CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200327

STATISTICAL REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA # :	200327
Drug Name:	Teflaro™ (ceftaroline fosamil for injection)
Indication:	Acute bacterial skin and Skin Structure Infections
Applicant:	Cerexa (a wholly owned subsidiary of Forest Laboratories, Inc.)
Stamp Date:	December 30, 2009
PDUFA Goal Date:	October 30, 2010
Reviewer Completion Date:	October 8, 2010
Biometrics Division:	Division of Biometrics IV
Medical Division:	Division of Anti-Infective and Ophthalmology Drug Products
Documents Reviewed:	\\CDSESUB1\EVSPROD\NDA200327\0000
Statistical Reviewer:	Christopher Kadoorie, PhD
Concurring Reviewers:	Thamban Valappil, PhD
Clinical Team Leader:	Janice Pohlman, MD
Clinical Reviewers:	Neil Rellosa, MD
Project Manager:	Carmen DeBellas, Pharm D

TABLE OF CONTENTS

List of Tables

List of Figures

1. EXECUTIVE SUMMARY

1.1 Introduction

The Applicant submitted NDA 200327 on December 30, 2009 to support approval of Teflaro™ (ceftaroline fosamil for injection) for the indications of Community Acquired Bacterial Pneumonia (CABP) and Acute Bacterial Skin and Skin Structure Infections (ABSSSI). This statistical review addresses the issues related to ABSSSI indication. For statistical issues related to the CABP indication, refer to the statistical review of Dr. Daniel Rubin.

For the ABSSSI indication, this application included two Phase 3 ABSSSI studies, studies P903-06 and P903-07 (hereinafter referred to as studies 06 & 07) to support the efficacy and safety of ceftaroline. Studies 06 and 07 assessed clinical response at test of cure (TOC), 8-15 days after the end of a 5-14 day course of therapy, as the primary endpoint in a non-inferiority design with a pre-specified non-inferiority margin of 10%. Although Study 06 & 07 designs had been previously agreed to by the Agency, these designs are no longer considered appropriate for demonstrating non-inferiority. Based on a major re-thinking within the Agency and among outside experts in ABSSSI, non-inferiority comparisons for endpoints analyzed at later time points such as at TOC may not be meaningfully interpreted since there is no available historical data to support the NI margin. In contrast, NI margins based on earlier time points such as at 48-72 hours (Day 3) after start of study therapy may be supported by historical studies (Snodgrass et. al, 1937)[1,2]. Due to these considerations, this review primarily considers the responder rate endpoint defined as "cessation of spread of lesion with absence of fever" in the FDA modified ITT analysis population. The FDA-MITT is a subset of the Applicant's modified ITT (MITT) which excluded MITT patients with lesion sizes ≤ 75 cm^2, major abscesses with < 5 cm of surrounding erythema or infection types of 'other' or of 'ulcer.' The FDA-MITT included 797 (58%) of the Applicant's MITT subjects across both studies. In this review, the analysis population considered will be the FDA-MITT unless otherwise stated.

An anti-infective advisory committee (AIDAC) was held on September 7, 2010 to discuss issues in making a determination of the safety and efficacy of Teflaro™. Based on considerations of Reviewer sensitivity analyses at the Day 3 endpoint as well as other evidence, the AIDAC voted unanimously (18 votes to 0) that Teflaro™ was safe and effective for the ABSSSI indication.

1.2 Conclusions and Recommendations

Based on my review of the data, non-inferiority studies 06 & 07 provided adequate evidence supporting the efficacy of ceftaroline (administered as 1 hour IV infusion every 12 hours for 5 to 14 days) in treating patients with ABSSSI infections. Findings relied primarily on Reviewer sensitivity analyses for the key endpoint of responder rates based on cessation of spread of lesion with absence of fever at 48-72 hours (Day 3) in FDA-MITT patients. Responder rates favored ceftaroline over the comparator: 74.0% vs.

64.6%, a 9.4% difference (95% CI: 0.03%, 18.8%) in Study 06 and 74.0% vs. 68.1%, a 5.9% difference (95% CI: -3.6%, 15.5%) in Study 07. These analyses provided evidence of non-inferiority (NI) of ceftaroline to vancomycin/aztreonam (active comparator) within a 3.6% NI margin for both studies. In additional sensitivity analyses to evaluate the robustness of findings, ceftaroline was observed to be similar (or favorable) to the comparator regardless of the degree of change in lesion size required for a responder (e.g. cessation vs. % reduction), timing of responder rates (e.g. Day 3 vs. EOT), definition of a responder (e.g. cessation/percent reduction without the fever component) and choice of endpoint (e.g. investigator assessment of clinical cure rate at EOT, rates of absence of erythema, swelling and tenderness). In these analyses, treatment comparisons on Day 3 favored ceftaroline in both studies while comparisons at EOT favored ceftaroline in Study 06 but did not favor either treatment in Study 07.

However, it should be noted that there were several limitations in applying the Reviewer sensitivity analyses to Study 06 & 07 as discussed in Section 5. General limitations included uncertainties in reliably measuring lesion size, NI margin justification from historical studies, the post-hoc nature of testing hypotheses, interpretation of responder rates and the types of patients/symptoms addressed. In addition, further limitations specific to Study 06 & 07 included higher rates of missing data, investigator errors & biases in measuring lesion size, influence of prior antibiotics use, influence of concomitant antipyretic & anti-inflammatory use, dependence on baseline fever status, discordance of responder rates with investigator assessment at EOT and reductions in sample size. Despite these limitations, overall findings from studies 06 & 07 were considered to be adequately robust in supporting the efficacy of ceftaroline.

1.3 Brief Overview of Clinical Studies

There were two Phase 3 clinical studies presented in this submission. A brief overview of studies 06 & 07 as submitted by the Applicant is shown below.

Table 1: Applicant's Overview of Studies 06 & 07

Comparison of Studies 06 & 07	Study 06	Study 07
Type of Study:	Phase 3 multicenter, randomized, double-blind comparative study to evaluate the safety and efficacy of ceftaroline vs. vancomycin + Aztreonam in adults with ABSSSI	
Objective:	Determine the noninferiority in clinical cure rate of ceftaroline treatment compared to vancomycin plus aztreonam at the Test-of-cure (TOC) Visit in the Clinically Evaluable and MITT populations of adult subjects with ABSSSI	
Treatment Arms:	Two arms: Ceftaroline (600mg, q12h) and Vancomycin (1g IV q12h) plus Aztreonam (1g IV q12h)	
Sample Size:	702 ITT patients	694 ITT patients
Co-Primary Endpoints:	Per-subject clinical cure rate at the TOC visit in the CE and MITT populations.	
Study Design:	Baseline: within 24 hours of first dose of study drug, randomization	

	Study drug administration: Day 1 to EOT (IV, q12h for 5 to 14 days) TOC: 8 to 15 days after last dose of study drug LFU: 21 to 35 days after last dose of study drug
Statistical Methods:	Non-inferiority in clinical cure rate of ceftaroline in comparison with vancomycin plus aztreonam was determined by estimating two-sided 95% CIs around the observed treatment difference in proportions (ceftaroline minus vancomycin plus aztreonam). If lower limits of the 95% CI exceeded -10% for both co-primary endpoints, non-inferiority was concluded.

Source: Applicant Table

Statistical Reviewer Comments: *The above table describes the Applicant's Study 06 & 07 characteristics. However, evidence in this submission primarily relied on Reviewer sensitivity analyses with different characteristics as described in Section 3.1.1 "FDA Reviewer Sensitivity Analysis: Population and Endpoints."*

1.4 Major Statistical Issues and Findings

The major statistical issue in this submission was that the Applicant's primary analyses in Studies 06 & 07 were based on non-inferiority comparisons of clinical cure rates at a TOC visit occurring 8-15 days after the last dose of study drug. However, the proposed non-inferiority margin of 10% for these comparisons could not be scientifically justified from historical data. There are also further issues relating to the analysis population and the type/severity of ABSSSIs that can be considered for non-inferiority comparisons.

To address these issues, Reviewer sensitivity analyses considered responder rates at Day 3 as a key endpoint. Responders were defined as patients having cessation of spread of lesion and absence of fever at Day 3. Sensitivity analyses also considered the FDA-MITT analysis population which excluded patients with lesion sizes of < 75 cm^2 at baseline, patients with major abscesses with < 5 cm of surrounding erythema, patients with infection types of 'ulcer' or 'other.' In contrast to NI margins based on a clinical response endpoint at TOC, NI margins based on earlier time points such as at 48-72 hours after start of study therapy may be supported by historical studies (Snodgrass 1937). In the two Snodgrass studies of 1937, the treatment effect of sulphanilamide and prontosil compared to UV light in patients with cellulitis/erysipelas was approximately 17% for a composite primary endpoint of cessation of spread of lesion and resolution of fever at a 48-72 hour timepoint.

However, there were several limitations in applying responder rate analyses to Studies 06 and 07. General limitations included uncertainties in reliably measuring lesion size, NI margin justification from historical studies, the post-hoc nature of testing, interpretations of findings and the types of patients/symptoms addressed. In addition, further limitations specific to Study 06 & 07 included higher rates of missing data, measurement errors in lesions, influence of prior antibiotics, influence of concomitant antipyretics and anti-inflammatories, dependence on baseline fever status, discordance with investigator assessment at EOT and reductions in sample size. These limitations are discussed in Section 5.

2. INTRODUCTION

2.1 Class and Indication

Ceftaroline fosamil is the prodrug of ceftaroline, which is a cephalosporin antibiotic with broad spectrum activity against both gram-positive and gram-negative organisms.

The Applicant's proposed indication for Ceftaroline fosamil is for the treatment of ABSSSIs caused by susceptible isolates of the following gram-positive and gram-negative microorganisms: *Staphylococcus aureus* (including methicillin-susceptible [MSSA] and -resistant [MRSA] isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, (b) (4) *Escherichia coli, Klebsiella pneumoniae*, *Klebsiella oxytoca*, (b) (4).

2.2 History of Drug Development for ABSSSI

The following is a brief timeline of some of the key events (not all) in the history of drug development of ceftaroline for ABSSSI:

December 2004: Peninsula Pharmaceuticals, Inc. submitted an IND 71, 371 application to develop (b) (4) (ceftaroline fosamil for injection) for the treatment of ABSSSI and CABP.

June 2005: The sponsorship of IND 71,371 was transferred to Cerexa, Inc.

February 28, 2006: Cerexa was granted fast track designation from the Division for (b) (4) for the treatment of ABSSSI.

October 24, 2006: End-of-Phase 2 meeting. The Phase 3 development of ceftaroline fosamil for the treatment of ABSSSI was discussed with the Division. The discussion included endpoints and NI margin for the pivotal Phase 3 ABSSSI studies.

June 1, 2007: The Division agreed that a noninferiority study design at 10% non-inferiority margin was acceptable to support an indication of ABSSSI.

July 7, 2009: Type B Pre-NDA Meeting. The objective of the Pre-NDA meeting was to obtain concurrence on the content and format of the NDA. The Division and Applicant also agreed to maintain the 7-20 day test of cure TOC window when analyzing efficacy data for the pivotal ABSSSI studies. Sensitivity analyses would be conducted using the protocol-defined window of 8 to 15 days post-EOT in each clinical study report.

December 29, 2009: NDA 200327 was submitted for ceftaroline for the CABP and ABSSSI indications.

September 7, 2010: An anti-infective advisory committee (AIDAC) was held on September 7, 2010 to discuss issues in making a determination of the safety and efficacy of Teflaro™. Based on considerations of Reviewer sensitivity analyses at the Day 3 endpoint as well as other evidence, the AIDAC voted unanimously (18 votes to 0) that Teflaro™ was safe and effective for the ABSSSI indication.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

Applicant's Study Design and Endpoints

The study design and endpoints described in this section relate to those described by the Applicant for Study 06 & 07. Note that evaluation of evidence in this submission relied primarily on reviewer sensitivity analyses which differed from the Applicant's design and endpoints as discussed in Section 3.1.1 "FDA Reviewer Sensitivity Analysis: Population and Endpoints". Subheadings of the study design and endpoints below refer to both studies 06 and 07 unless otherwise stated.

Studies 06 & 07 are both Phase 3, multicenter, randomized, double-blind, comparative studies to evaluate the safety and efficacy of ceftaroline versus vancomycin plus aztreonam in adults with ABSSSI. The dosing schedule and study design are described in Tables 2 & 3.

Table 2: Standard Dosing Schedule

Treatment Group	Dosing Schedule	
	Infusion A 60 (± 10) minutes	**Infusion B** 60 (± 10) minutes
Ceftaroline	Ceftaroline fosamil (600 mg) q12h	Placebo q12h
Vancomycin + Aztreonam	Vancomycin (1 g) q12h	Aztreonam (1 g) q12h

Source: Adapted from Applicant Table

Table 3: Applicant's Study 06 & 07 Design

Visit:	Baseline	On therapy	TOC	LFU
Timing	Within 24 hours before first dose of study drug	Day 1 to EOT	8 to 15 days after last dose of study drug	21 to 35 days after last dose of study drug
Description	Confirmation of study eligibility Randomization to Treatment	IV study drug therapy for 5 to 14 days On-therapy clinical and laboratory assessments EOT assessments performed on last day of study drug administration	Subjects returned to study center for assessment of efficacy and safety.	Subjects returned to study center for final assessment of efficacy and safety.

Study 06 & 07 included subjects from 55 & 56 study centers across Latin America, Eastern and Western Europe and the US. Study 06 was conducted from February 2007 to November 2007 and Study 07 was conducted from March 2007 to December 2007. The primary objective in these studies were to determine the noninferiority in clinical cure rate of ceftaroline compared with that of vancomycin plus aztreonam at the TOC (8-15 days after EOT) in CE and MITT Populations of adult subjects with ABSSSI.

The Applicant's co-primary endpoints were clinical cure rates at TOC evaluated in the MITT and CE populations. Additional secondary endpoints included: 1) microbiological success rate at TOC, 2) clinical response at EOT, 3) clinical and microbiological response by pathogen at TOC, 4) clinical relapse at late follow-up (LFU), and 5) microbiological reinfection or recurrence at LFU.

Applicant's Inclusion Criteria

1. Age 18 years or more
2. Skin and/or skin structure infection (SSSI) that met EITHER of the following criteria:
   - Involved deeper soft tissue or required significant surgical intervention such as a wound infection (surgical or traumatic), a major abscess, an infected ulcer, or deep and extensive cellulitis

OR

   - Cellulitis or abscess of a lower extremity in subjects with diabetes mellitus or well documented peripheral vascular disease (PVD)
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 38ºC oral (greater than 38.5ºC rectal or tympanic) or hypothermia (less than 35ºC)
- White blood cell (WBC) count greater than 10,000/mm^3
- Greater than 10% immature neutrophils (bands) irrespective of WBC count

4. Need for hospitalization, or treatment in an emergency room or urgent care setting
5. Subject's infection expected to require at least 5 days of IV antimicrobial therapy
6. Females of child-bearing potential less than 2 years postmenopausal had to agree to and comply with using highly effective methods of birth control while in study
7. Written informed consent, willingness and ability to comply with all study procedures

Statistical Reviewer Comments: *The above describe the Applicant's main criteria for inclusion into Study 06 & 07. However, evidence in this submission relied primarily on Reviewer sensitivity analyses of the FDA-MITT population. Inclusion criteria for the FDA-MITT population were more stringent that the Applicant's MITT as discussed in Section 3.1.1 'FDA Reviewer Sensitivity Analysis: Population and Endpoints'.*

Applicant's Analysis Populations

The analysis populations defined by the Applicant and the number of subjects included in the analysis populations is shown below.

- **ITT:** All randomized subjects
- **MITT:** All randomized subjects who received any amount of study drug
- **Clinical MITT (cMITT):** All subjects in the MITT who met the study-specific minimal disease criteria for ABSSSI
- **Clinically Evaluable (CE):** All subjects in cMITT for whom sufficient information regarding the ABSSSI site was available to determine the subject's outcome
- **Microbiological MITT (mMITT):** All subjects in cMITT with at least one bacterial pathogen identified at baseline from culture
- **Microbiologically Evaluable (ME) :** Subjects from CE with at least one bacterial pathogen identified at baseline from culture

Table 4: Analysis Populations, Number of Subjects

	Study 06		Study 07	
Population # (% of ITT)	Ceftaroline	Vancomycin + Aztreonam	Ceftaroline	Vancomycin + Aztreonam
ITT	353 (100%)	349 (100%)	348 (100%)	346 (100%)
MITT	351 (99%)	347 (99%)	342 (98%)	338 (98%)
CE	316 (90%)	300 (86%)	294 (84%)	292 (84%)
mMITT	271 (77%)	263 (75%)	269 (77%)	259 (75%)
ME	244 (69%)	227 (65%)	224 (64%)	219 (63%)

Source: Adapted from Applicant Table

Applicant's Clinical Outcome Assessment

Clinical outcome assessments were made at the EOT and TOC Visits. Clinical outcome was classified by the Investigator as 'cure', 'failure', or 'indeterminate'. A favorable clinical response was the outcome of 'clinical cure'. An unfavorable clinical response was either 'clinical failure' or 'indeterminate' (MITT analysis only). Subjects who were considered clinically cured at the TOC assessment were reassessed at LFU for evidence of continuing favorable response (Success) of the original ABSSSI or relapse of symptoms (Failure). A 'clinical failure' occurring at an earlier time point was carried forward to the TOC Visit. Subjects for whom data were unavailable at LFU were assigned an 'indeterminate' outcome. Clinical outcome categories are defined in Table 5.

Table 5: Clinical Response Definition

Outcome	Definition
Clinical Cure	Total resolution of all signs and symptoms of the ABSSSI, or improvement to such an extent that further antimicrobial therapy was not necessary **Note**: for subjects with an underlying skin ulcer or wound, healing of the ulcer or wound was not required for an outcome of cure
Clinical Failure	Any of the following: 1. Persistence, incomplete resolution, or worsening in signs and symptoms of the ABSSSI that required alternative antimicrobial therapy 2. A surgical intervention that was performed as an adjunct or follow-up therapy due to failure of the study drug to adequately treat the infection. Minor surgical interventions conducted at the bedside and considered standard adjunctive therapy to appropriate antimicrobial treatment (eg, suture removal, needle aspiration, superficial debridement of devitalized tissue, limited incision and drainage, or routine wound care), surgical intervention on SSSI lesions other than the index lesion, surgeries not related to the SSSI, or execution of planned surgical interventions did not constitute evidence of study drug failure. 3. New signs and symptoms associated with the original ABSSSI or a new ABSSSI at the same anatomical site 4. Subject required alternative antimicrobial therapy to treat the ABSSSI, including oral step-down therapy. Extension of study drug therapy to 21 days was allowed with prior approval of the Medical Monitor and did not constitute evidence of study drug failure. 5. Treatment-limiting AE leading to study drug discontinuation, when subject required alternative antimicrobial therapy to treat the ABSSSI, including oral step-down therapy. 6. Diagnosis of osteomyelitis 8 or more days after randomization. 7. Death wherein ABSSSI was considered causative
Indeterminate	Study data were not available for evaluation of efficacy, for any reason including: treatment change prior to completing at least 48 hours of study drug therapy (except if the subject had a treatment limiting AE, in which case, regardless of the number of hours of therapy, the subject was a treatment failure), death wherein ABSSSI was clearly noncontributory, loss to follow-up, or extenuating circumstances that precluded classification as a cure or failure (e.g., diagnosis of osteomyelitis 7 or fewer days after randomization)

Source: Applicant Table

FDA Reviewer Sensitivity Analysis: Population and Endpoints

As stated earlier, non-inferiority comparisons for endpoints analyzed at later time points such as at TOC in the Applicant's primary analysis may not be meaningfully interpreted since there is no available historical literature to support the NI margin. In contrast, NI margins based on earlier time points such as at 48-72 hours (Day 3) after start of study therapy may be supported by historical studies, Snodgrass et. al, (1937). Due to these considerations, Reviewer sensitivity analyses were conducted at earlier time points, primarily Day 3, to assess treatment effects in the FDA-MITT population.

The key endpoint of FDA Reviewer analyses was based on responder rates at Day 3 in the FDA-MITT population. Responders had to satisfy the following two criteria at 48-72 hours (Day 3):

- Cessation of spread of lesion from baseline in both the length and width of lesion measurements AND
- Absence/resolution of fever

Additionally, patients who were assessed as 'clinical failures' on Day 3 or determined by the FDA clinical review team as 'clinical failures' (Study 06- Patient # 201206561 in comparator arm) were considered as 'nonresponders.' Patients with missing lesion measurements and/or temperature readings on Day 3 were also considered as 'nonresponders'.

The FDA-MITT population excluded MITT patients with the following lesion characteristics at baseline:

- Lesion size < 75 cm^2
- Major abscesses without at least 5 cm of surrounding erythema
- Infection types of 'ulcer' or 'other'

Additional secondary endpoints analyzed in the Reviewer sensitivity analyses included:

- Responder rates at Day 3 and EOT in which responders required % reductions in lesion size area ($\geq 10\%, \geq 20\%$ at Day 3; $\geq 75\%, \geq 90\%, \geq 95\%$ at EOT) Investigator assessment of clinical response at EOT
- Rates for cessation/percent reduction in lesion size from baseline (Day 3, EOT)
- Rates of absence in erythema, swelling, tenderness (EOT)
- Analyses by baseline pathogen in FDA-mMITT subjects
- Responder rates by subgroup (Day 3)

Other exploratory/sensitivity analyses of interest included:

- Responder rates and rates for cessation/percent reduction at additional time points such as Day 2, 4, 5
- Responder rates and rates for meeting % reductions in lesion area at Day 3 using additional cut-offs such as $\geq 30\%, \geq 50\%, \geq 75\%$
- Changes in the distributions of % reductions in lesion area from Days 2 to 5.
- Rates of missing data

- Responder rates using a carry forward approach for patients with missing data who were not clinical failures on or prior to Day 3
- Concordance/discordance of responder rates with EOT assessment

Additional details regarding Reviewer sensitivity analysis endpoints can be found in Section 3.1.3 'FDA Reviewer Analyses: Statistical Methodologies'.

3.1.2 Subject Disposition, Demographic and Baseline Characteristics

Subject disposition, demographic and baseline characteristics were assessed for only the FDA-MITT analysis population. Note that evaluation of evidence from studies 06 & 07 in this review relied primarily on responder rate analyses at Day 3 in the FDA-MITT.

Disease Severity at Baseline

Table 6 shows baseline characteristics of disease severity for ceftaroline and vancomycin + aztreonam patients in Study 06 & 07. Baseline characteristics identified by the FDA clinical reviewer included those relating to medical history: age (> 65, >75), diabetes, PVD, renal function and signs and symptoms fever, elevated WBC, bacteremia, infection area, degree of tenderness.

Table 6: Baseline Characteristics of Disease Severity in FDA-MITT Patients

Baseline Characteristics of Disease Severity	Study 06			Study 07		
	Ceftaroline (n=200) # (%)	Vancomycin + Aztreonam (n=209) # (%)	Total (N=409)	Ceftaroline (n=200) # (%)	Vancomycin + Aztreonam (n=188) # (%)	Total (N=388)
Medical history, n (%)						
> 65 years	32 (16.0)	36 (17.2)	68 (16.6)	30 (15.0)	22 (11.7)	52 (13.4)
> 75 years	13 (6.5)	14 (6.7)	27 (6.6)	13 (6.5)	10 (5.3)	23 (5.9)
Diabetes	29 (14.5)	47 (22.5)	76 (18.6)	33 (16.5)	29 (15.4)	62 (16.0)
PVD	19 (9.5)	25 (12.0)	44(10.8)	17 (8.5)	14 (7.4)	31 (8.0)
Renal function (CrCl in mL/min)						
> 80	163/199 (81.9)	162/208 (77.9)	325/407 (79.9)	163 (81.5)	139 (73.9)	302 (77.8)
> 50 to 80	28/199 (14.1)	38/208 (18.3)	66/407 (16.2)	28 (14.0)	43 (22.9)	71 (18.3)
> 30 to 50	8/199 (4.0)	8/208 (3.8)	16/407 (3.9)	9 (4.5)	6 (3.2)	15 (3.9)
≤ 30	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Signs and symptoms (s/s), n (%)						
Fever	88 (44.0)	91 (43.5)	179 (43.8)	82 (41.0)	88 (46.8)	170 (43.8)
Elevated WBC count (> 10^3/mm^3)	76/181 (42.0)	88/183 (46.6)	164/370 (44.3)	87/175 (49.7)	80/164 (48.8)	167/339 (49.3)
Bacteremia	14 (7.0)	5 (2.4)	19 (4.6)	7 (3.5)	11 (5.9)	18 (4.6)
Infection area(cm^2) median (range)	247 (75, 3150)	255 (75, 2451)	253 (75, 3150)	224 (76, 2860)	237 (80, 495)	225 (76, 4950)
Tenderness						
Absent	3 (1.5)	1 (0.5)	4 (1.0)	2 (1.0)	1 (0.5)	3 (0.7)
Mild	8 (4.0)	4 (1.9)	12 (2.9)	18 (9.0)	19 (10.1)	37 (9.5)
Moderate	70 (35.0)	80 (38.3)	150 (36.7)	68 (34.0)	57 (30.3)	125 (32.2)
Severe	119 (59.5)	124 (59.3)	243 (59.4)	112 (56.0)	111 (59.0)	223 (57.5)

Source: Reviewer Table

In Table 6, baseline characteristics were generally similar between the two studies. Fewer patients with mild/absent degree of tenderness at baseline were noted in Study 06. Baseline characteristics were also generally similar in treatment comparisons within each group. In Study 06, ceftaroline vs. comparator, fewer ceftaroline patients with diabetes (14.5% vs. 22.5%) but more with bacteremia (7.0% vs. 2.4%) at baseline were noted. In Study 07, fewer ceftaroline patients with moderate renal dysfunction (14.0% vs. 22.9%) and fever (41.0% vs. 46.8%) at baseline were noted.

Statistical Reviewer Comments: *In Study 07, lower rates for baseline fever of (41.0% vs. 46.8%) in ceftaroline vs. comparator may favor ceftaroline in responder rate comparisons. Responder rates were observed to be substantially higher in ceftaroline patients without baseline fever (Table 16).*

Types of Skin Infections at Baseline

Table 7 shows the distribution of infection types at baseline for FDA-MITT patients in Study 06 & 07. This distribution differed from that of the Applicant's MITT. In addition to requiring lesion sizes be ≥ 75 cm^2, FDA Reviewer criteria also excluded patients with infection types of 'ulcer' and 'other' as well as major abscesses with less than 5 cm of surrounding erythema. This led to a greater proportion of patients with cellulitis who were included in the FDA-MITT, 54% in Study 06 and 49% in Study 07.

Table 7: Types of Skin Infections at Baseline

	Study 06			**Study 07**		
Type of infection:	**Ceftaroline (n=200)** # (%)	**Vancomycin +Aztreonam (n=209)** # (%)	**Total (N=409)**	**Ceftaroline (n=200)** # (%)	**Vancomycin + Aztreonam (n=188)** # (%)	**Total (N=388)**
Deep/extensive cellulitis	111(55.5)	111 (53.1)	222 (54.3)	88 (44.0)	103 (54.8)	191 (49.2)
Major abscess (with ≥ 5cm of surrounding erythema)	43 (21.5)	46 (22.0)	89 (21.8)	69 (34.5)	50 (26.6)	119 (30.7)
Infected wound	30 (15.0)	27 (12.9)	57 (13.9)	29 (14.5)	24 (12.8)	53 (13.7)
Lower extremity ABSSSI, subject with diabetes or PVD	13 (6.5)	18 (8.6)	31 (7.6)	8 (4.0)	8 (4.3)	16 (4.1)
Infected bite	3 (1.5)	7 (3.3)	10 (2.4)	6 (3.0)	3 (1.6)	9 (2.3)

Source: Reviewer Table

In Table 7, distributions of infection types (irrespective of treatment) in Study 06 vs. Study 07 differed substantially in the number of patients with major abscesses (21.8% vs. 30.7%) but were generally similar otherwise. Distributions of infection types between treatments (i.e. ceftaroline vs. vancomycin + aztreonam) were similar in Study 06 but differed in Study 07 with more ceftaroline patients having a major abscess (34.5% vs. 26.6%) but fewer having deep/extensive cellulitis (44.0% vs. 54.8%).

Infection Size at Baseline

Table 8 shows a comparison of length, width and area measurements of primary lesions for patients in Study 06 and Study 07. These distributions differed from those of the Applicant since FDA Reviewer criteria required patients with lesion sizes of ≥ 75 cm^2 to be included in the FDA-MITT.

Table 8: Infection Size at Baseline

Measure	Study 06			Study 07		
	Ceftaroline (n=200) # (%)	**Vancomycin +Aztreonam (n=209)** # (%)	**Total (N=409)**	**Ceftaroline (n=200)** # (%)	**Vancomycin +Aztreonam (n=188)** # (%)	**Total (N=388)**
Infection length (cm)						
Mean ± SD	20.5 ± 10.2	22.6 ± 12.0	21.6 ± 11.2	22.2 ± 10.2	22 ± 13.0	22.1 ± 11.6
Median (range)	18 (5, 65)	19 (7.5, 68.6)	18 (5, 68.6)	20 (6, 65)	18 (7, 99)	20 (6, 99)
Infection width (cm)						
Mean ± SD	17.1 ± 9.8	17.6 ± 10.5	17.4 ± 10.1	15.4 ± (9.6)	16.2 ± (10.1)	15.8 ± (9.9)
Median (range)	14.5 (5, 55)	15 (5, 61.3)	15 (5, 61.3)	12 (4, 54)	12 (5, 54)	12 (4, 54)
Infection area (cm^2)						
Mean ± SD	412.1 ± 464.3	458.6 ± 459.5	435.9 ± 461.9	393.1 ± 450.9	426.5 ± 593.9	409.3 ± 524.7
Median (range)	246.9 (75, 3150)	255 (75, 2451)	253 (75, 3150)	224 (75.6, 2860)	237 (80, 4950)	225 (75.6, 4950)

Source: Reviewer Table

In Table 8, lesion sizes at baseline tended to be larger in Study 06 than in Study 07 based on the mean and median of lesion areas. Within each study, lesions tended to be slightly smaller for ceftaroline vs. vancomycin + aztreonam. This trend of smaller lesion sizes at baseline for ceftaroline patients was not considered to meaningfully influence sensitivity analyses comparisons based on % changes in lesion size from baseline.

