken down by studies.

Table 92. Incidence of TEAEs representing Potential Renal Impairment

Indication	Trial/Study	Ceftaroline Group n (%)	Comparator or Placebo Group n (%)
ABSSSI	Phase 3	9/692 (1.3%)	5/686 (0.7%)
CABP	Phase 3	10/608 (1.6%)	5/611 (0.8%)
	Trial P903-17 (IM ceftaroline)	0	0
	Study P903-15 (pediatric PK)	0	0

Categorized by PT and SOC, the incidences of TEAE related to the renal system are as follows:

Table 93. Incidence of Treatment-Emergent Adverse Events Indicating Potential Renal Impairment for Phase 3 Trials

	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 TEAE Indicating Potential Renal Impairment	9 (1.3)	5 (0.7)	10 (1.6)	5 (0.8)	19 (1.5)	10 (0.8)
Investigations	7 (1.0)	2 (0.3)	4 (0.7)	3 (0.5)	11 (0.8)	5 (0.4)
Blood creatinine increased	5 (0.7)	2 (0.3)	3 (0.5)	0	8 (0.6)	2 (0.2)
Creatinine renal clearance decreased	3 (0.4)	0	1 (0.2)	3 (0.5)	4 (0.3)	3 (0.2)
Glomerular filtration rate decreased	0	0	1 (0.2)	0	1 (0.1)	0
Renal and Urinary Disorders	3 (0.4)	3 (0.4)	7 (1.1)	2 (0.3)	10 (0.8)	5 (0.4)
Renal failure	1 (0.1)	0	6 (1.0)	0	7 (0.5)	0
Renal Impairment	2 (0.3)	0	0	0	2 (0.2)	0
Renal failure acute	1 (0.1)	3 (0.4)	0	2 (0.3)	1 (0.1)	5 (0.4)
Renal failure chronic	0	0	1 (0.2)	0	1 (0.1)	0

Source: Integrated Summary of Safety (ABSSSI and CABP), p. 200.
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, the number of TEAEs representing potential renal impairment was assessed to be low and similar between the ceftaroline and comparator treatment groups (1.5% [19/1300] and 0.8% [10/1297, respectively), with study drug-related events occurring in 11 patients (0.8%) in the ceftaroline group and 6 patients (0.5%) in the comparator. Eight patients (0.6%) in the ceftaroline group experienced renal failure or acute renal failure compared with five patients (0.4%) in the comparator group. Three of the eight cases in ceftaroline treated patients were SAEs assessed by the Investigator as unrelated to study drug because of underlying comorbidities, pre-existing renal failure, concomitant medications, and remoteness of renal failure from study drug administration. Two of the eight patients were assessed as related to ceftaroline. However, because of underlying medical conditions, concomitant medications, and timing of the TEAE, the Applicant disagreed with the Investigator assessment of association between ceftaroline and renal failure.

Four patients (3 in the ceftaroline group and 1 in the comparator group) experienced renal disorder TEAEs that resulted in drug discontinuation or study withdrawal. Because of pre-existing renal disease, underlying medical conditions, and concomitant nephrotoxic medications, the Applicant disagreed with the Investigator assessment of association between ceftaroline and renal failure. According to the Applicant, none of

the AEs of potential renal impairment in these 3 patients were related to ceftaroline administration.

The number of patients with PCS creatinine, BUN values, or CrCl values in the pooled Phase 3 ABSSSI and CABP trials,was low and similar in the ceftaroline (1.4%, 0.7%, and 0.7%, respectively) and comparator groups (1.9%, 1.6%, and 1.3%, respectively).

Table 94. PCS Postbaseline Renal Chemistry Values for Pooled Phase 3 Trials Safety Population.

Clinical Laboratory Parameter Criterion	*cSSSI (06, 07)*		*CABP (08, 09)*		*Pooled Phase 3 Studies (06, 07, 08, 09)*	
	Ceftaroline (N = 692) n/N1 (%)	*Vancomycin plus Aztreonam (N = 686) n/N1 (%)*	*Ceftaroline (N = 613) n/N1 (%)*	*Ceftriaxone (N = 615) n/N1 (%)*	*Ceftaroline (N = 1305) n/N1 (%)*	*Pooled Comparators (N = 1301) n/N1 (%)*
Serum Creatinine > 1.5 mg/dL and > 50% Increase from Baseline	6/ 676 (0.9)	14/ 664 (2.1)	12/ 599 (2.0)	10/ 596 (1.7)	18/1275 (1.4)	24/1260 (1.9)
Maximum Serum Creatinine Level						
> 1.5 to 2.0 mg/dL	5/ 6 (83.3)	10/ 14 (71.4)	4/ 12 (33.3)	4/ 10 (40.0)	9/ 18 (50.0)	14/ 24 (58.3)
> 2.0 mg/dL to 3.0 mg/dL	0/ 6	3/ 14 (21.4)	6/ 12 (50.0)	2/ 10 (20.0)	6/ 18 (33.3)	5/ 24 (20.8)
> 3.0 mg/dL to 5.0 mg/dL	1/ 6 (16.7)	0/ 14	1/ 12 (8.3)	3/ 10 (30.0)	2/ 18 (11.1)	3/ 24 (12.5)
> 5.0 mg/dL	0/ 6	1/ 14 (7.1)	1/ 12 (8.3)	1/ 10 (10.0)	1/ 18 (5.6)	2/ 24 (8.3)
Blood Urea Nitrogen > 1.5 × ULN and > 50% Increase from Baseline	2/ 676 (0.3)	8/ 664 (1.2)	7/ 599 (1.2)	12/ 596 (2.0)	9/1275 (0.7)	20/1260 (1.6)
CrCl > 50% Decrease from Baseline	3/ 676 (0.4)	7/ 663 (1.1)	6/ 599 (1.0)	9/ 596 (1.5)	9/1275 (0.7)	16/1259 (1.3)

Notes: N1 = Subjects who have both a baseline and at least one postbaseline assessment for each parameter, with the exception of the maximum serum creatinine section, where it is the count of subjects who met the elevated serum creatinine criteria.
Source: Integrated Summary of Safety (ABSSSI and CABP), p. 230)

Medical Officer Comment:
Overall, the incidence rates of TEAEs that represent potential renal impairment, TEAEs that led to either premature drug discontinuation or study withdrawal, and the number of patients with post-baseline renal chemistry value changes that are potentially clinically significant, are low. However, the Medical Officer disagrees with the Applicant that the incidences between the ceftaroline and comparator groups are similar and comparable. As noted in Table 93, in TEAE categories that represent potential renal impairment (laboratory investigations, renal failure, renal impairment, acute and chronic renal failure), the incidence of TEAEs in the ceftaroline group was higher compared to the comparator group. In the pooled ABSSSI studies where vancomycin, an antibacterial that can potentially cause nephrotoxicity (renal failure, increased BUN and creatinine, interstitial nephritis), was used as a comparator, the incidence of TEAEs of potential renal impairment in the ceftaroline group was higher compared to the vancomycin plus aztreonam group.

When the incidence of patients who experienced post-baseline renal chemistry value changes in the pooled Phase 3 safety population vs the ABSSSI and CABP studies is

compared, it becomes evident that the lower incidence of PCS renal chemistry value changes in the pooled Phase 3 trials is driven by the higher incidence of the PCS changes in the vancomycin-aztreonam group in the ABSSSI studies.

Applicant analysis of the patients who experienced renal TEAEs, some of which were SAEs with death as outcomes, resulted in the assessment that the TEAEs, SAEs, and deaths, are all unrelated to the administration of ceftaroline. The Medical Officer, in part, agrees that it is difficult to ascribe the TEAEs, deaths, and SAEs related to nephrotoxicity to ceftaroline because of the presence of pre-existing renal disease, multiple underlying medical conditions that predispose and/or cause renal disease (hypertension, diabetes, shock, etc.), concomitant medications that may be nephrotoxic, and temporal remoteness of the event to ceftaroline administration. However, in some patients, especially in those who responded with discontinuation of ceftaroline, it is difficult to entirely rule out ceftaroline as the etiology of the renal disorder.

In summary, the incidence of clinically significant renal TEAEs and PCS changes in renal function tests is low overall but higher in ceftaroline-treated groups. Association between these events and ceftaroline is difficult to rule out in the current safety population. Nonclinical studies demonstrated that the renal system may potentially be a target organ system for toxicity from ceftaroline. Therefore, the Medical Officer recommends that renal adverse events be monitored as part of post-marketing safety surveillance reporting.

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 reportedly suggests 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 PCS decreases in hematocrit (Hct), hemoglobin (Hgb), and 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 TEAEs representing potential drug-induced anemia (e.g. anemia, hemoglobin decreased). Table 95 summarizes the incidence data when broken down.

Table 95. Incidence of patients with TEAEs of potential drug-induced anemia broken down by study

Trial/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%)	3/611 (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% vs 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 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.

Table 96 summarizes the incidences of PCS postbaseline hematology values for the pooled Phase 3 trials safety population. The PCS decreases in Hct, Hgb, and RBC count values occurred at similar frequencies in the ceftaroline and comparator groups (1.2%, 1.5%. 1.4%, respectively compared to 1.7%, 1.9%, and 2.3% respectively), with the overall magnitude of PCS decreases similar in both treatment groups. There were 8 patients with PCS decreases in their RBC counts of unknown significance because of the absence of corresponding PCS decreases in Hgb or Hct and no corresponding SAEs. All 23 patients in the ceftaroline group with PCS decreases in hematological parameters were reviewed and none developed SAEs representing potential drug-induced anemia. All except two patients, either had a surgical procedure or a medical condition that may have been associated with the anemia during the study. The mean hematological parameter values were similar between the two treatment groups.

In the Phase 2 IM and IV ABSSSI trials, the incidence of patients with direct Coombs' test seroconversion was higher in the ceftaroline group compared to the comparator group (21.6% and 15% and 4.8% and 5.0%, respectively). In the Phase 2 and Phase 3 ABSSSI and CABP trials, patients who seroconverted to positive postbaseline results did not develop evidence of hemolytic anemia. None of these patients, when evaluated for hemolytic anemia using laboratory criteria consisting of a positive Coombs' test, a decrease in Hgb of > 1.5 mg/dL, and either an increase in lactate dehydrogenase (LDH) of > 2x baseline or total bilirubin of > 3x the ULN, developed hemolytic anemia. Lastly,

no TEAEs representing potential drug-induced anemia or PCS hematology values were observed in the overall pooled safety population.

In summary, in the pooled Phase 3 studies, the frequency of potential drug-induced anemia was rare and similar between the two treatment groups. Despite the higher incidence of direct Coombs' test seroconversion in the ceftaroline group, no case of hemolytic anemia developed in either treatment group.

Table 96. Incidence of PCS Postbaseline Hematology Values for Phase 3 Studies.

Clinical Laboratory Parameter and PCS Criterion	ABSSSI (Trial 06, 07)		CABP (Trial 08, 09)		Pooled Phase 3 Trials (Trials 06, 07, 08, 09)	
	Ceftaroline (N=692) n/N1 (%)	Vancomycin plus Aztreonam (N=686) n/N1 (%)	Ceftaroline (N=608) n/N1 (%)	Ceftriaxone (N=611) n/N1 (%)	Ceftaroline (N=1300) n/N1 (%)	Pooled Comparators (N=1297) n/N1 (%)
Hematocrit (%)						
< 0.8 x LLN and decrease from baseline > 20%	8/586 (1.4)	16/573 (2.8)	4/420 (1.0)	1/411 (0.2)	12/1006 (1.2)	17/984 (1.7)
> 1.3 x ULN and increase from baseline > 30%	0	0	0	0	0	0
Hemoglobin (g/dL)						
< 0.8 x LLN and decrease from baseline > 20%	12/611 (2.0)	19/604 (3.1)	4/485 (0.8)	2/482 (0.4)	16/1096 (1.5)	21/1089 (1.9)
> 1.3 x ULN and increase from baseline > 30%	0	0	0	0	0	0
Platelet count (10^3/uL)						
< 0.65 x LLN and decrease from baseline > 50%	3/573 (0.5)	0/562	1/432 (0.2)	1/421 (0.2)	4/1005 (0.4)	1/983 (0.1)
> 1.5 x ULN and increase from baseline > 100%	10/573 (1.7)	9/562 (1.6)	16/432 (3.7)	25/421 (5.9)	26 (1005 (2.6)	34/983 (3.5)
White blood cell count (10^3/uL)						
< 0.65 x LLN and decrease from baseline > 60%	2/611 (0.3)	1/604 (0.2)	1/485 (0.2)	3/482 (0.6)	3/1096 (0.3)	4/1086 (0.4)
> 1.6 x ULN and increase from baseline > 100%	3/611 (0.5)	4/604 (0.7)	4/485 (0.8)	5/482 (0.6)	3/1096 (0.6)	4/1086 (0.4)
Direct Antiglobulin Test (Coombs)						
Positive	**69/594 (11.6)**	**25/582 (4.3)**	**51/523 (9.8)**	**24/537 (1.0)**	**120/1117 (10.7)**	**49/1119 (4.4)**

Source: Adapted from the Integrated Summary of Safety (ABSSSI and CABP), p. 208.
Nine patients were excluded from Trial P903-09 in the CABP trials because of data integrity.
Abbreviations: PCS: Potentially Clinically Significant; LLN: Lower Limit of Normal; ULN: Upper Limit of Normal; N1: Number of patients with a baseline and at least one post-dose assessment for the parameter, with the exception of the Direct Antiglobulin (Coombs), where a negative baseline assessment and at least one post-dose assessment are required.

Medical Officer Comment:
Analyses of the pooled safety population from the ceftaroline development program and the safety population from the pooled Phase 3 trials for ABSSSI and CABP demonstrate that the effect of ceftaroline on hematological parameters is small and comparable to the comparator's effect. However, if the treatment effect on hematological parameters is examined by indication, it is apparent that the similarity of treatment effect on Hct, Hgb, and RBC count is driven by the lower incidence of anemia in the ceftaroline group compared to the vancomycin/aztreonam group. If the CABP trials are analyzed separately, the frequency of PCS decreases in Hct and Hgb is low but the incidence of PCS decrease in Hct and Hgb is higher in the ceftaroline group (1.0% and 0.8%, respectively) compared to the ceftriaxone group (0.2% and 0.4%, respectively).

The frequency of seroconversion of direct Coombs' test in both the ABSSSI and CABP trials is higher in the ceftaroline treatment group. Seroconversion of the direct Coombs' test has been observed in patients exposed to cephalosporins such as ceftriaxone and cefepime in as many as 16% of patients. It is concerning that in ABSSSI trials, 11.6% of patients treated with ceftaroline developed positive direct Coombs' test compared to 4.3% of patients treated with vancomycin/aztreonam. More concerning is the finding that in the CABP studies, compared to 4.5 % of patients treated with ceftriaxone who seroconverted to a positive direct Coombs' test, twice as many patients treated with ceftaroline (9.8%) developed a positive direct Coombs' test. As none of these patients developed clinical and laboratory evidence of hemolytic anemia, the significance of this finding is unknown.

It is therefore necessary to continue monitoring for the potential of ceftaroline to cause drug-induced anemia and to explore the significance of seroconversion of the direct Coombs' test, as part of surveillance in postmarketing safety reports.

TEAEs Indicating Potential Liver Injury

While the hepatic system was not considered a focus of toxicity with ceftaroline use, nonclinical studies in a 4 week repeat dose study in rats showed AST elevations at doses representing approximately 20 times the human equivalent exposure given therapeutic doses.

Across the pooled Clinical Pharmacology studies and Phase 2 and Phase 3 clinical trials, 39 patients (2.3% or 39/1701) in the ceftaroline group developed TEAEs representing potential liver injury compared to 51 (3.5% or 51/1452) in the comparator/placebo groups.

Table 97 summarizes the incidence of TEAEs representing potential liver injury in the safety population broken down by study phases.

