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**TITLE PAGE**



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**Ceftaroline Fosamil for Injection in Complicated Skin and Skin Structure Infections  
and Community-acquired Bacterial Pneumonia  
NDA 200327**

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## **2.0     TABLES OF CONTENTS, TABLES & FIGURES**

## 2.1 OVERALL TABLE OF CONTENTS

1.0 TITLE PAGE .....	1
2.0 TABLES OF CONTENTS, TABLES & FIGURES .....	2
2.1 Overall Table of Contents .....	3
2.2 List of In-Text Tables .....	9
2.3 List of In-Text Figures .....	13
3.0 ABBREVIATIONS .....	14
4.0 EXECUTIVE SUMMARY .....	17
4.1 INTRODUCTION .....	17
4.2 REGULATORY AND DEVELOPMENT HISTORY .....	18
4.3 BACKGROUND .....	20
4.3.1 Community-acquired Bacterial Pneumonia .....	20
4.3.2 Complicated Skin and Skin Structure Infection .....	22
4.4 CLINICAL DEVELOPMENT PROGRAM & EFFICACY .....	23
4.5 SAFETY SUMMARY .....	27
4.6 RISK BENEFIT SUMMARY .....	28
5.0 CEFTAROLINE OVERVIEW .....	30
5.1 CHEMISTRY .....	30
5.2 NONCLINICAL SAFETY EVALUATION .....	31
5.2.1 In Vivo Studies .....	31
5.3 MICROBIOLOGY .....	32

5.3.1 Mechanism of Action .....	32
5.3.2 Resistance Studies .....	33
5.3.3 In Vitro Spectrum of Activity .....	33
5.3.4 In Vitro Synergy Studies .....	36
5.3.5 In Vivo Efficacy in Animal Infection Models .....	36
5.4 CLINICAL PHARMACOLOGY OVERVIEW .....	36
5.4.1 Pharmacokinetics .....	37
5.4.2 Distribution .....	37
5.4.3 Metabolism .....	37
5.4.4 Excretion .....	38
5.4.5 Special Populations .....	38
5.4.5.1 Renal Impairment .....	38
5.4.5.2 Age and Gender Effects .....	38
5.4.6 In Vitro Drug Interactions .....	39
5.4.7 Pharmacokinetics/Pharmacodynamics, Target Attainment, and Dose Justification .....	39
6.0 COMMUNITY-ACQUIRED BACTERIAL PNEUMONIA STUDY DESIGN AND EFFICACY .....	41
6.1 STUDY DESIGN .....	41
6.1.1 Statistical Methods .....	45
6.2 ANALYSIS POPULATIONS .....	47
6.3 REGIONS OF ENROLLMENT .....	48

6.4 PREMATURE DISCONTINUATIONS FROM STUDY DRUG .....	50
6.5 DEMOGRAPHICS, BASELINE CHARACTERISTICS, AND BASELINE PATHOGENS .....	51
6.5.1 Demographics and Baseline Characteristics .....	51
6.5.2 Severity of Disease .....	53
6.5.3 Baseline Pathogens .....	55
6.6 CLINICAL RESPONSE AT TEST OF CURE – THE PRIMARY EFFICACY VARIABLE .....	57
6.7 SECONDARY EFFICACY ANALYSES .....	58
6.7.1 Clinical Response at End of Therapy .....	58
6.7.2 Clinical Response by Baseline Pathogen at Test of Cure .....	59
6.7.3 Clinical Relapse and Microbiological Reinfection or Recurrence at Late Follow-up .....	60
6.8 CLINICAL CURE RATE BY RELEVANT SUBGROUPS .....	61
6.8.1 Clinical Cure Rates by Demographics and Baseline Characteristics .....	61
6.9 FDA-DEFINED EXPLORATORY ANALYSIS .....	63
6.9.1 FDA-defined Clinical Response at Day 4 .....	63
7.0 COMPLICATED SKIN AND SKIN STRUCTURE STUDY DESIGN AND EFFICACY .....	65
7.1 STUDY DESIGN .....	65
7.1.1 Statistical Methods .....	70

7.2 ANALYSIS POPULATIONS .....	71
7.3 REGIONS OF ENROLLMENT .....	72
7.4 PREMATURE DISCONTINUATIONS OF STUDY DRUG .....	73
7.5 DEMOGRAPHICS, BASELINE CHARACTERISTICS, AND BASELINE PATHOGENS .....	74
7.5.1 Demographics and Baseline Characteristics .....	74
7.5.2 Severity of Disease .....	76
7.5.3 Baseline Pathogens .....	79
7.6 CLINICAL RESPONSE AT TEST OF CURE – THE PRIMARY EFFICACY VARIABLE .....	80
7.7 SECONDARY EFFICACY ANALYSES .....	82
7.7.1 Clinical Response at End of Therapy .....	82
7.7.2 By-pathogen Clinical Response at Test of Cure .....	83
7.7.3 Clinical Relapse and Microbiological Reinfection or Recurrence at Late Follow-up .....	84
7.8 CLINICAL CURE RATE BY RELEVANT SUBGROUPS .....	85
7.8.1 Clinical Cure Rates by Region .....	85
7.8.2 Clinical Cure Rates by Demographics and Baseline Characteristics .....	86
7.9 FDA-DEFINED EXPLORATORY ANALYSES .....	89
7.9.1 Clinical Cure Rates by Exclusion of Subjects with Abscesses Alone .....	89

7.9.2 FDA-defined Clinical Response at Day 3 .....	90
7.9.3 FDA-defined Secondary Endpoints at End of Therapy .....	91
8.0 SAFETY .....	93
8.1 SAFETY DATABASE .....	93
8.2 EXTENT OF EXPOSURE .....	94
8.3 SUMMARY OF ADVERSE EVENTS .....	96
8.3.1 Common Adverse Events .....	97
8.3.2 Deaths and Serious Adverse Events .....	99
8.3.2.1 Deaths .....	99
8.3.2.2 Serious Adverse Events .....	105
8.3.3 Discontinuation of Study Medication or Study Due to an Adverse Event .....	105
8.4 SAFETY EVENTS OF INTEREST .....	106
8.4.1 Renal Safety .....	106
8.4.2 Hepatic Safety .....	113
8.4.3 Potential Allergic Reactions (Including Hypersensitivity) .....	116
8.4.4 Direct Coombs Seroconversion .....	118
8.4.5 Seizures .....	120
8.4.6 Clostridium difficile-associated Diarrhea .....	120
8.4.7 Cardiac Effects .....	121
8.5 CLINICAL LABORATORY TESTS .....	122

8.6 VITAL SIGNS .....	123
8.7 SAFETY CONCLUSIONS .....	123
9.0 RISK BENEFIT ANALYSIS .....	125
9.1 MICROBIOLOGICAL BENEFITS .....	125
9.2 BIOPHARMACEUTIC BENEFITS .....	126
9.3 CLINICAL BENEFITS .....	126
9.3.1 Benefits in Community-acquired Bacterial Pneumonia .....	127
9.3.2 Benefits in Complicated Skin and Skin Structure Infections .....	129
9.4 LIMITATIONS AND RISKS .....	130
9.5 CONCLUSIONS .....	132
10.0 REFERENCES .....	134
11.0 APPENDICES .....	141
Appendix 11.1: Selection of Noninferiority Margins For Community-Acquired Bacterial Pneumonia Studies .....	141
Appendix 11.2: Selection of Noninferiority Margins for Complicated Skin and Skin Structure Infection Studies .....	164
Appendix 11.3: End of Text Tables .....	178
Table 11.3–1. Incidence of Serious Adverse Events, Phase 3 Studies for cSSSI and CABP—Safety Population .....	179
Table 11.3–2. Incidence of Adverse Events Leading to Discontinuation of Study Drug or Withdrawal from Study, Phase 3 Studies for cSSSI and CABP—Safety Population .....	189



## 2.2 LIST OF IN-TEXT TABLES

Table 4.4–1. Clinical Response at Test of Cure, Phase 3 Community-acquired Bacterial Pneumonia Studies—MITTE and CE Populations .....	25
Table 4.4–2. Clinical Response at Test of Cure, Phase 3 cSSSI Studies—MITT and CE Populations .....	26
Table 5.3.1–1. Inhibition of Modified Penicillin-binding Protein 2a in Methicillin-resistant Staphylococcus aureus and Penicillin-binding Protein 2x in Penicillin Nonsusceptible Streptococcus pneumoniae .....	32
Table 5.3.3–1. In Vitro Activity of Ceftaroline and Comparator Agents against Organisms, Including Those Causing Skin and Respiratory Infections, Isolated in United States Medical Centers in 2008 .....	33
Table 6.1–1. Study Visit Overview, Studies P903-08 and P903-09 .....	42
Table 6.1–2. Clinical Outcome Categories .....	45
Table 6.3–1. Enrollment by Region, Phase 3 Community-acquired Bacterial Pneumonia Studies—MITTE Population .....	49
Table 6.4–1. Premature Discontinuation of Study Drug, Phase 3 Community-acquired Bacterial Pneumonia Studies —MITTE Population .....	51
Table 6.5.1–1. Demographics and Baseline Characteristics, Phase 3 Community-acquired Bacterial Pneumonia Studies—MITTE Population .....	52
Table 6.5.2–1. Severity Markers for Community-acquired Bacterial Pneumonias: Clinical Parameters, Phase 3 Studies—MITTE Population .....	54
Table 6.5.3–1. Subjects with Pathogenic Organisms Identified at Baseline from Respiratory or Blood Specimens or Urinary Antigen Tests, Phase 3 Community-acquired Bacterial Pneumonia Studies—mMITTE Population .....	56
Table 6.7.1–1. Clinical Response at End of Therapy, Phase 3 Community-acquired Bacterial Pneumonia Studies—CE and MITTE Populations .....	58

Table 6.7.2–1. Clinical Response at the Test of Cure Visit by Baseline Pathogen, Pooled Phase 3 Community-acquired Bacterial Pneumonia Studies—mMITTE Population .....	60
Table 6.8.1–1. Clinical Cure Rates at Test of Cure by Demographic and Baseline Characteristics, Pooled Phase 3 Community-acquired Bacterial Pneumonia Studies—CE Population .....	61
Table 6.9.1–1. Clinical Response of Signs and Symptoms at Study Day 4, Noninferiority Tests, Phase 3 Community-acquired Bacterial Pneumonia Studies — FDA-mMITT Population .....	64
Table 7.1–1. Study Visit Overview, P903-06 and P903-07 .....	66
Table 7.1–2. Clinical Outcome Categories .....	69
Table 7.3–1. Enrollment by Region Groups, Phase 3 Complicated Skin and Skin Structure Studies—MITT Population .....	73
Table 7.4–1. Premature Discontinuation From Study Drug, Phase 3 Complicated Skin and Skin Structure Studies—MITT Population .....	74
Table 7.5.1–1. Demographics and Baseline Characteristics, Phase 3 Complicated Skin and Skin Structure Studies—MITT Population .....	75
Table 7.5.2–1. Markers for Complicated Skin and Skin Structure Infections - Clinical Parameters, Phase 3 Studies—MITT Population .....	77
Table 7.5.3–1. Subjects with Pathogenic Organisms From Cultures From the Primary Infection Site or Blood at Baseline, Phase 3 Complicated Skin and Skin Structure Studies—mMITT Population .....	80
Table 7.6–1. Clinical Response at Test of Cure, Phase 3 Complicated Skin and Skin Structure Studies—ME and mMITT Populations .....	82
Table 7.7.1–1. Clinical Response at End of Therapy, Phase 3 Complicated Skin and Skin Structure Studies—MITT and CE Populations .....	83
Table 7.7.2–1. Clinical Response at Test of Cure by Baseline Pathogen,	

Pooled Phase 3 Complicated Skin and Skin Structure Infection Studies—mMITT Population .....	84
Table 7.8.1–1. Clinical Cure Rates at Test of Cure by Region Groups, Pooled Phase 3 Complicated Skin and Skin Structure Infection Studies—CE Population .....	85
Table 7.8.2–1. Clinical Cure Rates at Test of Cure by Demographics and Baseline Characteristics, Pooled Phase 3 Complicated Skin and Skin Structure Infection Studies —CE Population .....	87
Table 7.9.1–1. Clinical Response at Test of Cure Excluding Subjects with Abscesses, Noninferiority Tests, Study P903-06— MITT and CE Populations .....	89
Table 7.9.1–2. Clinical Response at Test of Cure Excluding Subjects with Abscesses, Noninferiority Tests, Study P903-07—MITT and CE Populations .....	90
Table 7.9.2–1. FDA Exploratory Endpoint at Study Day 3, Noninferiority Tests, Phase 3 Complicated Skin and Skin Structure Infection Studies — FDA-MITT Population .....	91
Table 7.9.3–1 Reduction in Infection Area at End of Therapy, Phase 3 Complicated Skin and Skin Structure Infection Studies — FDA-MITT Population .....	92
Table 8.1–1. Number of Subjects in Safety Database .....	93
Table 8.2–1 Extent of Exposure, Pooled Clinical Pharmacology, Phase 2, and Phase 3 Studies .....	95
Table 8.3–1. Summary of Adverse Events, Phase 3 Studies—Safety Population .....	96
Table 8.3.1–1. Incidence of Common ( $\geq 1\%$ ) Treatment-Emergent Adverse Events, Phase 3 Studies —Safety Population .....	98
Table 8.3.2.1–1. Incidence of Death, Phase 3 Studies—Safety Population .....	101

Table 8.3.2.1–2. Listing of All Subjects Who Died in Phase 3 Studies—Safety Population .....	103
Table 8.4.1–1. Summary of Renal Events, Phase 3 Studies—Safety Population .....	107
Table 8.4.1–2. Distribution of Maximum Values for Potentially Clinically Significant Creatinine Values, Phase 3 Studies—Safety Population .....	108
Table 8.4.1–3. Summary of Independent Nephrology Review of All Renal Events, Phase 3 Studies—Safety Population .....	109
Table 8.4.2–1. Incidence of Treatment-Emergent Adverse Events Indicating Potential Liver Injury, Phase 3 Studies—Safety Population .....	114
Table 8.4.2–2. Potentially Clinically Significant Postbaseline Hepatic Chemistry Values, Phase 3 Studies—Safety Population .....	115
Table 8.4.3–1. Incidence of Treatment-Emergent-Adverse Events by Discrete Category of Rash, Hypersensitivity, or Pruritus, Phase 3 Studies—Safety Population .....	116
Table 8.4.3–2. Incidence of Severe or Serious Potential Allergic Reactions, Phase 3 Studies—Safety Population .....	117
Table 8.4.4–1. Selected Potentially Clinically Significant Hematology Values, Phase 3 Studies—Safety Population .....	119

## 2.3 LIST OF IN-TEXT FIGURES

Figure 6.2–1. Analysis Populations, Pooled Community-acquired Bacterial Pneumonia Studies .....	47
Figure 6.6–1. Clinical Response and Confidence Intervals for the Difference in Clinical Cure Rates at Test of Cure, Phase 3 Community-acquired Bacterial Pneumonia Studies—MITTE and CE Populations .....	57
Figure 7.2–1. Analysis Populations, Pooled Phase 3 Complicated Skin and Skin Structure Studies .....	71
Figure 7.6–1. Clinical Response and Confidence Intervals for the Difference in Clinical Cure Rates at Test of Cure, Phase 3 Complicated Skin and Skin Structure Studies—MITT and CE Populations .....	81

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### **ABBREVIATIONS**

%T > MIC	percent time during the dosing interval that plasma free drug concentration exceeded the minimum inhibitory concentration
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATS	American Thoracic Society
AUC	area under the time concentration curve
CA-MRSA	community-acquired methicillin-resistant <i>Staphylococcus aureus</i>
CAP	community-acquired pneumonia
CABP	community-acquired bacterial pneumonia
CE	clinically evaluable
CI	confidence interval
C <sub>max</sub>	maximum plasma drug concentration
COPD	chronic obstructive pulmonary disease
CrCl	creatinine clearance
cSSSI	complicated skin and skin structure infection
ECG	electrocardiogram
EOT	end of therapy
ESBL	extended-spectrum beta-lactamase
ESRD	end-stage renal disease
FDA	Food and Drug Administration
FDA-MITT	FDA-defined modified intent-to-treat
FDA-mMITT	FDA-defined microbiological modified intent-to-treat
Hgb	hemoglobin
ICH	International Conference on Harmonisation
ICU	intensive care unit

IM	intramuscular
IND	Investigational New Drug (application)
ITT	intent-to-treat
IV	intravenous
LDH	lactate dehydrogenase
LFU	late follow-up
MDRSP	multidrug-resistant <i>Streptococcus pneumoniae</i>
ME	microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
MIC <sub>90</sub>	minimum concentration that inhibits 90% of organisms
MITT	modified intent-to-treat
MITTE	modified intent-to-treat efficacy
mMITT	microbiological modified intent-to-treat
mMITTE	microbiological modified intent-to-treat efficacy
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
MSSA	methicillin-susceptible <i>Staphylococcus aureus</i>
OPAT	outpatient parenteral antimicrobial therapy
PBP	penicillin-binding protein
PCS	potentially clinically significant
PD	pharmacodynamic
PK	pharmacokinetic
PORT	Pneumonia Outcomes Research Team
PRSP	penicillin-resistant <i>Streptococcus pneumoniae</i>
PVD	peripheral vascular disease
PVL	Panton-Valentine leukocidin
q12h	every 12 hours

q24h	every 24 hours
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate by Bazett's formula
QTcF	QT interval corrected for heart rate by Fridericia's formula
QTcIb	QT interval corrected for heart rate with an individual subject correction formula based on the baseline QT-RR slope
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SIRS	systemic inflammatory response syndrome
SOC	system organ class
SSSI	skin and skin structure infection
T <sub>½</sub>	terminal elimination half-life
TEAE	treatment-emergent adverse event
TOC	test of cure
ULN	upper limit of normal
VISA	vancomycin-intermediate <i>Staphylococcus aureus</i>
VRSA	vancomycin-resistant <i>Staphylococcus aureus</i>
WBC	white blood cell



## **4.0 EXECUTIVE SUMMARY**

### **4.1 INTRODUCTION**

Ceftaroline is a next-generation cephalosporin antibiotic with broad-spectrum activity against clinically important gram-positive and gram-negative bacteria, including contemporary resistant gram-positive phenotypes such as methicillin-resistant *Staphylococcus aureus* (MRSA), multidrug-resistant *Streptococcus pneumoniae* (MDRSP), and penicillin-resistant *Streptococcus pneumoniae* (PRSP). Like other beta-lactams, ceftaroline inhibits penicillin-binding proteins (PBPs), which are membrane-bound enzymes of the cytoplasmic membrane involved in the biosynthesis of the bacterial cell wall. Ceftaroline exhibits unique properties that distinguish it from other beta-lactams, in that it has potent bactericidal activity against resistant gram-positive organisms due to its high affinity for PBPs, ie, PBP2a in MRSA and PBP2x in PRSP.

Ceftaroline is administered as the N-phosphonoamino water-soluble prodrug ceftaroline fosamil, which is rapidly converted to active ceftaroline in plasma. In this document, ‘ceftaroline fosamil’ is used when necessary to clearly differentiate the prodrug from the bioactive form and when specifically referring to the form of the drug administered to subjects (ie, when describing dosages or proposed labeling). However, for brevity, the name ‘ceftaroline’ is used to describe treatment groups, in table headers and footnotes, and in general results discussions.

Ceftaroline fosamil for Injection is proposed for the treatment of patients with community-acquired bacterial pneumonia (CABP) or complicated skin and skin structure infection (cSSSI) caused by susceptible strains of the following designated microorganisms:

CABP: Ceftaroline fosamil for Injection at a dose of 600 mg intravenous (IV) every 12 hours (q12h) for 5 to 7 days is effective for the treatment of CABP caused by susceptible isolates of the following gram-positive and gram-negative microorganisms: *Streptococcus pneumoniae* (including MDRSP and cases with concurrent bacteremia), methicillin-susceptible *Staphylococcus aureus* (MSSA), *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Klebsiella pneumoniae*, and *Escherichia coli*.

cSSSI: Ceftaroline fosamil for Injection at a dose of 600 mg IV q12h for 5 to 14 days is effective for the treatment of cSSSI caused by susceptible isolates of the following gram-positive and gram-negative microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus anginosus* group (includes *S. anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*), *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Morganella morganii*.

The core of the development program of ceftaroline in CABP and cSSSI consisted of 4 large, global, randomized, placebo-controlled Phase 3 studies in 1240 subjects with CABP (Studies P903-08 and P903-09) and 1396 subjects with cSSSI (Studies P903-06 and P903-07). All 4 studies demonstrated the noninferiority of ceftaroline in the primary efficacy endpoint compared with ceftriaxone in CABP and vancomycin plus aztreonam in cSSSI. The safety of ceftaroline has been evaluated in 1745 randomized and treated subjects in Phase 1 to 3 studies, of whom 1305 subjects received ceftaroline 600 mg IV q12h in the Phase 3 CABP and cSSSI studies, demonstrating that ceftaroline is well tolerated with a safety profile similar to that observed for the comparator agents and consistent with known cephalosporin class effects. The safety and efficacy data support a positive benefit/risk assessment for the use of ceftaroline in the current and future evolving environment of microbial resistance in CABP and cSSSI.

#### **4.2 REGULATORY AND DEVELOPMENT HISTORY**

The data analyses presented in this briefing book are based on FDA draft guidance documents that were available at the time of study design and on additional requests by the agency and discussions between the FDA and Sponsor that occurred before 31 Jul 2010. The IND for ceftaroline was submitted in December 2004 for the treatment of cSSSI and CABP. A Phase 2 study comparing IV ceftaroline to IV vancomycin plus aztreonam in patients with cSSSI was conducted in 2005. In 2006, FDA granted Cerexa (which became a subsidiary of Forest Laboratories Inc. in January 2007) fast track designation to Ceftaroline fosamil for Injection for the treatment of cSSSI.

The Phase 3 development of ceftaroline for the treatment of cSSSI, including final agreements on the primary endpoints (per-subject clinical cure rate at test of cure (TOC) in the coprimary clinically evaluable (CE) and modified intent-to-treat (MITT) Populations) and 10% noninferiority margin, was discussed and agreed upon with the FDA between October 2006 (End-of-Phase 2 meeting) and June 2007. Final study design and protocols for the Phase 3 cSSSI studies were consistent with existing FDA guidelines. The Phase 3 cSSSI trials (2 identically designed studies comparing ceftaroline to a combination of vancomycin plus aztreonam) were initiated in February and March 2007 and completed in November and December 2007, respectively. Further discussions with the FDA, post NDA submission, led to additional post-hoc sensitivity and exploratory analyses, including clinical cure at TOC among subjects without abscess and clinical response at Study Day 3 in a new exploratory population.

The Phase 3 development of ceftaroline for the treatment of CABP, including final agreements on the primary endpoints (clinical response at TOC in the coprimary CE and modified intent-to-treat efficacy [MITTE] Populations) and 10% noninferiority margin in subjects with moderate-to-severe CABP, defined as Pneumonia Outcomes Research Team [PORT] Risk Class of III or greater, was discussed and agreed upon with the FDA between October 2006 (End-of-Phase 2 meeting) and September 2007.

On 22 Nov 2006, the FDA and Cerexa agreed on the primary endpoint and analysis populations. Cerexa submitted a request for Special Protocol Assessment on 26 Jan 2007 for the Phase 3 CABP protocols. On 15 Mar 2007, the FDA's Division of Anti-Infective Drug Products advised that Cerexa should not include treatment with a long-acting concomitant macrolide or an option for an oral switch in these studies because concomitant non-study drug antimicrobials could confound the assessment of efficacy of ceftaroline. On 17 Apr 2007, Cerexa informed the Division that, due to incompatibility with Infectious Diseases Society of America/ American Thoracic Society (ATS) guidelines (Mandell et al, 2007) with respect to the lack of adjunctive macrolide therapy, enrollment in the United States would be difficult. However, to meet the Agency's needs, on 01 Jun 2007, Cerexa and the FDA agreed that Study P903 09 would be an IV only study with no adjunctive therapy and that Study P903 08 would allow for only 24 hours (2 doses) of an adjunctive short-acting macrolide (clarithromycin) with no option for an oral switch.

One potentially substantive study design change that occurred during the conduct of both Phase 3 CABP studies was an entry criterion change in protocol Amendment 2 wherein subjects in PORT Risk Class II were no longer eligible for enrollment in either study. This change was made to comply with review suggestions from the FDA. Specifically, on 11 Sep 2007, the Division acknowledged and accepted the use of a 10% noninferiority margin in evaluating clinical efficacy only among subjects with moderate-to-severe CABP, defined as PORT Risk Class of III or greater. The planned primary and secondary efficacy analyses changed in protocol Amendment 2 from inclusion of subjects in PORT Risk Class II, III, or IV to include only subjects in PORT Risk Class III or IV. Both studies had already enrolled some subjects in PORT Risk Class II; therefore, the total sample sizes in both studies were increased to adequately power the primary analysis. As a consequence, subjects in PORT Risk Class II who were enrolled before Amendment 2 were excluded from the coprimary efficacy analysis populations (MITTE and CE). The Statistical Analysis Plans (SAPs) for the CABP studies were submitted to the Division for review and comment, and Division recommendations were incorporated into the SAPs prior to database lock and unblinding. Final study designs and protocols for the Phase 3 CABP studies were consistent with existing FDA guidelines (Section 6.1).

The Phase 3 CABP trials were initiated in July 2007 and January 2008 and completed in August and December 2008, respectively. Further discussions with the FDA, post NDA submission, led to additional post-hoc exploratory analyses, including clinical response at Study Day 4 in a separately defined population with microbiological isolates.

## 4.3 BACKGROUND

### 4.3.1 Community-acquired Bacterial Pneumonia

Community-acquired bacterial pneumonia is a commonly occurring serious infection that requires systemic antibiotic therapy and is associated with substantial morbidity, mortality, and considerable healthcare costs. Together with influenza, community-acquired pneumonia (CAP) is the eighth leading cause of death in the United States (File and Marrie, 2010). CAP accounts for over 4 million office visits in the United States, and the hospitalization rate has increased to over 1600 per 100,000 persons over the last decade (File and Marrie, 2010). Approximately 1 million episodes of CAP occur in adults 65 years of age or older each year in the United States (Jackson et al, 2004).

Despite advances in antimicrobial therapy, rates of mortality due to CAP have not substantially decreased over the past several decades (Feikin et al, 2000). This observation is in part due to an increased percentage of population at risk (ie, patients of advanced age and immunocompromised patients) and to the emergence of highly resistant or highly virulent pathogens. The rising incidence of drug resistance in *S. pneumoniae*, the most common causative organism in CAP, has led to challenges in the treatment of patients with severe or invasive disease due to this pathogen. In particular, the increasing incidence of drug resistance among *S. pneumoniae* “replacement strains” not covered by the current pneumococcal vaccines is alarming. For example, the incidence of *S. pneumoniae* serotype 19A has increased 4-fold since 1994 and the incidence of invasive pneumococcal disease due to penicillin-resistant serotype 19A increased from 6% to 35% from 1998 to 2005 (Moore et al, 2008). The current estimated prevalence of MDRSP, among patients with respiratory disease due to *S. pneumoniae*, is 20% (Richter et al, 2009). The same study reported the current prevalence of *S. pneumoniae* with intermediate penicillin resistance to be approximately 18% and with penicillin resistance (minimum inhibitory concentration [MIC]  $\geq 2$   $\mu\text{g/mL}$ ) to be 15%. Drug resistance was detected in approximately 29% of isolates to erythromycin, 21% to trimethoprim/sulfamethoxazole, 16% to tetracycline, 5% to beta-lactams such as amoxicillin and ceftriaxone, and 1% to fluoroquinolones (Richter et al, 2009). A report of vancomycin tolerance in *S. pneumoniae* due to a mutation in the *vncS* gene is also worrisome (Novak et al, 1999), as vancomycin is considered one of the antibiotics of last resort for this CAP pathogen.

In addition, *S. aureus*, including MRSA, has emerged as an important pathogen in CAP. Approximately 25% of cases of CAP are due to *S. aureus* and these cases are associated with increased mortality (Kollef et al, 2005). Community-acquired MRSA (CA-MRSA) has been associated with a severe, necrotizing form of CAP (Gillet et al, 2007). This form of CAP is associated with Panton-Valentine leukocidin (PVL) production and has an overall mortality rate of 56%; refractory shock, airway bleeding, and leukopenia have been associated with fatal outcomes in these patients. The incidence of severe MRSA CAP appears to be rising, with increasing reports during recent influenza seasons (Centers for Disease Control, 2007, 2009). These data underscore the need for new antibiotics for the treatment of severe CABP due to CA-MRSA.

Toxicities and substantial treatment-limiting adverse events (AEs) are of concern regarding the currently available antibiotic agents for CABP. For example, multiple approved antibiotics for CABP have label safety warnings that make these agents unsuitable therapeutic agents for certain patients, including carbapenems (seizures), fluoroquinolones (tendinopathy and tendon rupture, QT prolongation, hematological toxicities, central nervous system effects, peripheral neuropathy), linezolid (myelosuppression), macrolides (fetal toxicity), and tigecycline (fetal harm, GI toxicity). In addition, higher risk for drug-associated toxicities may occur if combination therapy is required for CABP, for example in cases where a specific anti-MRSA agent (eg, vancomycin or linezolid) is required as an addition to the initial empiric regimen in suspected cases of MRSA infection. Ceftaroline offers a broad spectrum of activity against common gram-positive and gram-negative pathogens including potent in vitro activity against MDRSP and MRSA, and the aforementioned treatment-limiting drug reactions have not been observed in the ceftaroline development program. Ceftaroline does not appear to have any toxicity beyond that expected for other members of the cephalosporin class such as hypersensitivity (Section 8.4.3) or *C. difficile*-associated diarrhea (Section 8.4.6).

In summary, ceftaroline addresses the unmet medical needs in the treatment of CABP. Specifically, monotherapy with ceftaroline is associated with high clinical cure rates and favorable microbiological outcomes, and ceftaroline has increased effectiveness for CABP compared with ceftriaxone (especially with regard to gram-positive, eg *S. pneumoniae*, infections; Section 6.7.2). Its broader spectrum of activity and enhanced bactericidal activity against highly resistant and highly virulent gram-positive organisms offer potential advantages over other available cephalosporins. This activity, due to its uniquely strong affinity for specific microbial PBPs (eg, PBP2a and PBP2x), allows for ceftaroline to be administered as a monotherapy for CABP as defined by the FDA, in covering both sensitive and resistant community-acquired typical pathogens. The efficacy of ceftaroline against CA-MRSA could not be evaluated in the CABP studies due to FDA guidance for an IV-only study with ceftriaxone as a comparator. Finally, ceftaroline has a safety profile consistent with available marketed cephalosporins, a class of antibiotics with a long history of clinical use.

Appropriate and effective antibiotic therapy is one of the most important factors in ensuring successful treatment of CAP and new antibiotics for treatment of infections caused by resistant organisms are needed (Spellberg et al, 2008). Considering the public health need for new drugs to treat moderate-to-severe CABP, the results of the studies described below indicate that ceftaroline represents an important anti-infective option for the treatment of CABP.

#### 4.3.2 Complicated Skin and Skin Structure Infection

Complicated skin and skin structure infection is a group of common infections that requires systemic antibiotic therapy, surgical management, and hospitalization, and may be life-threatening or severe (DiNubile and Lipsky, 2004; Elston, 2005; Eron et al, 2003; Nichols and Florman, 2001). Severe cSSSI requiring hospitalization or medical attention is increasing in incidence; from 1997 to 2005 the overall rate of doctor visits for cSSSI increased from 32.1 to 48.1 visits per 1000 population, reaching 14.2 million visits in the United States (Hersh et al, 2008). Furthermore, when cSSSI is complicated by the presence of antimicrobial-resistant pathogens or highly virulent pathogens (eg, CA-MRSA), an appropriate therapeutic choice is increasingly challenging and suboptimal patient outcomes often result (Howell-Jones, 2005).

Many microbial species cause cSSSI, the most common being *S. aureus*. In fact, the global SENTRY Antimicrobial Surveillance Program demonstrated that *S. aureus* was the most prevalent cause of nosocomial and community-acquired skin and skin structure infections (SSSI) and bloodstream infections in almost all geographic regions (Diekema et al, 2001; Moet et al, 2007). In the United States, MRSA causes approximately 35% to 72% of SSSIs (Moet et al, 2007; Awad et al, 2007; King et al, 2006). In addition, CA-MRSA cSSSIs have been associated with worse outcomes than those with methicillin-sensitive *S. aureus* (MSSA); this phenomenon may be related to increased virulence of CA-MRSA (Davis et al, 2007). Similarly, nosocomial MRSA cSSSIs, such as surgical site infections, tend to be associated with relatively high morbidity and mortality rates (Cosgrove, 2006; Engemann et al, 2003). Appropriate and effective antibiotic therapy is one of the most important factors in ensuring successful treatment of cSSSI. Therefore, new antibiotics for treatment of infections caused by *S. aureus* (including MRSA) and other bacterial pathogens are needed (Stevens et al, 2005; Dryden, 2008).

It is important to note that gram-negative pathogens (eg, enteric and water-borne gram-negative bacilli) may also cause cSSSI (Stevens et al, 2005). Empiric antimicrobial coverage against both gram-positive and gram-negative pathogens must be considered in every case of cSSSI, with consideration of patient risk factors and the type of cSSSI (Stevens et al, 2005). For example, broad-spectrum empiric antibiotic therapy with gram-negative pathogen coverage should be considered for many types of cSSSI including surgical site or traumatic wound infections, necrotizing skin infections, cSSSI associated with human or animal bites, and cSSSI in immunocompromised subjects.

Current treatments that are approved for the indication of cSSSI in the United States include cefotaxime, ceftriaxone, daptomycin, ertapenem, levofloxacin, linezolid, meropenem, piperacillin/tazobactam, telavancin, tigecycline, and vancomycin. Vancomycin continues to be widely used for cSSSI to cover suspected or documented MRSA, but the emergence of infections due to vancomycin-nonsusceptible *S. aureus* poses challenges (Sievert et al, 2008; Pillai et al, 2009). There are also recent reports of *S. aureus* nonsusceptibility to daptomycin (Tenover et al, 2009, Kirby et al, 2009) and linezolid (Mendes et al, 2008; Toh et al, 2007). There are some limitations to agents with anti-MRSA activity with regard to toxicity and the emergence of resistance. The following agents used for the treatment of MRSA have safety warnings: linezolid (myelosuppression), tigecycline (fetal harm and hepatic dysfunction), telavancin (renal toxicity and teratogenicity), and vancomycin (ototoxicity) (Zyvox [linezolid] package insert, 2007; Tygacil [tigecycline] package insert, 2009; Vibativ [telavancin] package insert, 2009; Vancocin [vancomycin] package insert, 2008). Because all of the above anti-MRSA agents (with the exception of tigecycline) have activity against gram-positive organisms only, a second agent is often required to cover gram-negative organisms.

In summary, ceftaroline addresses the unmet medical needs of cSSSI as evidenced by its efficacy and safety compared with currently available marketed products. Specifically, monotherapy with ceftaroline is associated with high success rates in cSSSI compared with a combination antibiotic regimen (ie, vancomycin plus aztreonam). Its broader in vitro spectrum of activity and enhanced bactericidal activity against highly resistant and highly virulent gram-positive organisms offer potential advantages over other available agents. This activity, due to its uniquely strong affinity for specific microbial PBPs (eg, PBP2a and PBP2x), allows for ceftaroline to be administered as a monotherapy for cSSSI, in covering both sensitive and resistant community-acquired bacterial pathogens. Finally, as noted above, ceftaroline has a safety profile consistent with the cephalosporin drug class. Monotherapy with ceftaroline offers a new effective treatment option for cSSSI, including coverage for infections caused by MRSA, without a safety liability.

#### **4.4 CLINICAL DEVELOPMENT PROGRAM & EFFICACY**

Evidence for the antimicrobial activity, efficacy, and safety of ceftaroline was derived from preclinical microbiological surveillance studies, studies in animal models of pneumonia, thigh infection, peritonitis, endocarditis and pneumonia, and Phase 1 - 3 clinical studies in humans. A total of 17 clinical studies (3153 subjects) have been conducted and completed with ceftaroline fosamil, including 11 Phase 1 clinical pharmacology studies (305 subjects), 2 Phase 2 cSSSI studies (242 subjects), and 4 Phase 3 studies (2606 subjects).

Preclinical pharmacokinetic (PK) studies determined that systemic exposure to ceftaroline increases approximately in proportion to increases in dose within the dose range of 50 to 1000 mg. The terminal elimination half-life ( $T_{1/2}$ ) of ceftaroline is approximately 2.5 hours in subjects with normal renal function and no appreciable accumulation is observed following multiple q12h doses. Ceftaroline is predominantly eliminated by the kidneys, and dosage adjustment is recommended for patients with creatinine clearance (CrCL) < 50 mL/min. Ceftaroline does not appear to be metabolized by the liver and does not inhibit or induce the cytochrome P450 system.

Preliminary population PK modeling based on MIC data for clinically relevant pathogens, PK/ pharmacodynamic (PD) targets from animal models of infection, and PK data from Phase 1 subjects with normal renal function and mild and moderate renal impairment and Phase 2 subjects with cSSSI were used to carry out Monte Carlo simulations in order to establish an optimal dosing regimen for use in the Phase 3 studies. Monte Carlo simulations revealed that subjects with normal renal function dosed with ceftaroline fosamil 600 mg q12h as a 1-hour infusion would achieve sufficient plasma exposure to provide 90% probability of target attainment for a percent time that plasma free drug concentrations exceed the MIC (%T > MIC) target of 40% for pathogens with an MIC up to and including 2 µg/mL. The target attainment analyses also supported doses of 600 mg q12h in subjects with mild renal impairment and 400 mg q12h in subjects with moderate renal impairment. These dose regimens were selected for the Phase 3 CABP and cSSSI studies.

The Phase 3 CABP studies were adequate and well controlled, multicenter, randomized, double-blind, active-controlled studies in adult subjects (Study P903-08 and Study P903-09). Ceftaroline fosamil was administered at a dose of 600 mg for 5 to 7 days for the treatment of moderate-to-severe CABP (PORT Risk Class III - IV). The active comparator regimen was ceftriaxone 1 g IV every 24 hours (q24h). Studies P903-08 and P903-09 were identical in design with the exception that subjects in Study P903-08 were administered 2 oral doses of adjunctive clarithromycin at 500 mg each during the initial 24 hours on study to provide initial coverage against atypical organisms. The primary efficacy endpoint was clinical response at TOC in the coprimary CE and MITTE Populations (Table 4.4–1). In the pooled Phase 3 CABP studies, the clinical cure rate at TOC in the CE Population was 84.3% in the ceftaroline group compared with 77.7% in the ceftriaxone group (95% CI 1.6, 11.8); in the MITTE Population, the clinical cure rate was 82.6% in the ceftaroline group and 76.6% in the ceftriaxone group (95% CI 1.4, 10.7). The observed clinical cure rate was higher in the ceftaroline group compared with the ceftriaxone group in each individual Phase 3 CABP study as well, with the lower limit of the 95% CI around the treatment differences in cure rates (ceftaroline – ceftriaxone) being greater than the prespecified noninferiority boundary of -10% in each coprimary population in each study. The noninferiority of ceftaroline compared with ceftriaxone was supported by efficacy results in each of the predefined secondary and subgroup analyses, as well as post-hoc exploratory analyses suggested by the FDA.