3.1.3 Statistical Methodologies

As mentioned previously, non-inferiority comparisons for endpoints analyzed at later time points such as at TOC in the Applicant's primary analyses may not be meaningfully interpreted since there is no available historical literature to support the NI margin. In contrast, NI margins based on earlier time points such as at 48-72 hours (Day 3) after start of study therapy may be supported by historical studies (Snodgrass et. al, 1937). Due to these considerations, Reviewer sensitivity analyses were conducted at earlier time points, primarily Day 3, to assess treatment effects in the FDA-MITT population. Statistical methodologies as originally presented by the Applicant and statistical methodologies based on FDA Reviewer sensitivity analyses are both described below.

Applicant's Statistical Methodologies

The Applicant's primary hypothesis tested H_0: $r_1 - r_2 \leq -10\%$ vs. H_1: $r_1 - r_2 > -10\%$ where r_1 is the clinical cure rate in the ceftaroline treatment group, r_2 is the clinical cure rate in the vancomycin plus aztreonam treatment group, and the NI margin is 10%.

To test H_0, a two-sided 95% CI for the observed difference in clinical cure rates (ceftaroline treatment group minus vancomycin plus aztreonam treatment group) was calculated for each population. If the lower limit of the 95% CI for the difference for each of the two populations exceeded –10%, then H_0 was rejected and the non-inferiority of ceftaroline to vancomycin plus aztreonam will be declared.

Computation of confidence intervals: The two-sided 95% CI for NI testing was based on the difference of clinical cure rates (ceftaroline minus vancomycin plus aztreonam) and was computed using the method proposed by Miettinen and Nurminen (1985) [3]. For notation purposes, assume the comparison is between 2 groups denoted by 1 and 2, in which 1 represents the active group and 2 represents the control group. Based on Miettinen and Nurminen (1985), the two-sided 95% CI is given by the roots for $RD = r_1 - r_2$ of the equation:

$$c_a^2 = \frac{(\hat{r}_1 - \hat{r}_2 - RD)^2}{\tilde{V}_{\hat{r}_1 - \hat{r}_2}}$$

where c_a^2 is the cut point of size a from the chi-square distribution, RD is the difference between the two true rates ($RD = r_1 - r_2$); $\hat{r}_1$ = the observed rate in Group 1, $\hat{r}_2$ = the observed rate in Group 2; and

$$\tilde{V}_{r_1 - r_2} = \left[\frac{\tilde{r}_1(1-\tilde{r}_1)}{n_1} + \frac{\tilde{r}_2(1-\tilde{r}_2)}{n_2} \right] \frac{n_1 + n_2}{n_1 + n_2 + 1}$$

where n_1 = # of subjects in Group 1, n_2 = # of subjects in Group 2; $\tilde{r}_1 = \tilde{r}_2 + RD$; and $\tilde{r}_2$ is the maximum likelihood estimate for r_2 as a function of RD and under the constraint $r_1 = r_2 + RD$. This statistical method is based on the CI approach and corresponds to the non-inferiority test (a p-value approach) proposed by Farrington and Manning (1990) [4].

If it is concluded that the clinical cure rate of ceftaroline treatment group is non-inferior to that of the vancomycin plus aztreonam treatment group, then a test of superiority will be performed. The p-value of the Fisher's Exact test will be used to test the null hypothesis that there is no difference between the treatment groups in clinical cure rate versus the alternative hypothesis that there is a difference between the treatment groups. Superiority of ceftaroline will be concluded if the Fisher's Exact two-sided p-value is less than or equal to 0.05.

Reviewer comments: *Reviewer analyses computed conservative 95% confidence intervals based on normal approximation to the binomial distribution using a continuity correction = $(1/n_1 + 1/n_2)^{-1}$. Since normal approximation methods may not be valid in*

estimating 95% confidence limits in samples with high cure rates (p) or limited sample size (n), exact binomial 95% confidence intervals were computed in cases with np(1-p) < 5 in one or more comparison groups.

NI margin (delta) selection: The Applicant used a 10% non-inferiority margin to determine treatment efficacy in the primary analysis of Study 06 & 07.

Interim analyses: No interim data analysis was performed.

Missing data: The Applicant analyses compared subjects according to the group to which they were randomized. By definition, subjects who receive the wrong study drug were not included in the CE and ME populations. Primary efficacy analyses were based on the MITT and CE populations (co-primary populations). A missing clinical response at the TOC visit in the MITT Population will be counted as indeterminate in the analyses.

For the MITT Population, the proportion of MITT subjects with a clinical cure is defined by: # of clinical cures / (# of clinical cures + # of clinical failures + # of indeterminates). Since subjects in the CE Population must have sufficient information for determination of clinical outcome, the proportion of CE subjects with a clinical cure is defined as: (# of clinical cures) / (# of clinical cures + # of clinical failures).

Multiple comparisons adjustment: In the Applicant's primary hypotheses, both comparisons (CE and MITT) were required to be significant in the primary efficacy analysis so that no adjustments for multiple comparisons were necessary.

Covariates: No adjustments for covariates were made to the primary analyses in the main analyses.

FDA Reviewer Analyses: Statistical Methodologies

In Reviewer sensitivity analyses, responder rates, as described in Section 3.1.1, were evaluated using the lower 95% confidence limit of the treatment difference ('ceftaroline' minus 'vancomycin + aztreonam'). Estimation of 95% confidence limits for the treatment difference in clinical cure rates at Day 3 was performed using normal approximation to the binomial distribution with a continuity correction of $(1/n_1 + 1/n_2)^{-1}$. Since normal approximation methods may not be valid in estimating 95% confidence limits in samples with high cure rates (p) or limited sample size (n), exact binomial 95% confidence intervals were computed in cases with $np(1-p) < 5$ in one or more comparison groups. The 95% confidence intervals computed in secondary and other FDA Reviewer sensitivity analyses followed the same approach as described for the primary analysis, however confidence intervals were not computed in cases with $n < 10$ in either sample.

Additional secondary endpoints analyzed in the Reviewer sensitivity analyses included:

- Responder rates at Day 3 and EOT in which responders required % reductions in lesion size area ($\geq 10\%$, $\geq 20\%$ at Day 3; $\geq 75\%$, $\geq 90\%$, $\geq 95\%$ at EOT)
  Investigator assessment of clinical response at EOT

- Rates for cessation/percent reduction in lesion size from baseline (Day 3, EOT)
- Rates of absence in erythema, swelling, tenderness (EOT)
- Analyses by baseline pathogen in FDA-mMITT subjects
- Responder rates by subgroup (Day 3)

Other exploratory/sensitivity analyses of interest included:

- Responder rates and rates for cessation/percent reduction at additional time points such as Day 2, 4, 5
- Responder rates and rates for meeting % reductions in lesion area at Day 3 using additional cut-offs such as ≥ 30%, ≥ 50%, ≥ 75%
- Changes in the distributions of % reductions in lesion area from Days 2 to 5.
- Rates of missing data
- Responder rates using a carry forward approach
- Concordance/discordance of responder rates with EOT assessment

The following points apply to the FDA Reviewer sensitivity analyses described above (unless otherwise stated):

- The outcome of 'responder' was determined based on a change in lesion size component (i.e. cessation/percent reduction) and an absence of fever component. 'Responders' could be overridden by a clinical assessment of 'failure' at EOT on the Study Day analyzed (e.g. Day 3).
- Responder rates required only cessation of spread for the change in lesion size component, unless otherwise stated.
- Responder rates were assessed at Day 3, unless otherwise stated.
- Patients with missing responder rate (or rate for cessation/ percent reduction) data for at the specified visit were considered as non-responders (or failures).
- Cessation of spread of lesion was determined based on no increase from baseline in both the lesion length and width dimensions.
- Percent reduction of lesion spread was computed using % reduction in lesion area
- The outcome of 'cessation/percent reduction of lesion size' could not be overridden by additional criteria (e.g. clinical assessment).
- Reviewer sensitivity analyses of investigator assessment of clinical response at EOT use clinical response criteria as defined by the Applicant. However, patients with missing/indeterminate clinical responses were considered as failures.
- In other Reviewer sensitivity analyses, patients with missing data for an outcome on the Day analyzed (e.g. Day 3, EOT) were evaluated as failures or non-responders, unless otherwise stated.

3.1.4 Results of Analyses

In the Applicant's primary analysis, clinical cure rates were compared between ceftaroline and the comparator (vancomycin + aztreonam) at the TOC visit using a 10% NI margin for both the MITT and CE populations.

Table 9: Applicant's Analyses of Clinical Cure Rates at TOC

	Study 06			Study 07		
Analysis Population	**Ceftaroline** n/N (%)	**Comparator** n/N (%)	**Ceftaroline - Comparator (95% CI)**	**Ceftaroline** n/N (%)	**Comparator** n/N (%)	**Ceftaroline - Comparator (95% CI)**
MITT	304/351 (86.6)	297/347 (85.6)	1.0 (-4.2, 6.2)	291/342 (85.1)	289/338 (85.5)	-0.4 (-5.8, 5.0)
CE	288/316 (91.1)	280/300 (93.3)	-2.2 (-6.6, 2.1)	271/294 (92.2)	269/292 (92.1)	0.1 (-4.4, 4.5)

Source: Applicant Table

Statistical Reviewer Comments: *Due to the lack of historical data in the literature supporting a NI margin of 10% for a clinical response endpoint at the TOC visit, results from the Applicant's primary analyses may not be meaningfully interpreted and may lack sufficient evidence in demonstrating non-inferiority. Consequently, additional FDA sensitivity analyses were conducted to assess non-inferiority. Based on the available literature, a NI margin was considered to be better supported in the FDA Reviewer analysis of the key endpoint (i.e. cessation of spread of lesion and absence of fever) at Day 3 than in the Applicant's analyses of clinical cure rates at TOC.*

FDA Reviewer Sensitivity Analysis Results

The FDA Reviewer sensitivity analysis compared treatments based on responder rates and examined robustness to differences in the degree of change in lesion size required for a responder (e.g. cessation vs. % reduction), timing of responder rates (e.g. Day 3 vs. EOT) and the definition of a responder (e.g. cessation/percent reduction of lesion size with no fever component). A key secondary endpoint in the Reviewer sensitivity analyses was the investigator assessment of clinical cure rates at EOT. Consistency of findings in responder rates at Day 3 (with or without the fever component) and clinical cure rates at EOT was considered to be especially meaningful. Additional secondary endpoints included analyses by pathogen, rates of absence in erythema, swelling, tenderness at EOT and subgroup analyses.

Responder Rates

The FDA Reviewer analyses defined a key endpoint of responder rate differences (ceftaroline – vancomycin plus aztreonam) based on the cessation of spread of lesion plus absence of fever at Day 3. However, due to concerns with the sensitivity of the cessation component of this endpoint as well as with potential misclassification errors and biases associated with investigator measurements of lesion length and/or width, further sensitivity analyses of responder rates were conducted for various levels of % reduction. These sensitivity analyses required responders to have at least a 10% or 20% reduction in lesion area along with absence of fever at Day 3. This placed a stricter requirement on the change in lesion size component used in the responder rate endpoint.

Additional sensitivity analyses were also examined to confirm that treatment comparisons in responder rates would remain consistent across later time points such as at the end-of-

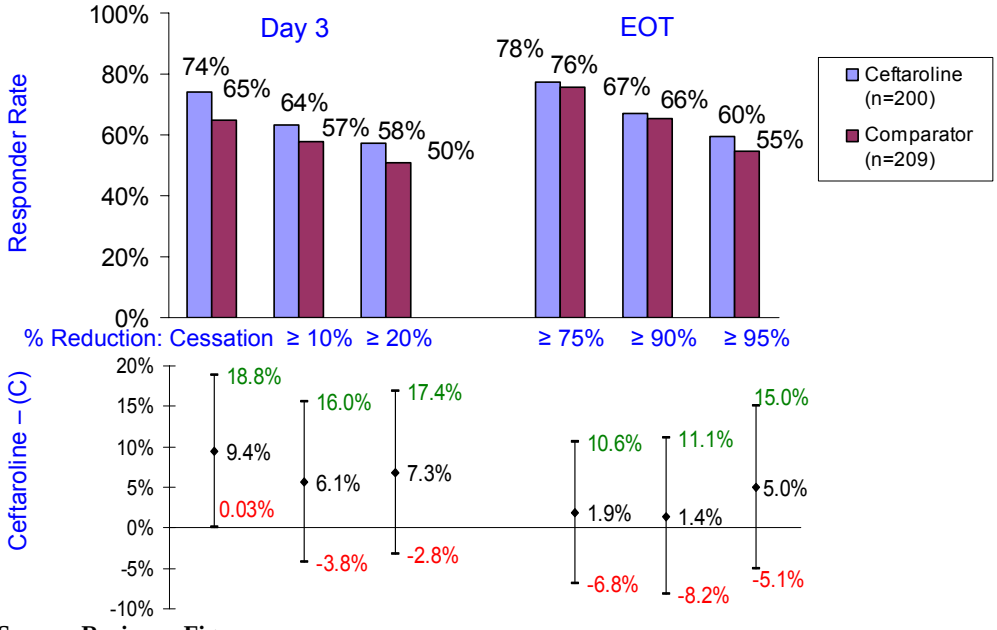
therapy when requiring at least a 75%, 90% or 95% reduction in lesion area for a responder. Results of these analyses are shown in Table 10 and in Figures 1 & 2 below.

Table 10: Responder Rates

Cessation / % Reduction for Responder	Study 06 (N=409)			Study 07 (N=388)		
	Ceftaroline N=200 # (%)	Vancomycin + Aztreonam N=209 # (%)	Difference (95% CI)	Ceftaroline N=200 # (%)	Vancomycin + Aztreonam N=188 # (%)	Difference (95% CI)
Day 3						
Cessation	**148 (74.0)**	**135 (64.6)**	**9.4 (0.03, 18.8)**	**148 (74.0)**	**128 (68.1)**	**5.9 (-3.6, 15.5)**
≥ 10%	127 (63.5)	120 (57.4)	6.1 (-3.8, 16.0)	133 (66.5)	115 (61.2)	5.3 (-4.7, 15.4)
≥ 20%	115 (57.5)	105 (50.2)	7.3 (-2.8, 17.4)	120 (60.0)	105 (55.9)	4.1 (-6.2, 14.5)
EOT						
≥ 75%	155 (77.5)	158 (75.6)	1.9 (-6.8, 10.6)	144 (72.0)	137 (72.9)	-0.9 (-10.3, 8.5)
≥ 90%	134 (67.0)	137 (65.6)	1.4 (-8.2, 11.1)	122 (61.0)	111 (59.0)	2.0 (-8.3, 12.2)
≥ 95%	119 (59.5)	114 (54.5)	5.0 (-5.1, 15.0)	108 (54.0)	98 (52.1)	1.9 (-8.6, 12.3)

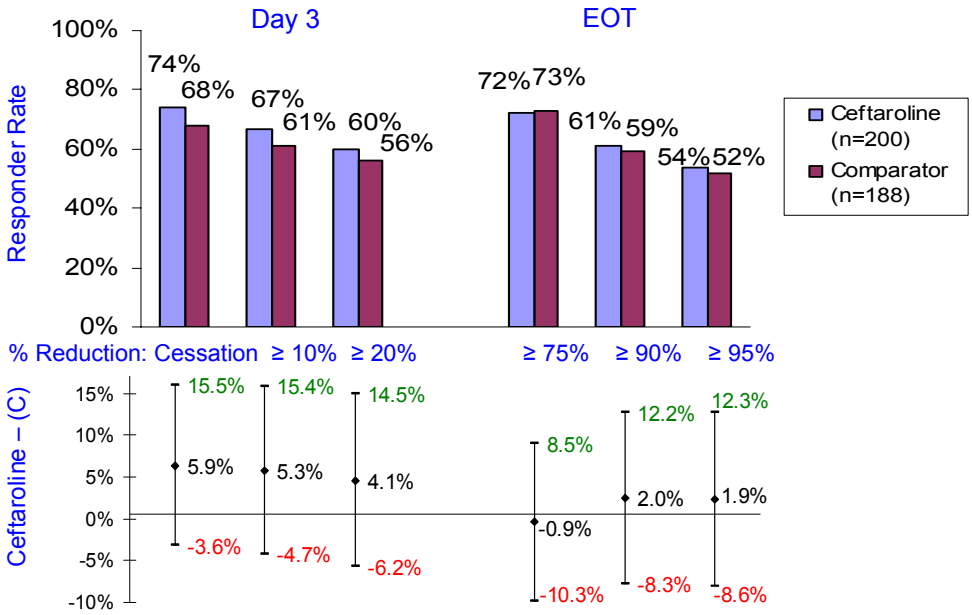
Source: Reviewer Table

Figure 1: Responder Rates- Study 06



Source: Reviewer Figure

Figure 2: Responder Rates - Study 07



Source: Reviewer Figure

As shown in Table 10 and Figures 1 & 2, the Reviewer key sensitivity endpoint of responder rates at Day 3 (i.e. cessation of lesion size from baseline and absence of fever at Day 3) favored ceftaroline by 9.4% (95% CI: 0.03%, 18.8%) in Study 06 and by 5.9% (95% CI: -3.6%, 15.5%) in Study 07. In analyses requiring a 10% or 20% reduction in lesion size from baseline in defining a responder, treatment differences favored ceftaroline with lower limits for treatment differences (ceftaroline – comparator) at Day 3 at or above -6.2% in both studies.

For responder rate analyses conducted at EOT requiring larger reductions in lesion size from baseline (i.e. ≥ 75%, ≥ 90% and ≥ 95% reductions) for responders, treatment differences in Study 06 also favored ceftaroline over the comparator, however these differences were not as large as the differences observed at Day 3. In Study 07, treatment differences at EOT were not considered to be substantial, slightly favoring the comparator for ≥ 75% reductions and ceftaroline for ≥ 90% and ≥ 95% reductions.

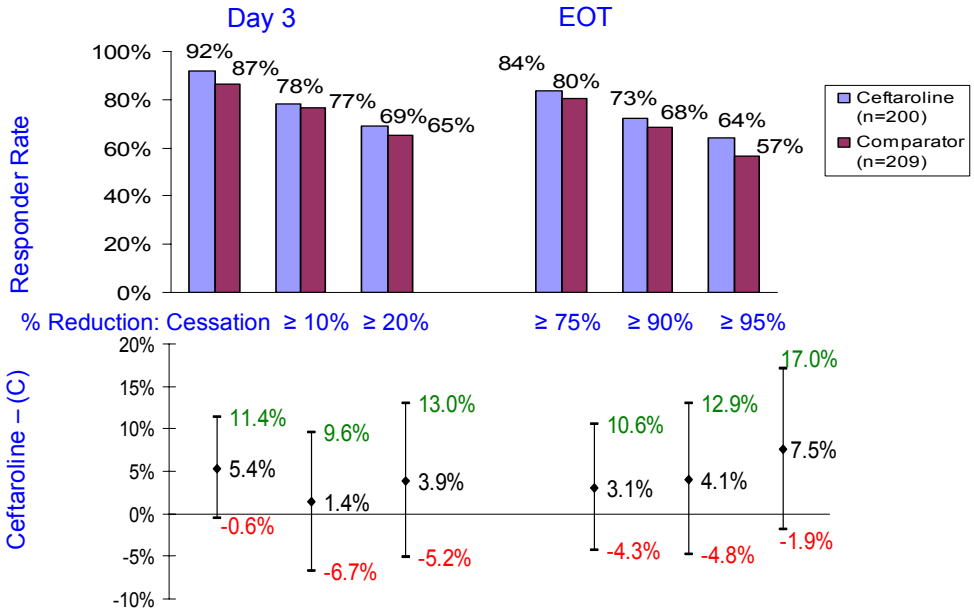
Rates for Cessation/Percent Reduction of Lesion Spread

Table 11: Rates for Cessation/Percent Reduction of Lesion Spread

Cessation / % Reduction in Lesion Area	Study 06 (N=409)			Study 07 (N=388)		
	Ceftaroline N=200 # (%)	Vancomycin + Aztreonam N=209 # (%)	Difference (95% CI)	Ceftaroline N=200 # (%)	Vancomycin + Aztreonam N=188 # (%)	Difference (95% CI)
Day 3						
Cessation	**184 (92.0)**	**181 (86.6)**	**5.4 (-0.6, 11.4)**	**179 (89.5)**	**167 (88.8)**	**0.7 (-5.5, 6.9)**
≥ 10%	156 (78.0)	160 (76.6)	1.4 (-6.7, 9.6)	159 (79.5)	147 (78.2)	1.3 (-6.8, 9.4)
≥ 20%	138 (69.0)	136 (65.1)	3.9 (-5.2, 13.0)	143 (71.5)	130 (69.1)	2.4 (-6.7, 11.5)
EOT						
≥ 75%	167 (83.5)	168 (80.4)	3.1 (-4.3, 10.6)	159 (79.5)	157 (83.5)	-4.0 (-11.7, 3.7)
≥ 90%	145 (72.5)	143 (68.4)	4.1 (-4.8, 12.9)	130 (65.0)	124 (66.0)	-1.0 (-10.4, 8.5)
≥ 95%	128 (64.0)	118 (56.5)	7.5 (-1.9, 17.0)	114 (57.0)	105 (55.9)	1.2 (-8.7, 11.0)

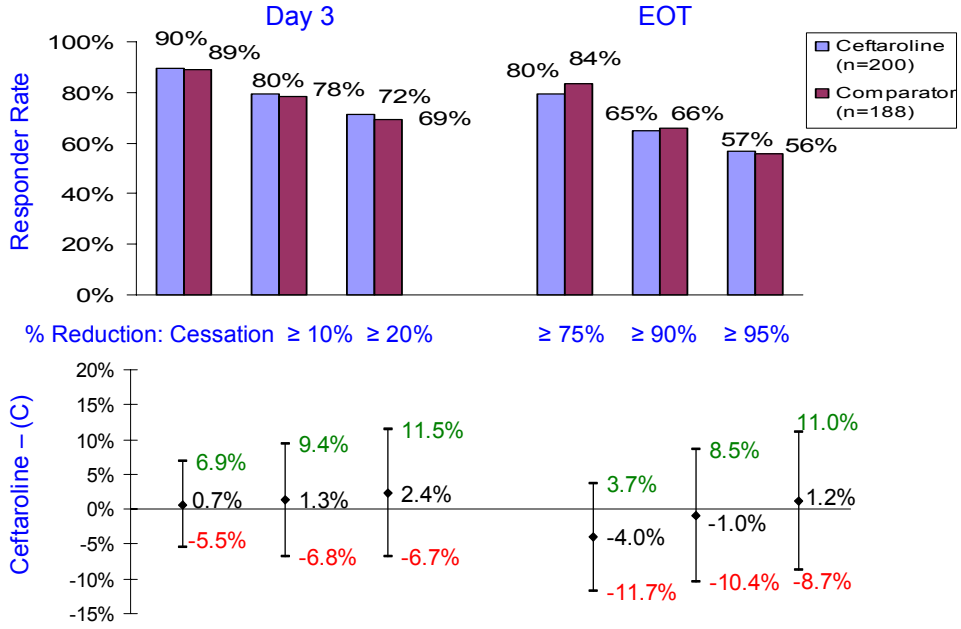
Source: Reviewer Table

Figure 3: Rates for Cessation/Percent Reduction of Lesion Spread – Study 06



Source: Reviewer Figure

Figure 4: Rates for Cessation/Percent Reduction of Lesion Spread – Study 07



Source: Reviewer Figure

In Table 11 & Figures 3-4, treatment differences at Day 3 for cessation of spread favored ceftaroline by 5.4% (95% CI: -0.6%, 11.4%) in Study 06 and by 0.7% (95% CI: -5.5%, 6.9%) in Study 07. Differences for meeting ≥ 10% and ≥ 20% reductions in lesion area at Day 3 also favored ceftaroline with lower limits at or above -6.8% across both studies.

Treatment differences at EOT for meeting ≥ 75%, ≥ 90% and ≥ 95% reductions in lesion area from baseline favored ceftaroline in Study 06 with lower limits at or above -4.8%. In contrast, differences in Study 07 (ceftaroline – comparator) were less favorable to ceftaroline in meeting a ≥ 75% reduction at -4.0% (95% CI: -11.7%, 3.7%) and did not favor either treatment substantially in meeting ≥ 90% and ≥ 95% reductions (i.e. -1.0% & 1.2%).

Clinical Cure Rates at EOT

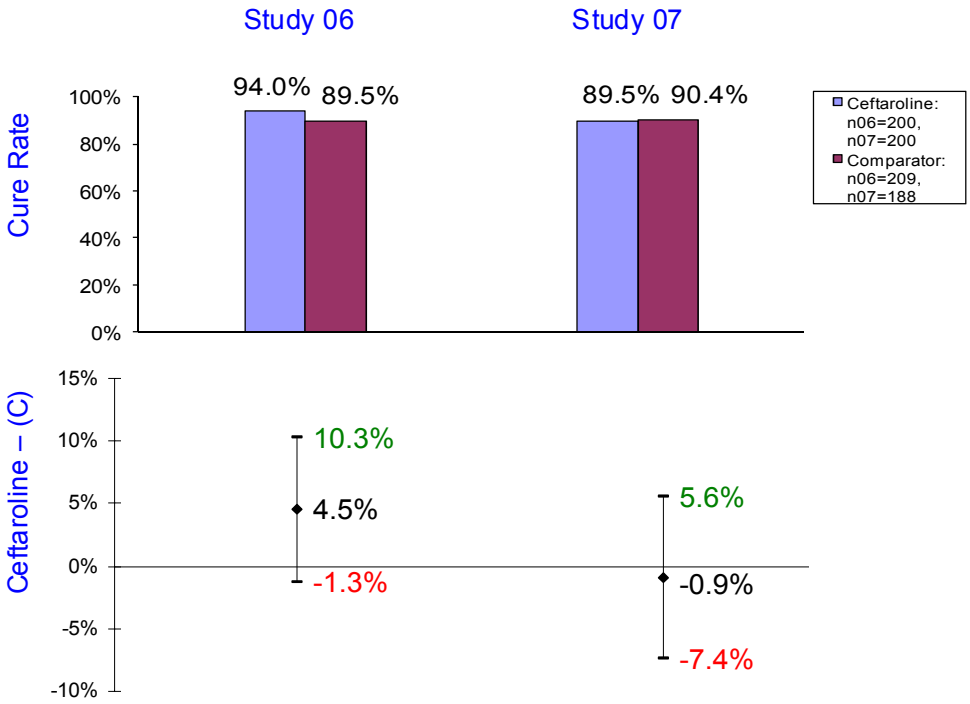
Investigator assessment of clinical cure rates at EOT was a key secondary endpoint in Reviewer sensitivity analyses. Since this endpoint is more established than the responder rate endpoint and addresses a broader range of patient signs and symptoms over a longer period of time (EOT vs. Day 3), consistency of responder rate differences at Day 3 (with and without the fever component) and clinical cure rates at EOT was viewed as especially meaningful. Comparisons of clinical cure rates at EOT for Studies 06 & 07 are shown in Table 12 & Figure 5.

Table 12: Clinical Cure Rates at EOT

Study 06 (N=409)			Study 07 (N=388)		
Ceftaroline (N=200) n/N (%)	**Comparator (N=209)** n/N (%)	**Difference (95% CI)**	**Ceftaroline (N=200)** n/N (%)	**Compator (N=188)** n/N (%)	**Difference (95% CI)**
188/200 (94.0)	187/209 (89.5)	4.5 (-1.3, 10.3)	179/200 (89.5)	170/188 (90.4)	-0.9 (-7.4, 5.6)

Source: Reviewer Table

Figure 5: Clinical Cure Rates at EOT



Source: Reviewer Figure

In Study 06, clinical cure rates at EOT based on investigator assessment in the FDA-MITT were higher for ceftaroline vs. vancomycin + aztreonam at 94.0% vs. 89.5%, a difference of 4.5% (95% CI: -1.3, 10.3). The lower limit for this difference was at -1.3% which was consistent with the lower limit of 0.03% observed for Study 06 key responder rate analyses based on cessation with absence of fever at Day 3. This finding was also consistent with Study 06 comparisons for rates of cessation (without the fever component) at Day 3 in which a lower limit of -0.6% was observed for the treatment difference. Consistency in responder rates (with or without the fever component) at Day 3 and clinical cure rates at EOT was shown in Study 06 and this provided meaningful evidence supporting the efficacy of ceftaroline.

In Study 07, comparisons did not show the same degree of consistency with responder rate comparisons that was observed in Study 06. Clinical cure rates at EOT were slightly lower for ceftaroline vs. vancomycin + aztreonam at 89.5% vs. 90.4%, a difference of -0.9% (95% CI: -7.4%, 5.6%). The lower limit for this difference of -7.4% was less favorable than both the lower limit of -3.6% observed for the key responder rate differences at Day 3 and the lower limit of -5.5% observed for differences in rates of cessation of spread at Day 3. While evidence based on these comparisons was not as robust as in Study 06, it was still viewed as being generally consistent with assumptions of non-inferiority.

Analyses by Baseline Pathogen

In Table 13, secondary analyses of responder rates, rates for cessation of spread and clinical cure rates at EOT considered the *S. aureus* (MRSA, MSSA) and *S.pyogenes* pathogens in FDA-mMITT subjects (i.e. subjects included in both the FDA-MITT and Sponsor mMITT populations). There were some imbalances in the numbers of patients included for some of the treatment comparisons (ceftaroline vs. comparator). In Study 06, there 18 vs. 26 patients with *S.pyogenes* and in Study 07 there were 57 vs. 43 patients with MRSA.