Table 97. Incidence of TEAE Representing Potential Liver Injury Broken Down by Trials

Trial/Study	Number of Patients with TEAEs representing potential liver injury (%)	
	Ceftaroline	Comparator Drug/Placebo
Phase 2 ABSSSI Trials	6/165 (3.6%)	4/77 (1.3%)
Phase 3 ABSSSI Trials	19/692 (2.7%)	29/686 (4.2%)
Phase 3 CABP Trials	14/608 (2.3%)	18/611 (2.9%)
P903-17 (IM Ceftaroline)	0/36	0
P903-15 (Phase 1 pediatric PK study)	0/9	No subjects

Summarized from Integrated Summary of Safety (ABSSSI and CABP), p. 211.
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, the incidences of patients who developed TEAEs representing potential liver injury were similar between the ceftaroline group (2.5% or 33/1300) and the comparator group (3.6% or 47/1297). Five patients (2 treated with ceftaroline and 3 treated with ceftriaxone) enrolled in the CABP trials, experienced SAEs representing potential liver injury. One patient who received ceftriaxone in Trial P903-08 for CABP had no known comorbid conditions, underlying liver disease or concomitant medications that may have contributed to liver injury. The other four patients had histories of concomitant paracetamol administration, CHF and circulatory disease, cardiac dysrhythmia, or alcohol abuse. Two patients with SAEs had outcomes of death; one patient treated with ceftaroline died due to pulmonary embolism with evidence of congestive hepatic hyperemia and nutmeg liver on autopsy and the other patient treated with ceftriaxone and possible history of alcohol abuse died of multi-organ failure and hepatic failure.

One patient treated with ceftaroline developed a hepatic-related TEAE of unrelated cytolytic hepatitis of unknown etiology that resulted in study drug discontinuation or study withdrawal.

The frequencies of TEAEs indicating potential liver injury are found in Appendix 12. Hepatic-related TEAEs occurred infrequently and were comparable between the ceftaroline and comparator treatment groups. The number of patients developing hepatic-related investigation TEAEs appears to be slightly greater in the comparator treatment groups [40/1297 patients (3.1%)] compared to the ceftaroline group [27/1300 patients (2.1%)].

Evaluation for PCS elevation of hepatic enzymes indicated that six patients had postbaseline ALT or AST values greater than 10 times the ULN (2 patients in the ceftaroline group and 4 patients in the comparator groups). Two of these patients, both in the CABP trials and treated with ceftaroline, developed SAEs representative of liver injury, with one subsequently dying from pulmonary embolism. Twelve patients had postbaseline ALT or AST values greater than 5 and less than 10 times the ULN (5 patients treated with ceftaroline and 7 patients treated with the comparator). Of these twelve patients, only one patient in the comparator group had an SAE representative of liver injury or which led to study drug discontinuation or study withdrawal. Lastly, the

frequencies of postbaseline total bilirubin elevations greater than 1.5 and greater than 2.0 times the ULN and alkaline phosphatase elevations greater than 2.0 times ULN were infrequent and comparable between the ceftaroline and comparator treatment groups. The incidences of PCS hepatic chemistry values were low and comparable in both treatment groups. The mean hepatic chemistry values were similar between treatment groups. (See Appendix 13)

No patient in either treatment group met Hy's law (transaminase > 3x ULN and TB > 2x ULN without ALP>2x ULN), except for two patients treated with ceftriaxone (Appendix 16). One patient with underlying gallbladder disease met the laboratory criteria for Hy's law and another patient developed liver failure and died of multiorgan failure.

Review of the box plot and scatter plot figures provided by the Applicant shows that there was no meaningful change in hepatic chemistry parameters observed between the two treatment groups. (See Appendix 14 and 15 for box and scatter plots for ALT and bilirubin, respectively).

No TEAEs representing potential liver injury, leading to study drug discontinuation or study withdrawal occurred in any Clinical Pharmacology or any Phase 2 ABSSSI trial. No patient developed PCS hepatic chemistry values and met laboratory criteria for Hy's law. The incidence of TEAEs and PCS chemistry values were similar between the ceftaroline and comparator treatment groups. Trends or safety concerns indicating potential liver injury with ceftaroline use were not observed.

Medical Officer Comment:
The clinical data obtained from the pooled safety population indicates that the frequency of TEAEs and PCS chemistry values representing potential hepatic injury are low and similar between the ceftaroline and comparator treatment groups. Only two patients in the comparator-treated group met the criteria for Hy's Law. Thus, potential hepatic toxicity from ceftaroline treatment may not be of major concern.

TEAEs Indicating Potential Antibiotic-Associated Diarrhea

In the majority of nonclinical studies, gastrointestinal AEs were not observed although loose stools were occasionally observed. Stool excretion of ceftaroline is low (around 6% of the dose) and ceftaroline had a very minor effect on the intestinal microflora in healthy adults with minimal demonstrated risk of development of microbial resistance. Overall, pooled Phase 3 trials demonstrated that the incidence of antibiotic-associated diarrhea was similar between the ceftaroline and comparator groups (4.5% or 58/1300 vs 3.2% or 42/1297, respectively). Gastroenteritis secondary to *Clostridium difficile (C. difficile)* was rare and occurred in two patients (0.2%) in the ceftaroline- and one patient (<0.1%) in the comparator-treated groups.

Across the pooled safety population from the Clinical Pharmacology studies and all Phase 2 and Phase 3 clinical trials, 74 patients (4.3% or 74/1701) in the ceftaroline group and 49 patients (3.4% or 49/1452) in the comparator/placebo groups experienced TEAEs representing potential antibiotic-associated diarrhea. The incidence of these TEAEs by trials is summarized in Table 98.

Table 98. Incidence of TEAE Representing Potential Antibiotic-Associated Diarrhea Broken Down by Studies/Trials

Trial/Study	Number of Patients with TEAEs representing potential antibiotic-associated diarrhea (%)	
	Ceftaroline	Comparator Drug/Placebo
Clin. Pharmacology Studies	6/236 (2.5%)	2/78 (2.6%)
Phase 2 ABSSSI Trials	9/165 (5.5%)	5/77 (6.5%)
Phase 3 ABSSSI Trials	33/692 (4.8%)	26/686 (3.8%)
Phase 3 CABP Trials	25/608 (4.1%)	16/611 (2.6%)
P903-17 (IM Ceftaroline)	3/36 (8.3%)	0
P903-15 (Phase 1 pediatric PK study)	0/9	No patients

Source: Integrated Summary of Safety (ABSSSI and CABP), p 220.
Nine patients were excluded from Trial P903-09 in the CABP trials because of data integrity.

Two patients treated with ceftaroline (0.2%), one of whom was reported as an SAE, and one patient treated with the comparator (<0.1%) experienced *C. difficile* confirmed colitis. Four patients, two in each group, experienced TEAEs of potential antibiotic-associated diarrhea that resulted in premature study drug discontinuation or study withdrawal. These were all assessed as related to the study drug. None of the patients who developed the TEAEs and SAE representing potential antibiotic-associated diarrhea had an outcome of death.

Overall, the incidences of TEAEs representing potential antibiotic-associated diarrhea, including *C. difficile* colitis, were low and similar number of patients in both treatment groups.

Table 99. Incidence of TEAEs of Potential Antibiotic-Associated Diarrhea in Pooled Phase 3 Trials

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=1300) n (%)	Pooled Comparators (N=1297) n (%)
Patients with at Least One TEAE Indicating Potential Antibiotic-Associated Diarrhea	33 (4.8)	26 (3.8)	25 (4.1)	16 (2.6)	58 (4.5)	42 (3.2)
Gastrointestinal Disorders	32 (4.6)	26 (3.8)	25 (4.1)	16 (2.6)	57(4.4)	42 (3.2)
Diarrhoea	32 (4.6)	26 (3.8)	25 (4.1)	16 (2.6)	57(4.4)	42 (3.2)
Infections and Infestations	2 (0.3)	1 (0.1)	0	0	2 (0.2)	1 (0.1)
Clostridium difficile colitis	2 (0.3)	1 (0.1)	0	0	2 (0.2)	1 (0.1)

Source: Adapted from Integrated Summary of Safety (ABSSSI and CABP), p. 221.
Nine patients were excluded from Trial P903-09 in the CABP trials because of data integrity.

Medical Officer Comment:
For the pooled safety population, the incidence of TEAEs of antibiotic-associated diarrhea is low. However, it appears that the incidence of diarrhea in the safety population is slightly higher in the ceftaroline-treated patients than in the comparator-treated patients. The significance of the difference is difficult to ascertain, given the low incidence of antibiotic-associated diarrhea. Monitoring for these events post-marketing should be done to better assess the significance of the observed difference.

7.4.6 Immunogenicity

An antigenicity study to examine potential induction of PCA and ASA found ceftaroline to be a non-inducer. However, when combined with an adjuvant, ceftaroline was found to be negative in the ASA assay but positive in the PCA assay, suggesting that ceftaroline has the potential to sensitize under conditions of immunostimulation.

Across the pooled safety population of Clinical Pharmacology studies and all Phase 2 and Phase 3 clinical trials, 91/1701 patients (5.3%) in the ceftaroline group and 115/1452 patients (7.9%) in the comparator/placebo group had potential allergic TEAEs. Broken down by studies/trials, Table 100 summarizes the incidences of potential allergic TEAEs.

Table 100. Incidence of TEAEs of potential allergic reactions broken down by studies/trials.

Trial/Study	Number of Patients with TEAEs representing potential allergic reactions(%)	
	Ceftaroline	Comparator Drug/Placebo
Clin. Pharmacology Studies	10/236 (4.2%)	No data
Phase 2 ABSSSI Trials	11/165 (6.7%)	4/77 (5.2%)
Phase 3 ABSSSI Trials	61/692 (8.8%)	101/686 (14.7%)
Phase 3 CABP Trials	9/608 (1.5%)	10/611 (1.6%)
P903-17 (IM Ceftaroline)	1/36 (2.8%)	0
P903-15 (Phase 1 pediatric PK study)	0/9	No patients

Source: Adapted from Integrated Summary and Safety (ABSSSI and CABP), p. 223.
Nine patients were excluded from Trial P903-09 in the CABP trials because of data integrity.

In the pooled Phase 3 trials, the incidences of TEAEs that represent potential allergic reactions were similar between the ceftaroline and comparator treatment groups (5.4% (70/1300) vs 8.6% (111/1297), respectively). Five patients, three in the ceftaroline treatment group and 2 in the ceftriaxone treatment group in the pooled ABSSSI and CABP trials, developed SAEs representing potential allergic reactions (Table 100). The patients treated with ceftaroline developed SAEs of hypersensitivity, anaphylactoid reaction, and anaphylactic shock while both patients treated with ceftriaxone developed hypersensitivity. Of the three patients in the ceftaroline group, only one patient developed systemic symptoms such as facial swelling, cyanosis, and difficulty breathing

as manifestations of the SAE anaphylactic shock. All three patients recovered completely.

All TEAEs of potential allergic reaction, except for two in the comparator treatment group) were assessed as related to the study drug. All TEAEs resulted in premature drug discontinuation or study withdrawal; 15 patients treated with ceftaroline and 23 patients treated with the comparator were discontinued from study drug and/or withdrawn from the study.

In the pooled Phase 3 trials, the incidences of patients with potential allergic TEAEs categorized as any rash, hypersensitivity, and/or pruritus, were higher in the vancomycin/aztreonam treatment group compared to the ceftaroline treatment group in the ABSSSI studies (14.7% or 101/686 vs 8.8% or 61/692, respectively). The incidences of these TEAEs were similar between the ceftriaxone group and the ceftaroline group in the CABP trials (1.6% (10/611) and 1.5% (9/608), respectively). (See Appendix 17) In the Phase 2 ABSSSI trials, none of the patients with potential allergic reactions died or experienced SAEs.

In summary, the frequency of patients with potential allergic TEAEs were similar in the ceftaroline and comparator treatment groups in the safety population. The Applicant states that the risk of allergic reactions to ceftaroline appears to be similar to the comparators.

Medical Officer Comment:
Allergic reactions manifested as rash, hypersensitivity, and pruritus appear to occur at similar rates between ceftaroline and a cephalosporin comparator and at higher rates when the vancomycin/aztreonam comparator is utilized. TEAEs developed by patients in the ceftaroline group were generally mild to moderate in severity except for the three SAEs developed by patients given ceftaroline, only one of which was classified as a true anaphylactic shock. The safety data demonstrates that ceftaroline can potentially cause allergic reactions similar to those caused by cephalosporins in terms of the type of reaction, frequency, and severity.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The majority of the studies in the ceftaroline development program utilized a dosage of 600 mg every 12 hours given as two sequential 30-minute intravenous infusions and 400 mg every 12 hours (for patients with moderate renal impairment). Four Clinical Pharmacology studies (Study P903-01, 903-05, 903-17, and 903-20) utilized different doses of ceftaroline (from 50 to 2000 mg) as part of dose-ranging studies and the thorough QT study (1500 mg dose of ceftaroline).

A total of 120 adult male and female patients in the pooled Clinical Pharmacology studies received a single dose or multiple doses considered higher than the Phase 2 or Phase 3 protocol recommended dose noted above. Forty-nine of 120 patients (40.8%) experienced at least one TEAE, all of which were assessed as mild or moderate in intensity except for a single patient. This particular patient with ESRD enrolled in Study P903-20 and given a 2000 mg single dose of ceftaroline experienced severe nausea. Four of the 120 patients had premature discontinuation of study drug after developing mild urticaria, mild pruritus, moderate rash, and mild phlebitis. None of the patients in the Clinical Pharmacology studies developed serious TEAEs or deaths.

Analyses of safety data from these studies suggest that ceftaroline, even when given in supratherapeutic doses, has a good safety and tolerability profile as TEAEs were generally mild. No SAEs, severe TEAEs, and deaths occurred during dose-exploration studies.

Medical Officer Comment:
Despite the lack of safety data from dose-exploration studies, it appears that ceftaroline was well tolerated in PK studies with a limited number of healthy patients receiving higher than the recommended therapeutic dose and TEAEs that did develop were generally mild.

7.5.2 Time Dependency for Adverse Events

No data presented.

7.5.3 Drug-Demographic Interactions

Age
For the pooled Phase 3 ABSSSI and CABP trials, the incidence of TEAEs in the ceftaroline and comparator treatment groups were higher in patients 65 years or older (52.4% (208/ 397) and 47.3% (196/ 414), respectively) than in patients younger than 65 years (42.8% (389/ 908) and 46.3% (411/ 887), respectively). However, the incidence of TEAEs in each age category were similar between the two treatment groups. In both treatment groups, there was a higher incidence of TEAEs in patients 75 years and older than younger patients. These observations were expected because of the increased comorbidities in an elderly population. (See Table 101)

Table 101. Incidence of TEAEs by Age Category from Pooled Phase 3 Trials

No. of Patients with at least one TEAE n/N (%)	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 (%)

< 65	252/572 (44.1)	273/556 (49.1)	137/331 (40.8)	138/328 (41.7)	389/ 903 (42.8)	411/ 884 (46.3)
≥ 65	57/120 (47.5)	53/130 (40.8)	151/277 (54.5)	143/283 (50.4)	208/ 397 (52.4)	196/ 413 (47.3)
< 75	284/638 (44.5)	299/636 (47.0)	207/476 (43.0)	212/481 (43.7)	491/1114 (43.9)	511/1117 (45.6)
≥ 75	25/ 54 (46.3)	27/ 50 (54.0)	81/132 (61.4)	69/130 (53.1)	106/ 186 (57.0)	96/ 180 (53.3)

Source: Adapted from Integrated Summary of Safety (ABSSSI and CABP). Table 12.1.1-1, p. 256.
Nine patients were excluded from Trial P903-09 in the CABP trials because of data integrity

Gender

For the pooled safety population from the Phase 3 trials, a modest increase (<10 %) was observed between the incidence of TEAEs in females compared to males. For each gender, the incidence of TEAEs was similar between the two treatment groups. (Table 102)

Table 102. TEAEs by Gender for Pooled Phase 3 Trials

No. of Patients with at least one TEAE n/N (%)	ABSSSI (Trial 06, 07)		CABP (Trial 08, 09)		Pooled Phase 3 Trial (Trial 06, 07, 08, 09)	
	Ceftaroline (N=692) n (%)	Vancomycin plus Aztreonam (N=686) n (%)	Ceftaroline (N=613) n (%)	Ceftriaxone (N=615) n (%)	Ceftaroline (N=1305) n (%)	Pooled Comparators (N=1301) n (%)
	309/692 (44.7)	326/686 (47.5)	288/613 (47.0)	281/615 (45.7)	597/1305 (45.7)	607/1301 (46.7)
Male	185/443 (41.8)	186/420 (44.3)	167/376 (44.1)	180/395 (45.2)	352/ 819 (42.8)	366/ 815 (44.7)
Female	124/249 (49.8)	140/266 (52.6)	121/232 (51.7)	101/216 (46.5)	245/ 481 (50.7)	241/ 482 (49.9)

Source: Adapted from Integrated Summary of Safety (ABSSSI and CABP), Table 12.1.2-1. p. 257.
Nine patients were excluded from Trial P903-09 in the CABP trials because of data integrity

Race and Ethnic Origin

Most patients in the pooled safety population of the Phase 3 trials were white (82.8%). The second largest group was of unknown race, comprising 9% of the total population. There were markedly fewer black, Asian, and multi-racial patients enrolled. Because the proportion of nonwhite patients was small, meaningful conclusions between race categories can not be made. Between the ceftaroline and the comparator treatment groups, the incidence of TEAEs in the white race was similar.