Table 4.4–1 provides a summary of the primary efficacy endpoint, clinical response at TOC in the coprimary CE and MITTE Populations of the Phase 3 CABP studies.

**Table 4.4–1. Clinical Response at Test of Cure, Phase 3 Community-acquired Bacterial Pneumonia Studies—MITTE and CE Populations**

<i>Population/Clinical Response</i>	<i>P903-08</i>		<i>P903-09</i>		<i>Pooled Phase 3 Studies (08, 09)</i>	
	<i>Ceftaroline n (%)</i>	<i>Ceftriaxone n (%)</i>	<i>Ceftaroline n (%)</i>	<i>Ceftriaxone n (%)</i>	<i>Ceftaroline n (%)</i>	<i>Ceftriaxone n (%)</i>
<b>MITTE</b>						
N	291	300	289	273	580	573
Clinical Cure	244 (83.8)	233 (77.7)	235 (81.3)	206 (75.5)	479 (82.6)	439 (76.6)
Crude difference (95% CI)	6.2 (-0.2, 12.6)		5.9 (-1.0, 12.7)		6.0	
Weighted difference (95% CI)					6.0 (1.4, 10.7)	
<b>CE</b>						
N	224	234	235	215	459	449
Clinical Cure	194 (86.6)	183 (78.2)	193 (82.1)	166 (77.2)	387 (84.3)	349 (77.7)
Crude difference (95% CI)	8.4 (1.4, 15.4)		4.9 (-2.5, 12.5)		6.6	
Weighted difference (95% CI)					6.7 (1.6, 11.8)	

Abbreviations: CE = clinically evaluable; MITTE = modified intent-to-treat efficacy.

Notes: Crude difference = difference in clinical cure rates (ceftaroline treatment group minus ceftriaxone treatment group). Weighted difference = weighted difference (stratified by study) in clinical cure rates (ceftaroline treatment group minus ceftriaxone treatment group). Confidence intervals are calculated using Miettinen and Nurminen method without adjustments except for pooled studies (stratified by study). Noninferiority margin of 10% is used.

The Phase 3 cSSSI studies were adequate and well controlled, multicenter, randomized, double-blind, active-controlled studies in adult subjects (Studies P903-06 and P903-07). Ceftaroline fosamil was administered as monotherapy at a dose of 600 mg q12h for 5 to 14 days for the treatment of cSSSI. The active comparator regimen was vancomycin 1 g IV q12h plus aztreonam 1 g IV q12h. Studies P903-06 and P903-07 were identical in design. The primary efficacy endpoint was clinical response at TOC in the coprimary CE and MITT Populations (Table 4.4–2). In the pooled Phase 3 cSSSI studies, the clinical cure rate at TOC in the CE Population was 91.6% in the ceftaroline group compared with 92.7% in the vancomycin plus aztreonam group (95% CI -4.2, 2.0); in the MITT Population, the clinical cure rate was 85.9% in the ceftaroline group and 85.5% in the vancomycin plus aztreonam group (95% CI -3.4, 4.0). The results were similar in each individual study, demonstrating that ceftaroline was noninferior to vancomycin plus aztreonam in subjects with cSSSI, as evidenced by the lower limit of the 95% CI around the differences (ceftaroline – vancomycin plus aztreonam) in cure rates being greater than the prespecified noninferiority boundary of -10%. The noninferiority of ceftaroline monotherapy compared with vancomycin plus aztreonam was supported by efficacy results in each of the predefined secondary and subgroup analyses, as well as post-hoc exploratory analyses suggested by the FDA.

Table 4.4–2 provides an overall summary of the primary efficacy endpoint, clinical response at TOC, in the coprimary analysis populations (CE and MITT) of the Phase 3 cSSSI studies.

**Table 4.4–2. Clinical Response at Test of Cure, Phase 3 cSSSI Studies—MITT and CE Populations**

<i>Population/ Clinical Response</i>	<i>P903-06</i>		<i>P903-07</i>		<i>Pooled Phase 3 Studies (06, 07)</i>	
	<i>Ceftaroline n (%)</i>	<i>Vancomycin plus Aztreonam n (%)</i>	<i>Ceftaroline n (%)</i>	<i>Vancomycin plus Aztreonam n (%)</i>	<i>Ceftaroline n (%)</i>	<i>Vancomycin plus Aztreonam n (%)</i>
<b>MITT</b>						
N	351	347	342	338	693	685
Clinical Cure	304 (86.6)	297 (85.6)	291 (85.1)	289 (85.5)	595 (85.9)	586 (85.5)
Crude difference (95% CI)	1.0 (-4.2, 6.2)		-0.4 (-5.8, 5.0)		0.3	
Weighted difference (95% CI)					0.3 (-3.4, 4.0)	

**Table 4.4–2. Clinical Response at Test of Cure, Phase 3 cSSSI Studies—MITT and CE Populations**

<i>Population/ Clinical Response</i>	<i>P903-06</i>		<i>P903-07</i>		<i>Pooled Phase 3 Studies (06, 07)</i>	
	<i>Ceftaroline n (%)</i>	<i>Vancomycin plus Aztreonam n (%)</i>	<i>Ceftaroline n (%)</i>	<i>Vancomycin plus Aztreonam n (%)</i>	<i>Ceftaroline n (%)</i>	<i>Vancomycin plus Aztreonam n (%)</i>
<b>CE</b>						
N	316	300	294	292	610	592
Clinical Cure	288 (91.1)	280 (93.3)	271 (92.2)	269 (92.1)	559 (91.6)	549 (92.7)
Crude difference (95% CI)	-2.2 (-6.6, 2.1)		0.1 (-4.4, 4.5)		-1.1	
Weighted difference (95% CI)					-1.1 (-4.2, 2.0)	

Abbreviations: CE = clinically evaluable; MITT = modified intent-to-treat.

Notes: Crude difference = difference in clinical cure rates (ceftaroline treatment group minus comparator treatment group). Weighted difference = weighted difference (stratified by study) in clinical cure rates (ceftaroline treatment group minus comparator treatment group). Confidence intervals are calculated using Miettinen and Nurminen method without adjustments except for pooled studies (stratified by study). Noninferiority margin of 10% is used.

## 4.5 SAFETY SUMMARY

The safety profile of ceftaroline was evaluated in 1745 subjects treated with ceftaroline, including 1305 subjects in the Phase 3 CABP and cSSSI studies. The incidences of treatment-emergent adverse events (TEAEs) experienced by subjects receiving ceftaroline were similar compared with subjects receiving comparator therapies. No TEAE had an incidence of > 5% in subjects receiving ceftaroline. In the pooled Phase 3 studies, the most common TEAEs in the ceftaroline group were diarrhea, headache, and nausea. Most of the TEAEs were mild or moderate in severity and were assessed as unrelated to study drug administration. The incidences of death, serious adverse events (SAEs), and discontinuation of study drug or withdrawal from the study due to an adverse event (AE) in ceftaroline-treated subjects were low and similar compared with subjects receiving comparator therapies.

Additional safety analyses with regard to known cephalosporin class effects were performed, revealing no unique clinically significant safety signals for ceftaroline based on the clinical trial experience in patients and normal volunteers. An independent review of all renal safety data by the Sponsor and 2 blinded nephrologists identified no clinically meaningful differences between the treatment groups, and no adverse renal effects were detected beyond those expected for the cephalosporin class. The incidences of subjects in the ceftaroline and comparator groups with TEAEs representing potential liver injury or potential allergic events were low and similar between treatment groups. Rates of seroconversion to a positive direct Coombs test were higher in the ceftaroline compared to the comparator groups (10.7% vs 4.4%, respectively); however, the observed incidence rates were within the expected range of Coombs seroconversion associated with cephalosporins, and was not associated with clinical events of hemolytic anemia or an increased incidence of abnormal hematological laboratory findings. Seizures were rare, and the 2 observed cases of seizure in the ceftaroline group occurred 2 or more days after completion of study drug treatment. Finally, *Clostridium difficile*-associated diarrhea was rare, occurring in 2 subjects in the ceftaroline group and 1 subject in the comparator group in the pooled Phase 3 studies. Of note, ceftaroline had little effect on the intestinal microflora and was not measurable in the feces in a Phase 1 study that evaluated the effect of ceftaroline on the intestinal microflora in healthy subjects.

In summary, ceftaroline was well tolerated in adults treated for CABP and cSSSI and had a safety profile consistently reflective of the cephalosporin class.

#### **4.6 RISK BENEFIT SUMMARY**

CABP and cSSSI are very common infectious diseases associated with rising morbidity and mortality, hospitalization and office visits, and associated health care costs. New antibiotics that are safe and highly active against emergent drug-resistant pathogens such as MRSA, MDRSP, and other highly resistant gram-positive bacteria are needed to address the existing unmet medical needs in the management of CABP and cSSSI. Ceftaroline is well suited to fill this niche and represents an important addition to the armamentarium of prescribing clinicians for the following reasons:

- A broad spectrum of activity including a wide range of gram-positive and gram-negative bacteria, including excellent in vitro activity against emerging resistant pathogens such as hospital-associated and CA-MRSA, MDRSP, PRSP, vancomycin-intermediate *Staphylococcus aureus* (VISA), and vancomycin-resistant *Staphylococcus aureus* (VRSA). This in vitro spectrum of activity offers clear advantages over other available cephalosporins.
- Its unique mechanism of action featuring strong affinity for modified PBPs, such as PBP2a in MRSA and PBP2x in PRSP, contributes to its potent activity against contemporary resistant gram-positive phenotypes.

- Low propensity for resistance development against common cSSSI or CABP pathogens, ie, spontaneous resistant mutants were not observed for *S. aureus* or *S. pneumoniae* when plating on media containing 4 times MIC of ceftaroline (spontaneous mutation frequency  $\leq 10^{-10}$ ) or in serial passage studies.
- Not metabolized by the liver and not an inhibitor or inducer of major cytochrome P450 enzymes, making clinically relevant drug-drug interactions through hepatic mechanisms unlikely.
- Effective in the treatment of CABP, with evidence of increased effectiveness of ceftaroline over ceftriaxone in clinical cure at TOC in both Phase 3 CABP studies. Ceftriaxone is currently considered one of the antibiotics of first choice for the empiric treatment of CABP in the United States and worldwide.
- Effective in the treatment of cSSSI as monotherapy, with ceftaroline noninferior to combination therapy with vancomycin plus aztreonam in clinical cure at TOC in both Phase 3 cSSSI studies. Monotherapy with ceftaroline offers greater simplicity as a treatment regimen compared to combination therapy.
- Ceftaroline does not have any toxicity beyond that expected for other members of the cephalosporin class.

In summary, ceftaroline offers a well tolerated, safe, and effective therapy that will benefit patients with either CABP or cSSSI. The totality of clinical data supports a positive benefit/risk assessment for the use of ceftaroline in the current and future evolving environment of microbial resistance in CABP and cSSSI. Ceftaroline addresses distinct areas of unmet medical need and has the potential to improve the treatment of CABP and cSSSI compared with currently available products, as evidenced by its effectiveness in the treatment of CABP and cSSSI.

## **5.0** **CEFTAROLINE OVERVIEW**

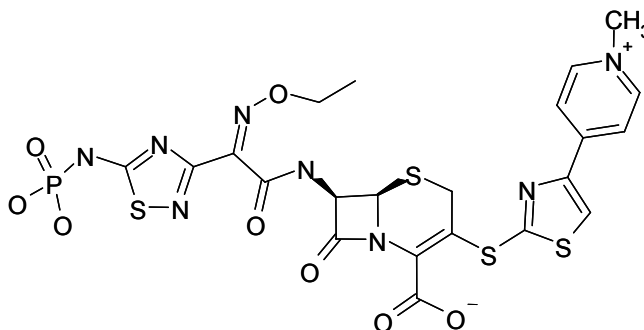
### **5.1** **CHEMISTRY**

Ceftaroline fosamil is a sterile, parenteral prodrug cephalosporin antibiotic.

**Chemical name:**

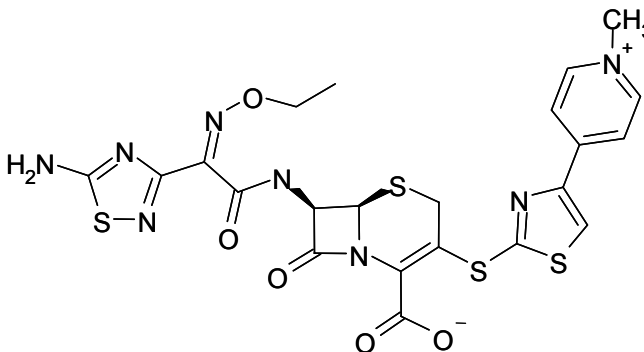
(6R,7R)-7-[(2Z)-2-(ethoxyimino)-2-[5-(phosphonoamino)-1,2,4-thiadiazol-3-yl]acetamido]-3-[[4-(1-methylpyridin-1-ium-4-yl)-1,3-thiazol-2-yl]sulfanyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate

**Structural Formula of Ceftaroline Fosamil:**



The N-phosphonoamino water-soluble prodrug is rapidly converted in plasma into the bioactive ceftaroline.

**Structural Formula of Ceftaroline**



## 5.2 NONCLINICAL SAFETY EVALUATION

### 5.2.1 In Vivo Studies

The kidney was considered the target organ in the toxicity studies using supratherapeutic doses of ceftaroline. In 4- and 13-week repeat-dose studies in rats, cloudy/discolored urine and crystalluria were observed. Microscopic changes included collecting duct hypertrophy and/or vacuolation, deposition of foreign material associated with granuloma formation, basophilic tubules, tubular dilatation, casts, and pyelitis. These changes were reduced in severity following a 4-week recovery period and were observed at plasma levels (based on the maximum plasma concentration [ $C_{max}$ ] and area under the plasma concentration-time curves [AUCs]) greater than those measured in clinical studies (4-27 times that of the proposed clinical dose based on plasma  $C_{max}$  values and ~ 1 to 3 times that of the proposed clinical dose based on AUC). There were similar findings in a 4-week monkey study, however, no renal toxicity was observed in the 13-week monkey study.

In the spleen, histopathological changes were observed in 4-week rat and monkey repeat-dose studies and included hypertrophy of the germinal centers, hyperplasia of lymph follicles, and congestion. These findings did not resolve following cessation of treatment with the exception of lymph node hyperplasia. No splenic changes were observed in 13-week studies in either species.

Although ceftaroline fosamil was not considered to be a sensitizer in a guinea pig antigenicity study, it may have sensitization potential under conditions of increased immunostimulation (ie, in the presence of adjuvant). There was no evidence of sensitization in repeat-dose studies in rats and monkeys.

Seizures are a known class effect of cephalosporins (DeSarro et al, 1989). Only at doses approximately 14 times the respective ceftaroline fosamil human plasma  $C_{max}$  levels at therapeutic levels, did ceftaroline fosamil demonstrate proconvulsant activity in rats by significantly reducing seizure latency time following pentylenetetrazole administration. Similar, if not greater, exposure margins were observed in acute rat and monkey toxicology studies. In the rat and monkey 4-week repeat-dose studies, tonic/clonic convulsions were induced at doses representing 4 to 26 times the exposure at the proposed clinical dose based on  $C_{max}$ .

The major toxicological findings observed in IV repeat-dose animal studies are known class effects of cephalosporins and occurred at dose levels above those administered clinically. Based on the preclinical safety data, ceftaroline is not expected to induce these events at the human dose equivalent. Furthermore, the findings with ceftaroline suggest no unique safety concerns.

### 5.3 MICROBIOLOGY

Ceftaroline is a new cephalosporin with broad spectrum activity against pathogens frequently associated with skin and respiratory infections. In particular, ceftaroline is active against resistant gram-positive organisms such as MRSA and MDRSP. Among the gram-negative pathogens, ceftaroline is active against beta-lactamase-producing *H. influenzae* but its activity against common members of the *Enterobacteriaceae* is limited to nonextended-spectrum beta-lactamase (ESBL)-producing strains. Ceftaroline is not active against nonfermentative gram-negative species.

#### 5.3.1 Mechanism of Action

In common with other beta-lactams, ceftaroline exerts its bactericidal effect by binding to PBPs, which are membrane-bound enzymes of the cytoplasmic membrane. Penicillin-binding proteins play an essential role in the biosynthesis of the bacterial cell wall and their inhibition is a lethal event for the bacteria. One resistance mechanism that gram-positive bacteria have widely used to evade the action of beta-lactam antibiotics is the acquisition of modified PBPs that no longer bind the antibiotic with high affinity. The potent activity of ceftaroline and corresponding low MIC values against MRSA and MDRSP are attributed to its ability to bind with high affinity to the modified PBP2a in MRSA and the modified PBP2x in penicillin nonsusceptible *S. pneumoniae* (Table 5.3.1–1).

**Table 5.3.1–1. Inhibition of Modified Penicillin-binding Protein 2a in Methicillin-resistant *Staphylococcus aureus* and Penicillin-binding Protein 2x in Penicillin Nonsusceptible *Streptococcus pneumoniae***

<i>Antibiotic</i>	<i>MRSA Strain 67-0</i>		<i>Antibiotic</i>	<i>Penicillin Nonsusceptible S. pneumoniae 2039</i>	
	<i>MIC (μg/mL)</i>	<i>Target Inhibition (PBP2a) IC<sub>50</sub> (μg/mL)</i>		<i>MIC (μg/mL)</i>	<i>Target Inhibition (PBP2x) IC<sub>50</sub> (μg/mL)</i>
Ceftaroline	0.5 - 1	0.16	Ceftaroline	0.12	0.17
Oxacillin	128	408	Penicillin	1 - 2 <sup>a</sup>	0.79
Ceftriaxone	>128	677	Ceftriaxone	1 - 2	0.64

Abbreviations: IC<sub>50</sub> = concentration that inhibits 50% activity; MIC = minimum inhibitory concentration;

MRSA = methicillin-resistant *Staphylococcus aureus*; PBP = penicillin binding protein.

a Clinical and Laboratory Standards Institute (2007).

Source: Moisan et al, 2008.



### 5.3.2 Resistance Studies

By virtue of its bactericidal mode of action, ceftaroline has low propensity for resistance development. In fact, resistance to ceftaroline occurs at low frequency in vitro for all key pathogens. Spontaneous resistant mutants at 4 times the MIC of ceftaroline have not been observed for *S. aureus* ( $< 10^{-10}$ ) and *S. pneumoniae* ( $< 10^{-9}$ ) (Hinshaw et al, 2008). Spontaneous resistance at 4 times the MIC was also not detected for *H. influenzae* ( $< 10^{-9}$ ) and *Moraxella catarrhalis* ( $10^{-10}$ ). Serial passage resistance development studies with *S. aureus*, *S. pyogenes*, *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* showed that all organisms maintained MICs that were equal to, or only 1- to 2-fold dilutions greater than, the starting culture. In gram-negative species, reduced susceptibility to ceftaroline and other cephalosporins is often the result of the activity of beta-lactamases, and *Enterobacteriaceae* that produce ESBL enzymes or that hyperproduce AmpC are resistant to ceftaroline (MICs  $\geq 32$  ug/mL) (Mushtaq et al, 2007). Ceftaroline causes insignificant induction of AmpC beta-lactamases among the *Enterobacteriaceae* at concentrations equal to or below the MIC (Mushtaq and Livermore, 2010).

### 5.3.3 In Vitro Spectrum of Activity

Ceftaroline has been evaluated in numerous studies for its in vitro activity against a wide collection of bacteria that have included historical isolate collections, clinical isolates with varying resistance phenotypes, and recent clinical isolates from surveillance studies. The activities of ceftaroline and comparator agents against contemporary United States clinical isolates collected in 2008 from sources including skin and respiratory infections are shown in Table 5.3.3–1.

**Table 5.3.3–1. In Vitro Activity of Ceftaroline and Comparator Agents against Organisms, Including Those Causing Skin and Respiratory Infections, Isolated in United States Medical Centers in 2008**

Organism	N	Agent	MIC (µg/mL)		
			Range	50%	90%
<i>Staphylococcus aureus</i> (oxacillin-susceptible)	1711	Ceftaroline	$\leq 0.008 - 0.5$	0.25	0.25
		Ceftriaxone	0.5 - 16	4	4
		Vancomycin	$\leq 0.12 - 2$	1	1
		Linezolid	0.25 - 2	2	2
		Daptomycin	$\leq 0.06 - 1$	0.25	0.5
<i>Staphylococcus aureus</i> (oxacillin-resistant)	2254	Ceftaroline	0.12 - 2	1	1
		Ceftriaxone	$\leq 0.25 - > 32$	$> 32$	$> 32$
		Vancomycin	0.25 - 2	1	1
		Linezolid	0.25 - $> 8$	2	2
		Daptomycin	0.12 - 4	0.25	0.5

**Table 5.3.3–1. In Vitro Activity of Ceftaroline and Comparator Agents against Organisms, Including Those Causing Skin and Respiratory Infections, Isolated in United States Medical Centers in 2008**

<i>Organism</i>	<i>N</i>	<i>Agent</i>	<i>MIC (µg/mL)</i>		
			<i>Range</i>	<i>50%</i>	<i>90%</i>
Coagulase-negative staphylococci	638	Ceftaroline	≤ 0.008 - 2	0.25	0.5
		Ceftriaxone	≤ 0.25 - > 32	8	> 32
		Vancomycin	0.25 - 4	1	2
		Linezolid	0.25 - > 8	1	1
		Daptomycin	≤ 0.06 - 4	0.25	0.5
Beta-hemolytic streptococci	327	Ceftaroline	≤ 0.008 - 0.06	≤ 0.008	0.03
		Ceftriaxone	≤ 0.25 - 0.5	≤ 0.25	≤ 0.25
		Vancomycin	0.25 - 1	0.5	0.5
		Linezolid	0.12 - 2	1	1
		Daptomycin	≤ 0.06 - 0.5	0.12	0.25
Viridans group streptococci (all isolates)	110	Ceftaroline	≤ 0.008 - 1	0.03	0.12
		Ceftriaxone	≤ 0.25 - 16	≤ 0.25	1
		Vancomycin	≤ 0.12 - 1	0.5	0.5
		Linezolid	0.25 - 2	1	1
		Daptomycin	≤ 0.06 - 2	0.25	0.5
<i>Streptococcus pneumoniae</i> (all isolates)	894	Ceftaroline	≤ 0.008 - 0.5	0.015	0.12
		Ceftriaxone	≤ 0.25 - 8	≤ 0.25	1
		Penicillin	≤ 0.03 - > 4	≤ 0.03	4
		Levofloxacin	≤ 0.5 - > 4	1	1
<i>Streptococcus pneumoniae</i> (penicillin-resistant, MIC ≥ 2 µg/mL)	195	Ceftaroline	0.03 - 0.5	0.12	0.25
		Ceftriaxone	≤ 0.25 - 8	1	2
		Penicillin	2 - > 4	4	4
		Levofloxacin	≤ 0.5 - > 4	1	1
<i>Streptococcus pneumoniae</i> (penicillin-resistant, MIC ≥ 8 µg/mL)	9	Ceftaroline	0.25 - 0.5	0.5	NA
		Ceftriaxone	2 - 8	4	NA
		Penicillin	> 4	> 4	NA
		Levofloxacin	≤ 0.5 - 1	1	NA
<i>Haemophilus influenzae</i> (beta-lactamase-negative)	275	Ceftaroline	≤ 0.008 - 0.06	≤ 0.008	0.015
		Ceftriaxone	≤ 0.25 - 0.5	≤ 0.25	≤ 0.25
		Ampicillin	≤ 1 - 4	≤ 1	≤ 1
		Levofloxacin	≤ 0.5	≤ 0.5	≤ 0.5
<i>Haemophilus influenzae</i> (beta-lactamase-positive)	106	Ceftaroline	≤ 0.008 - 0.12	≤ 0.008	0.03
		Ceftriaxone	≤ 0.25 - 0.5	≤ 0.25	≤ 0.25
		Ampicillin	2 - >16	16	>16
		Levofloxacin	≤ 0.5	≤ 0.5	≤ 0.5

**Table 5.3.3–1. In Vitro Activity of Ceftaroline and Comparator Agents against Organisms, Including Those Causing Skin and Respiratory Infections, Isolated in United States Medical Centers in 2008**

<i>Organism</i>	<i>N</i>	<i>Agent</i>	<i>MIC (µg/mL)</i>		
			<i>Range</i>	<i>50%</i>	<i>90%</i>
<i>Escherichia coli</i> (all isolates)	1076	Ceftaroline	0.015 – > 16	0.12	0.5
		Ceftriaxone	≤ 0.25 – > 32	≤ 0.25	≤ 0.25
		Ampicillin	≤ 1 – > 16	> 16	> 16
		Levofloxacin	≤ 0.5 – > 4	≤ 0.5	> 4
<i>Klebsiella spp.</i> (all isolates)	706	Ceftaroline	≤ 0.008 – > 16	0.12	> 16
		Ceftriaxone	≤ 0.25 – > 32	≤ 0.25	16
		Ampicillin	≤ 1 – > 16	> 16	> 16
		Levofloxacin	≤ 0.5 – > 4	≤ 0.5	> 4

Abbreviation: MIC = minimum inhibitory concentration; NA = not applicable.

Almost all of the key skin and respiratory pathogens collected in the United States surveillance study were inhibited by ceftaroline concentrations that were ≤ 2 µg/mL. Ceftaroline was developed because of its activity against MRSA and subsequent studies have shown that ceftaroline is active against both hospital-associated MRSA and CA-MRSA, including PVL-producing organisms (Saravolatz et al, 2010). Among *S. pneumoniae*, ceftaroline retains activity against multi-drug-resistant strains including the emerging serotypes such as 19A (Jacobs et al, 2009).

Ceftaroline is active against ceftazidime-susceptible members of the *Enterobacteriaceae* such as *E. coli* and *K. pneumoniae*, with minimum concentrations that inhibit 90% of organisms (MIC<sub>90</sub>s) of 0.5 and 0.25 µg/mL, respectively (Ge et al, 2008). The MIC<sub>90</sub>s for ceftaroline against ceftazidime-resistant *Enterobacteriaceae* and the nonfermenting gram-negative bacilli are typically > 16 µg/mL. However, ceftaroline retains activity against *H. influenzae* regardless of its ability to produce beta-lactamase. The activity of ceftaroline against *H. influenzae* includes beta-lactamase negative ampicillin-resistant isolates (MIC<sub>90</sub> = 0.03 µg/mL) (Sader et al, 2005), which have mutations affecting PBP3.

Among the anaerobes, ceftaroline is active against gram-positive strains and its activity against gram-negative anaerobes is restricted to non-beta-lactamase-producing organisms (Citron et al, 2010). Ceftaroline was active against a collection of *C. difficile* clinical isolates, including fluoroquinolone-resistant strains, with MICs to ceftaroline ranging from 0.015 to 8 µg/mL (Snydman et al, 2009).

#### **5.3.4 In Vitro Synergy Studies**

The activity of ceftaroline in combination with other antibacterial agents has been evaluated in checkerboard and time-kill synergy studies at concentrations relevant to the clinical experience. No instances of antagonism were detected and most combinations showed no interactions (Schaadt et al, 2007). Results from time-kill synergy studies suggest that there is potential for synergy of ceftaroline with aminoglycosides against ceftaroline nonsusceptible gram-negative organisms (Vidailiac et al, 2009).

#### **5.3.5 In Vivo Efficacy in Animal Infection Models**

Ceftaroline fosamil has been evaluated for in vivo activity in numerous animal infection models against a variety of gram-positive and gram-negative pathogens. Efficacy has been successfully demonstrated in the mouse lung, thigh, and peritonitis models. Ceftaroline has been shown to be efficacious against MRSA infections in various models ranging from peritonitis, pneumonia, and thigh infections in the mouse to endocarditis and osteomyelitis in the rabbit (Forest Labs, data on file; Jacqueline et al, 2007; Antimicrob Agents Chemother; Jacqueline et al, 2007; Abstract B-1358). Several endocarditis studies in rabbit utilized simulated human dosing via computer-controlled infusion pumps to mimic the ceftaroline PK observed in healthy humans. Efficacy was assessed by determining the log<sub>10</sub> reduction in colony counts in infected tissues following treatment compared to controls. In each study, ceftaroline achieved bactericidal effects. In the endocarditis model with simulated human dosing, infections by MRSA isolates with MIC of 1 and 2 µg/mL were effectively treated. Additionally, ceftaroline demonstrated superior efficacy to ceftriaxone against PRSP in a rabbit pneumonia model following the administration of simulated human dosing regimens. The ceftaroline MIC for the PRSP was 0.25 µg/mL. The reduction in bacterial burden in the lung was 5-log<sub>10</sub>-fold greater in ceftaroline-treated animals than ceftriaxone-treated animals (Croiser-Bertin et al, 2009).

### **5.4 CLINICAL PHARMACOLOGY OVERVIEW**

Eleven Phase 1 studies have been conducted with ceftaroline. These include studies that evaluated the pharmacokinetics in healthy adult subjects; subjects with mild, moderate, and severe renal impairment; subjects with end-stage renal disease (ESRD) receiving intermittent hemodialysis; subjects 65 years of age and older; and adolescent subjects 12 to 17 years of age. Phase 1 studies were also conducted to provide information on the pharmacokinetics of ceftaroline following intramuscular (IM) injection of ceftaroline fosamil, the mass balance and metabolite profiling of ceftaroline in humans following administration of [<sup>14</sup>C] ceftaroline fosamil, the effect of ceftaroline on the QTc interval, and the effects of ceftaroline on the intestinal microflora. In addition, in vitro studies were conducted to evaluate the protein binding, blood distribution, and in vitro metabolism of ceftaroline, as well as the inhibition and induction potential of ceftaroline on the cytochrome P450 enzyme system.

#### **5.4.1 Pharmacokinetics**

Single- and multiple-dose studies demonstrated that the prodrug ceftaroline fosamil is rapidly converted in plasma to active ceftaroline following IV infusion. The  $C_{\max}$  and AUC values for ceftaroline increased approximately in proportion to increases in dose within the dose range of 50 to 1000 mg, and no accumulation of ceftaroline fosamil or active ceftaroline was observed with either q12h or q24h multiple-dose regimens in healthy adult subjects. The time of maximum plasma concentration for ceftaroline generally occurred near the end of the infusion, and the  $T_{1/2}$  of ceftaroline was approximately 2.5 hours in healthy adult subjects with normal renal function. Following IV infusion of [ $^{14}\text{C}$ ] ceftaroline fosamil, 88% of the dose of radioactivity was excreted in urine and 6% was excreted in feces, confirming that urinary excretion is the principal route of elimination. A significant percentage of the ceftaroline fosamil dose was excreted in the urine as ceftaroline ( $\approx 40\% - 70\%$ ). Additionally, renal clearance of ceftaroline was generally independent of dose and approximately equal to, or less than, glomerular filtration rate. Therefore, active renal transport is not considered to play a major role in urinary excretion of this compound.

#### **5.4.2 Distribution**

The plasma protein binding of ceftaroline in vitro was generally low (mean  $\pm$  SD of  $20\% \pm 6.1\%$ ) and concentration-independent in human plasma over the clinically relevant concentration range. Results of a blood cell partition study indicate that ceftaroline was unable to effectively penetrate into red blood cells (RBCs). The mean penetration rate of ceftaroline (ceftaroline concentration in lung tissue/ceftaroline concentration in plasma) into rabbit lung tissue after IV administration of ceftaroline fosamil was approximately 45%.

#### **5.4.3 Metabolism**

Ceftaroline fosamil is transformed to ceftaroline by hydrolysis of the phosphate amide group and ceftaroline is further metabolized by hydrolysis of the beta-lactam ring to yield ceftaroline M-1, which lacks antimicrobial activity. The conversion of ceftaroline fosamil to active ceftaroline appears to be mediated by phosphatase enzymes. In vitro oxidative metabolic studies with liver microsomes demonstrated that the metabolism of ceftaroline is not dependent upon cytochrome P450 enzymes. The metabolic transformations of ceftaroline fosamil seen in humans were also observed in rats and monkeys.

#### **5.4.4 Excretion**

Ceftaroline and its metabolites are eliminated primarily by the kidneys. Following administration of a single 600-mg IV dose of radiolabeled ceftaroline fosamil to healthy male adults, approximately 88% of radioactivity was recovered in urine and 6% in feces. The majority of the radioactivity (~ 90%) was recovered within 48 hours. Of the radioactivity recovered in urine, approximately 64% was excreted as ceftaroline and approximately 6% as ceftaroline-M-1.

#### **5.4.5 Special Populations**

##### **5.4.5.1 Renal Impairment**

Following administration of a single 600-mg IV dose of ceftaroline fosamil, the mean AUC of ceftaroline in subjects with mild ( $50 \text{ mL/min} < \text{CrCl} \leq 80 \text{ mL/min}$ ) or moderate ( $30 \text{ mL/min} < \text{CrCl} \leq 50 \text{ mL/min}$ ) renal impairment was increased by 19% and 52%, respectively, compared to mean values in healthy subjects with normal renal function ( $\text{CrCl} > 80 \text{ mL/min}$ ). Following administration of a single 400-mg IV dose of ceftaroline fosamil, the mean AUC of ceftaroline in subjects with severe ( $\text{CrCl} \leq 30 \text{ mL/min}$ ) renal impairment was increased by 115% compared to mean values in healthy subjects with normal renal function who received a single 400-mg dose. No dosage adjustment is considered necessary for patients with mild renal impairment. Dosage adjustment is recommended in patients with moderate and severe renal impairment ( $\text{CrCl} \leq 50 \text{ mL/min}$ ).

Pharmacokinetic/pharmacodynamic analyses and Monte Carlo simulations support a dose regimen of 400 mg ceftaroline fosamil infused over 1 hour q12h in subjects with moderate or severe renal impairment. This dose regimen should provide similar PK/PD target attainment while minimizing increases in drug exposure relative to subjects with normal renal function or mild renal impairment dosed with 600 mg of ceftaroline fosamil infused over 1 hour q12h.

When a single 400-mg dose of ceftaroline fosamil was administered to 6 subjects with ESRD 4 hours before hemodialysis, the mean recovery of ceftaroline in the dialysate following a 4-hour dialysis session was 76.5 mg, or 21.6% of the administered dose.

##### **5.4.5.2 Age and Gender Effects**

Following administration of a 600-mg IV dose of ceftaroline fosamil to healthy elderly subjects ( $\geq 65$  years), the mean AUC of ceftaroline was modestly higher (~ 33%) than that in healthy young adult subjects (18 - 45 years). The  $C_{\text{max}}$  was not significantly different between the elderly and younger subjects. The difference in AUC was attributable to decreased renal function in the elderly subjects and was not believed to be clinically significant. Dosage adjustment beyond that recommended for impaired renal function is therefore not necessary in subjects 65 years of age or older.

The pharmacokinetics of ceftaroline were evaluated in adolescent subjects (12 - 17 years) with normal renal function. The mean values of  $C_{\max}$  and AUC for ceftaroline observed in adolescent subjects who received 8 mg/kg ceftaroline fosamil (or 600 mg for subjects weighing > 75 kg) were about 10% and 23% less than the values observed in adult subjects following administration of a 600-mg dose of ceftaroline fosamil.

In Phase 1 studies in healthy subjects,  $C_{\max}$  and AUC for ceftaroline were similar between male and female subjects, although there was a trend for slightly higher AUC (6% - 15%) and  $C_{\max}$  (17% - 22%) values in female subjects. Population PK analysis of data from Phase 1, Phase 2, and Phase 3 studies did not identify clinically meaningful increases in ceftaroline exposure based on gender.

#### **5.4.6 In Vitro Drug Interactions**

In vitro studies in human liver microsomes indicated that neither ceftaroline fosamil nor ceftaroline inhibits the major cytochrome P450 isoenzymes (CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4). In vitro studies in human hepatocytes also demonstrated that ceftaroline fosamil, ceftaroline, and ceftaroline M-1 are not inducers of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A4/5 activity. Therefore, ceftaroline is not expected to inhibit or induce the clearance of drugs that are metabolized by these metabolic pathways in a clinically relevant manner.

Exploratory population PK analysis did not identify any clinically relevant increases in ceftaroline exposure (ie,  $C_{\max}$  and AUC) in subjects with cSSSI or CABP who were taking concomitant medications that are known inhibitors, inducers, or substrates of the cytochrome P450 system.

#### **5.4.7 Pharmacokinetics/Pharmacodynamics, Target Attainment, and Dose Justification**

In common with most beta-lactams, %T > MIC is the most appropriate parameter to predict efficacy of ceftaroline. The PK/PD relationship for ceftaroline was initially evaluated in the murine neutropenic thigh infection model with several organisms including *S. aureus* and *S. pneumoniae* (Andes and Craig, 2006). The mean free-drug %T > MIC required for stasis ranged from 26% for *S. aureus* to 39% for *S. pneumoniae*, regardless of the resistance phenotype.

Prior to starting Phase 3 studies, a preliminary population PK model was used, along with MIC data for clinically relevant pathogens and PK/PD targets from nonclinical animal models of infection, to carry out Monte Carlo simulations in order to estimate the probability of PK/PD target attainment for various dosing regimens (Ge et al, 2007, Abstract A-34). The initial population PK model was developed using PK data from Phase 1 subjects with normal renal function and mild and moderate renal impairment and Phase 2 subjects with cSSSI (Ge et al, 2007; Abstract A-35). Monte Carlo simulations showed that subjects with normal renal function dosed with ceftaroline fosamil 600 mg q12h as a 1-hour infusion would achieve sufficient plasma exposure to provide 90% probability of target attainment for a %T > MIC target of 40% for pathogens with an MIC up to and including 2 µg/mL. The target attainment analyses also supported doses of 600 mg q12h in subjects with mild renal impairment and 400 mg q12h in subjects with moderate renal impairment. These dose regimens were thus selected for the Phase 3 studies in CABP and cSSSI.

After the completion of Phase 3, an updated population PK model was developed in order to include additional data from the Phase 1, 2, and 3 studies. The additional data included higher doses of ceftaroline fosamil, data from subjects with severe renal impairment and ESRD, data from subjects over the age of 65 years, and data from subjects with cSSSI and CABP. The updated PK model was then used to predict ceftaroline free-drug %T > MIC values for microbiologically evaluable (ME) subjects in the Phase 2/ 3 studies in cSSSI and Phase 3 studies in CABP. Of the subjects for whom a free-drug %T > MIC could be generated, the mean free-drug %T > MIC (based on each subject's baseline pathogen) was 90.4% in the Phase 2/ 3 cSSSI studies and 96.8% in the CABP studies. The high success rates for all efficacy endpoints in the Phase 3 studies (described in Section 6.0 and Section 7.0) and the high free-drug %T > MIC values over the MIC ranges studied demonstrate that the dose regimens used in the Phase 2/ 3 cSSSI and Phase 3 CABP studies were appropriate.