Table 13: Analyses by Baseline Pathogen in FDA-mMITT

	Study 06 (N=295)		**Study 07 (N=312)**	
Endpoint *Pathogen*	**Ceftaroline (N=143)** n/N (%)	**Vancomycin + Aztreonam (N=152)** n/N (%)	**Ceftaroline (N=164)** n/N (%)	**Vancomycin + Aztreonam (N=148)** n/N (%)
Responder Rate (Day 3)				
S.aureus	77/104 (74%)	72/114 (63)	110/140 (79)	84/121 (69)
MRSA	34/45 (76)	30/41 (73)	50/57 (88)	35/43 (81)
MSSA	44/61 (72)	42/73 (58)	58/81 (72)	50/79 (63)
S.pyogenes	9/18 (50)	13/26 (50)	16/28 (57)	15/23 (65)
Rate for Cessation of Spread of Lesion (Day 3)				
S.aureus	99/104 (95%)	100/114 (88)	133/140 (95)	107/121 (88)
MRSA	42/45 (93)	34/41 (83)	52/57 (91)	38/43 (88)
MSSA	59/61 (97)	66/73 (90)	79/81 (98)	70/79 (89)
S.pyogenes	17/18 (94)	24/26 (92)	26/28 (93)	22/23 (96)
Clinical Cure Rate (EOT)				
S.aureus	98/104 (94)	104/114 (91)	131/140 (93)	112/121(93)
MRSA	43/45 (96)	35/41 (85)	49/57 (86)	40/43 (93)
MSSA	57/61(93)	69/73(95)	80/81 (99)	73/79 (92)
S.pyogenes	18/18 (100)	24/26 (92)	25/28 (89)	21/23 (91)

Source: Reviewer Table

Treatment differences in responder rates favored ceftaroline by 10 to 11% in patients with *S.aureus* for both studies. However, for MRSA, differences in Study 06 favored

ceftaroline by only 3% (76% vs. 73%). For *S.pyogenes*, differences in Study 07 favored the comparator by 8%, 65% vs. 57%. However, inferences regarding treatment differences for *S.pyogenes* are limited due to the small patient numbers.

Treatment differences in rates of cessation of spread favored ceftaroline over the comparator in patients with a *S.aureus* pathogen at baseline in both studies. However, for MRSA, differences in Study 07 favored ceftaroline by only 3% (91% vs. 88%). In patients with *S.pyogenes,* there were no notable treatment differences in rates of cessation.

Treatment differences in clinical cure rates at EOT showed ceftaroline patients with MRSA to fare better vs. the comparator in Study 06 at 96% vs. 85%. However, a reversal of this trend was observed in Study 07 for MRSA at 86% vs. 93%. For MSSA, treatment differences were primarily observed in Study 07 at 99% vs. 92%. For *S.pyogenes,* there were no notable differences given the high degree of variability from small patient numbers.

Overall findings from Table 13 show ceftaroline as being generally similar or slightly favorable to the comparator for the *S.aureus* pathogen. However, inferences for MRSA and MSSA may be unclear especially based on comparisons of clinical cure rates at EOT which were inconsistent across studies. Comparisons for *S.pyogenes* were limited by small numbers and failed to show a meaningful treatment difference based on comparisons of responder rates, rates for cessation of spread and clinical cure rates.

Rates of Absence in Erythema, Swelling and Tenderness

Another secondary endpoint was the rate of absence in erythema, swelling and tenderness at EOT (Table 14). These signs and symptoms were identified by the clinical review team as being the most informative in assessing improvements in patients with ABSSSI. Improvements based on absence vs. presence would also allow for a more meaningful interpretation compared to improvements on an ordinal scale (e.g. severe to moderate, moderate to mild) which are considered to be more subjective. Due to the small numbers of patients with absence in these signs and symptoms at Day 3, only the EOT time point was considered.

Table 14: Rates of Absence in Erythema, Swelling and Tenderness

	Study 06 (N=409)			**Study 07 (N=388)**		
Sign or Symptom	**Ceftaroline (N=200)** # (%)	**Vancomycin + Aztreonam (N=209)** # (%)	**Ceftaroline - Vancomycin + Aztreonam (95% CI)**	**Ceftaroline (N=200)** # (%)	**Vancomycin + Aztreonam (N=188)** # (%)	**Ceftaroline - Vancomycin + Aztreonam (95% CI)**
Erythema	127 (63.5)	134 (64.1)	-0.6 (-10.4, 9.2)	131 (65.5)	123 (65.4)	0.1 (-9.9, 10.1)
Swelling	138 (69.0)	127 (60.8)	8.2 (-1.5, 17.9)	113 (56.5)	99 (52.7)	3.8 (-6.6, 14.3)
Tenderness	146 (73.0)	146 (69.9)	3.1 (-6.1, 12.4)	120 (60.0)	106 (56.4)	3.6 (-6.7, 14.0)

Source: Reviewer Table

In Studies 06 & 07, rates of absence in erythema were similar between ceftaroline vs. the comparator. However, rates of absence in swelling favored ceftaroline over the comparator by 69.0% vs. 60.8%, a difference of 8.2% (95% CI: -1.5, 17.9) in Study 06 and by 56.5% vs. 52.7%, a difference of 3.8% (95% CI: -6.6, 14.3) in Study 07. Differences in tenderness also favored ceftaroline in Study 06 & 07 by 3.1% and 3.6%. Note that rates of absence for swelling and tenderness were substantially higher in Study 06 vs. 07 across both treatment arms.

3.1.5 Efficacy Conclusions

Sensitivity analyses provided evidence supporting the non-inferiority (NI) of ceftaroline to vancomycin/aztreonam within a 3.6% NI margin for both studies. In additional sensitivity analyses to evaluate the robustness of findings, ceftaroline was observed to be similar (or favorable) to the comparator regardless of the degree of change in lesion size required for a responder (e.g. cessation vs. % reduction), timing of responder rates (e.g. Day 3 vs. EOT), definition of a responder (cessation/percent reduction without the fever component) and choice of endpoint (e.g. investigator assessment of clinical cure rate at EOT, rates of absence of erythema, swelling and tenderness. In these analyses, treatment comparisons on Day 3 favored ceftaroline in both studies while comparisons at EOT tended favored ceftaroline in Study 06 but did not favor either treatment in Study 07. There were several limitations with Reviewer sensitivity analyses as noted in Section 5. However, despite these limitations, results were considered to support the efficacy of ceftaroline.

3.2 Evaluation of Safety

Details on drug safety are available in the review of Dr. Porcalla.

4. SPECIAL/SUBGROUP POPULATIONS

4.1 Subgroup Analyses

Reviewer subgroup analyses assessed several variables which could potentially confound responder rates including the infection type, geographical regions, baseline fever status, prior antibiotics use, concomitant use of antipyretics and anti-inflammatory drugs. Similar analyses were also conducted for rates of cessation of spread of lesion with results shown in the Appendix. It should be noted that subgroup analyses were limited by a high degree of variability resulting from the small number of subjects included in each subgroup. For these reasons, confidence intervals for treatment differences in subgroups were not considered to be informative and are not included in the tables.

4.1.1 Analyses by Infection Types

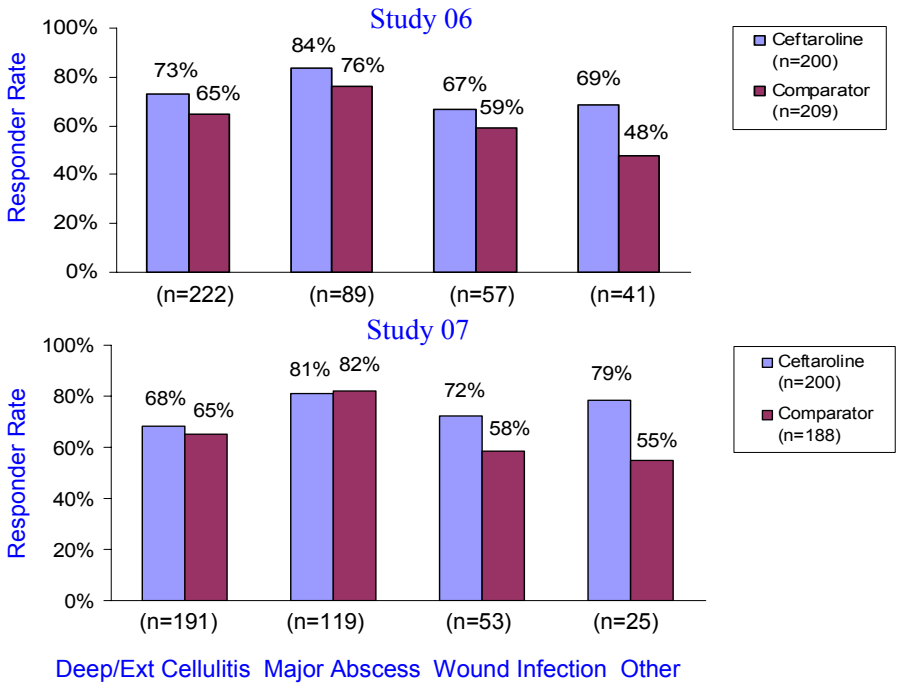
Responder rates (Table 15 & Figure 6) and rates for cessation (Appendix Table 24) were evaluated in FDA-MITT subjects for infection types of 'deep/extensive cellulitis', 'major abscess', 'wound infection' and 'other'). The 'other' category included lower extremity infections in patients with diabetes or PVD and bite infections. Compared to Study 06, Study 07 included more patients with major abscesses, especially in the ceftaroline arm at 69/200 (34.5%) vs. 43/200 (21.5%).

Table 15: Responder Rates by Infection Type

	Study 06 (N=409)		**Study 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 (%)
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)
Other	11/16 (68.8)	12/25 (48.0)	11/14 (78.6)	6/11 (54.5)

Source: Reviewer Table

Figure 6: Responder Rates by Infection Type



Source: Reviewer Figure

In Table 15 & Figure 6, responder rates in Study 06 favored ceftaroline over the comparator for all infection types. In Study 07, responder rates favored ceftaroline for all infection types except for major abscesses where responder rates favored the comparator slightly (82.0% vs. 81.2%).

In Appendix Table 24, rates for cessation of spread in Study 06 also favored ceftaroline for all infection types but only slightly in patients with deep/extensive cellulitis (90.1% vs. 89.2%). In Study 07, rates for cessation of spread favored ceftaroline vs. comparator for all infection types except for major abscesses (88.4% vs. 92.0%).

4.1.2 Analyses by Region

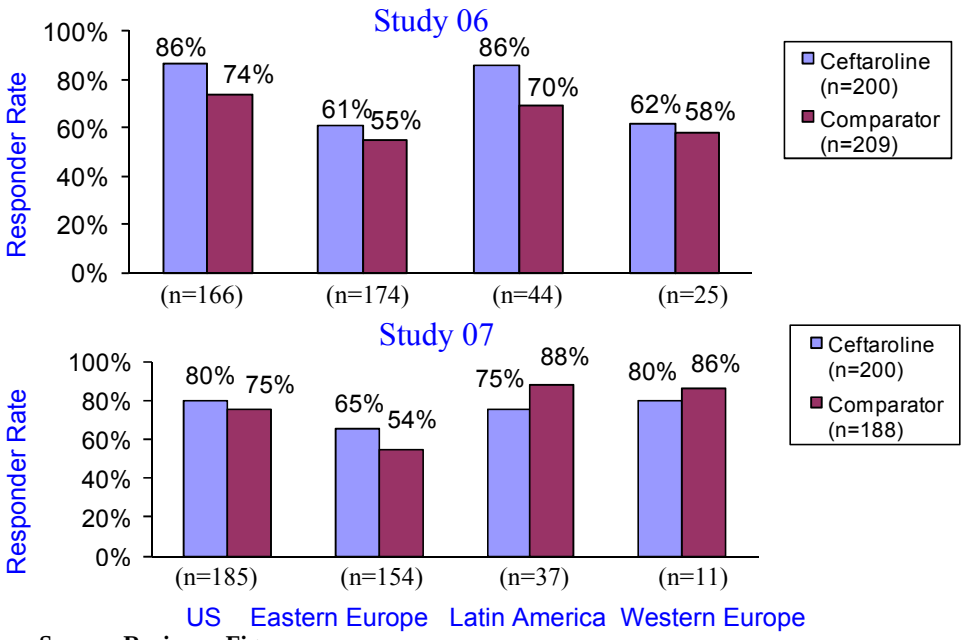
Responder rates (Table 16 & Figure 7) and rates for cessation of spread (Appendix Table 25) were evaluated in the U.S., Eastern Europe, Latin America and Western Europe. Analyses primarily considered the US and Eastern European regions since 85% of FDA-MITT subjects were from U.S. or Eastern Europe. (Patients from Poland and Hungary were considered as Western European by the Applicant but considered as Eastern European in Reviewer analyses).

Table 16: Responder Rates by Region

	Study 06 (N=409)		**Study 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 (%)
US	70/81 (86.4)	63/85 (74.1)	80/100 (80.0)	64/85 (75.3)
Eastern Europe	52/85 (61.2)	49/89 (55.1)	49/75 (65.3)	43/79 (54.4)
Latin America	18/21 (85.7)	16/23 (69.6)	15/20 (75.0)	15/17 (88.2)
Western Europe	8/13 (61.5)	7/12 (58.3)	4/5 (80.0)	6/7 (85.7)

Source: Reviewer Table

Figure 7: Responder Rates by Region



Source: Reviewer Figure

Table 16 & Figure 7 show that responder rates (regardless of treatment) were substantially higher in the US vs. Eastern Europe in both studies. In the US, responder rates favored ceftaroline over the comparator by 12% (86% vs. 74%) in Study 06 and by 5% (80% vs. 75%) in Study 07. In Eastern Europe, responder rates favored ceftaroline by 6% (61% vs. 55%) in Study 06 and by 11% (65% vs. 54%) in Study 07. Comparisons of responder rates in Latin America and Western Europe were limited by small numbers but tended to favor ceftaroline in Study 06 and the comparator in Study 07.

Appendix Table 25 shows that rates for cessation of spread favored ceftaroline over the comparator in the US and Eastern Europe for both studies. Study 06 comparisons in the US were especially favorable to ceftaroline (91.4% vs. 78.8%). Comparisons in Latin America and Western Europe were limited by small numbers and did not show any clear trends in treatment differences across studies.

4.1.3 Analyses by Baseline Fever Status

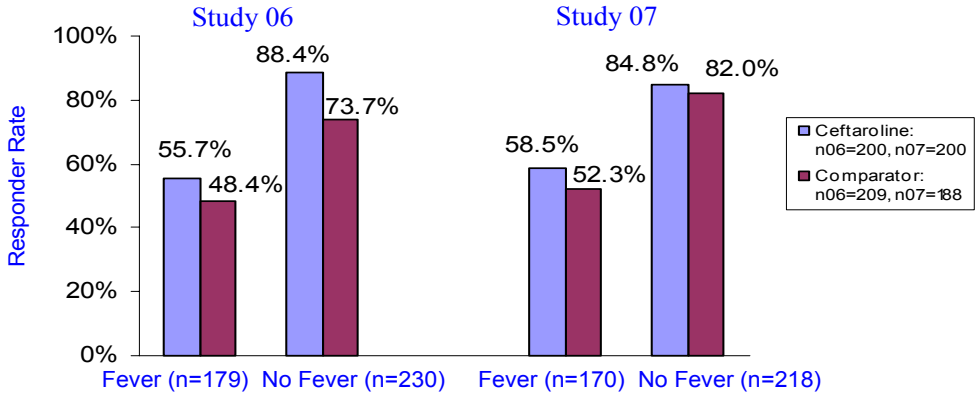
Subgroup analyses by baseline fever status were also performed for responder rates (Table 17 & Figure 8) and rates for cessation of spread (Table 26). Presence of fever was determined using FDA clinical reviewer criteria in which patients with a highest daily uncorrected temperature reading of $\geq 38^{0}$ Celsius by any route of administration were considered as having fever at baseline. Approximately 44% of patients in each of the two studies had fever at baseline based on these criteria.

Table 17: Responder Rates by Baseline Fever Status

	Study 06 (N=409)		Study 07 (N=388)	
Fever at Baseline (≥38°C)?	**Ceftaroline (N=200)** n/N (%)	**Vancomycin + Aztreonam (N=209)** n/N (%)	**Ceftaroline (N=200)** n/N (%)	**Vancomycin + Aztreonam (N=188)** n/N (%)
Fever	49/ 88 (55.7)	44/91 (48.4)	48/82 (58.5)	46/88 (52.3)
No Fever	99/112 (88.4)	91/118 (73.7)	100/118 (84.8)	82/100 (82.0)

Source: Reviewer Table

Figure 8: Responder Rates by Baseline Fever Status



Source: Reviewer Figure

In Table 17 & Figure 8, responder rates in both studies favored ceftaroline over the comparator regardless of baseline fever status. Treatment differences in Study 06 were more favorable than in Study 07 especially among patients with no baseline fever. It should also be noted that regardless of the treatment received, responder rates in both studies were substantially lower in patients with fever at baseline.

In Appendix Table 26, rates for cessation of spread also favored ceftaroline regardless of baseline fever status but to a lesser extent than with responder rates. Rates for cessation of spread in both studies were also observed to be slightly higher in patients with vs. without baseline fever. This indicates that differences in responder rates by baseline fever status were primarily due to the fever component of the responder definition.

Overall findings indicate a strong dependence of responder rates (primarily the fever component) on baseline fever status. Due to this dependence, comparisons of responder rates become less clear among patients with baseline fever because the responder rate endpoint may be driven primarily by the fever vs. cessation of spread component. This can confound treatment differences in cessation of spread component. This also creates uncertainty in assumptions relating to NI margin justification which would be influenced by the proportion of patients with baseline fever. These issues are further discussed in Section 4.2.6.

4.1.4 Analyses by Prior Antibiotics Use

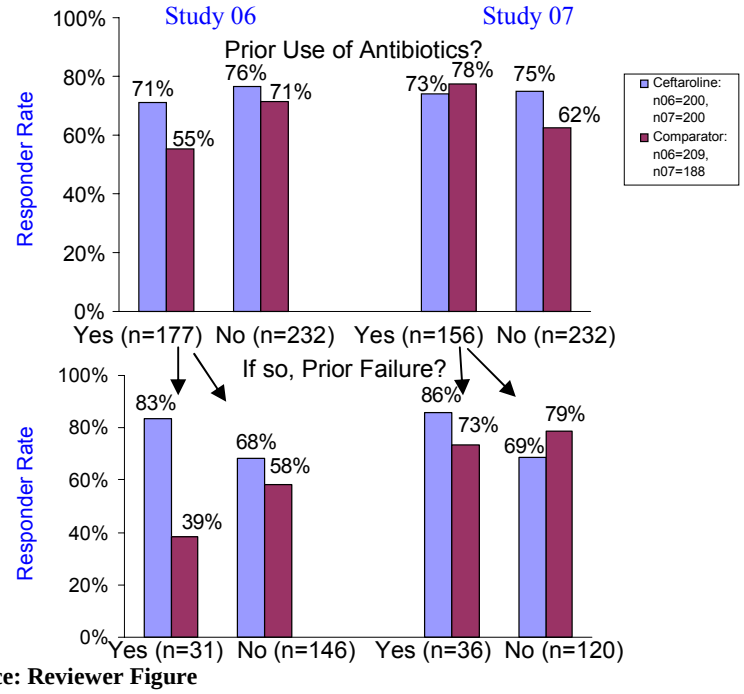
Responder rates (Table 18 & Figure 9) and rates for cessation of spread (Table 27) were analyzed by prior use of antibiotics and by prior failures in those with prior use. Based on FDA clinical Reviewer considerations, any prior systemic antibiotics use within 24 hours of start of study of therapy could potentially confound responder rates at Day 3. According to the Applicant's exclusion criteria designed for evaluating a TOC endpoint 8 to 15 days post-therapy, > 24 hours of prior use of antibiotics within 72 hours of start of study drug was not permitted unless the subject was deemed a prior failure by the investigator.

Table 18: Responder Rates by Prior Antibiotics Use

	Study 06 (N=409)		Study 07 (N=388)	
Prior antibiotics use within 24 hours of start of study drug?	**Ceftaroline (N=200)** # (%)	**Vancoymycin +Aztreonam (N=209)** # (%)	**Ceftaroline (N=200)** # (%)	**Vancoymycin +Aztreonam (N=188)** # (%)
Yes	64/ 90 (71.1)	48/87 (55.2)	62/85 (72.9)	55/71 (77.5)
No	84/110 (76.4)	87/122 (71.3)	86/115 (74.8)	73/117 (62.4)
If so, Prior Failure?				
Yes	15/18 (83.3)	5/13 (38.5)	18/21 (85.7)	11/15 (73.3)
No	49/72 (68.1)	43/74 (58.1)	44/64 (68.8)	44/56 (78.6)

Source: Reviewer Table

Figure 9: Responder Rates by Prior Use of Antibiotics



Source: Reviewer Figure

In Table 18 & Figure 9, responder rates (ceftaroline vs. comparator) among patients taking prior antibiotics within 24 hours of the start of study drug favored ceftaroline in Study 06, 71.1% vs. 55.2% but was less favorable to ceftaroline in Study 07, 72.9% vs. 77.5%. Among patients not taking prior antibiotics, responder rates favored ceftaroline in both studies, 76.4% vs. 71.3% in Study 06 and 74.8% vs. 62.4% in Study 07. Approximately 8% & 9% of patients in Studies 06 & 07 had used prior antibiotics and were assessed as prior failures. Among these patients, responder rates tended to favor ceftaroline over the comparator, however inferences were limited due to small numbers.

In Appendix Table 27, rates for cessation of spread in Study 06 favored ceftaroline over the comparator regardless of prior antibiotics use. In Study 07, rates favored the comparator in patients taking prior antibiotics (82.4% vs. 85.9%) but favored ceftaroline in patients not taking prior antibiotics (94.8% vs. 90.6%). Among prior failures, rates tended to favor ceftaroline over the comparator, however inferences were limited due to small numbers.

Overall, responder rates and rates for cessation of spread in patients not taking prior antibiotics appeared to favor ceftaroline in both studies, especially in Study 07. However, it is important to note that use of prior antibiotics can potentially confound treatment differences at early time points and the extent of the impact is difficult to ascertain after the study is completed. In a non-inferiority design, this can potentially lead to falsely concluding non-inferiority.

4.1.5 Analyses by Concomitant Antipyretics and Anti-Inflammatory Use

Subgroup analyses of responder rates (Table 19 & Figure 10) and rates for cessation of spread (Appendix Table 28) were also performed by use of concomitant antipyretics and anti-inflammatories. Based on FDA clinical reviewer considerations, use of antipyretics (on Day 1 or 2) and use of anti-inflammatories (on Day 1, 2 or 3) can potentially confound treatment differences in responder rates at Day 3. In each of the studies, roughly 70% of patients used antipyretics and nearly 80% of patients had used anti-inflammatories.

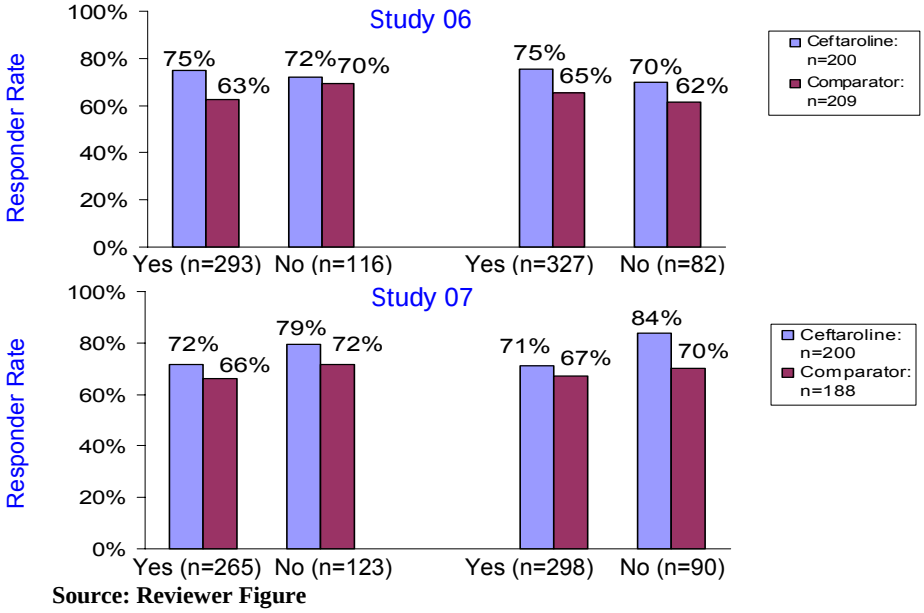
Table 19: Responder Rates by Concomitant Antipyretic & Anti-Inflammatory Use

	Study 06 (N=409)		**Study 07 (N=388)**	
	Ceftaroline (N=200) n/N (%)	**Comparator (N=209)** n/N (%)	**Ceftaroline (N=200)** n/N (%)	**Comparator (N=188)** n/N (%)
Concomitant Use of Antipyretics on Days 1 or 2?				
Yes	107/143 (74.8)	94/150 (62.7)	98/137 (71.5)	85/128 (66.4)
No	41/57 (71.9)	41/59 (69.5)	50/63 (79.4)	43/60 (71.7)
Concomitant Use of Anti-Inflammatories on Days 1, 2 or 3?				
Yes	118/157 (75.2)	111/170 (65.3)	112/157 (71.3)	95/141 (67.4)
No	30/43 (69.8)	24/39 (61.5)	36/43 (83.7)	33/47 (70.2)

Source: Reviewer Table

Figure 10: Responder Rates by Concomitant Antipyretic & Anti-Inflammatory Use

Use of Antipyretics (Day 1 or 2)? Use of Anti-inflammatories (Days 1, 2 or 3)?



Source: Reviewer Figure

Table 19 & Figure 10 show that in both studies responder rates favored ceftaroline over the comparator regardless of use of antipyretics or anti-inflammatories. In Study 06, treatment differences favored ceftaroline more in patients taking antipyretics (75% vs. 63%) vs. not taking antipyretics (72% vs. 70%). In Study 07, treatment differences favored ceftaroline less in patients taking anti-inflammatories (71% vs. 67%) vs. not taking anti-inflammatories (84% vs. 70%).

Appendix Table 28 shows that in Study 06 rates for cessation of spread favored ceftaroline over the comparator in patients with or without concomitant use of antipyretics or anti-inflammatory medications. In Study 07, differences did not substantially favor either treatment in patients with concomitant use of antipyretics or anti-inflammatories but tended to favor ceftaroline in patients without concomitant use of antipyretics or anti-inflammatories.

Overall, these subgroup analyses did not indicate that ceftaroline patients may benefit more from the concomitant use of antipyretics or anti-inflammatories. However, it is important to note that such concomitant use can potentially confound treatment differences at early time points and this could potentially lead to false conclusions of non-inferiority.

It should be further noted that assessing the extent of the impact from such confounding was difficult for several reasons. First, there were limited numbers of patients not using antipyretics or anti-inflammatories. Second, the influence of antipyretics (and anti-inflammatories) on fever was difficult to assess because the case report forms used in

Studies 06 & 07 did not record the exact timing of temperature readings, only the highest daily temperature. Third, there is potential confounding from other factors (e.g. prior antibiotic use, baseline fever status, missing data).

4.2 Exploratory/Sensitivity Analyses

Exploratory/sensitivity analyses were conducted by the Reviewer to better assess the robustness of findings for rates for cessation of spread and responder rates under a broader set of assumptions. These analyses considered the following:

- Responder rates and rates for cessation/percent reduction at additional time points such as Day 2, 4, 5
- Responder rates and rates for meeting % reductions in lesion area at Day 3 using additional cut-offs such as ≥ 30%, ≥ 50%, ≥ 75%
- Changes in the distributions of % reductions in lesion area from Days 2 to 5
- Rates of missing data
- Responder rates using a carry forward approach
- Concordance/discordance of responder rates with EOT assessment

4.2.1 Analyses at Days 2-5

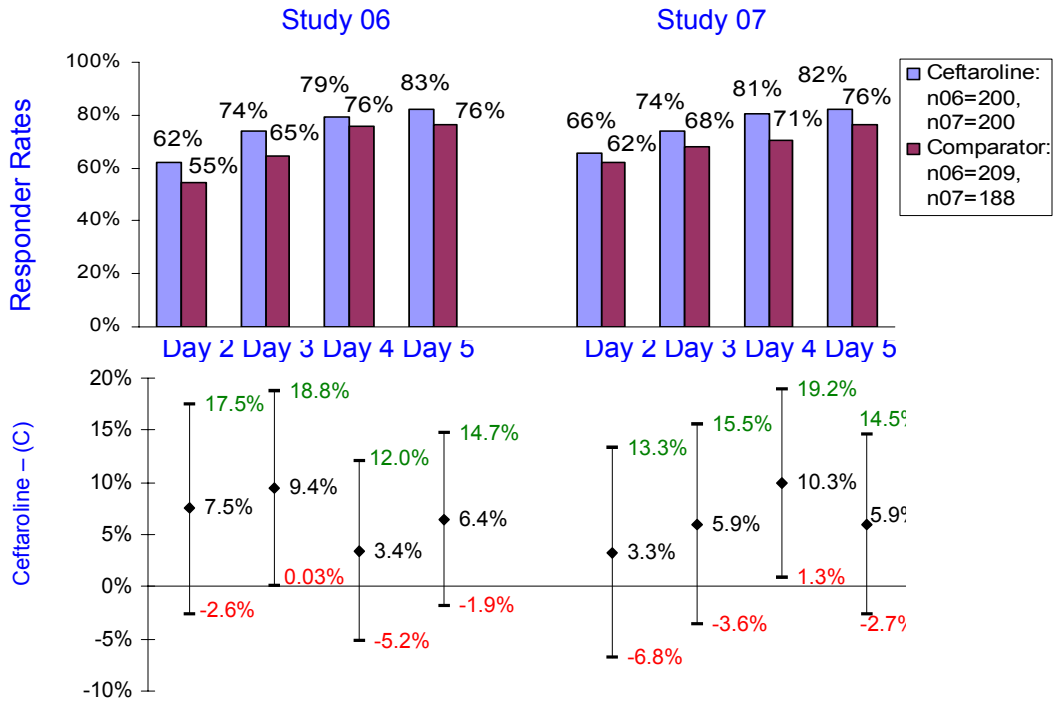
Responder rates (Table 20 & Figure 11) and rates for cessation of spread (Appendix Table 29) were analyzed across Days 2 to 5. While analyses at Day 3 were considered to be most meaningful, analyses at Days 2, 4, 5 were considered useful in exploring the robustness of Day 3 findings with respect to timing of assessment.