By ethnic origin, the majority of the safety population from the Phase 3 trials were non-Hispanic (83.2%). The incidence of TEAEs in both treatment groups was higher for Hispanic patients compared with non-Hispanic patients, although the numbers of non-Hispanic patients were less. Between the two treatment groups for each ethnicity, the incidence of TEAEs was similar. (See Table 103)

Table 103. TEAEs by Ethnic Origin for Pooled Phase 3 Trials

No. of Patients with at least one TEAE n/N (%)	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=610) n (%)	Ceftaroline (N=1300) n (%)	Pooled Comparators (N=1297) n (%)
	309/692 (44.7)	326/686 (47.5)	288/613 (47.0)	281/615 (45.7)	597/1305 (45.7)	607/1301 (46.7)
Hispanic	85/146 (58.2)	85/136 (62.5)	55/ 79 (69.6)	52/ 78 (66.7)	140/ 225 (62.2)	137/ 214 (64.0)
Non-Hispanic	224/546 (41.0)	241/550 (43.8)	233/529 (43.6)	229/533 (42.6)	457/1075 (42.3)	470/1083 (43.2)

Source: Adapted from Integrated Summary of Safety (ABSSSI and CABP), Table 12.1.4-1. p. 259.
Nine patients were excluded from Trial P903-09 in the CABP trials because of data integrity

Body Mass Index

In the safety population, the proportion of patients who are underweight (BMI < 18.5 kg/m^2) and morbidly obese (BMI > 40 kg/m^2) was small (3.3% and 4.4%, respectively) compared to those with normal weight (BMI 18.5 to ≤ 25.0 kg/m^2) at 36.8%, overweight (BMI 25 to <30 kg/m^2) at 32.3%, and obese (BMI 30 to <40 kg/m^2) at 23.1%. Meaningful comparisons between the categories can not be made. However, an observed trend is that the incidence of TEAEs in both treatment groups increased with increasing BMI.

Table 104. TEAEs by Body Mass Index in Phase 3 Safety Population

No. of Patients with at least one TEAE n/N (%)	ABSSSI (Trial 06, 07)		CABP (Trial 08, 09)		Pooled Phase 3 Studies (Studies 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 (%)
	309/692 (44.7)	326/686 (47.5)	283/608 (46.5)	278/611 (45.5)	592/1300 (45.5)	604/1297 (46.6)
< 18.5	7/15 (46.7)	3/7 (42.9)	16/40 (40.0))	6/20 (30.0)	23/55 (41.8)	9/27 (33.3)
18.5 - < 25.0	85/237 (35.9)	92/224 (41.1)	113/257 (44.0)	120/238 (50.4)	198/494 (40.1)	212/462 (45.9)
25 - < 30	91/216 (42.1)	104/227 (45.8)	87/187 (46.5)	88/210 (41.9)	178/403 (44.2)	192/437 (43.9)
30 - < 40	92/178 (51.7)	92/180 (51.1)	58/112 (51.8)	59/131 (45.0)	150/ 290 (51.7)	151/311 (48.6)
≥ 40	33/44 (75.0)	34/47 (72.3)	9/12 (75.0)	5/12 (41.7)	42/56 (75.0)	39/59 (66.1)
Missing	1/2 (50.0)	1/1 (100.0)	NA	NA	1/2 (50.0)	1/1 (100.0)

Source: Adapted from Integrated Summary of Safety (ABSSSI and CABP), Table 12.1.5-1. p 260.
Nine patients were excluded from Trial P903-09 in the CABP trials because of data integrity

7.5.4 Drug-Disease Interactions

Renal Clearance

The proportion of enrolled patients with severe renal impairment (CrCl < 30 ml/min) was small (1.0%) since it was an exclusion criterion for the Phase 3 trials. Thus, comparisons between categories of renal insufficiency may be inconclusive. The proportion of patients with normal renal function, mild renal impairment, and moderate renal impairment was 67.2%, 22.9%, and 8.8%, respectively. A general trend was observed with higher incidence of TEAEs in patients with moderate renal impairment than in patients with normal renal function. The frequency of TEAEs was similar between treatment groups.

Table 105. TEAEs by Creatinine Clearance/Renal Impairment Categories for Pooled Phase 3 Trials

	ABSSSI (Trial 06, 07)		CABP (Trial 08, 09)		Pooled Phase 3 Trial (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 (%)
No. of Patients with at least one TEAE n/N (%)	309/692 (44.7)	326/686 (47.5)	283/608 (46.5)	278/611 (45.5)	592/1300 (45.5)	604/1297 (46.6)
> 80 mL/min	248/568 (43.7)	276/560 (49.3)	120/303 (39.6)	122/316 (38.6)	368/ 873 (42.1)	398/ 876 (45.4)
> 50 and ≤ 80 mL/min	46/99 (46.5)	35/98 (35.7)	101/201 (50.2)	104/197 (52.8)	147/300 (49.0)	139/295 (47.1)
> 30 and ≤ 50 mL/min	14/23 (60.9)	14/26 (53.8)	54/91 (59.3)	46/88 (52.3)	68/114 (59.6)	60/114 (52.6)
≤ 30 mL/min	1/2 (50.0)	1/2 (50.0)	8/13 (61.5)	6/10 (60.0)	9/15 (60.0)	7/12 (58.3)

Source: Adapted from Integrated Summary of Safety (ABSSSI and CABP), Table 12.1.6-1, p. 261.
Nine patients were excluded from Trial P903-09 in the CABP trials because of data integrity

Diabetes mellitus

As an important comorbidity for ABSSSI, the incidence of AEs in patients with diabetes mellitus enrolled in the Phase 3 ABSSSI trials was investigated. In the pooled Phase 3 ABSSSI trials, 18% were diabetic. It appears that the proportion of patients with DM who experienced TEAEs was higher than in patients without DM (63.1% [77/122] and 55.8% [67/120] compared with 40.7% [232/570] and 45.8% [259/566], respectively).

Table 106. TEAEs Categorized by Diabetes mellitus from Pooled ABSSSI Safety Population .

	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 (%)
No. of Patients, N1						
Diabetic	62	68	60	52	122	120
Non-Diabetic	289	279	281	287	570	566
Number of Patients with at Least One TEAE	165/351 (47.0)	167/347 (48.1)	144/341 (42.2)	159/339 (46.9)	309/692 (44.7)	326/686 (47.5)
Diabetic	36/62 (58.1)	36/68 (52.9)	41/60 (68.3)	31/52 (59.6)	77/122 (63.1)	67/120 (55.8)
Non-Diabetic	129/289 (44.6)	131/279 (47.0)	103/281 (36.7)	128/287 (44.6)	232/570 (40.7)	259/566 (45.8)

Source: Supporting Table 9.2.2.1.1.1. Integrated Summary of Safety (ABSSSI and CABP). P. 8375.
Abbreviations: N1: Number of patients in each specified diabetes mellitus status.

7.5.5 Drug-Drug Interactions

Drug-Food Interactions
Except for cephalosporins with an N-methyl-tetrazole-thiol side chain such as cefoperazone, cefamandole, and cefotetan, which can cause a disulfiram-type reaction when co-administered with alcohol or alcohol-containing medications, cephalosporins are typically not associated with drug-food interactions. More importantly, ceftaroline is being administered intravenously so drug-food interactions are not expected.

Drug-Drug Interactions
As stated, several factors make ceftaroline drug interactions unlikely. In vivo drug interactions through hepatic mechanisms are unlikely. Interaction of ceftaroline with drugs that are highly protein-bound is also unlikely. Lastly, interactions with drugs that inhibit active renal section are not expected. Because of these factors, drug-drug interactions are not expected with ceftaroline and formal clinical pharmacokinetic (PK) studies were not performed to investigate potential drug interactions.

In patients with ABSSSI and CABP taking concomitant medications that are known inhibitors, inducers, and substrates of the cytochrome P450 system, exploratory PK analysis did not identify any clinically relevant increases in ceftaroline exposure as reflected by C_{max} and AUC.

The TEAEs of patients from the pooled Phase 3 trials who were taking specific concomitant medications were analyzed to evaluate potential safety concerns with concomitant administration of ceftaroline and other medications. Incidences of the 10 most common TEAEs by specific concomitant medications were analyzed as the basis for such information. The following medications were selected:

- Probenecid – competitively inhibits renal excretion of drugs such as penicillins, increasing their plasma concentration and prolonging their effects;
- Warfarin – interacts with antibiotics through their effect on the intestinal microflora and on vitamin K levels;
- Furosemide – a loop diuretic that can potentially affect ceftaroline excretion; and
- Most common concomitant medications: acetylsalicylic acid (ASA), paracetamol, metamizole.

Interactions between ceftaroline and these medications were not expected based on their known pharmacodynamic properties.

No safety data was obtained for patients taking probenecid as its use was an exclusion criterion. For warfarin, the number of patients in the pooled Phase 3 trials was small, so no meaningful comparison between patients taking warfarin and those who were not could be performed. In the Phase 3 trials, 19% of patients received concomitant ASA. The incidence of TEAEs in the ceftaroline and the comparator treatment groups were generally higher, but similar between the patients who received ASA (57.3% vs 53.8%, respectively) than in those who did not (43.2% vs 44.9%, respectively). This unequal distribution may be attributed to the fact that ASA may be used to treat common AEs such as fever, minor aches and pains, and inflammation. Similarly, paracetamol is commonly used as an analgesic and an antipyretic. In the Phase 3 trials, 14.5% of patients received concomitant paracetamol. The incidences of TEAEs in the ceftaroline and comparator groups were higher, but similar in the two treatment groups, among patients who received paracetamol (66.5% vs 63.1%, respectively), than in those who did not (42.5% vs 43.7, respectively). This could be explained by the use of paracetamol for many common AEs. Lastly, metamizole, a nonsteroidal anti-inflammatory drug, is given to relieve pain and reduce fever. In the Phase 3 studies, 14.6% of patients received concomitant metamizole. The incidence of TEAEs in the ceftaroline and comparator groups was lower, but similar in the two treatment groups, in the patients who received metamizole (39.8% vs 39.0%, respectively) than in those who did not (46.7% vs 48.0%, respectively).

Medical Officer Comment:
The potential for ceftaroline to interact with other medications appears to be minimal based on its pharmacodynamic properties, exploratory PK analysis, and on the safety data generated from patients taking specific concomitant medications in the pooled Phase 3 studies.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Nonclinical studies such as the Ames bacterial reverse mutation assay, the micronucleus testing in rats and mice, and tests using Chinese hamster lung and ovary cells, demonstrate the low potential of ceftaroline to induce cellular mutations and

carcinogenicity. Based on these findings and on the recommended short duration of treatment and intermittent clinical use of ceftaroline, long-term chronic use and carcinogenicity studies have not been conducted with ceftaroline.

7.6.2 Human Reproduction and Pregnancy Data

Nonclinical studies were not performed to assess whether ceftaroline or its prodrug crosses the placental barrier. Nonclinical reproductive studies performed in rats during early pregnancy at IV doses resulting in exposure to ceftaroline up to 8 times the human exposure at a dose of 600 mg every 12 hours demonstrated no maternal toxicity and no fetal effects.

However, rabbit reproductive studies during early pregnancy where rabbits were given doses resulting in exposure to ceftaroline similar to human exposure at a dose of 600 mg every 12 hours, resulted in spontaneous abortions and an increased incidence of angulated hyoid alae, a common skeletal variation in rabbits. The Applicant attributed these effects to the high sensitivity of rabbits to broad-spectrum antibiotics.

Clinical experience on the effects of ceftaroline and its prodrug on human pregnancies is limited as patients who were pregnant were excluded from participating in studies/trials. Likewise, no studies have been performed with ceftaroline to determine its presence in human milk. However, three patients with elevated human chorionic gonadotropin (HCG) levels were inadvertently exposed to a study drug during Clinical Pharmacology or Phase 3 trials. Two of these patients developed a pregnancy and one patient developed a blighted ovum. One patient (enrolled in Study P903-05 [Thorough QT Study]) who developed a pregnancy received 1500 mg of ceftaroline as a single dose followed by a single dose of moxifloxacin. Her pregnancy was unremarkable and resulted in the delivery of a live baby girl with no postpartum AEs in either the neonate or the mother. The other pregnant patient received 600 mg of linezolid during Study P903-19, with the pregnancy resulting in stillbirth at 26.6 weeks.

Medical Officer Comment:
Based on nonclinical experience in rats and rabbits and on inadvertent human exposure to ceftaroline during pregnancy, it is difficult to determine the effects of ceftaroline on human reproduction and pregnancy.

7.6.3 Pediatrics and Assessment of Effects on Growth

As a cephalosporin with a limited duration of exposure, adverse effects on human growth are not expected. With safety data in the pediatric population limited to one Clinical Pharmacology study where 9 pediatric patients aged 12 to 17 years were given a single dose of ceftaroline, the effect of ceftaroline on human growth has not yet been explored. The Applicant intends to study ceftaroline in the pediatric population for severe or life-threatening infections.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

In the pooled Clinical Pharmacology, Phase 2, and Phase 3 trials, no AEs of acute overdose of ceftaroline were reported. In the event of an overdose, it is recommended that the drug be discontinued and supportive treatment be given. Although no information is available on the use of hemodialysis to treat overdosage, ceftaroline can be removed by hemodialysis so that in ESRD patients given 400 mg of ceftaroline, the mean total recovery of ceftaroline after a 4 hour hemodialysis session was 76.5 mg or 21.6% of the dose.

A study of the effects of ceftaroline overdose has not been performed but an analysis of patients who received doses higher than the protocol recommended doses based on the dose received and the patient's CrCl values were presented by the Applicant.

Patients considered to have received higher than the recommended doses of ceftaroline should fulfill the following criteria:

- Receipt of more than 600 mg every 12h;
- Receipt of unadjusted doses for patients with moderate renal impairment;
- Receipt of ceftaroline at any dose for patients with severe renal impairment; and
- Receipt of doses exceeding the expected number of every 12 hour doses during the patient's duration of therapy.

Based on these criteria, in the pooled Phase 3 trials, 6 patients (5.0%) were identified to have received higher than the recommended doses of ceftaroline. The frequencies of patients with TEAEs were higher in these patients (64.6%) than in those who did not (44.8%), as can be seen in Appendix 18. Of the 65 patients exposed to higher than recommended doses, 62/65 (95.4%) had baseline CrCl values of less than or equal to 80 mL/min; 31/65 patients (47.7%) had CrCl values of less than or equal to 50 mL/min, indicating that the baseline renal status of patients who received the higher doses was different from the patients who were appropriately dosed. Because of this, no meaningful conclusion can be made regarding the incidence of TEAEs in patients given the higher doses.

As a drug class, cephalosporins are not associated with abuse and withdrawal potential, in the absence of a known chemical or pharmacological basis. During the ceftaroline drug development program, no TEAE representing drug abuse was identified. No study drug accountability issues were encountered during monitoring of the ceftaroline clinical study sites.

7.7 Additional Submissions / Safety Issues

Following NDA submission, ceftaroline was not actively being studied in clinical trials not marketed anywhere in the world. The Applicant submitted a 120-day Safety Report on April 28, 2010 indicating that there was no new safety information to report.
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8 Postmarketing Experience

None.