## **6.0 COMMUNITY-ACQUIRED BACTERIAL PNEUMONIA STUDY DESIGN AND EFFICACY**

### **6.1 STUDY DESIGN**

The Phase 3 CABP program included 2 studies: Studies P903-08 and P903-09 were adequate and well controlled, multicenter, multinational, randomized, double-blinded, active-controlled studies. Adult subjects with CABP were randomized 1:1 to the ceftaroline (P903-08, n = 304; P903-09, n = 317) or ceftriaxone (P903-08, n = 309; P903-09, n = 310) groups. The duration of treatment with study medication was 5 to 7 days. The ceftaroline fosamil doses of 600 mg q12h in subjects with normal renal function and mild renal impairment and 400 mg q12h in subjects with moderate renal impairment used in the Phase 3 studies were selected based on a 90% PK/PD target attainment for organisms with an MIC  $\leq 2$   $\mu\text{g/mL}$  (Section 5.4.7). In addition, the dosing regimen of 600 mg q12h used in the Phase 2 cSSSI study was shown to be efficacious and well tolerated.

The active comparator regimen was ceftriaxone 1 g IV q24h. Subjects randomized to ceftriaxone received placebo infusions to match the ceftaroline q12h dosing regimen. Ceftriaxone was chosen as the active-control agent in both Phase 3 CABP studies because it is currently approved for the treatment of lower respiratory tract infections caused by susceptible typical community-acquired pathogens (Rocephin® [ceftriaxone sodium] package insert, 2004). It is used globally and widely accepted as a standard of care therapy for CAP (Mandell et al, 2007). The dose of ceftriaxone used in the Phase 3 CABP studies was 1 g IV q24h as described in the FDA approved package insert (Rocephin® [ceftriaxone sodium] package insert, 2004).

Prior antibiotics were restricted to the allowance of a single dose of a short-acting antibiotic in the 96 hours prior to randomization; strict exclusion criteria prohibited the prior use of any long-acting antibiotics such as long-acting beta-lactams (eg, ceftriaxone), respiratory fluoroquinolones (eg, levofloxacin, moxifloxacin, gatifloxacin), or macrolides (eg, azithromycin).

Studies P903-08 and P903-09 were identical in design (including objectives, inclusion and exclusion criteria, analysis populations, and dosage regimens) with the exception that subjects in Study P903-08 were administered 2 oral doses of adjunctive clarithromycin at 500 mg each during the initial 24 hours on study. The brief course of clarithromycin (two doses of 500 mg q12h starting on Study Day 1) was administered in Study P903-08 to provide initial coverage against atypical organisms (eg, if baseline *Legionella pneumophila* urinary antigen testing was delayed) and was a necessary addition in an attempt to employ a study design that could be used in the United States. Unlike Study P903-08, no adjunctive macrolide therapy was allowed in Study P903-09.

The visit schedule, subject population, length of therapy, efficacy endpoints, and statistical considerations in each study were consistent with existing guidelines (eg, the US FDA Draft Guidance for Industry: CAP—Developing Antimicrobial Drugs for Treatment [US FDA, 1998 Jul]; US FDA Draft Guidance for Industry: Developing Antimicrobial Drugs—General Considerations for Clinical Trials [US FDA, 1998 Jul].

Table 6.1–1 provides the study visit overview for P903-08 and P903-09 schematically.

**Table 6.1–1. Study Visit Overview, Studies P903-08 and P903-09**

<i>Baseline</i>	<i>Study Drug Administration</i>	<i>TOC</i>	<i>LFU</i>
<b>Within 24 hours before first dose of study drug</b>	<b>Day 1 to EOT</b>	<b>8 to 15 days after last dose of study drug</b>	<b>21 to 35 days after last dose of study drug</b>
Confirmation of study eligibility	IV study drug therapy for 5 to 7 days		
Randomization to treatment	On-therapy clinical and laboratory assessments	Subjects returned to study center for assessment of efficacy and safety.	Subjects returned to study center for final assessment.
	EOT assessments performed on last day that study drug was administered or at the time of withdrawal from the study.		

Abbreviations: EOT = end of therapy; IV = intravenous; LFU = late follow-up; TOC = test of cure.

Pooling of the 2 studies for the integrated summaries of efficacy and safety was appropriate since both studies were well controlled Phase 3, multicenter, randomized, double-blind, active-controlled studies, with identical designs (with the exception that subjects in Study P903-08 were administered 2 oral doses of adjunctive clarithromycin), in adult subjects. The appropriateness of pooling was further supported by similarities in the key results of the 2 studies, including similar baseline demographic characteristics of the subject populations, clinical markers for CABP (eg, signs, symptoms), clinical cure rates between treatment groups, and microbiological results.

Subject selection criteria were defined rigorously in the ceftaroline Phase 3 CABP protocols. In line with the CABP Draft Guidance for Industry (US FDA, 2009 Mar), CAP severity of disease was defined according to the PORT scale of CAP severity (Fine et al, 1997), in which Risk Class I was associated with the lowest risk for mortality and Risk Class V represented the highest risk. The protocols were designed to ensure that subjects were enrolled only with new or progressive pulmonary infiltrate(s) on chest radiography, clinical signs and symptoms consistent with CABP, and disease of moderate-to-severe severity (ie, PORT Risk Class III or IV) to warrant hospitalization in a general medical ward and administration of IV antimicrobial therapy. Subjects were hospitalized for the duration of IV study drug administration and no switch to oral therapy was permitted.

Key inclusion criteria included:

- Adult subjects (18 years or older) with acute onset ( $\leq 7$  days' duration) illness who required hospitalization and treatment with IV antimicrobials, in PORT Risk Class III or IV, and who had 3 or more of the following clinical signs or symptoms consistent with lower respiratory tract infection:
  - Fever  $> 38^{\circ}\text{C}$  oral or hypothermia ( $< 35^{\circ}\text{C}$ )
  - White blood cell (WBC) count  $> 10,000$  cells/ $\text{mm}^3$  or  $< 4,500$  cells/ $\text{mm}^3$
  - Greater than 15% immature neutrophils (bands) irrespective of WBC count
  - New or increased cough
  - Purulent sputum or change in sputum character
  - Auscultatory findings consistent with pneumonia (eg, rales, egophony, findings of consolidation)
  - Dyspnea, tachypnea, or hypoxemia ( $\text{O}_2$  saturation  $< 90\%$  on room air or  $\text{pO}_2 < 60$  mmHg)
- Radiographically-confirmed pneumonia (new or progressive pulmonary infiltrate(s) on chest radiograph or chest computed tomography scan) consistent with bacterial pneumonia

Key exclusion criteria included:

- Respiratory infection that was confirmed or suspected to be attributable to sources other than community-acquired bacterial pathogens (eg, ventilator-associated, hospital-acquired, healthcare-associated), noninfectious causes (eg, cancer, aspiration), confirmed or suspected pathogens that were resistant to ceftaroline and/or ceftriaxone, such as *Pseudomonas aeruginosa*, MRSA, or atypical organisms (eg, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Legionella* spp.)
- CABP that required treatment in an intensive care unit (ICU) setting
- Receipt of a long-acting antimicrobial (eg, ceftriaxone, levofloxacin, moxifloxacin, gatifloxacin, azithromycin) for the treatment of CABP within 96 hours before randomization or receipt of more than a single dose of oral or IV short-acting antimicrobial for the treatment of CABP within 96 hours before randomization, unless there was unequivocal clinical evidence of treatment failure after at least 48 hours of the prior systemic antimicrobial therapy and isolation of an organism that was resistant to that therapy

- Severely impaired renal function ( $\text{CrCl} \leq 30 \text{ mL/min}$ ) estimated by the Cockcroft-Gault (1976) formula; evidence of significant hepatic, hematologic, immunologic, or immediately life-threatening disease, or history of any hypersensitivity or allergic reaction to any beta-lactam antimicrobial

Analysis populations are described in Section 6.2.

The primary objective in the individual Phase 3 CABP studies was the demonstration of noninferiority of ceftaroline to ceftriaxone in the primary efficacy endpoint of clinical response at TOC in the coprimary CE and MITTE Populations (only subjects in PORT Risk Class III and IV).

Prespecified secondary efficacy endpoints included clinical response at end of therapy (EOT) in the MITTE and CE Populations, by-subject microbiological response at TOC in the microbiological modified intent-to-treat (mMITT), microbiological modified intent-to-treat efficacy (mMITTE), and ME Populations, overall (combined clinical and radiographic) response at TOC in the MITTE and CE Populations, clinical and microbiological responses by baseline pathogen at TOC in the mMITTE and ME Populations, relapse at late follow-up (LFU) in those subjects who were clinically cured at the TOC visit, and reinfection or recurrence at LFU in those subjects who had a favorable clinical and microbiological outcome at TOC.

Clinical response categories are described in Table 6.1–2.

Rigorous study conduct, which was ensured throughout the studies, included activities such as pre-enrollment qualification of all sites, Investigator meetings in all regions, protocol training required before site initiation, blinding procedures reviewed at each site, strict site initiation procedures, intensive monitoring of sites during and after active enrollment to ensure protocol adherence, enforcement of ICH compliance, and extensive auditing (> 30% of sites and subjects).

**Table 6.1–2. Clinical Outcome Categories**

<b><i>Outcome</i></b>	<b><i>Definition</i></b>
Clinical Cure	Total resolution of all signs and symptoms of pneumonia (ie, CABP), or improvement to such an extent that further antimicrobial therapy was not necessary. Clinical improvement includes the absence of fever for $\geq 24$ continuous hours in addition to a substantial improvement in signs and symptoms of CABP. Substantial improvement includes a return to pre-CABP baseline levels for subjects with decreased pulmonary function.
Clinical Failure	Any of the following: <ul style="list-style-type: none"> <li>• Persistence, incomplete clinical resolution, or worsening in signs and symptoms of CABP that required alternative antimicrobial therapy</li> <li>• Treatment-limiting AE leading to discontinuation of study drug therapy, when subject required alternative antimicrobial therapy to treat the pneumonia</li> <li>• Death up to and including TOC, or up to and including 28 days after EOT for those subjects without a clinical response assessment at TOC</li> </ul>
Indeterminate	Study data were not available for evaluation of efficacy, for any reason, including treatment change before completing at least 48 hours of study drug therapy, lost to follow-up, or extenuating circumstances that precluded classification as a cure or failure.

Abbreviations: AE = adverse event; CABP = community-acquired bacterial pneumonia; EOT = end of therapy; TOC = test of cure.

### **6.1.1 Statistical Methods**

For the primary objective of establishing noninferiority of ceftaroline with respect to ceftriaxone in the coprimary populations, the lower limit of the 95% CI for the difference (ceftaroline - ceftriaxone) in the proportions of subjects with an outcome of clinical cure was obtained using the Miettinen and Nurminen method for comparing proportions. Noninferiority was shown if the lower limit was greater than or equal to -0.100. The FDA accepted the use of a 1-sided significance level of 0.025 for statistical significance of the test of noninferiority. Since the statistical test in each coprimary population had to meet this requirement, the Type I error is controlled at the (one-sided) 2.5% significance level. Descriptive statistics, including the numbers and percentages for categorical variables, and the numbers, means, standard deviations, medians, minimums and maximums for continuous variables are provided when appropriate.

The noninferiority margin for the primary efficacy analysis was prospectively defined as 10% in the study protocols and SAPs, which were submitted to the FDA before database lock and unblinding. The FDA acknowledged and accepted the use of a noninferiority margin of 10% in evaluating clinical efficacy in subjects with moderate-to-severe CABP as defined by a PORT Risk Class of III or more in September 2007. The justification of the noninferiority margin is described in detail in Appendix 11.1.

For 2 key secondary endpoints, the hierarchical testing procedure of Westfall and Krishen (2001) was utilized to control the overall Type I error at 2.5% (one-sided).

- By-subject clinical cure rate at EOT in both the MITTE and CE Populations using a noninferiority margin of 10%
- By-subject microbiological favorable outcome rate at TOC in the mMITT Population using a noninferiority margin of 15% based on the CABP Draft Guidance for Industry (US FDA, 2009 Mar)

For analyses of pooled data, the Miettinen and Nurminen method stratified by study and using Cochran-Mantel-Haenszel weights was used.

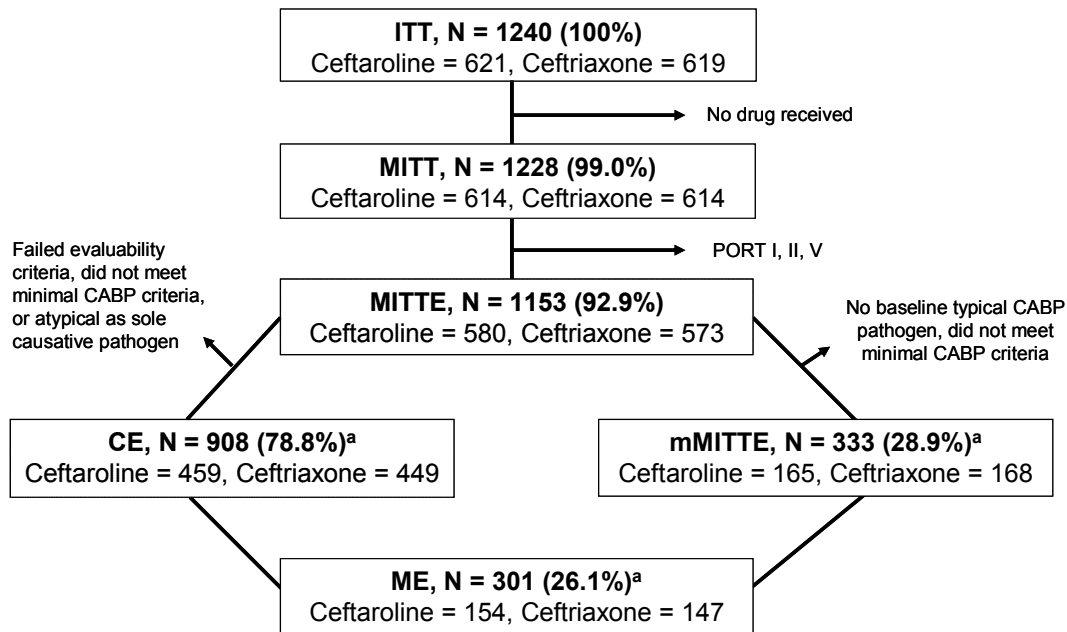
The sample size determination was based on a point estimate of the overall (combined clinical and radiographic) success rate of 90% in both the ceftaroline and ceftriaxone groups, which is consistent with the literature and the clinical cure rate. Using a noninferiority margin of 10% (accepted by the FDA for subjects in PORT Risk Class III or greater), 90% power, and a two-sided alpha of 0.05, based on the sample size determination method of Farrington and Manning (1990), a total of 205 evaluable (PORT Risk Class III or greater) subjects in each treatment group was required. Assuming that approximately 60 subjects in Study P903-08 and 76 subjects in Study P903-09 with PORT Risk Class II had already been enrolled (Section 4.2), and assuming that 75% of the randomized population would be evaluable for the CE Population, a total sample size of 610 subjects (305 subjects in each treatment group) was required in Study P903-08 and 626 subjects (313 subjects in each treatment group) was required in Study P903-09. Prior to database lock and unblinding of the study, the FDA requested that the primary endpoint of both Phase 3 CABP studies be changed to clinical response alone at TOC rather than overall success (combined clinical response and radiographic success). The primary endpoint was subsequently changed to clinical response at TOC in the coprimary populations of both Phase 3 CABP studies, and the prior primary endpoint of overall success was maintained as a secondary endpoint. The estimated sample size specified above was determined to provide at least 90% power for the primary endpoint of clinical response as well.

To assess the consistency of ceftaroline efficacy in CABP, treatment group differences were examined for a variety of subgroups defined by baseline characteristics (Section 6.8).

## 6.2 ANALYSIS POPULATIONS

An overview of the numbers of subjects included in each population is presented in Figure 6.2–1. Overall, the 2 treatment groups were similar in the number of subjects included in the various populations.

**Figure 6.2–1. Analysis Populations, Pooled Community-acquired Bacterial Pneumonia Studies**



Abbreviations: CABP = community-acquired bacterial pneumonia; CE = clinically evaluable; ITT = intent-to-treat; ME = microbiologically evaluable; MITT = modified intent-to-treat; MITTE = modified intent-to-treat efficacy; mMITTE = microbiological modified intent-to-treat efficacy; PORT = Pneumonia Outcomes Research Team.

<sup>a</sup> Percentage based on MITTE Population

The analysis populations of the CABP studies are described below:

- Intent-to-treat (ITT) Population: all randomized subjects
- MITT Population: all randomized subjects who received any amount of study drug. Subjects given study drug opposite from the randomized assignment were analyzed for efficacy in the treatment group assigned. The Safety Population was analyzed by the treatment actually received.
- mMITT Population: all subjects in the MITT Population who met the minimal disease criteria for CABP and had at least 1 typical bacterial pathogen identified at baseline from an appropriate specimen.

- MITTE Population: all subjects in the MITT Population who were in PORT Risk Class of III or IV
- mMITTE Population: all subjects in the MITTE Population who met the minimal disease criteria for CABP and had at least 1 typical bacterial pathogen identified at baseline from an appropriate specimen.
  - A pathogen was defined as an organism consistent with a CABP pathogen and isolated from a blood culture or an appropriate respiratory sample (any pleural fluid, transthoracic, deep bronchial [eg, bronchoalveolar lavage], deep tracheal culture, or appropriate sputum sample [ $\leq 10$  squamous epithelial cells/low-power field on Gram stain]) at baseline.
  - Subjects with serological evidence of a sole atypical infection (ie, *M. pneumoniae*, *C. pneumoniae*, or *L. pneumophila*) were excluded from the mMITTE Population
- CE Population: all subjects in the MITTE Population who met the minimal disease criteria for CABP, met the evaluability criteria detailed in the protocol and SAP, and did not have an atypical isolate as the sole causative CABP pathogen
- ME Population: subjects from the CE Population who had at least 1 typical bacterial pathogen identified at baseline from an appropriate microbiological specimen at baseline.

### 6.3 REGIONS OF ENROLLMENT

Table 6.3–1 provides a summary of enrollment by region for the Phase 3 CABP studies in the MITTE Population. Enrollment was highest in Eastern Europe followed by Western Europe, Latin America, and Asia. In the pooled Phase 3 CABP studies, enrollment by region was similar between the ceftaroline and ceftriaxone groups. Subject treatment, subject care, sample collection and analysis, and data capture was standardized across regions in the multinational Phase 3 CABP studies by the use of a universal protocol that mandated the type, timing, and methods for specific assessments and procedures.

Few subjects were enrolled in the United States (approximately 2% of the pooled MITTE Population). Due to the lack of a full course of adjunctive macrolide therapy in either Phase 3 CABP study (ie, inconsistency with Infectious Disease Society of America / ATS Guidelines [Mandell et al, 2007]), and other difficulties with conforming to the protocol requirements (eg, strict prior antibiotic exclusion criteria), only 13 of the 198 contacted sites in the United States agreed to participate in Study P903-08.

Despite relatively low enrollment of subjects from sites in the United States, the results of these studies are directly applicable to subjects with CABP in the United States. The subject demographic and baseline characteristics, CABP characteristics, and microbial pathogens identified in the multinational Phase 3 CABP studies correspond with those that would be expected among subjects hospitalized with CABP in the United States.



The use of the standardized PORT scoring system, which is based on demographic factors, laboratory values, and chest radiography and is utilized to predict mortality and make site-of-care decisions in the United States, ensured the inclusion of a uniform cohort of subjects requiring hospitalization and IV therapy (ie, PORT Risk Class III or IV) that can be generalized to the United States.

In addition, the distributions of subject demographic and baseline characteristics in the Phase 3 CABP studies are similar to those observed among subjects hospitalized to non-ICU medical wards in the United States in several large retrospective cohort and prospective observational studies (Restrepo et al, 2008; Lave et al, 1996; Fine et al, 1990). In the pooled Phase 3 CABP studies, subjects were predominantly male (approximately 63%), non-Hispanic (approximately 87%), and white (approximately 93%) and had a mean body mass index of approximately 26 kg/m<sup>2</sup> and a median age of approximately 64 years (range 18 to 99 years) (Section 6.5.1). Other baseline characteristics of subjects in the Phase 3 CABP studies included a history of structural lung disease including chronic obstructive pulmonary disease (COPD) (approximately 27%), a history of smoking (approximately 51%), and presence of multilobar infiltrates (approximately 28%). The most common causative CABP pathogens were *S. pneumoniae*, *S. aureus*, and *H. influenzae*. Among subjects enrolled in the large United States cohort studies, subjects were predominantly male (48% to 75%) and white (85%), had a mean age of 57 to > 65 years (range 18 to 101 years), and had incidences of smoking history of 31% to 34%, multilobar infiltrates of 30%, and underlying COPD of 15% to 25% (Restrepo et al, 2008; Lave et al, 1996; Fine et al, 1990). The most common causative CABP pathogens in the cohort studies were *S. pneumoniae*, *S. aureus*, and *H. influenzae*, as seen in the Phase 3 CABP studies.

Finally, the antimicrobial (including ceftaroline and ceftriaxone) MIC distributions for all key baseline pathogens isolated in the Phase 3 CABP studies were analyzed according to geographic origin and compared with MIC distributions for recent United States surveillance isolates collected in 2008. The similar MIC ranges of ceftaroline and currently available antibiotics for CABP (including cephalosporins, macrolides, and fluoroquinolones) suggest similar antimicrobial susceptibility profiles. For example, the mode MIC for ceftaroline was  $\leq 0.015$   $\mu\text{g/mL}$  against both clinical and United States surveillance *S. pneumoniae* isolates, 0.25  $\mu\text{g/mL}$  against both clinical and surveillance *S. aureus* isolates, and  $\leq 0.015$   $\mu\text{g/mL}$  against both clinical and surveillance *H. influenzae* isolates.

In summary, these data from the medical literature and microbiology analyses suggest that the efficacy results from Studies P903-08 and P903-09 are applicable to subjects hospitalized with CABP in the United States.

**Table 6.3–1. Enrollment by Region, Phase 3 Community-acquired Bacterial Pneumonia Studies—MITTE Population**

<b>Region Group</b>	<b>P903-08</b>		<b>P903-09</b>		<b>Pooled Phase 3 Studies (08, 09)</b>	
	<i>Ceftaroline</i> (N = 291) n (%)	<i>Ceftriaxone</i> (N = 300) n (%)	<i>Ceftaroline</i> (N = 289) n (%)	<i>Ceftriaxone</i> (N = 273) n (%)	<i>Ceftaroline</i> (N = 580) n (%)	<i>Ceftriaxone</i> (N = 573) n (%)
Eastern Europe	128 (44.0)	134 (44.7)	136 (47.1)	127 (46.5)	264 (45.5)	261 (45.5)
Western Europe	106 (36.4)	105 (35.0)	100 (34.6)	98 (35.9)	206 (35.5)	203 (35.4)
Latin America	16 (5.5)	16 (5.3)	48 (16.6)	44 (16.1)	64 (11.0)	60 (10.5)
Asia	13 (4.5)	15 (5.0)	5 (1.7)	4 (1.5)	18 (3.1)	19 (3.3)
Africa	17 (5.8)	18 (6.0)	0	0	17 (2.9)	18 (3.1)
US	11 (3.8)	12 (4.0)	0	0	11 (1.9)	12 (2.1)

Abbreviation: MITTE = modified intent-to-treat efficacy.

#### 6.4 PREMATURE DISCONTINUATIONS FROM STUDY DRUG

Table 6.4–1 provides a summary of subjects for the Phase 3 CABP studies who completed study drug administration and the numbers and percentages of subjects who prematurely discontinued study drug in the MITTE Population. In the pooled Phase 3 CABP studies, approximately 93% of subjects in each treatment group completed study drug administration. The most common reasons for premature discontinuation of study drug were insufficient therapeutic effect, treatment-limiting AE, and withdrew consent. Insufficient therapeutic effect was due to clinical worsening, lack of clinical progress, or isolation of a resistant pathogen.

**Table 6.4–1. Premature Discontinuation of Study Drug, Phase 3 Community-acquired Bacterial Pneumonia Studies —MITTE Population**

	<i>P903-08</i>		<i>P903-09</i>		<i>Pooled Phase 3 Studies (08, 09)</i>	
	<i>Ceftaroline (N = 291) n (%)</i>	<i>Ceftriaxone (N = 300) n (%)</i>	<i>Ceftaroline (N = 289) n (%)</i>	<i>Ceftriaxone (N = 273) n (%)</i>	<i>Ceftaroline (N = 580) n (%)</i>	<i>Ceftriaxone (N = 573) n (%)</i>
<b>Completed study drug</b>	<b>277 (95.2)</b>	<b>283 (94.3)</b>	<b>271 (93.8)</b>	<b>246 (90.1)</b>	<b>548 (94.5)</b>	<b>529 (92.3)</b>
Prematurely discontinued from study drug	14 (4.8)	17 (5.7)	18 (6.2)	27 (9.9)	32 (5.5)	44 (7.7)
<b>Reason for premature discontinuation of study drug</b>						
Adverse event	5 (1.7)	4 (1.3)	7 (2.4)	8 (2.9)	12 (2.1)	12 (2.1)
Pregnancy/nursing	0	0	0	0	0	0
Significant laboratory abnormality	0	0	0	0	0	0
Insufficient therapeutic effect	2 (0.7)	6 (2.0)	8 (2.8)	12 (4.4)	10 (1.7)	18 (3.1)
Clinical worsening, lack of clinical progress	2 (0.7)	6 (2.0)	7 (2.4)	10 (3.7)	9 (1.6)	16 (2.8)
Due to resistant pathogen	0	0	1 (0.3)	2 (0.7)	1 (0.2)	2 (0.3)
Withdrew consent	5 (1.7)	6 (2.0)	2 (0.7)	4 (1.5)	7 (1.2)	10 (1.7)
Lost to follow-up	0	0	0	2 (0.7)	0	2 (0.3)
Other	2 (0.7)	1 (0.3)	1 (0.3)	1 (0.4)	3 (0.5)	2 (0.3)

Abbreviation: MITTE = modified intent-to-treat efficacy.

## 6.5 DEMOGRAPHICS, BASELINE CHARACTERISTICS, AND BASELINE PATHOGENS

### 6.5.1 Demographics and Baseline Characteristics

Table 6.5.1–1 provides the demographic and baseline characteristics for all subjects. The demographic characteristics of subjects in the ceftaroline and ceftriaxone groups were well balanced. Demographics and baseline characteristics in the CE Population were similar to those in the MITTE Population. Approximately 76% of subjects were 50 years or older. Approximately 61% of subjects were in PORT Risk Class III and approximately 37% were in PORT Risk Class IV in the coprimary populations for the pooled efficacy analysis in both treatment groups. This population is consistent with the CABP Draft Guidance for Industry (US FDA, 2009 Mar), which specifies fewer than 25% of subjects in PORT Risk Class II and more than 25% of subjects in PORT Risk Class IV.

**Table 6.5.1–1. Demographics and Baseline Characteristics, Phase 3 Community-acquired Bacterial Pneumonia Studies—MITTE Population**

<i>Demographic or Baseline Parameter</i>	<i>P903-08</i>		<i>P903-09</i>		<i>Pooled Phase 3 Studies (08, 09)</i>	
	<i>Ceftriaxone (N = 291)</i>	<i>Ceftriaxone (N = 300)</i>	<i>Ceftriaxone (N = 289)</i>	<i>Ceftriaxone (N = 273)</i>	<i>Ceftriaxone (N = 580)</i>	<i>Ceftriaxone (N = 573)</i>
Age years						
Median	64.0	63.5	62.0	64.0	63.0	64.0
Min, Max	20, 94	18, 91	18, 99	18, 91	18, 99	18, 91
Age group - I (years) n (%)						
< 65	148 (50.9)	152 (50.7)	159 (55.0)	140 (51.3)	307 (52.9)	292 (51.0)
≥ 65	143 (49.1)	148 (49.3)	130 (45.0)	133 (48.7)	273 (47.1)	281 (49.0)
Age group - II (years) n (%)						
≤ 50	75 (25.8)	74 (24.7)	67 (23.2)	54 (19.8)	142 (24.5)	128 (22.3)
> 50	216 (74.2)	226 (75.3)	222 (76.8)	219 (80.2)	438 (75.5)	445 (77.7)
Gender n (%)						
Male	187 (64.3)	191 (63.7)	175 (60.6)	175 (64.1)	362 (62.4)	366 (63.9)
Female	104 (35.7)	109 (36.3)	114 (39.4)	98 (35.9)	218 (37.6)	207 (36.1)
Ethnicity n (%)						
Non-Hispanic	262 (90.0)	274 (91.3)	243 (84.1)	228 (83.5)	505 (87.1)	502 (87.6)
Hispanic	29 (10.0)	26 (8.7)	46 (15.9)	45 (16.5)	75 (12.9)	71 (12.4)
Race n (%)						
White	260 (89.3)	268 (89.3)	278 (96.2)	264 (96.7)	538 (92.8)	532 (92.8)
Black or African American	17 (5.8)	15 (5.0)	0	0	17 (2.9)	15 (2.6)
Other	14 (4.8)	17 (5.7)	11 (3.8)	9 (3.3)	25 (4.3)	26 (4.5)
PORT Risk Class n (%)						
III	190 (65.3)	182 (60.7)	170 (58.8)	171 (62.6)	360 (62.1)	353 (61.6)
IV	101 (34.7)	118 (39.3)	119 (41.2)	102 (37.4)	220 (37.9)	220 (38.4)
Structural lung disease <sup>a</sup> n (%)	64 (22.0)	60 (20.0)	96 (33.2)	87 (31.9)	160 (27.6)	147 (25.7)
Prior Pneumonia n (%)	61 (21.0)	51 (17.0)	62 (21.5)	41 (15.0)	123 (21.2)	92 (16.1)
Creatinine clearance (mL/min) <sup>b</sup> n (%)						
> 80	152 (52.2)	152 (50.7)	128 (44.3)	136 (49.8)	280 (48.3)	288 (50.3)
> 50 and ≤ 80	88 (30.2)	95 (31.7)	111 (38.4)	95 (34.8)	199 (34.3)	190 (33.2)
> 30 and ≤ 50	47 (16.2)	48 (16.0)	41 (14.2)	37 (13.6)	88 (15.2)	85 (14.8)
≤ 30	4 (1.4)	5 (1.7)	9 (3.1)	5 (1.8)	13 (2.2)	10 (1.7)
Prior systemic antibiotic use <sup>c</sup> n (%)	137 (47.1)	143 (47.7)	100 (34.6)	117 (42.9)	237 (40.9)	260 (45.4)
Bacteremia n (%)	8 (2.7)	9 (3.0)	15 (5.2)	11 (4.0)	23 (4.0)	20 (3.5)

Abbreviations: MITTE = modified intent-to-treat efficacy; PORT = Pneumonia Outcomes Research Team;

<sup>a</sup> Structural lung disease was defined as any clinically significant parenchymal or bronchial disease, eg, chronic obstructive pulmonary disease (including emphysema or chronic bronchitis), bronchiectasis, and pulmonary fibrosis.

<sup>b</sup> Central laboratory values of creatinine clearance were used if available. Otherwise, case report form creatinine clearance values were used.

<sup>c</sup> Single dose of a short-acting antibiotic.

### 6.5.2 Severity of Disease

Table 6.5.2–1 provides an overall summary of severity markers for CABP for the MITTE Population in the Phase 3 CABP studies. By definition, only subjects with PORT Class III or IV could be included in the MITTE Population. Severity markers for CABP were generally similar in the individual Phase 3 CABP studies compared with the pooled Phase 3 CABP studies and were well balanced between the ceftazidime and ceftriaxone groups. Severity markers for CABP in the CE Population were similar to those in the MITTE Population.

The subject demographics and disease characteristics (Table 6.5.1–1 and Table 6.5.2–1) clearly indicate that all enrolled subjects had “moderate-to-severe” CABP (ie, hospitalized subjects in PORT Risk Classes III and IV). The subjects enrolled in the Phase 3 CABP studies had clinical signs suggestive of moderate to severe disease, such as fever or hypoxia (approximately 73% of subjects in the MITTE Population), pleural effusion (approximately 19%), and multilobar disease (approximately 28%). In addition, approximately 30% of subjects in the MITTE Population met modified ATS criteria for severe CAP, and approximately 75% of subjects met systemic inflammatory response syndrome (SIRS) criteria (defined in Table 6.5.2–1). Finally, all subjects enrolled on the Phase 3 CABP studies had “higher risk for mortality”, as defined by the FDA (Tygacil [tigecycline] package insert, 2009). In the approval of tigecycline for CAP, the FDA performed a post-hoc analysis on approximately 69% of enrolled subjects with “higher risk for mortality”, defined as age of 50 years or older, PORT Risk Class of at least III, or the presence of *S. pneumoniae* bacteremia. Specifically, 100% of the subjects in the Phase 3 CABP studies met this FDA definition, as 76.6% of subjects were at least 50 years old, 100% had a PORT Risk Class of III or greater, and 9.3% of the subjects in the ME Population had *S. pneumoniae* bacteremia.

The ceftazidime Phase 3 CABP studies enrolled more severe disease than recent FDA registration trials. For example, the Phase 3 ceftazidime CABP studies included approximately 62% of subjects with PORT Risk Class III disease and 38% of subjects with PORT Risk Class IV disease. This compares with 27.0% and 19.3% of subjects in the tigecycline studies, 23.4% and 22.5% of subjects in the ertapenem studies, and 30.3% and 27.6% of subjects in the daptomycin studies with PORT Risk Class III and IV, respectively (Tanaseanu et al, 2008; Pertel et al, 2008; Ortiz-Ruiz et al, 2004). In general, past registration trials have included subjects with PORT Risk Classes I and/or II and allowed a course of oral switch therapy after a brief IV course of study drug, often in the outpatient setting. The ceftazidime Phase 3 CABP studies required a full course of IV therapy in the hospital, with no allowed outpatient or oral therapy.

Together, these data suggest that the subjects enrolled in the Phase 3 CABP studies had symptoms, physical examination findings, and radiographic findings consistent with moderate-to-severe CABP and, specifically, a severity of CABP that required hospitalization and IV therapy.

**Table 6.5.2–1. Severity Markers for Community-acquired Bacterial Pneumonias: Clinical Parameters, Phase 3 Studies—MITTE Population**

<b>Marker</b>	<b>P903-08</b>		<b>P903-09</b>		<b>Pooled Phase 3 Studies (08, 09)</b>	
	<i>Ceftaroline</i> (N = 291) n (%)	<i>Ceftriaxone</i> (N = 300) n (%)	<i>Ceftaroline</i> (N = 289) n (%)	<i>Ceftriaxone</i> (N = 273) n (%)	<i>Ceftaroline</i> (N = 580) n (%)	<i>Ceftriaxone</i> (N = 573) n (%)
PORT Risk Class						
III (PORT Score 71-90)	190 (65.3)	182 (60.7)	170 (58.8)	171 (62.6)	360 (62.1)	353 (61.6)
IV (PORT Score 91-130)	101 (34.7)	118 (39.3)	119 (41.2)	102 (37.4)	220 (37.9)	220 (38.4)
Modified ATS severe CAP criteria met						
Yes	82 (28.2)	89 (29.7)	99 (34.3)	80 (29.3)	181 (31.2)	169 (29.5)
SIRS criteria met						
Yes	231 (79.4)	232 (77.3)	203 (70.2)	193 (70.7)	434 (74.8)	425 (74.2)
Presence of bacteremia						
Yes	8 (2.7)	9 (3.0)	15 (5.2)	11 (4.0)	23 (4.0)	20 (3.5)
Fever or hypoxia						
Yes	230 (79.0)	230 (76.7)	197 (68.2)	187 (68.5)	427 (73.6)	417 (72.8)
Fever (> 38°C Orally or > 38.5°C rectally or tympanically)						
Yes	198 (68.0)	186 (62.0)	136 (47.1)	133 (48.7)	334 (57.6)	319 (55.7)
Hypoxia (PaO <sub>2</sub> < 60 mmHg or O <sub>2</sub> saturation < 90%)						
Yes	101 (34.7)	103 (34.3)	114 (39.4)	96 (35.2)	215 (37.1)	199 (34.7)
Pleural effusion <sup>b</sup>						
Yes	56 (19.2)	65 (21.7)	43 (14.9)	53 (19.4)	99 (17.1)	118 (20.6)
Pulmonary infiltrate status						
Multilobar	90 (31.0)	89 (29.7)	77 (26.6)	70 (25.6)	167 (28.8)	159 (27.7)

Abbreviations: ATS = American Thoracic Society; MITTE = modified intent-to-treat efficacy; PORT = Pneumonia Outcomes Research Team; SIRS = systemic inflammatory response syndrome.

Notes: Modified ATS Severe CAP criteria include the presence of 3 or more of the following 9 symptoms at baseline: respiratory rate ≥ 30 breaths/minute, O<sub>2</sub> < 90% or PaO<sub>2</sub> < 60 mmHg, multilobar infiltrates, confusion/disorientation, blood urea nitrogen level ≥ 20 mg/dL, leukopenia (white blood cell count < 4000 cells/mm<sup>3</sup>), thrombocytopenia (platelet count < 100,000 cells/mm<sup>3</sup>), hypothermia (core temperature < 36°C), systolic blood pressure < 90 mmHg or diastolic blood pressure ≤ 60 mmHg. SIRS criteria include the presence of ≥ 2 of the following 4 symptoms at baseline: temperature < 36°C or > 38°C, heart rate > 90 beats per minute, respiratory rate > 20, white blood cell count < 4000 or > 12,000 or immature neutrophils > 10%.

a Subjects who had fever but do not have PaO<sub>2</sub> < 60 mmHg or O<sub>2</sub> saturation collected at baseline and subjects who had hypoxia but do not have temperature collected at baseline are excluded

b Pleural effusion includes subjects with pleural effusion on either the right or left side of any size.

### 6.5.3 Baseline Pathogens

Table 6.5.3–1 provides a summary of the pathogenic organisms identified from specimens obtained from the respiratory tract or blood, or from *S. pneumoniae* urinary antigen testing for the Phase 3 CABP studies in the mMITTE Population. Appropriate respiratory tract specimens included pleural fluid, transthoracic samples, deep bronchial samples (eg, bronchoalveolar lavage), deep tracheal cultures, or appropriate sputum samples ( $\leq 10$  squamous epithelial cells/low-power field on Gram stain).

*Streptococcus pneumoniae* was the most commonly identified pathogen. Of the *S. pneumoniae* isolates with baseline susceptibility testing performed, 16.7% (13/78) were MDRSP isolates (defined as resistance to two or more antimicrobial classes of drugs, including penicillin, macrolides, tetracycline, fluoroquinolones, chloramphenicol, trimethoprim/sulfamethoxazole, and second generation cephalosporins). The percentage of MDRSP among subjects in the Phase 3 CABP studies is consistent with the prevalence of MDRSP reported in the United States (Richter et al, 2009).

Other commonly identified pathogen included *S. aureus*, *H. influenzae*, *H. parainfluenzae*, *K. pneumoniae*, and *E. coli*. As expected in CABP and given the study exclusion criteria, the isolation of MRSA was rare (n = 2 isolates).