Table 20: Responder Rates, Days 2-5

	Study 06 (N=409)			**Study 07 (N=388)**		
	Ceftaroline N=200 n (%)	**Vancomycin + Aztreonam N=209** n (%)	**Difference (95% CI)**	**Ceftaroline N=200** n (%)	**Vancomycin + Aztreonam N=188** n (%)	**Difference (95% CI)**
Day 2	124 (62.0)	114 (54.5)	7.5 (-2.6, 17.5)	131 (65.5)	117 (62.2)	3.3 (-6.8, 13.3)
Day 3	**148 (74.0)**	**135 (64.6)**	**9.4 (0.03, 18.8)**	**148 (74.0)**	**128 (68.1)**	**5.9 (-3.6, 15.5)**
Day 4	158 (79.0)	158 (75.6)	3.4 (-5.2, 12.0)	162 (81.0)	133 (70.7)	10.3 (1.3, 19.2)
Day 5	165 (82.5)	159 (76.1)	6.4 (-1.9, 14.7)	164 (82.0)	143 (76.1)	5.9 (-2.7, 14.5)

Source: Reviewer Table

Figure 11: Responder Rates, Days 2-5



Source: Reviewer Figure

In Table 20 & Figure 11, responder rates in both studies favored ceftaroline over the comparator for all comparisons across Days 2 to 5, with differences ranging from 3.3% to 10.3% and lower limits at or above -6.8%. These findings show that responder rate differences which favored ceftaroline in the key sensitivity analysis were generally robust to timing based on the day specified for the analysis. These findings also show that differences in responder rates favoring ceftaroline were generally consistent between studies from Day 2 to Day 5.

Appendix Table 29 shows for Study 06 that rates for cessation of spread favored ceftaroline over the comparator, especially from Day 3 to Day 5 where treatment differences were from 5.4% to 6.4% with lower limits between -1.1% and -0.1%. In contrast, rates in Study 07 were generally similar between treatments from Days 2 to 4 and lower in ceftaroline patients at Day 5 with a difference of -3.0% (-9.6%, 3.6%).

4.2.2 Analyses for Various % Reductions

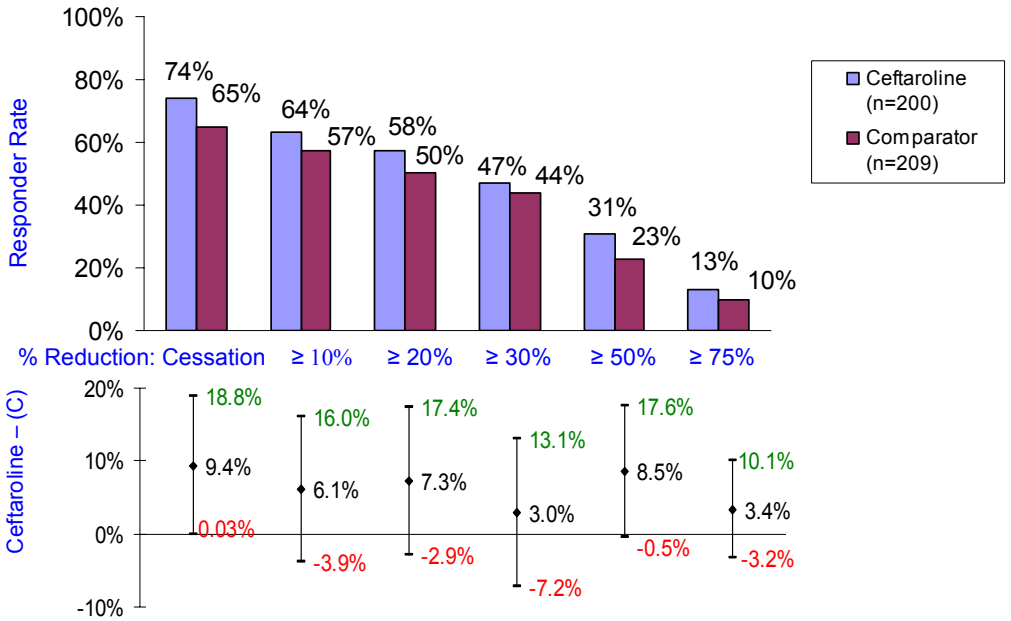
Responder rates (Table 21 & Figures 12 & 13) and rates for cessation of spread (Appendix Table 30) were explored based on various % reductions in lesion size from baseline. These analyses included larger % reductions (e.g. reductions in lesion area of ≥ 30%, ≥ 50%, ≥ 75%) than had been considered in earlier sensitivity analyses.

Table 21: Responder Rates for Cessation/Various % Reductions in Lesion Area

Cessation / % Reduction for Responder	Study 06 (N=409)			Study 07 (N=388)		
	Ceftaroline N=200 # (%)	Vancomycin + Aztreonam N=209 # (%)	Difference (95% CI)	Ceftaroline N=200 # (%)	Vancomycin + Aztreonam N=188 # (%)	Difference (95% CI)
Cessation	**148 (74.0)**	**135 (64.6)**	**9.4 (0.03, 18.8)**	**148 (74.0)**	**128 (68.1)**	**5.9 (-3.6, 15.5)**
≥ 10%	127 (63.5)	120 (57.4)	6.1 (-3.9, 16.0)	133 (66.5)	115 (61.2)	5.3 (-4.7, 15.4)
≥ 20%	115 (57.5)	105 (50.2)	7.3 (-2.9, 17.4)	120 (60.0)	105 (55.9)	4.1 (-6.2, 14.5)
≥ 30%	94 (47.0)	92 (44.0)	3.0 (-7.2, 13.1)	106 (53.0)	92 (48.9)	4.1 (-6.4, 14.5)
≥ 50%	62 (31.0)	47 (22.5)	8.5 (-0.5, 17.6)	73 (36.5)	58 (30.9)	5.6 (-4.3, 15.6)
≥ 75%	26 (13.0)	20 (9.6)	3.4 (-3.2, 10.1)	41 (20.5)	23 (12.2)	8.3 (0.5, 16.1)

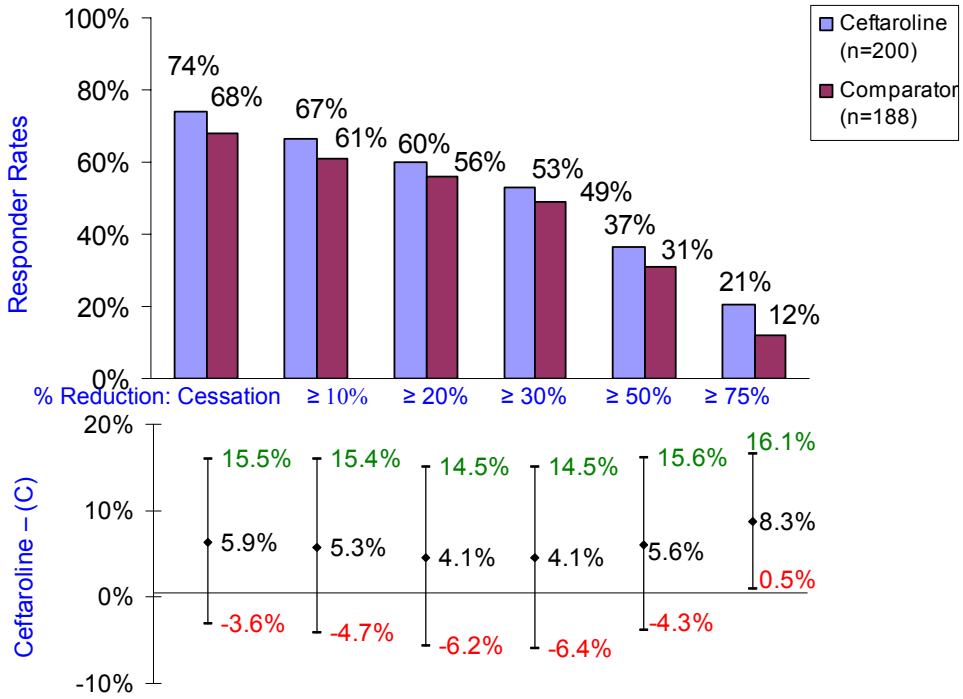
Source: Reviewer Table

Figure 12: Responder Rates for Cessation/Various % Reductions- Study 06



Source: Reviewer Figure

Figure 13: Responder Rates for Cessation/Various % Reductions- Study 07



Source: Reviewer Figure

In Table 21 and Figures 12 & 13 above, responder rate differences in both studies favored ceftaroline for all specified % reductions with lower confidence limits above -7.2%. Treatment differences appeared to be especially favorable to ceftaroline for larger % reductions. In Study 06, treatment differences in responder rates based on a ≥ 50% reduction favored ceftaroline by 8.5% (95% CI: -0.5%, 17.6%) while in Study 07, differences based on a ≥ 75% reduction favored ceftaroline by 8.3% (95% CI: 0.5%, 16.1%).

Appendix Table 30 shows that differences in rates of cessation/percent reduction of spread of lesion at Day 3 also favored ceftaroline but differences were not as strong or as consistent as in responder rate comparisons. In both studies, treatment differences appeared to be more favorable to cefaroline for larger % reductions such as a ≥ 50% or ≥ 75%.

Overall findings show that differences in responder rates and rates for cessation of spread were robust to the specified % reduction even for larger % reductions. It is also important to note that favorable treatment differences at larger % reductions may be especially meaningful because in these comparisons there is likely to be misclassification of responders due to investigator biases or measurement errors.

4.2.3 Comparisons of Distributions for % Reduction in Lesion Area

In Appendix Figures 15 & 16, Reviewer analyses also compared the distributions for the % reduction in lesion area from Day 2 to Day 5 using side-by-side comparisons of box plots (ceftaroline in green vs. the comparator in red). In both studies, especially Study 06, ceftaroline box plots started to separate from the comparator box plots at Day 3. Separation in the box plots also appeared to be most evident for the upper quartiles which corresponded to larger % reductions in lesion area. As stated earlier, favorable treatment differences at larger % reductions may be especially meaningful because in these comparisons there is likely to be misclassification of responders due to investigator biases or measurement errors.

4.2.4 Analyses of Missing Data

Table 22: Missing Responder Rate Data by EOT Outcome

EOT Outcome	Study 06 (N=409)		Study 07 (N=388)	
	Ceftaroline (N=200) # Missing (%)	**Vancomycin + Aztreonam (N=209)** # Missing (%)	**Ceftaroline (N=200)** # Missing (%)	**Vancomycin + Aztreonam (N=209)** # Missing (%)
Total	**5 (2.5%)**	**11 (5.3)**	**8 (4.0)**	**8 (4.3)**
EOT Cure	4 (2.0%)	4 (1.9)	2 (1.0)	4 (2.1)
EOT Failure	0 (0)	5 (2.4)	3 (1.5)	3 (1.6)
EOT Indeterminate	1 (0.5)	2 (1.0)	3 (1.5)	1 (0.5)

Source: Reviewer Table

Table 22 shows missing data for responder rate analyses at Day 3 by the patient's investigator assessment at EOT. A total of 32 patients (16 in each study) had missing missing responder rate data at Day 3. In Study 06, the ceftaroline arm had less missing data, primarily among EOT failures, 0 (0%) vs. 5 (2.4%). In Study 07, both treatment arms had similar rates of missing data, 8 (4.0%) vs. 8 (4.3%). The ceftaroline arm, however, had a slightly lower rate of missing data among EOT cures and a slightly higher rate among EOT indeterminates. In both studies, the handling of missing data as 'non-responders' in sensitivity analyses at Day 5 did not appear to substantially favor either treatment.

Missing data for cessation of spread assessments were similar to missing data for responder rates. However, there were three patients with missing responder rate data who were missing only data for the temperature component and could be assessed for changes in lesion size: 1 in ceftaroline arm (Study 06), 2 in comparator arm (Study 06 & 07). These three patients were clinical cures at EOT.

Appendix Table 31 shows missing responder rate data at Days 2-5 and at EOT for FDA-MITT subjects. Considering all subjects across both studies, missing data rates increased from Day 3 to Day 4 (4.0% to 6.1%) and from Day 4 to Day 5 (6.1% to 7.5%) but were substantially lower by the EOT visit (1.5%). In Study 06, missing data rates were lower in the ceftaroline vs. comparator arm with differences most pronounced at Day 5, 5.5% vs. 10.0%. In Study 06, missing data rates were lower in the ceftaroline vs. comparator arm with differences most pronounced at Day 5, 5.5% vs. 10.0%. In Study 07, missing data rates tended to be slightly higher in the ceftaroline arm with differences most pronounced at Day 5, 8.5% vs. 5.9%.

Overall, these results suggest missing data may influence responder rates and rates for cessation of spread, especially at Days 4 and 5 where rates of missing data were highest. In Section 4.2.5, sensitivity analyses assess the influence of missing data.

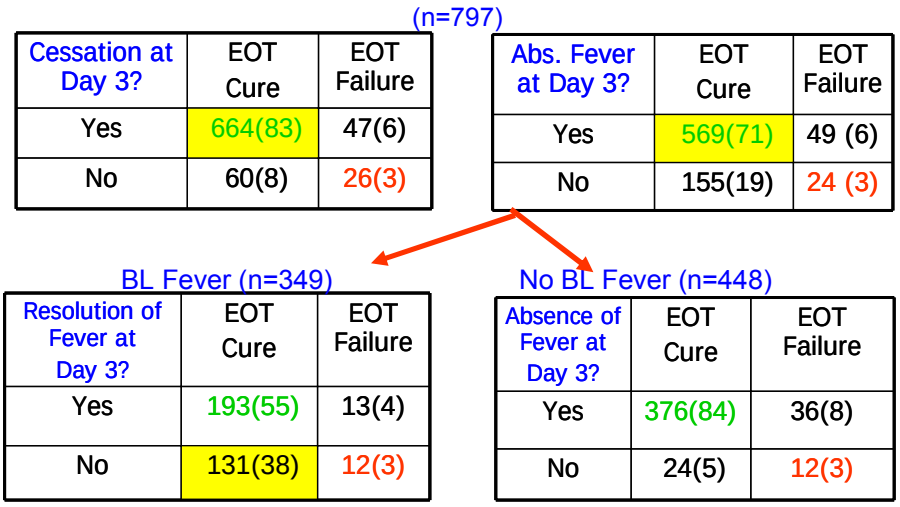
4.2.5 Responder Rates Using a Carry Forward Approach

In Appendix Table 32, sensitivity analyses were performed from Day 2 to Day 5 using a carry forward approach in which patients with missing responder rate data at Day x (x = 2, 3, 4, 5) as a result of no longer being in the study at Day x could have lesion and temperature measurements carried forward from an earlier visit to Day x, provided they had not been assessed as a 'clinical failure' at EOT on or prior to Day x. In comparison to the Reviewer's primary approach which considered all missing cases as non-responders from Day 2-5 (Table 20), the carry forward approach showed identical treatment differences at Day 2 for both studies and at Day 3 for Study 07. At Day 3 in Study 06, the treatment difference (95% CI) decreased by 1.0% from 9.4% (0.03%, 18.8%) to 8.4% (-0.9%, 17.8%). At Days 4 & 5, treatment differences decreased by 1.9% & 1.9% in Study 06 (i.e. benefitting comparator more) and increased by 1.4% & 2.0% in Study 07 (i.e. benefitting ceftaroline more). Similar trends were observed when comparing the two approaches for the cessation of spread endpoint. (There was one patient in the Study 07 comparator arm who was re-classified as having 'cessation' using a carry forward approach at Day 5 but remained a 'non-responder' due to a missing temperature reading).

4.2.6 Concordance/Discordance of Responder Rates with EOT Assessment

Exploratory analyses of concordance/discordance of responder rates with EOT showed that responder outcomes at Day 3 often diverged from the outcomes at EOT based on clinical assessment (Figure 14). This divergence was observed more for the absence of fever component (71% positive concordance) than for the cessation component (83% positive concordance). Further subgroup analyses of patients with and without fever at baseline showed strong divergence among patients with fever at baseline. Within this subgroup, 38% of patients failed to have resolution of fever at Day 3 but were clinical cures at EOT. This finding raises concerns regarding the clinical significance of fever and responder rates at Day 3, especially among patients with fever at baseline.

Figure 14: Convergence/Divergence of Responder Rates with EOT Assessment



Source: Reviewer Figure

5. LIMITATIONS

As mentioned earlier, there were several limitations with the FDA Reviewer approach of conducting analyses based on responder rates. These limitations were divided into two categories: 'Limitations (General)' and 'Limitations (Studies 06 & 07)'. 'Limitations (General)' would include limitations that would occur regardless of the study design specified, while 'Limitations (Studies 06 & 07)' would refer to limitations specific to the Study 06 & 07 designs.

5.1 Limitations (General)

The general limitations of Reviewer analyses based on responder rates at 48-72 hours (Day 3) included NI margin justification, the post-hoc nature of the testing, interpretations of responder rates and the types of infections included. Note that these limitations would be independent of the study designs used.

5.1.1 Uncertainties in Reliably Measuring Lesion Size

Currently, there is not a validated approach to ensure accurate and consistent measurements of lesion sizes across study sites in a clinical trial. Approaches utilizing digital photo planimetry may hold the most potential for ensuring accurate and consistent measurements, however, implementation of these approaches in a clinical trial setting is still in the exploratory stage.

5.1.2 NI Margin Justification from Historical Studies

While non-inferiority analyses based on responder rate at Day 3 would allow for a more meaningful interpretation of the findings in comparison to analyses of clinical cure rates at TOC, there are some limitations with the justification of an appropriate NI margin at Day 3. For example, justification of the NI margin relied upon two historical studies (i.e. Snodgrass et. al, 1937) in which cessation of spread and resolution of fever were evaluated at 48 hours in patients with fever at baseline. However, in Studies 06 and 07 responder rates were evaluated over a later time period of 48 to 72 hours and in a different study population which was mostly afebrile at baseline (i.e. 56% afebrile). This creates uncertainty in the NI margin since the treatment effect on responder rates is substantially lower in patients evaluated at 72 hours vs. 48 hours (i.e. Snodgrass et. al, 1937). There is also potential uncertainty in the treatment effect in patients with vs. without fever at baseline as suggested in the current studies (Table 17).

There were also several other limitations in justifying a NI margin based on the Snodgrass studies (e.g. infection type, mortality, pathogen representation, etc.) Further work is needed to explore potential effects of timing (48 hours vs. 72 hours), fever status at baseline and other factors in justifying NI margins for responder rates at Day 3.

5.1.3 Post-hoc Nature of Testing Hypotheses

The post-hoc nature of testing statistical hypotheses using FDA Reviewer responder rate analyses reduced the strength of the evidence in these analyses due to potential inflation of the overall type I error rate. However, it should be noted that FDA Reviewer definitions of the analysis population and responder rate endpoint were specified in a blinded manner, looking only at the overall data without knowledge of the individual treatment effects. This would serve to minimize potential inflation of the overall type I error rate in drawing inferences based on responder rate comparisons.

5.1.4 Interpretation of Responder Rates

Responder rate differences are based on a composite measure of both cessation of spread of lesion component and an absence/resolution of fever component. This composite measure may be difficult to interpret because the two components are conceptually different measures, spread of lesion being a key symptom of the skin infection and temperature being a sign of a systemic infection. Interpretations become less clear if there are inconsistencies in treatment differences in each of the individual component. Interpretations also become less clear if overall rates for cessation are higher than overall rates for absence/resolution of fever. In this case, differences in responder rates may be "driven" primarily by the fever component as discussed in Section 5.2.5.

5.1.5 Types of Patients/Symptoms Addressed

Responder rate analyses address only a subgroup of patients meeting certain characteristics for inclusion. Since the FDA-MITT includes only patients with baseline lesion sizes of 75 cm^2 or greater, responder rate analyses may not address certain types of important skin infections such smaller lesions occurring on the face, neck, hands, feet etc.

Responder rate analyses also address only one symptom (i.e. change in lesion size) and one sign of infection (i.e. fever) rather than overall patient improvements based on a broad range of signs and symptoms such as in a clinical assessment. Therefore, important patient symptoms such as pain would not be addressed in responder rate analyses. There are also concerns that too much importance may be placed on the one sign and/or symptom used in defining responders. For example, presence of fever at Day 3 may not be a reliable indicator of the effectiveness of the antibiotic in patients with fever at baseline (Figure 14).

5.2 Limitations (Specific to Studies 06 & 07)

There were also several other limitations with Reviewer sensitivity analyses based on responder rates which were specific to the Study 06 & 07 designs. These limitations included higher rates of missing data, measurement errors in lesion size, use of prior antibiotics, use of concomitant antipyretics and anti-inflammatory drugs, differences by baseline fever status, divergence of responder rates at Day 3 with clinical outcomes at EOT (esp. for fever component) and reductions in sample size.

5.2.1 Higher Rates of Missing Data

There was also a high rate of missing data when examining responder rates at Day 3 (4% missing). The influence of missing data was especially apparent in assessing the cessation of spread of lesion. In Studies 06 & 07, 14/400 (4%) and 15/388 (4%) had missing lesion measurements while 30/400 (8%) and 27/388 (7%) had an observed increase in lesion size (either length or width) at Day 3. Patients with missing lesion measurements in Studies 06 & 07 therefore accounted for 14/44 (32%) and 15/42 (36%) of patients assessed as not having cessation of spread of lesion at Day 3. This indicates that variability in missing data rates among treatments can substantially impact comparisons based on cessation of spread of lesion. For these reasons, exploratory analyses considered the effect of using a carry forward approach for patients with missing responder rate data at Day x (x = 2, 3, 4, 5) since they were no longer in the study at Day x and had not been assessed as a 'clinical failure' (e.g. patients who were lost-to-follow-up or had extenuating circumstances). These patients could have lesion and temperature measurements carried forward from an earlier visit to Day x.

5.2.2 Investigator Errors & Biases in Measuring Lesion Size

Inferences based on the Applicant's measurements of spread of lesion may be limited by possible investigator measurement error in lesion sizes and misclassification biases.

Studies 06 & 07 were not designed to assess treatment differences in lesion sizes but were rather intended only for descriptive statistics. Therefore, there was limited emphasis on precise lesion size measurement, no standardization to ensure accuracy & consistency, no verification of measurements and no estimation of measurement error. Studies 06 & 07 also measured length and width of lesions by ruler to the nearest cm with lesion area = length x width. This approach is problematic because l x w assumes a rectangle whereas lesions have varieties of shapes. There is also human error, subjectivity & other factors.

Reviewer observation of the lesion measurement data in studies 06 & 07 also suggested potential errors and biases. There was high variability among investigators, inconsistent precisions used by investigator (cm vs. mm), highly disproportionate % changes in length vs. width and other inconsistencies and irregularities. Examples of some of the inconsistencies and irregularities could be clearly observed for Site #5007 and Site #5014. In site #5007, 44/46 (96%) vs. 128/363 (35.3%) at other Study 06 sites had a reduction in lesion area of 100% at EOT, $p=3.3*10^{-16}$. In Site #5014, 18/60 (30%) vs. 11/328 (3.4%) at other Study 07 sites had a reduction in lesion area of 0% at Day 3, $p=5.4*10^{-14}$.

To account for potential measurement error, sensitivity analyses were conducted in which a 10% or 20% reduction in lesion size area was required for responders at Day 3. Similar analyses were conducted for the change in lesion size (i.e. without the fever component). Further analyses also explored larger % reductions at Day 3 (i.e. $\geq 30\%$, $\geq 50\%$ & $\geq 75\%$). Results were generally consistent regardless of the required reduction.

5.2.3 Influence of Prior Antibiotics Use

Study 06 & 07 were not designed to control for the use of prior antibiotics in non-inferiority comparisons at early time points. Consequently, there was substantial use of prior antibiotics which can potentially confound the treatment effect at Day 3 for both the responder rate and rates of cessation of spread endpoints. Approximately 43% & 40% of Study 06 & 07 patients included in the FDA-MITT had used prior antibiotics within 24 hours of study drug. Subgroup analyses were performed for subjects using and not using prior antibiotics. While ceftaroline patients not using prior antibiotics appeared to fare well vs. the comparator in both studies, the extent of impact of prior antibiotic use is difficult to ascertain based on post-hoc subgroup analyses. It should be further noted that any kind of noise in the response in an NI trial can lead to false conclusions of non-inferiority

5.2.4 Influence of Concomitant Antipyretic & Anti-inflammatory Use

As with the use of prior antibiotics, concomitant use of antipyretics or anti-inflammatory drugs can also potentially confound responder rates. In studies 06 & 07, the effect of concomitant use on responder rates was especially difficult to assess for several reasons. First, the CRF only recorded a patient's highest temperature within 24 hrs (no hour/minute of each reading). The hour/minute in which the concomitant med. was taken was missing for many patient records. Second, a large proportion of the patients were

using antipyretics or anti-inflammatory drugs. Across both studies, approximately 70% & 80% of patients used antipyretics (Days 2 or 3) or anti-inflammatory drugs (Days 1, 2 or 3). Additionally, there were other confounders such as prior antibiotics use which made assessment of the effects of antipyretics or anti-inflammatory drugs on responder rates difficult.

5.2.5 Dependence on Baseline Fever Status

Responder rates in patients with baseline fever were observed to be approximately 30% lower in those patients with baseline fever (Table 17). This finding may make interpretations of study findings less clear because NI margin justification in patients with baseline fever may not be applicable to patients without baseline fever. Additionally, since rates of resolution of fever at Day 3 were also approximately 30 to 40% lower than rates for cessation of spread of lesion in patients with baseline fever in both studies (Appendix Table 26, rows 1 & 3), the interpretation of responder rates in patients with baseline fever may be problematic because rates for resolution of fever at Day 3 may be driven by the responder rate endpoint.

Due to these considerations, establishing a NI margin in patients not having baseline fever may be challenging. It should also be noted that causal effects of baseline fever on responder rates may be difficult to ascertain due to the fever component of the responder rate and other confounders such as age and diabetes. As shown in the Appendix Table 33, older patients ($\geq$ 65 years and $\geq$ 75 years) and patients with diabetes tended to be less likely to have fever at baseline.

5.2.6 Discordance of Responder Rates with EOT Assessment

The Reviewer evaluated concordance/discordance between responder rates at Day 3 and clinical cure rates based on investigator assessment at EOT. Results indicated a strong discordance among patients with baseline fever. In this subgroup, 38% of patients failed to have resolution of fever at Day 3 but were clinical cures at EOT. This finding indicates that failure to satisfy the absence/resolution of fever component at Day 3 may not be clinically relevant in patients with baseline fever. This would also call into question the clinical relevance of the responder rate endpoint which relies on the fever component. Due to this limitation, as well AC meeting discussions pertaining to the fever component, the Reviewer performed extensive analyses evaluating only the cessation of spread of lesion endpoint (i.e. without the fever component) which are included in this review.

5.2.7 Reductions in Sample Size

Only 58% of patients in the Applicant's MITT population could be included in the FDA-MITT for Reviewer sensitivity analyses. Due to large treatment effects favoring ceftaroline in the key sensitivity analysis of responder rates at Day 3, lack of power due to a limited sample size did not appear to affect these analyses. However, the limited sample size did limit the Reviewer in conducting meaningful subgroup analyses based on

a FDA-MITT population. It should also be noted that since the FDA-MITT is not protected by the randomization, subgroups may not be appropriately balanced with respect to factors potentially affecting responder rates.

6. ADVISORY COMMITTEE MEETING

On September 7, 2010, an anti-infective advisory committee (AIDAC) was held to discuss issues in making a determination of the safety and efficacy of Teflaro™. Based on considerations of Reviewer sensitivity analyses at the Day 3 endpoint as well as other evidence, the AIDAC unanimously agreed (18 votes to 0) that both safety and efficacy of ceftaroline were demonstrated for the requested indication of ABSSSI. Although members commented that evidence was not as impressive as for the CABP indication, they felt that data on lesion resolution was compelling. Some members expressed concerns with potential unblinding in the trials due to monitoring of vancomycin levels and suggested weight-based dosing of vancomycin for future trials. There were also concerns regarding the validity of lesion measurement and members suggested the use of digital photography and computer analysis.

One committee member noted that the sensitivity analyses at Day 3 had greater sensitivity to changes in treatments than would have been observed based on a TOC endpoint. This member also emphasized the need for analyses that consider only the cessation of spread component, mentioning that the Foundation for the National Institutes of Health (FINH) working group recognizes that endpoints in ABSSSI and CABP should be based on measures of symptoms rather than on signs (e.g. temperature, heart rate, SBP).

7. SUMMARY AND CONCLUSIONS

Non-inferiority studies 06 & 07 provided adequate evidence supporting the efficacy of ceftaroline in treating patients with ABSSSI infections. Findings relied primarily on Reviewer sensitivity analyses for the key endpoint of responder rates based on cessation of spread of lesion with absence of fever at 48-72 hours (Day 3) in FDA-MITT patients. Responder rates favored ceftaroline over the comparator: 74.0% vs. 64.6%, a 9.4% difference (95% CI: 0.03%, 18.8%) in Study 06 and 74.0% vs. 68.1%, a 5.9% difference (95% CI: -3.6%, 15.5%) in Study 07. These analyses provided evidence of non-inferiorityof ceftaroline to vancomycin/aztreonam within a 3.6% NI margin for both studies. In additional sensitivity analyses to evaluate the robustness of findings, ceftaroline was observed to be similar (or favorable) to the comparator regardless of the degree of change in lesion size required for a responder (e.g. cessation vs. % reduction), timing of responder rates (e.g. Day 3 vs. EOT), definition of a responder (e.g. cessation/percent reduction without the fever component) and choice of endpoint (e.g. investigator assessment of clinical cure rate at EOT, rates of absence of erythema, swelling and tenderness). In these analyses, treatment comparisons on Day 3 favored ceftaroline in both studies while comparisons at EOT favored ceftaroline in Study 06 but did not favor either treatment in Study 07.