9 Appendices

Appendix 1. Calendar Days on Study Drug for Phase 3 ABSSSI Studies Safety Population. (Source: Integrated Summary of Safety Appendix. Table 3.1.1.1.1)

Calendar Days on Study Drug
Phase 3 Studies for cSSSI
Safety Population

	P903-06		P903-07		Pooled Phase 3 Studies (06, 07)	
	Ceftaroline (N=351)	Vancomycin plus Aztreonam (N=347)	Ceftaroline (N=341)	Vancomycin plus Aztreonam (N=339)	Ceftaroline (N=692)	Vancomycin plus Aztreonam (N=686)
Days on Study Drug						
Distribution n (%)						
1 - 4	12 (3.4)	20 (5.8)	23 (6.7)	23 (6.8)	35 (5.1)	43 (6.3)
5 - 7	153 (43.6)	130 (37.5)	162 (47.5)	163 (48.1)	315 (45.5)	293 (42.7)
8 - 10	111 (31.6)	124 (35.7)	102 (29.9)	95 (28.0)	213 (30.8)	219 (31.9)
11 - 14	69 (19.7)	64 (18.4)	43 (12.6)	47 (13.9)	112 (16.2)	111 (16.2)
15	5 (1.4)	4 (1.2)	2 (0.6)	3 (0.9)	7 (1.0)	7 (1.0)
> 15	1 (0.3)	5 (1.4)	9 (2.6)	8 (2.4)	10 (1.4)	13 (1.9)
n	351	347	341	339	692	686
Mean	8.5	8.6	8.2	8.2	8.4	8.4
SD	2.99	3.17	3.29	3.37	3.15	3.28
Median	8.0	8.0	7.0	7.0	7.0	8.0
Min, Max	1, 19	1, 19	1, 22	1, 21	1, 22	1, 21
Days on Aztreonam						
Distribution n (%)						
0	NA	15 (4.3)	NA	26 (7.7)	NA	41 (6.0)
1 - 4	NA	117 (33.7)	NA	147 (43.4)	NA	264 (38.5)
5 - 7	NA	129 (37.2)	NA	118 (34.8)	NA	247 (36.0)
8 - 10	NA	65 (18.7)	NA	29 (8.6)	NA	94 (13.7)
11 - 14	NA	18 (5.2)	NA	15 (4.4)	NA	33 (4.8)
15	NA	1 (0.3)	NA	1 (0.3)	NA	2 (0.3)
> 15	NA	2 (0.6)	NA	3 (0.9)	NA	5 (0.7)
n	NA	347	NA	339	NA	686
Mean	NA	5.7	NA	4.6	NA	5.1
SD	NA	3.24	NA	3.59	NA	3.46
Median	NA	5.0	NA	4.0	NA	5.0
Min, Max	NA	0, 19	NA	0, 21	NA	0, 21

Appendix 2. Calendar Days on Study Drug for Phase 3 CABP Studies Safety Population. (Source: Integrated Summary of Safety Appendix. Table 3.1.1.2.1)

Calendar Days on Study Drug
Phase 3 Studies for CAP
Safety Population

	P903-08		P903-09		Pooled Phase 3 Studies (08, 09)	
	Ceftaroline (N=298)	Ceftriaxone (N=308)	Ceftaroline (N=315)	Ceftriaxone (N=307)	Ceftaroline (N=613)	Ceftriaxone (N=615)
Days on Study Drug Distribution n (%)						
1 - 4	14 (4.7)	14 (4.5)	12 (3.8)	18 (5.9)	26 (4.2)	32 (5.2)
5 - 7	273 (91.6)	287 (93.2)	291 (92.4)	279 (90.9)	564 (92.0)	566 (92.0)
8	11 (3.7)	7 (2.3)	12 (3.8)	10 (3.3)	23 (3.8)	17 (2.8)
> 8	0	0	0	0	0	0
n	298	308	315	307	613	615
Mean	6.4	6.5	6.5	6.5	6.5	6.5
SD	1.1	1.1	1.0	1.1	1.1	1.1
Median	7.0	7.0	7.0	7.0	7.0	7.0
Min, Max	1, 8	1, 8	1, 8	1, 8	1, 8	1, 8
Number of Doses of Clarithromycin n (%)						
0	2 (0.7)	3 (1.0)	NA	NA	2 (0.3)	3 (0.5)
1	2 (0.7)	1 (0.3)	NA	NA	2 (0.3)	1 (0.2)
2	294 (98.7)	304 (98.7)	NA	NA	294 (48.0)	304 (49.4)
> 2	0	0	NA	NA	0	0
n	298	308	NA	NA	298	308
Mean	2.0	2.0	NA	NA	2.0	2.0
SD	0.2	0.2	NA	NA	0.2	0.2
Median	2.0	2.0	NA	NA	2.0	2.0
Min, Max	0, 2	0, 2	NA	NA	0, 2	0, 2

Appendix 3. Demographic and Baseline Characteristics of the Phase 3 Studies for ABSSSI Safety Population (Source: Integrated Summary of Safety Appendix. Table 2.2.1.1)

Table 2.2.1.1
Demographic and Baseline Characteristics
Phase 3 Studies for cSSSI
Safety Population

	P903-06		P903-07		Pooled Phase 3 Studies (06, 07)	
	Ceftaroline (N=351)	Vancomycin plus Aztreonam (N=347)	Ceftaroline (N=341)	Vancomycin plus Aztreonam (N=339)	Ceftaroline (N=692)	Vancomycin plus Aztreonam (N=686)
Age (years)						
n	351	347	341	339	692	686
Mean	47.2	49.2	47.8	47.5	47.5	48.4
SD	17.0	17.2	17.0	16.1	17.0	16.6
Median	48.0	48.0	47.0	48.0	47.5	48.0
Min, Max	18, 90	18, 87	18, 93	18, 96	18, 93	18, 96
Age Group - I (years) n (%)						
<65	293 (83.5)	269 (77.5)	279 (81.8)	287 (84.7)	572 (82.7)	556 (81.0)
>=65	58 (16.5)	78 (22.5)	62 (18.2)	52 (15.3)	120 (17.3)	130 (19.0)
Age Group - II (years) n (%)						
<75	325 (92.6)	317 (91.4)	313 (91.8)	319 (94.1)	638 (92.2)	636 (92.7)
>=75	26 (7.4)	30 (8.6)	28 (8.2)	20 (5.9)	54 (7.8)	50 (7.3)
Sex n (%)						
Male	220 (62.7)	218 (62.8)	223 (65.4)	202 (59.6)	443 (64.0)	420 (61.2)
Female	131 (37.3)	129 (37.2)	118 (34.6)	137 (40.4)	249 (36.0)	266 (38.8)
Ethnicity n (%)						
Hispanic	83 (23.6)	77 (22.2)	63 (18.5)	59 (17.4)	146 (21.1)	136 (19.8)
Non-Hispanic	268 (76.4)	270 (77.8)	278 (81.5)	280 (82.6)	546 (78.9)	550 (80.2)

Appendix 4. Demographic and Baseline Characteristics of the Phase 3 Studies for CABP Safety Population (Source: Integrated Summary of Safety Appendix. Table 2.2.2.1)

Table 2.2.2.1
Demographic and Baseline Characteristics
Phase 3 Studies for CAP
Safety Population

	P903-08		P903-09		Pooled Phase 3 Studies (08, 09)	
	Ceftaroline (N=298)	Ceftriaxone (N=308)	Ceftaroline (N=315)	Ceftriaxone (N=307)	Ceftaroline (N=613)	Ceftriaxone (N=615)
Age (years)						
n	298	308	315	307	613	615
Mean	61.0	61.0	59.0	60.0	60.0	60.5
SD	16.7	16.6	17.0	15.5	16.9	16.1
Median	64.0	63.0	60.0	61.0	62.0	62.0
Min, Max	20, 94	18, 91	18, 99	18, 91	18, 99	18, 91
Age Group - I (years) n (%)						
<65	153 (51.3)	158 (51.3)	183 (58.1)	173 (56.4)	336 (54.8)	331 (53.8)
>=65	145 (48.7)	150 (48.7)	132 (41.9)	134 (43.6)	277 (45.2)	284 (46.2)
Age Group - II (years) n (%)						
<75	230 (77.2)	236 (76.6)	251 (79.7)	249 (81.1)	481 (78.5)	485 (78.9)
>=75	68 (22.8)	72 (23.4)	64 (20.3)	58 (18.9)	132 (21.5)	130 (21.1)
Sex n (%)						
Male	190 (63.8)	196 (63.6)	189 (60.0)	202 (65.8)	379 (61.8)	398 (64.7)
Female	108 (36.2)	112 (36.4)	126 (40.0)	105 (34.2)	234 (38.2)	217 (35.3)
Ethnicity n (%)						
Hispanic	29 (9.7)	27 (8.8)	50 (15.9)	51 (16.6)	79 (12.9)	78 (12.7)
Non-Hispanic	269 (90.3)	281 (91.2)	265 (84.1)	256 (83.4)	534 (87.1)	537 (87.3)

Appendix 5-A. Schedule of Assessments and Procedures for ABSSSI Studies (P903-06 and P903-07.

	Assessment or Procedure	***Base-line***	***Study Drug Administration***					***EOT[4]***	***TOC[5]***	***LFU[6]***
			Day 1[1]	*Day 2*	*Day 3[2]*	*Day 4-14*	*Day 15-21[3]*			
	Informed consent [7]	X								
	Medical and surgical history	X								
Clinical	Prior and concomitant medications	X[8]	X	X	X	X	X	X	X	X[9]
	Physical examination[10]	X			X	X	X	X	X	
	Vital signs[11]	X	X	X	X	X	X	X	X	
	Temperature[12]	X	X	X	X	X	X	X	X	
	Record height and weight	X								
	12-lead ECG[13]	X			X			X	X	
	Clinical assessment of cSSSI[14]	X	X	X	X	X	X	X	X	
	Record cSSSI site procedures	X	X	X	X	X	X	X	X	
	Record adverse events		X	X	X	X	X	X	X	
	Record serious adverse events		X	X	X	X	X	X	X	X
Laboratory	PT/INR, PTT[15]	X			X	X	X	X[16]	X	
	Safety laboratory tests (CBC with differential and comprehensive metabolic panel) [15]	X			X	X	X	X[16]	X	
	Direct and indirect Coombs' tests	X						X	X	
	UA[17], microscopy	X			X			X[16]	X	
	Pregnancy test [18]	X						X[19]		
	Estimate CrCl	X								
	Measure C-reactive protein	X								
Micro	Microbiological assessment[20]	X	X[21]	X[21]	X[21]	X[21]	X[21]	X[22]	X[23]	X[24]
	Blood for culture [25]	X	X[26]	X[26]	X[26]	X[26]	X[26]	X[26]	X[26]	X[27]
	Study drug randomization[28]	X								
	Administration of study drug		X	X	X	X	X	X[29]		

Abbreviations: CBC complete blood count; CrCl = creatinine clearance; cSSSI = complicated skin and skin structure infection; ECG = electrocardiogram; EOT = End-of-Therapy; INR = international normalized ratio; LFU = Late Follow-Up; PT = prothrombin time; PTT = partial thromboplastin time; TOC = Test-of-Cure; UA = urinalysis

1 Study Day 1 was the first day of study drug administration; subsequent study days were consecutive calendar days.

2 For investigational sites participating in the PK portion of the study, blood PK samples were obtained from subjects on Study Day 3.

3 Therapy beyond 14 days was anticipated only in unusual cases and permitted only after approval by the Sponsor's Medical Monitor.

4 EOT assessments were performed on the last day study drug was administered.

5 TOC assessments were performed 8 to 15 days after administration of the last dose of study drug.

6 LFU assessments were performed 21 to 35 days after administration of the last dose of study drug.

7 Written informed consent had to be obtained before initiating any study related assessments or procedures.

8 Prior medications, including all antimicrobial agents, taken within 4 weeks before baseline (screening) were recorded.

9 Only concomitant antimicrobial agents were recorded between TOC and LFU Visits.

10 Complete physical examination were performed at baseline and directed physical examination on Study Days 3, 7, 10, 14, 18, and 21 (± 1 day for each study day), and at the EOT and TOC Visits.

11 Vital signs were recorded daily while subject remained on study drug therapy.

12 The highest daily temperature (oral, rectal, or tympanic) was recorded while subject remained on study drug therapy.

13 ECG recordings were obtained at baseline, on Study Day 3 (± 1 day), and at the EOT and TOC.

14 Clinical assessment of the cSSSI site and measurement of length and width of the skin infection was performed at baseline, on Study Days 1-5, on Study Days 7, 10, 14, 18, and 21 (± 1 day for each study day), and at the EOT and TOC Visits.

15 PT/INR, PTT, and safety laboratory tests were performed at baseline, on Study Days 3, 7, 10, 14, 18, and 21 (± 1 day for each study day), and at EOT and TOC Visits.

16 Not performed if Study Day 3, 7, 10, 14, 18, or 21 assessments were within prior 24 hours.

17 UA and urine microscopy were performed at baseline, on Study Day 3 (±1 day), and at the EOT and TOC Visits.

18 Urine pregnancy test was performed for women of childbearing potential and those who were fewer than 2 years postmenopausal.

19 If the pregnancy test was positive at the EOT Visit, the reporting requirements in Section 10.1.9 of the study protocol (Appendix 16.1.1) were followed.

20 Appropriate cSSSI site specimens for culture and susceptibility testing were obtained at baseline, culture, and Gram's stain was performed.

21 Microbiological assessment of cSSSI site specimen was performed when medically indicated, but only if a focus of infection was present.

22 Microbiological assessment at EOT was performed if the subject was discontinued from study drug for insufficient therapeutic effect and a focus of infection was present.

23 Microbiological assessment at TOC was performed if a focus of infection was present.

24 Microbiological assessment was performed in subjects experiencing clinical relapse, if clinically appropriate and a focus of infection was present.

25 Blood for culture was obtained at baseline. Blood cultures were to be repeated upon receipt of a positive result (rather than daily) until sterilization was confirmed in those subjects with a positive result at baseline.

26 Blood for culture was obtained if the previous blood culture was positive.

27 Blood for culture was obtained if medically indicated and the subject relapsed clinically.

28 Verification that the subject met all study inclusion and exclusion criteria before randomization.

29 Administration of study drug could occur on the same calendar day as the EOT Visit, and if so was to be completed before the EOT assessments.

Appendix 5-B. Schedule of Assessments and Procedures for CABP Studies (Study P903-08 and P903-09)

	Assessment or Procedure	Baseline	Study Treatment Regimen				EOT[3]	TOC[4]	LFU[5]
			Study Day 1[1]	Study Day 2	Study Day 3[2]	Study Days 4 - 6			
	Informed consent[6]	X							
	Medical, surgical, and smoking history	X							
Clinical	Prior and concomitant medications	X[7]	X	X	X	X	X	X	X[8]
Clinical	Evaluate signs and symptoms of CABP[9]	X	X	X	X	X	X	X	X
Clinical	Physical examination[10]	X			X		X	X	
Clinical	Vital signs[11]	X	X	X	X	X	X	X	
Clinical	Height and weight	X							
Clinical	12-lead ECG[12]	X			X		X	X	
Clinical	CXR or CT scan[13]	X						X	X
Clinical	Record adverse events[14]		X	X	X	X	X	X	
Clinical	Record serious adverse events[14]		X	X	X	X	X	X	X
Laboratory	PT/INR, PTT	X			X		X[15]	X	
Laboratory	Safety laboratory tests (CBC with differential and comprehensive metabolic panel)[16]	X			X		X[15]	X	
Laboratory	Measure C-reactive protein	X							
Laboratory	Direct and indirect Coombs' tests	X					X	X	
Laboratory	UA[17], microscopy	X			X		X[15]	X	
Laboratory	Pregnancy test[18]	X					X[19]		
Laboratory	Obtain blood pH and partial pressure of arterial oxygen from ABG[20]	X							
Laboratory	Estimate creatinine clearance	X							
Microbiology	Sputum analysis	X[21]	X[22]	X[22]	X[22]	X[22]	X[23]	X[24]	X[25]
Microbiology	Pleural fluid analysis	X[26]	X[26]	X[26]	X[26]	X[26]	X[26]		
Microbiology	*Legionella pneumophila*[27] and pneumococcal urinary antigen tests	X							
Microbiology	Serology tests for atypical pathogens	X							X
Microbiology	Blood for culture	X	X[28]	X[28]	X[28]	X[28]	X[28]	X[28]	X[25]
	Determine PORT score and Risk Class	X							
	Study drug randomization[29]	X							
	Administration of study drug therapy		X	X	X	X	X[30]		
	Administration of adjunctive therapy		X						

Abbreviations: ABG = arterial blood gas; CABP = community-acquired bacterial pneumonia; CBC = complete blood count; CT = computed tomography; CXR = chest radiograph; ECG = electrocardiogram; EOT = End-of-Therapy; INR = International Normalized Ratio; LFU = Late Follow-up; PORT = Pneumonia Outcomes Research Team; PT = prothrombin time; PTT = partial thromboplastin time; TOC = Test-of-cure; UA = urinalysis.