The recovery rate of typical pathogens in the Phase 3 CABP studies (approximately 29% in the pooled MITTE Population) was not unexpected based on a review of the scientific literature (File, 2003). The expected typical pathogen recovery rates from United States studies detailed in a recent review were 19.9% to 32.9% (File, 2003). The typical pathogen recovery was also similar to that of other NDA registration trials; for example, the linezolid Phase 3 CAP study, which had similar sputum Gram stain criteria to those of the Phase 3 ceftriaxone CABP studies, revealed a typical pathogen recovery rate of approximately 29%. Note that the incidence of subjects with serological evidence of sole atypical pathogens in the Phase 3 CABP studies was approximately 12% and that these subjects were excluded from the CE, mMITTE, and ME Populations per protocol. Every effort was made to collect adequate microbiological samples from every subject in the Phase 3 CABP studies. There were no exclusion criteria related to the inability to produce sputum (eg, dry or nonproductive cough) and no “enhancement” inclusion criteria related to the inclusion of only subjects with a positive sputum Gram stain or culture. The Phase 3 CABP studies enrolled subjects with moderate-to-severe CAP requiring hospitalization and IV therapy, regardless of sputum production or Gram stain positivity.

**Table 6.5.3–1. Subjects with Pathogenic Organisms Identified at Baseline from Respiratory or Blood Specimens or Urinary Antigen Tests, Phase 3 Community-acquired Bacterial Pneumonia Studies—mMITTE Population**

<b>Baseline Pathogen</b>	<b>P903-08</b>		<b>P903-09</b>		<b>Pooled Phase 3 Studies (08, 09)</b>	
	<i>Ceftaroline</i> (N = 75) n (%)	<i>Ceftriaxone</i> (N = 80) n (%)	<i>Ceftaroline</i> (N = 90) n (%)	<i>Ceftriaxone</i> (N = 88) n (%)	<i>Ceftaroline</i> (N = 165) n (%)	<i>Ceftriaxone</i> (N = 168) n (%)
<b>Gram-positive organisms (aerobes)</b>	<b>36 (48.0)</b>	<b>43 (53.8)</b>	<b>56 (62.2)</b>	<b>54 (61.4)</b>	<b>92 (55.8)</b>	<b>97 (57.7)</b>
Any <i>Streptococcus pneumoniae</i>	27 (36.0)	30 (37.5)	42 (46.7)	40 (45.5)	69 (41.8)	70 (41.7)
Positive via urinary antigen only	14 (18.7)	16 (20.0)	14 (15.6)	15 (17.0)	28 (17.0)	31 (18.5)
Positive via respiratory specimen or blood culture	13 (17.3)	14 (17.5)	28 (31.1)	25 (28.4)	41 (24.8)	39 (23.2)
MDRSP	2 (2.7)	1 (1.3)	2 (2.2)	8 (9.1)	4 (2.4)	9 (5.4)
Non-MDRSP	11 (14.7)	13 (16.3)	26 (28.9)	15 (17.0)	37 (22.4)	28 (16.7)
PRSP	0	0	0	0	0	0
PISP	0	0	1 (1.1)	1 (1.1)	1 (0.6)	1 (0.6)
PSSP	13 (17.3)	14 (17.5)	27 (30.0)	22 (25.0)	40 (24.2)	36 (21.4)
<i>Staphylococcus aureus</i>	10 (13.3)	14 (17.5)	15 (16.7)	16 (18.2)	25 (15.2)	30 (17.9)
MRSA	0	1 (1.3)	0	1 (1.1)	0	2 (1.2)
MSSA	10 (13.3)	13 (16.3)	15 (16.7)	15 (17.0)	25 (15.2)	28 (16.7)
<i>Streptococcus agalactiae</i>	0	0	1 (1.1)	0	1 (0.6)	0
<i>Streptococcus pyogenes</i>	0	0	0	1 (1.1)	0	1 (0.6)
<b>Gram-negative organisms (aerobes)</b>	<b>44 (58.7)</b>	<b>44 (55.0)</b>	<b>46 (51.1)</b>	<b>47 (53.4)</b>	<b>90 (54.5)</b>	<b>91 (54.2)</b>
<i>Haemophilus influenzae</i>	5 (6.7)	10 (12.5)	15 (16.7)	14 (15.9)	20 (12.1)	24 (14.3)
<i>Haemophilus parainfluenzae</i>	8 (10.7)	10 (12.5)	9 (10.0)	8 (9.1)	17 (10.3)	18 (10.7)
<i>Klebsiella pneumoniae</i>	8 (10.7)	5 (6.3)	7 (7.8)	8 (9.1)	15 (9.1)	13 (7.7)
<i>Escherichia coli</i>	8 (10.7)	7 (8.8)	4 (4.4)	6 (6.8)	12 (7.3)	13 (7.7)

Abbreviations: MDRSP = multidrug-resistant *S. pneumoniae*; mMITTE = microbiological modified intent-to-treat efficacy; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*; PISP = penicillin-intermediate-susceptible *S. pneumoniae*; PRSP = penicillin-resistant *S. pneumoniae*; PSSP = penicillin-susceptible *S. pneumoniae*.

Notes: MRSA and MSSA are considered distinct pathogens. Subjects with both MRSA and MSSA are only counted once in the overall tabulation for *S. aureus*. Similarly, any of the 6 combinations of MDRSP/non-MDRSP with PISP/PSSP/PRSP within a subject is considered a distinct pathogen. However, subjects with any combination of these are only counted once in the overall tabulation of *S. pneumoniae* as well as overall tallies for any of the phenotypes (ie, MDRSP, PSSP, etc). Subjects with the same pathogen from a respiratory specimen, urinary antigen testing and blood specimen are counted only once for that pathogen.

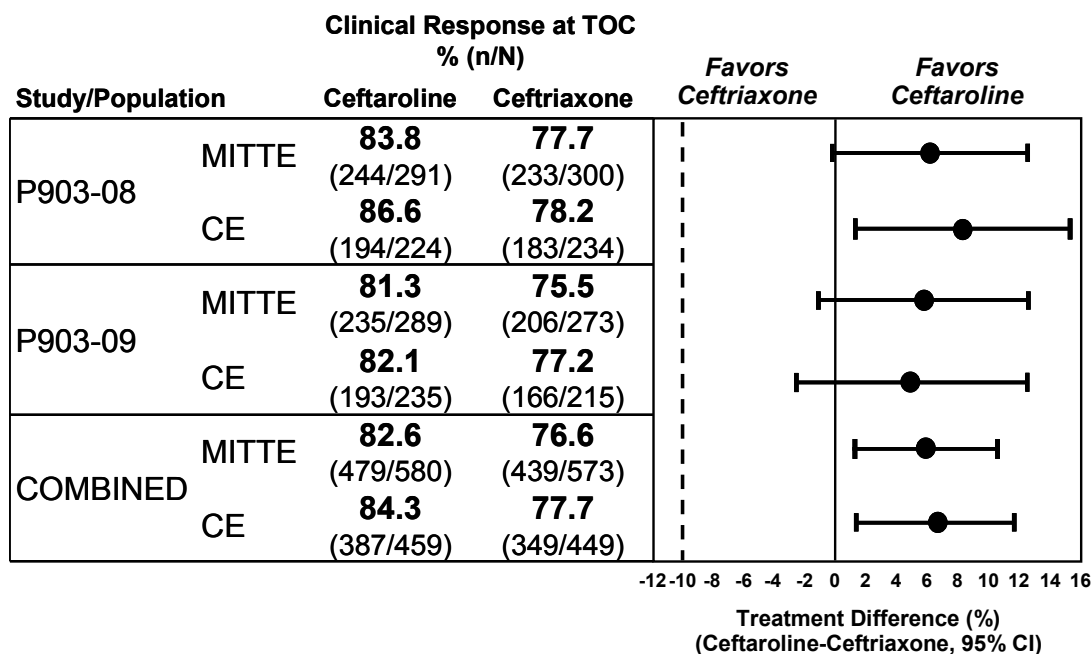


## 6.6 CLINICAL RESPONSE AT TEST OF CURE – THE PRIMARY EFFICACY VARIABLE

Most of the subjects in the ceftaroline and ceftriaxone groups received 5 to 8 calendar days of study drug (8 calendar days represented seven 24-hour days) and the median duration of ceftaroline fosamil or ceftriaxone therapy was 7.0 days (Section 8.2).

These large pivotal Phase 3 studies were consistent in demonstrating that ceftaroline is noninferior to ceftriaxone in subjects with CABP as evidenced by the lower limit of the 95% CI around the treatment difference in cure rates (ceftaroline – ceftriaxone) being greater than the prespecified noninferiority boundary of -10% in the coprimary CE and MITTE Populations of each study (Figure 6.6–1). When the two Phase 3 CABP studies were pooled, the lower limit of the 95% CI around the treatment difference (ceftaroline – ceftriaxone) was also greater than zero in both the CE and MITTE Populations (Figure 6.6–1).

**Figure 6.6–1. Clinical Response and Confidence Intervals for the Difference in Clinical Cure Rates at Test of Cure, Phase 3 Community-acquired Bacterial Pneumonia Studies—MITTE and CE Populations**



Abbreviations: CE = clinically evaluable; MITTE = modified intent-to-treat efficacy; TOC = test of cure.

Notes: Dots indicate difference in clinical cure rates defined as ceftaroline group minus ceftriaxone group. Bars indicate the lower and upper bounds of the CI. Confidence intervals are calculated using Miettinen and Nurminen method without adjustments except for pooled studies (stratified by study). Lower bound of 10% noninferiority margin is indicated by a vertical dashed line.

## 6.7 SECONDARY EFFICACY ANALYSES

### 6.7.1 Clinical Response at End of Therapy

Table 6.7.1–1 provides a summary of clinical response at EOT by treatment group for the Phase 3 CABP studies in the CE and MITTE Populations. Clinical cure rates at EOT were approximately 2% to 4% higher than those seen at TOC and the treatment difference (ceftaroline - ceftriaxone) were similar at EOT compared with TOC.

Per the hierarchical testing procedure of key secondary endpoints conducted for the individual studies (described in Section 6.1.1), ceftaroline was shown to be noninferior to ceftriaxone for the clinical cure rate at EOT in the CE and MITTE Populations of each study as evidenced by the lower limit of the 95% CI around the treatment difference (ceftaroline - ceftriaxone) being greater than the prespecified noninferiority boundary of -10%. In fact, the lower limit of the 95% CI in 3 of the 4 analyses were greater than zero.

**Table 6.7.1–1. Clinical Response at End of Therapy, Phase 3 Community-acquired Bacterial Pneumonia Studies—CE and MITTE Populations**

<i>Population/ Clinical Response</i>	<i>P903-08</i>		<i>P903-09</i>	
	<i>Ceftaroline n (%)</i>	<i>Ceftriaxone n (%)</i>	<i>Ceftaroline n (%)</i>	<i>Ceftriaxone n (%)</i>
<b>CE Population</b>				
N	224	234	235	215
Clinical Cure	197 (87.9)	188 (80.3)	202 (86.0)	172 (80.0)
Clinical Failure <sup>a</sup>	27 (12.1)	46 (19.7)	32 (13.6)	43 (20.0)
Crude difference (95% CI)	7.6 (0.9, 14.3)		6.0 (-1.0, 13.0)	
<b>MITTE Population</b>				
N	291	300	289	273
Clinical Cure	253 (86.9)	242 (80.7)	249 (86.2)	215 (78.8)
Clinical Failure <sup>a</sup>	30 (10.3)	52 (17.3)	35 (12.1)	50 (18.3)
Indeterminate	8 (2.7)	6 (2.0)	5 (1.7)	8 (2.9)
Crude difference (95% CI)	6.3 (0.3, 12.3)		7.4 (1.1, 13.8)	

Abbreviations: CE = clinically evaluable; MITTE = modified intent-to-treat efficacy.

Notes: Crude difference = difference in clinical cure rates (ceftaroline treatment group minus ceftriaxone treatment group). Weighted difference = weighted difference (stratified by study) in clinical cure rates (ceftaroline treatment group minus ceftriaxone treatment group). Confidence intervals are calculated using Miettinen and Nurminen method without adjustments except for pooled studies (stratified by study). Noninferiority margin of 10% is used.

a Subjects with indeterminate outcome at EOT due to death are counted as clinical failures.

### 6.7.2 Clinical Response by Baseline Pathogen at Test of Cure

Table 6.7.2–1 provides a summary of clinical response at TOC by baseline pathogen for the Phase 3 CABP studies in the mMITTE Population.

Clinical cure rates at TOC among subjects with any baseline gram-positive aerobic pathogens were higher in the ceftriaxone group compared with the ceftazidime group in the pooled Phase 3 CABP studies. Specifically, the lower limit of the 95% CI around the treatment difference was +5.5% in favor of ceftriaxone. This treatment difference was driven in large part by the clinical cure rates associated with *S. pneumoniae*, the most frequently isolated pathogen, for which the treatment difference was 17% in favor of ceftriaxone (ceftazidime, 85.5%; ceftriaxone, 68.6%) and the lower limit of the 95% CI was greater than zero. The clinical cure rate for MDRSP was higher in the ceftriaxone group than in the ceftazidime group (ceftazidime, 100%; ceftriaxone, 22.2%), but the numbers of MDRSP were small in this subject population. In subjects with *S. pneumoniae* bacteremia, the clinical cure rate was higher in the ceftriaxone group (14/17, 82.4%) than in the ceftazidime group (7/11, 63.6%). Clinical cure rates were also higher for *S. aureus* in the ceftriaxone group compared with the ceftazidime group, for which the treatment difference was 12% in favor of ceftriaxone (ceftazidime, 72%; ceftriaxone, 60%).

Clinical cure rates at TOC among subjects with any baseline gram-negative aerobes were similar for the 2 treatment groups. *Haemophilus influenzae* was the most frequently isolated gram-negative pathogen and clinical cure rates were similar between treatment groups (approximately 84%). Clinical cure rates for other common gram-negative pathogens, including *H. parainfluenzae*, *E. coli*, and *K. pneumoniae*, were similar between treatment groups.

**Table 6.7.2–1. Clinical Response at the Test of Cure Visit by Baseline Pathogen, Pooled Phase 3 Community-acquired Bacterial Pneumonia Studies—mMITTE Population**

<b>Baseline Pathogen/ Clinical Response<sup>a</sup></b>	<b>Pooled Phase 3 Studies (08, 09)</b>		<b>Weighted Difference (95% CI)</b>
	<b>Ceftaroline n(%)</b>	<b>Ceftriaxone n(%)</b>	
<b>Gram-positive organisms (aerobes)</b>	<b>77/92 (83.7)</b>	<b>64/97(66.0)</b>	<b>17.9(5.5, 29.8)</b>
<i>Streptococcus pneumoniae</i> <sup>b</sup>	59/69 (85.5)	48/70(68.6)	17.0(2.9, 30.7)
MDRSP	4/4 (100)	2/9(22.2)	
<i>Staphylococcus aureus</i> <sup>c</sup>	18/25 (72.0)	18/30 (60.0)	12.7 (-13.1, 36.3)
MSSA	18/25 (72.0)	17/28 (60.7)	12.2 (-13.8, 36.3)
<b>Gram-negative organisms (aerobes)</b>	<b>75/90 (83.3)</b>	<b>76/91 (83.5)</b>	<b>-0.2 (-11.4, 10.8)</b>
<i>Escherichia coli</i>	10/12 (83.3)	9/13 (69.2)	
<i>Haemophilus influenzae</i>	17/20 (85.0)	20/24(83.3)	
<i>Haemophilus parainfluenzae</i>	16/17 (94.1)	15/18 (83.3)	
<i>Klebsiella pneumoniae</i>	14/15 (93.3)	10/13 (76.9)	

Abbreviations: MDRSP = multidrug-resistant *Streptococcus pneumoniae*; mMITTE = microbiological modified intent-to-treat efficacy; MSSA = methicillin-susceptible *Staphylococcus aureus*.

- a Subjects with the same pathogen from a respiratory specimen, urinary antigen testing and blood specimen are counted only once for that pathogen.
- b Subjects with any combinations of MDRSP are counted once in the overall tabulation for *S. pneumoniae* as well as the individual phenotypes.
- c Subjects with both MRSA and MSSA are counted only once at the level of *S. aureus*, but are counted once each at the level of MRSA and MSSA.

Notes: Weighted difference = weighted difference (stratified by study) in clinical cure rates (ceftaroline treatment group minus ceftriaxone treatment group). Confidence intervals are calculated when the total sample size for a pathogen is at least 10 subjects in each treatment group using Miettinen and Nurminen method for stratified designs (stratified by study).

### 6.7.3 Clinical Relapse and Microbiological Reinfection or Recurrence at Late Follow-up

Eleven (1.6%) subjects (ceftaroline, n = 7; ceftriaxone, n = 4) in the CE Population of the Phase 3 CABP studies who were a clinical cure at TOC had a clinical relapse at LFU. None of the subjects with clinical relapse at LFU had evidence of microbiological reinfection or recurrence. In addition, with the exception of 1 subject, none of the subjects with clinical relapse had a causative pathogen at baseline. This subject had a history of bronchiectasis, diabetes, and congestive heart failure, and entered the study with multilobar CABP due to *H. influenzae* (ceftaroline MIC 0.015 µg/mL) and *S. pneumoniae* (no susceptibilities available). The subject was a clinical cure at both EOT (Study Day 7) and TOC (Study Day 20). This subject was rehospitalized on Study Day 27 with clinical relapse and worsened left-sided infiltrate on chest x-ray; repeated cultures were negative at LFU.

## 6.8 CLINICAL CURE RATE BY RELEVANT SUBGROUPS

### 6.8.1 Clinical Cure Rates by Demographics and Baseline Characteristics

Table 6.8.1–1 provides a summary of clinical cure rates at TOC for the CE Population in the pooled Phase 3 CABP studies by demographics and baseline characteristics for the 2 treatment groups. Confidence intervals were calculated for all subgroups with at least 10 observations in each group in each study.

Clinical cure rates were higher in the ceftaroline group (approximately 86%) than the ceftriaxone group (approximately 75%) for subjects with no prior systemic antibacterial treatment (the corresponding lower limit of the 95% CI was 4.5); however, the cure rates were similar between treatment groups (approximately 72% in each group) for subjects with prior systemic antibacterial treatment.

Point estimates of the treatment differences for all other subgroups of sufficient size (ie, those comprising at least one third of the overall population) were of comparable magnitude to the overall population demonstrating the robustness of the conclusions. Not surprisingly, observed treatment differences (ceftaroline - ceftriaxone) among smaller subgroups were more variable, but all such differences in point estimates favored ceftaroline. Further, for all subgroups with a large enough sample size to calculate a 95% CI around the treatment difference in cure rates (ceftaroline - ceftriaxone), the 95% CI included zero or the lower limit of the 95% CI was greater than zero.

**Table 6.8.1–1. Clinical Cure Rates at Test of Cure by Demographic and Baseline Characteristics, Pooled Phase 3 Community-acquired Bacterial Pneumonia Studies—CE Population**

<i>Demographic or Baseline Parameter</i>	<i>Pooled Phase 3 Studies (08, 09)</i>		
	<i>Ceftaroline (N = 459) n/N (%)</i>	<i>Ceftriaxone (N = 449) n/N (%)</i>	<i>Weighted Difference (95% CI)</i>
<b>Age group</b>			
< 65	192/227 (84.6)	172/230 (74.8)	9.7 (2.3, 17.1)
≥ 65	195/232 (84.1)	177/219 (80.8)	3.4 (-3.7, 10.5)
<b>Gender</b>			
Male	235/283 (83.0)	220/293 (75.1)	8.0 (1.4, 14.7)
Female	152/176 (86.4)	129/156 (82.7)	3.7 (-4.1, 11.8)
<b>Creatinine clearance (mL/min)</b>			
> 80	183/210 (87.1)	177/226 (78.3)	8.8 (1.7, 15.9)
> 50 and ≤ 80	133/164 (81.1)	115/151 (76.2)	5.3 (-3.8, 14.4)
> 30 and ≤ 50	62/75 (82.7)	50/63 (79.4)	3.5 (-9.7, 17.2)
≤ 30	9/10 (90.0)	7/9 (77.8)	12.2

**Table 6.8.1–1. Clinical Cure Rates at Test of Cure by Demographic and Baseline Characteristics, Pooled Phase 3 Community-acquired Bacterial Pneumonia Studies—CE Population**

<b>Demographic or Baseline Parameter</b>	<b>Pooled Phase 3 Studies (08, 09)</b>		
	<i>Ceftaroline</i> (N = 459) n/N (%)	<i>Ceftriaxone</i> (N = 449) n/N (%)	<i>Weighted Difference</i> (95% CI)
Body mass index (kg/m <sup>2</sup> )			
Underweight (< 18.5)	22/25 (88.0)	13/17 (76.5)	11.5 (-11.8, 37.7) <sup>a</sup>
Normal Weight (18.5, < 25.0)	154/188 (81.9)	121/166 (72.9)	9.6 (0.9, 18.4)
Overweight (25.0, < 30.0)	132/156 (84.6)	129/158 (81.6)	3.0 (-5.4, 11.4)
Obese (30.0, < 40.0)	69/79 (87.3)	78/99 (78.8)	8.5 (-3.0, 19.4)
Morbidly Obese (≥ 40.0)	10/11 (90.9)	8/9 (88.9)	2.0
PORT Risk Class			
Risk Class III	249/287 (86.8)	217/274 (79.2)	7.5 (1.3, 13.8)
Risk Class IV	138/172 (80.2)	132/175 (75.4)	4.7 (-4.1, 13.5)
Presence of bacteremia			
Yes	15/21 (71.4)	10/17 (58.8)	12.6 (-17.6, 41.6) <sup>a</sup>
No	372/438 (84.9)	339/432 (78.5)	6.5 (1.4, 11.7)
Any prior systemic antibacterial			
Yes	152/185 (82.2)	158/194 (81.4)	0.7 (-7.2, 8.6)
No	235/274 (85.8)	191/255 (74.9)	11.2 (4.5, 18.0)
Structural lung disease <sup>b</sup>			
Yes	108/138 (78.3)	93/122 (76.2)	2.2 (-8.0, 12.5)
No	279/321 (86.9)	256/327 (78.3)	8.6 (2.8, 14.4)

Abbreviations: CE = clinically evaluable; PORT = Pneumonia Outcomes Research Team.

Notes: The denominator is the number of subjects in the specified subgroup. Weighted difference = weighted difference (stratified by study) in clinical cure rates (ceftaroline treatment group minus ceftriaxone treatment group). Confidence intervals are calculated when the sample size is at least 10 subjects in each treatment group using Miettinen and Nurminen method without adjustments except for weighted difference (stratified by study).

- a For this subgroup, a CI for the crude difference in clinical cure rates (ceftaroline treatment group minus ceftriaxone treatment group) is provided.
- b Structural lung disease is defined as any clinically significant parenchymal or bronchial disease, eg, chronic obstructive pulmonary disease (including emphysema or chronic bronchitis), bronchiectasis, and pulmonary fibrosis.

## 6.9 FDA-DEFINED EXPLORATORY ANALYSIS

### 6.9.1 FDA-defined Clinical Response at Day 4

The Division requested that the Sponsor conduct a post-hoc exploratory analysis of clinical response based on signs and symptoms at Study Day 4 in the FDA-defined microbiological modified intent-to-treat (FDA-mMITT) Population. The FDA-defined analysis population consisted of subjects in the MITT Population with  $\geq 1$  acceptable baseline typical pathogen (defined below). Subjects with an acceptable typical pathogen and serological evidence of coinfection with an atypical pathogen (ie, *L. pneumophila*, *M. pneumoniae*, or *C. pneumoniae*) were also included in this FDA-mMITT Population. Subjects with *H. parainfluenzae* as the sole causative pathogen were excluded from the analysis population.

An acceptable baseline typical pathogen was defined as:

- Pathogen isolated from an acceptable baseline specimen (ie, blood, pleural fluid, broncho-alveolar lavage transthoracic, deep tracheal, or adequate sputum specimen [ $\leq 10$  squamous epithelial cells/LPF and  $> 10$  WBC/LPF])
  - Typical pathogens include *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *S. aureus*, or *S. pyogenes* and are acceptable for subjects classified as PORT Risk Class II or above
  - Enteric Gram-negative rods (ie, *K. pneumoniae*, *E. coli*, *Citrobacter freundii* complex, *Citrobacter koseri*, *Enterobacter cloacae*, *K. oxytoca*, *Proteus mirabilis*, *Serratia liquefaciens*, *Enterobacter aerogenes*, *Serratia marcescens*) only acceptable if the subject classified as PORT Risk Class III or above
- Positive urinary antigen test for *S. pneumoniae*

The FDA-defined exploratory outcome was clinical response at Study Day 4. Subjects were considered a responder if they met both “clinical stability” and “clinical symptom improvement” criteria at Study Day 4.

For clinical stability, a subject must have met all of the following criteria on Study Day 4:

- Temperature  $\leq 37.8^{\circ}\text{C}$  (uncorrected temperature, measured orally, rectally, or tympanically)
- Heart rate  $\leq 100$  beats per minute
- Respiratory rate  $\leq 24$  breaths per minute
- Systolic blood pressure  $\geq 90$  mmHg
- Oxygen saturation  $\geq 90\%$
- Absence of confusion/disorientation

For clinical symptom improvement, a subject was deemed a “success” if none of the following 4 symptoms were classified as worsening, and at least 1 was classified as improving, on Study Day 4: cough, dyspnea, chest pain, and sputum production.

The FDA exploratory clinical response results at Study Day 4 in the FDA-mMITT Population is provided for Study P903-08 and Study P903-09 (Table 6.9.1–1). This exploratory endpoint was not contemplated in the original study design, data collection was not optimized for this outcome measure, and the study was not powered with respect to this endpoint, however, treatment differences of 14.1% in Study P903-08 and 9.0% were observed in Study P903-09 in favor of ceftaroline. The lower limit of the 95% CI around the treatment difference (ceftaroline - ceftriaxone) was greater than zero for the pooled Phase 3 CABP studies.

**Table 6.9.1–1. Clinical Response of Signs and Symptoms at Study Day 4, Noninferiority Tests, Phase 3 Community–acquired Bacterial Pneumonia Studies — FDA-mMITT Population**

<i><b>By-subject Clinical Response at Study Day 4</b></i>	<i><b>P903-08</b></i>		<i><b>P903-09</b></i>		<i><b>Pooled Phase 3 Studies (08, 09)</b></i>	
	<i>Ceftaroline n(%)</i>	<i>Ceftriaxone n(%)</i>	<i>Ceftaroline n(%)</i>	<i>Ceftriaxone n(%)</i>	<i>Ceftaroline n(%)</i>	<i>Ceftriaxone n(%)</i>
N	69	72	82	81	151	153
Responders	49 (71.0)	41 (56.9)	57 (69.5)	49 (60.5)	106 (70.2)	90 (58.8)
Nonresponder	20 (29.0)	31 (43.1)	25 (30.5)	32 (39.5)	45 (29.8)	63 (41.2)
Crude difference (95% CI)	14.1 (-1.9, 29.3)		9.0 (-5.7, 23.4)			
Weighted difference (95% CI)					11.4 (0.6, 21.9)	

Abbreviation: FDA-mMITTE = FDA microbiological modified intent-to-treat.

Notes: Crude difference = difference in clinical cure rates (ceftaroline treatment group minus ceftriaxone treatment group). Weighted difference = weighted difference (stratified by study) in clinical cure rates (ceftaroline treatment group minus ceftriaxone treatment group). Confidence intervals are calculated using Miettinen and Nurminen method without adjustments except for pooled studies (stratified by study).



## **7.0** **COMPLICATED SKIN AND SKIN STRUCTURE STUDY DESIGN AND EFFICACY**

### **7.1** **STUDY DESIGN**

The Phase 3 cSSSI program included 2 studies: Studies P903-06 and P903-07 were adequate and well controlled, multicenter, multinational, randomized, double-blinded, active-controlled studies conducted under identical protocols. Adult subjects with cSSSI were randomized 1:1 to the ceftaroline (P903-06, n = 353; P903-07, n = 348) or vancomycin plus aztreonam (P903-06, n = 349; P903-07, n = 346) groups. The duration of treatment with study medication was 5 to 14 days. The dose of ceftaroline fosamil was 600 mg IV administered q12h for subjects with normal renal function or mild renal impairment and 400 mg IV q12h for subjects with moderate renal impairment. Subjects randomized to ceftaroline received placebo infusions to match the comparator dosing regimen. The rationale for the ceftaroline fosamil dose of 600 mg q12h, the same dose used in the Phase 3 CABP studies, is discussed in Section 6.1.

The active comparator regimen was vancomycin 1 g IV q12h plus aztreonam 1 g IV q12h. This regimen is in accordance with the approved dosage regimens recommended for vancomycin and aztreonam in this population. Vancomycin was chosen as the active comparative agent best suited for the Phase 3 cSSSI studies because of its acceptance in clinical practice worldwide as a highly effective, standard-of-care therapy for cSSSI (Stevens et al, 2005). Aztreonam was chosen in combination because it is recommended for community-acquired gram-negative infections and is a recommended therapy for gram-negative cSSSI in expert guidelines (Stevens et al, 2005); it has no overlapping activity with the gram-positive activity of vancomycin. The initial vancomycin dosage regimen was consistent with the dosage and administration recommendations in the approved package insert; 1 g q12h administered as 1-hour IV infusions (Vancocin [vancomycin] package insert, 2008). Subsequent doses of vancomycin could be decreased to < 1 g q12h for subjects with moderate renal impairment or increased for subjects who weighed 90 kg or more. The aztreonam dosage regimen used in the Phase 3 cSSSI studies was 1 g q12h as a 1-hour IV infusion, which is consistent with the recommended dosage for adults (Azactam [aztreonam] package insert, 2007). Aztreonam treatment could be discontinued at any time if infection with a gram-negative pathogen was neither identified nor suspected.

The visit schedule, subject population, length of therapy, efficacy endpoints, and statistical considerations in each study are consistent with the current US FDA Guidance for Industry: Uncomplicated and Complicated Skin and Skin Structure Infections—Developing Antimicrobial Drugs for Treatment (US FDA, 1998 Jul).

The study visit overview for Studies P903-06 and P903-07 is shown schematically in Table 7.1–1.

**Table 7.1–1. Study Visit Overview, P903-06 and P903-07**

<b><i>BASELINE</i></b>	<b><i>STUDY DRUG ADMINISTRATION</i></b>	<b><i>TOC Visit</i></b>	<b><i>LFU Visit</i></b>
<b>Within 24 hours before first dose of study drug</b>	<b>Day 1 to EOT</b>	<b>8 to 15 days after last dose of study drug</b>	<b>21 to 35 days after last dose of study drug</b>
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

Abbreviations: EOT = end of therapy; IV = intravenous; LFU = late follow-up; TOC = test of cure.

Pooling of the 2 studies for the integrated summaries of efficacy and safety was appropriate since both studies were well controlled Phase 3, randomized, multicenter, double-blind, active-controlled studies, with identical designs, in adult subjects. The appropriateness of pooling was further supported by similarities in the key results of the 2 studies, including similar baseline demographic characteristics of the subject populations, clinical markers for cSSSI (eg, signs, symptoms, types of infections), clinical cure rates between treatment groups, and microbiological results.

Subject selection criteria were defined rigorously in the Phase 3 cSSSI protocols. The protocols were designed to ensure that subjects were enrolled only if their skin or skin structure infection was complicated (ie, met predefined cSSSI criteria) and of sufficient severity to warrant hospitalization and/or IV antimicrobial therapy. Most subjects were hospitalized at the time of randomization and IV study drug was administered in the hospital setting; outpatient parenteral antimicrobial therapy (OPAT) was permitted if prespecified conditions were met (eg, OPAT site prequalified by Sponsor, Investigator capable of performing face-to-face assessments, subject showed adequate improvement on study medication to warrant hospital discharge). No switch to oral therapy was permitted.

Key inclusion criteria included:

- Adult subjects (18 years or older) who required initial hospitalization or treatment in an emergency room or urgent care setting who had 3 or more of the following clinical signs (local, systemic, or both) of SSSI:
  - Fever  $> 38^{\circ}\text{C}$  oral or hypothermia ( $< 35^{\circ}\text{C}$ )
  - WBC count  $> 10,000/\text{mm}^3$
  - Greater than 10% immature neutrophils (bands) irrespective of WBC count
  - Purulent or seropurulent drainage or discharge
  - Erythema
  - Fluctuance
  - Heat or localized warmth
  - Pain or tenderness to palpation
- Skin and skin structure infection expected to require at least 5 days of IV antimicrobial therapy and that met **EITHER** of the following criteria:
  - Involved deeper soft tissue (defined as subdermal tissue including subcutaneous fat) or required significant surgical intervention (defined as a major operative procedure that could be performed within 48 hours after initiating study drug therapy, not including commonly performed minor procedures at the bedside), such as:
    - Wound infection (defined by the presence of either purulent or seropurulent discharge from the surgical or traumatic wound or  $\geq 5$  cm of erythema [ie, cellulitis] surrounding the wound margin)
    - Major abscess (defined by the presence of a loculated fluid collection with  $\geq 2$  cm of erythema [ie, cellulitis] extending from the abscess margin and acute onset within 7 days)
    - Infected ulcer
    - Deep and extensive cellulitis (defined as involving deeper soft tissue with a surface area  $\geq 10\text{ cm}^2$ )

**OR**

- Cellulitis (defined by the presence of advancing erythema, edema, and heat) or abscess on the lower extremity that occurs in subjects with diabetes mellitus (defined as subjects with a history of diabetes mellitus and taking insulin, insulin analogues, or oral hypoglycemic agents) or well documented peripheral vascular disease (PVD; defined as arterial or venous vascular disease resulting in ischemia of the lower extremities as manifest by ulceration, poor wound healing, or the absence of readily palpable dorsalis pedis and posterior tibial pulses).

Key exclusion criteria included:

- Uncomplicated SSSI
- More than 24 hours of treatment with an antimicrobial (other than topical antimicrobials) for the treatment of current cSSSI within 96 hours before randomization, unless there was documented treatment failure on prior antimicrobial therapy or requirement for concomitant antimicrobial therapy (including systemic antifungal therapy)
- Severely impaired renal function ( $\text{CrCl} \leq 30 \text{ mL/min}$ ) estimated by the Cockcroft-Gault (1976) formula or evidence of significant hepatic, hematologic, immunologic, or immediately life-threatening disease
- History of any hypersensitivity or allergic reaction to any beta-lactam antimicrobial

Analysis populations are described in Section 7.2.

The primary objective in the Phase 3 cSSSI studies was the demonstration of noninferiority of ceftaroline to the comparator regimen in the primary efficacy endpoint of clinical cure rate at TOC in the coprimary CE and MITT Populations. The clinical response of each subject was determined by the Investigator by assessing the subject's clinical signs and symptoms at the specified evaluation visit compared with the signs and symptoms present at baseline. Prespecified secondary efficacy endpoints included clinical response at EOT in the MITT and CE Populations, by-subject microbiological response at TOC in the mMITT and ME Populations, clinical and microbiological responses by baseline pathogen at TOC in the mMITT and ME Populations, relapse at LFU in those subjects who were clinically cured at the TOC visit, and reinfection or recurrence at LFU in those subjects who had a favorable microbiological outcome at the TOC visit.

Clinical outcome categories are described in Table 7.1–2.

Rigorous study conduct, which was ensured throughout the studies, included activities such as pre-enrollment qualification of all sites, Investigator meetings in all regions, protocol training required before site initiation, blinding procedures reviewed at each site, strict site initiation procedures, intensive monitoring of sites during and after active enrollment to ensure protocol adherence, enforcement of ICH compliance, and extensive auditing (> 30% of sites and subjects).

**Table 7.1–2. Clinical Outcome Categories**

<b><i>Outcome</i></b>	<b><i>Definition</i></b>
Clinical Cure	Total resolution of all signs and symptoms of the cSSSI, or improvement to such an extent that further antimicrobial therapy was not necessary  <b>Note:</b> 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: <ol style="list-style-type: none"> <li>1. Persistence, incomplete resolution, or worsening in signs and symptoms of the cSSSI that required alternative antimicrobial therapy</li> <li>2. A surgical intervention that was performed as an adjunct or follow-up therapy <i>due to failure of the study drug</i> 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.</li> <li>3. New signs and symptoms associated with the original cSSSI or a new cSSSI at the same anatomical site</li> <li>4. Subject required alternative antimicrobial therapy to treat the cSSSI, 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.</li> <li>5. Treatment-limiting AE leading to study drug discontinuation, when subject required alternative antimicrobial therapy to treat the cSSSI, including oral step-down therapy.</li> <li>6. Diagnosis of osteomyelitis 8 or more days after randomization.</li> <li>7. Death wherein cSSSI was considered causative</li> </ol>
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 cSSSI was clearly noncontributory, lost to follow-up, or extenuating circumstances that precluded classification as a cure or failure (eg, diagnosis of osteomyelitis 7 or fewer days after randomization)

Abbreviations: AE = adverse event; cSSSI = complicated skin and skin structure infection; SSSI = skin and skin structure infection.

### 7.1.1 Statistical Methods

For the primary objective of establishing noninferiority of ceftaroline with respect to vancomycin plus aztreonam in the coprimary populations, the lower limit of the 95% CI for the difference (ceftaroline - vancomycin plus aztreonam) in the proportions of subjects with an outcome of clinical cure was obtained using the Miettinen and Nurminen method for comparing proportions. Noninferiority was shown if the lower limit was greater than or equal to -0.100. The FDA accepted the use of a 1-sided significance level of 0.025 for statistical significance of the test of noninferiority. Since the statistical test in each coprimary population had to meet this requirement, the Type I error is controlled at the (one-sided) 2.5% significance level. Descriptive statistics, including the numbers and percentages for categorical variables, and the numbers, means, standard deviations, medians, minimums and maximums for continuous variables are provided when appropriate.

The noninferiority margin for the primary efficacy analysis was prospectively defined as 10% in the analysis plan submitted to the FDA before database lock and unblinding. At the End-of-Phase 2 meeting (October 24, 2006) and subsequent meetings between the FDA and Cerexa, the FDA accepted a 10% noninferiority margin for the two pivotal Phase 3 cSSSI studies (P903-06 and P903-07). The selection and justification of the noninferiority margin is described in detail in Appendix 11.2.

For 2 key secondary endpoints, the hierarchical testing procedure of Westfall and Krishen (2001) was utilized to control the overall Type I error at 2.5% (one-sided).

- By-subject clinical cure rate at EOT in both the MITT and CE Populations using a noninferiority margin of 10%
- By-subject microbiological favorable outcome rate at TOC in the mMITT and ME Populations using a noninferiority margin of 10%

For analyses of pooled data, the Miettinen and Nurminen method stratified by study and using Cochran-Mantel-Haenszel weights was used.

The sample size was based on a point estimate of the clinical cure rate of 85% in both the ceftaroline group and vancomycin plus aztreonam group, which is consistent with the literature and the overall clinical response rate in the MITT Population from the Phase 2 IV study. Using a noninferiority margin of 10%, 90% power, and a two-sided alpha of 0.05, based on the sample size determination method of Farrington and Manning (1990), a total of 276 evaluable subjects in each treatment group was required. Assuming 80% of the randomized population would be evaluable for the CE Population, a total sample size of 690 subjects was required (345 subjects in each treatment group).