There were several limitations in applying the Reviewer sensitivity analyses to Study 06 & 07. General limitations included uncertainties in reliably measuring lesion size, NI margin justification from historical studies, the post-hoc nature of testing hypotheses, interpretation of responder rates and the types of patients/symptoms addressed. In addition, further limitations specific to Study 06 & 07 included higher rates of missing data, investigator errors & biases in measuring lesion size, influence of prior antibiotics use, influence of concomitant antipyretic & anti-inflammatory use, dependence on baseline fever status, discordance of responder rates with investigator assessment at EOT and reductions in sample size. Despite these limitations, overall findings from studies 06 & 07 were considered to be adequately robust in supporting the efficacy of ceftaroline.

REFERENCES

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

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

3. Miettinen O, Nurminen M. Comparative analysis of two rates, *Statistics in Medicine*. 1985;4(2):213-226.

4. Farrington CP, Manning G. Test statistics and sample size formulae for comparative binomial trials with null hypothesis of non-zero risk difference or non-unity relative risk. *Statistics in Medicine.* December 1990; 9(12):1447-1454

APPENDIX

Efficacy Analyses

Table 23: Rates for Cessation/Percent Reduction in Lesion Area at Day 3 & EOT

Cessation / % Reduction in Lesion Area	Study 06 (N=409)			Study 07 (N=388)		
	Ceftaroline N=200 n (%)	**Vancomycin + Aztreonam N=209** n (%)	**Difference (95% CI)**	**Ceftaroline N=200** n (%)	**Vancomycin + Aztreonam N=188** n (%)	**Difference (95% CI)**
Day 3						
Cessation	**184 (92.0)**	**181 (86.6)**	**5.4 (-0.6, 11.4)**	**179 (89.5)**	**167 (88.8)**	**0.7 (-5.5, 6.9)**
≥ 10%	156 (78.0)	160 (76.6)	1.4 (-6.7, 9.6)	159 (79.5)	147 (78.2)	1.3 (-6.8, 9.4)
≥ 20%	138 (69.0)	136 (65.1)	3.9 (-5.2, 13.0)	143 (71.5)	130 (69.1)	2.4 (-6.7, 11.5)
EOT						
≥ 75%	167 (83.5)	168 (80.4)	3.1 (-4.3, 10.6)	159 (79.5)	157 (83.5)	-4.0 (-11.7, 3.7)
≥ 90%	145 (72.5)	143 (68.4)	4.1 (-4.8, 12.9)	130 (65.0)	124 (66.0)	-1.0 (-10.4, 8.5)
≥ 95%	128 (64.0)	118 (56.5)	7.5 (-1.9, 17.0)	114 (57.0)	105 (55.9)	1.1 (-8.7, 11.0)

Subgroup Analyses for Cessation of Spread

Table 24: Rates for Cessation of Spread by Infection Type

	Study 06 (N=409)		Study 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 (%)
Deep/Extensive Cellulitis	100/111 (90.1)	99/111 (89.2)	78/88 (88.6)	87/103 (84.5)
Major Abscess	42/43 (97.7)	40/46 (87.0)	61/69 (88.4)	46/50 (92.0)
Wound Infection	27/30 (90.0)	22/27 (81.5)	27/29 (93.1)	24/24 (100)
Other	15/16 (93.8)	20/25 (80.0)	13/14 (92.9)	10/11 (90.9)

Source: Reviewer Table

Table 25: Rates for Cessation of Spread by Geographical Region

	Study 06 (N=409)		Study 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 (%)
US	74/81 (91.4)	67/85 (78.8)	83/100 (83.0)	69/85 (81.2)
Eastern Europe	83/85 (97.6)	83/89 (93.3)	74/75 (98.7)	75/79 (94.9)
Latin America	19/21 (90.5)	20/23 (87.0)	17/20 (85.0)	16/17 (94.1)
Western Europe	8/13 (61.5)	11/12 (91.7)	5/5 (100)	7/7 (100)

Source: Reviewer Table

Table 26: Rates for Cessation of Spread and Absence of Fever by Baseline Fever

	Study 06 (N=409)		Study 07 (N=388)	
Fever at Baseline (≥38°C)?	**Ceftaroline (N=200)** # (%)	**Vancomycin + Aztreonam (N=209)** # (%)	**Ceftaroline (N=200)** # (%)	**Vancomycin + Aztreonam (N=188)** # (%)
Cessation of Spread at Day 3				
Fever	82/ 88 (93.2)	83/91 (91.2)	76/82 (92.7)	80/88 (90.9)
No Fever	102/112 (91.1)	98/118 (83.1)	103/118 (87.3)	87/100 (87.0)
Absence of Fever at Day 3				
Fever	56/ 88 (63.6)	46/91 (50.5)	51/82 (62.2)	53/88 (60.2)
No Fever	106/112 (94.6)	105/118 (89.0)	111/118 (94.1)	90/100 (90.0)

Source: Reviewer Table

Table 27: Rates for Cessation of Spread by Prior Antibiotics Use

	Study 06 (N=409)		Study 07 (N=388)	
Prior antibiotics use within 24 hours of start of study drug?	**Ceftaroline (N=200)** # (%)	**Vancoymycin +Aztreonam (N=209)** # (%)	**Ceftaroline (N=200)** # (%)	**Vancoymycin +Aztreonam (N=188)** # (%)
Yes	81/ 90 (90.0)	75/87 (86.2)	70/85 (82.4)	61/71 (85.9)
No	103/110 (93.6)	106/122 (86.9)	109/115 (94.8)	106/117 (90.6)
If so, Prior Failure?				
Yes	17/18 (94.4)	11/13 (84.6)	21/21 (100)	14/15 (93.3)
No	64/72 (88.9)	64/74 (86.5)	49/64 (76.6)	47/56 (83.9)

Source: Reviewer Table

Table 28: Rates for Cessation of Spread by Concomitant Antipyretic & Anti-Inflammatory Use

	Study 06 (N=409)		Study 07 (N=388)	
	Ceftaroline (N=200) n/N (%)	**Comparator (N=209)** n/N (%)	**Ceftaroline (N=200)** n/N (%)	**Comparator (N=188)** n/N (%)
Concomitant Use of Antipyretics on Days 1 or 2?				
Yes	134/143 (93.7)	132/150 (88.0)	119/137 (86.7)	112/128 (87.5)
No	50/57 (87.7)	49/59 (83.1)	60/63 (95.2)	55/60 (91.7)
Concomitant Use of Anti-Inflammatories on Days 1, 2 or 3?				
Yes	147/157 (93.6)	150/170 (88.2)	137/157 (87.3)	123/141 (87.2)
No	37/43 (86.0)	31/39 (79.5)	42/43 (97.7)	44/47 (93.6)

Source: Reviewer Table

Exploratory/Sensitivity Analyses for Cessation of Spread (Tables)

Table 29: Rates for Cessation of Spread, Days 2-5

	Study 06 (N=409)			Study 07 (N=388)		
	Ceftaroline N=200 # (%)	**Vancomycin + Aztreonam N=209** # (%)	**Difference (95% CI)**	**Ceftaroline N=200** # (%)	**Vancomycin + Aztreonam N=188** # (%)	**Difference (95% CI)**
Day 2	179 (89.5)	183 (87.6)	1.9 (-4.7, 8.6)	175 (87.5)	166 (88.3)	-0.8 (-7.8, 6.2)
Day 3	**184 (92.0)**	**181 (86.6)**	**5.4 (-1.1, 11.8)**	**179 (89.5)**	**167 (88.8)**	**0.7 (-6.0, 7.4)**
Day 4	185 (92.5)	181 (86.6)	5.9 (-0.5, 12.3)	178 (89.0)	167 (88.8)	0.2 (-6.5, 7.0)
Day 5	185 (92.5)	180 (86.1)	6.4 (-0.1, 12.8)	176 (88.0)	171 (91.0)	-3.0 (-9.6, 3.6)

Source: Reviewer Table

Table 30: Rates for Cessation/Percent Reduction in Lesion Size on Day 3

Cessation / % Reduction in Lesion Area	Study 06 (N=409)			Study 07 (N=388)		
	Ceftaroline N=200 # (%)	**Vancomycin + Aztreonam N=209** #(%)	**Difference (95% CI)**	**Ceftaroline N=200** # (%)	**Vancomycin + Aztreonam N=188** # (%)	**Difference (95% CI)**
Cessation	**184 (92.0)**	**181 (86.6)**	**5.4 (-0.6, 11.4)**	**179 (89.5)**	**167 (88.8)**	**0.7 (-5.5, 6.9)**
≥ 10%	156 (78.0)	160 (76.6)	1.4 (-6.7, 9.6)	159 (79.5)	147 (78.2)	1.3 (-6.8, 9.4)
≥ 20%	138 (69.0)	136 (65.1)	3.9 (-5.2, 13.0)	143 (71.5)	130 (69.1)	2.4 (-6.7, 11.5)
≥ 30%	114 (57.0)	119 (56.9)	0.1 (-9.6, 9.7)	132 (61.0)	113 (60.1)	0.9 (-8.8, 10.6)
≥ 50%	72 (36.0)	58 (27.8)	8.3 (-0.8, 17.3)	88 (44.0)	72 (38.3)	5.7 (-4.1, 15.5)
≥ 75%	28 (14.0)	21 (10.0)	4.0 (-2.4, 10.3)	47 (23.5)	30 (16.0)	7.5 (-0.3, 15.4)

Source: Reviewer Table

Table 31: Missing Responder Rate Data by Study Day

	Study 06 (N=409)		Study 07 (N=388)		Total
	Ceftaroline (n=200) # Missing (%)	**Vancomycin + Aztreonam (n=209)** # Missing (%)	**Ceftaroline (n=200)** # Missing (%)	**Vancomycin + Aztreonam (n=188)** # Missing (%)	**All Patients N=797** # Missing (%)
Day 2	7 (3.5%)	9 (4.3%)	7 (3.5%)	4 (2.1%)	27 (3.4%)
Day 3	5 (2.5%)	11 (5.3%)	8 (4.0%)	8 (4.3%)	32 (4.0%)
Day 4	8 (4.0%)	18 (8.6%)	13 (6.5%)	10 (5.3%)	49 (6.1%)
Day 5	11 (5.5%)	21 (10.0%)	17 (8.5%)	11 (5.9%)	60 (7.5%)
EOT	2 (1.0%)	4 (1.9%)	4 (2.0%)	2 (1.1%)	12 (1.5%)

Source: Reviewer Table

Table 32: Responder Rates Using a Carry Forward Approach for Missing Data

	Study 06 (N=409)			Study 07 (N=388)		
	Ceftaroline N=200 # (%)	**Vancomycin + Aztreonam N=209** # (%)	**Difference (95% CI)**	**Ceftaroline N=200** # (%)	**Vancomycin + Aztreonam N=188** # (%)	**Difference (95% CI)**
Day 2	124 (62.0)	114 (54.5)	7.5 (-2.6, 17.5)	131 (65.5)	117 (62.2)	3.3 (-6.8, 13.3)
Day 3	**148 (74.0)**	**137 (65.6)**	**8.4 (-0.9, 17.8)**	**149 (74.5)**	**129 (68.6)**	**5.9 (-3.6, 15.4)**
Day 4	158 (79.0)	162 (77.5)	1.5 (-7.0, 10.0)	166 (83.0)	134 (71.3)	11.7 (2.9, 20.5)
Day 5	166 (83.0)	164 (78.5)	4.5 (-3.6, 12.6)	169 (84.5)	144 (76.6)	7.9 (-0.5, 16.3)

Source: Reviewer Table

Table 33: Age and Diabetes in Patients by Fever Status at Baseline

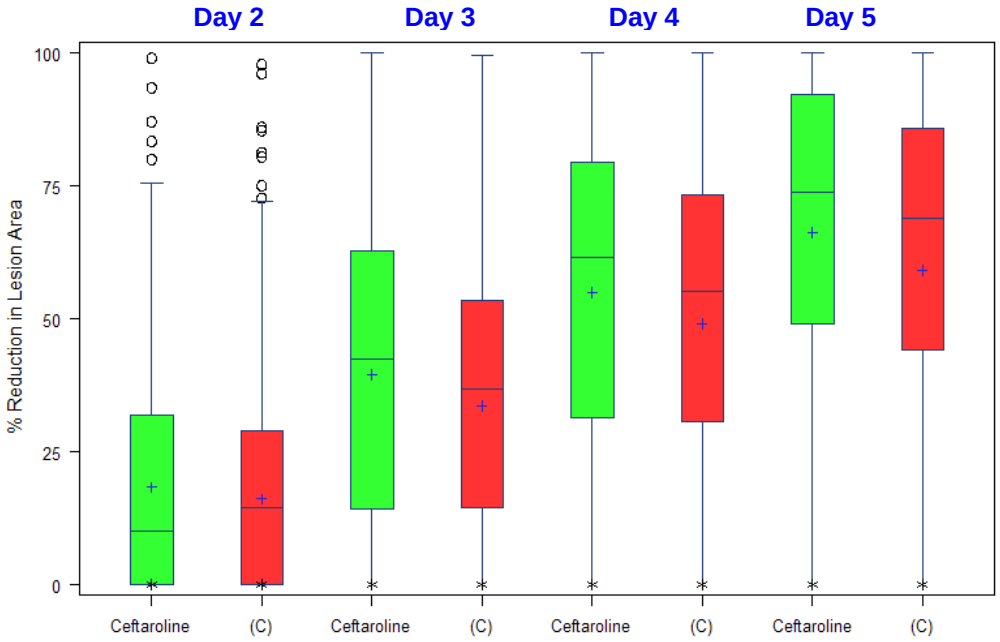
Study 06	**Ceftaroline (n=200)**		**Comparator (n=209)**		**Total (N=409)**	
Baseline fever?	**Yes (n=88)**	**No (n=112)**	**Yes (n=91)**	**No (n=118)**	**Yes (n=179)**	**No (n=230)**
Age:						
Mean ± std	45.8 ± 16.3	47.3 ± 18.1	46.7 ± 16.9	49.4 ± 16.9	46.3 ± 16.6	48.4 ± 17.5
Median	47.0	48.0	46.0	49.0	46.0	48.0
> 65 yrs, n (%)	11 (12.5)	21 (18.8)	16 (17.6)	20 (16.9)	27 (15.1)	41 (17.8)
> 75 yrs, n (%)	4 (4.5)	9 (8.0)	4 (4.4)	10 (8.5)	8 (4.5)	19 (8.3)
Diabetes, n (%):	14 (15.9)	15 (13.4)	16 (17.6)	31 (26.3)	30 (16.8)	46 (20.0)

Study 07	**Ceftaroline (n=200)**		**Comparator (n=188)**		**Total (N=388)**	
Baseline fever?	**Yes (n=82)**	**No (n=118)**	**Yes (n=88)**	**No (n=100)**	**Yes (n=170)**	**No (n=218)**
Age:						
Mean ± std	46.3 ± 13.8	47.7 ± 18.4	49.3 ± 14.8	46.4 ± 17.1	47.9 ± 14.4	47.1± 17.8
Median	45.5	45.5	50.5	46.5	48.0	46.0
> 65 yrs, n (%)	7 (8.5)	23 (19.5)	10 (11.4)	12 (12.0)	17 (10.0)	35 (16.1)
> 75 yrs, n (%)	3 (3.7)	10 (8.5)	3 (3.4)	7 (7.0)	6 (3.5)	17 (7.8)
Diabetes, n (%):	9 (11.0)	24 (20.3)	10 (11.4)	19 (19.0)	19 (11.2)	43 (19.7)

Source: Reviewer Table

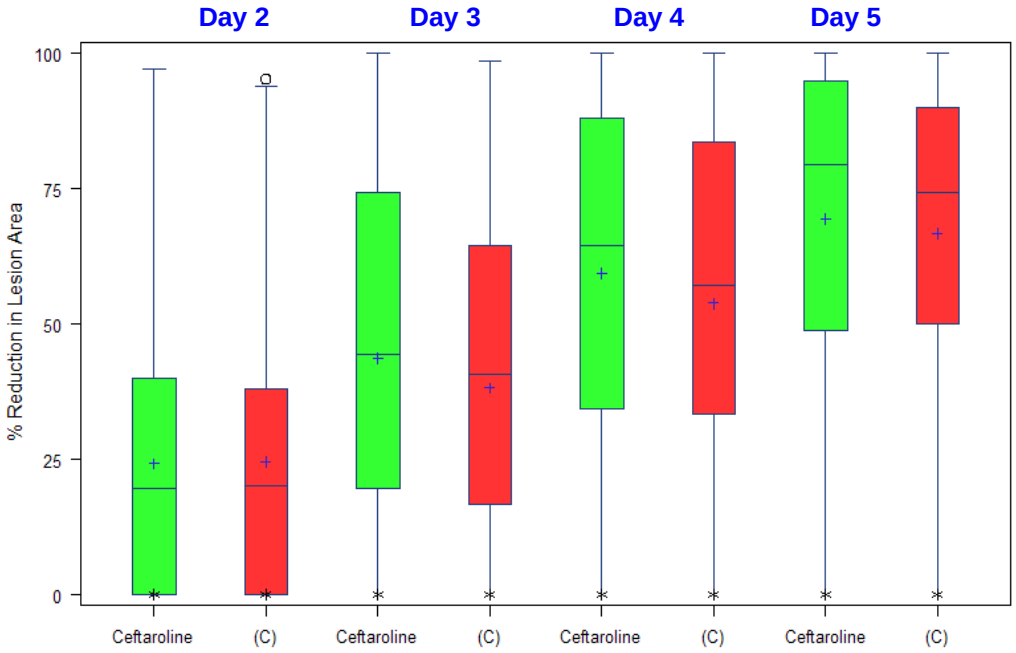
Exploratory/Sensitivity Analyses for Cessation of Spread (Figures)

Figure 15: % Reduction in Lesion Area- Study 06



Source: Reviewer Figure

Figure 16: % Reduction in Lesion Area- Study 07



Source: Reviewer Figure

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Christopher Kadoorie, Ph.D.

Date: 10/08/2010

Concurring Reviewer: Thamban Valappil, Ph.D, Statistical Team Leader

cc:
Project Manager/ Carmen DeBellas, Pharm. D.
Medical Team Leader/Janice Pohlman, M.D., M.P.H.
Medical Reviewer/Neil Rellosa, M.D.,
Deputy Division Dir/ Katherine Laessig, M.D.
Division Dir/ Wiley Chambers, M.D.
Primary Statistical Reviewer/ Christopher Kadoorie, Ph.D.
Statistical Team Leader/ Thamban Valappil, Ph.D.
Biometrics Deputy Division Director/ Daphne Lin, Ph.D.
Biometrics Division Director/ Mohammad Huque, Ph.D.
Mathematical Statistician/Lillian Patrician M.S., M.B.A.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTOPHER E KADOORIE
10/08/2010

THAMBAN I VALAPPIL
10/08/2010

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	200327
Drug Name:	Teflaro™ (ceftaroline fosamil for injection)
Indication:	Community-acquired bacterial pneumonia
Applicant:	Cerexa, Inc. (a subsidiary of Forest Laboratories, Inc.)
Stamp Date:	December 30, 2009
PDUFA Goal Date:	October 30, 2010
Reviewer Completion Date:	September 30, 2010
Review Priority:	Standard
Biometrics Division:	Division of Biometrics IV
Medical Division:	Division of Anti-Infective and Ophthalmology Products
Data Sources:	\\CDSESUB1\EVSPROD\NDA200327
Statistical Reviewer:	Daniel Rubin, Ph.D.
Concurring Reviewer(s):	Thamban Valappil, Ph.D.
Clinical Reviewer:	Ariel Porcalla, M.D.
Clinical Team Leader:	Janice Pohlman, M.D.
Project Manager:	Carmen DeBellas, Pharm.D.

TABLE OF CONTENTS

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The Applicant Cerexa, Inc. is seeking approval of the new cephalosporin antibiotic ceftaroline for the treatment of community-acquired bacterial pneumonia (CABP). The submission is based on the results of two phase 3 clinical trials comparing ceftaroline to ceftriaxone, another antibiotic in the cephalosporin class. Both studies were non-inferiority trials that used as a primary endpoint an investigator-assessment of clinical cure, at the test-of-cure visit 8-15 days after the end of 5-7 days of therapy. Prespecified non-inferiority goals were met in both trials, and numerical trends in the results favored ceftaroline over ceftriaxone. However, the main statistical issue was that between the time of study completion and the Applicant's submission, the scientific viewpoint of FDA reviewers had evolved, and the Applicant's 10% non-inferiority margin for the test-of-cure endpoint was no longer considered justifiable. Therefore, FDA reviewers assessed whether the totality of evidence still provided substantiation of efficacy, in light of concerns about the adequacy of the prespecified endpoint and margin justification.

Based on conducting a responder analysis by defining a signs and symptoms endpoint at an earlier time than the test-of-cure, and conducting several other additional analyses, this reviewer concluded that ceftaroline demonstrated non-inferiority to ceftriaxone for the treatment of CABP. Nevertheless, although the two trials provided evidence of efficacy, the FDA reviewers' responder analysis had several important limitations that are discussed in this document.

The safety review of ceftaroline was performed by the medical reviewer Dr. Ariel Porcalla, who found that the drug had a similar safety profile to other cephalosporin antibiotics.

An FDA anti-infective advisory committee was convened on September 7, 2010 to discuss the application. Based on the FDA reviewers' responder analysis and other considerations, the committee voted 21-0 that ceftaroline was safe and effective for the treatment of CABP.

The labeling of ceftaroline should make clear that the two trials enrolled subjects who were not at high risk for mortality, and that there were limited patients enrolled from the United States. It should also clearly state that ceftaroline was not shown to be superior to ceftriaxone, but only non-inferior to ceftriaxone. Finally, the labeling should note that virtually no subjects with methicillin-resistant *Staphylococcus aureus* (MRSA) were enrolled in the two clinical trials.

1.2 Brief Overview of Clinical Studies

Ceftaroline has shown in vitro activity against typical pathogens implicated in community-acquired pneumonia, as well as in vitro activity against methicillin-resistant *Staphylococcus aureus* (MRSA). The drug has been tested in phase 1 trials of healthy volunteers, and in a phase 2 trial of subjects with bacterial skin infections.

The phase 3 trials under review were randomized, double-blind, multicenter, multinational, non-inferiority studies of subjects with community-acquired bacterial pneumonia. The trials were designed to evaluate whether ceftaroline was or was not unacceptably worse than a comparator

antibiotic, ceftriaxone. The two clinical trials had similar protocols. Subjects were randomly assigned to ceftaroline or ceftriaxone, which was then given intravenously for 5-7 days with no allowed switch to oral therapy. The one major difference between the two trials was that in the first study, two adjunctive doses of oral clarithromycin were given to all subjects.

Subjects enrolled in the studies needed to have radiographically-confirmed pneumonia, as well as certain signs and symptoms of the disease. The inclusion criteria also required subjects to be in PORT Risk Class III or IV, but this requirement was based on an amendment while the studies were not yet completed, so some enrolled subjects were in other risk classes. Exclusion criteria also limited subjects to at most one dose of a short-acting systemic antimicrobial drug in the 96 hours prior to randomization.

The prespecified primary analysis was to compare clinical cure rates at the test-of-cure among subjects assigned to ceftaroline or ceftriaxone, using a non-inferiority margin of 10%. In both studies non-inferiority testing was conducted in two co-primary analysis populations: the Modified Intent-to-Treat Efficacy (MITTE) population containing subjects in PORT Risk Class III-IV who received any amount of study drug, and the Clinically Evaluable (CE) population containing MITTE subjects who sufficiently complied with the protocol. These populations had their own limitations, as they included subjects who did not have microbiological confirmation of bacterial pathogens, and the CE population did not have randomization protection.

1.3 Statistical Issues and Findings

1.3.1 Applicant's Prespecified Primary Analysis

Clinical response rates at the test-of-cure in the two trials were as follows for the co-primary MITTE population (subjects in PORT Risk Class III-IV who received any study drug) and CE population (MITTE subjects who sufficiently complied with the protocol):

Table 1: Clinical Cure Rates at Test-of-Cure Visit; MITTE and CE Populations

Study P903-08	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)
Study P903-09	Ceftaroline	Ceftriaxone	Difference (95% CI)
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 reviewer. Nine subjects excluded from Study P903-09 for reasons of data integrity.

These results showed that the prespecified 10% non-inferiority margin was met in both studies for each of the two co-primary analysis populations. Nevertheless, this reviewer did not consider these results alone to provide substantial evidence of efficacy. The two trials were non-inferiority studies, and the Applicant did not provide FDA reviewers with historical data that supported a non-inferiority margin for the late test-of-cure endpoint. The Applicant's margin justification relied on data showing an antibiotic treatment effect for mortality, and extrapolating that effect to clinical response. But, non-inferiority margins cannot necessarily be extrapolated across endpoints. The problem with an endpoint at the test-of-cure 8-15 days after the end of 5-7

days of therapy was that there was no historical data to quantify a treatment effect, and there may have been spontaneous resolution by such a late time, so this endpoint may not have been able to differentiate an effective antibiotic from an ineffective one without a superiority finding.

1.3.2 Mortality Results

Observed mortality rates were relatively low the two trials, which raised uncertainties about the severity of subjects in comparison to historical data. The strongest historical evidence for an antibiotic treatment effect is for an effect on reducing mortality in patients with pneumococcal pneumonia or lobar pneumonia likely to be caused by *S. pneumoniae,* and the most important public health benefit of antibiotic therapy for pneumonia is in its ability to prevent death. Community-acquired pneumonia remains a leading cause of mortality in the United States, particularly among the elderly. However, because of exclusion criteria, subjects in the two trials under review were not generally at risk of death.

Table 2: 30-Day All-Cause Mortality; MITTE Population

Study	Ceftaroline	Ceftriaxone	Odds Ratio (Exact 95% CI)
Study P903-08	4/291 (1.4)	5/300 (1.7)	0.82 (0.16, 3.86)
Study P903-09	7/284 (2.5)	5/269 (1.9)	1.33 (0.36, 5.40)

Data Source: FDA reviewer. Nine subjects excluded from Study P903-09 for reasons of data integrity.

1.3.3 Margin Examination Using Daptomycin Trials

This reviewer made an initial assessment of efficacy by re-examining the non-inferiority margin for the prespecified clinical response endpoint. This margin analysis used two CABP trials of the ceftriaxone comparator and daptomycin, which was later found to have been unexpectedly deactivated. As daptomycin may have still had some antimicrobial activity, a treatment effect for ceftriaxone over daptomycin was considered conservative for an effect over the (not included) placebo, which is what was needed for a margin. The daptomycin trials had similar designs to the ceftaroline trials, and used clinical response at the test-of-cure as the primary endpoint. The table below shows results in pooled trials of daptomycin and ceftriaxone.

Table 3: Clinical Cure Rates at TOC; Pooled Daptomycin Studies; ITT Population

	Ceftriaxone	Daptomycin	Difference (95% CI)
PORT I-IV			
All ITT subjects	326/421 (77.4)	293/413 (70.9)	6.5 (0.6, 12.4)
No long-acting prior therapy	270/337 (80.1)	236/328 (72.0)	8.2 (1.7, 14.6)
No prior therapy	190/234 (81.2)	154/221 (69.7)	11.5 (3.6, 19.4)
PORT III-IV			
All ITT subjects	178/236 (74.4)	164/247 (66.4)	9.0 (0.9, 17.0)
No long-acting prior therapy	**145/183 (79.2)**	**131/195 (67.2)**	**12.1 (3.1, 20.8)**
No prior therapy	101/124 (81.5)	88/136 (64.7)	16.7 (6.0, 27.1)

Data Source: FDA reviewer.

A margin justification for the ceftriaxone comparator was needed for the group of subjects in PORT Risk Class III-IV who were given no long-acting prior antibiotics, corresponding to the prespecified primary analysis population for the two ceftaroline studies. A random effects meta-analysis of the two daptomycin studies yielded an estimated ceftriaxone control effect (M1) of 3%, and a non-inferiority margin (M2) of 1.5% based on a 50% preservation fraction. While this resulting margin was small, the 95% confidence intervals in the co-primary MITTE analysis of the two ceftaroline studies both suggested that the clinical cure rate for ceftaroline was at most 1% worse than the ceftriaxone rate. Hence, this reviewer considered whether this margin analysis provided enough of a buffer to aid the interpretation of efficacy for ceftaroline; the daptomycin studies suggested at least a small treatment effect for the ceftriaxone comparator, and ceftaroline did not seem to lose much if any of this treatment effect.

Unfortunately, this analysis had significant limitations. It was post-hoc and exploratory, and the 3% control (ceftriaxone) effect over putative placebo (daptomycin) was so small that it may not have been robust to uncertainties in the justification process. Therefore, this reviewer concluded that this margin analysis could only provide supportive evidence of efficacy for ceftaroline.

1.3.4 FDA Reviewers' Day 4 Responder Analysis

Based on the current thinking of FDA reviewers regarding an antibiotic treatment effect on signs and symptoms of the disease, the strongest historical evidence is for an effect relatively early in the course of therapy, such as from Days 3-5 in the treatment course. FDA reviewers concluded that an early endpoint was most appropriate for CABP trials, because spontaneous resolution was less of a factor at an early time, facilitating the differentiation of effective and ineffective antibiotics. Therefore, FDA reviewers assessed efficacy by defining an early endpoint at Day 4 in terms of signs and symptoms of disease that were measured on case report forms. To be considered a responder at Day 4, a subject had to meet two sets of criteria. First, he or she had to be in stable condition according the following consensus treatment guidelines of the Infectious Diseases Society of America and the American Thoracic Society:

- Temperature $\leq$ 37.8°C
- Heart rate $\leq$ 100 beats/min
- Respiratory rate $\leq$ 24 breaths/min
- Systolic blood pressure $\geq$ 90 mm Hg
- Oxygen saturation $\geq$ 90%
- Normal mental status

Second, by Day 4 a responder needed to show improvement from baseline values on at least one of the following four symptoms, while not worsening from baseline of any of these symptoms:

- Cough
- Dyspnea
- Pleuritic chest pain
- Sputum production

Furthermore, the FDA reviewers' responder analysis was conducted in a population of subjects (the FDA-mITT population) that required microbiologically-confirmed bacterial pneumonia.