1. Study Day 1 was the first day of study drug administration; subsequent study days were consecutive calendar days.
2. For investigational sites participating in the PK portion of the study, blood PK samples were obtained from subjects on Study Day 3.
3. EOT assessments were performed on the last day study drug therapy was administered. If the last dose of the study drug occurred at night, the EOT assessments (with the exception of the ECG recording) could be performed in the morning of the following day. Subjects discontinuing early from the study drug or withdrawing from the study should have had all EOT assessments performed on the day of discontinuation or withdrawal.
4. TOC assessments were performed 8 to 15 days after the last dose of study drug was administered.
5. LFU assessments were performed 21 to 35 days after administration of the last dose of study drug.
6. Written informed consent was obtained before initiating any study assessment or procedure.
7. Prior medications, including all antimicrobial agents, taken within 4 weeks before baseline (screening) were recorded.
8. Only concomitant antimicrobial agents between TOC and LFU were recorded.
9. Signs and symptoms of CABP were evaluated at baseline, daily while subject remained on the study drug, and at EOT, TOC, and LFU. Signs and symptoms were not obtained at TOC or LFU if the subject was previously deemed a failure.
10. Complete physical examination was performed at baseline and directed physical examination was performed on Study Day 3 (± 1 day), and at EOT and TOC.
11. Vital signs (heart rate, blood pressure, respiratory rate, and temperature) were recorded at baseline, daily while subject remained on the study drug, and at EOT and TOC. The highest daily temperature measured and the site collected (oral, rectal, or tympanic) were recorded. Oxygen saturation was recorded at baseline, daily while subject remained on the study drug, at EOT, and if medically indicated at TOC.
12. ECG recordings were obtained at baseline, on Study Day 3 (± 1 day), and at EOT and TOC.
13. Radiographs were not obtained at TOC and LFU if the subject was previously deemed a failure.
14. AEs and SAEs were collected from time of first dose.
15. Not performed if Study Day 3 safety laboratory tests were performed within prior 24 hours.
16. Safety laboratory tests were performed at baseline, on Study Day 3 (± 1 day), and at EOT and TOC.
17. Urinalysis may have been semiquantitative if standard practice at the respective hospital laboratory; see Appendix 6 of protocol (Appendix 16.1.1) for detailed information.
18. Urine pregnancy test was performed for women of childbearing potential and those who were fewer than 2 years postmenopausal.
19. If the pregnancy test was positive at EOT, the Investigator was to follow the reporting requirements in Section 10.1.9 of the protocol (Appendix 16.1.1).
20. Performed at the discretion of the Investigator.
21. An appropriate sputum specimen was obtained at baseline, and culture and susceptibility testing were performed.
22. Sputum culture and susceptibility testing were repeated if medically indicated during study drug administration.
23. Sputum assessment was performed at EOT if the subject was deemed a clinical failure or if medically indicated.
24. Sputum assessment was performed at TOC if the subject was deemed a clinical failure (unless the subject was already deemed a clinical failure at EOT) or if medically indicated.
25. Sputum assessment and/or blood culture were performed at LFU if medically indicated in subjects experiencing clinical relapse.
26. Pleural fluid assessment was performed on any study day, only if medically indicated; repeat pleural fluid samples were not required.
27. Results of the *L. pneumophila* urinary antigen test (a rapid in vitro immunochromatographic assay) had to be available before enrollment. Subjects with a positive result at baseline were not to be enrolled in the study.
28. Blood for culture was obtained if the previous blood culture was positive or if medically indicated. Blood for culture was not obtained at TOC if the subject was a failure at EOT.
29. Before randomization, study personnel verified that the subject met all study inclusion and exclusion criteria.
30. Administration of study drug may have occurred on the same calendar day as EOT, and if so was completed before EOT assessments began.

Appendix 6. TEAEs by Decreasing Incidence of Preferred Term in Ceftaroline Clinical Pharmacology Studies (Source: Integrated Summary of Safety Appendix Table 4.1.4.3.2. p. 310)

Treatment Emergent Adverse Events by Decreasing Incidence of Preferred Term in Ceftaroline
Clinical Pharmacology Studies
Safety Population

	Healthy Population (01, 02, 04, 05, 11, 13, 14, 17, 18, 20)		Special Populations (02, 04, 11, 18)		Pooled Clinical Pharmacology Studies (01, 02, 04, 05, 11, 13, 14, 17, 18, 20)	
	Ceftaroline (N=195)	Placebo (N=78)	Ceftaroline (N=41)	Placebo (N=0)	Ceftaroline (N=236)	Placebo (N=78)
Preferred Term	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Subjects with at Least One TEAE	76 (39.0)	25 (32.1)	15 (36.6)	NA	91 (38.6)	25 (32.1)
Nausea	21 (10.8)	4 (5.1)	3 (7.3)	NA	24 (10.2)	4 (5.1)
Headache	16 (8.2)	3 (3.8)	4 (9.8)	NA	20 (8.5)	3 (3.8)
Vomiting	7 (3.6)	0	1 (2.4)	NA	8 (3.4)	0
Dizziness	5 (2.6)	1 (1.3)	2 (4.9)	NA	7 (3.0)	1 (1.3)
Urine colour abnormal	6 (3.1)	0	1 (2.4)	NA	7 (3.0)	0
Urine odour abnormal	6 (3.1)	0	1 (2.4)	NA	7 (3.0)	0
Diarrhoea	5 (2.6)	2 (2.6)	1 (2.4)	NA	6 (2.5)	2 (2.6)
Contusion	5 (2.6)	2 (2.6)	0	NA	5 (2.1)	2 (2.6)
Dermatitis contact	5 (2.6)	5 (6.4)	0	NA	5 (2.1)	5 (6.4)
Infusion site pain	5 (2.6)	0	0	NA	5 (2.1)	0
Rash	4 (2.1)	0	0	NA	4 (1.7)	0
Abdominal pain	3 (1.5)	2 (2.6)	0	NA	3 (1.3)	2 (2.6)
Nasopharyngitis	3 (1.5)	1 (1.3)	0	NA	3 (1.3)	1 (1.3)
Pruritus	3 (1.5)	0	0	NA	3 (1.3)	0
Skin odour abnormal	3 (1.5)	0	0	NA	3 (1.3)	0
Anxiety	1 (0.5)	0	1 (2.4)	NA	2 (0.8)	0
Chills	2 (1.0)	0	0	NA	2 (0.8)	0
Chromaturia	2 (1.0)	0	0	NA	2 (0.8)	0
Excoriation	2 (1.0)	0	0	NA	2 (0.8)	0
Feeling hot	2 (1.0)	0	0	NA	2 (0.8)	0
Infusion site anaesthesia	2 (1.0)	0	0	NA	2 (0.8)	0
Infusion site inflammation	2 (1.0)	0	0	NA	2 (0.8)	0
Muscle spasms	1 (0.5)	0	1 (2.4)	NA	2 (0.8)	0
Oedema peripheral	1 (0.5)	0	1 (2.4)	NA	2 (0.8)	0
Oropharyngeal pain	2 (1.0)	0	0	NA	2 (0.8)	0
Orthostatic hypotension	2 (1.0)	0	0	NA	2 (0.8)	0

	Healthy Population (01, 02, 04, 05, 11, 13, 14, 17, 18, 20)		Special Populations (02, 04, 11, 18)		Pooled Clinical Pharmacology Studies (01, 02, 04, 05, 11, 13, 14, 17, 18, 20)	
	Ceftaroline (N=195)	Placebo (N=78)	Ceftaroline (N=41)	Placebo (N=0)	Ceftaroline (N=236)	Placebo (N=78)
Preferred Term	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Vaginal infection	1 (0.5)	1 (1.3)	0	NA	1 (0.4)	1 (1.3)
Vein pain	0	1 (1.3)	0	NA	0	1 (1.3)
Anorexia	1 (0.5)	0	0	NA	1 (0.4)	0
Anxiety	1 (0.5)	0	1 (2.4)	NA	2 (0.8)	0
Arthralgia	1 (0.5)	0	0	NA	1 (0.4)	0
Back pain	1 (0.5)	0	0	NA	1 (0.4)	0
Blood pressure diastolic increased	1 (0.5)	0	0	NA	1 (0.4)	0
Blood pressure increased	0	0	1 (2.4)	NA	1 (0.4)	0
Bradycardia	1 (0.5)	0	0	NA	1 (0.4)	0
Chills	2 (1.0)	0	0	NA	2 (0.8)	0
Chromaturia	2 (1.0)	0	0	NA	2 (0.8)	0
Cough	1 (0.5)	0	0	NA	1 (0.4)	0
Dermatitis allergic	0	0	1 (2.4)	NA	1 (0.4)	0
Disturbance in attention	1 (0.5)	0	0	NA	1 (0.4)	0
Dry mouth	1 (0.5)	0	0	NA	1 (0.4)	0
Dry skin	1 (0.5)	0	0	NA	1 (0.4)	0
Dry throat	1 (0.5)	0	0	NA	1 (0.4)	0
Dysgeusia	1 (0.5)	0	0	NA	1 (0.4)	0
Dyspnoea	1 (0.5)	0	0	NA	1 (0.4)	0
Excoriation	2 (1.0)	0	0	NA	2 (0.8)	0
Feeling hot	2 (1.0)	0	0	NA	2 (0.8)	0
Graft thrombosis	0	0	1 (2.4)	NA	1 (0.4)	0
Hiccups	0	0	1 (2.4)	NA	1 (0.4)	0
Hypoaesthesia	1 (0.5)	0	0	NA	1 (0.4)	0
Hypotension	1 (0.5)	0	0	NA	1 (0.4)	0
Infusion site anaesthesia	2 (1.0)	0	0	NA	2 (0.8)	0
Infusion site erythema	1 (0.5)	0	0	NA	1 (0.4)	0
Infusion site inflammation	2 (1.0)	0	0	NA	2 (0.8)	0

Appendix 7. SAEs by Decreasing Incidence of Preferred Term in the Pooled Phase 3 Studies

Serious Adverse Events by Decreasing Incidence of Preferred Term in the Pooled Ceftaroline Group
Phase 3 Studies for cSSSI and CAP
Safety Population

	cSSSI (06, 07)				CAP (08, 09)				Pooled Phase 3 Studies (06, 07, 08, 09)			
Preferred Term	Ceftaroline (N=692) n(%)		Vancomycin plus Aztreonam (N=686) n(%)		Ceftaroline (N=613) n(%)		Ceftriaxone (N=615) n(%)		Ceftaroline (N=1305) n(%)		Pooled Comparators (N=1301) n(%)	
Subjects with at Least One SAE	30	(4.3)	28	(4.1)	69	(11.3)	72	(11.7)	99	(7.6)	100	(7.7)
Pneumonia	0		1	(0.1)	9	(1.5)	9	(1.5)	9	(0.7)	10	(0.8)
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	(0.5)
Respiratory failure	1	(0.1)	0		4	(0.7)	1	(0.2)	5	(0.4)	1	(0.1)
Chronic obstructive pulmonary disease	0		0		4	(0.7)	6	(1.0)	4	(0.3)	6	(0.5)
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 neoplasm malignant	0		0		3	(0.5)	0		3	(0.2)	0	
Renal failure	1	(0.1)	0		2	(0.3)	0		3	(0.2)	0	
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)
Convulsion	1	(0.1)	0		1	(0.2)	0		2	(0.2)	0	
Lung abscess	0		0		2	(0.3)	4	(0.7)	2	(0.2)	4	(0.3)
Malignant neoplasm progression	1	(0.1)	0		1	(0.2)	0		2	(0.2)	0	
Pleurisy	1	(0.1)	0		1	(0.2)	2	(0.3)	2	(0.2)	2	(0.2)
Pulmonary oedema	0		0		2	(0.3)	0		2	(0.2)	0	
Sepsis	0		1	(0.1)	2	(0.3)	1	(0.2)	2	(0.2)	2	(0.2)
Sudden death	0		0		2	(0.3)	0		2	(0.2)	0	
Urinary tract infection	0		0		2	(0.3)	1	(0.2)	2	(0.2)	1	(0.1)
Abdominal pain	1	(0.1)	0		0		0		1	(0.1)	0	
Accidental overdose	1	(0.1)	0		0		0		1	(0.1)	0	
Acute prerenal failure	1	(0.1)	0		0		0		1	(0.1)	0	
Acute pulmonary oedema	1	(0.1)	0		0		1	(0.2)	1	(0.1)	1	(0.1)
Anaemia	0		1	(0.1)	1	(0.2)	0		1	(0.1)	1	(0.1)
Anaphylactic shock	1	(0.1)	0		0		0		1	(0.1)	0	
Anaphylactoid reaction	1	(0.1)	0		0		0		1	(0.1)	0	
Anoxic encephalopathy	0		0		1	(0.2)	0		1	(0.1)	0	
Aortic aneurysm	0		0		1	(0.2)	0		1	(0.1)	0	
Aortic dissection	0		0		1	(0.2)	0		1	(0.1)	0	
Back pain	1	(0.1)	0		0		0		1	(0.1)	0	
Bacteraemia	1	(0.1)	0		0		0		1	(0.1)	0	
Bradycardia	1	(0.1)	1	(0.1)	0		0		1	(0.1)	1	(0.1)
Bronchitis	0		0		1	(0.2)	0		1	(0.1)	0	
Cardiac arrest	0		0		1	(0.2)	0		1	(0.1)	0	
Cardiac failure	0		0		1	(0.2)	0		1	(0.1)	0	
Cardiovascular insufficiency	0		0		1	(0.2)	0		1	(0.1)	0	
Catheter related infection	1	(0.1)	0		0		0		1	(0.1)	0	
Central line infection	1	(0.1)	0		0		0		1	(0.1)	0	
Cerebrovascular accident	1	(0.1)	0		0		1	(0.2)	1	(0.1)	1	(0.1)
Clostridium difficile colitis	1	(0.1)	0		0		0		1	(0.1)	0	
Colon cancer	0		0		1	(0.2)	0		1	(0.1)	0	
Diabetes mellitus	0		0		1	(0.2)	1	(0.2)	1	(0.1)	1	(0.1)
Diabetes mellitus inadequate control	0		1	(0.1)	1	(0.2)	0		1	(0.1)	1	(0.1)
Dislocation of joint prosthesis	1	(0.1)	0		0		0		1	(0.1)	0	
Disseminated intravascular coagulation	0		0		1	(0.2)	0		1	(0.1)	0	
Duodenal ulcer	0		0		1	(0.2)	0		1	(0.1)	0	
Electrocardiogram ST segment elevation	1	(0.1)	0		0		0		1	(0.1)	0	
Empyema	0		0		1	(0.2)	2	(0.3)	1	(0.1)	2	(0.2)
Gastritis	0		0		1	(0.2)	0		1	(0.1)	0	
Gastrointestinal perforation	0		0		1	(0.2)	0		1	(0.1)	0	
Haematochezia	1	(0.1)	0		0		0		1	(0.1)	0	
Hepatic failure	0		0		1	(0.2)	1	(0.2)	1	(0.1)	1	(0.1)
Hyperglycaemia	1	(0.1)	0		0		0		1	(0.1)	0	

Appendix 8. Incidence of Treatment Emergent Adverse Events in Clinical Pharmacology Studies (Source: Integrated Summary of Safety. Table 4.1.2.3.2. p. 305-309.