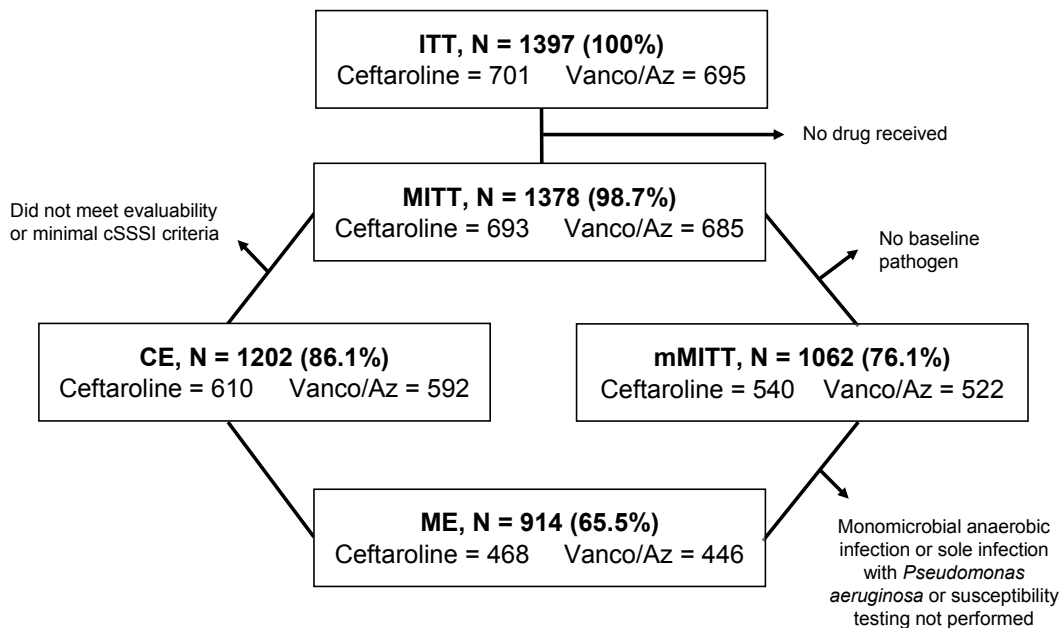
As recommended by the FDA and in addition to the planned analyses, an additional post-hoc cSSSI analysis was conducted to evaluate clinical cure rates at TOC for the CE and MITT Populations excluding subjects with abscesses alone (Section 7.9).

To explore the homogeneity of ceftaroline efficacy in cSSSI, treatment group differences were examined for a variety of subgroups defined by baseline characteristics (Section 7.8).

## 7.2 ANALYSIS POPULATIONS

An overview of the numbers of subjects included in each population is presented in Figure 7.2–1. Overall, the 2 treatment groups were similar in the number of subjects included in the various populations.

**Figure 7.2–1. Analysis Populations, Pooled Phase 3 Complicated Skin and Skin Structure Studies**



Abbreviations: cSSSI = complicated skin and skin structure infections; CE = clinically evaluable; ITT = intent-to-treat; ME = microbiologically evaluable; MITT = modified intent-to-treat; mMITT = microbiological modified intent-to-treat; Vanco/Az = vancomycin plus aztreonam.

The analysis populations of the Phase 3 cSSSI studies are described below:

- ITT Population: all randomized subjects
- MITT Population: all randomized subjects who received any amount of study drug. Subjects given study drug opposite from the randomized assignment were analyzed for efficacy in the treatment group assigned. The Safety Population was analyzed by the treatment actually received.
- mMITT Population: all subjects in the MITT Population who met the study-specific minimal disease criteria for cSSSI and had at least 1 bacterial pathogen identified at baseline from culture
- CE Population: all subjects in the MITT Population who met the study-specific minimal disease criteria for cSSSI and met the evaluability criteria detailed in the protocol and SAP
- ME Population: subjects from the CE Population who had at least 1 bacterial pathogen identified at baseline from culture.

The MITT and CE Populations were considered the coprimary populations for the primary endpoint analysis of noninferiority in Studies P903-06 and P903-07.

### **7.3 REGIONS OF ENROLLMENT**

Table 7.3–1 provides an overall summary of enrollment by region (MITT Population) in the Phase 3 cSSSI studies. In the pooled Phase 3 cSSSI studies, enrollment was highest in the United States followed by Eastern Europe, Western Europe, and Latin America. Enrollment by region was similar between the ceftriaxone and vancomycin plus aztreonam groups.

Subject treatment, subject care, sample collection and analysis, and data capture was standardized across regions in the multinational Phase 3 cSSSI studies by the use of a universal protocol that mandated the type, timing, and methods for specific assessments and procedures. Clinical cure rates by region are provided in Section 7.8.1.



**Table 7.3–1. Enrollment by Region Groups, Phase 3 Complicated Skin and Skin Structure Studies—MITT Population**

<b>Region Group or Protocol Amendment</b>	<b>P903-06</b>		<b>P903-07</b>		<b>Pooled Phase 3 Studies (06, 07)</b>	
	<i>Ceftaroline (N = 351) n(%)</i>	<i>Vancomycin plus Aztreonam (N = 347) n(%)</i>	<i>Ceftaroline (N = 342) n(%)</i>	<i>Vancomycin plus Aztreonam (N = 338) n(%)</i>	<i>Ceftaroline (N = 693) n(%)</i>	<i>Vancomycin plus Aztreonam (N = 685) n(%)</i>
<b>Region</b>						
US	133 (37.9)	131 (37.8)	170 (49.7)	168 (49.7)	303 (43.7)	299 (43.6)
Eastern Europe	145 (41.3)	147 (42.4)	106 (31.0)	104 (30.8)	251 (36.2)	251 (36.6)
Western Europe	42 (12.0)	41 (11.8)	41 (12.0)	41 (12.1)	83 (12.0)	82 (12.0)
Latin America	31 (8.8)	28 (8.1)	25 (7.3)	25 (7.4)	56 (8.1)	53 (7.7)
<b>US and Non-US</b>						
US	133 (37.9)	131 (37.8)	170 (49.7)	168 (49.7)	303 (43.7)	299 (43.6)
Non-US	218 (62.1)	216 (62.2)	172 (50.3)	170 (50.3)	390 (56.3)	386 (56.4)

Abbreviation: MITT = modified intent-to-treat.

#### 7.4 PREMATURE DISCONTINUATIONS OF STUDY DRUG

Table 7.4–1 (MITT Population) provides an overall summary of subjects in the Phase 3 cSSSI studies who completed study drug administration and the numbers and percentages of subjects who prematurely discontinued study drug. In the pooled Phase 3 cSSSI studies, approximately 91% of subjects in each treatment group completed study drug administration. The most common reasons for premature discontinuation of study drug were AEs, insufficient therapeutic effect, and lost to follow-up. The “other” category for premature discontinuation from study drug administration included protocol deviation, delayed shipment of study drug, and subject noncompliance.

**Table 7.4–1. Premature Discontinuation From Study Drug, Phase 3 Complicated Skin and Skin Structure Studies—MITT Population**

	<i>P903-06</i>		<i>P903-07</i>		<i>Pooled Phase 3 Studies (06, 07)</i>	
	<i>Ceftaroline (N = 351) n (%)</i>	<i>Vancomycin plus Aztreonam (N = 347) n (%)</i>	<i>Ceftaroline (N = 342) n (%)</i>	<i>Vancomycin plus Aztreonam (N = 338) n (%)</i>	<i>Ceftaroline (N = 693) n (%)</i>	<i>Vancomycin plus Aztreonam (N = 685) n (%)</i>
<b>Completed study drug</b>	<b>325 (92.6)</b>	<b>315 (90.8)</b>	<b>316 (92.4)</b>	<b>304 (89.9)</b>	<b>641 (92.5)</b>	<b>619 (90.4)</b>
Prematurely discontinued from study drug	26 (7.4)	32 (9.2)	26 (7.6)	34 (10.1)	52 (7.5)	66 (9.6)
<b>Reason for premature discontinuation of study drug</b>						
Adverse event	13 (3.7)	15 (4.3)	7 (2.0)	17 (5.0)	20 (2.9)	32 (4.7)
Insufficient therapeutic effect	3 (0.9)	5 (1.4)	9 (2.6)	9 (2.7)	12 (1.7)	14 (2.0)
Clinical worsening, lack of clinical progress	0	3 (0.9)	4 (1.2)	8 (2.4)	4 (0.6)	11 (1.6)
Significant surgical intervention	2 (0.6)	0	2 (0.6)	1 (0.3)	4 (0.6)	1 (0.1)
Due to resistant pathogen	1 (0.3)	2 (0.6)	3 (0.9)	0	4 (0.6)	2 (0.3)
Withdrew consent	1 (0.3)	0	1 (0.3)	1 (0.3)	2 (0.3)	1 (0.1)
Lost to follow-up	5 (1.4)	7 (2.0)	4 (1.2)	2 (0.6)	9 (1.3)	9 (1.3)
Other	4 (1.1)	5 (1.4)	5 (1.5)	5 (1.5)	9 (1.3)	10 (1.5)

Abbreviation: MITT = modified intent-to-treat.

## 7.5 DEMOGRAPHICS, BASELINE CHARACTERISTICS, AND BASELINE PATHOGENS

### 7.5.1 Demographics and Baseline Characteristics

Table 7.5.1–1 provides the demographic and baseline characteristics of subjects (MITT Population) in the Phase 3 cSSSI studies. The demographic and baseline characteristics of subjects in the ceftaroline and the vancomycin plus aztreonam groups were well balanced. Demographics and baseline characteristics in the CE Population were similar to those in the MITT Population.

**Table 7.5.1–1. Demographics and Baseline Characteristics, Phase 3 Complicated Skin and Skin Structure Studies—MITT Population**

<i>Demographic or Baseline Parameter</i>	<i>P903-06</i>		<i>P903-07</i>		<i>Pooled Phase 3 Studies (06, 07)</i>	
	<i>Ceftaroline (N = 351)</i>	<i>Vancomycin plus Aztreonam (N = 347)</i>	<i>Ceftaroline (N = 342)</i>	<i>Vancomycin plus Aztreonam (N = 338)</i>	<i>Ceftaroline (N = 693)</i>	<i>Vancomycin plus Aztreonam (N = 685)</i>
Age (years)						
n	351	347	342	338	693	685
Median	48.0	48.0	47.0	48.0	48.0	48.0
Min, Max	18, 90	18, 87	18, 93	18, 96	18, 93	18, 96
Age group (years) n (%)						
< 65	293 (83.5)	269 (77.5)	280 (81.9)	286 (84.6)	573 (82.7)	555 (81.0)
≥ 65	58 (16.5)	78 (22.5)	62 (18.1)	52 (15.4)	120 (17.3)	130 (19.0)
Sex n (%)						
Male	220 (62.7)	218 (62.8)	224 (65.5)	201 (59.5)	444 (64.1)	419 (61.2)
Female	131 (37.3)	129 (37.2)	118 (34.5)	137 (40.5)	249 (35.9)	266 (38.8)
Ethnicity n (%)						
Non-Hispanic	268 (76.4)	270 (77.8)	279 (81.6)	279 (82.5)	547 (78.9)	549 (80.1)
Hispanic	83 (23.6)	77 (22.2)	63 (18.4)	59 (17.5)	146 (21.1)	136 (19.9)
Race n (%)						
White	260 (74.1)	258 (74.4)	246 (71.9)	254 (75.1)	506 (73.0)	512 (74.7)
Asian	3 (0.9)	4 (1.2)	3 (0.9)	1 (0.3)	6 (0.9)	5 (0.7)
Black or African American	15 (4.3)	20 (5.8)	33 (9.6)	21 (6.2)	48 (6.9)	41 (6.0)
Multi-race/Other	9 (2.6)	5 (1.4)	5 (1.5)	8 (2.4)	14 (2.0)	13 (1.9)
Unknown <sup>a</sup>	64 (18.2)	60 (17.3)	55 (16.1)	54 (16.0)	119 (17.2)	114 (16.6)
BMI (kg/m <sup>2</sup> ) distribution n (%)						
Underweight (< 18.5)	8 (2.3)	4 (1.2)	7 (2.0)	3 (0.9)	15 (2.2)	7 (1.0)
Normal weight (18.5, < 25.0)	114 (32.5)	100 (28.8)	124 (36.3)	123 (36.4)	238 (34.3)	223 (32.6)
Overweight (25.0, < 30.0)	111 (31.6)	126 (36.3)	105 (30.7)	101 (29.9)	216 (31.2)	227 (33.1)
Obese/ Morbidly Obese (≥ 30.0)	116 (33.0)	116 (33.4)	106 (31.0)	111 (32.8)	222 (32.0)	227 (33.1)
Subjects with DM	62 (17.7)	68 (19.6)	60 (17.5)	52 (15.4)	122 (17.6)	120 (17.5)
Subjects with PVD	47 (13.4)	53 (15.3)	46 (13.5)	40 (11.8)	93 (13.4)	93 (13.6)

**Table 7.5.1–1. Demographics and Baseline Characteristics, Phase 3 Complicated Skin and Skin Structure Studies—MITT Population**

<b>Demographic or Baseline Parameter</b>	<b>P903-06</b>		<b>P903-07</b>		<b>Pooled Phase 3 Studies (06, 07)</b>	
	<i>Ceftaroline (N = 351)</i>	<i>Vancomycin plus Aztreonam (N = 347)</i>	<i>Ceftaroline (N = 342)</i>	<i>Vancomycin plus Aztreonam (N = 338)</i>	<i>Ceftaroline (N = 693)</i>	<i>Vancomycin plus Aztreonam (N = 685)</i>
Creatinine clearance (mL/min) <sup>b</sup>						
> 80	291 (82.9)	283 (81.6)	278 (81.3)	276 (81.7)	569 (82.1)	559 (81.6)
> 50 and ≤ 80	48 (13.7)	46 (13.3)	51 (14.9)	52 (15.4)	99 (14.3)	98 (14.3)
> 30 and ≤ 50	11 (3.1)	16 (4.6)	12 (3.5)	10 (3.0)	23 (3.3)	26 (3.8)
≤ 30	1 (0.3)	2 (0.6)	1 (0.3)	0	2 (0.3)	2 (0.3)
Previous antibiotic usage <sup>c</sup>	148 (42.2)	143 (41.2)	128 (37.4)	117 (34.6)	276 (39.8)	260 (38.0)

Abbreviations: BMI = body mass index; DM = diabetes mellitus; MITT = modified intent-to-treat; PVD = peripheral vascular disease.

- a In Studies P903-06 and P903-07, the case report form (CRF) did not capture race and ethnicity as separate categories, subjects were allowed to report more than 1 ethnicity/race, and Hispanic or Latino was an acceptable choice for ethnicity/race. In this integrated analysis, ethnicity (ie, Hispanic/ non-Hispanic) was extracted from the race/ethnicity category, subjects reporting multiple races (excluding Hispanic/Latino) or reporting 'Other' were counted in the category Multi-race/Other, and subjects who reported solely 'Hispanic or Latino' were assigned a race of Unknown.
- b Central laboratory values of creatinine clearance were used if available. Otherwise, CRF creatinine clearance values were used.
- c Previous systemic antibiotic usage within 96 hours prior to first dose of study drug.

## 7.5.2 Severity of Disease

Table 7.5.2–1 provides an overall summary of severity markers for cSSSI for the MITT Population in the Phase 3 cSSSI studies. Severity markers for cSSSI in the CE Population were similar to those in the MITT Population. The characteristics of the study population (ie, a relatively high percentage of subjects with fever, elevated WBC count, no previous antibiotic usage, prior treatment failures, and bacteremia) and description of the infection site (ie, infection type and location) were consistent with what would be expected for subjects with complicated skin infections and were similar between the treatment groups.

The subject demographics and disease characteristics (Table 7.5.1–1 and Table 7.5.2–1) clearly indicate that all enrolled subjects had signs and symptoms consistent with complicated infection that required initial hospitalization and systemic IV therapy. In the MITT Population, 98% of subjects in each treatment group had deep skin structure involvement and other characteristic signs of cSSSI including fluctuance, discharge, lymphangitic spread, bullae, ulceration, and necrosis of the primary infection site. Many subjects enrolled in the Phase 3 cSSSI studies had other clinical signs suggestive of relatively severe cSSSI, such as baseline lesion size  $\geq 75 \text{ cm}^2$  (approximately 73%), the presence of at least one systemic sign (approximately 54% had fever, leukocytosis, or bacteremia), complicated infection involving the head or neck (approximately 5%), or bacteremia (approximately 4%). Of the subjects who had abscess, the abscess was required to have at least 2 cm of surrounding cellulitis extending from the abscess margin. The median infection area was approximately  $156 \text{ cm}^2$  for the ceftaroline group and  $150 \text{ cm}^2$  for the vancomycin plus aztreonam group. Finally, approximately 54% of subjects had at least 2 severe signs or symptoms at baseline, and approximately 23% of subjects met SIRS criteria at baseline (defined in Table 7.5.2–1).

**Table 7.5.2–1. Markers for Complicated Skin and Skin Structure Infections - Clinical Parameters, Phase 3 Studies—MITT Population**

<b>Markers</b>	<b>P903-06</b>		<b>P903-07</b>		<b>Pooled Phase 3 Studies (06, 07)</b>	
	<i>Ceftaroline</i> (N = 351) n (%)	<i>Vancomycin plus Aztreonam</i> (N = 347) n (%)	<i>Ceftaroline</i> (N = 342) n (%)	<i>Vancomycin plus Aztreonam</i> (N = 338) n (%)	<i>Ceftaroline</i> (N = 693) n (%)	<i>Vancomycin plus Aztreonam</i> (N = 685) n (%)
Systemic signs <sup>a</sup>						
Subjects with at Least 1 Systemic Sign	199 (56.7)	193 (55.6)	179 (52.3)	170 (50.3)	378 (54.5)	363 (53.0)
Subjects with severe signs and/or symptoms at baseline						
Subjects with 2 or more severe signs and/or symptoms	191 (54.4)	203 (58.5)	181 (52.9)	176 (52.1)	372 (53.7)	379 (55.3)
Fever						
No (Temperature $\leq 38^\circ\text{C}$ )	229 (65.2)	237 (68.3)	252 (73.7)	247 (73.1)	481 (69.4)	484 (70.7)
Yes (Temperature $> 38^\circ\text{C}$ )	121 (34.5)	110 (31.7)	90 (26.3)	91 (26.9)	211 (30.4)	201 (29.3)
Missing	1 (0.3)	0	0	0	1 (0.1)	0
Elevated WBC count						
No ( $\leq 10,000 \text{ cells/mm}^3$ )	194 (55.3)	187 (53.9)	180 (52.6)	177 (52.4)	374 (54.0)	364 (53.1)
Yes ( $> 10,000 \text{ cells/mm}^3$ )	120 (34.2)	126 (36.3)	126 (36.8)	128 (37.9)	246 (35.5)	254 (37.1)
Missing	37 (10.5)	34 (9.8)	36 (10.5)	33 (9.8)	73 (10.5)	67 (9.8)
Subjects with at least 2 severe signs and symptoms OR fever OR elevated WBC count						
Yes	261 (74.4)	257 (74.1)	245 (71.6)	235 (69.5)	506 (73.0)	492 (71.8)

**Table 7.5.2–1. Markers for Complicated Skin and Skin Structure Infections - Clinical Parameters, Phase 3 Studies—MITT Population**

<b>Markers</b>	<b>P903-06</b>		<b>P903-07</b>		<b>Pooled Phase 3 Studies (06, 07)</b>	
	<i>Ceftaroline</i> (N = 351) n (%)	<i>Vancomycin</i> plus <i>Aztreonam</i> (N = 347) n (%)	<i>Ceftaroline</i> (N = 342) n (%)	<i>Vancomycin</i> plus <i>Aztreonam</i> (N = 338) n (%)	<i>Ceftaroline</i> (N = 693) n (%)	<i>Vancomycin</i> plus <i>Aztreonam</i> (N = 685) n (%)
Baseline lesion size $\geq 75$ cm <sup>2</sup>						
Yes	259 (73.8)	275 (79.3)	246 (71.9)	223 (66.0)	505 (72.9)	498 (72.7)
Previous antibiotic usage <sup>b</sup>						
Any prior systemic antibacterial	148 (42.2)	143 (41.2)	128 (37.4)	117 (34.6)	276 (39.8)	260 (38.0)
SIRS criteria met <sup>c</sup>						
Yes	81 (23.1)	79 (22.8)	74 (21.6)	84 (24.9)	155 (22.4)	163 (23.8)
Presence of bacteremia						
No	327 (93.2)	331 (95.4)	330 (96.5)	317 (93.8)	657 (94.8)	648 (94.6)
Yes	20 (5.7)	11 (3.2)	9 (2.6)	15 (4.4)	29 (4.2)	26 (3.8)
No Culture	4 (1.1)	5 (1.4)	3 (0.9)	6 (1.8)	7 (1.0)	11 (1.6)
Description of infection						
Infected wound	54 (15.4)	43 (12.4)	48 (14.0)	39 (11.5)	102 (14.7)	82 (12.0)
Abscess	103 (29.3)	102 (29.4)	140 (40.9)	134 (39.6)	243 (35.1)	236 (34.5)
Major abscess	99 (96.1)	101 (99.0)	139 (99.3)	133 (99.3)	238 (97.9)	234 (99.2)
Abscess in lower extremity cSSSI in subjects with DM or PVD	4 (3.9)	1 (1.0)	1 (0.7)	1 (0.7)	5 (2.1)	2 (0.8)
At least 1 dimension > 5 cm	86 (83.5)	89 (87.3)	125 (89.3)	121 (90.3)	211 (86.8)	210 (89.0)
No Dimension > 5 cm	17 (16.5)	13 (12.7)	15 (10.7)	13 (9.7)	32 (13.2)	26 (11.0)
Concomitant bacteremia	6 (5.8)	4 (3.9)	4 (2.9)	3 (2.2)	10 (4.1)	7 (3.0)
Infected ulcer	23 (6.6)	31 (8.9)	31 (9.1)	21 (6.2)	54 (7.8)	52 (7.6)
Infected burn	25 (7.1)	20 (5.8)	1 (0.3)	2 (0.6)	26 (3.8)	22 (3.2)
Infected bite	7 (2.0)	7 (2.0)	6 (1.8)	4 (1.2)	13 (1.9)	11 (1.6)
Cellulitis	138 (39.3)	139 (40.1)	111 (32.5)	134 (39.6)	249 (35.9)	273 (39.9)
Deep/extensive cellulitis	121 (87.7)	120 (86.3)	103 (92.8)	123 (91.8)	224 (90.0)	243 (89.0)
Cellulitis in lower extremity cSSSI in subjects with DM or PVD	17 (12.3)	19 (13.7)	8 (7.2)	11 (8.2)	25 (10.0)	30 (11.0)
Other	1 (0.3)	5 (1.4)	5 (1.5)	4 (1.2)	6 (0.9)	9 (1.3)

**Table 7.5.2–1. Markers for Complicated Skin and Skin Structure Infections - Clinical Parameters, Phase 3 Studies—MITT Population**

<b>Markers</b>	<b>P903-06</b>		<b>P903-07</b>		<b>Pooled Phase 3 Studies (06, 07)</b>	
	<i>Ceftaroline</i> (N = 351) n (%)	<i>Vancomycin</i> plus <i>Aztreonam</i> (N = 347) n (%)	<i>Ceftaroline</i> (N = 342) n (%)	<i>Vancomycin</i> plus <i>Aztreonam</i> (N = 338) n (%)	<i>Ceftaroline</i> (N = 693) n (%)	<i>Vancomycin</i> plus <i>Aztreonam</i> (N = 685) n (%)
<b>Anatomical Site of Primary Infection</b>						
Head and/or neck	26 (7.4)	19 (5.5)	19 (5.6)	14 (4.1)	45 (6.5)	33 (4.8)
Lower limb (leg and/or foot)	192 (54.7)	191 (55.0)	146 (42.7)	148 (43.8)	338 (48.8)	339 (49.5)
Other location	133 (37.9)	137 (39.5)	177 (51.8)	176 (52.1)	310 (44.7)	313 (45.7)

Abbreviations: cSSSI = complicated skin and skin structure infections; DM = diabetes mellitus; MITT = modified intent-to-treat; PVD = peripheral vascular disease; SIRS = systemic inflammatory response syndrome; WBC = white blood cell.

- a Systemic signs were fever > 38°C oral, WBC count > 10,000/mm<sup>3</sup>, or > 10% immature neutrophils (bands) irrespective of WBC count.
- b Previous systemic antibiotic usage within 96 hours prior to first dose of study drug.
- c SIRS criteria are defined as the presence of ≥ 2 of the following 4 symptoms at baseline: temperature < 36°C or > 38°C, heart rate > 90 beats per minute, respiratory rate > 20, white blood cell count < 4000 or > 12,000 or immature neutrophils > 10%.

### 7.5.3 Baseline Pathogens

Table 7.5.3–1 provides a summary of the numbers and percentages of subjects (mMITT Population) in the Phase 3 cSSSI studies with the most frequently identified pathogens from culture of the primary infection site or blood at baseline. Specimens from the primary site of infection included deep tissue cultures, cultures during surgical procedures, cultures of the leading edge needle aspirate or punch biopsy for cellulitis, and cultures of deep site specimens via biopsy or needle aspirate for other infections. Superficial swabs of infected areas were not acceptable specimens.

Most subjects (78%) had cSSSI due to *S. aureus*, with MRSA accounting for approximately 42% (179/425) of *S. aureus* isolates in the ceftaroline group and 37% (151/409) in the vancomycin plus aztreonam group. Of the *S. aureus* isolates that were analyzed for the presence of the PVL gene, approximately 45% (161/361) were PVL-positive in the ceftaroline group and 43% (145/335) were PVL-positive in the vancomycin plus aztreonam group. Among MRSA isolates, approximately 73% (179/246) were PVL positive, approximately 61% (149/246) were USA 300 strains, and approximately 83% (204/233) were staphylococcal cassette chromosome mec type IV.

The recovery rate of pathogens in the Phase 3 cSSSI studies was approximately 77% in the pooled MITT Population.

**Table 7.5.3–1. Subjects with Pathogenic Organisms From Cultures From the Primary Infection Site or Blood at Baseline, Phase 3 Complicated Skin and Skin Structure Studies—mMITT Population**

<b>Baseline Pathogen</b>	<b>P903-06</b>		<b>P903-07</b>		<b>Pooled Phase 3 Studies (06, 07)</b>	
	<i>Ceftaroline</i> (N = 271)	<i>Vancomycin</i> plus <i>Aztreonam</i> (N = 263)	<i>Ceftaroline</i> (N = 269)	<i>Vancomycin</i> plus <i>Aztreonam</i> (N = 259)	<i>Ceftaroline</i> (N = 540)	<i>Vancomycin</i> plus <i>Aztreonam</i> (N = 522)
<b>Gram-positive pathogens (aerobes) n (%)</b>	<b>245 (90.4)</b>	<b>244 (92.8)</b>	<b>244 (90.7)</b>	<b>241 (93.1)</b>	<b>489 (90.6)</b>	<b>485 (92.9)</b>
<i>Staphylococcus aureus</i>	199 (73.4)	200 (76.0)	226 (84.0)	209 (80.7)	425 (78.7)	409 (78.4)
MSSA	108 (39.9)	120 (45.6)	137 (50.9)	138 (53.3)	245 (45.4)	258 (49.4)
MRSA	93 (34.3)	80 (30.4)	86 (32.0)	71 (27.4)	179 (33.1)	151 (28.9)
<i>Streptococcus pyogenes</i>	25 (9.2)	34 (12.9)	38 (14.1)	28 (10.8)	63 (11.7)	62 (11.9)
<i>Streptococcus agalactiae</i>	17 (6.3)	15 (5.7)	10 (3.7)	6 (2.3)	27 (5.0)	21 (4.0)
<i>Streptococcus anginosus</i> group	9 (3.3)	10 (3.8)	6 (2.2)	8 (3.1)	15 (2.8)	18 (3.4)
<i>Streptococcus dysgalactiae</i>	6 (2.2)	9 (3.4)	8 (3.0)	8 (3.1)	14 (2.6)	17 (3.3)
<b>Gram-negative pathogens (aerobes) n (%)</b>	<b>57 (21.0)</b>	<b>63 (24.0)</b>	<b>51 (19.0)</b>	<b>48 (18.5)</b>	<b>108 (20.0)</b>	<b>111 (21.3)</b>
<i>Escherichia coli</i>	10 (3.7)	15 (5.7)	13 (4.8)	6 (2.3)	23 (4.3)	21 (4.0)
<i>Klebsiella pneumoniae</i>	11 (4.1)	11 (4.2)	7 (2.6)	8 (3.1)	18 (3.3)	19 (3.6)
<i>Klebsiella oxytoca</i>	5 (1.8)	4 (1.5)	7 (2.6)	4 (1.5)	12 (2.2)	8 (1.5)
<i>Morganella morganii</i>	6 (2.2)	4 (1.5)	6 (2.2)	3 (1.2)	12 (2.2)	7 (1.3)

Abbreviations: mMITT = microbiological modified intent-to-treat; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*.

Notes: Subjects with a baseline pathogen of both MRSA and MSSA are included once in the overall *S. aureus* category. The overall count of subjects with *S. aureus* includes subjects whose isolates were not tested for susceptibility and, therefore, do not contribute to either the MRSA or MSSA count.

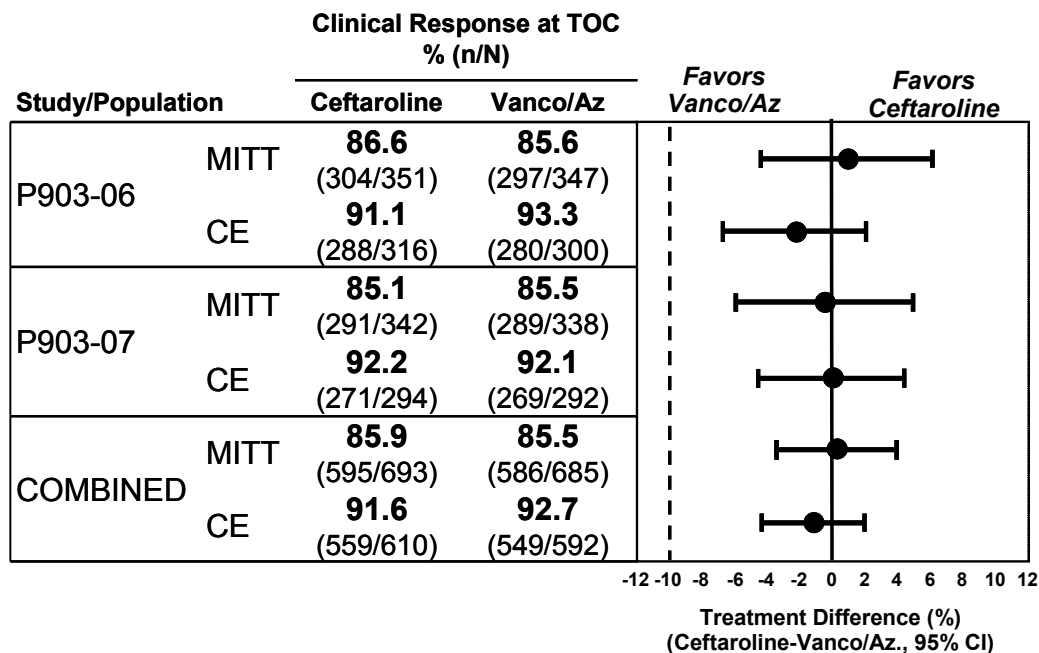
## 7.6 CLINICAL RESPONSE AT TEST OF CURE – THE PRIMARY EFFICACY VARIABLE

Most of the subjects in the ceftaroline and vancomycin plus aztreonam groups received 5 to 14 calendar days of study drug and the median duration of ceftaroline fosamil and vancomycin therapy was 7.0 and 8.0 days, respectively (Section 8.2).



The results of the primary endpoint (clinical response at TOC) in the coprimary MITT and CE Populations of the individual pivotal Phase 3 cSSSI studies demonstrated that monotherapy with ceftaroline is noninferior to vancomycin plus aztreonam in subjects with cSSSI, as evidenced by the lower limit of the 95% CI around the difference (ceftaroline – vancomycin plus aztreonam) in clinical cure rates being greater than the prespecified noninferiority boundary of -10% (Figure 7.6–1). In the individual pivotal Phase 3 cSSSI studies and in the pooled Phase 3 studies, the clinical cure rates were high and similar between treatment groups in both the CE Population (ranging from 91% to 93%) and MITT Population (ranging from 85% to 87%). The results are displayed in Figure 7.6–1.

**Figure 7.6–1. Clinical Response and Confidence Intervals for the Difference in Clinical Cure Rates at Test of Cure, Phase 3 Complicated Skin and Skin Structure Studies—MITT and CE Populations**



Abbreviations: CE = clinically evaluable; MITT = modified intent-to-treat; TOC = test of cure; vanco/az = vancomycin plus aztreonam.

Notes: Dots indicate difference in clinical cure rates defined as ceftaroline group minus comparator group. Bars indicate the lower and upper bounds of the CI. Confidence intervals are calculated using Miettinen and Nurminen method without adjustments except for pooled studies (stratified by study). Lower bound of 10% noninferiority margin is indicated by a vertical dashed line.

Table 7.6–1 provides an overall summary of clinical response at TOC in the microbiological populations (mMITT and ME Populations) of the Phase 3 cSSSI studies. The clinical cure rates at TOC were high and similar to those in the coprimary analysis populations. Clinical response by pathogen is summarized in Section 7.7.2.

**Table 7.6–1. Clinical Response at Test of Cure, Phase 3 Complicated Skin and Skin Structure Studies—ME and mMITT Populations**

<i>Population/ Clinical Response</i>	<i>P903-06</i>		<i>P903-07</i>		<i>Pooled Phase 3 Studies (06, 07)</i>	
	<i>Ceftaroline n (%)</i>	<i>Vancomycin plus Aztreonam n (%)</i>	<i>Ceftaroline n (%)</i>	<i>Vancomycin plus Aztreonam n (%)</i>	<i>Ceftaroline n (%)</i>	<i>Vancomycin plus Aztreonam n (%)</i>
<b>mMITT</b>						
N	271	263	269	259	540	522
Clinical Cure	235 (86.7)	226 (85.9)	234 (87.0)	227 (87.6)	469 (86.9)	453 (86.8)
Clinical Failure	21 (7.7)	13 (4.9)	17 (6.3)	15 (5.8)	38 (7.0)	28 (5.4)
Indeterminate	15 (5.5)	24 (9.1)	18 (6.7)	17 (6.6)	33 (6.1)	41 (7.9)
Crude difference (95% CI)	0.8 (-5.1, 6.7)		-0.7 (-6.4, 5.1)		0.1	
Weighted difference (95% CI)					0.1 (-4.0, 4.2)	
<b>ME</b>						
N	244	227	224	219	468	446
Clinical Cure	225 (92.2)	215 (94.7)	209 (93.3)	206 (94.1)	434 (92.7)	421 (94.4)
Clinical Failure	19 (7.8)	12 (5.3)	15 (6.7)	13 (5.9)	34 (7.3)	25 (5.6)
Crude difference (95% CI)	-2.5 (-7.2, 2.1)		-0.8 (-5.5, 4.0)		-1.7	
Weighted difference (95% CI)					-1.7 (-4.9, 1.6)	

Abbreviations: ME = microbiologically evaluable; mMITT = microbiological modified intent-to-treat.

Notes: Crude difference = difference in clinical cure rates (ceftaroline treatment group minus comparator treatment group). Weighted difference = weighted difference (stratified by study) in clinical cure rates (ceftaroline treatment group minus comparator treatment group). Confidence intervals are calculated using Miettinen and Nurminen method without adjustments except for pooled studies (stratified by study).

## 7.7 SECONDARY EFFICACY ANALYSES

### 7.7.1 Clinical Response at End of Therapy

Table 7.7.1–1 provides a summary of clinical response at EOT by treatment in the MITT and CE Populations in the Phase 3 cSSSI studies. Clinical cure rates at EOT were similar to clinical cure rates observed at TOC in the CE Population.

Per the hierarchical testing procedure of key secondary endpoints conducted for the individual studies (described in Section 7.1.1), ceftaroline was shown to be noninferior to vancomycin plus aztreonam for the clinical cure rate at EOT in the CE and MITT Populations of each study as evidenced by the lower limit of the 95% CI around the treatment difference (ceftaroline - vancomycin plus aztreonam) being greater than the prespecified noninferiority boundary of -10%.

**Table 7.7.1–1. Clinical Response at End of Therapy, Phase 3 Complicated Skin and Skin Structure Studies—MITT and CE Populations**

<i>Population/Clinical Response</i>	<i>P903-06</i>		<i>P903-07</i>	
	<i>Ceftaroline n (%)</i>	<i>Vancomycin plus Aztreonam n (%)</i>	<i>Ceftaroline n (%)</i>	<i>Vancomycin plus Aztreonam n (%)</i>
<b>MITT</b>				
N	351	347	342	338
Clinical Cure	322 (91.7)	313 (90.2)	304 (88.9)	302 (89.3)
Clinical Failure	19 (5.4)	19 (5.5)	22 (6.4)	26 (7.7)
Indeterminate	10 (2.8)	15 (4.3)	16 (4.7)	10 (3.0)
Crude difference (95% CI)	1.5 (-2.8,5.9)		-0.5 (-5.2,4.3)	
<b>CE</b>				
N	316	300	294	292
Clinical Cure	298 (94.3)	282 (94.0)	274 (93.2)	271 (92.8)
Clinical Failure	18 (5.7)	18 (6.0)	20 (6.8)	21 (7.2)
Crude difference (95% CI)	0.3 (-3.5,4.2)		0.4 (-3.9,4.7)	

Abbreviations: CE = clinically evaluable; MITT = modified intent-to-treat.

Notes: Crude difference = difference in clinical cure rates (ceftaroline treatment group minus comparator treatment group). Weighted difference = weighted difference (stratified by study) in clinical cure rates (ceftaroline treatment group minus comparator treatment group). Confidence intervals are calculated using Miettinen and Nurminen method without adjustments except for pooled studies (stratified by study).

## 7.7.2 By-pathogen Clinical Response at Test of Cure

Table 7.7.2–1 provides a summary of clinical response at TOC by baseline pathogen from primary infection site or blood cultures for the mMITT Population in the Phase 3 cSSSI studies.

Clinical cure rates at TOC among subjects with gram-positive aerobic pathogens were high and similar in the 2 treatment groups (ceftaroline, 87.7%; vancomycin plus aztreonam, 86.6%). The clinical cure rates associated with *S. aureus* were high and similar between treatment groups, regardless of methicillin susceptibility. The clinical cure rates were also high and similar between treatment groups for other gram-positive pathogens, such as *S. pyogenes*.

Clinical cure rates at TOC among subjects with gram-negative aerobic pathogens were high and similar in the 2 treatment groups (ceftaroline, 85.2%; vancomycin plus aztreonam, 87.4%).