Patients were required to have adequate specimens for at least one of the following organisms: *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pyogenes, Staphylococcus aureus, Klebsiella pneumoniae, Citrobacter freundii* complex, *Citrobacter koseri*, *Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Proteus mirabilis, Serratia liquefaciens, Serratia marcescens.*

Results of the FDA reviewer's responder analysis using a Day 4 signs and symptoms endpoint and microbiological intent-to-treat population provided evidence of efficacy, as differences in response rates favored ceftaroline and lower confidence limits were sufficiently close to zero.

Table 4: Responder Rates for Day 4 Signs and Symptoms Endpoint; FDA-mITT

Day 4 Signs/Symptoms	Ceftaroline	Ceftriaxone	Difference (95% CI)
Study P903-08	48/69 (69.6)	42/72 (58.3)	11.2 (-4.6, 26.5)
Study P903-09	58/84 (69.0)	51/83 (61.4)	7.6 (-6.8, 21.8)

Data Source: FDA reviewer. One subject excluded from Study P903-09 FDA-mITT for reasons of data integrity.

To assess the sensitivity of conclusions to the choices made in defining the responder analysis, results were also examined when modifying the definition of the signs and symptoms endpoint, the timing of assessment, and the analysis population. This reviewer found results to be relatively robust to such modifications.

1.3.5 Day 3 Symptoms Endpoint and Biomarker Concern

The symptom improvement criteria involving cough, dyspnea, chest pain, and sputum production that was used in the FDA reviewers' responder analysis was unofficially suggested by members of a working group of the Biomarkers Consortium of the Foundation for the National Institute of Health. In fact, group members recommended that CABP trials only use these symptom criteria for the primary analysis, and not use vital signs or clinician assessments. The arguments were that vital signs were biomarkers that did not directly capture how a patient felt, functioned, or survived, that they had not been validated as surrogate endpoints, and that clinician assessments were themselves often influenced by such biomarkers. Additionally, the FNIH group unofficially recommended assessing the symptoms-based endpoint at Day 3 rather than Day 4 of therapy. In view of the biomarker argument, this reviewer examined the Day 3 symptoms endpoint in the same microbiological intent-to-treat population (the FDA-mITT population) used for the FDA reviewers' responder analysis.

Table 5: Responder Rates for Day 3 Symptoms Endpoint; FDA-mITT Population

Day 3 Symptoms	Ceftaroline	Ceftriaxone	Difference (95% CI)
Study P903-08	63/69 (91.3)	58/72 (80.6)	10.7 (-0.8, 22.6)
Study P903-09	70/84 (83.3)	69/83 (83.1)	0.2 (-11.4, 11.8)

Data Source: FDA reviewer. One subject excluded from Study P903-09 FDA-mITT for reasons of data integrity.

Results in Study P903-08 favored ceftaroline and approached superiority findings, but evidence of efficacy was not seen in Study P903-09 when using this early symptoms-based endpoint. This review also discusses results for the early symptoms endpoint in different analysis populations and under various modifications.

2. INTRODUCTION

2.1 Overview

Ceftaroline is an antibiotic developed by the biopharmaceutical company Cerexa, Inc., which in the class of antibiotics known as cephalosporins. These drugs work by inhibiting bacterial cell wall synthesis during cell division. Ceftaroline fosamil is the water-soluble prodrug of the bioactive ceftaroline. Ceftaroline has shown in vitro activity against both Gram-positive and Gram-negative pneumonia pathogens, but it does not have activity against the atypical pathogens *Legionella pneumophila*, *Chlamydophila pneumoniae*, or *Mycoplasma pneumoniae*. It also does not have activity against *Pseudomonas aeruginosa*, a common pathogen in hospital-associated pneumonia, and ceftaroline can be deactivated by extended-spectrum beta-lactamase (ESBL) produced by Enterobacteriaceae. Although ceftaroline has shown in vitro activity against methicillin-resistant *S. aureus* (MRSA), suspected MRSA subjects were excluded from the two clinical studies of pneumonia, and there were virtually no MRSA cases in either of the two trials under review. The safety and tolerability of the drug has been examined in phase 1 studies, and also in a phase 2 study of subjects with skin infections.

This review assessed the evidence of efficacy in two phase 3 non-inferiority trials that compared ceftaroline to a control antibiotic, ceftriaxone, for the treatment of community-acquired bacterial pneumonia. The main issue in the application was that after the studies were completed, the thinking of FDA reviewers had evolved regarding the acceptability of the primary endpoint. Hence, this reviewer assessed whether the totality of evidence in the application still provided substantiation of efficacy. As part of this assessment, this reviewer defined and examined another efficacy endpoint. This reviewer also examined two community-acquired pneumonia trials evaluating the ceftriaxone comparator and daptomycin, to see if these could quantify the control (ceftriaxone) treatment effect to justify a meaningful non-inferiority margin.

2.2 Community-Acquired Bacterial Pneumonia

Bacterial pneumonia is a lower respiratory tract infection caused by a bacterial pathogen. Community-acquired bacterial pneumonia (CABP) refers to bacterial pneumonia in individuals who have not recently been hospitalized, differentiating it from hospital-associated pneumonia. The disease is a leading cause of death in the United States, especially among elderly patients. The "bacterial" in CABP refers to the fact that pneumonia can also be caused by other sources, such as viruses or fungi. Diagnostics for pneumonia do not have perfect sensitivity or specificity. Diagnoses can utilize radiography (e.g., chest X-rays) as well as signs and symptoms such as cough or fever. The specificity of bacterial pneumonia diagnoses can be enhanced by using microbiological evidence, such as from blood or sputum cultures, which can identify the bacterial pathogen. Bacterial pneumonia is caused by both Gram-positive pathogens (e.g., *S. pneumoniae, S. aureus*) and Gram-negative pathogens (e.g., *H. influenzae, K. pneumoniae*). The severity and mortality risk of a patient presenting with pneumonia is often expressed through a Pneumonia Outcomes Research Team score, known as a PORT score, which has five risk classes ranging from the least severe Risk Class I to the most severe Risk Class V. The PORT score is determined algorithmically by demographics, comorbidities, physical examination results, and other factors. Bacterial pneumonia is treated with antibiotics, for durations that can last from

five days to two weeks. For moderate or severe pneumonia, this usually requires intravenous therapy. Placebo-controlled clinical trials are considered unethical when evaluating new therapies for community-acquired pneumonia.

2.3 Specific Trials Reviewed

The two phase 3 CABP trials reviewed were Study P903-08 and Study P903-09. Both had similar designs and protocols, and they took place over 2007 and 2008. Each was a randomized, double-blind, multicenter, multinational, two-arm non-inferiority trial. The comparator drug in both studies was ceftriaxone, another cephalosporin antibiotic that is commonly used for treating CABP. Both trials enrolled slightly over 600 total subjects, used 1:1 randomization, and treated patients with 5-7 days of intravenous therapy. In both trials, the primary objective was to show that ceftaroline was non-inferior to ceftriaxone in terms of clinical cure rates, based on a non-inferiority margin of 10%. The major difference between the two trials was that all subjects in Study P903-08 were given two doses of adjunctive clarithromycin, an antibiotic in the macrolide class with activity against atypical pathogens not covered by cephalosporins. Because clarithromycin also had activity against some typical CABP pathogens, a concern was that it could potentially mask inferiority of the investigational drug.

2.4 Data Sources

The clinical study reports and datasets can be found at the following location:
\\CDSESUB1\EVSPROD\NDA200327

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design

The two CABP studies considered in this review were phase 3, multicenter, multinational, 1:1 randomized, double-blind, active-controlled non-inferiority trials of IV ceftaroline fosamil versus IV ceftriaxone, given for 5-7 days. No switches to oral therapy were allowed. Two adjunctive doses of oral clarithromycin (500 mg q12h) were administered to subjects in Study P903-08, but not in Study P903-09. The studies both had slightly over 300 subjects randomized to each treatment arm. Except for the adjunctive clarithromycin, Study P903-08 and Study P903-09 had almost identical designs in terms of sample sizes, inclusion and exclusion criteria, comparators, and endpoints. Hence, this reviewer's summaries will apply to both trials. Much of the wording used to describe the designs comes from the Applicant's study reports.

3.1.1.1 Inclusion and Exclusion Criteria

Subjects were males and females 18 or more years of age requiring initial hospitalization for pneumonia, or treatment in an emergency room or urgent care setting by the standard of care, with an infection requiring initial treatment with IV antimicrobials. Bacterial pneumonia was diagnosed through the following criteria:

Radiographically confirmed pneumonia (new or progressive pulmonary infiltrate(s) on chest radiograph [CXR] or chest computed tomography [CT] scan consistent with bacterial pneumonia)

AND

Acute illness (≤ 7 days' duration) with at least three of the following clinical signs or symptoms consistent with a lower respiratory tract infection:

- New or increased cough
- 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)
- Fever greater than 38°C oral (> 38.5°C rectally or tympanically) or hypothermia (< 35°C)
- 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

AND

PORT Risk Class III or IV.

Subjects with CABP suitable for outpatient therapy with an oral antimicrobial agent were excluded, as were subjects with confirmed or suspected respiratory tract infections attributable to sources other than CABP (e.g., hospital-associated pneumonia), subjects with noninfectious causes of pulmonary infiltrates (e.g., pulmonary embolism), and subjects with pleural empyema.

Because ceftaroline and ceftriaxone had no activity against atypical organisms *M. pneumoniae*, *C. pneumoniae*, or *Legionella pneumophila*, subjects were excluded if these pathogens were confirmed or suspected based upon the epidemiological context, or if *L. pneumophila* was confirmed at baseline through urinary antigen testing.

Microbiologically documented or suspected infection with a pathogen known to be resistant to ceftriaxone led to exclusion, as did epidemiological or clinical context suggesting such a pathogen. These pathogens included *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA). Epidemiological clues to potential MRSA infection included residence in a nursing home or assisted living facility, existence of an ongoing local MRSA infection outbreak, known skin colonization with MRSA, recent skin or skin structure infection due to MRSA, intravenous drug use, and concomitant influenza. Subjects with risk factors for MRSA infection who had a predominance of Gram-positive cocci in clusters on sputum Gram stains were also excluded.

Other exclusion criteria concerned safety (e.g., exclusion due to immediately life threatening conditions, severely impaired renal function, pregnancy) and standard items for clinical trials

(e.g., exclusion for previous participation in a ceftaroline study, unwillingness to adhere to the study-specific procedures and restrictions).

Subjects who had previous treatment with an antimicrobial for CABP within 96 hours of randomization could be included only if they received a single dose of an oral or IV short-acting antibiotic, or if there was both unequivocal clinical evidence of treatment failure following at least 48 hours of prior systemic therapy and isolation of an organism that was resistant to this therapy. Disallowed prior antibiotics were as follows:

Table 6: Prior Antibiotics Allowed; 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, Cefruoxime, Cephalexin, Loracarbef	Cefixime (400 mg), Ceftriaxone
Fluoroquinolones	
Ciprofloxacin, Norfloxacin	Gatifloxacin, Gemifloxacin, Grepafloxacin, Levofloxacin, Moxifloxacin, Sparfloxacin
Macrolides and Ketolides	
Clarithromycin, Erythromycin, Roxithromycin	Azithromycin, Clarithromycin XL (extended release), Dirithromycin, Telithromycin
Penicillins and Carbapenems	
Amoxicillin, Amoxicillin-Clavulanate, Amoxicillin-Sulbactam, Ampicillin, Ampicillin-Sulbactam, Dicloxacillin, Imipenem, Meropenem, Nafcillin, Oxacillin, Penicillin-G, Penicillin-V, Piperacillin, Piperacillin-Tazobactam, Ticarcillin-Clavulanate	Ertapenem, Penicillin-G, Benzathine/Procaine
Tetracyclines	
Doxycycline (100 mg), Minocycline, Tetracycline	Doxycycline (200 mg), Minocycline Extended Release
Other Antibiotics	
Clindamycin, Co-trimoxazole	

Source: Study P903-08, CSR, Appendix 2; Study P903-09; CSR Appendix 2.

3.1.1.2 Study Visits

The 1:1 randomization to ceftaroline or ceftriaxone arms was implemented with an interactive voice response system, and was stratified by country and PORT Risk Class.

Baseline confirmation of eligibility was to occur within 24 hours of the first dose of the study drug, and Day 1 was defined as the first day of study drug administration.

After the baseline visit, subjects were monitored throughout 5-7 days of therapy, subsequently had an end-of-therapy (EOT) visit, returned for a test-of-cure (TOC) visit 8-15 days later, and finally had a late follow-up (LFU) visit.

Table 7: Study Visits

Baseline	Study Drug Administration	End-of-Therapy (EOT) visit	Test-of-Cure (TOC) visit	Late Follow-up (LFU) visit
Confirmation of eligibility, and randomization	5-7 days of therapy with the study drug	Last day drug administered, or withdrawal time	8-15 days after the last dose of study drug	21-35 days after last dose of study drug

Source: Study P903-08, CSR, Table 9.5.1-1; Study P903-09, CSR, Table 9.5.1-1.

Investigators assessed signs and symptoms of pneumonia at different study visits. The vital signs assessed at all study visits except the late follow-up (LFU) visit were:

- Highest temperature of the day
- Heart rate
- Respiratory rate
- Systolic and diastolic blood pressure
- Oxygen saturation

The signs and symptoms of CABP assessed at all study visits were:

- 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, mild, moderate, severe)
- Sputum (presence, amount, change in character from baseline, purulence)

3.1.1.3 Dosing

Unless an adjustment was needed due to renal impairment, subjects in the ceftaroline arm received 600 mg IV q12h as two consecutive infusions of IV ceftaroline, at 300 mg infused over 30 (+/- 10) minutes q12h (+/- 2 hours) for 5-7 days. The 600 mg dose was split into two infusions was to maintain the blind. Subjects in the ceftriaxone arm received a dose of 1 g infused over 30 (+/- 10) minutes followed by an infusion of IV saline placebo infused over 30 (+/- 10) minutes q24 (+/- 2) hours for 5-7 days. The following table shows this dosing:

Table 8: Study Drug Dosing Overview; Dosing Without Adjustment for Renal Impairment

Treatment Group	First Daily Dose		Second Daily Dose	
	Infusion 1 30 (+/- 10) min	Infusion 2 30 (+/- 10) min	Infusion 1 30 (+/- 10) min	Infusion 2 30 (+/- 10) min
Ceftaroline	Ceftaroline (300 mg)	Ceftaroline (300 mg)	Ceftaroline (300 mg)	Ceftaroline (300 mg)
Ceftriaxone	Ceftriaxone (1 g)	Placebo	Placebo	Placebo

Source: Study P903-08, CSR, Table 9.4.1-1; Study P903-09, CSR, Table 9.4.1-1.

3.1.1.4 Concomitant Medication

Concomitant systemic antimicrobial agents, other than those listed as part of study drug therapy, were not permitted. Probenecid was not allowed within three days before dosing with study drug therapy or during administration of the study drug. All other concomitant medications were allowed.

3.1.1.5 Applicant's Primary Endpoint

The prespecified primary endpoint in Study P903-08 and Study P903-09 was an investigator assessment of clinical response at the TOC visit. Clinical response was classified by the investigator as *Clinical Cure, Clinical Failure, or Indeterminate*. This investigator assessment was also made at the EOT visit. A *Clinical Failure* at the EOT was carried forward to the TOC. In both studies, all subjects who were classified as *Clinical Cure* at the TOC were also classified as *Clinical Cure* at the EOT. Equivalently, all subjects who were not *Clinical Cures* at the EOT were not *Clinical Cures* at the TOC. The protocol-defined clinical response was programmed to be *Clinical Failure* for subjects who died at any time up to and including the TOC visit, or up to and including 28 days after the EOT for subjects without a clinical response assessment at the TOC. In the clinical response assessments at the EOT and TOC, subjects were considered clinical cures if they had total resolution of signs and symptoms of the baseline infection, or improvement of the infection to such an extent that no further antimicrobial therapy was necessary. Improvement required the absence of fever (temperature ≤ 38°C oral or ≤ 38.5°C rectally or tympanically) for at least 24 continuous hours with temperature recorded twice daily, in addition to a substantial improvement in signs and symptoms of CABP. This substantial improvement required a return to pre-CABP baseline levels for subjects with decreased pulmonary function (e.g., subjects with COPD).

Table 9: Clinical Response Categories

Outcome	Definition
Clinical Cure	Total resolution of all signs and symptoms of pneumonia, or improvement such that further antimicrobial therapy was not necessary.
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.

Source: Study P903-08, CSR, Table 9.5.2.2.1-1; Study P903-09, CSR, Table 9.5.2.2.1-1.

3.1.1.6 Radiographic Outcomes

Radiographic assessments were also made at baseline, the TOC visit, and the LFU visit. These were performed at the study site by a local radiologist, and subjects were classified as *Radiographic Success*, *Radiographic Failure*, or *Indeterminate*.

3.1.1.7 Microbiological Outcomes

For subjects with a baseline CABP pathogen identified, a microbiological outcome at the TOC visit was derived using electronic microbiology data from a central laboratory and from pathogen information 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*.

3.1.1.8 Applicant's Analysis Populations

The Applicant defined the following seven populations, including the co-primary Modified Intent-to-Treat Efficacy (MITTE) and Clinically Evaluable (CE) populations:

Table 10: Study Populations

Population	Description of Analysis Population
ITT	Intent-to-Treat. All randomized subjects.
MITT	Modified Intent-to-Treat. All randomized subjects who received any amount of study drug.
MITTE	Modified Intent-to-Treat Efficacy (**co-primary population**). All MITT subjects in PORT Risk Class III or IV at baseline.
CE	Clinically Evaluable (**co-primary population**). All subjects in the MITTE population who met the inclusion criteria for CABP and all evaluability criteria, including subjects who received at least the prespecified minimal amount of the intended dose and duration of study drug therapy, for whom sufficient information regarding the infection was available to determine the subject's outcome. Subjects with *M. pneumoniae* or *C. pneumoniae* as the sole causative pathogen of infection, and all subjects with *L. pneumophila* infections were excluded from the CE population.
mMITT	Microbiological Modified Intent-to-Treat. All subjects in the MITT population who met the inclusion criteria for CABP, and had at least one typical bacterial organism consistent with a CABP pathogen identified from a microbiological specimen (e.g., blood, sputum, or pleural fluid). Subjects with *M. pneumoniae* or *C. pneumoniae* as the sole causative pathogen of infection, and all subjects with *L. pneumophila* infections were excluded from the mMITT population.
mMITTE	Microbiological Modified Intent-to-Treat Efficacy. All subjects in the mMITT population in PORT Risk Class III or IV at baseline.
ME	Microbiologically Evaluable. All subjects in both the CE and mMITTE populations.

Source: Study P903-08, CSR, Section 9.7.1.1; Study P903-09, CSR, Section 9.7.1.1.

Because dropping out before receiving any study drug would not normally be related to any aspect of the therapy in a blinded study, this reviewer considered the ITT, MITT, MITTE, mMITT, and mMITTE populations to have the protection of randomization, in that differences in outcomes could be attributed to treatment or chance, and not to confounding by other factors. This reviewer did not consider the CE population to be protected from confounding by

randomization, as subjects were excluded due to post-baseline events. This review therefore focuses on the MITTE population when describing the Applicant's prespecified results.

3.1.1.9 Applicant's Objectives

The primary objective in both trials was to determine whether ceftaroline was non-inferior to ceftriaxone in the co-primary MITTE and CE populations, in terms of clinical cure rates at the test-of-cure (TOC) visit.

Secondary objectives were to:

- Evaluate the clinical response at the end-of-therapy (EOT)
- Evaluate the microbiological success rate at the TOC
- Evaluate the overall (clinical and radiographic) success rate at the TOC
- Evaluate the clinical and microbiological response by pathogen at the TOC
- Evaluate clinical relapse at the LFU visit
- Evaluate microbiological reinfection/recurrence at the LFU visit
- Evaluate safety

3.1.1.10 Pathogen Identification

In Study P903-08 and P903-09, pathogens could be identified through the following means:

- Sputum samples for culture
- Pleural fluid samples for culture
- Blood cultures
- Blood samples for serology testing
- Urine samples for antigen testing

For defining which subjects belonged to the mMITT population, or the population with a microbiologically-confirmed CABP pathogen at baseline, the following organisms were always counted as typical CABP pathogens:

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

Aside from a list of organisms that were never to be counted as CABP pathogens (e.g., fungi, coryneform bacteria) other organisms were determined to be baseline CABP pathogens on a case-by-case basis via a blinded manual review by the Applicant.

3.1.2 Data Integrity

In Study P903-09, there were data integrity concerns with one investigator in India who enrolled seven subjects. Allegations of fraud had been made against the investigator in a different study.

In an inspection of the investigator's site, the Applicant could not locate any source documents, even though the contract research organization (CRO) had claimed 100% verification of source material. This CRO was responsible for two other Indian sites in Study P903-09 that enrolled two other total subjects.

Because this reviewer could not be certain of data integrity for the nine subjects enrolled at sites monitored by this CRO, these subjects are excluded from all analyses presented in this review.

3.1.3 Patient Disposition at Baseline

Baseline characteristics were examined in the co-primary MITTE population (all randomized subjects in PORT Risk Class III-IV who received any amount of study drug) to assess if the randomization balanced baseline factors over treatment arms. This reviewer also assessed patient severity, as subjects with mild cases can artificially make treatments appear similar.

The two arms appeared balanced on the baseline factors considered, and ages, PORT Risk Classes, and CABP signs and symptoms also appeared sufficient for non-inferiority trials.

Age is a risk factor for death in community-acquired pneumonia, and slightly under half of MITTE subjects were over 65 years old. Bacteremia is another important risk factor for mortality, but few subjects were bacteremic at baseline.

Most subjects were from Eastern Europe. The Applicant's study reports included Hungary and Poland as part of Western Europe, but this reviewer did not. The North American region only contained sites in the United States, but the number of sites was limited, and Study P903-09 had no sites in the US. The following table shows countries where subjects were enrolled.

Table 11: Countries of Study P903-08 and Study P903-09

Region	Countries
Africa	South Africa
Asia	India, Malaysia, Thailand
Eastern Europe	Bulgaria, Estonia, Georgia, Hungary, Latvia, Lithuania, Poland, Romania, Russia, Serbia, Ukraine
Latin America	Argentina, Brazil, Chile, Mexico, Peru
North America	United States
Western Europe	Austria, Germany, Switzerland

Source: Study P903-08, CSR, Section 11.1.1.4-1; Study P903-09, CSR, Section 11.1.1.4-1.

Slightly under half the enrolled subjects were given antibiotics in the 96 hours prior to randomization, although they were only allowed one dose of a short-acting antimicrobial. Most of these prior antibiotics were given within 24 hours of the first dose of study drug, presumably to begin treatment while consent was obtained for study enrollment. Ideally, subjects in non-inferiority trials would not have prior therapy. Common prior antibiotics were amoxicillin-clavulanic acid, cefotaxime, ciprofloxacin, and Unacid.

Around one-half of subjects had mild, moderate, or severe renal function, around one-fifth had COPD, and around one-half had ever smoked cigarettes.

Table 12: Baseline Disposition; MITTE Population

	Study P903-08		Study P903-09	
	Ceftaroline	Ceftriaxone	Ceftaroline	Ceftriaxone
Total Subjects	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 (98)	264 (98)
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)
50-64	74 (25)	81 (27)	96 (34)	92 (34)
≥ 65	143 (49)	148 (49)	130 (46)	132 (49)
PORT Risk Class				
III	190 (65)	182 (61)	168 (59)	169 (63)
IV	101 (35)	118 (39)	116 (41)	100 (37)
Bacteremia				
Yes	8 (3)	9 (3)	14 (5)	11 (4)
No	283 (97)	291 (97)	270 (95)	258 (96)
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 (79)	212 (79)
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 (5)	13 (5)
Prior Antibiotics				
Yes	137 (47)	143 (48)	95 (33)	113 (42)
No	154 (53)	157 (52)	189 (67)	156 (58)
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)
Lung Disease				
Yes	64 (22)	60 (20)	95 (33)	87 (32)
No	227 (78)	240 (80)	189 (67)	182 (68)
Smoking History				
Yes	156 (54)	141 (47)	148 (52)	144 (54)
No	135 (46)	159 (53)	136 (48)	125 (46)

Data Source: FDA reviewer. Nine subjects excluded from Study P903-09 for reasons of data integrity.
[1] Hungary and Poland were included in Eastern Europe by the Applicant and in Western Europe by this reviewer.

The next tables show the number of subjects in each of the prespecified analysis populations, as well as subjects with different bacterial pathogens. Few subjects were lost in moving from the ITT population (all randomized subjects) to the MITT population (subjects who received any amount of study drug), or the MITTE population (MITT subjects in PORT Risk Class III or IV). About three quarters of subjects met all evaluability criteria (CE population). Well under half of

subjects were in populations requiring microbiological pathogen confirmation (mMITT, mMITTE, ME).

Table 13: Sample Sizes of the Applicant's Analysis Populations

	Study P903-08		Study 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)

Data Source: FDA reviewer. Nine subjects excluded from Study P903-09 for reasons of data integrity.

Table 14: Subjects in mMITT Population with Various Baseline Pathogens

	Study P903-08		Study P903-09	
	Ceftaroline	Ceftriaxone	Ceftaroline	Ceftriaxone
Total Subjects	75	82	98	102
Chlamydophila pneumoniae	2 (3)	3 (4)	3 (3)	4 (4)
Citrobacter freundii complex	0 (0)	0 (0)	0 (0)	2 (2)
Citrobacter koseri	1 (1)	1 (1)	1 (1)	0 (0)
Enterobacter aerogenes	0 (0)	0 (0)	2 (2)	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)	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 (0)	2 (2)	0 (0)
Pseudomonas aeruginosa	1 (1)	0 (0)	3 (3)	2 (2)
Serratia liquefaciens	0 (0)	1 (1)	1 (1)	1 (1)
Serratia marcescens	3 (4)	2 (2)	0 (0)	1 (1)
Staphylococcus aureus	10 (13)	14 (17)	16 (16)	19 (19)
Streptococcus pneumoniae	27 (36)	30 (37)	47 (48)	44 (43)

Data Source: FDA reviewer. Nine subjects excluded from Study P903-09 for reasons of data integrity.

3.1.4 Applicant's Efficacy Results

3.1.4.1 Clinical Response at TOC and EOT

The Applicant's prespecified statistical procedure was to test for non-inferiority in primary, secondary, and tertiary analyses using the hierarchical method of Westfall and Krishen (2001), which controls the overall Type I error rate. Non-inferiority in TOC cure rates was first to be tested using a 10% margin in the co-primary MITTE population (all randomized subjects in PORT Risk Class III-IV receiving any study drug) and CE population (all MITTE subjects who met evaluability criteria). A two-sided 95% confidence interval for the observed difference in clinical cure rates (ceftaroline – ceftriaxone) was to be constructed using the method of Miettinen and Nurminen (1985), with non-inferiority concluded if the lower limit of the 95% confidence interval exceeded -10%. If non-inferiority was met in both the co-primary MITTE and CE populations, the next step was to test for non-inferiority in terms of clinical cure rates at the EOT in these two populations, again using a 10% margin. If non-inferiority was again met in both groups, the last step was to test for non-inferiority of ceftaroline in terms of favorable microbiological outcomes, using a 15% margin in the mMITT population. Although multiple tests were to be done, the hierarchical nature of the procedure ensured the probability of a false positive was controlled below $\alpha = 0.05/2 = 0.025$ in each study.

The Applicant met all prespecified non-inferiority goals in both studies, and numerical trends for (ceftaroline – ceftriaxone) differences in cure rates favored ceftaroline. The tables below show results for the Applicant's primary and secondary analyses of clinical cure rates in the co-primary MITTE and CE populations at the TOC and EOT.

Table 15: Study P903-08 Primary and Secondary Analysis; MITTE and CE Populations

Primary Analysis: Clinical Cure at TOC	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)
Secondary Analysis: Clinical Cure at EOT	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)

Data Source: Study P903-08, CSR, Table 11.1.1.1-1., 11.1.1.2.1-1.

Table 16: Study P903-09 Primary and Secondary Analysis; MITTE and CE Populations

Primary Analysis: Clinical Cure at TOC	Ceftaroline	Ceftriaxone	Difference (95% CI)
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)
Secondary Analysis: Clinical Cure at EOT	Ceftaroline	Ceftriaxone	Difference (95% CI)
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 reviewer. Nine subjects excluded from Study P903-09 for reasons of data integrity.

The lower confidence limits exceeded zero in some of these primary and secondary analyses, and this gave increased confidence in the treatment effect. However, a superiority claim was not possible, because this would have required replicated evidence of superiority over the two trials

and a further examination of the totality of evidence. The sequential testing also did not include an adjustment for superiority testing; when testing a single hypothesis for non-inferiority, there is no inflation of the Type I error rate to claim superiority if the lower confidence limit exceeds zero, but this is not necessarily true with hierarchical testing (Dmitrienko and Tamhane, 2007).

The following table shows clinical cure rates in the Applicant's microbiological (mMITT) population, containing only subjects with microbiologically-confirmed bacterial pneumonia.

Table 17: Clinical Cure Rates at TOC and EOT; mMITT Population

Study P903-08	Ceftaroline	Ceftriaxone	Difference (95% CI)
Clinical Cure at TOC	66/75 (88.0)	62/82 (75.6)	12.4 (0.2, 24.4)
Clinical Cure at EOT	66/75 (88.0)	64/82 (78.0)	10 (-2.0, 21.8)
Study P903-09	Ceftaroline	Ceftriaxone	Difference (95% CI)
Clinical Cure at TOC	78/98 (79.6)	78/102 (76.5)	3.1 (-8.5, 14.6)
Clinical Cure at EOT	81/98 (82.7)	82/102 (80.4)	2.3 (-8.7, 13.1)

Data Source: FDA reviewer. Nine subjects excluded from Study P903-09 for reasons of data integrity.