	Healthy Population (01, 02, 04, 05, 11, 13, 14, 17, 18, 20)		Special Populations (02, 04, 11, 18)		Pooled Clinical Pharmacology Studies (01, 02, 04, 05, 11, 13, 14, 17, 18, 20)	
System Organ Class/ Preferred Term	Ceftaroline (N=195) n(%)	Placebo (N=78) n(%)	Ceftaroline (N=41) n(%)	Placebo (N=0) n(%)	Ceftaroline (N=236) n(%)	Placebo (N=78) n(%)
Subjects with at Least One TEAE	76 (39.0)	25 (32.1)	15 (36.6)	NA	91 (38.6)	25 (32.1)
Blood and lymphatic system disorders	1 (0.5)	1 (1.3)	0	NA	1 (0.4)	1 (1.3)
Lymphadenopathy	1 (0.5)	0	0	NA	1 (0.4)	0
Neutropenia	0	1 (1.3)	0	NA	0	1 (1.3)
Cardiac disorders	2 (1.0)	0	0	NA	2 (0.8)	0
Bradycardia	1 (0.5)	0	0	NA	1 (0.4)	0
Palpitations	1 (0.5)	0	0	NA	1 (0.4)	0
Eye disorders	0	1 (1.3)	0	NA	0	1 (1.3)
Keratitis	0	1 (1.3)	0	NA	0	1 (1.3)
Gastrointestinal disorders	26 (13.3)	9 (11.5)	4 (9.8)	NA	30 (12.7)	9 (11.5)
Nausea	21 (10.8)	4 (5.1)	3 (7.3)	NA	24 (10.2)	4 (5.1)
Vomiting	7 (3.6)	0	1 (2.4)	NA	8 (3.4)	0
Diarrhoea	5 (2.6)	2 (2.6)	1 (2.4)	NA	6 (2.5)	2 (2.6)
Abdominal pain	3 (1.5)	2 (2.6)	0	NA	3 (1.3)	2 (2.6)
Abdominal distension	1 (0.5)	1 (1.3)	0	NA	1 (0.4)	1 (1.3)
Dry mouth	1 (0.5)	0	0	NA	1 (0.4)	0
Paraesthesia oral	1 (0.5)	0	0	NA	1 (0.4)	0
Stomach discomfort	1 (0.5)	1 (1.3)	0	NA	1 (0.4)	1 (1.3)
Aphthous stomatitis	0	1 (1.3)	0	NA	0	1 (1.3)
Change of bowel habit	0	1 (1.3)	0	NA	0	1 (1.3)
Tongue ulceration	0	1 (1.3)	0	NA	0	1 (1.3)
General disorders and administration site conditions	19 (9.7)	3 (3.8)	2 (4.9)	NA	21 (8.9)	3 (3.8)
Infusion site pain	5 (2.6)	0	0	NA	5 (2.1)	0
General disorders and administration site conditions (Cont)						
Chills	2 (1.0)	0	0	NA	2 (0.8)	0
Feeling hot	2 (1.0)	0	0	NA	2 (0.8)	0
Infusion site anaesthesia	2 (1.0)	0	0	NA	2 (0.8)	0
Infusion site inflammation	2 (1.0)	0	0	NA	2 (0.8)	0
Oedema peripheral	1 (0.5)	0	1 (2.4)	NA	2 (0.8)	0
Infusion site erythema	1 (0.5)	0	0	NA	1 (0.4)	0
Infusion site paraesthesia	1 (0.5)	0	0	NA	1 (0.4)	0
Infusion site phlebitis	1 (0.5)	0	0	NA	1 (0.4)	0
Infusion site swelling	1 (0.5)	0	0	NA	1 (0.4)	0
Infusion site thrombosis	1 (0.5)	0	0	NA	1 (0.4)	0
Injection site reaction	1 (0.5)	0	0	NA	1 (0.4)	0
Malaise	1 (0.5)	0	0	NA	1 (0.4)	0
Oedema	0	0	1 (2.4)	NA	1 (0.4)	0
Catheter site haematoma	0	1 (1.3)	0	NA	0	1 (1.3)
Infusion site extravasation	0	1 (1.3)	0	NA	0	1 (1.3)
Infusion site haematoma	0	1 (1.3)	0	NA	0	1 (1.3)
Infections and infestations	7 (3.6)	2 (2.6)	0	NA	7 (3.0)	2 (2.6)
Nasopharyngitis	3 (1.5)	1 (1.3)	0	NA	3 (1.3)	1 (1.3)
Upper respiratory tract infection	2 (1.0)	0	0	NA	2 (0.8)	0
Vaginal infection	1 (0.5)	1 (1.3)	0	NA	1 (0.4)	1 (1.3)
Viral infection	1 (0.5)	0	0	NA	1 (0.4)	0
Injury, poisoning and procedural complications	8 (4.1)	2 (2.6)	2 (4.9)	NA	10 (4.2)	2 (2.6)
Contusion	5 (2.6)	2 (2.6)	0	NA	5 (2.1)	2 (2.6)
Injury, poisoning and procedural complications (Cont)						
Excoriation	2 (1.0)	0	0	NA	2 (0.8)	0
Graft thrombosis	0	0	1 (2.4)	NA	1 (0.4)	0
Skin laceration	0	0	1 (2.4)	NA	1 (0.4)	0
Sunburn	1 (0.5)	0	0	NA	1 (0.4)	0
Investigations	8 (4.1)	0	2 (4.9)	NA	10 (4.2)	0
Urine colour abnormal	6 (3.1)	0	1 (2.4)	NA	7 (3.0)	0
Blood pressure diastolic increased	1 (0.5)	0	0	NA	1 (0.4)	0
Blood pressure increased	0	0	1 (2.4)	NA	1 (0.4)	0
Lymph node palpable	1 (0.5)	0	0	NA	1 (0.4)	0
Metabolism and nutrition disorders	1 (0.5)	0	0	NA	1 (0.4)	0
Anorexia	1 (0.5)	0	0	NA	1 (0.4)	0
Musculoskeletal and connective tissue disorders	5 (2.6)	1 (1.3)	1 (2.4)	NA	6 (2.5)	1 (1.3)
Muscle spasms	1 (0.5)	0	1 (2.4)	NA	2 (0.8)	0
Arthralgia	1 (0.5)	0	0	NA	1 (0.4)	0
Back pain	1 (0.5)	0	0	NA	1 (0.4)	0
Musculoskeletal stiffness	1 (0.5)	0	0	NA	1 (0.4)	0
Myalgia	1 (0.5)	0	0	NA	1 (0.4)	0
Tendon pain	1 (0.5)	0	0	NA	1 (0.4)	0
Pain in extremity	0	1 (1.3)	0	NA	0	1 (1.3)
Nervous system disorders	23 (11.8)	6 (7.7)	6 (14.6)	NA	29 (12.3)	6 (7.7)
Headache	16 (8.2)	3 (3.8)	4 (9.8)	NA	20 (8.5)	3 (3.8)

System Organ Class/ Preferred Term	Healthy Population (01, 02, 04, 05, 11, 13, 14, 17, 18, 20) Ceftaroline (N=195) n(%)	Healthy Population (01, 02, 04, 05, 11, 13, 14, 17, 18, 20) Placebo (N=78) n(%)	Special Populations (02, 04, 11, 18) Ceftaroline (N=41) n(%)	Special Populations (02, 04, 11, 18) Placebo (N=0) n(%)	Pooled Clinical Pharmacology Studies (01, 02, 04, 05, 11, 13, 14, 17, 18, 20) Ceftaroline (N=236) n(%)	Pooled Clinical Pharmacology Studies (01, 02, 04, 05, 11, 13, 14, 17, 18, 20) Placebo (N=78) n(%)
Nervous system disorders (Cont)						
Dizziness	5 (2.6)	1 (1.3)	2 (4.9)	NA	7 (3.0)	1 (1.3)
Paraesthesia	2 (1.0)	0	0	NA	2 (0.8)	0
Disturbance in attention	1 (0.5)	0	0	NA	1 (0.4)	0
Dizziness postural	1 (0.5)	1 (1.3)	0	NA	1 (0.4)	1 (1.3)
Dysgeusia	1 (0.5)	0	0	NA	1 (0.4)	0
Hypoaesthesia	1 (0.5)	0	0	NA	1 (0.4)	0
Sinus headache	0	0	1 (2.4)	NA	1 (0.4)	0
Somnolence	1 (0.5)	0	0	NA	1 (0.4)	0
Syncope vasovagal	1 (0.5)	1 (1.3)	0	NA	1 (0.4)	1 (1.3)
Tremor	0	1 (1.3)	0	NA	0	1 (1.3)
Psychiatric disorders	1 (0.5)	0	1 (2.4)	NA	2 (0.8)	0
Anxiety	1 (0.5)	0	1 (2.4)	NA	2 (0.8)	0
Renal and urinary disorders	8 (4.1)	0	1 (2.4)	NA	9 (3.8)	0
Urine odour abnormal	6 (3.1)	0	1 (2.4)	NA	7 (3.0)	0
Chromaturia	2 (1.0)	0	0	NA	2 (0.8)	0
Respiratory, thoracic and mediastinal disorders	5 (2.6)	2 (2.6)	1 (2.4)	NA	6 (2.5)	2 (2.6)
Oropharyngeal pain	2 (1.0)	0	0	NA	2 (0.8)	0
Cough	1 (0.5)	0	0	NA	1 (0.4)	0
Dry throat	1 (0.5)	0	0	NA	1 (0.4)	0
Dyspnoea	1 (0.5)	0	0	NA	1 (0.4)	0
Hiccups	0	0	1 (2.4)	NA	1 (0.4)	0
Haemoptysis	0	1 (1.3)	0	NA	0	1 (1.3)
Nasal congestion	0	1 (1.3)	0	NA	0	1 (1.3)

Appendix 9. Incidence of PCS Postbaseline Coagulation Values in Pooled Phase 3 Studies. (Source: Integrated Summary of Safety (ABSSSI and CABP), p. 232).

Clinical Laboratory Parameter (Unit) PCS Criterion	***cSSSI (06, 07)***		***CABP (08, 09)***		***Pooled Phase 3 Studies (06, 07, 08, 09)***	
	Ceftaroline (N = 692) n/N1 (%)	*Vancomycin plus Aztreonam (N = 686) n/N1 (%)*	*Ceftaroline (N = 613) n/N1 (%)*	*Ceftriaxone (N = 615) n/N1 (%)*	*Ceftaroline (N = 1305) n/N1 (%)*	*Pooled Comparators (N = 1301) n/N1 (%)*
Activated Partial Thromboplastin (sec)						
< 0.5 × LLN and decrease from baseline > 50%	0/554	0/554	0/492	0/498	0/1046	0/1052
> 2.0 × ULN and increase from baseline > 100%	9/554 (1.6)	15/554 (2.7)	9/492 (1.8)	5/498 (1.0)	18/1046 (1.7)	20/1052 (1.9)
International Normalized Ratio						
< 0.5 × LLN and decrease from baseline > 50%	1/558 (0.2)	0/553	0/506	0/508	1/1064 (0.1)	0/1061
> 2.0 × ULN and increase from baseline > 100%	9/558 (1.6)	6/553 (1.1)	8/506 (1.6)	8/508 (1.6)	17/1064 (1.6)	14/1061 (1.3)
Prothrombin Time (sec)						
< 0.5 × LLN and decrease from baseline > 50%	0/558	0/555	0/507	0/512	0/1065	0/1067
> 2.0 × ULN and increase from baseline > 100%	9/558 (1.6)	8/555 (1.4)	12/507 (2.4)	11/512 (2.1)	21/1065 (2.0)	19/1067 (1.8)

Abbreviations: LLN = Lower limit of normal value, PCS = Potentially clinically significant, ULN = Upper limit of normal value.
N1 = Number of subjects with a baseline and at least one post-dose assessment for the parameter.

Appendix 10. PCS Postbaseline Chemistry Values in the Pooled Phase 3 Studies (Source: Integrated Summary of Safety (ABSSSI and CABP), pp. 235-8.)

Clinical Laboratory Parameter (Unit) PCS Criterion	*cSSSI (06, 07)*		*CABP (08, 09)*		*Pooled Phase 3 Studies (06, 07, 08, 09)*	
	Ceftaroline (N = 692) n/N1 (%)	*Vancomycin plus Aztreonam (N = 686) n/N1 (%)*	*Ceftaroline (N = 613) n/N1 (%)*	*Ceftriaxone (N = 615) n/N1 (%)*	*Ceftaroline (N = 1305) n/N1 (%)*	*Pooled Comparators (N = 1301) n/N1 (%)*
Alanine Aminotransferase (SGPT) (U/L)						
> 3.0 × ULN and increase from baseline > 200%	8/648 (1.2)	17/644 (2.6)	13/552 (2.4)	18/544 (3.3)	21/1200 (1.8)	35/1188 (2.9)
Albumin (g/dL)						
< 0.5 × LLN and decrease from baseline > 50%	1/656 (0.2)	0/649	1/553 (0.2)	2/546 (0.4)	2/1209 (0.2)	2/1195 (0.2)
> 1.5 × ULN and increase from baseline > 50%	0/656	0/649	0/553	0/546	0/1209	0/1195
Alkaline Phosphatase (U/L)						
< 0.5 × LLN and decrease from baseline > 80%	0/673	0/663	0/598	0/596	0/1271	0/1259
> 2.0 × ULN and increase from baseline > 100%	0/673	3/663 (0.5)	7/598 (1.2)	9/596 (1.5)	7/1271 (0.6)	12/1259 (1.0)
Aspartate Aminotransferase (SGOT) (U/L)						
> 3.0 × ULN and increase from baseline > 200%	9/639 (1.4)	14/635 (2.2)	6/537 (1.1)	13/527 (2.5)	15/1176 (1.3)	27/1162 (2.3)
Bicarbonate (HCO3) (mEq/L)						
< 0.7 × LLN and decrease from baseline > 40%	0/655	0/647	0/553	1/545 (0.2)	0/1208	1/1192 (0.1)
> 1.3 × ULN and increase from baseline > 40%	1/655 (0.2)	0/647	0/553	0/545	1/1208 (0.1)	0/1192
Bilirubin, Direct (Conjugated) (mg/dL)						
> 2.5 × ULN and increase from baseline > 150%	0/615	1/604 (0.2)	0/451	2/433 (0.5)	0/1066	3/1037 (0.3)
Bilirubin, Total (mg/dL)						
> 2.5 × ULN and increase from baseline > 150%	0/656	1/649 (0.2)	0/553	1/546 (0.2)	0/1209	2/1195 (0.2)
Calcium (mg/dL)						
< 0.7 × LLN and decrease from baseline > 30%	1/676 (0.1)	1/662 (0.2)	0/599	2/596 (0.3)	1/1275 (0.1)	3/1258 (0.2)
> 1.3 × ULN and increase from baseline > 30%	0/676	0/662	0/599	0/596	0/1275	0/1258
Chloride (mEq/L)						
< 0.8 × LLN and decrease from baseline > 20%	0/676	0/662	0/599	0/595	0/1275	0/1257
> 1.2 × ULN and increase from baseline > 20%	0/676	0/662	0/599	0/595	0/1275	0/1257
Cholesterol, Total (mg/dL)						
> 1.3 × ULN and increase from baseline > 50%	1/676 (0.1)	1/662 (0.2)	1/599 (0.2)	0/596	2/1275 (0.2)	1/1258 (0.1)
Creatine Kinase (U/L)						
< 0.4 × LLN and decrease from baseline > 60%	0/652	0/646	0/552	0/545	0/1204	0/1191
> 4.0 × ULN and increase from baseline > 300%	15/652 (2.3)	10/646 (1.5)	4/552 (0.7)	5/545 (0.9)	19/1204 (1.6)	15/1191 (1.3)