**Table 7.7.2–1. Clinical Response at Test of Cure by Baseline Pathogen, Pooled Phase 3 Complicated Skin and Skin Structure Infection Studies—mMITT Population**

<b>Baseline Pathogen/ Clinical Response</b>	<b>Pooled Phase 3 Studies (06, 07)</b>		<b>Weighted Difference (95% CI)</b>
	<i>Ceftaroline</i> n (%)	<i>Vancomycin plus Aztreonam</i> n (%)	
<b>Gram-positive organisms (aerobes)</b>	<b>429/489 (87.7)</b>	<b>420/485 (86.6)</b>	<b>1.1 (-3.1, 5.4)</b>
<i>Staphylococcus aureus</i> <sup>a</sup>	377/425 (88.7)	356/409 (87.0)	1.6 (-2.8, 6.1)
MSSA	221/245 (90.2)	233/258 (90.3)	-0.1 (-5.5, 5.2)
MRSA	155/179 (86.6)	124/151 (82.1)	4.4 (-3.4, 12.6)
<i>Streptococcus pyogenes</i>	56/63 (88.9)	57/62 (91.9)	-1.8 (-13.3, 9.5)
<i>Streptococcus agalactiae</i>	25/27 (92.6)	19/21 (90.5)	
<i>Streptococcus anginosus</i> group	12/15 (80.0)	16/18 (88.9)	
<i>Streptococcus dysgalactiae</i>	14/14 (100.0)	15/17 (88.2)	
<b>Gram-negative organisms (aerobes)</b>	<b>92/108 (85.2)</b>	<b>97/111 (87.4)</b>	<b>-2.2 (-11.7, 7.1)</b>
<i>Escherichia coli</i>	21/23 (91.3)	19/21 (90.5)	
<i>Klebsiella pneumoniae</i>	17/18 (94.4)	14/19 (73.7)	
<i>Klebsiella oxytoca</i>	10/12 (83.3)	7/8 (87.5)	
<i>Morganella morganii</i>	11/12 (91.7)	5/7 (71.4)	

Abbreviations: mMITT = microbiological modified intent-to-treat; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*.

Notes: The overall count of subjects with *S. aureus* includes subjects whose isolates were not tested for susceptibility and, therefore, do not contribute to either the MRSA or the MSSA count. Subjects with both MSSA and MRSA were counted only once. Weighted difference = weighted difference (stratified by study) in clinical cure rates (ceftaroline treatment group minus comparator treatment group). Confidence intervals for pooled studies are calculated when the sample size for a pathogen is at least 10 subjects in each treatment group using Miettinen and Nurminen method for stratified designs (stratified by study).

a Subjects with both MRSA and MSSA were counted only once.

### **7.7.3 Clinical Relapse and Microbiological Reinfection or Recurrence at Late Follow-up**

Eleven (1.0%) subjects (ceftaroline, n = 6; vancomycin plus aztreonam, n = 5) in the CE Population of the Phase 3 cSSSI studies who were a clinical cure at TOC had a clinical relapse at LFU.

Of the 11 subjects with clinical relapse, 2 subjects had microbiological reinfections, both in the ceftaroline group. One subject with an infected wound due to *K. pneumoniae* at baseline had a polymicrobial reinfection attributed to *E. coli*, MRSA, *P. mirabilis*, and *Enterococcus faecalis* at LFU. The other subject with an infected ulcer due to *P. aeruginosa* and MRSA at baseline had a microbiological reinfection due to *P. aeruginosa* (with a different susceptibility profile from that isolated at baseline) and MSSA. The different species and susceptibility profiles of the pathogens isolated from the primary sites of infection from these subjects at LFU, compared with those isolated at baseline, suggest that reinfection, rather than recurrence, led to clinical relapse.

## 7.8 CLINICAL CURE RATE BY RELEVANT SUBGROUPS

### 7.8.1 Clinical Cure Rates by Region

Table 7.8.1–1 provides a summary of clinical cure rates at TOC by region group and treatment group for the pooled Phase 3 cSSSI studies in the CE Population. Confidence intervals were calculated for all subgroups with at least 10 observations in each group in each study. In the CE Population of the pooled Phase 3 cSSSI studies, the clinical cure rates were similar in the ceftaroline group compared with the vancomycin plus aztreonam group for subjects in Eastern Europe, Latin America, and the United States. Clinical cure rates were lower in the ceftaroline group compared with the vancomycin plus aztreonam group for subjects in Western Europe; however, the difference in the number of failures (5 subjects) was not large enough to suggest a regional difference in efficacy. For the regions with sufficient subjects enrolled to calculate a 95% CI around the treatment difference in cure rates (ceftaroline - vancomycin plus aztreonam), the 95% CIs overlapped with each other and included zero.

**Table 7.8.1–1. Clinical Cure Rates at Test of Cure by Region Groups, Pooled Phase 3 Complicated Skin and Skin Structure Infection Studies—CE Population**

<b>Region</b>	<b>Pooled Phase 3 Studies (06, 07)</b>		
	<i>Ceftaroline</i> (N = 610) n/N (%)	<i>Vancomycin plus Aztreonam</i> (N = 592) n/N (%)	Weighted Difference (95% CI)
Eastern Europe	235/241 (97.5)	238/240 (99.2)	-1.7 (-4.6, 0.8)
Latin America	46/54 (85.2)	41/48 (85.4)	-0.4 (-14.5, 14.5)
Western Europe	62/74 (83.8)	66/73 (90.4)	-7.0 (-18.6, 3.9)
US	216/241 (89.6)	204/231 (88.3)	1.3 (-4.4, 7.1)

Abbreviation: CE = clinically evaluable.

Notes: The denominator is the number of subjects in the specified subgroup. Weighted difference = weighted difference (stratified by study) in clinical cure rates (ceftaroline treatment group minus comparator treatment group). Confidence intervals are calculated when the sample size is at least 10 subjects in each treatment group using Miettinen and Nurminen method without adjustments except for weighted difference (stratified by study).

Subjects in Eastern Europe had higher clinical cure rates in both treatment groups in the pooled Phase 3 cSSSI studies compared with cure rates associated with other regions. However, the difference in clinical cure rates between treatment groups in Eastern Europe was similar to that observed in the other regions. Analysis of demographics and baseline characteristics between Eastern Europe and the rest of the world in the pooled Phase 3 cSSSI studies revealed that subjects in Eastern Europe did not have less severe disease than subjects in the rest of the world had. In fact, a higher percentage of subjects in Eastern Europe than in the rest of the world had cellulitis (approximately 48% vs 33%), had PVD (approximately 21% vs 10%), had fever, elevated, or immature neutrophils (approximately 72% vs 42%), had infection area  $\geq 75 \text{ cm}^2$  (approximately 88% vs 65%), met SIRS criteria (approximately 34% vs 16%), had polymicrobial infections (approximately 41% vs 19%), and had cSSSI due to *S. pyogenes* (approximately 23% vs 4%), respectively. A lower percentage of subjects in Eastern Europe than in the rest of the world had abscess (approximately 16% vs 44%) and diabetes mellitus (approximately 10% vs 24%), respectively. The higher incidences of acute cSSSI due to *S. pyogenes* in Eastern Europe may have contributed to the higher observed cure rates in this region, as *S. pyogenes* is a highly susceptible pathogen to antibacterial therapy.

When subjects enrolled in Eastern Europe were excluded from the pooled Phase 3 cSSSI studies in an exploratory sensitivity analysis, ceftaroline was still noninferior to vancomycin plus aztreonam in both of the coprimary populations in both studies, therefore, confirming the robustness of the study results.

### **7.8.2 Clinical Cure Rates by Demographics and Baseline Characteristics**

Table 7.8.2–1 provides a summary of clinical cure rates at TOC for the CE Population in the pooled Phase 3 cSSSI studies by demographics and baseline characteristics for the 2 treatment groups. Confidence intervals were calculated for all subgroups with at least 10 observations in each group in each study. Point estimates of the treatment differences for all subgroups of sufficient size (ie, those comprising at least one third of the overall population) were of comparable magnitude to the overall population demonstrating the robustness of the conclusions. Not surprisingly, observed treatment differences (ceftaroline - vancomycin plus aztreonam) among smaller subgroups were more variable, but generally were also greater than -10%. Further, for all subgroups with a large enough sample size to calculate a 95% CI around the treatment difference in cure rates (ceftaroline - vancomycin plus aztreonam), the 95% CI included zero.

Among the small number of subjects with bacteremia, the clinical cure rate in the ceftaroline group (22/26; 84.6%) was lower than in the vancomycin plus aztreonam group (21/21; 100.0%). Of the 4 subjects in the ceftaroline group who had bacteremia and were also assessed as a clinical failure, 2 subjects had clinical failure due to a treatment-limiting AE (*C. difficile*-associated diarrhea and allergic rash). The third subject had a clinical failure due to the need for surgical intervention to treat the infection. Therefore, none of these 3 cases of clinical failure was due directly to the bacteremia. The fourth subject had a deep and severe leg ulcer infection due to *P. aeruginosa* (ceftaroline MIC > 16 µg/mL) and *M. morganii* (ceftaroline MIC = 1 µg/mL) isolated from both blood and primary infection site cultures at baseline. This subject's failure was associated with a ceftaroline-nonsusceptible pathogen (*P. aeruginosa*).

**Table 7.8.2–1. Clinical Cure Rates at Test of Cure by Demographics and Baseline Characteristics, Pooled Phase 3 Complicated Skin and Skin Structure Infection Studies —CE Population**

<i>Demographic or Baseline Parameter</i>	<i>Pooled Phase 3 Studies (06, 07)</i>		
	<i>Ceftaroline (N = 610) n/N (%)</i>	<i>Vancomycin plus Aztreonam (N = 592) n/N (%)</i>	<i>Weighted Difference (95% CI)</i>
Age group			
< 65	461/499 (92.4)	438/474 (92.4)	-0.1 (-3.5, 3.4)
≥ 65	98/111 (88.3)	111/118 (94.1)	-6.3 (-14.5, 1.1)
Sex			
Male	366/395 (92.7)	337/363 (92.8)	-0.2 (-3.9, 3.7)
Female	193/215 (89.8)	212/229 (92.6)	-2.8 (-8.4, 2.5)
Creatinine clearance (mL/min)			
> 80	458/496 (92.3)	442/476 (92.9)	-0.5 (-3.9, 2.8)
>50 and ≤ 80	83/92 (90.2)	85/90 (94.4)	-4.0 (-12.6, 4.1)
>30 and ≤ 50	17/20 (85.0)	20/24 (83.3)	1.7 (-22.6, 24.3) <sup>a</sup>
≤ 30	1/2 (50.0)	2/2 (100.0)	-50.0
BMI (kg/m <sup>2</sup> )			
Underweight (< 18.5)	11/14 (78.6)	5/5 (100.0)	-21.4
Normal Weight (18.5, < 25.0)	189/203 (93.1)	172/187 (92.0)	1.1 (-4.3, 6.7)
Overweight (25.0, < 30.0)	188/197 (95.4)	200/210 (95.2)	0.3 (-4.2, 4.7)
Obese/ Morbidly Obese (≥ 30.0)	171/195 (87.7)	171/189 (90.5)	-2.8 (-9.2, 3.6)

**Table 7.8.2–1. Clinical Cure Rates at Test of Cure by Demographics and Baseline Characteristics, Pooled Phase 3 Complicated Skin and Skin Structure Infection Studies —CE Population**

<i>Demographic or Baseline Parameter</i>	<i>Pooled Phase 3 Studies (06, 07)</i>		
	<i>Ceftriaxone (N = 610) n/N (%)</i>	<i>Vancomycin plus Aztreonam (N = 592) n/N (%)</i>	<i>Weighted Difference (95% CI)</i>
<b>Diabetes mellitus</b>			
No	463/500 (92.6)	449/482 (93.2)	-0.5 (-3.8, 2.8)
Yes	96/110 (87.3)	100/110 (90.9)	-3.5 (-12.2, 5.0)
<b>Presence of bacteremia</b>			
No	532/578 (92.0)	521/564 (92.4)	-0.3 (-3.5, 2.8)
Yes	22/26 (84.6)	21/21 (100.0)	-15.4 (-33.8, 1.5) <sup>a</sup>
<b>Previous systemic antibacterial usage</b>			
No	356/377 (94.4)	353/374 (94.4)	0.0 (-3.4, 3.4)
Any	203/233 (87.1)	196/218 (89.9)	-2.8 (-8.8, 3.2)
<b>Description of infection</b>			
Cellulitis	213/229 (93.0)	222/243 (91.4)	1.7 (-3.4, 6.7)
Abscess	187/205 (91.2)	179/190 (94.2)	-3.0 (-8.4, 2.3)
Infected wound	73/84 (86.9)	65/73 (89.0)	-2.2 (-12.8, 8.7)
Infected ulcer	48/53 (90.6)	47/50 (94.0)	-3.5 (-15.7, 8.3)
Infected burn	25/25 (100.0)	18/18 (100.0)	0.0 (-13.6, 17.9) <sup>a</sup>
Infected bite	9/9 (100.0)	9/9 (100.0)	0.0

Abbreviation: BMI = body mass index; CE = clinically evaluable; cSSSI = complicated skin and skin structure infection.

Notes: The denominator is the number of subjects in the specified subgroup. Weighted difference = weighted difference (stratified by study) in clinical cure rates (ceftriaxone treatment group minus comparator treatment group). Confidence intervals are calculated when the sample size is at least 10 subjects in each treatment group using Miettinen and Nurminen method without adjustments except for weighted difference (stratified by study).

- a For this subgroup, a CI for the crude difference in clinical cure rates (ceftriaxone treatment group minus comparator treatment group) is provided.



## 7.9 FDA-DEFINED EXPLORATORY ANALYSES

### 7.9.1 Clinical Cure Rates by Exclusion of Subjects with Abscesses Alone

Based on guidance from the Division, a post-hoc exploratory analysis excluding subjects with abscess alone was conducted. Clinical cure rates at TOC for the MITT and CE Populations excluding subjects with abscesses alone are provided for Study P903-06 (Table 7.9.1–1) and Study P903-07 (Table 7.9.1–2). The noninferiority of ceftaroline compared with vancomycin plus aztreonam was maintained in both of the coprimary populations in both studies, as the lower limit of the 95% CI around the treatment difference (ceftaroline - vancomycin plus aztreonam) was greater than -10%. Similar results were observed in the MITT and CE Populations using the planned analysis, which included subjects with abscesses (Section 7.6), therefore, confirming the robustness of the study results.

**Table 7.9.1–1. Clinical Response at Test of Cure Excluding Subjects with Abscesses, Noninferiority Tests, Study P903-06— MITT and CE Populations**

<i>Population Excluding Subjects with Abscesses</i>	<i>Clinical Response</i>	<i>Ceftaroline n (%)</i>	<i>Vancomycin plus Aztreonam n (%)</i>	<i>Difference<sup>a</sup> (95% CI<sup>b</sup>)</i>
MITT, N		248	245	
	Clinical Cure	219 (88.3)	214 (87.3)	1.0 ( -4.9, 6.9)
	Clinical Failure	19 (7.7)	17 (6.9)	
	Indeterminate	10 (4.0)	14 (5.7)	
CE, N		226	221	
	Clinical Cure	208 (92.0)	205 (92.8)	-0.7 (-5.8, 4.4)
	Clinical Failure	18 (8.0)	16 (7.2)	

Abbreviations: CE = clinically evaluable; MITT = modified intent-to-treat.

a Difference = ceftaroline group minus comparator group.

b CIs are calculated using the Miettinen and Nurminen method without adjustment.

**Table 7.9.1–2. Clinical Response at Test of Cure Excluding Subjects with Abscesses, Noninferiority Tests, Study P903-07—MITT and CE Populations**

<i>Population Excluding Subjects with Abscesses</i>	<i>Clinical Response</i>	<i>Ceftaroline n (%)</i>	<i>Vancomycin plus Aztreonam n (%)</i>	<i>Difference<sup>a</sup> (95% CI<sup>b</sup>)</i>
MITT, N		202	204	
	Clinical Cure	175 (86.6%)	176 (86.3%)	0.4 (-6.4, 7.1)
	Clinical Failure	17 (8.4%)	20 (9.8%)	
	Indeterminate	10 (5.0%)	8 (3.9%)	
CE, N		179	181	
	Clinical Cure	164 (91.6%)	165 (91.2%)	0.5 (-5.6, 6.5)
	Clinical Failure	15 (8.4%)	16 (8.8%)	

Abbreviations: CE = clinically evaluable; MITT = modified intent-to-treat.

a Difference = ceftaroline group minus comparator group.

b CIs are calculated using the Miettinen and Nurminen method without adjustment.

### 7.9.2 FDA-defined Clinical Response at Day 3

The Division requested that the Sponsor conduct a post-hoc exploratory analysis of clinical response at Study Day 3 in the FDA-defined modified intent-to-treat (FDA-MITT) Population. The FDA-MITT Population consisted of subjects in the MITT Population who met the following criteria:

- Lesion size  $\geq 75 \text{ cm}^2$
- Infection type of infected wound, major abscess with surrounding erythema of  $\geq 5 \text{ cm}$ , deep/extensive cellulitis, lower extremity SSSI in subjects with diabetes mellitus or PVD, or infected arthropod bite

The FDA-defined exploratory endpoint was clinical response at Study Day 3. Subjects were considered a clinical responder if they met the following criteria:

- Cessation of infection spread (no increase in baseline lesion width or length measurement)
- Afebrile at study day 3, using 2 different temperature cutoffs (either  $< 37.6^\circ \text{C}$  or temperature  $< 37.8^\circ \text{C}$ )

Subjects who did not meet both of these criteria were considered as non-responders. In addition, subjects who were considered clinical failures on study day 3 or that had missing or incomplete information on study day 3 were also considered non-responders.

Clinical response at Study Day 3 in the FDA-MITT Population is provided for individual and pooled Phase 3 cSSSI studies for temperature  $\leq 37.6^{\circ}\text{C}$  (Table 7.9.2–1). This exploratory endpoint was not contemplated in the original study design, data collection was not optimized for this outcome measure, and the study was not powered with respect to this endpoint, however, treatment differences of 9.4% in Study P903-06 and 5.9% in Study P903-07 were observed in favor of ceftaroline. The lower limit of the 95% CI around the treatment difference (cefataroline - vancomycin plus aztreonam) was greater than zero in the pooled Phase 3 cSSSI studies. Results were similar for clinical response at Study Day 3 in the FDA-MITT Population using an afebrile temperature cutoff of  $\leq 37.8^{\circ}\text{C}$ .

**Table 7.9.2–1. FDA Exploratory Endpoint at Study Day 3, Noninferiority Tests, Phase 3 Complicated Skin and Skin Structure Infection Studies — FDA-MITT Population**

<i>By-subject Clinical Response at Study Day 3</i>	<i>P903-06</i>		<i>P903-07</i>		<i>Pooled Phase 3 Studies (06, 07)</i>	
	<i>Cefataroline n (%)</i>	<i>Vancomycin plus Aztreonam n (%)</i>	<i>Cefataroline n (%)</i>	<i>Vancomycin plus Aztreonam n (%)</i>	<i>Cefataroline n (%)</i>	<i>Vancomycin plus Aztreonam n (%)</i>
N	200	209	200	188	400	397
Responder (cessation of lesion spread and afebrile, temperature $\leq 37.6^{\circ}\text{C}$ )	148 (74.0)	135 (64.6)	148 (74.0)	128 (68.1)	296 (74.0)	263 (66.2)
Nonresponder	52 (26.0)	74 (35.4)	52 (26.0)	60 (31.9)	104 (26.0)	134 (33.8)
Crude difference (95% CI)	9.4 (0.4, 18.2)		5.9 (-3.1, 14.9)			
Weighted difference (95% CI)					7.7 (1.3, 14.0)	

Abbreviation: FDA-MITT = FDA modified intent-to-treat.

Notes: Crude difference = difference in clinical cure rates (cefataroline treatment group minus comparator treatment group). Weighted difference = weighted difference (stratified by study) in clinical cure rates (cefataroline treatment group minus comparator treatment group). Confidence intervals are calculated using Miettinen and Nurminen method without adjustments except for pooled studies (stratified by study).

### 7.9.3 FDA-defined Secondary Endpoints at End of Therapy

FDA-defined exploratory secondary endpoint analyses at EOT included the following:

- Absolute and percent reduction in the area of lesion measurement from baseline (percent reduction from baseline at EOT was also computed based on reduction in lesion length and width measurements separately)
- Absence of tenderness
- Absence of swelling

- Absence of erythema
- Investigator assessment of clinical response

The absolute and percent decrease in the infection area from baseline at EOT was similar in the two treatment groups (Table 7.9.3–1). The percent change in the infection area from baseline was also similar in both treatment groups for both studies with an approximate decrease of 85% by EOT. The incidences of absence of tenderness, erythema, and swelling at EOT were high and similar between treatment groups in both studies. Clinical cure rates at EOT in these additional secondary endpoints were higher in the ceftaroline group compared with the vancomycin plus aztreonam group in each study individually and in the pooled analysis.

**Table 7.9.3–1 Reduction in Infection Area at End of Therapy, Phase 3 Complicated Skin and Skin Structure Infection Studies — FDA-MITT Population**

<b>Reduction in Lesion Area</b>	<b>P903-06</b>		<b>P903-07</b>		<b>Pooled Phase 3 Studies (06, 07)</b>	
	<i>Ceftaroline n (%)</i>	<i>Vancomycin plus Aztreonam n (%)</i>	<i>Ceftaroline n (%)</i>	<i>Vancomycin plus Aztreonam n (%)</i>	<i>Ceftaroline n (%)</i>	<i>Vancomycin plus Aztreonam n (%)</i>
N	199	206	196	186	395	392
Mean absolute change from baseline in infection area, cm <sup>2</sup>	-369.2	-373.2	-324.6	-378.7	-347.1	-375.8
Mean percent change from baseline in infection area	-88.7	-82.7	-85.6	-87.2	-87.2	-84.9

Abbreviation: FDA MITT = FDA modified intent-to-treat.

## **8.0                      SAFETY**

### **8.1                      SAFETY DATABASE**

Table 8.1–1 provides the number of subjects exposed to ceftaroline and comparators in the completed studies in the clinical development program.

The ceftaroline program consisted of a total of 3153 subjects, 1745 of whom were treated with ceftaroline (1608 adult subjects received IV ceftaroline, 98 adult subjects received IM ceftaroline in a Phase 2 study, 36 adult subjects received IM ceftaroline in a Phase 1 study, and 9 adolescent subjects received IV ceftaroline) and 1462 of whom were treated with a comparator (note that 54 subjects received ceftaroline, placebo, and moxifloxacin in the crossover study [P903-05], and are, therefore, only counted once in the total column). Of those treated with ceftaroline, 1452 subjects with normal renal function or mild to severe renal impairment were assigned to receive the proposed recommended dose. This number includes 6 subjects in the Clinical Pharmacology studies, 13 subjects in the CABP studies, and 2 subjects in the cSSSI studies with severe renal impairment who received the proposed recommended ceftaroline fosamil dose of 400 mg for severe renal impairment. Subjects with severe renal impairment in the CABP and cSSSI studies were identified based on baseline CrCl values from the central laboratory, but were enrolled in the studies based on CrCl values from the local laboratory that reflected moderate renal impairment.

The Phase 3 CABP and cSSSI studies, comprising the core of the clinical database, included a total of 2606 subjects: 1305 subjects who received ceftaroline and 1301 subjects who received comparators.

**Table 8.1–1.                      Number of Subjects in Safety Database**

<b><i>Study Grouping Study Subgrouping Study</i></b>	<b><i>Ceftaroline fosamil (Recommended Dose)<sup>a</sup></i></b>	<b><i>Comparator</i></b>	<b><i>Total</i></b>
Clinical Pharmacology (Total)	275 (80)	84	305
Clinical Pharmacology (adults administered IV)	236 (80)	78	260
Single-dose studies (dose range 50 mg to 2000 mg IV)	192 (62)	70	208
Multiple-dose studies	44 (18)	8	52
Pooled Phase 3 CABP studies	613 (613)	615	1228

**Table 8.1–1. Number of Subjects in Safety Database**

<i>Study Grouping Study Subgrouping Study</i>	<i>Ceftaroline fosamil (Recommended Dose)<sup>a</sup></i>	<i>Comparator</i>	<i>Total</i>
Phase 2 and Phase 3 cSSSI studies			
Phase 2 cSSSI studies	165 (67)	77	242
Pooled Phase 3 cSSSI studies	692 (692)	686	1378
Pooled Phase 2 and Phase 3 IV cSSSI studies	759 (759)	718	1477
Total Phase 3 CABP and cSSSI studies	1305 (1305)	1301	2606
Total all studies	1745 (1452)	1462	3153

Abbreviations: CABP = community-acquired bacterial pneumonia; cSSSI = complicated skin and skin structure infection; IV = intravenous.

- a Proposed recommended dose refers to 600 mg ceftaroline fosamil (IV administered over 1 hour) for adult subjects with normal renal function or mild renal impairment or 400 mg ceftaroline fosamil for adult subjects with moderate or severe renal impairment.

## 8.2 EXTENT OF EXPOSURE

The clinical Safety Population consisted of all subjects who received any amount of study drug. Subjects given study drug opposite from the randomized assignment were analyzed, in the safety population, in the treatment group corresponding to the study drug actually received for the majority of the dosing period. Two subjects, 1 in a cSSSI study and 1 in a CABP study, who were randomized to the ceftaroline group received only comparator study drug. None of the subjects in the Phase 2 and Phase 3 studies randomized to any comparator group received ceftaroline.

Table 8.2–1 provides a summary of ceftaroline exposure by dose and by dose regimen for the ceftaroline program.

In the pooled Phase 3 CABP studies, the median duration of ceftaroline fosamil or ceftriaxone therapy was 7.0 days. Most of the subjects in the pooled Phase 3 CABP studies received 5 to 8 calendar days of study drug; no subjects received therapy for more than 8 calendar days.

In the pooled Phase 3 cSSSI studies, the median durations of ceftaroline fosamil and vancomycin therapy were 7.0 and 8.0 days, respectively. Most of the subjects in the pooled Phase 3 cSSSI studies received between 5 to 14 calendar days of study drug. Approximately 94% of the subjects in the vancomycin plus aztreonam group of the pooled Phase 3 cSSSI studies received at least 1 day of aztreonam therapy, and the median duration of aztreonam therapy was 5 days.

**Table 8.2–1                      Extent of Exposure, Pooled Clinical Pharmacology, Phase 2, and Phase 3 Studies**

<i>Ceftriaxone Dose</i>	<i>Days on Study Drug</i>	<i>Ceftriaxone n (%)</i>	<i>Comparator or Placebo n (%)</i>
<b>Pooled Clinical Pharmacology Studies (P903-01, 02, 04, 05, 11, 13, 14, 17, 18, 20)</b>			
N		236	78
Single Dose Studies 50 - 2000 mg	1	192 (81.4)	70 (89.7)
Multiple Dose Studies 300 - 600 mg q12h, 600 mg q8h, 800 mg q24h	7 - 14	44 (18.6)	8 (10.3)
<b>Phase 2 IM Study (P903-19)</b>			
N		98	45
600 mg (or 400 mg for moderate renal impairment) q12h	1 - 4	6 (6.1)	3 (6.7)
	5 - 7	45 (45.9)	22 (48.9)
	8 - 10	30 (30.6)	16 (35.6)
	11 - 14	17 (17.3)	4 (8.9)
	15	0	0
	> 15	0	0
<b>Phase 2 IV Study (P903-03)</b>			
N		67	32
600 mg (or 400 mg for moderate renal impairment) q12h	1 - 4	4 (6.0)	4 (12.5)
	5 - 7	18 (26.9)	9 (28.1)
	8 - 10	27 (40.3)	11 (34.4)
	11 - 14	15 (22.4)	6 (18.8)
	15	1 (1.5)	1 (3.1)
	> 15	2 (3.0)	1 (3.1)
<b>Pooled Phase 3 CABP Studies (08, 09)</b>			
N		613	615
600 mg (or 400 mg for moderate renal impairment) q12h	1 - 4	26 (4.2)	32 (5.2)
	5 - 7	564 (92.0)	566 (92.0)
	8 - 10	23 (3.8)	17 (2.8)
	11 - 14	0	0
	> 14	0	0

**Table 8.2–1 Extent of Exposure, Pooled Clinical Pharmacology, Phase 2, and Phase 3 Studies**

<i>Ceftaroline Dose</i>	<i>Days on Study Drug</i>	<i>Ceftaroline n (%)</i>	<i>Comparator or Placebo n (%)</i>
<b><i>Pooled Phase 3 cSSSI Studies (06, 07)</i></b>			
N		692	686
600 mg (or 400 mg for moderate renal impairment) q12h	1 - 4	35 (5.1)	43 (6.3)
	5 - 7	315 (45.5)	293 (42.7)
	8 - 10	213 (30.8)	219 (31.9)
	11 - 14	112 (16.2)	111 (16.2)
	> 14	17 (2.5)	20 (2.9)

Abbreviations: CABP = community-acquired bacterial pneumonia; cSSSI = complicated skin and skin structure infection; IM = intramuscular; IV = intravenous; NA = not applicable; q8h = every 8 hours; q12h = every 12 hours.

### 8.3 SUMMARY OF ADVERSE EVENTS

Table 8.3–1 provides an overview of safety for the Phase 3 studies, which represent the core of the clinical safety database and are the focus of this safety discussion.

In the pooled Phase 3 CABP and cSSSI studies, the incidences of TEAEs, deaths, SAEs, and discontinuations of study drug or study due to TEAEs in the ceftaroline group were similar to those in the comparator group. Treatment-emergent adverse events, deaths, SAEs, and discontinuations are further discussed in Section 8.3.1, Section 8.3.2.1, Section 8.3.2.2, and Section 8.3.3, respectively.

**Table 8.3–1. Summary of Adverse Events, Phase 3 Studies—Safety Population**

	<b><i>Pooled CABP Studies (08, 09)</i></b>		<b><i>Pooled cSSSI Studies (06, 07)</i></b>		<b><i>Pooled Phase 3 Studies (06, 07, 08, 09)</i></b>	
	<i>Ceftaroline (N = 613) n (%)</i>	<i>Ceftriaxone (N = 615) n (%)</i>	<i>Ceftaroline (N = 692) n (%)</i>	<i>Vancomycin plus Aztreonam (N = 686) n (%)</i>	<i>Ceftaroline (N = 1305) n (%)</i>	<i>Pooled Comparators (N = 1301) n (%)</i>
Number of subjects with						
Any TEAE	288 (47.0)	281 (45.7)	309 (44.7)	326 (47.5)	597 (45.7)	607 (46.7)
Any SAE	69 (11.3)	72 (11.7)	30 (4.3)	28 (4.1)	99 (7.6)	100 (7.7)
Discontinuations due to TEAE	27 (4.4)	25 (4.1)	21 (3.0)	33 (4.8)	48 (3.7)	58 (4.5)
Deaths <sup>a</sup>	15 (2.4)	12 (2.0)	3 (0.4)	0	18 (1.4)	12 (0.9)

Abbreviations: CABP = community-acquired bacterial pneumonia; cSSSI = complicated skin and skin structure infection; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

- a An additional 9 deaths were spontaneously reported after LFU in the Phase 3 CABP (1 in the ceftaroline group and 4 in the ceftriaxone group) and cSSSI (2 in the ceftaroline group and 2 in the vancomycin plus aztreonam group) studies.



### **8.3.1 Common Adverse Events**

Table 8.3.1–1 provides AEs that occurred at a rate  $\geq 1\%$  in the ceftaroline group in the Phase 3 studies.

In the pooled Phase 3 CABP and cSSSI studies, the incidences of TEAEs were similar in the pooled ceftaroline and pooled comparators group. No individual TEAEs occurred in 5% or more of subjects in the pooled Phase 3 CABP and cSSSI subjects. The most common TEAEs in the ceftaroline group were diarrhea, headache, and nausea. By comparison, the most common TEAEs in the comparator group were pruritus, nausea, and diarrhea. Most TEAEs in the pooled Phase 3 CABP and cSSSI studies were mild or moderate in severity and the incidences of TEAEs in the ceftaroline and comparator group were similar in each category (mild, 24.1% vs 23.0%; moderate, 16.6% vs 17.8%; and severe, 5.0% vs 5.8%, respectively). No severe TEAE occurred in more than 1% of subjects in either treatment group. In the pooled Phase 3 CABP and cSSSI studies, the percentages of subjects with 1 or more TEAEs assessed by the Investigator as related to study drug were similar for the ceftaroline and the comparator group (19.4% vs 20.1%, respectively).

In the pooled Phase 3 CABP studies, the incidences of TEAEs were similar in the ceftaroline and ceftriaxone treatment groups. Most TEAEs in the pooled Phase 3 CABP studies were mild or moderate in severity and the incidences of TEAEs in the ceftaroline and comparator groups were similar in each category (mild, 24.5% vs 20.0%; moderate, 16.2% vs 18.4%; severe, 6.4% vs 7.3%, respectively). The incidences of TEAEs assessed as related to study drug were similar for the ceftaroline and the ceftriaxone groups (14.7% vs 13.2%, respectively).

In the pooled Phase 3 cSSSI studies, the incidences of TEAEs were similar in ceftaroline and vancomycin plus aztreonam groups. Most TEAEs in the pooled Phase 3 cSSSI studies were mild or moderate in severity and the incidences of TEAEs in the ceftaroline and comparator groups were similar in each category (mild, 23.8% vs 25.7%; moderate, 17.1% vs 17.3%; severe, 3.8% vs 4.5%, respectively). The incidences of TEAEs assessed as related to study drug were similar for the ceftaroline and the vancomycin plus aztreonam groups (23.6% vs 26.4%, respectively).

**Table 8.3.1–1. Incidence of Common ( $\geq 1\%$ ) Treatment-Emergent Adverse Events, Phase 3 Studies — Safety Population**

<b>System Organ Class Preferred Term</b>	<b>Pooled CABP Studies (08, 09)</b>		<b>Pooled cSSSI Studies (06, 07)</b>		<b>Pooled Phase 3 Studies (06, 07, 08, 09)</b>	
	<i>Ceftaroline (N = 613) n(%)</i>	<i>Ceftriaxone (N = 615) n(%)</i>	<i>Ceftaroline (N = 692) n(%)</i>	<i>Vancomycin plus Aztreonam (N = 686) n(%)</i>	<i>Ceftaroline (N = 1305) n(%)</i>	<i>Pooled Comparators (N = 1301) n(%)</i>
Subjects with at Least 1 TEAE	288 (47.0)	281 (45.7)	309 (44.7)	326 (47.5)	597 (45.7)	607 (46.7)
Gastrointestinal disorders						
Diarrhea	26 (4.2)	16 (2.6)	34 (4.9)	26 (3.8)	60 (4.6)	42 (3.2)
Nausea	14 (2.3)	14 (2.3)	41 (5.9)	35 (5.1)	55 (4.2)	49 (3.8)
Constipation	9 (1.5)	6 (1.0)	18 (2.6)	18 (2.6)	27 (2.1)	24 (1.8)
Vomiting	7 (1.1)	2 (0.3)	20 (2.9)	18 (2.6)	27 (2.1)	20 (1.5)
Abdominal pain	5 (0.8)	3 (0.5)	9 (1.3)	7 (1.0)	14 (1.1)	10 (0.8)
General disorders and administration site conditions						
Pyrexia	4 (0.7)	5 (0.8)	9 (1.3)	16 (2.3)	13 (1.0)	21 (1.6)
Investigations						
Blood pressure increased	5 (0.8)	4 (0.7)	9 (1.3)	9 (1.3)	14 (1.1)	13 (1.0)
Alanine aminotransferase increased	5 (0.8)	6 (1.0)	8 (1.2)	12 (1.7)	13 (1.0)	18 (1.4)
Metabolism and nutrition disorders						
Hypokalemia	14 (2.3)	15 (2.4)	10 (1.4)	15 (2.2)	24 (1.8)	30 (2.3)
Nervous system disorders						
Headache	21 (3.4)	9 (1.5)	36 (5.2)	31 (4.5)	57 (4.4)	40 (3.1)
Dizziness	3 (0.5)	2 (0.3)	14 (2.0)	8 (1.2)	17 (1.3)	10 (0.8)
Psychiatric disorders						
Insomnia	19 (3.1)	14 (2.3)	17 (2.5)	17 (2.5)	36 (2.8)	31 (2.4)
Skin and subcutaneous tissue disorders						
Pruritus	1 (0.2)	3 (0.5)	24 (3.5)	56 (8.2)	25 (1.9)	59 (4.5)
Rash	2 (0.3)	2 (0.3)	22 (3.2)	17 (2.5)	24 (1.8)	19 (1.5)
Pruritus generalized	0	0	15 (2.2)	19 (2.8)	15 (1.1)	19 (1.5)
Vascular disorders						
Hypertension	14 (2.3)	16 (2.6)	9 (1.3)	10 (1.5)	23 (1.8)	26 (2.0)
Phlebitis	17 (2.8)	13 (2.1)	3 (0.4)	5 (0.7)	20 (1.5)	18 (1.4)

Abbreviations: CABP = community-acquired bacterial pneumonia; cSSSI = complicated skin and skin structure;  
TEAE = treatment-emergent adverse event.

### **8.3.2 Deaths and Serious Adverse Events**

#### **8.3.2.1 Deaths**

Table 8.3.2.1–1 summarizes incidences of on-study death by SAE preferred term in the Phase 3 studies and Table 8.3.2.1–2 provides a list of all subjects who died, the SAE leading to death, the study days on study drug, the Study Days of their deaths, and the causality assessment of the Investigator.

In the safety population of the pooled Phase 3 CABP and cSSSI studies, 30 subjects in the ceftaroline and comparator groups (18 [1.4%] vs 12 [0.9%], respectively) died on or before the day of LFU evaluations or within 30 days after EOT when LFU evaluations had not been done. The SAEs leading to death were generally similar between the ceftaroline and comparator groups with the exception of the terms: “sudden death” (2 versus 0, respectively) and terms representing underlying neoplasms (5 versus 0, respectively). A review of the clinical circumstances leading to the 30 deaths above revealed that 7 subjects died of sudden events of uncertain etiology (4 in the ceftaroline group and 3 in the comparator group). However, 2 subjects in the ceftaroline group and 3 subjects in the comparator group were not recorded by the Investigator as a sudden death, as the death was presumed to be due to an underlying malignant neoplasm progression, acute cardiac failure, cardiac arrest, or cardio-respiratory arrest. Overall, the incidences of death representing a sudden event of uncertain etiology were balanced between the ceftaroline and the comparator groups.

Similarly, although no subject’s death in the comparator group was attributed to an underlying neoplastic process by the Investigator, one ceftriaxone-treated subject had an underlying mesothelioma and diffuse pulmonary microemboli (to which death was attributed) discovered at autopsy. These subjects, who died from an underlying neoplastic process, likely had undiagnosed neoplasms at baseline. In the Phase 3 CABP and cSSSI studies, ceftaroline would not likely cause or alter such an underlying neoplastic process given the short duration of treatment received by these subjects ( $\leq 7$  days), the maximum follow-up period of approximately 5 weeks post therapy, and a lack of any in vitro or in vivo non-clinical evidence of mutagenicity.

Only 1 death in each treatment group was assessed by the Investigator as possibly related to study drug. One case of sudden death in the ceftaroline group was considered possibly related to study drug because no other etiology was identified (ie, no autopsy was performed and no preceding clinical event could be cited to explain the sudden death). The possibly study-drug-related death in the ceftriaxone group was attributed to multiorgan failure. A detailed summary of these subjects is provided below.