These microbiological ITT results also supported the efficacy of ceftaroline. The table below shows clinical response rates at TOC among subjects with different baseline pathogens. Clinical response rates were higher for ceftaroline than ceftriaxone among subjects with *S. pneumoniae*, but for the other baseline pathogens the numbers were too small for meaningful observations.

Table 18: Clinical Cure Rates at TOC by Baseline Pathogen; mMITT Population

	Study P903-08		**Study 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)	9/14 (64.3)	10/16 (62.5)	12/19 (63.2)
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 reviewer. Nine subjects excluded from Study P903-09 for reasons of data integrity.

Clinical cure rates were also examined by prior antibiotic use. Cure rates were higher for ceftaroline than ceftriaxone among subjects with no prior therapy, while rates were more similar among subjects given prior antibiotics. Although these were exploratory subgroups, the apparent effect modification in this direction was a finding that supported the efficacy of ceftaroline.

Table 19: Clinical Cure Rates at TOC by Prior Antibiotic Use; MITTE Population

Study P903-08	Ceftaroline	Ceftriaxone	Difference (95% CI)
Prior Antibiotics	105/137 (76.6)	112/143 (78.3)	-1.7 (-11.5, 8.1)
No Prior Antibiotics	139/154 (90.3)	121/157 (77.1)	13.2 (5.1, 21.4)
Study P903-09	Ceftaroline	Ceftriaxone	Difference (95% CI)
Prior Antibiotics	80/95 (84.2)	91/113 (80.5)	3.7 (-7.0, 14.0)
No Prior Antibiotics	151/189 (79.9)	112/156 (71.8)	8.1 (-0.9, 17.3)

Data Source: FDA reviewer. Nine subjects excluded from Study P903-09 for reasons of data integrity.

3.1.4.2 Mortality Results

Mortality rates were low in both CABP trials. Higher rates can be seen in observational studies, where rates can reach 20% among PORT V subjects. Studies P903-08 and P903-09 excluded subjects in PORT Risk Class V, subjects requiring ICU admission, subjects requiring multiple antibiotics, and subjects with life-threatening diseases such as sepsis or respiratory failure. The reason given by the Applicant for these exclusions was that such subjects may have required combination therapy. There is historical evidence for an antibiotic treatment effect on mortality, but mortality rates in the co-primary MITTE population were too low for meaningful efficacy inferences. Fleming and Powers (2008) recommended using a mortality endpoint for community-acquired pneumonia trials and a non-inferiority margin of 1.67 on the odds ratio scale, and ceftaroline did not meet this efficacy standard in either study.

Table 20: 30-Day All-Cause Mortality; MITTE Population

	Ceftaroline	Ceftriaxone	Odds Ratio (Exact 95% CI)
Study P903-08	4/291 (1.4)	5/300 (1.7)	0.82 (0.16, 3.86)
Study P903-09	7/284 (2.5)	5/269 (1.9)	1.33 (0.36, 5.40)

Data Source: FDA reviewer. Nine subjects excluded from Study P903-09 for reasons of data integrity.

Mortality rates were still low when restricting to subgroups generally considered to be at higher risk. The table below shows rates in the pooled CABP studies by age, bacteremic status, and PORT Risk Class. Mortality rates generally remained below 5% in both study arms among these groups at greater risk, and there were no deaths among subjects with bacteremia at baseline.

Table 21: 30-Day All Cause Mortality, Pooled CABP Studies; MITTE Population

Population	Ceftaroline	Ceftriaxone	Odds Ratio (Exact 95% CI)
All MITTE Subjects	11/575 (1.9)	10/569 (1.8)	1.09 (0.42, 2.89)
Age ≥ 75	5/130 (3.8)	7/128 (5.5)	0.69 (0.17, 2.61)
Baseline Bacteremia	0/22 (0.0)	0/20 (0.0)	N/A
PORT IV	6/217 (2.8)	7/218 (3.2)	0.86 (0.23, 3.04)

Data Source: FDA reviewer. Nine subjects excluded from Study P903-09 for reasons of data integrity.

3.1.4.3 Radiographic Results

Radiographic outcomes were concordant with the investigator-assessed clinical responses. The protocol in each study defined a subject as being an *Overall Success* if he or she was a clinical cure at the TOC and the radiographic response at the TOC was either *Radiographic Success* or *Indeterminate*. Using this stringent definition of an overall responder, only one MITTE subject in each study was reclassified from a success to a failure after incorporating radiographic results.

3.1.5 Review Issues and Additional Analyses

A non-inferiority trial is a study that examines whether a new drug is not unacceptably worse than a comparator drug based on a prespecified and justified non-inferiority margin. It differs from a superiority trial, in which the objective is to examine whether the new treatment is better

than a comparator, which most commonly is a placebo. Non-inferiority trials are common when evaluating new antibiotics in serious diseases, as placebo controls are often considered unethical.

Unfortunately, non-inferiority trials have several drawbacks. First, it is necessary to conservatively quantify a non-inferiority margin, or an amount by which the active control is superior to placebo on the primary endpoint. If it is known with near certainty that the active control drug is at least 15% better than placebo, and the non-inferiority trial establishes that the difference between the new treatment and active control is at most 5%, then the non-inferiority trial has provided indirect evidence of efficacy relative to placebo. However, if it is only known that the control is somewhere between 5-10% better than the placebo, then there is no evidence that the new treatment is any better than an inert substance.

The two principles that underpin the reliability of a non-inferiority trial are assay sensitivity and constancy. Assay sensitivity refers to the capability to differentiate effective from ineffective treatments based on the results of a clinical trial. The constancy assumption stipulates that the quantitative estimate of the active control – placebo treatment effect remains consistent from the historical to the contemporary NI trial, and is questionable when there are dissimilarities between the studies with respect to important design and conduct features. As NI trials lack placebo arms, data external to the trial that reliably and quantitatively estimate the magnitude of benefit of the active control drug compared to placebo are required.

In the case of pneumonia, the difficulty in justifying a non-inferiority margin is that antibiotics were discovered before randomized placebo-controlled trials were common. By the time randomized trials began to affect clinical practice, placebo-controls were considered unethical for treating pneumonia. Hence, there is a dearth of Level I evidence that can be used to justify a non-inferiority margin.

Non-inferiority trials also present another challenge. Protocol violations, unevaluable data, or enrollment of patients in mild condition tend to make treatment arms appear similar, which can mask inferiority of the investigational drug. For example, if many subjects have had prior effective therapy, or actually have viral pneumonia instead of bacterial pneumonia, then it will be difficult to differentiate an effective antibiotic from an ineffective one because outcomes will be similar under either drug. This is a key difference between superiority and non-inferiority trials: lax study conduct typically makes it difficult to meet objectives in a superiority trial, but perversely can make it easier to meet objectives in a non-inferiority trial.

The two CABP studies under review each used a 10% non-inferiority margin for a primary endpoint of investigator-assessed clinical response at the test-of-cure (TOC) visit, 8-15 days after the end of therapy. The current thinking of FDA reviewers is that historical data do not justify a margin when using such an endpoint. The Applicant's margin justification was based on extrapolating an antibiotic treatment effect for mortality to an effect on clinical response, but this extrapolation was not necessarily valid.

Historical data may provide evidence for an antibiotic treatment effect on improvement in patient signs and symptoms at a time earlier than 8-15 days after the end of therapy. Evidence for and against an early clinical response endpoint was discussed at the 12/09/2009 meeting of the

FDA's Anti-Infective advisory committee (Bullowa, 1937; Flippin et al., 1939; Meakins and Hanson, 1939; Wilson et al., 1939; Finland et al., 1940). When "historical data" or "historical studies" are mentioned in this document, this reviewer refers to these discussions.

In addition to examining ceftaroline results for the primary clinical response endpoint, this reviewer conducted several other analyses. First, to assess whether a small non-inferiority margin could be justified for the ceftriaxone comparator, two trials were examined that compared ceftriaxone to daptomycin for the treatment of pneumonia. Second, because historical evidence of an antibiotic treatment effect on clinical response was for an effect relatively early in the treatment course, FDA reviewers considered results when defining an endpoint earlier in the course of therapy than at the TOC or EOT.

3.1.6 Margin Examination Using Daptomycin Trials

Although historical evidence supporting a 10% non-inferiority margin for a clinical response endpoint at test-of-cure has not been identified, this reviewer conducted a post-hoc assessment of whether a small margin could be empirically justified. Placebo-controlled trials are considered unethical for CABP, but two recent trials compared ceftriaxone to daptomycin, which was later shown to have been deactivated by interaction with lung surfactant (Pertel et al., 2008). As daptomycin may still have had some antibacterial activity, this reviewer considered it as a conservative substitute for a placebo arm.

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

This reviewer's margin analysis with the daptomycin trials examined the same group of subjects used for the prespecified primary analysis in the ceftaroline trials: subjects in PORT Risk Class III-IV who were only allowed one dose of a short-acting systemic antimicrobial in the 96 hours prior to randomization.

To begin the margin analysis with daptomycin trials, FDA reviewers first classified prior antibiotic therapy as being long-acting or short-acting. Any prior therapy that was allowed for ceftaroline subjects (e.g., clarithromycin) was considered short-acting, while drugs that were disallowed (e.g., azithromycin, levofloxacin, ceftriaxone) were considered long-acting. Some prior CABP antibiotics administered in the daptomycin trials were not explicitly identified as

being allowed or disallowed. Of these, FDA reviewers only considered lincomycin to be a long-acting drug. Drugs not explicitly allowed or disallowed in the ceftaroline trials that were considered short-acting included cephalexin, cefazolin, ceftizoxime, and ofloxacin.

The tables below show results in the ITT population (subjects who received any study drug) in separate and pooled daptomycin trials, by PORT Risk Class and prior therapy.

Table 22: Clinical Cure Rates in DAP-00-05 and DAP-00-08, ITT Population

	Study DAP-00-05		Study DAP-00-08	
	Ceftriaxone	Daptomycin	Ceftriaxone	Daptomycin
PORT I-IV				
All ITT subjects	258/335 (77.0)	231/326 (70.9)	68/86 (79.1)	62/87 (71.3)
No long-acting prior therapy	212/261 (81.2)	179/248 (72.2)	58/76 (76.3)	57/80 (71.2)
No prior therapy	142/173 (82.1)	111/155 (71.6)	48/61 (78.7)	43/66 (65.2)
PORT III-IV				
All ITT subjects	128/175 (73.1)	131/192 (68.2)	50/61 (82.0)	33/55 (60.0)
No long-acting prior therapy	**103/130 (79.2)**	**101/145 (69.7)**	**42/53 (79.2)**	**30/50 (60.0)**
No prior therapy	68/84 (81.0)	67/95 (70.5)	33/40 (82.5)	21/41 (51.2)

Data Source: FDA reviewer.

Table 23: Clinical Cure Rates at TOC; Pooled Daptomycin Studies; ITT Population

	Ceftriaxone	Daptomycin	Difference (95% CI)
PORT I-IV			
All ITT subjects	326/421 (77.4)	293/413 (70.9)	6.5 (0.6, 12.4)
No long-acting prior therapy	270/337 (80.1)	236/328 (72.0)	8.2 (1.7, 14.6)
No prior therapy	190/234 (81.2)	154/221 (69.7)	11.5 (3.6, 19.4)
PORT III-IV			
All ITT subjects	178/236 (74.4)	164/247 (66.4)	9.0 (0.9, 17.0)
No long-acting prior therapy	**145/183 (79.2)**	**131/195 (67.2)**	**12.1 (3.1, 20.8)**
No prior therapy	101/124 (81.5)	88/136 (64.7)	16.7 (6.0, 27.1)

Data Source: FDA reviewer.

In attempting a margin justification, FDA reviewers combined the two trials using the DerSimonian and Laird (1986) random effects model. For subjects in PORT Risk Class III-IV given no long-acting prior antibiotics, this meta-analysis model gave an estimate of 12.1% for the ceftriaxone – daptomycin difference in clinical cure rates, with a 95% confidence interval of (3.2%, 20.1%). The lower limit of this interval therefore yielded a control effect (M1) of 3% for the clinical response endpoint. A fraction of M1 needed to be preserved based on clinical judgment to derive the NI margin. For example, a rule of thumb is to use 50% preservation, which resulted in a margin (M2) of 1.5%. While this resulting margin was small, the 95% confidence intervals of the co-primary MITTE analysis in Study P903-08 and Study P903-09 suggested that the clinical cure rate for ceftaroline was at most 1% worse than the ceftriaxone rate. Hence, this reviewer considered whether the margin analysis provided enough of a buffer to aid interpretation of the ceftaroline efficacy results.

3.1.7 Conclusions and Limitations of Margin Analysis

There were significant limitations in using daptomycin data to justify a non-inferiority margin. First, this was an attempted post-hoc justification performed by FDA reviewers, and non-inferiority trials traditionally require a prespecified and justified margin as part of the protocol. Clearly, the Type I error rate was not being controlled in this post-hoc margin analysis.

In addition, the Applicant's gatekeeping procedure for testing non-inferiority hypotheses did not appear to have the closed testing protection that would allow one to first meet a 10% NI margin, and then use a lower confidence limit to test for non-inferiority using a smaller margin, even if the smaller margin is justified. A sequential gatekeeping procedure can require a multiplicity adjustment for such testing (Dmitrienko and Tamhane, 2007).

Further, the idea to examine daptomycin subjects without long-acting prior therapy was based on the post-hoc subgroup analysis in Pertel et al. (2008), and such analyses are best considered exploratory.

Also, the control (ceftriaxone) effect of 3% that resulted was small, and large NI margins are more robust to uncertainties in the justification process.

Given the limitations, this reviewer concluded that the daptomycin studies could not be used to provide a rigorous, empirical justification of a non-inferiority margin for a clinical response endpoint at the test-of-cure. However, as an exploratory analysis, the daptomycin trials suggested at least a small treatment effect on clinical response for the ceftriaxone comparator, and ceftaroline did not seem to lose much if any of this effect. This reviewer therefore concluded the margin analysis provided indirect supportive evidence of efficacy for ceftaroline.

3.1.8 Day 4 Responder Analysis

Based on historical evidence for an antibiotic treatment effect at an early time in the course of therapy, FDA reviewers defined an early efficacy endpoint. The historical data concerning an antibiotic treatment effect supported the conclusion that patient signs and symptoms improved dramatically after several days of therapy. Finland et al. (1940) provided estimates of an effect on symptom resolution at 48-72 hours after therapy. Bullowa (1939), Flippin et al. (1939), and Meakins and Hanson (1939) gave estimates of a treatment effect for clinical recovery at Day 3. Wilson et al. (1939) estimated treatment effects for mean days to clinical improvement, fall in temperature, and clinical recovery of 2.5, 3.4, and 4.2 days. The FDA reviewers' responder analysis used an endpoint defined at Day 4, which was 72-96 hours after the first dose of the study drug. For most subjects this was halfway through the duration of therapy. FDA reviewers considered Day 4 to be in line with where the historical evidence showed the existence of an antibiotic treatment effect. In defining the Day 4 endpoint, FDA reviewers used a definition that combined sign and symptom measurements. Study P903-08 and Study P903-09 had no overall clinician assessment of patient well-being until the EOT, which for most subjects occurred on Day 7. Therefore, FDA reviewers defined the responder analysis endpoint directly in terms of the sign and symptom measurements available at Day 4 from the patient case report forms.

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

1. Clinical stability, as defined by the Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS) Consensus Guidelines for the Management of Community-Acquired Pneumonia in Adults. The IDSA/ATS criteria for clinical stability were as follows, and were primarily determined by vital signs:
   - 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 required the ability to maintain oral intake, and involved oxygen partial pressure in addition to oxygen saturation, but these were not captured on case report forms at Day 4. FDA reviewers defined normal mental status as confusion/disorientation being recorded as absent. The criteria were originally proposed as a guide for determining whether discharge or a switch to oral therapy were acceptable for CABP patients, and were based on time-to-stability studies of Halm et al. (1998).

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

   This symptom-based endpoint was unofficially recommended by members of a working group of the Biomarkers Consortium of the Foundation for the National Institutes of Health. To be classified as a responder at Day 4, a subject had to have improved from baseline on at least one of the four symptoms, and could not have worsened from baseline values on any of the four components. For cough, dyspnea, and chest pain, this was determined through investigator recordings of whether symptoms were absent, mild, moderate, or severe. For sputum, worsening or improvement was determined first by examining investigator assessments of whether sputum was present or absent at baseline and at Day 4, and if present on both days, then whether its character was recorded as worsened, unchanged, or improving from baseline.

Subjects were classified as failures if there were insufficient data on Day 4 to determine if the sign and symptom criteria were satisfied. The most common reason for missing Day 4 data was that the end-of-therapy visit occurred before this time. No subject with an EOT visit at Day 4 or earlier was classified by the investigator as a clinical cure. The impact of missing data on the results is discussed in more detail in Section 3.1.9.

In line with the recommendation of the 12/09/2009 Anti-Infective Drugs Advisory Committee, the population utilized for analysis (the FDA-mITT population) included only subjects with

microbiologically-confirmed bacterial pneumonia. The changes to the Applicant's prespecified microbiological population dealt with the list of acceptable pathogens and adequacy criteria for sputum samples. The FDA-mITT population included randomized patients who received any amount of study therapy and had demonstration of a baseline pathogen as follows:

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

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

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

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

- FDA reviewers included patients from whom *Legionella* spp. was identified in addition to a typical pathogen. The Applicant excluded these subjects from microbiological populations.

The table below shows the baseline disposition of the FDA-mITT population used by FDA reviewers for the responder analysis. Baseline characteristics were similar to those of the Applicant's co-primary MITTE population that was previously discussed.

At baseline, only 5% of FDA-mITT subjects met the IDSA/ATS clinical stability criteria used in the responder analysis and 98% of FDA-mITT subjects had at least two of the four symptoms of cough, dyspnea, chest pain, and sputum production recorded as being present.

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

Table 24: Baseline Disposition; FDA-mITT Population

	Study P903-08		Study P903-09	
	Ceftaroline	Ceftriaxone	Ceftaroline	Ceftriaxone
Total Subjects	69	72	84	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)
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)
Bacteremia				
Yes	8 (12)	10 (14)	14 (17)	11 (13)
No	61 (88)	62 (86)	70 (83)	72 (87)
Region				
Africa	3 (4)	4 (6)	0 (0)	0 (0)
Asia	2 (3)	4 (6)	0 (0)	0 (0)
Eastern Europe[1]	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[1]	8 (12)	12 (17)	1 (1)	2 (2)
Lung Disease				
Yes	17 (25)	14 (19)	26 (31)	27 (33)
No	52 (75)	58 (81)	58 (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)

Data Source: FDA reviewer. Nine subjects excluded from Study P903-09 for reasons of data integrity.
[1] Hungary and Poland were included in Eastern Europe by the Applicant and in Western Europe by this reviewer.

The next table shows results for the FDA reviewers' responder analysis using the Day 4 signs and symptoms endpoint in the FDA-mITT population. Although sample sizes were small due to the requirement of microbiological confirmation, the responder analysis results provided evidence of efficacy for ceftaroline, as the lower confidence limit for the ceftaroline - ceftriaxone difference in response rates exceeded -10% in both studies.

Table 25: Responder Rates for Day 4 Signs and Symptoms Endpoint; FDA-mITT

Day 4 Signs/Symptoms	Ceftaroline	Ceftriaxone	Difference (95% CI)
Study P903-08	48/69 (69.6)	42/72 (58.3)	11.2 (-4.6, 26.5)
Study P903-09	58/84 (69.0)	51/83 (61.4)	7.6 (-6.8, 21.8)

Data Source: FDA reviewer. One subject excluded from Study P903-09 FDA-mITT for reasons of data integrity.

Results for the FDA-mITT population were also examined using the Applicant-defined primary efficacy endpoint (clinical response at TOC) and secondary endpoint (clinical response at EOT).

Table 26: Investigator-Assessed Clinical Response; FDA-mITT Population

Study P903-08	Ceftaroline	Ceftriaxone	Difference (95% CI)
TOC	60/69 (87.0)	51/72 (70.8)	16.1 (2.7, 29.3)
EOT	60/69 (87.0)	53/72 (73.6)	13.3 (0.2, 26.4)
Study P903-09	Ceftaroline	Ceftriaxone	Difference (95% CI)
TOC	66/84 (78.6)	64/83 (77.1)	1.5 (-11.2, 14.2)
EOT	69/84 (82.1)	66/83 (79.5)	2.6 (-9.5, 14.7)

Data Source: FDA reviewer. One subject excluded from Study P903-09 FDA-mITT for reasons of data integrity.

These Investigator-assessed clinical response rates were higher under ceftaroline than the ceftriaxone comparator in Study P903-08. Although clinical response rates continued to favor ceftaroline in Study P903-09, the magnitude of the treatment difference was smaller.

The early signs and symptoms endpoint was predictive of later clinical response at the EOT or TOC, but by no means was a perfect predictor. Among FDA-mITT subjects in Studies P903-08 and P903-09 who were Day 4 responders on sign and symptom criteria, 90% and 85% were investigator-assessed clinical cures at the EOT, while clinical cure rates in the two studies were only 63% and 72% among those who were not Day 4 responders.

The table below shows per-subject response rates with the Day 4 signs and symptoms endpoint, by baseline pathogen. Ceftaroline success rates were higher than ceftriaxone rates for *S. pneumoniae*, and numbers were too small for other pathogens to make meaningful observations.

Table 27: Day 4 Sign and Symptom Response Rates by Pathogen, FDA-mITT Population

	Study P903-08		**Study P903-09**	
Baseline Pathogen	Ceftaroline	Ceftriaxone	Ceftaroline	Ceftriaxone
S. pneumoniae	19/27 (70.4)	17/32 (53.1)	35/47 (74.5)	25/43 (58.1)
S. aureus	4/9 (44.4)	5/15 (33.3)	10/15 (66.7)	11/16 (68.8)
H. influenzae	5/6 (83.3)	10/13 (76.9)	11/14 (78.6)	10/15 (66.7)
M. catarrhalis	0/1 (0)	1/1 (100)	1/3 (33.3)	1/2 (50.0)
E. coli	3/8 (37.5)	5/6 (83.3)	1/4 (25)	4/7 (57.1)
E. cloacae	6/6 (100)	4/7 (57.1)	2/2 (100)	3/4 (75.0)
K. oxytoca	3/3 (100)	4/4 (100)	3/3 (100)	2/2 (100)
K. pneumoniae	8/9 (88.9)	1/3 (33.3)	5/8 (62.5)	5/8 (62.5)

Data Source: FDA reviewer. One subject excluded from Study P903-09 FDA-mITT for reasons of data integrity.

Day 4 sign and symptom results were also examined by prior antibiotic use. This reviewer considered the group of subjects with both microbiologically-confirmed bacterial pneumonia and no prior antibiotic use to be optimal for the non-inferiority setting. However, the sample sizes

were very small for this subgroup, and there was too much uncertainty for this analysis to provide meaningful conclusions. When restricting to the small group of FDA-mITT subjects with no prior antibiotics, it did not appear that either study could provide evidence of efficacy.

Table 28: Day 4 Signs and Symptoms Endpoint Results by Prior Therapy; FDA-mITT

Study P903-08	Ceftaroline	Ceftriaxone	Difference (95% CI)
Prior Antibiotics	21/30 (70.0)	21/37 (56.8)	13.2 (-10.1, 34.8)
No Prior Antibiotics	27/39 (69.2)	21/35 (60.0)	9.2 (-12.4, 30.3)
Study 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)

Data Source: FDA reviewer. One subject excluded from Study P903-09 FDA-mITT for reasons of data integrity.

The responder analysis results supported the efficacy of ceftaroline, but selection of an analysis population and endpoint involved making choices and cutoffs. To examine the robustness of the evidence, FDA reviewers considered results when modifications were made to the following:

- The definition of the endpoint. Results were examined when separately using the IDSA/ATS clinical stability definition and the symptom resolution definition.

Table 29: Day 4 Results for Clinical Stability and Symptom Resolution; FDA-mITT

Study P903-08	Ceftaroline	Ceftriaxone	Difference (95% CI)
Signs and Symptoms	48/69 (69.6)	42/72 (58.3)	11.2 (-4.6, 26.5)
Clinical Stability	49/69 (71.0)	44/72 (61.1)	9.9 (-5.8, 25.1)
Symptom Resolution	66/69 (95.7)	63/72 (87.5)	8.2 (-1.2, 18.4)
Study P903-09	Ceftaroline	Ceftriaxone	Difference (95% CI)
Signs and Symptoms	58/84 (69)	51/83 (61.4)	7.6 (-6.8, 21.8)
Clinical Stability	62/84 (73.8)	56/83 (67.5)	6.3 (-7.5, 20.0)
Symptom Resolution	75/84 (89.3)	70/83 (84.3)	4.9 (-5.5, 15.7)

Data Source: FDA reviewer. One subject excluded from Study P903-09 FDA-mITT for reasons of data integrity.

- The timing of assessment. Results were examined at Day 3, Day 4, and the EOT.

Table 30: Signs and Symptoms Endpoint at Day 3, Day 4, and EOT; FDA-mITT

Study P903-08	Ceftaroline	Ceftriaxone	Difference (95% CI)
Day 3	35/69 (50.7)	30/72 (41.7)	9.1 (-7.4, 25.0)
Day 4	48/69 (69.6)	42/72 (58.3)	11.2 (-4.6, 26.5)
EOT	59/69 (85.5)	55/72 (76.4)	9.1 (-4.0, 22.1)
Study P903-09	Ceftaroline	Ceftriaxone	Difference (95% CI)
Day 3	48/84 (57.1)	47/83 (56.6)	0.5 (-14.4, 15.4)
Day 4	58/84 (69.0)	51/83 (61.4)	7.6 (-6.8, 21.8)
EOT	66/84 (78.6)	65/83 (78.3)	0.3 (-12.3, 12.9)

Data Source: FDA reviewer. One subject excluded from Study P903-09 FDA-mITT for reasons of data integrity.

- The analysis population. Results for the Day 4 responder analysis were examined in Applicant's co-primary MITTE and CE populations and the Applicant's microbiological intent-to-treat population (mMITT).

Table 31: Day 4 Signs and Symptoms Endpoint Results; MITTE, CE, and mMITT

Study P903-08	Ceftaroline	Ceftriaxone	Difference (95% CI)
MITTE	194/291 (66.7)	185/300 (61.7)	5.0 (-2.7, 12.7)
CE	150/224 (67.0)	145/234 (62.0)	5.0 (-3.8, 13.7)
mMITT	54/75 (72.0)	53/82 (64.6)	7.4 (-7.3, 21.6)
Study P903-09	Ceftaroline	Ceftriaxone	Difference (95% CI)
MITTE	194/284 (68.3)	165/269 (61.3)	7.0 (-1.0, 14.9)
CE	165/232 (71.1)	137/214 (64.0)	7.1 (-1.6, 15.7)
mMITT	66/98 (67.3)	64/102 (62.7)	4.6 (-8.6, 17.6)

Data Source: FDA reviewer. Nine subjects excluded from Study P903-09 for reasons of data integrity.

These analyses showed that non-inferiority results were relatively robust to the endpoint definition in terms of signs and symptoms, timing of assessment, and analysis population.

3.1.9 Impact of Missing Data and Protocol Violations

Unevaluable data or protocol violations can be problematic in non-inferiority trials by artificially making treatment arms appear similar. Such problems can mask inferiority of a new drug, even if there is a sound justification for the non-inferiority margin from historical data.

Recall that in the previously-given results, subjects were classified as non-responders on the Day 4 signs and symptoms endpoint if there were insufficient data to determine whether they met clinical stability criteria or symptom resolution criteria. There were 11 total FDA-mITT subjects in the two studies with incomplete data on Day 4: Study P903-08 had missing data for 3 subjects assigned to ceftaroline and 4 subjects assigned to ceftriaxone, while Study P903-09 had incomplete data for 2 ceftaroline subjects and 2 ceftriaxone subjects. For 9 of the 11 total subjects with incomplete data, there was missingness because the end-of-therapy occurred on Days 1-3, so sign and symptom measurements were not recorded on Day 4. Of these 9 subjects with early end-of-therapy visits, 4 were investigator-assessed clinical failures, 5 had indeterminate clinical responses, and none were investigator-assessed clinical cures. The two subjects with missing Day 4 data who did not have early end-of-therapy visits were both assigned to ceftaroline, and were clinical cures at the EOT on Day 7. The most conservative method (i.e., conservative for the treatment difference) of handling missing data was to classify all ceftriaxone subjects with incomplete data as Day 4 responders, and classify all ceftaroline subjects with incomplete data as Day 4 non-responders (i.e., best-worst analysis). When this was done for the 11 subjects with missing data, the ceftaroline – ceftriaxone difference in response rates still favored ceftaroline in both studies, and lower confidence limits for differences still exceeded -10% in both studies. Thus, this reviewer concluded that the non-inferiority findings were not driven by missing data.

Even when subjects in non-inferiority trials have complete data, protocol violations can make interpretation difficult. This was the reason why the Applicant made the Clinically Evaluable (CE) population (i.e., a "per-protocol" population) co-primary for efficacy analysis. However, a concern with the CE population was that subjects were excluded due to post-baseline events, so randomization did not necessarily provide protection against confounding. The table below

shows the number of FDA-mITT subjects who were excluded from the CE population for various reasons. The most common reason was that subjects in Study P903-09 were not in the MITTE population because they were not in PORT Risk Class III or IV.