Clinical Laboratory Parameter (Unit) PCS Criterion	*cSSSI (06, 07)*		*CABP (08, 09)*		*Pooled Phase 3 Studies (06, 07, 08, 09)*	
	Ceftaroline (N = 692) n/N1 (%)	*Vancomycin plus Aztreonam (N = 686) n/N1 (%)*	*Ceftaroline (N = 613) n/N1 (%)*	*Ceftriaxone (N = 615) n/N1 (%)*	*Ceftaroline (N = 1305) n/N1 (%)*	*Pooled Comparators (N = 1301) n/N1 (%)*
Gamma Glutamyl Transferase (GGT) (U/L)						
> 3.0 × ULN and increase from baseline > 200%	4/673 (0.6)	8/661 (1.2)	12/598 (2.0)	15/595 (2.5)	16/1271 (1.3)	23/1256 (1.8)
Glucose (mg/dL)						
< 0.6 × LLN and decrease from baseline > 40%	1/653 (0.2)	1/645 (0.2)	0/548	0/541	1/1201 (0.1)	1/1186 (0.1)
> 3.0 × ULN and increase from baseline > 200%	2/653 (0.3)	4/645 (0.6)	2/548 (0.4)	1/541 (0.2)	4/1201 (0.3)	5/1186 (0.4)
Lactate Dehydrogenase (U/L)						
< 0.4 × LLN and decrease from baseline > 60%	0/636	0/630	0/563	1/557 (0.2)	0/1199	1/1187 (0.1)
> 4.0 × ULN and increase from baseline > 300%	0/636	0/630	1/563 (0.2)	1/557 (0.2)	1/1199 (0.1)	1/1187 (0.1)
Magnesium (mg/dL)						
< 0.5 × LLN and decrease from baseline > 65%	0/675	0/662	0/599	0/596	0/1274	0/1258
> 3.0 × ULN and increase from baseline > 200%	0/675	0/662	0/599	0/596	0/1274	0/1258
Phosphorus (mg/dL)						
< 0.5 × LLN and decrease from baseline > 50%	0/672	1/662 (0.2)	0/594	1/591 (0.2)	0/1266	2/1253 (0.2)
> 3.0 × ULN and increase from baseline > 200%	0/672	0/662	0/594	0/591	0/1266	0/1253
Potassium (mEq/L)						
< 0.8 × LLN and decrease from baseline > 20%	4/666 (0.6)	0/659	2/591 (0.3)	3/587 (0.5)	6/1257 (0.5)	3/1246 (0.2)
> 1.2 × ULN and increase from baseline > 20%	0/666	2/659 (0.3)	0/591	2/587 (0.3)	0/1257	4/1246 (0.3)
Protein, Total (g/dL)						
< 0.5 × LLN and decrease from baseline > 50%	1/676 (0.1)	0/662	0/599	0/596	1/1275 (0.1)	0/1258
> 1.5 × ULN and increase from baseline > 50%	0/676	0/662	0/599	0/596	0/1275	0/1258
Sodium (mEq/L)						
< 0.85 × LLN and decrease from baseline > 10%	0/676	0/664	0/599	0/596	0/1275	0/1260
> 1.1 × ULN and increase from baseline > 10%	1/676 (0.1)	1/664 (0.2)	5/599 (0.8)	0/596	6/1275 (0.5)	1/1260 (0.1)
Uric Acid (Urate) (mg/dL)						
> 2.0 × ULN and increase from baseline > 200%	0/676	0/662	0/599	0/596	0/1275	0/1258

Abbreviations: LLN = Lower limit of normal value; PCS = Potentially clinically significant, ULN = Upper limit of normal value.
N1 = Number of subjects with a baseline and at least one post-dose assessment for the parameter.

Appendix 11. PCS Vital Sign Value Changes in Pooled Phase 3 Studies (Source: Integrated Summary of Safety (ABSSSI and CABP), pp 243-4).

Vital Sign PCS Criteria	***cSSSI (06, 07)***		***CABP (08, 09)***		***Pooled Phase 3 Studies (06, 07, 08, 09)***	
	Ceftaroline (N = 692) n/N1(%)	*Vancomycin plus Aztreonam (N = 686) n/N1(%)*	*Ceftaroline (N = 613) n/N1(%)*	*Ceftriaxone (N = 615) n/N1(%)*	*Ceftaroline (N = 1305) n/N1(%)*	*Pooled Comparators (N = 1301) n/N1(%)*
Systolic BP (mmHg)						
≥ 180 and Increase ≥ 20	11/ 690 (1.6)	11/ 681 (1.6)	13/ 613 (2.1)	18/ 614 (2.9)	24/1303 (1.8)	29/1295 (2.2)
≤ 90 and Decrease ≥ 20	18/ 690 (2.6)	16/ 681 (2.3)	20/ 613 (3.3)	11/ 614 (1.8)	38/1303 (2.9)	27/1295 (2.1)
Diastolic BP (mmHg)						
≥ 105 and Increase ≥ 15	13/ 690 (1.9)	15/ 681 (2.2)	7/ 613 (1.1)	7/ 614 (1.1)	20/1303 (1.5)	22/1295 (1.7)
≤ 50 and Decrease ≥ 15	37/ 690 (5.4)	33/ 681 (4.8)	15/ 613 (2.4)	14/ 614 (2.3)	52/1303 (4.0)	47/1295 (3.6)
Pulse Rate (bpm)						
≥ 120 and Increase ≥ 15	7/ 690 (1.0)	7/ 681 (1.0)	12/ 613 (2.0)	6/ 614 (1.0)	19/1303 (1.5)	13/1295 (1.0)
≤ 50 and Decrease ≥ 15	14/ 690 (2.0)	8/ 681 (1.2)	8/ 613 (1.3)	7/ 614 (1.1)	22/1303 (1.7)	15/1295 (1.2)

Abbreviations: N1 = number of subjects with the vital sign parameter assessed at baseline and at least once postdose; PCS = potentially clinically significant.

Appendix 12. Incidence of TEAEs Indicating Potential Liver Injury in Pooled Phase 3 Studies.

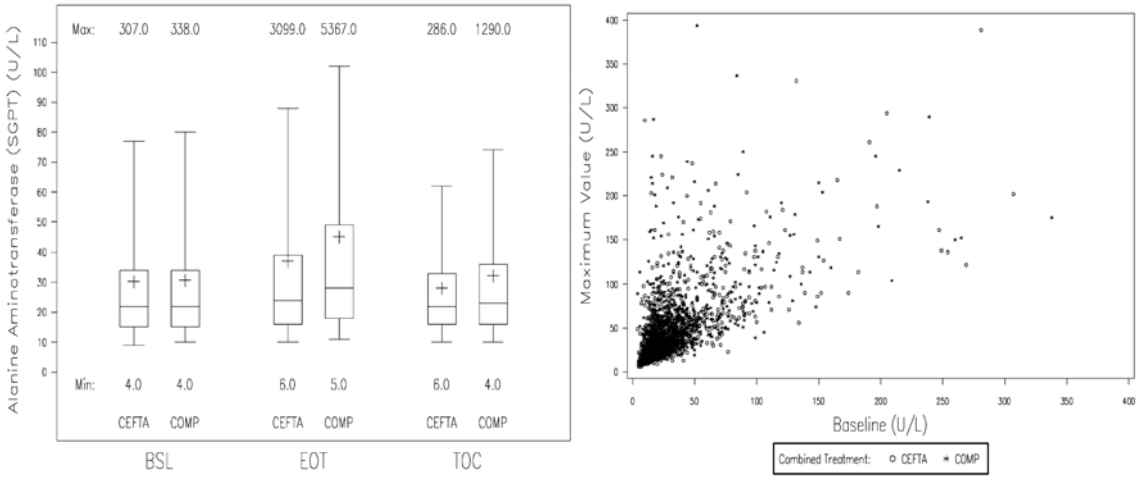
System Organ Class/ Preferred Term	***cSSSI (06, 07)***		***CABP (08, 09)***		***Pooled Phase 3 Studies (06, 07, 08, 09)***	
	Ceftaroline (N = 692) n(%)	*Vancomycin plus Aztreonam (N = 686) n(%)*	*Ceftaroline (N = 613) n(%)*	*Ceftriaxone (N = 615) n(%)*	*Ceftaroline (N = 1305) n(%)*	*Pooled Comparators (N = 1301) n(%)*
Subjects with at Least One TEAE Indicating Potential Liver Injury	19 (2.7)	29 (4.2)	14 (2.3)	18 (2.9)	33 (2.5)	47 (3.6)
Hepatobiliary disorders	2 (0.3)	2 (0.3)	4 (0.7)	5 (0.8)	6 (0.5)	7 (0.5)
Hepatitis	0	0	2 (0.3)	0	2 (0.2)	0
Cytolytic hepatitis	0	1 (0.1)	1 (0.2)	1 (0.2)	1 (0.1)	2 (0.2)
Hepatic failure	0	1 (0.1)	1 (0.2)	1 (0.2)	1 (0.1)	2 (0.2)
Hepatitis toxic	1 (0.1)	0	0	0	1 (0.1)	0
Hepatomegaly	1 (0.1)	0	0	0	1 (0.1)	0
Acute hepatic failure	0	0	0	1 (0.2)	0	1 (0.1)
Hepatocellular injury	0	0	0	1 (0.2)	0	1 (0.1)
Liver disorder	0	0	0	1 (0.2)	0	1 (0.1)
Investigations	17 (2.5)	27 (3.9)	10 (1.6)	13 (2.1)	27 (2.1)	40 (3.1)
Alanine aminotransferase increased	8 (1.2)	12 (1.7)	5 (0.8)	6 (1.0)	13 (1.0)	18 (1.4)
Aspartate aminotransferase increased	7 (1.0)	13 (1.9)	4 (0.7)	4 (0.7)	11 (0.8)	17 (1.3)
Gamma-glutamyltransferase increased	5 (0.7)	4 (0.6)	5 (0.8)	3 (0.5)	10 (0.8)	7 (0.5)
Hepatic enzyme increased	1 (0.1)	6 (0.9)	2 (0.3)	4 (0.7)	3 (0.2)	10 (0.8)
Transaminases increased	2 (0.3)	0	1 (0.2)	1 (0.2)	3 (0.2)	1 (0.1)
Liver function test abnormal	1 (0.1)	4 (0.6)	1 (0.2)	0	2 (0.2)	4 (0.3)

Appendix 13. PCS Postbaseline Hepatic Chemistry Values for Pooled Phase 3 Studies

Clinical Laboratory Parameter Criterion	*cSSSI (06, 07)*		*CABP (08, 09)*		*Pooled Phase 3 Studies (06, 07, 08, 09)*	
	Ceftaroline (N = 692) n/N1 (%)	*Vancomycin plus Aztreonam (N = 686) n/N1 (%)*	*Ceftaroline (N = 613) n/N1 (%)*	*Ceftriaxone (N = 615) n/N1 (%)*	*Ceftaroline (N = 1305) n/N1 (%)*	*Pooled Comparators (N = 1301) n/N1 (%)*
ALT > 3 × ULN	4/542 (0.7)	12/527 (2.3)	10/430 (2.3)	13/422 (3.1)	14/972 (1.4)	25/949 (2.6)
ALT > 5 × ULN	3/542 (0.6)	5/527 (0.9)	3/430 (0.7)	1/422 (0.2)	6/972 (0.6)	6/949 (0.6)
ALT > 10 × ULN	0/542	3/527 (0.6)	1/430 (0.2)	0/422	1/972 (0.1)	3/949 (0.3)
AST > 3 × ULN	6/510 (1.2)	13/488 (2.7)	5/401 (1.2)	6/388 (1.5)	11/911 (1.2)	19/876 (2.2)
AST > 5 × ULN	1/510 (0.2)	5/488 (1.0)	3/401 (0.7)	4/388 (1.0)	4/911 (0.4)	9/876 (1.0)
AST > 10 × ULN	0/510	3/488 (0.6)	2/401 (0.5)	1/388 (0.3)	2/911 (0.2)	4/876 (0.5)
Total Bilirubin > 1.5 × ULN	1/628 (0.2)	1/619 (0.2)	1/507 (0.2)	3/501 (0.6)	2/1135 (0.2)	4/1120 (0.4)
Total Bilirubin > 2 × ULN	1/628 (0.2)	1/619 (0.2)	0/507	1/501 (0.2)	1/1135 (0.1)	2/1120 (0.2)
ALP > 2 × ULN	0/592	2/565 (0.4)	3/526 (0.6)	6/518 (1.2)	3/1118 (0.3)	8/1083 (0.7)
Potential Hy's Law ALT or AST > 3 × ULN, ALP < 2 × ULN and						
Total Bilirubin > 1.5 × ULN	0/655	0/649	0/549	1/545 (0.2)	0/1204	1/1194 (0.1)
Total Bilirubin > 2 × ULN	0/656	0/649	0/552	1/545 (0.2)	0/1208	1/1194 (0.1)

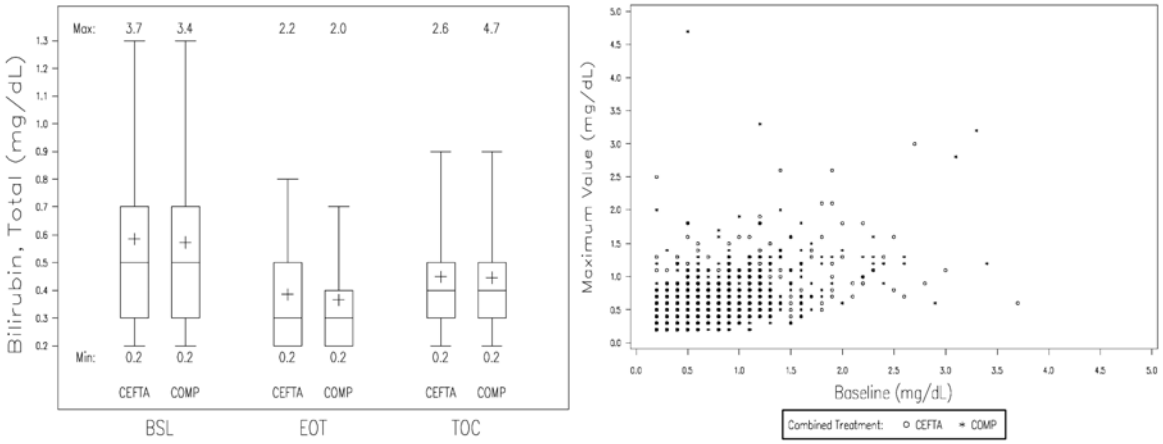
Notes: N1 = Number of subjects with at least one postbaseline assessment and a normal baseline value (≤ ULN) of the laboratory parameter. For potential Hy's Law, ALT, AST, ALP, and total bilirubin do not need to be normal at baseline, but potential Hy's Law laboratory criteria must not be met at baseline.

Appendix 14. Box and scatter pots for ALT (Maximum vs Baseline) by Treatment Group of Pooled Phase 3 Studies



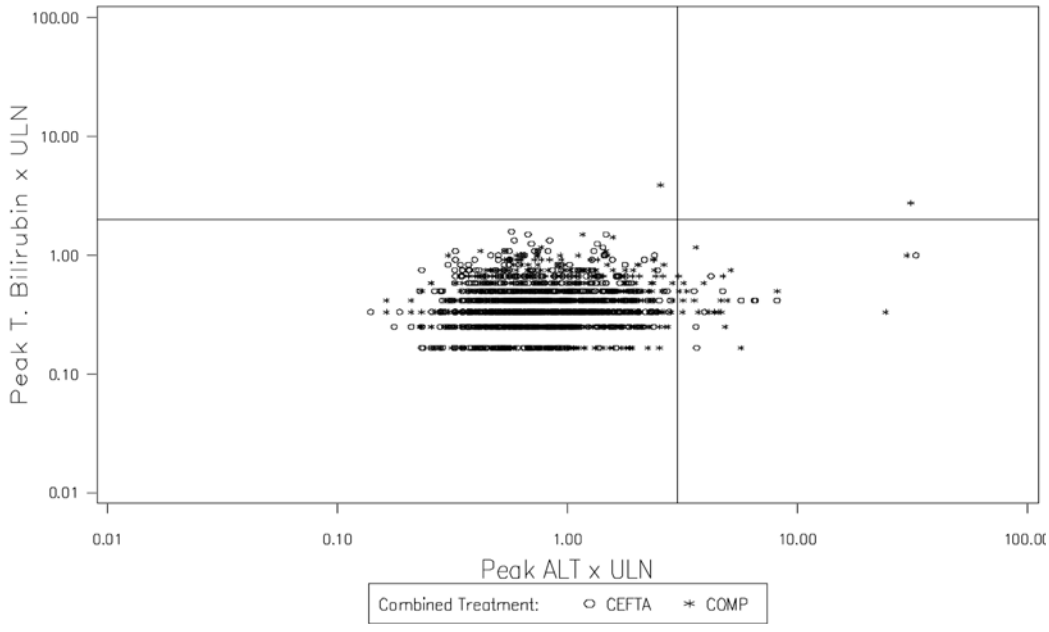
Legend: CEFTA = Ceftaroline, COMP = Pooled comparator (Ceftriaxone and Vancomycin plus Aztreonam. Baseline is defined as the last assessment prior to the first dose of study drug.