- Subject 2034-08238 (sudden death in ceftaroline group) was a 73-year-old white female with a medical history that included smoking. The subject received ceftaroline fosamil for 2 days for the treatment of right middle lobe CABP (PORT Risk Class III) with no identified pathogen at baseline. The subject was febrile but hemodynamically stable at baseline and electrocardiogram (ECG) testing revealed sinus rhythm and atrial premature complexes. No AEs were noted during study drug administration on Study Days 1 and 2. Laboratory results were unremarkable. On Study Day 3, the subject was found unresponsive. The subject was intubated without difficulty (ie, there was no report of throat swelling), and no rash, hives or other evidence of a drug reaction was noted during resuscitation. The resuscitation was unsuccessful and the subject died. The Investigator reported that the subject did not have any previous exposure to cephalosporin drug therapy nor any allergies or sensitivity to penicillin, cephalosporin, or beta-lactam medications. The cardiologist suspected that the subject died due to a suspected myocardial infarction. An autopsy was not performed. The Investigator reported an SAE of sudden death as possibly related to study drug with an alternative etiology of myocardial infarction.
- Subject 6626-08148 (multi-organ disorder in ceftriaxone group) was a 60-year-old white male with a medical history that included smoking and hypertension. The subject received ceftriaxone for 6 days for the treatment of bilateral CABP (PORT Risk Class IV) with no pathogen isolated at baseline. According to the Investigator, the subject also had a history of a current alcohol abuse without liver disease or paracetamol or acetaminophen indigestion. Baseline laboratory results included: alanine aminotransferase (ALT) 16 U/L, aspartate aminotransferase (AST) 19 U/L, lactate dehydrogenase (LDH) 182 U/L, total bilirubin 0.4 mg/dL, international normalized ratio 1.1, serum creatinine 0.8 mg/dL, and CrCl 104.4 mL/min. Additionally, on Study Day 1, an ultrasound of the liver revealed normal liver size and structure. On Study Day 6, laboratory results revealed serum creatinine and CrCl of 1.6 mg/dL and 52.8 ml/min, respectively, an elevated D-Dimer, ALT 214 U/L, AST 231 U/L, LDH 521 U/L, and negative serology for Hepatitis A and B and human immunodeficiency virus. On Study Day 7, the subject experienced an SAE of hepatic failure with worsening liver function by laboratory testing (ALT 2010 U/L, AST 4110 U/L, LDH 3022 U/L, total bilirubin 11  $\mu$ mol/L, and international normalized ratio 2.1). The subject experienced an SAE of multi-organ disorder on Study Day 11, and on Study Day 14, the subject died. No liver biopsy or autopsy was performed. The cause of death was reported as multiorgan disorder. The Investigator reported the SAEs of hepatic failure and multi-organ disorder to be possibly related to the study drug.

Of the remaining 28 deaths, 4 (2 in each treatment group in the Phase 3 CABP studies) were determined by the Investigator to be caused by the underlying primary infection. The remaining 24 deaths in the pooled ceftaroline and pooled comparator groups (15 vs 9, respectively) were considered unlikely to be related to study drug or the underlying primary infection and were more likely related to underlying severe disease (eg, cardiomyopathy, chronic pulmonary disease, myopathy, malignancy), were temporally unrelated to the study drug treatment period, or both.

In addition to the on-study deaths (Table 8.3.2.1–1), 3 subjects in the pooled ceftaroline group and 6 subjects in the pooled comparator group died after LFU or > 30 days after EOT when no LFU was done; 4 of these subjects were in the cSSSI studies (2 vs 2, respectively) and 5 were in the CABP studies (1 vs 4, respectively).

In summary, no clinically meaningful difference between the ceftaroline and comparator groups was observed with regard to the incidence or nature of deaths during the Phase 3 CABP and cSSSI studies.

**Table 8.3.2.1–1. Incidence of Death, Phase 3 Studies—Safety Population**

<b>System Organ Class Preferred Term</b>	<b>Pooled CABP Studies (08, 09)</b>		<b>Pooled cSSSI Studies (06, 07)</b>		<b>Pooled Phase 3 Studies (06, 07, 08, 09)</b>	
	<i>Ceftaroline (N = 613) n (%)</i>	<i>Ceftriaxone (N = 615) n (%)</i>	<i>Ceftaroline (N = 692) n (%)</i>	<i>Vancomycin plus Aztreonam (N = 686) n (%)</i>	<i>Ceftaroline (N = 1305) n (%)</i>	<i>Pooled Comparators (N = 1301) n (%)</i>
Deaths <sup>a</sup>	15 (2.4)	12 (2.0)	3 (0.4)	0	18 (1.4)	12 (0.9)
Cardiac disorders	2 (0.3)	7 (1.1)	1 (0.1)	0	3 (0.2)	7 (0.5)
Cardiac arrest	1 (0.2)	0	0	0	1 (0.1)	0
Cardiac failure	1 (0.2)	0	0	0	1 (0.1)	0
Cardiopulmonary failure	0	1 (0.2)	1 (0.1)	0	1 (0.1)	1 (0.1)
Cardiac failure acute	0	1 (0.2)	0	0	0	1 (0.1)
Cardio-respiratory arrest	0	2 (0.3)	0	0	0	2 (0.2)
Cardiomyopathy	0	1 (0.2)	0	0	0	1 (0.1)
Coronary artery disease	0	1 (0.2)	0	0	0	1 (0.1)
Myocardial infarction	0	1 (0.2)	0	0	0	1 (0.1)
General disorders and administration site conditions	2 (0.3)	1 (0.2)	0	0	2 (0.2)	1 (0.1)
Sudden death	2 (0.3)	0	0	0	2 (0.2)	0
Multi-organ disorder	0	1 (0.2)	0	0	0	1 (0.1)

**Table 8.3.2.1–1. Incidence of Death, Phase 3 Studies—Safety Population**

<b>System Organ Class Preferred Term</b>	<b>Pooled CABP Studies (08, 09)</b>		<b>Pooled cSSSI Studies (06, 07)</b>		<b>Pooled Phase 3 Studies (06, 07, 08, 09)</b>	
	<i>Ceftaroline (N = 613) n (%)</i>	<i>Ceftriaxone (N = 615) n (%)</i>	<i>Ceftaroline (N = 692) n (%)</i>	<i>Vancomycin plus Aztreonam (N = 686) n (%)</i>	<i>Ceftaroline (N = 1305) n (%)</i>	<i>Pooled Comparators (N = 1301) n (%)</i>
Infections and infestations	3 (0.5)	1 (0.2)	0	0	3 (0.2)	1 (0.1)
Pneumonia	1 (0.2)	1 (0.2)	0	0	1 (0.1)	1 (0.1)
Sepsis	1 (0.2)	0	0	0	1 (0.1)	0
Septic shock	1 (0.2)	0	0	0	1 (0.1)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	4 (0.7)	0	1 (0.1)	0	5 (0.4)	0
Malignant neoplasm progression	1 (0.2)	0	1 (0.1)	0	2 (0.2)	0
Lung neoplasm malignant	1 (0.2)	0	0	0	1 (0.1)	0
Metastases to liver	1 (0.2)	0	0	0	1 (0.1)	0
Metastatic neoplasm	1 (0.2)	0	0	0	1 (0.1)	0
Respiratory, thoracic and mediastinal disorders	4 (0.7)	3 (0.5)	1 (0.1)	0	5 (0.4)	3 (0.2)
Respiratory failure	2 (0.3)	0	1 (0.1)	0	3 (0.2)	0
Interstitial lung disease	1 (0.2)	0	0	0	1 (0.1)	0
Pulmonary embolism	1 (0.2)	2 (0.3)	0	0	1 (0.1)	2 (0.2)
Acute respiratory failure	0	1 (0.2)	0	0	0	1 (0.1)

Abbreviations: CABP = community-acquired bacterial pneumonia; cSSSI = complicated skin and skin structure infection.

- a An additional 9 deaths were spontaneously reported after LFU, 5 in the Phase 3 CABP studies (1 in the ceftaroline group of pancreatic neoplasm and 4 in the ceftriaxone group of myopathy, pneumonia, chronic obstructive pulmonary disease, and pseudomonal lung infection) and 4 in the Phase 3 cSSSI studies (2 in the ceftaroline group of multiorgan failure and myocardial infarction and 2 in the vancomycin plus aztreonam group of recurrent chronic lymphocytic leukemia and the other of unknown cause).

**Table 8.3.2.1–2. Listing of All Subjects Who Died in Phase 3 Studies—Safety Population**

<i>Subject ID</i>	<i>Cause of Death</i>	<i>Age/ Gender</i>	<i>Last Day of Study Drug</i>	<i>Study Day of Death</i>	<i>Investigator Assessment of Relationship to Study Drug</i>
<b><i>Subjects who died <u>before</u> LFU or <u>within</u> 30 days after EOT when there was no LFU</i></b>					
<b>cSSSI, ceftaroline group</b>					
0002-06674	Respiratory failure	90/F	4	7	NR
5007-06358	Malignant neoplasm progression	68/F	5	17	NR
6609-06196	Cardio-pulmonary failure	58/F	15	38	NR
<b><i>Subjects who died <u>before</u> LFU or <u>within</u> 30 days after EOT when there was no LFU</i></b>					
<b>CABP, ceftaroline group</b>					
1004-08340	Sudden death	71/M	5	31	NR
2034-08238	Sudden death	73/F	2	3	Possibly Related
6635-08316	Metastases to liver	74/M	7	24	NR
6642-08567	Cardiac failure	87/F	7	14	NR
6827-08190	Sepsis	82/F	4	32	NR
6829-08528	Respiratory failure <sup>a</sup>	49/M	4	16	NR
2015-09618	Nosocomial pneumonia	69/M	7	16	NR
5012-09074	Pulmonary embolism	78/M	6	12	NR
5101-09115	Malignant lung neoplasm	67/M	7	24	NR
5203-09541	Metastatic neoplasm	70/M	7	31	NR
6602-09365	Respiratory failure	57/M	6	28	NR
6608-09621	Interstitial lung disease	80/M	6	10	NR
6613-09346	Malignant neoplasm progression	84/M	7	11	NR
6804-09374	Cardiac arrest	87/M	7	8	NR
9008-09619	Septic shock <sup>a</sup>	57/M	5	13	NR
<b>CABP, ceftriaxone group</b>					
0044-08030	Cardiorespiratory arrest	91/M	2	2	NR
2031-08249	Pneumonia <sup>a</sup>	50/M	2	23	NR
6531-08393	Cardiopulmonary failure <sup>a</sup>	81/M	3	14	NR
6626-08148	Multi-organ disorder	60/M	6	14	Possibly Related
6828-08570	Acute cardiac failure	80/F	7	13	NR
8206-08236	Cardiomyopathy	68/M	7	12	NR
5011-09250	Cardio-respiratory arrest	68/M	4	5	NR
5011-09540	Pulmonary embolism	75/F	7	27	NR
6511-09215	Myocardial infarction	88/F	7	19	NR
6612-09481	Acute respiratory failure	78/M	5	6	NR
7004-09012	Coronary artery disease	82/M	7	22	NR
7004-09332	Pulmonary embolism	84/F	2	3	NR

**Table 8.3.2.1–2. Listing of All Subjects Who Died in Phase 3 Studies—Safety Population**

<i>Subject ID</i>	<i>Cause of Death</i>	<i>Age/ Gender</i>	<i>Last Day of Study Drug</i>	<i>Study Day of Death</i>	<i>Investigator Assessment of Relationship to Study Drug</i>
<b><i>Subjects who died after LFU or more than 30 days after EOT when there was no LFU</i></b>					
<b>cSSSI, ceftaroline group</b>					
2016-07561	Multi-organ failure	61/M	2	45	NR
5017-07652	Myocardial infarction	74/F	5	45	NR
<b>cSSSI, vancomycin plus aztreonam group</b>					
2106-07694	Unknown <sup>b</sup>	54/M	14	66	NR
6511-07312	Recurrent chronic lymphocytic leukemia	72/F	3	43	NR
<b>CABP, ceftaroline group</b>					
5528-08119	Pancreatic neoplasm	91/F	7	68	NR
<b>CABP, ceftriaxone group</b>					
5027-08585	Myopathy	62/M	2	50	NR
6204-08575	Pneumonia	70/M	7	43	NR
6634-08108	COPD	65/M	7	47	NR
6506-09105	Pseudomonal lung infection	58/M	7	70	NR
<b>Phase 2 Studies: No deaths occurred</b>					
<b>Phase 1 Studies: No deaths occurred</b>					

Abbreviations: CABP = community-acquired bacterial pneumonia; COPD = chronic obstructive pulmonary disease; cSSSI = complicated skin and skin structure infection; EOT = end of therapy; F = female; ID = identification number; LFU = late follow-up; M = male; NR = not related or unlikely to be related

a The Investigator indicated the cause of death was related to CABP.

b The Investigator indicated the cause could not be specified but was probably due to cardiovascular disease, arrhythmia, infarct, or pulmonary embolism.



### **8.3.2.2      *Serious Adverse Events***

End-of-text Table 11.3–1 summarizes incidences of SAEs by Medical Dictionary for Regulatory Activities (MedDRA) preferred term in the Phase 3 studies.

In the pooled Phase 3 CABP and cSSSI studies, SAEs occurred in similar percentages of subjects receiving ceftaroline or comparator drugs (7.6% vs 7.7%, respectively). The most common SAEs in the ceftaroline or comparator group (occurring in 4 or more subjects in either group) represented complications attributable to the respiratory system (pulmonary embolism [0.5% vs 0.3%], respiratory failure [0.4% vs 0.1%], and pleural effusion [0.4% vs 0.5%], comorbidities (COPD [0.3% vs 0.5%]), or worsening of the underlying infection (pneumonia [0.7% vs 0.8%], pyothorax [0.3% vs 0], lung abscess [0.2% vs 0.3%], and cellulitis [0.3% vs 0.1%], respectively. The instances of worsening of the underlying infection were recorded as SAEs because they resulted in prolongation of hospitalization or rehospitalization. The only other SAE terms that occurred in more than 2 subjects in the ceftaroline group were malignant neoplasm (3 subjects) and renal failure (3 subjects) (discussed in more detail in Section 8.4.1). The majority of SAEs were assessed as unrelated to study drug and the incidence of SAEs assessed as related to study drug was similar in the pooled ceftaroline and pooled comparator groups.

In the pooled Phase 3 CABP studies and the pooled Phase 3 cSSSI studies, the incidences of SAEs in the ceftaroline and comparator groups were similar (11.3% vs 11.7% for CABP and 4.3% vs 4.1% for cSSSI, respectively) (Table 11.3–1). As many of the SAEs observed in CABP and cSSSI were related to the underlying primary infection, the greater incidence of SAEs in the CABP studies likely represents higher morbidity and mortality associated with CABP relative to cSSSI. Additionally, the subjects in the CABP studies were generally older (median age approximately 64 vs 48 years, respectively) with more underlying comorbidities (including chronic obstructive lung disease) at baseline.

### **8.3.3      *Discontinuation of Study Medication or Study Due to an Adverse Event***

End-of-text Table 11.3–2 summarizes the incidences of TEAEs by MedDRA preferred term leading to discontinuation of study drug or withdrawal from study in the Phase 3 studies.

In the pooled Phase 3 CABP and cSSSI studies, the incidences of TEAEs resulting in premature discontinuation from study drug or withdrawal from study were low and similar in the ceftaroline and comparator groups (3.7% vs 4.5%, respectively). The most common TEAEs resulting in premature discontinuation of study drug or withdrawal from study in the pooled ceftaroline and pooled comparator groups were hypersensitivity (4 vs 6 subjects), rash (2 vs 4 subjects), pneumonia (2 vs 3 subjects), pruritus generalized (2 vs 3 subjects), erythema (0 vs 5 subjects), pulmonary embolism (2 vs 2 subjects), and urticaria (1 vs 3 subjects), respectively.

In the pooled Phase 3 CABP studies and the pooled Phase 3 cSSSI studies analyzed separately by indication, the incidences of TEAEs resulting in premature discontinuation from study drug or withdrawal from study were also low and similar in the ceftaroline and comparator groups.

## 8.4 SAFETY EVENTS OF INTEREST

Although cephalosporin antibiotics are generally well tolerated with low incidences of adverse reactions, the range of observed cephalosporin class effects include: local irritation; gastrointestinal intolerance including nausea and diarrhea (including *C. difficile*-associated diarrhea); allergic phenomena including potential anaphylaxis; nephrotoxicity; hepatotoxicity; hematologic effects such as positive Coombs testing, hemolytic anemia, aplastic anemia, and neutropenia; decreased seizure threshold; and superinfection (Karchmer, 2000). The primary findings observed in the ceftaroline toxicology studies, at doses generally higher than the maximum recommended human equivalent dose, included tonic/clonic convulsions, renal toxicity, local irritation at the injection site, anemia, and neutropenia. Based on the combination of the known cephalosporin class effects and the ceftaroline toxicology findings, the clinical data were further analyzed for the following safety events of interest: Renal Safety (Section 8.4.1), Hepatic Safety (Section 8.4.2), Potential Allergic Reactions (Section 8.4.3), Direct Coombs Seroconversion (Section 8.4.4), Seizures (Section 8.4.5), and *C. difficile*-associated diarrhea (Section 8.4.6). In addition, although cardiac toxicities are not typical of the cephalosporin class and no cardiac signal was detected in the ceftaroline toxicology studies, a brief review of Cardiac Effects (Section 8.4.7) is included in this section due to observed toxicities with other antibacterials (eg, Zithromax [azithromycin for injection] package insert, 2009) and Avelox [moxifloxacin] package insert, 2008).

### 8.4.1 Renal Safety

Table 8.4.1–1 provides the incidences of subjects with TEAEs representing potential renal impairment, subjects with potentially clinically significant [PCS] renal chemistry values, and subjects with any renal event (ie, subjects with a renal TEAE and/or PCS renal chemistry values) in the Phase 3 studies.

In the pooled Phase 3 CABP and cSSSI studies, the incidence of TEAEs representing potential renal impairment (eg, renal failure, renal impairment, blood creatinine increased, CrCl decreased, and glomerular filtration rate decreased) were low in both groups although higher in the pooled ceftaroline group compared to the pooled comparators group (1.5% vs 0.8%, respectively). Conversely, subjects with PCS renal chemistry values were low in both groups and lower in the pooled ceftaroline group compared to the pooled comparators group for serum creatinine (1.4% vs 1.9%) and creatinine clearance (0.7% vs 1.3%). Overall, the incidences of subjects with any renal event were evaluated and found to be low and similar between treatment groups (2.7% vs 2.5%, respectively).

Furthermore, the incidences of subjects with any renal event were similar between the pooled Phase 3 CABP studies and pooled Phase 3 cSSSI studies and between comparator groups within each indication.

**Table 8.4.1–1. Summary of Renal Events, Phase 3 Studies—Safety Population**

	<i>Pooled CABP Studies (08, 09)</i>		<i>Pooled cSSSI Studies (06, 07)</i>		<i>Pooled Phase 3 Studies (06, 07, 08, 09)</i>	
	<i>Ceftaroline n/N (%)</i>	<i>Ceftriaxone n/N (%)</i>	<i>Ceftaroline n/N (%)</i>	<i>Vancomycin plus Aztreonam n/N (%)</i>	<i>Ceftaroline n/N (%)</i>	<i>Pooled Comparators n/N (%)</i>
<b>Any Renal Event</b>	18/613 (2.9)	15/615 (2.4)	17/692 (2.5)	18/686 (2.6)	35/1305 (2.7)	33/1301 (2.5)
AE representing potential renal impairment	10/613 (1.6)	5/615 (0.8)	9/692 (1.3)	5/686 (0.7)	19/1305 (1.5)	10/1301 (0.8)
PCS renal chemistry parameters, n/N1 (%)						
Serum creatinine (> 1.5 mg/dL and > 50% increase from baseline)	12/599 (2.0)	10/596 (1.7)	6/676 (0.9)	14/664 (2.1)	18/1275 (1.4)	24/1260 (1.9)
Creatinine clearance (> 50% decrease from baseline)	6/599 (1.0)	9/596 (1.5)	3/676 (0.4)	7/663 (1.1)	9/1275 (0.7)	16/1259 (1.3)

Abbreviations: AE = adverse event; CABP = community-acquired bacterial pneumonia; cSSSI = complicated skin and skin structure infection; N1 = subjects who have both a baseline and at least 1 postbaseline assessment for each parameter, with the exception of the maximum serum creatinine section, in which it is the count of subjects who met the elevated serum creatinine criteria; PCS = potentially clinically significant.

Table 8.4.1–2 provides the incidences and distribution of subjects in the Phase 3 studies by the maximum PCS serum creatinine values.

In the pooled Phase 3 CABP and cSSSI studies, the distribution of the maximum serum creatinine values reported were similar between treatment groups. The majority in both treatment groups had maximum creatinine values of < 3 mg/dL. In the ceftaroline group, 3 subjects had maximum creatinine values > 3 mg/dL and none of these subjects had SAEs reported that represent potential renal impairment. Two of these 3 subjects had preexisting renal impairment and the third subject had only 1 abnormal creatinine value with rapid normalization of creatinine noted. In the pooled comparators group, 5 subjects had maximum creatinine values > 3 mg/dL and 1 subject had a renal SAE (Subject 5014-07467 with acute renal failure discussed below).

The incidences of subjects with PCS renal chemistry values were similar in the pooled Phase 3 CABP studies and pooled Phase 3 cSSSI studies and were similar or lower in the ceftaroline group versus the comparator groups.

**Table 8.4.1–2. Distribution of Maximum Values for Potentially Clinically Significant Creatinine Values, Phase 3 Studies—Safety Population**

<b>Clinical Laboratory Parameter Criterion</b>	<b>Pooled CABP Studies (08, 09)</b>		<b>Pooled cSSSI Studies (06, 07)</b>		<b>Pooled Phase 3 Studies (06, 07, 08, 09)</b>	
	<i>Ceftaroline</i> (N = 613) n/N1 (%)	<i>Ceftriaxone</i> (N = 615) n/N1 (%)	<i>Ceftaroline</i> (N = 692) n/N1 (%)	<i>Vancomycin plus Aztreonam</i> (N = 686) n/N1 (%)	<i>Ceftaroline</i> (N = 1305) n/N1 (%)	<i>Pooled Comparators</i> (N = 1301) n/N1 (%)
Serum creatinine > 1.5 mg/dL and > 50% increase from baseline	12/599 (2.0)	10/596 (1.7)	6/676 (0.9)	14/664 (2.1)	18/1275 (1.4)	24/1260 (1.9)
Maximum serum creatinine level						
> 1.5 to 2.0 mg/dL	4/599 (0.7)	4/596 (0.7)	5/676 (0.7)	10/664 (1.5)	9/1275 (0.7)	14/1260 (1.1)
> 2.0 mg/dL to 3.0 mg/dL	6/599 (1.0)	2/596 (0.4)	0/676	3/664 (0.5)	6/1275 (0.5)	5/1260 (0.4)
> 3.0 mg/dL to 5.0 mg/dL	1/599 (0.2)	3/596 (0.5)	1/676 (0.1)	0/664	2/1275 (0.2)	3/1260 (0.2)
> 5.0 mg/dL	1/599 (0.2)	1/596 (0.2)	0/676	1/664 (0.2)	1/1275 (0.1)	2/1260 (0.2)

Abbreviations: CABP = community-acquired bacterial pneumonia; cSSSI = complicated skin and skin structure infection; N1 = subjects who have both a baseline and at least 1 postbaseline assessment for each parameter, with the exception of the maximum serum creatinine section, in which it is the count of subjects who met the elevated serum creatinine criteria.

To further evaluate the clinical significance of the renal TEAEs and the PCS renal chemistry values observed in the Phase 3 CABP and cSSSI studies and the lack of concordance between them, relevant study data for all subjects with any renal event was analyzed by 2 nephrologists (Julia Lewis, M.D. and Jamie Dwyer, M.D. from Vanderbilt University) independently. The independent and blinded reviews identified 53 subjects with evidence of acute renal injury (28 in the pooled ceftaroline group and 25 in the pooled comparators group). The number of subjects with renal events that were identified as possibly or likely to be study drug related by the nephrology review were similar between the pooled ceftaroline group and pooled comparators group (5 versus 4, respectively) (Table 8.4.1–3).

**Table 8.4.1–3. Summary of Independent Nephrology Review of All Renal Events, Phase 3 Studies—Safety Population**

	<i>Pooled CABP Studies (08, 09)</i>		<i>Pooled cSSSI Studies (06, 07)</i>		<i>Pooled Phase 3 Studies (06, 07, 08, 09)</i>	
	<i>Ceftaroline N = 613 n (%)</i>	<i>Ceftriaxone N = 615 n (%)</i>	<i>Ceftaroline N = 692 n (%)</i>	<i>Vancomycin plus aztreonam N = 686 n (%)</i>	<i>Ceftaroline N = 1305 n (%)</i>	<i>Pooled Comparators N = 1301 n (%)</i>
<b>Any Renal Event</b>	18 (2.9)	15 (2.4)	17 (2.5)	18 (2.6)	35 (2.7)	33 (2.5)
Assessed as acute renal injury	16 (2.6)	11 (1.8)	12 (1.7)	14 (2.0)	28 (2.1)	25 (1.9)
Assessed as possibly or likely study-drug related	3 (0.5)	1 (0.2)	2 (0.3)	3 (0.4)	5 (0.4)	4 (0.3)

Abbreviations: CABP = community-acquired bacterial pneumonia; cSSSI = complicated skin and skin structure infection.

In the Phase 3 CABP and cSSSI studies, 3 subjects in the pooled ceftaroline group and 1 subject in the pooled comparators group had SAEs representing renal impairment. One SAE (acute renal failure) in the vancomycin plus aztreonam group (Subject 5014-07467) was assessed as related to study drug by the Investigator; however, no SAE was assessed as possibly related to study drug by the nephrology review and no renal SAE was assessed as the cause of any subject's death. Detailed summaries of the subjects with renal SAEs follow.

In the pooled Phase 3 CABP studies, 2 subjects in the ceftaroline group experienced SAEs of renal failure representing potential renal impairment.

- Subject 5012-09074 (renal failure in the ceftaroline group) was a 78-year-old male with a history of pancreatitis who received ceftaroline for 6 days for the treatment of CABP. The subject also had a medical history of smoking; structural lung disease; chronic bronchitis; pulmonary embolism; atrial fibrillation; atherosclerosis of aorta, cerebral, and renal arteries; myocardial ischemia with 2 myocardial infarctions; chronic pyelonephritis; and prostatic adenoma. Baseline creatinine was 1.4 mg/dL (CrCl 38.1 mL/min). On Study Day 3, the subject was noted to have moderate atrial fibrillation. On Study Day 5, the subject developed moderate acute pancreatitis (ALT 933 U/L, AST 798 U/L, and total bilirubin of 1.6 mg/dL [amylase and lipase values not reported]). On Study Day 6, the subject developed pulmonary embolism, renal failure (no hemodialysis performed), and hepatic failure and ceftaroline was discontinued. Laboratory results on Study Day 6 included ALT 3099 U/L, AST 2707 U/L, total bilirubin 1.5 mg/dL, and creatinine 2.4 mg/dL. On Study Day 10, the subject developed disseminated intravascular coagulation. On Study Day 12, the subject experienced sudden increased dyspnea and died on the same day. The Investigator reported the death to be due to pulmonary embolism. The SAEs were assessed by the Investigator as unrelated to study drug. Based on the underlying atherosclerotic disease (including the renal arteries), atrial fibrillation, decreased cardiac output, pulmonary emboli and hepatic failure, relationship of the renal failure to ceftaroline treatment appears highly unlikely.
- Subject 2015-09618 (renal failure in the ceftaroline group) was a 69-year-old white male who received ceftaroline for 7 days for the treatment of CABP. The subject had a medical history of smoking, structural lung disease, asthma, diabetes, bladder diverticulum, hematuria, prostatic adenoma, and hydronephrosis with chronic renal insufficiency (baseline creatinine and CrCl of 1.1 mg/dL and 51.2 mL/min, respectively). On Study Day 8, the subject experienced exacerbation of COPD that required mechanical ventilation (Study Day 13). On Study Day 14, the subject developed nosocomial pneumonia and shock. On Study Day 15 the subject's creatinine was 1.45 mg/dL and CrCl was 32.9 mL/min (based on these findings, an SAE of renal failure was recorded). The subject was treated with furosemide and no hemodialysis was performed. The subject died on Study Day 16, according to the Investigator, due to nosocomial pneumonia. All SAEs were assessed by the Investigator as unrelated to study drug. Based on the subject's underlying comorbidities, remote onset of renal failure (8 days after ceftaroline treatment), and the subject developing nosocomial pneumonia and shock, relationship of the renal failure to ceftaroline treatment appears highly unlikely.

In the pooled Phase 3 cSSSI studies, 1 subject in the ceftaroline group (with renal failure) and 1 subject in the vancomycin plus aztreonam group (with acute renal failure) experienced SAEs representing potential renal impairment.

- Subject 2016-07561 (renal failure in the ceftaroline group) was a 61-year-old Hispanic white male who received 3 doses of ceftaroline 400 mg for cellulitis of the leg. The subject had a medical history of ischemic cardiomyopathy, diabetes, hypertension, cerebrovascular accident, and renal failure (pretreatment creatinine values were 3.0 and 4.5 mg/dL). On Study Day 2, the subject experienced an SAE of acute pulmonary edema assessed by the Investigator as unrelated to study drug; study drug, however, was prematurely discontinued to control the volume of fluid administered. The subject was transferred to the ICU, intubated, and mechanically ventilated. Following a *S. aureus* bacteremia from a central line infection on Study Day 17, the subject's clinical condition continued to deteriorate resulting in worsening of his renal failure (requiring hemodialysis) on Study Day 21 and death on Study Day 45 from multi-organ failure. The Investigator assessed all the subject's SAEs to be unrelated to study drug. The onset of worsening of renal failure approximately 3 weeks after study drug discontinuation (after 2 days of administration) occurred in a setting of acute pulmonary edema, decreased cardiac output, and hypotension, in a subject with multiple comorbidities and renal disease present at baseline, and therefore, is highly unlikely to be related to treatment with ceftaroline.
- Subject 5014-07467 (acute renal failure in the vancomycin plus aztreonam group) was a 23-year-old white male who received vancomycin plus aztreonam for 3 days for the treatment of cellulitis of the arm. The subject had a medical history of hypertension, proteinuria, and microhematuria. The subject underwent debridement and incision and drainage of the underlying skin infection. Baseline creatinine was 1.0 mg/dL. The subject developed back pain on Study Day 2 and acute renal failure on Study Day 3 (creatinine 6.1 mg/dL, CrCl 16.2 mL/min). Additional local laboratory results on Study Day 2 showed creatinine of 5.0 mg/dL. The acute renal failure resolved on Study Day 14. The Investigator assessed the acute renal failure to be related to study drug. However, the nephrology review assessed the event to be unlikely to be related to study drug as the subject had underlying hypertension with an indication of underlying renal disease (proteinuria, hematuria, and back pain), citing also that the acute renal failure could have been a complication of the subject's surgery and the rapid rise in serum creatinine observed from baseline would be unusual for drug-induced nephrotoxicity.

Additionally, in the Phase 2 cSSSI studies, 1 subject, in the vancomycin plus aztreonam group, had a renal SAE of “interstitial nephritis” which was assessed as possibly related to study drug by the Investigator and the blinded nephrology review. No other subject in the Phase 2 cSSSI studies had a PCS renal chemistry value recorded.

- Subject 2002-00001 (interstitial nephritis in the vancomycin plus aztreonam group) was a 54-year-old white female who received vancomycin for 10 days for the treatment of facial cellulitis. The subject had a medical history of diabetes, cellulitis of the right foot, pyelonephritis, and alcohol abuse. On Study Day 10, study drug was discontinued due to an increase in serum creatinine from a baseline value of 1.2 mg/dL to 2.9 mg/dL, with further increase to 4.5 mg/dL on Study Day 12. The subject was discharged from the hospital on Study Day 21 with a serum creatinine value of 1.9 mg/dL. The Investigator assessed the interstitial nephritis as related to study drug.

In summary, none of the renal SAEs recorded in the subjects in the ceftaroline groups in the Phase 3 CABP or cSSSI studies was assessed by the Investigator or by the nephrology review as related to study drug based on the baseline or concurrent comorbidities and the temporal course of clinical events in each case.

In the Phase 3 CABP and cSSSI studies, 4 subjects in the pooled ceftaroline group or pooled comparators group (3 vs 1, respectively) had renal TEAEs that led to discontinuations of study drug or study. The one TEAE representing potential renal impairment and leading to discontinuation of study drug in the pooled comparators group was the SAE of acute renal failure (Subject 5014-07467) discussed above. In the ceftaroline group, the three TEAEs included one SAE mentioned above (Subject 5012-09074) and two TEAEs of increased blood creatinine that were assessed by the Investigator as related to study drug. Of these, only 1 TEAE in the ceftaroline group (Subject 0010-06389 with increased blood creatinine) was assessed as possibly related to study drug by the nephrology review. Detailed summaries of these 2 subjects follow.

- Subject 7008-09290 (increased blood creatinine in the ceftaroline group) was an 80-year-old white male who received 4 days of ceftaroline (400 mg q12h) for the treatment of CABP. The subject had multiple underlying comorbidities with baseline creatinine of 3.9 mg/dL and CrCl of 17.4 mL/min. Study drug was discontinued on Study Day 4 after a TEAE of increased blood creatinine was recorded on Day 3 (creatinine 4.0 mg/dL). The TEAE of increased blood creatinine was considered resolved on Study Day 19 (creatinine 1.9 mg/dL). The Investigator assessed the TEAE of increased serum creatinine to be related to study drug. However, the subject appears to have underlying renal failure prior to starting study drug without any appreciable increase in creatinine while on study drug. Therefore, relationship of the subject’s renal impairment to therapy with ceftaroline appears highly unlikely.



- Subject 0010-06389 (increased blood creatinine in the ceftaroline group) was a 37-year-old Hispanic male who was treated with ceftaroline for 4 days for cellulitis of the leg. The subject had a medical history of hypertension. Study drug was discontinued on Study Day 5 after a TEAE of increased blood creatinine was recorded (creatinine increased to 2.0 mg/dL from 1.5 mg/dL at baseline). The Investigator assessed the modestly increased blood creatinine to be related to study drug. However, the subject was hypertensive and was receiving potentially nephrotoxic concomitant medications (atenolol, captopril, and clonidine). Therefore, causal relationship to ceftaroline is uncertain.

The results of the clinical studies reveal a renal safety profile similar to the profiles of the comparators studied and do not indicate any adverse renal effects beyond those expected for the cephalosporin class.

#### **8.4.2 Hepatic Safety**

Table 8.4.2–1 provides the incidences of subjects in the Phase 3 studies with TEAEs representing potential liver injury.

In the pooled Phase 3 CABP and cSSSI studies, the incidences of subjects in the pooled ceftaroline group and pooled comparators group with TEAEs representing potential liver injury (eg, hepatitis, cytolytic hepatitis, hepatic failure, hepatitis toxic, hepatomegaly, hepatocellular injury, liver disorder, ALT increased, AST increased, gamma-glutamyltransferase increased, hepatic enzyme increased, transaminases increased, liver function test abnormal) were similar (2.5% vs 3.6%, respectively).

The incidence of subjects with TEAEs representing potential liver injury was similar between the pooled Phase 3 CABP studies and pooled Phase 3 cSSSI studies and between treatment groups within each indication.

**Table 8.4.2–1. Incidence of Treatment-Emergent Adverse Events Indicating Potential Liver Injury, Phase 3 Studies—Safety Population**

<b>System Organ Class/ Preferred Term</b>	<b>Pooled CABP Studies (08, 09)</b>		<b>Pooled cSSSI Studies (06, 07)</b>		<b>Pooled Phase 3 Studies (06, 07, 08, 09)</b>	
	<i>Ceftaroline (N = 613) n (%)</i>	<i>Ceftriaxone (N = 615) n (%)</i>	<i>Ceftaroline (N = 692) n (%)</i>	<i>Vancomycin plus Aztreonam (N = 686) n (%)</i>	<i>Ceftaroline (N = 1305) n (%)</i>	<i>Pooled Comparators (N = 1301) n (%)</i>
Subjects with at least 1 TEAE indicating potential liver injury	14 (2.3)	18 (2.9)	19 (2.7)	29 (4.2)	33 (2.5)	47 (3.6)
Hepatobiliary disorders	4 (0.7)	5 (0.8)	2 (0.3)	2 (0.3)	6 (0.5)	7 (0.5)
Hepatitis	2 (0.3)	0	0	0	2 (0.2)	0
Cytolytic hepatitis	1 (0.2)	1 (0.2)	0	1 (0.1)	1 (0.1)	2 (0.2)
Hepatic failure	1 (0.2)	1 (0.2)	0	1 (0.1)	1 (0.1)	2 (0.2)
Hepatitis toxic	0	0	1 (0.1)	0	1 (0.1)	0
Hepatomegaly	0	0	1 (0.1)	0	1 (0.1)	0
Acute hepatic failure	0	1 (0.2)	0	0	0	1 (0.1)
Hepatocellular injury	0	1 (0.2)	0	0	0	1 (0.1)
Liver disorder	0	1 (0.2)	0	0	0	1 (0.1)
Investigations	10 (1.6)	13 (2.1)	17 (2.5)	27 (3.9)	27 (2.1)	40 (3.1)
Alanine aminotransferase increased	5 (0.8)	6 (1.0)	8 (1.2)	12 (1.7)	13 (1.0)	18 (1.4)
Aspartate aminotransferase increased	4 (0.7)	4 (0.7)	7 (1.0)	13 (1.9)	11 (0.8)	17 (1.3)
Gamma-glutamyltransferase increased	5 (0.8)	3 (0.5)	5 (0.7)	4 (0.6)	10 (0.8)	7 (0.5)
Hepatic enzyme increased	2 (0.3)	4 (0.7)	1 (0.1)	6 (0.9)	3 (0.2)	10 (0.8)
Transaminases increased	1 (0.2)	1 (0.2)	2 (0.3)	0	3 (0.2)	1 (0.1)
Liver function test abnormal	1 (0.2)	0	1 (0.1)	4 (0.6)	2 (0.2)	4 (0.3)

Abbreviations: CABP = community-acquired bacterial pneumonia; cSSSI = complicated skin and skin structure infection; TEAE = treatment-emergent adverse event.

Table 8.4.2–2 provides the incidences of subjects in the Phase 3 studies with elevated postbaseline transaminase, total bilirubin, and alkaline phosphatase values.

In the pooled Phase 3 CABP and cSSSI studies, the incidences of subjects with postbaseline alanine transferase values greater than 3, 5, or 10 times upper limit of normal (ULN) in the pooled ceftaroline group and pooled comparators group were similar. The incidences of postbaseline total bilirubin elevations > 1.5 and > 2.0 times ULN and alkaline phosphatase elevations > 2.0 times ULN were infrequent and similar in both the pooled ceftaroline group and pooled comparators group.