Table 32: FDA-mITT Subjects Excluded from the CE Population

	Study P903-08		Study P903-09	
	Ceftaroline	Ceftriaxone	Ceftaroline	Ceftriaxone
Not in MITTE	0/69 (0)	2/72 (2.8)	9/84 (10.7)	10/83 (12.0)
Did not meet disease criteria	0/69 (0)	0/72 (0)	1/84 (1.2)	0/83 (0)
Exclusion criterion violation	0/69 (0)	2/72 (2.8)	0/84 (0)	0/83 (0)
Prior antibiotic violation	0/69 (0)	3/72 (4.2)	0/84 (0)	0/83 (0)
Atypical as sole pathogen or *L. pneumophila*	2/69 (2.9)	4/72 (5.6)	0/84 (0)	2/83 (2.4)
Received both study drugs	0/69 (0)	0/72 (0)	0/84 (0)	0/83 (0)
Unblinding	0/69 (0)	0/72 (0)	0/84 (0)	0/83 (0)
> 24 h of concomitant systemic antibiotic, other than for treatment failure	0/69 (0)	1/72 (1.4)	3/84 (3.6)	3/83 (3.6)
Less than 80% compliance	0/69 (0)	0/72 (0)	0/84 (0)	0/83 (0)
Wrong study drug	0/69 (0)	0/72 (0)	0/84 (0)	0/83 (0)
Dose not met[1]	1/69 (1.4)	2/72 (2.8)	1/84 (1.2)	3/83 (3.6)
Indeterminate TOC response, not clinical failure at EOT	X	X	X	X
TOC window violation	X	X	X	X
TOC assessment missing, not clinical failure at EOT	X	X	X	X

[1] At least 48 hours of study drug needed to be an evaluable failure or at least 72 hours of study drug to be an evaluable success.

Data Source: FDA reviewer. One subject excluded from Study P903-09 FDA-mITT for reasons of data integrity.

The last three rows in the table are not filled in because this reviewer considered such TOC visit violations to be irrelevant when evaluating efficacy using the Day 4 signs and symptoms endpoint, as these rows describe events occurring after Day 4. This reviewer examined the impact of protocol violations by defining a new clinically evaluable population (the FDA-CE population) that retained the protection of randomization. Starting from the FDA-mITT population used for the responder analysis, subjects were excluded due to violations in the table above that occurred before the administration of any study drug (i.e., exclusion for not being in the MITTE population, not meeting disease criteria, an exclusion criterion violation, a prior antibiotic violation, or the presence of *L. pneumophila* or a sole atypical pathogen). This FDA-CE population only protected against evaluability problems due to baseline events, but from the above table this reviewer concluded that the two types of post-baseline violations that occurred (> 24 h of a concomitant systemic antibiotic, dose not met) were infrequent. The table below

shows response rates for the Day 4 signs and symptoms endpoint using the FDA-CE population. This analysis was meant to assess the impact of unevaluable data or protocol violations on non-inferiority results, while preserving the integrity of randomization. Response rates were higher for ceftaroline than ceftriaxone in both studies, and lower confidence limits for treatment differences exceeded -10%. The analysis provided evidence that the non-inferiority findings were not driven by protocol violations.

Table 33: Responder Rates for Day 4 Signs and Symptoms Endpoint; FDA-CE Population

Day 4 Signs/Symptoms	Ceftaroline	Ceftriaxone	Difference (95% CI)
Study P903-08	47/67 (70.1)	37/63 (58.7)	11.4 (-5.0, 27.4)
Study P903-09	53/75 (70.7)	44/71 (62.0)	8.7 (-6.6, 23.7)

Data Source: FDA reviewer.

Although FDA reviewers defined a Day 4 endpoint due to concerns about the Applicant's non-inferiority margin justification, this reviewer found that a side benefit of an early endpoint was that missingness or protocol violations were less problematic than at the test-of-cure, as the chance of missing data or noncompliance increased as subjects were followed for longer times.

3.1.10 Biomarker Concern and Day 3 Symptoms Endpoint

As has been discussed, the FDA reviewers' Day 4 responder analysis utilized symptom improvement criteria that involved cough, dyspnea, chest pain, and sputum production. These criteria were suggested by a working group of the Biomarkers Consortium of the Foundation for the National Institutes of Health. In fact, members of this group unofficially recommended using only this symptoms-based endpoint for CABP trials, without including vital sign measurements. The argument was that signs such as temperature or pulse are biomarkers that do not directly capture how a patient feels, functions, or survives, and that they have not been validated as surrogate endpoints. A second difference between this unofficial FNIH endpoint and the FDA reviewers' signs and symptoms endpoint was the recommendation that the assessment be made on Day 3 instead of Day 4. In light of the biomarker argument, this section presents results using the unofficial FNIH Day 3 symptoms endpoint. Here subjects were classified as responders if at least one of cough, dyspnea, chest pain, or sputum production had shown improvement from baseline by Day 3, and if none of the four symptoms had worsened from baseline values. The table below shows response rates in the FDA-mITT population, which was comprised of subjects with microbiologically-confirmed bacterial pneumonia.

Table 34: Responder Rates for Day 3 Symptoms Endpoint; FDA-mITT Population

Day 3 Symptoms	Ceftaroline	Ceftriaxone	Difference (95% CI)
Study P903-08	63/69 (91.3)	58/72 (80.6)	10.7 (-0.8, 22.6)
Study P903-09	70/84 (83.3)	69/83 (83.1)	0.2 (-11.4, 11.8)

Data Source: FDA reviewer. One subject excluded from Study P903-09 FDA-mITT for reasons of data integrity.

Success rates in Study P903-08 were higher for ceftaroline than ceftriaxone, while rates were nearly identical in Study P903-09. The lower confidence limit for the treatment difference approached zero in Study P903-08, but fell below -10% in Study P903-09. Due to small sample sizes, there was much uncertainty in the treatment effect estimates.

In the FDA-mITT population in each study, the symptom measurements needed to evaluate the endpoint were not available for 3 subjects who had their end-of-therapy visits on Days 1-2. As in the previously-mentioned Day 4 analysis, these 6 subjects were classified as non-responders. Both studies had incomplete data for 1 ceftaroline FDA-mITT subject and 2 ceftriaxone subjects.

The next table shows per-subject response rates for the Day 3 symptoms endpoint by baseline pathogen. In accord with other analyses presented, success rates were higher for ceftaroline than ceftriaxone in subjects with *S. pneumoniae* but sample sizes were very small for other pathogens.

Table 35: Day 3 Symptom Response Rates by Pathogen; FDA-mITT Population

	Study P903-08		**Study P903-09**	
Baseline Pathogen	Ceftaroline	Ceftriaxone	Ceftaroline	Ceftriaxone
S. pneumoniae	25/27 (92.6)	23/32 (71.9)	40/47 (85.1)	33/43 (76.7)
S. aureus	8/9 (88.9)	14/15 (93.3)	12/15 (80.0)	14/16 (87.5)
H. influenzae	6/6 (100)	11/13 (84.6)	12/14 (85.7)	14/15 (93.3)
M. catarrhalis	1/1 (100)	1/1 (100)	2/3 (66.7)	2/2 (100)
E. coli	7/8 (87.5)	5/6 (83.3)	4/4 (100)	5/7 (71.4)
E. cloacae	6/6 (100)	6/7 (85.7)	2/2 (100)	4/4 (100)
K. oxytoca	3/3 (100)	4/4 (100)	2/3 (66.7)	1/2 (50.0)
K. pneumoniae	7/9 (77.8)	2/3 (66.7)	6/8 (75.0)	8/8 (100)

Data Source: FDA reviewer. One subject excluded from Study P903-09 FDA-mITT for reasons of data integrity.

The table below shows results by prior antibiotic use. Although subjects with both microbiologically-confirmed pneumonia and no prior therapy were perhaps ideal for non-inferiority studies, sample sizes were considered too small for meaningful observations.

Table 36: Day 3 Symptom Response Rates by Prior Antibiotic Use; FDA-mITT

Study P903-08	Ceftaroline	Ceftriaxone	Difference (95% CI)
Prior Antibiotics	28/30 (93.3)	28/37 (75.7)	17.7 (-0.2, 34.8)
No Prior Antibiotics	35/39 (89.7)	30/35 (85.7)	4.0 (-11.7, 20.7)
Study P903-09	Ceftaroline	Ceftriaxone	Difference (95% CI)
Prior Antibiotics	20/26 (76.9)	26/31 (83.9)	-6.9 (-28.6, 13.8)
No Prior Antibiotics	50/58 (86.2)	43/52 (82.7)	3.5 (-10.3, 17.9)

Data Source: FDA reviewer. One subject excluded from Study P903-09 FDA-mITT for reasons of data integrity.

Another idea arising from the FNIH discussions was to define a more stringent symptoms endpoint by requiring improvement on at least two of the four symptoms, while still requiring that none worsen from baseline. The table below shows response rates at Day 3 when using this more stringent symptoms endpoint. Results supported the efficacy of ceftaroline in both studies.

Table 37: Day 3 Response Rates with Stringent Symptoms Endpoint; FDA-mITT

Study P903-08	Ceftaroline	Ceftriaxone	Difference (95% CI)
Stringent Day 3 Symptoms Endpoint	58/69 (84.1)	56/72 (77.8)	6.3 (-6.9, 19.4)
Study P903-09	Ceftaroline	Ceftriaxone	Difference (95% CI)
Stringent Day 3 Symptoms Endpoint	67/84 (79.8)	55/83 (66.3)	13.5 (0.0, 26.7)

Data Source: FDA reviewer. One subject excluded from Study P903-09 FDA-mITT for reasons of data integrity.

This reviewer also examined response rates for the Day 3 symptoms endpoint across analysis populations: the Applicant's co-primary MITTE and Clinically Evaluable (CE) populations that did not require microbiological diagnoses, and the Applicant's microbiological intent-to-treat population (mMITT). Results generally favored ceftaroline, although in Study P903-09 there was no evidence of efficacy when restricting to the Applicant's microbiological population.

Table 38: Day 3 Symptoms Endpoint Results; MITTE, CE, and mMITT Populations

Study P903-08	Ceftaroline	Ceftriaxone	Difference (95% CI)
MITTE	250/291 (85.9)	241/300 (80.3)	5.6 (-0.5, 11.6)
Prior antibiotics	114/137 (83.2)	114/143 (79.7)	3.5 (-5.7, 12.6)
No prior antibiotics	136/154 (88.3)	127/157 (80.9)	7.4 (-0.6, 15.6)
CE	193/224 (86.2)	191/234 (81.6)	4.5 (-2.2, 11.3)
mMITT	69/75 (92.0)	68/82 (82.9)	9.1 (-1.5, 19.8)
Study P903-09	Ceftaroline	Ceftriaxone	Difference (95% CI)
MITTE	236/284 (83.1)	215/269 (79.9)	3.2 (-3.3, 9.7)
Prior antibiotics	75/95 (78.9)	90/113 (79.6)	-0.7 (-12.0, 10.3)
No prior antibiotics	161/189 (85.2)	125/156 (80.1)	5.1 (-2.9, 13.3)
CE	197/232 (84.9)	174/214 (81.3)	3.6 (-3.4, 10.7)
mMITT	81/98 (82.7)	88/102 (86.3)	-3.6 (-14.0, 6.6)

Data Source: FDA reviewer. Nine subjects excluded from Study P903-09 for reasons of data integrity.

3.1.11 Conclusions and Limitations

Results from the FDA reviewers' analysis using a Day 4 signs and symptoms endpoint supported the efficacy of ceftaroline, and agreed with the Applicant's prespecified results. As this reviewer examined sensitivity by modifying the endpoint definition, timing of assessment, or analysis population, the response rates were generally higher under ceftaroline than ceftriaxone, and the lower confidence limit for the treatment difference generally exceeded -10%.

However, there were several important limitations of this early responder analysis. First, it was post-hoc, and not specified in the Applicant's protocol or statistical analysis plan. Therefore, no Type I error rate was being controlled in this reviewer's analyses.

Requiring microbiological confirmation also meant that the FDA-mITT population was small in both studies. Thus, there was a great deal of uncertainty when estimating treatment effects.

Furthermore, the sign and symptom measurements were not standardized in terms of how or when they were assessed, which was not ideal in the non-inferiority setting.

Additionally, the sign and symptom components of the FDA reviewers' Day 4 endpoint can be manipulated pharmacologically by concomitant medication. For instance, the temperature component of the endpoint can be affected by antipyretics. Virtually all subjects were given some degree of non-antimicrobial concomitant therapy.

This reviewer also recognized that aside from mortality, no algorithmic combination of signs and symptoms would precisely correspond to the overall clinical responses assessed in historical studies. That is, a fully rigorous and empirical margin justification was not given for the FDA reviewers' signs and symptoms endpoint.

In non-inferiority trials, the "constancy assumption" is needed for efficacy conclusions. The assumption is that the historical trials used for margin justification were similar in terms of designs, subjects, and background conditions to the non-inferiority trials being conducted. The constancy assumption was questionable for Study P903-08 and Study P903-09 because there was little mortality, and historical studies cited in support of the early signs and symptoms endpoint included subjects at greater risk of death.

Finally, generalizability to American subjects was not clear. Study P903-09 had no subjects enrolled in the United States. Study P903-08 had only 27 American subjects, and only 5 in the FDA-mITT population used for FDA reviewers' responder analysis.

3.2 Evaluation of Safety

Please refer to the safety review of Dr. Ariel Porcalla, the medical reviewer for this application.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, and Age

Efficacy results were examined for various subgroups. This analysis was not prespecified, and no procedure was used to control for multiple comparisons, so conclusions drawn from these results were exploratory. This reviewer first assessed subgroups of the MITTE population, because it was a co-primary analysis population, and unlike the co-primary CE population it was considered to have randomization protection. The table below shows results for the pooled studies in terms of clinical cure rates at TOC, corresponding to the prespecified primary endpoint. Differences in rates and 95% confidence intervals are shown for subgroups in which there were at least 20 subjects in both the ceftaroline and ceftriaxone arms, and cure rates were higher for ceftaroline than ceftriaxone for all such subgroups.

This reviewer considered pooling appropriate because the analysis was exploratory, both studies used 1:1 randomization, the studies had similar protocols, and no heterogeneity was detected.

Subgroup results are also shown for the FDA-reviewers' responder analysis using a Day 4 signs and symptoms endpoint and the microbiologically-confirmed FDA-mITT population, after again pooling the two studies. Response rates under ceftaroline were again greater than or equal to the ceftriaxone rates in all subgroups examined with more than 20 subjects per arm.

In inspecting pooled results, the consistency of treatment differences favoring ceftaroline across subgroups defined by gender, race, or age was supportive evidence of efficacy for the drug.

Table 39: Clinical Cure at TOC by Gender/Race/Age; Pooled Study MITTE

Subgroup	Ceftaroline	Ceftriaxone	Difference (95% CI)
All MITTE Subjects	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 reviewer. Nine subjects excluded from Study P903-09 for reasons of data integrity.

Table 40: Day 4 Signs/Symptoms Endpoint by Gender/Race/Age; Pooled Study FDA-mITT

Subgroup	Ceftaroline	Ceftriaxone	Difference (95% CI)
All FDA-mITT Subjects	106/153 (69.3)	93/155 (60.0)	9.3 (-1.4, 19.8)
Sex			
Male	70/98 (71.4)	59/97 (60.8)	10.6 (-2.7, 23.6)
Female	36/55 (65.5)	34/58 (58.6)	6.8 (-11.0, 24.2)
Race			
White	97/143 (67.8)	77/146 (52.7)	15.1 (3.8, 26)
Black	3/3 (100)	2/2 (100)	X
Asian	3/3 (100)	2/5 (40)	X
American Indian	2/3 (66.7)	2/2 (100)	X
Age			
18-49	29/38 (76.3)	24/36 (66.7)	9.6 (-10.9, 29.8)
50-64	29/45 (64.4)	31/53 (58.5)	6.0 (-13.4, 24.6)
≥ 65	48/70 (68.6)	38/66 (57.6)	11.0 (-5.2, 26.7)

Data Source: FDA Reviewer. One subject excluded from Study P903-09 FDA-mITT for reasons of data integrity.

4.2 Other Subgroups/Populations

This reviewer also examined subgroups defined by PORT Risk Class, baseline bacteremia, region, prior antibiotic use, renal function, chronic lung disease, and smoking history. Clinical cure rates were again first assessed in the MITTE population after pooling the two studies. Results are shown in the table below, with confidence intervals given for treatment differences whenever there are at least 20 subjects in each arm. For all such subgroups examined, clinical cure rates were higher for ceftaroline than ceftriaxone.

Subgroup results were also assessed for the Day 4 endpoint and microbiological intent-to-treat population used in FDA reviewers' responder analysis. Response rates were lower under ceftaroline than ceftriaxone for PORT IV subjects and subjects with bacteremia, but differences were minor in light of chance effects due to small sample sizes and multiple comparisons.

This reviewer again considered the consistency of treatment differences favoring ceftaroline across these subgroups to be supportive evidence of efficacy.

Table 41: Clinical Cure at TOC; Various Subgroups; Pooled MITTE Populations

Subgroup	Ceftaroline	Ceftriaxone	Difference (95% CI)
All MITTE Subjects	475/575 (82.6)	436/569 (76.6)	6.0 (1.3, 10.7)
PORT Risk Class			
III	307/358 (85.8)	278/351 (79.2)	6.6 (1.0, 12.2)
IV	168/217 (77.4)	158/218 (72.5)	4.9 (-3.2, 13.1)
Bacteremia			
Yes	15/22 (68.2)	13/20 (65.0)	3.2 (-24.6, 31.0)
No	460/553 (83.2)	423/549 (77.0)	6.1 (1.4, 10.8)
Region			
Africa	15/17 (88.2)	16/18 (88.9)	X
Asia	11/13 (84.6)	11/15 (73.3)	X
Eastern Europe	351/424 (82.8)	319/419 (76.1)	6.6 (1.2, 12.1)
Latin America	53/64 (82.8)	48/60 (80)	2.8 (-11.1, 16.9)
North America	8/11 (72.7)	8/12 (66.7)	X
Western Europe	37/46 (80.4)	34/45 (75.6)	4.9 (-12.3, 22.1)
Prior Antibiotics			
Yes	185/232 (79.7)	203/256 (79.3)	0.4 (-6.8, 7.6)
No	290/343 (84.5)	233/313 (74.4)	10.1 (4.0, 16.3)
Renal Function			
$80 < CrCl$	230/272 (84.6)	213/281 (75.8)	8.8 (2.1, 15.4)
$50 < CrCl \leq 80$	156/194 (80.4)	143/185 (77.3)	3.1 (-5.1, 11.4)
$30 < CrCl \leq 50$	69/85 (81.2)	64/80 (80.0)	1.2 (-11, 13.5)
$CrCl \leq 30$	10/13 (76.9)	8/10 (80.0)	X
Lung Disease			
Yes	126/159 (79.2)	109/147 (74.1)	5.1 (-4.4, 14.6)
No	349/416 (83.9)	327/422 (77.5)	6.4 (1.1, 11.7)
Smoking History			
Yes	242/304 (79.6)	204/285 (71.6)	8.0 (1.1, 15.0)
No	233/271 (86.0)	232/284 (81.7)	4.3 (-1.9, 10.4)

Data Source: FDA reviewer. Nine subjects excluded from Study P903-09 for reasons of data integrity.

Table 42: Day 4 Signs/Symptoms Endpoint; Subgroup Analysis; Pooled FDA-mITT

Subgroup	Ceftaroline	Ceftriaxone	Difference (95% CI)
All FDA-mITT Subjects	106/153 (69.3)	93/155 (60.0)	9.3 (-1.4, 19.8)
PORT Risk Class			
III	63/83 (75.9)	46/82 (56.1)	19.8 (5.4, 33.5)
IV	38/61 (62.3)	39/61 (63.9)	-1.6 (-18.5, 15.3)
Bacteremia			
Yes	12/22 (54.5)	12/21 (57.1)	-2.6 (-30.8, 26.1)
No	94/131 (71.8)	81/134 (60.4)	11.3 (-0.1, 22.4)
Region			
Africa	3/3 (100)	4/4 (100)	X
Asia	2/2 (100)	1/4 (25.0)	X
Eastern Europe	78/114 (68.4)	62/103 (60.2)	8.2 (-4.5, 20.8)
Latin America	15/23 (65.2)	14/27 (51.9)	13.4 (-13.9, 38.5)
North America	0/2 (0)	3/3 (100)	X
Western Europe	8/9 (88.9)	9/14 (64.3)	X
Prior Antibiotics			
Yes	40/56 (71.4)	38/68 (55.9)	15.5 (-1.6, 31.5)
No	66/97 (68.0)	55/87 (63.2)	4.8 (-8.8, 18.5)
Renal Function			
$80 < CrCl$	55/74 (74.3)	42/63 (66.7)	7.7 (-7.6, 22.9)
$50 < CrCl \leq 80$	30/45 (66.7)	34/63 (54.0)	12.7 (-6.1, 30.3)
$30 < CrCl \leq 50$	18/25 (72.0)	14/25 (56.0)	16.0 (-10.6, 40.6)
$CrCl \leq 30$	2/6 (33.3)	1/1 (100)	X
Lung Disease			
Yes	29/43 (67.4)	24/41 (58.5)	8.9 (-11.6, 28.8)
No	77/110 (70.0)	69/114 (60.5)	9.5 (-3, 21.7)
Smoking History			
Yes	58/86 (67.4)	54/94 (57.4)	10.0 (-4.2, 23.7)
No	48/67 (71.6)	39/61 (63.9)	7.7 (-8.4, 23.7)

Data Source: FDA reviewer. One subject excluded from Study P903-09 FDA-mITT for reasons of data integrity.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The main statistical issue in Study P903-08 and Study P903-09 was the lack of an appropriate justification for the 10% non-inferiority margin used by the Applicant for the prespecified primary endpoint of clinical response at the test-of-cure. The Applicant's justification relied on historical data for an antibiotic treatment effect on mortality, but a margin for mortality cannot necessarily be extrapolated to a margin for clinical response. The historical evidence for an antibiotic effect on clinical response mainly deals with an effect early in the treatment course (i.e., Days 3-5). A margin for an early endpoint also cannot necessarily translate into a margin at the test-of-cure visit 8-15 days after the end-of-therapy, and an early endpoint may better differentiate effective and ineffective antibiotics.

Mortality rates in the two studies were too low to draw any meaningful efficacy inferences. Due to exclusion criteria, all-cause mortality rates were in the range of 1-2% over the two trials and

treatment arms, while mortality rates of 10% or higher can be seen in observational studies of severe CABP patients.

To assess efficacy, this reviewer first re-examined the non-inferiority margin for the prespecified clinical response endpoint and ceftriaxone comparator, using two recent trials comparing ceftriaxone to daptomycin for the treatment of CABP. Daptomycin was unexpectedly deactivated, and a margin for ceftriaxone over daptomycin was taken to be conservative for a margin over placebo. Applying random effects meta-analysis to the two daptomycin studies yielded a ceftriaxone effect (M1) of 3% for the clinical response endpoint among PORT III-IV subjects given no long-acting prior antibiotics. While this was small, and reduced to margin (M2) of 1.5% to preserve 50% of the treatment effect, results supported the efficacy of ceftaroline. Confidence intervals for the ceftaroline – ceftriaxone difference in clinical cure rates for the co-primary MITTE population of Study P903-08 and Study P903-09 showed ceftaroline to be no more than 1% worse than ceftriaxone. That is, the daptomycin studies suggested at least a small treatment effect for the ceftriaxone comparator, and ceftaroline appeared to lose little if any of this effect. However, this margin analysis had many limitations, primarily because it was post-hoc and exploratory. Therefore, this reviewer concluded that the margin analysis could only provide indirect and supportive evidence for the efficacy of ceftaroline.

Because the historical evidence for an antibiotic treatment effect on clinical response related to an effect early in the treatment course, FDA reviewers also conducted a responder analysis by defining an early signs and symptoms endpoint at Day 4. The population used for this responder analysis contained only subjects with microbiologically-confirmed bacterial pneumonia. The analysis provided evidence of efficacy for ceftaroline. Response rates in the two studies were 69.6% and 69.0% for ceftaroline and 58.3% and 61.4% for ceftriaxone, with treatment differences and 95% confidence intervals of 11.2% (-4.6, 26.5%) and 7.6% (-6.8%, 21.8%).

The robustness of the Day 4 responder analysis results was examined with respect to the specific choices made by FDA reviewers. Conclusions were relatively robust under modifications to the endpoint definition in terms of signs and symptoms, timing of the early assessment, and choice of analysis population.

This reviewer concluded that the non-inferiority findings could not be explained by missing data or protocol violations. A conservative best-worst analysis of subjects with missing sign and symptom measurements at Day 4 did not impact results in any meaningful way. Although an early endpoint was used by FDA reviewers due to non-inferiority margin considerations, a side benefit was that unevaluable data or protocol violations were less problematic at the early time. However, the drawback of the early endpoint was that it did not necessarily capture the overall well-being of patients, because it ignored what happened after Day 4 of therapy.

This reviewer also assessed outcomes when an early endpoint was defined only through symptom measurements, without vital signs such as temperature, pulse, or respiratory rate. Vital signs have been criticized because they are biomarkers, and have not undergone validation as surrogate endpoints. Using a Day 3 symptom improvement endpoint that has been unofficially recommended at meetings of the FNIH Biomarkers Consortium, results in Study P903-08

supported ceftaroline and approached superiority findings, but evidence of efficacy was not seen in Study P903-09 among subjects with microbiologically-confirmed bacterial pneumonia.

Exploratory analyses of pooled studies did not identify any potentially problematic subgroups.

There were signs of effect modification on clinical response by prior antibiotic use, in that the ceftaroline – ceftriaxone difference in success rates appeared larger for subjects without prior therapy. While this finding was encouraging for ceftaroline, it raised concerns about whether future studies should allow any prior antimicrobial therapy, even if it is short-acting.

The main limitation of this reviewer's efficacy assessment was that the choice of an early endpoint was post-hoc and exploratory. Also, the sign and symptom measurements were not standardized or optimized for such an endpoint assessment. Additionally, the endpoint components may have been affected by concomitant medication, as virtually all subjects were given non-antimicrobial concomitant therapy. Further, there was no rigorous justification for the FDA reviewers' early signs and symptoms endpoint; it was used because the historical literature based on cross-study comparisons only dealt with effects on signs and symptoms of the disease at an early time in the treatment course. Finally, generalizability to American subjects was not clear, because there were very few patients enrolled in the United States.

5.2 Conclusions and Recommendations

Although the thinking of FDA reviewers regarding the adequacy of the prespecified analysis plan had evolved between the time of study completion and the time of review, the totality of information in the application still provided evidence that ceftaroline was non-inferior to ceftriaxone for the treatment of community-acquired bacterial pneumonia.

Study P903-08 and Study P903-09 each met prespecified efficacy endpoints and showed numerical trends favoring ceftaroline over ceftriaxone. In spite of sample sizes suggesting the analysis would be underpowered, the FDA reviewers' responder analysis using an early endpoint and microbiological intent-to-treat population was concordant with the Applicant's prespecified analysis. The responder analysis results were also relatively robust to choices of an early signs and symptoms endpoint, timing of assessment, and analysis population. FDA reviewers additionally conducted an exploratory post-hoc examination of whether daptomycin trials could justify a non-inferiority margin for the prespecified clinical response endpoint, and this analysis provided indirect and supportive evidence of efficacy for ceftaroline.

While ceftaroline was shown to be non-inferior to ceftriaxone for the treatment of CABP, the labeling should clearly identify that superiority to ceftriaxone was not established.

Additionally, the label should note that very few subjects in Study P903-08 or Study P903-09 were from the United States, and that subjects studied were at low risk for mortality.

The labeling should also clearly explain that although ceftaroline has in vitro activity against MRSA, the efficacy and safety of ceftaroline has not been examined for community-acquired pneumonia patients with methicillin-resistant *Staphylococcus aureus*.

REFERENCES

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

DerSimonian, R. and Laird, N. Meta-analysis in clinical trials. *Controlled Clinical Trials*. 1986; 7:177-188.

Dmitrienko, A. and Tamhane, A.C. Gatekeeping procedures with clinical trial applications. *Pharmaceutical Statistics*. 2007; 6:171-180.

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

Fleming, T.R. and Powers, J.H. Issues in noninferiority trials: the evidence in community-acquired pneumonia. *Clinical Infectious Diseases*. 2008; 47:S108-120.

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

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

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

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

Miettinen, O. and Nurminen, M. Comparative analysis of two rates. *Statistics in Medicine.* 1985; 4:213-226.

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

Westfall P.H. and Krishen A. Optimally weighted, fixed sequence and gatekeeper multiple testing procedures. *Journal of Statistical Planning and Inference*. 2001; 99:25-41.

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

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Daniel Rubin, Ph.D.

Concurring Reviewers: Thamban Valappil, Ph.D., Statistical Team Leader

cc:
Division Director, Division of Biometrics IV/Mohammad Huque
Deputy Division Director, Division of Biometrics IV/Daphne Lin
Mathematical Statistician/Scott Komo
Mathematical Statistician/Lillian Patrician
Project Manager/Carmen DeBellas
Medical Reviewer/Ariel Porcalla
Medical Team Leader/Janice Pohlman
Deputy Division Director for Safety, Office of Antimicrobial Products/Sumati Nambiar
Director, Division of Anti-Infective and Ophthalmology Products/Wiley Chambers
Deputy Director, Division of Anti-Infective and Ophthalmology Products/Katherine Laessig
Microbiology Reviewer/Avery Goodwin
Microbiology Team Leader/Frederic Marsik
Clinical Pharmacology Reviewer/Aryun Kim
Clinical Pharmacology Team Leader/Charles Bonapace

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DANIEL B RUBIN
09/30/2010

THAMBAN I VALAPPIL
09/30/2010

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 200327 **Applicant: Cerexa Inc.** **Stamp Date: December 30, 2009**

Drug Name [redacted] **(b) (4)** **NDA/BLA Type:**
(ceftaroline fosamil for injection)

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			Datasets in initial submission were problematic. Revised datasets later submitted are acceptable.

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ____YES____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.		X		Review Issue
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.		X		A variety of approaches for missing data are

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

				not provided.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200327	ORIG-1	CEREXA INC	ceftaroline fosamil for injection

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTOPHER E KADOORIE
03/04/2010

SCOTT S KOMO
03/04/2010

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 200327 **Applicant: Cerexa** **Stamp Date: 12/30/2009**

Drug Name: Ceftaroline **NDA/BLA Type:**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? _____Yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.				Review issue
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200327	ORIG-1	CEREXA INC	ceftaroline fosamil for injection

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DANIEL B RUBIN
02/19/2010

THAMBAN I VALAPPIL
02/19/2010