Appendix 15. Box and Scatter Plots for Total Bilirubin by Treatment at Baseline, EOT, and TOC from Pooled Phase 3 Studies.



Legend: CEFTA = Ceftaroline, COMP = Pooled comparator (Ceftriaxone and Vancomycin plus Aztreonam. Baseline is defined as the last assessment prior to the first dose of study drug.

Appendix 16. Scatter Plots of Peak Post-Baseline Total Bilirubin versus Peak Post-Baseline ALT in Pooled Phase 3 Studies (Hy's Law)



Legend: CEFTA = Ceftaroline; Comp = Pooled comparators (Ceftriaxone and Vancomycin plus Aztreonem. Results on each axis are calculated in relation to patient-specific ULN, and plotted on the log10 scale.

Appendix 17. Incidence of TEAEs of Rash, Hypersensitivity, or Pruritus in Pooled Phase 3 Studies.

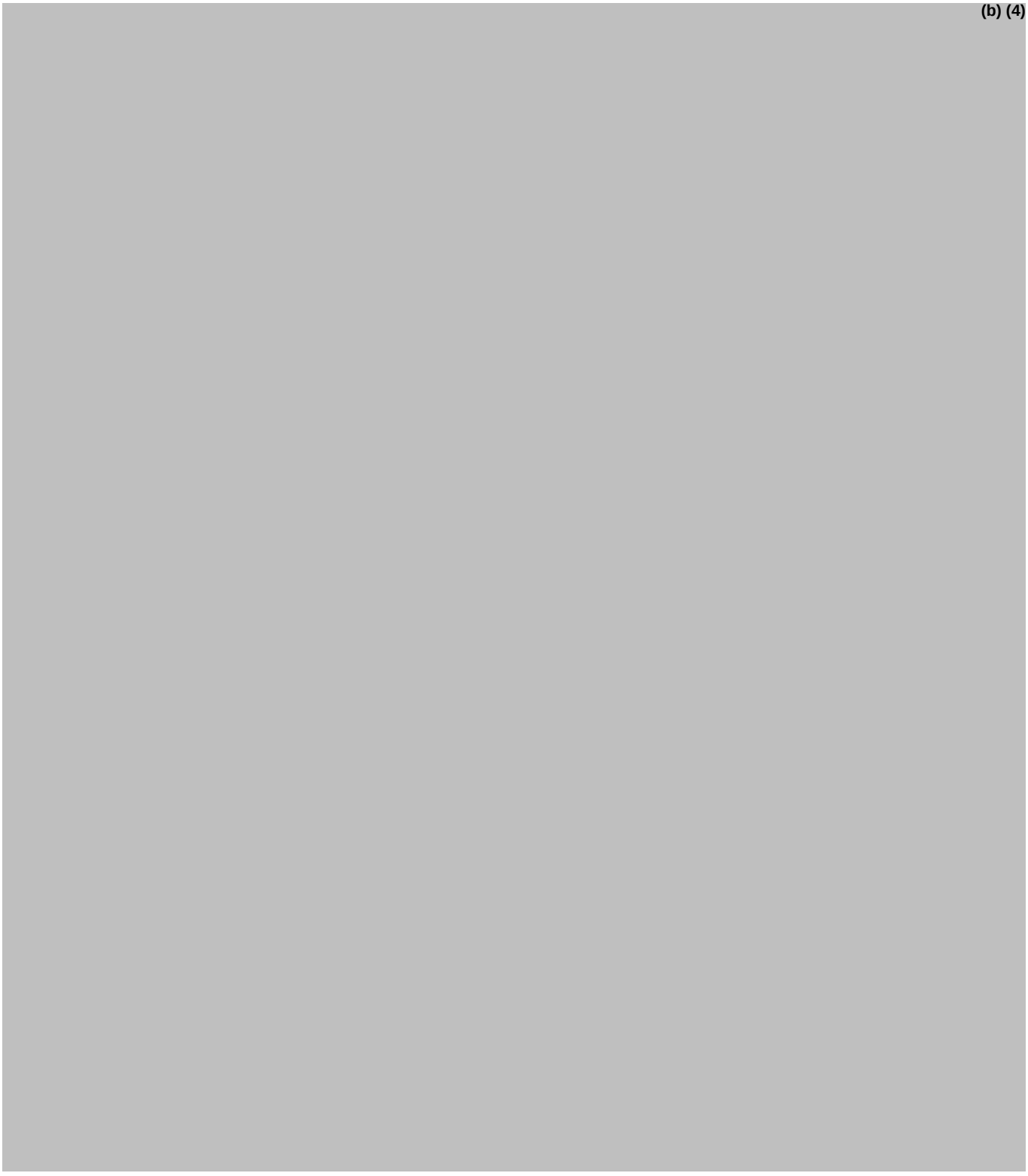
Preferred Term	***cSSSI (06, 07)***		***CABP (08, 09)***		***Pooled Phase 3 Studies (06, 07, 08, 09)***	
	Ceftaroline (N = 692) n(%)	*Vancomycin plus Aztreonam (N = 686) n(%)*	*Ceftaroline (N = 613) n(%)*	*Ceftriaxone (N = 615) n(%)*	*Ceftaroline (N = 1305) n(%)*	*Pooled Comparators (N = 1301) n(%)*
Subjects with at Least One Potential Allergic TEAE	61 (8.8)	101 (14.7)	9 (1.5)	10 (1.6)	70 (5.4)	111 (8.5)
Any Rash	31 (4.5)	37 (5.4)	6 (1.0)	5 (0.8)	37 (2.8)	42 (3.2)
Rash	15 (2.2)	15 (2.2)	2 (0.3)	2 (0.3)	17 (1.3)	17 (1.3)
Rash generalised	5 (0.7)	2 (0.3)	0	0	5 (0.4)	2 (0.2)
Dermatitis allergic	3 (0.4)	4 (0.6)	1 (0.2)	1 (0.2)	4 (0.3)	5 (0.4)
Rash maculo-papular	3 (0.4)	2 (0.3)	0	0	3 (0.2)	2 (0.2)
Dermatitis	1 (0.1)	0	1 (0.2)	0	2 (0.2)	0
Drug eruption	0	1 (0.1)	2 (0.3)	1 (0.2)	2 (0.2)	2 (0.2)
Erythema	2 (0.3)	12 (1.7)	0	0	2 (0.2)	12 (0.9)
Rash macular	1 (0.1)	0	0	0	1 (0.1)	0
Rash pruritic	1 (0.1)	2 (0.3)	0	0	1 (0.1)	2 (0.2)
Generalised erythema	0	1 (0.1)	0	0	0	1 (0.1)
Infusion site rash	0	1 (0.1)	0	0	0	1 (0.1)
Rash papular	0	0	0	1 (0.2)	0	1 (0.1)
Any Hypersensitivity	14 (2.0)	28 (4.1)	2 (0.3)	4 (0.7)	16 (1.2)	32 (2.5)
Hypersensitivity	4 (0.6)	8 (1.2)	1 (0.2)	1 (0.2)	5 (0.4)	9 (0.7)
Urticaria	3 (0.4)	8 (1.2)	1 (0.2)	1 (0.2)	4 (0.3)	9 (0.7)
Flushing	2 (0.3)	3 (0.4)	0	0	2 (0.2)	3 (0.2)
Anaphylactic reaction	1 (0.1)	0	0	0	1 (0.1)	0
Anaphylactic shock	1 (0.1)	0	0	0	1 (0.1)	0
Anaphylactoid reaction	1 (0.1)	0	0	0	1 (0.1)	0
Hyperaemia	1 (0.1)	0	0	0	1 (0.1)	0
Lip swelling	1 (0.1)	1 (0.1)	0	0	1 (0.1)	1 (0.1)
Swelling face	1 (0.1)	2 (0.3)	0	0	1 (0.1)	2 (0.2)
Allergic oedema	0	1 (0.1)	0	0	0	1 (0.1)
Angioedema	0	0	0	1 (0.2)	0	1 (0.1)
Infusion site urticaria	0	2 (0.3)	0	0	0	2 (0.2)
Laryngospasm	0	0	0	1 (0.2)	0	1 (0.1)
Pharyngeal oedema	0	1 (0.1)	0	0	0	1 (0.1)
Red man syndrome	0	3 (0.4)	0	0	0	3 (0.2)
Any Pruritus	31 (4.5)	65 (9.5)	1 (0.2)	3 (0.5)	32 (2.5)	68 (5.2)
Pruritus	17 (2.5)	50 (7.3)	1 (0.2)	3 (0.5)	18 (1.4)	53 (4.1)
Pruritus generalised	15 (2.2)	19 (2.8)	0	0	15 (1.1)	19 (1.5)
Pruritus allergic	0	1 (0.1)	0	0	0	1 (0.1)

Source: Integrated Summary of Safety (ABSSSI and CABP), p. 224-5.

Appendix 18. Overview of Adverse Events by Potential Ceftaroline Overdose for Phase 3 Studies.

	cSSSI (06, 07)	CAP (08, 09)	Pooled Phase 3 Studies (06, 07, 08, 09)
	Ceftaroline (N=692)	Ceftaroline (N=613)	Ceftaroline (N=1305)
Number of Subjects, N1			
Potentially Overdosed	17	48	65
Not Overdosed	675	565	1240
Number of Subjects with At Least One TEAE, n/N1(%)	309/ 692 (44.7)	288/ 613 (47.0)	597/1305 (45.7)
Potentially Overdosed	10/ 17 (58.8)	32/ 48 (66.7)	42/ 65 (64.6)
Not Overdosed	299/ 675 (44.3)	256/ 565 (45.3)	555/1240 (44.8)
Number of Deaths, n/N1(%)	3/ 692 (0.4)	15/ 613 (2.4)	18/1305 (1.4)
Potentially Overdosed	0/ 17	2/ 48 (4.2)	2/ 65 (3.1)
Not Overdosed	3/ 675 (0.4)	13/ 565 (2.3)	16/1240 (1.3)
Number of Subjects with SAEs Other than Death, n/N1(%)	28/ 692 (4.0)	61/ 613 (10.0)	89/1305 (6.8)
Potentially Overdosed	1/ 17 (5.9)	8/ 48 (16.7)	9/ 65 (13.8)
Not Overdosed	27/ 675 (4.0)	53/ 565 (9.4)	80/1240 (6.5)
Number of Subjects Who Discontinued Study Drug or Study Due to AEs, n/N1(%)	21/ 692 (3.0)	27/ 613 (4.4)	48/1305 (3.7)
Potentially Overdosed	0/ 17	4/ 48 (8.3)	4/ 65 (6.2)
Not Overdosed	21/ 675 (3.1)	23/ 565 (4.1)	44/1240 (3.5)

Source: Integrated Summary of Safety (ABSSSI and CABP), p. 3741



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9.2 Advisory Committee Meeting

The Anti-Infective Drugs Advisory Committee met on September 7, 2010 at the Hilton Washington, DC/Gaithersburg in Gaithersburg, MD to discuss the new drug application (NDA) 200327 for ceftaroline fosamil for injection which was submitted by Cerexa, Inc. for the treatment of adults with community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI)

9.2.1. Community-Acquired Bacterial Pneumonia (CABP)

For the morning session of the meeting, the committee discussed whether the information in the NDA demonstrated the safety and efficacy of ceftaroline for the treatment of CABP in adults. Seven voting members and one non-voting member of the AIDAC, twelve voting special government employee consultants, two voting regular government employee consultants, and several non-voting FDA participants/presentors were present.

After the meeting was called to order by Thomas Moore, MD, Committee Chair, Janice Pohlman, MD, MPH discussed the existing historical evidence that has become the basis of the Agency's current thinking on the validity of clinical endpoints and the timing of the assessment for both indications.

The Applicant, Cerexa, Inc., then presented their perspective on the microbiology, pharmacology (Ian Critchley, Ph. D.), clinical trial results that would support the efficacy (Dirk Thye, M.D.) and safety (David Friedland, M.D.) of ceftaroline as treatment for CABP. The FDA then presented their perspective of the Application. Avery Goodwin, Ph. D. presented the microbiologic information on ceftaroline and the FDA-proposed MIC breakpoints. Daniel Rubin, Ph. D. presented the sensitivity analyses performed by the FDA review team using an earlier assessment of a combined sign and symptom improvement criteria as an endpoint. Dr. Rubin presented robust results concordant with the Applicant's analysis, showing ceftaroline's efficacy as treatment for CABP. Ariel R. Porcalla, M.D., M.P.H. presented the FDA perspective on the safety of ceftaroline in the pooled safety population for both indications, indicating that the safety profile of ceftaroline is similar to those of existing cephalosporins.

The Committee was then asked to vote whether the application demonstrated the safety and efficacy for the indication of CABP.

All of the 21 voting members of the Advisory Committee agreed that both safety and efficacy of ceftaroline was demonstrated by the Applicant for the requested indication of CABP. Members felt that ceftaroline met the prespecified 10% noninferiority margin using the Applicant's analysis with primary endpoints assessed at the TOC visit. The members commended the FDA for the sensitivity analyses consistent with historical

evidence, stating that such analysis may become the paradigm on which study protocols for future clinical trials may be modeled.

The increased frequency of seroconversion of Coombs' test observed in the ceftaroline-treated group compared to the comparator group, the lack of evidence for ceftaroline's efficacy against CABP caused by methicillin-resistant *Staphylococcus aureus* (MRSA), and the disparate MIC breakpoints from the FDA and the Applicant, are some of the concerning issues members felt should be addressed in the labeling discussions with the Applicant.

9.2.2. Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

Initially, Applicant presentations were made by Cerexa, Inc. These presentations included discussions an overview of the treatment of ABSSSI, the pertinent microbiology and clinical pharmacology, clinical design and efficacy results, clinical safety, and comments of therapeutic perspective relevant to ABSSSI. Cerexa discussed their efficacy results based on their pre-specified primary endpoint of clinical response rate at the Test-of-Cure visit and their key secondary analyses. In addition, Cerexa Inc. discussed the results of the additional sensitivity analyses performed based on the most recent FDA draft guidance document for the treatment of acute bacterial skin and skin structure infections. The document recommends establishing primary efficacy endpoints based on cessation of lesion spread and resolution of fever at an earlier time point.

The majority of questions from the Committee of the Applicant focused on the use of vancomycin plus aztreonam as the comparator drug in the Phase 3 clinical trials and the number of microbiological isolates obtained for organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA).

Afterwards, the FDA presented their review and analysis of the data submitted for ceftaroline. The FDA statistical reviewer, Dr. Christopher Kadoorie, discussed the difficulty of establishing a non-inferiority margin based on the initial pre-specified analysis population and efficacy endpoints. He presented the results of sensitivity analyses looking at assessment based on cessation of lesion spread and reduction of fever at the Day 3 time point. In addition, he presented data on further analyses that looked at reduction in lesion size at various time points, prior antibiotic use, and concomitant medication use. Overall, these data ultimately supported the non-inferiority of ceftaroline relative to the comparator, Dr. Kadoorie highlighted limitations to these analyses including errors in measuring lesion size.

The Committee was then charged with voting on the following question: has the Applicant demonstrated the safety and efficacy of ceftaroline for the requested indication of ABSSSI? The Committee unanimously agreed that both safety and efficacy of ceftaroline was demonstrated for the indication of ABSSSI. The vote total

was 18 for yes, zero for no and no abstentions. Some members were concerned with potential unblinding in trials due to monitoring of vancomycin levels and suggested weight-based dosing in the design of future trials. In addition, some members were also concerned with the issue raised about accuracy of lesion measurement and measurement techniques were discussed for future trials. Lastly, concerns were raised about the potential for off-label use of ceftaroline for treatment of community-acquired bacterial pneumonia caused by MRSA and members urged that this should be clearly addressed in the labeling.

9.3 Literature Review/References

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/s/

ARIEL R PORCALLA

10/29/2010

The efficacy review for Acute Bacterial Skin and Skin Structure Infections was done by Neil Rellosa, MD.

JANICE K POHLMAN

10/29/2010