No subject in either treatment group met all criteria for Hy's law. One subject in the comparator group (in the Phase 3 CABP studies) met the laboratory criteria but these laboratory abnormalities were attributed to a diagnosis of cholecystitis. The incidences of subjects with PCS hepatic chemistry values were similar in the pooled Phase 3 CABP studies and pooled Phase 3 cSSSI studies.

**Table 8.4.2–2. Potentially Clinically Significant Postbaseline Hepatic Chemistry Values, Phase 3 Studies—Safety Population**

<b>Clinical Laboratory Parameter Criterion</b>	<b>Pooled CABP Studies (08, 09)</b>		<b>Pooled cSSSI Studies (06, 07)</b>		<b>Pooled Phase 3 Studies (06, 07, 08, 09)</b>	
	<i>Ceftaroline (N = 613)</i> <i>n/N1 (%)</i>	<i>Ceftriaxone (N = 615)</i> <i>n/N1 (%)</i>	<i>Ceftaroline (N = 692)</i> <i>n/N1 (%)</i>	<i>Vancomycin plus Aztreonam (N = 686)</i> <i>n/N1 (%)</i>	<i>Ceftaroline (N = 1305)</i> <i>n/N1 (%)</i>	<i>Pooled Comparators (N = 1301)</i> <i>n/N1 (%)</i>
ALT > 3 × ULN	10/430 (2.3)	13/422 (3.1)	4/542 (0.7)	12/527 (2.3)	14/972 (1.4)	25/949 (2.6)
ALT > 5 × ULN	3/430 (0.7)	1/422 (0.2)	3/542 (0.6)	5/527 (0.9)	6/972 (0.6)	6/949 (0.6)
ALT > 10 × ULN	1/430 (0.2)	0/422	0/542	3/527 (0.6)	1/972 (0.1)	3/949 (0.3)
Total bilirubin > 1.5 × ULN	1/507 (0.2)	3/501 (0.6)	1/628 (0.2)	1/619 (0.2)	2/1135 (0.2)	4/1120 (0.4)
Total bilirubin > 2 × ULN	0/507	1/501 (0.2)	1/628 (0.2)	1/619 (0.2)	1/1135 (0.1)	2/1120 (0.2)
ALP > 2 × ULN	3/526 (0.6)	6/518 (1.2)	0/592	2/565 (0.4)	3/1118 (0.3)	8/1083 (0.7)
Potential Hy's Law ALT or AST > 3 × ULN, ALP < 2 × ULN and						
Total bilirubin > 2 × ULN	0/552	1/545 (0.2)	0/656	0/649	0/1208	1/1194 (0.1)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine transferase; AST = aspartate aminotransferase; CABP = community-acquired bacterial pneumonia; cSSSI = complicated skin and skin structure infection; N1 = Number of subjects with at least 1 postbaseline assessment and a normal baseline value (≤ ULN) of the laboratory parameter. ULN = upper limit of normal.

Notes: For potential Hy's Law, ALT, AST, ALP, and total bilirubin do not need to be normal at baseline, but potential Hy's Law laboratory criteria must not be met at baseline.

### 8.4.3 Potential Allergic Reactions (Including Hypersensitivity)

Table 8.4.3–1 provides a summary of the numbers and percentages of subjects in the Phase 3 studies who experienced TEAEs that represented potential allergic reactions.

In the pooled Phase 3 CABP and cSSSI studies, the percentages of subjects with TEAEs representing potential allergic reactions (eg, rash, dermatitis, erythema, urticaria, anaphylactic reaction, angioedema, pruritus) in the pooled ceftaroline group and pooled comparators group were similar. Most of the potential allergic reactions in the pooled ceftaroline group and pooled comparators group were assessed by an Investigator as mild (3.1% vs 5.6%, respectively). The incidences of potential allergic reactions in the pooled ceftaroline group and pooled comparators group assessed as moderate (2.0% vs 2.5%, respectively) or severe (0.2% vs 0.4%, respectively) were low and similar. Similar results were observed for the discrete categories of any rash, any hypersensitivity, and any pruritus, with the incidences of any hypersensitivity and any pruritus being lower in the ceftaroline group.

The incidences of subjects with TEAEs that represented potential allergic reactions were lower in the pooled Phase 3 CABP studies than in the pooled Phase 3 cSSSI studies and were similar between treatment groups within each indication.

**Table 8.4.3–1. Incidence of Treatment-Emergent-Adverse Events by Discrete Category of Rash, Hypersensitivity, or Pruritus, Phase 3 Studies—Safety Population**

<b>Preferred Term</b>	<b>Pooled CABP Studies (08, 09)</b>		<b>Pooled cSSSI Studies (06, 07)</b>		<b>Pooled Phase 3 Studies (06, 07, 08, 09)</b>	
	<i>Cefaroline (N = 613) n (%)</i>	<i>Ceftriaxone (N = 615) n (%)</i>	<i>Cefaroline (N = 692) n (%)</i>	<i>Vancomycin plus Aztreonam (N = 686) n (%)</i>	<i>Cefaroline (N = 1305) n (%)</i>	<i>Pooled Comparators (N = 1301) n (%)</i>
Subjects with at least 1 potential allergic TEAE	9 (1.5)	10 (1.6)	61 (8.8)	101 (14.7)	70 (5.4)	111 (8.5)
Rash, drug eruption, erythema	6 (1.0)	5 (0.8)	31 (4.5)	37 (5.4)	37 (2.8)	42 (3.2)
Hypersensitivity, urticaria, anaphylaxis, possible angioedema	2 (0.3)	4 (0.7)	14 (2.0)	28 (4.1)	16 (1.2)	32 (2.5)
Red man syndrome	0	0	0	3 (0.4)	0	3 (0.2)
Pruritus	1 (0.2)	3 (0.5)	31 (4.5)	65 (9.5)	32 (2.5)	68 (5.2)

Abbreviations: CABP = community-acquired bacterial pneumonia; cSSSI = complicated skin and skin structure infection; TEAE = treatment-emergent adverse event.

Table 8.4.3–2 provides a summary of the percentages of subjects in the Phase 3 studies with severe or serious potential allergic reactions.

In the pooled Phase 3 CABP and cSSSI studies, the incidences of severe or serious potential allergic reactions were low and similar between treatment groups.

**Table 8.4.3–2. Incidence of Severe or Serious Potential Allergic Reactions, Phase 3 Studies—Safety Population**

<i>Preferred Term</i>	<i>Pooled CABP Studies (08, 09)</i>		<i>Pooled cSSSI Studies (06, 07)</i>		<i>Pooled Phase 3 Studies (06, 07, 08, 09)</i>	
	<i>Ceftaroline (N = 613)</i>	<i>Ceftriaxone (N = 615)</i>	<i>Ceftaroline (N = 692)</i>	<i>Vancomycin plus Aztreonam (N = 686)</i>	<i>Ceftaroline (N = 1305)</i>	<i>Pooled Comparators (N = 1301)</i>
Subjects with $\geq 1$ severe <sup>a</sup> or serious potential allergic reaction	0	1 (0.2%)	3 (0.4%)	5 (0.7% )	3 (0.2%)	6 (0.5%)
Any rash	0	0	1 (0.1%)	2 (0.3%)	1 (0.1%)	2 (0.2%)
Erythema	0	0	0	1 (0.1%)	0	1 (0.1%)
Rash	0	0	1 (0.1%)	1 (0.1%)	1 (0.1%)	1 (0.1%)
Any hypersensitivity	0	1 (0.2%)	3 (0.4%)	2 (0.3%)	3 (0.2%)	3 (0.2%)
Anaphylactic shock	0	0	1 (0.1%)	0	1 (0.1%)	0
Anaphylactoid reaction	0	0	1 (0.1%)	0	1 (0.1%)	0
Hypersensitivity	0	1 (0.2%)	1 (0.1%)	2 (0.3%)	1 (0.1%)	3 (0.2%)
Lip swelling	0	0	1 (0.1%)	0	1 (0.1%)	0
Any pruritus	0	0	0	1 (0.1%)	0	1 (0.1%)
Pruritus	0	0	0	1 (0.1%)	0	1 (0.1%)

Abbreviations: CABP = community-acquired bacterial pneumonia; cSSSI = complicated skin and skin structure infection.

<sup>a</sup> Severity as assessed by an Investigator.

Of the 9 subjects summarized in Table 8.4.3–2, 5 subjects had SAEs representing potential allergic reactions, 3 in the pooled ceftaroline group (hypersensitivity, anaphylactoid reaction, and anaphylactic shock) and 2 in the pooled comparators group (both of hypersensitivity). All of the SAEs were assessed by an Investigator as related to study drug. Only 1 subject (who had an SAE of anaphylactic shock) had notable systemic symptoms (ie. facial swelling, cyanosis, and difficulty breathing). This subject received corticosteroid and antihistamine therapy, but did not receive epinephrine. No SAEs representing potential allergic reactions had outcomes of death.

In the pooled Phase 3 CABP and cSSSI studies, 1.1% (15/1305) of subjects in the pooled ceftaroline group and 1.8% (23/1301) of subjects in the pooled comparators group had TEAEs of potential allergic reactions that resulted in premature discontinuation of study drug or withdrawal from study. All of these TEAEs, except for 2 in the vancomycin plus aztreonam group, were assessed by the Investigator as related to study drug.

The incidences of subjects with TEAEs that represented potential allergic reactions leading to premature discontinuation of study drug or withdrawal from study were lower in the pooled Phase 3 CABP studies than in the pooled Phase 3 cSSSI studies.

In summary, the incidences of subjects with potential allergic TEAEs were similar in the ceftaroline and comparator groups. While allergic reactions can occur with any antibiotic, including beta-lactam antibiotics as a class, the risk of allergic reactions to ceftaroline appears to be similar to, or less than, that of comparators studied in the CABP and cSSSI programs.

#### **8.4.4 Direct Coombs Seroconversion**

Coombs testing was performed at baseline, EOT, and TOC. Rates of seroconversion from a negative to a positive direct Coombs test in the pooled Phase 3 CABP and cSSSI studies were higher in the pooled ceftaroline group compared with the pooled comparators group (10.7% vs 4.4%, respectively). Accordingly, all subjects in both treatment groups were analyzed for evidence of hemolytic anemia based on a set of laboratory criteria suggested by an independent expert: a change to a positive direct Coombs test and a decrease in hemoglobin (Hgb) ( $> 1.5$  mg/dL) and either an increase in LDH ( $> 2$  times baseline) or total bilirubin ( $> 3$  times ULN). Two subjects met these laboratory-screening parameters in the ceftaroline group. Neither subject had a clinical presentation consistent with hemolytic anemia and both subjects had alternative etiologies for the abnormal laboratory findings (poorly differentiated neck cancer and an acute aortic dissection).

- Subject 5007-06358 (neck cancer in the ceftaroline group) was a 68 year-old woman with a history of neck cellulitis who received 4 days of ceftaroline fosamil. Her baseline Hgb was 10.7 g/dL and LDH was 1337 U/L. On Study Day 13, she had a positive direct Coombs test, her Hgb was 9.1 g/dL, and her LDH was 1398 U/L. She had a neck biopsy on Day 15 that revealed poorly differentiated cancer. She became hypotensive and died on Day 17.
- Subject 6642-08180 (aortic dissection in the ceftaroline group) was a 63 year-old man with hypertension who received 7 days of ceftaroline fosamil. His baseline Hgb was 13.4 g/dL and LDH was 194 U/L. On Study Day 8, he had chest pains, a weakly positive direct Coombs test, a Hgb of 10.6 g/dL, and an LDH of 486 U/L. On Day 9, an aortic dissection was diagnosed by computed tomography scan and he underwent emergency surgery and recovered on Day 24.

In summary, despite an observed higher incidence of Coombs seroconversion noted in the ceftaroline group, no subject in either treatment group met both laboratory and clinical criteria consistent with a diagnosis of hemolytic anemia.

Additionally, based on the literature, the incidence of direct Coombs test seroconversions after exposure to cephalosporins would be expected to be approximately 3% in subjects exposed to older cephalosporins to as high as 16% in subjects receiving cefepime (Gustaferro and Steckelberg, 1991; Maxipime package insert, 2009).

Table 8.4.4–1 provides the incidences of subjects in the Phase 3 studies with PCS hematology values.

With the exception of direct Coombs seroconversions, discussed above and for which a higher incidence was observed in the pooled ceftaroline group than in the pooled comparators group, the incidences of PCS decreases for hematocrit, Hgb, and RBC count values were low and similar in both treatment groups. The incidences of subjects with PCS hematology values were lower in the pooled Phase 3 CABP studies than in the pooled Phase 3 cSSSI studies. Differences between treatment groups within each indication did not show any consistent trend.

**Table 8.4.4–1. Selected Potentially Clinically Significant Hematology Values, Phase 3 Studies—Safety Population**

<b>Clinical Laboratory Parameter (Unit) PCS Criterion</b>	<b>Pooled CABP Studies (08, 09)</b>		<b>Pooled cSSSI Studies (06, 07)</b>		<b>Pooled Phase 3 Studies (06, 07, 08, 09)</b>	
	<i>Ceftaroline (N = 613) n/N1 (%)</i>	<i>Ceftriaxone (N = 615) n/N1 (%)</i>	<i>Ceftaroline (N = 692) n/N1 (%)</i>	<i>Vancomycin plus Aztreonam (N = 686) n/N1 (%)</i>	<i>Ceftaroline (N = 1305) n/N1 (%)</i>	<i>Pooled Comparators (N = 1301) n/N1 (%)</i>
<b>Hematocrit (%)</b>						
< 0.8 × LLN and decrease from baseline > 20%	4/420 (1.0)	1/411 (0.2)	8/586 (1.4)	16/573 (2.8)	12/1006 (1.2)	17/984 (1.7)
<b>Hemoglobin (g/dL)</b>						
< 0.8 × LLN and decrease from baseline > 20%	4/485 (0.8)	2/482 (0.4)	12/611 (2.0)	19/604 (3.1)	16/1096 (1.5)	21/1086 (1.9)
<b>Red blood cell count (10<sup>6</sup>/uL)</b>						
< 0.6 × LLN and decrease from baseline > 20%	3/485 (0.6)	4/482 (0.8)	12/611 (2.0)	21/603 (3.5)	15/1096 (1.4)	25/1085 (2.3)
<b>Direct antiglobulin (Coombs)</b>						
Positive	51/523 (9.8)	24/537 (4.5)	69/594 (11.6)	25/582 (4.3)	120/1117 (10.7)	49/1119 (4.4)

Abbreviations: CABP = community-acquired bacterial pneumonia; cSSSI = complicated skin and skin structure infection; ; LLN = lower limit of normal; N1 = number of subjects with a baseline and at least 1 post-dose assessment for the parameter, with the exception of direct antiglobulin (Coombs), where subjects must provide both a negative baseline assessment and at least 1 post-dose assessment; PCS = potentially clinically significant.

#### 8.4.5 Seizures

In the pooled Phase 3 CABP and cSSSI studies, 3 AEs (two in the pooled ceftaroline group and 1 in the pooled comparators group) representing seizures (convulsions) were observed. None of these AEs resulted in death or in premature discontinuation of study drug or withdrawal from study.

In the Phase 3 CABP studies, 1 subject in the ceftaroline group and 1 subject in the ceftriaxone group had AEs representing seizures. The subject in the ceftaroline group had a seizure 2 days after EOT and had no central nervous system medical history. The seizure was an SAE and assessed by the Investigator as possibly related to study drug, with an alternative etiology of idiopathic seizures with a possible alternate cause due to an interaction of their concomitant medications, which included a beta-agonist, tamsulosin, and theophylline. The AE of convulsion in the ceftriaxone group was reported as nonserious.

In the Phase 3 cSSSI studies, 1 subject in the ceftaroline group experienced a seizure 23 days after EOT and had a history of cerebral ischemia and syncope. The SAE of seizure was assessed by the Investigator as unrelated to study drug.

In summary, TEAEs representing seizures were rare in subjects administered ceftaroline. Both cases of seizure in the ceftaroline group occurred 2 or more days after completion of ceftaroline therapy and were unlikely to be directly caused by ceftaroline therapy.

#### 8.4.6 *Clostridium difficile*-associated Diarrhea

*Clostridium difficile* testing was not performed on stool samples as a routine protocol safety evaluation; therefore, any testing for *C. difficile* was performed at the discretion of the Investigator. Treatment-emergent adverse events reported as *C. difficile* were rare, occurring in 2 subjects in the ceftaroline group and 1 subject in the comparator group in the pooled Phase 3 cSSSI studies. No additional subject was identified with findings consistent with *C. difficile* based on a review of all subjects with diarrhea including concomitant medical treatment (ie oral vancomycin or metronidazole) and reasons for such treatment. No subjects died and 1 of the cases of *C. difficile* colitis in the ceftaroline group was reported as an SAE.

- Subject 3004-06679 (*C. difficile*-associated diarrhea in the ceftaroline group) was an 81 year-old woman with history of hip abscess associated with a recent hip replacement, hypertension, atrial fibrillation, intracranial trauma, and pulmonary embolism who received 11 days of ceftaroline fosamil and had moderate diarrhea starting on Day 6. On Day 11, she was diagnosed with *C. difficile*-associated diarrhea, which the Investigator considered to be a medically significant event and reported as an SAE, and ceftaroline was discontinued. She was treated with loperamide and metronidazole and recovered on Day 20.



- Subject 6505-06693 (*C. difficile*-associated diarrhea in the ceftaroline group) was a 70 year-old man with history of diabetes mellitus, PVD, diabetic nephropathy, coronary artery disease, hypertension, hypothyroidism, and hepatic steatosis who received 14 days of ceftaroline fosamil and had a nonserious AE of *C. difficile* colitis on Day 19, which was assessed as moderate in severity and recovered to stability.
- Subject 0002-06626 (*C. difficile*-associated diarrhea in the vancomycin plus aztreonam group) was a 66 year-old woman with history of hypertension, asthma, alcohol abuse, urinary tract infection, and constipation who received Bactrim, clindamycin, meropenem, and vancomycin prior to randomization. She received 11 days of vancomycin plus aztreonam and had AEs of mild diarrhea with abdominal pain Days 8-15. A nonserious AE of *C. difficile* colitis was reported on Day 11, which was treated with Flagyl and recovered to stability.

A Phase 1 study (P903-14) was performed to evaluate the effect of ceftaroline on the intestinal microflora in healthy subjects. Twelve healthy subjects (6 male and 6 female subjects), aged 20 to 41 years, inclusive, received ceftaroline 600 mg IV q12h for 7 days. Overall, ceftaroline had little effect on the intestinal microflora with no measurable fecal concentration. With little perturbation of the intestinal microflora, the risk of *C. difficile* infection would be expected (as observed in the Phase 3 studies) to be low and similar to that observed for the cephalosporin class.

#### **8.4.7 Cardiac Effects**

In the pooled Phase 3 studies, there were no imbalances in cardiac SAEs or deaths. The incidences of TEAEs in the Cardiac Disorders system organ class (SOC) were low and similar between the pooled ceftaroline group and the pooled comparators group (5.1% vs 5.1%, respectively) and the majority of events were considered by the Investigator to be unrelated to study drug. Serious adverse events within the Cardiac Disorders SOC were uncommon in both the pooled ceftaroline group and the pooled comparators group (0.8% vs 1.2%, respectively) and all were assessed as unrelated to study drug. Deaths due to SAEs within the Cardiac Disorders SOC were also uncommon in both the pooled ceftaroline group and the pooled comparators group (0.2% vs 0.5%, respectively).

A Clinical Pharmacology three-way crossover thorough QTc trial (Study P903-05) with moxifloxacin as a positive control was performed. Following a single supratherapeutic dose of ceftaroline fosamil (1500 mg), the largest least squares mean QTc difference (from time-matched placebo) was 0.66 msec (95% CI of -2.1 to 3.4) for ceftaroline and 15.70 msec (95% CI to 12.8 to 18.5) for moxifloxacin. The upper bound of the 90% CI of the largest least squares mean difference (between ceftaroline and placebo at each time point) in changes from baseline in QT interval corrected with an individual subject correction formula based on the baseline QT-RR slope (QTcIb) was < 10 msec for all time points. Additionally, assay sensitivity was confirmed since the lower limit of the 90% CI of the largest least squares mean difference between moxifloxacin and time-matched placebo in changes from baseline in QTcIb was > 5 msec for at least 1 time point. In summary, a supratherapeutic dose of ceftaroline did not result in a clinically meaningful increase in the QTcIb, nor were clinically meaningful increases observed in QTcF or QTcB.

A review of the clinical data including the thorough QTc study and Phase 3 ECG data, cardiac TEAEs, cardiac SAEs, and premature discontinuations from study drug or withdrawal from study due to cardiac TEAEs revealed no evidence of cardiac toxicity attributable to the administration of ceftaroline.

## **8.5 CLINICAL LABORATORY TESTS**

Potentially clinically significant renal, hepatic, and hematology parameters are discussed in Section 8.4.1, Section 8.4.2, and Section 8.4.4, respectively.

In the pooled Phase 3 CABP and cSSSI studies, the incidences of nonrenal and nonhepatic PCS chemistry values were low and similar between treatment groups. The most common PCS nonhepatic and nonrenal chemistry finding in the pooled ceftaroline group and pooled comparators group was increased creatine kinase (1.6% vs 1.3%, respectively). No associated TEAEs of muscle cramps, myalgias, myositis, or rhabdomyolysis were observed in either treatment group. The evaluation of the mean chemistry values and shifts over time was similar between treatment groups and revealed no findings showing trends or safety concerns in either group, indicating that ceftaroline has no observable effect on chemistry parameters above that of the comparators studied. Similar results were observed for each pooled indication.

In the pooled Phase 3 CABP and cSSSI studies, the percentages of subjects with PCS elevations in postbaseline coagulation parameter values in the pooled ceftaroline group and pooled comparators group were low and similar for activated partial thromboplastin (1.7% vs 1.9%, respectively), International Normalized Ratio (1.6% vs 1.3%, respectively), and prothrombin time (2.0% vs 1.8%, respectively). The evaluations of the mean coagulation values and shifts over time were similar between treatment groups and revealed no findings showing trends or safety concerns in either group, indicating that ceftaroline has no observable effect on coagulation parameters above that of the comparators studied. Similar results were observed for each pooled indication.

In summary, there were no clinically meaningful differences in mean hematology, coagulation, or chemistry values in the pooled Phase 3 CABP and cSSSI studies, nor within each pooled indication.

## **8.6 VITAL SIGNS**

Blood pressure and pulse rate were similar between treatment groups and generally stable over time. The frequency of shifts to PCS values was low (< 1% in any treatment group) and no notable differences between the ceftaroline and comparator groups were observed.

## **8.7 SAFETY CONCLUSIONS**

The safety profile of ceftaroline was evaluated in a large multinational clinical development program that included 1745 subjects treated with ceftaroline, including 1305 subjects in the Phase 3 CABP and cSSSI studies. The incidences of TEAEs experienced by subjects receiving ceftaroline were similar compared with subjects receiving comparator therapies in the pooled Phase 3 studies and when pooled by indication. No TEAE had an incidence of > 5% in subjects receiving ceftaroline. In the pooled Phase 3 studies, the most common TEAEs in the ceftaroline group were diarrhea, headache, and nausea. The most frequent TEAEs in the pooled comparator group were pruritus, nausea, and diarrhea. Most of the TEAEs were mild or moderate in severity and were assessed as unrelated to study drug administration.

There were 30 deaths in the Phase 3 CABP and cSSSI studies (18 in ceftaroline group and 12 in comparator group). Only 1 death in each treatment group was assessed as possibly related to study drug. The remaining deaths were more likely attributable to underlying comorbidities. Overall, no clinically meaningful difference between the ceftaroline and comparator groups was observed with regard to the incidence or nature of deaths during the Phase 3 CABP and cSSSI studies. Furthermore, the incidences of SAEs and premature discontinuation of study drug or withdrawal from the study due to an AE in ceftaroline-treated subjects were low and similar compared with subjects receiving comparator therapies.

Additional safety analyses (listed below) revealed no clinically significant safety signals.

- **Renal Safety:** All renal safety data were reviewed by the Sponsor and by 2 blinded nephrologists independently and no clinically meaningful imbalance between the treatment groups was identified. The results of the clinical studies reveal a renal safety profile similar to the profiles of the comparators studied and do not indicate any adverse renal effects beyond those expected for the cephalosporin class.

- **Hepatic Safety:** The incidences of subjects in the ceftaroline group and comparator groups with TEAEs representing potential liver injury were similar between treatment groups. In addition, the incidence of subjects with TEAEs representing potential liver injury or with PCS hepatic chemistry values was similar between the pooled Phase 3 CABP studies and pooled Phase 3 cSSSI studies. No subject in either treatment group met all criteria for Hy's law.
- **Potential Allergic Reactions:** The incidences of subjects with potential allergic TEAEs were similar in the ceftaroline and comparator groups. While allergic reactions can occur with any antibiotic, including beta-lactam antibiotics as a class, the risk of allergic reactions to ceftaroline appears to be similar to, or less than, that of comparators studied in the CABP and cSSSI studies.
- **Direct Coombs Seroconversion:** Cephalosporins are known to be associated with positive direct Coombs test results and the rates of seroconversion to a positive direct Coombs test were higher in the pooled ceftaroline group versus the pooled comparators group (10.7% vs 4.4%, respectively). However, this is within the expected range of Coombs seroconversion associated with cephalosporins, and no subject was identified with clinical findings or laboratory results that were consistent with hemolytic anemia.
- **Seizures:** TEAEs representing seizures were rare in subjects administered ceftaroline. Two TEAEs in the pooled ceftaroline group and 1 in the pooled comparators group representing seizures (convulsions) were observed in the pooled Phase 3 studies. None of these AEs resulted in death or premature discontinuation of study drug or withdrawal from study. Both cases of seizure in the ceftaroline group occurred 2 or more days after completion of ceftaroline therapy, and were unlikely to be directly caused by ceftaroline therapy.
- ***Clostridium difficile*-associated Diarrhea:** TEAEs representing *C. difficile*-associated diarrhea were rare, occurring in 2 subjects in the ceftaroline group and 1 subject in the comparator group in the pooled Phase 3 cSSSI studies. No subject died and one of the cases of *C. difficile* colitis in the ceftaroline group was reported as an SAE. In a Phase 1 study that evaluated the effect of ceftaroline on the intestinal microflora in healthy subjects, ceftaroline had little effect on the intestinal microflora and was not measurable in the feces.
- **Cardiac Effects:** A supratherapeutic dose of ceftaroline in the thorough QTc study did not result in a clinically meaningful increase in the QTcIb, QTcF, or QTcB. A review of the clinical data including ECGs, cardiac TEAEs, cardiac SAEs, and premature discontinuations from study drug or withdrawal from study due to cardiac TEAEs in the pooled Phase 3 studies revealed no evidence of cardiac toxicity attributable to the administration of ceftaroline.

In summary, ceftaroline was well tolerated in adults treated for CABP and cSSSI and had a safety profile consistently reflective of the cephalosporin class.

## **9.0 RISK BENEFIT ANALYSIS**

The totality of the preclinical, efficacy, and safety data supports a positive benefit/risk assessment for the use of ceftaroline in the current and future evolving environment of microbial resistance in CABP and cSSSI. Ceftaroline addresses the distinct areas of unmet medical needs (Section 4.3) and has the potential to improve the treatment of CABP and cSSSI, as evidenced by its effectiveness in treatment of CABP and cSSSI. Given the potential for ceftaroline to positively impact the unmet medical need of treating serious cSSSI infections due to resistant pathogens, the FDA designated ceftaroline as a fast-track product on 28 Feb 2006. Monotherapy with ceftaroline is associated with high success rates at EOT and TOC in cSSSI, and may have increased effectiveness compared with ceftriaxone in the treatment of CABP (especially with regard to gram-positive, eg *S. pneumoniae*, CABP). At early time points in both the cSSSI and CABP studies, ceftaroline had higher cure rates than the comparator. In addition, ceftaroline has a safety profile reflective of the cephalosporin class.

### **9.1 MICROBIOLOGICAL BENEFITS**

Ceftaroline is a cephalosporin antibiotic with a broad spectrum of activity including a wide range of gram-positive and gram-negative bacteria including *S. aureus* (MSSA and MRSA), *S. pneumoniae* (including multidrug-resistant strains), *S. pyogenes*, *S. agalactiae*, *S. dysgalactiae*, *S. anginosus* group (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *H. influenzae* (including beta-lactamase producing strains), *H. parainfluenzae*, *K. pneumoniae*, *K. oxytoca*, *M. morganii*, and *E. coli*. Among *S. aureus* strains, ceftaroline is active against both hospital-associated and CA-MRSA, as well as VISA and VRSA (Saravolatz et al, 2010). With regard to respiratory isolates from subjects with CABP, ceftaroline has better in vitro activity than either ceftriaxone or cefepime against either MRSA or PRSP (Morrissey et al. 2009). The unique mechanism of action of ceftaroline, featuring strong affinity for modified PBPs such as PBP2a in MRSA and PBP2x in PRSP, contributes to its potent activity against contemporary resistant gram-positive phenotypes. Its broader spectrum of activity, including bactericidal activity against highly resistant and highly virulent gram-positive organisms, offers clear advantages over other available cephalosporins.

Ceftaroline has a low propensity for resistance development against common cSSSI or CABP pathogens. Specifically, spontaneous resistant mutants were not observed for *S. aureus* or *S. pneumoniae* when plating on media containing 4 times MIC of ceftaroline (spontaneous mutation frequency  $\leq 10^{-10}$ ) or in serial passage studies. No resistance was observed in the Phase 3 CABP or cSSSI studies, except for one incident of decreased susceptibility. In this case, the ceftaroline MIC for *E. cloacae* was 1 µg/mL at baseline and 16 µg/mL at EOT. The baseline *E. cloacae* isolate was a typical AmpC-inducible strain, and it appeared that the EOT *E. cloacae* isolate underwent a regulatory mutation affecting the expression of AmpC beta-lactamase. However, the EOT *E. cloacae* isolate was not completely derepressed for AmpC upon further characterization.

Ceftaroline also exhibits the beneficial property of in vitro synergy with other antibiotics including meropenem against MRSA and an ESBL-producing isolate of *K. pneumoniae* and amikacin against *P. aeruginosa* and an ESBL-producing isolate of *E. coli*. Furthermore, time-kill synergy studies have demonstrated synergy between ceftaroline and aminoglycosides against common resistant gram-negative organisms. Ceftaroline has not demonstrated antagonism with other antimicrobial agents tested in checkerboard and time-kill synergy studies that involved key skin and respiratory pathogens.

Ceftaroline has little to no effect on the fecal microflora with regard to the development of microbial resistance or shifts in bacterial counts. The results of a study in healthy subjects suggested that this limited perturbation of the intestinal microflora may lead to decreased patient susceptibility for *C. difficile*-associated disease. In addition, no new colonizing aerobic or anaerobic bacteria with 4-fold or greater increased MICs to ceftaroline were identified in the fecal microflora.

Finally, the efficacy of ceftaroline against gram-positive and gram-negative bacteria was demonstrated in the mouse lung, thigh, and peritonitis infection models. Ceftaroline was also highly efficacious against MRSA and PRSP in rabbit models of endocarditis and pneumonia, respectively. In all of the aforementioned animal infection models, ceftaroline demonstrated equivalent or superior efficacy relative to the comparator agents.

## **9.2 BIOPHARMACEUTIC BENEFITS**

Ceftaroline is not metabolized by the liver and is not an inhibitor or inducer of major cytochrome P450 enzymes. Clinically relevant drug-drug interactions through hepatic mechanisms are therefore unlikely. Exploratory PK/PD population analyses did not identify any clinically relevant increases in ceftaroline exposure in subjects who received inhibitors, inducers, and substrates of the cytochrome P450 enzyme system. Additionally, in vitro studies have not demonstrated any antagonism between ceftaroline and other commonly used antibacterial agents (eg, vancomycin, linezolid, daptomycin, levofloxacin, azithromycin, amikacin, aztreonam, tigecycline, meropenem).

## **9.3 CLINICAL BENEFITS**

New antibiotics that are safe and highly active against emergent drug-resistant pathogens such as MRSA, MDRSP, and other highly resistant gram-positive bacteria are needed to address the existing unmet medical needs in the management of CABP and cSSSI, given the need for more effective antibiotics due to emerging resistant and virulent pathogens. Ceftaroline is well suited to fill this niche given its unique mechanism of action with high affinity for PBP2a (important in MRSA) and PBP2x (important in PRSP), potent in vitro activity against gram-positive pathogens (including MRSA and MDRSP), gram-negative spectrum of activity, low propensity for spontaneous resistant mutants to develop, and its demonstrated clinical efficacy in CABP and cSSSI (discussed below). Ceftaroline does not have any toxicity beyond that expected for other members of the cephalosporin class.

### 9.3.1 Benefits in Community-acquired Bacterial Pneumonia

Community-acquired pneumonia accounts for over 4 million office visits in the United States, and the hospitalization rate has increased to over 1600 per 100,000 persons over the last decade (File and Marrie, 2010). Approximately 1 million episodes of CAP occur in adults 65 years of age or older each year in the United States (Jackson et al, 2004). Despite advances in antimicrobial therapy, rates of mortality due to CAP have not substantially decreased over the past several decades (Feikin et al, 2000). The rising incidence of drug resistance in *S. pneumoniae*, the most common causative organism in CAP, has led to challenges in the treatment of patients with severe or invasive disease due to this pathogen. In particular, the increasing incidence of drug resistance among *S. pneumoniae* “replacement strains” not covered by the current pneumococcal vaccines is alarming (Moore et al, 2008). The current estimated prevalence of MDRSP among patients with respiratory disease due to *S. pneumoniae*, is 20% (Richter et al, 2009). The same study reported the current prevalence of *S. pneumoniae* with intermediate penicillin resistance to be approximately 18% and with penicillin resistance to be 15%. A report of vancomycin tolerance in *S. pneumoniae* is also worrisome, as vancomycin is considered an antibiotic of last resort for this CAP pathogen (Novak et al, 1999). In addition, *S. aureus*, including MRSA, has emerged as an important pathogen in CAP. Approximately 25% of cases of CAP are due to *S. aureus* and these cases are associated with increased mortality (Kollef et al, 2005). Community-acquired MRSA has been associated with a severe, necrotizing form of CAP with an overall mortality rate of 56% (Gillet et al, 2007). The incidence of severe MRSA CAP appears to be rising, with increasing reports during recent influenza seasons (Centers for Disease Control, 2007, 2009). Community-acquired MRSA was not studied in the CABP studies due to study design requirements. However, ceftaroline has excellent in vitro activity against MRSA and had high response rates against MRSA in the cSSSI studies. Future studies may evaluate the efficacy of ceftaroline against CA-MRSA in subjects with pneumonia.

Increasing antimicrobial resistance to the available antibiotics for CABP poses substantial treatment challenges (eg, the emergence of MDRSP and CA-MRSA as important causes of CABP). Toxicities and substantial treatment-limiting AEs are of additional concern regarding the currently available antibiotic agents for CABP. Another limitation of the approved antibiotics for CABP is that most cannot be utilized as monotherapy for the infection when coverage against MRSA and/or MDRSP is suspected.

Ceftaroline offers a unique advantage over the other available broad spectrum beta-lactam antibiotics indicated for CABP (ie, ampicillin/sulbactam, cefepime, cefotaxime, ceftriaxone, cefuroxime, cefepime, ertapenem, meropenem, piperacillin/tazobactam, and ticarcillin/clavulanate) in that it provides coverage against highly resistant gram-positive organisms such as VISA and VRSA in addition to the common community-acquired gram-positive and gram-negative etiologies of CABP. In contrast, linezolid, a narrow-spectrum agent approved for treatment of CABP, offers no additional coverage against gram-negative pathogens and must be used in combination with other antimicrobials when common gram-negative pathogens such as *H. influenzae* and *K. pneumoniae* are suspected (Zyvox [linezolid] package insert, 2007). It is reported that patients who initially received inappropriate antibiotic selection had early clinical failures and increased mortality compared with patients who received an appropriate antibiotic at the start of therapy (Kollef et al, 1999; Rosón et al, 2004). Ceftaroline has the opportunity to provide appropriate broad spectrum coverage for CABP, especially for cases in which resistant gram-positive pathogens such as MDRSP are suspected.

The efficacy of ceftaroline in the treatment of CABP is summarized in Section 6.0. There is substantial evidence that ceftaroline fosamil administered at a dose of 600 mg (400 mg in subjects with moderate renal impairment) IV q12h for 5 to 7 days is effective in the treatment of CABP caused by susceptible gram-positive and gram-negative pathogens based on the results of the 2 adequate and well controlled, multicenter, randomized, double-blind, active-controlled studies in adult subjects (Study P903-08 and Study P903-09). Each study met the primary objective of showing noninferior clinical cure rates at TOC as compared with ceftriaxone in subjects with CABP using the prespecified noninferiority margin of 10% in the coprimary CE and MITTE Populations.

Specifically, the lower limit of the 95% CI around the treatment difference (ceftaroline – ceftriaxone) was greater than zero in the CE Population and -0.2% in the MITTE Population in Study P903-08. When the two Phase 3 CABP studies were pooled, the lower limit of the 95% CI around the treatment difference (ceftaroline – ceftriaxone) was also greater than zero in both the CE and MITTE Populations. The clinical cure rates at TOC in the combined studies in the ME, mMITTE, and mMITT Populations further support the primary study conclusions of noninferiority of ceftaroline. These data clearly provide evidence of effectiveness of ceftaroline compared to a third-generation cephalosporin, the latter of which is considered one of the antibiotics of first choice for CABP in the United States and worldwide.



In addition, clinical cure rates for subjects with CABP due to gram-positive pathogens were markedly higher in the ceftaroline group compared to ceftriaxone (83.7% vs 64.6%, respectively) and the lower limit of the 95% CI around the weighted treatment difference of +6.0% was in favor of ceftaroline. This treatment difference was driven in large part by the clinical cure rates associated with *S. pneumoniae*, the most frequently isolated pathogen for which the treatment difference was more than 16% in favor of ceftaroline (ceftaroline, 86%; ceftriaxone, 70%) and the lower limit of the 95% CI was greater than zero. Clinical cure rates were also higher in the ceftaroline group than in the ceftriaxone group among subjects infected with MDRSP and among subjects with *S. pneumoniae* bacteremia.

Results of an additional post-hoc exploratory analysis in an FDA-defined population and using an FDA-defined key endpoint of clinical response based on signs and symptoms at Study Day 4 (Section 6.9.1) were consistent with results from the protocol-planned analyses, confirming the robustness of the study results.

### **9.3.2 Benefits in Complicated Skin and Skin Structure Infections**

Severe cSSSI requiring hospitalization or medical attention is increasing in incidence. When cSSSI is complicated by the presence of antimicrobial-resistant pathogens or highly virulent pathogens (eg, CA-MRSA), the choice of appropriate therapy is more challenging and suboptimal clinical outcomes may result. *Staphylococcus aureus* is the most prevalent cause of nosocomial and community-acquired SSSI and bloodstream infections in almost all geographic regions (Diekema et al, 2001; Moet et al, 2007). In the United States, MRSA causes approximately 35% to 72% of SSSIs (Moet et al, 2007; Awad et al, 2007; King et al, 2006). Patients with CA-MRSA cSSSI may have worse outcomes than those with MSSA; this phenomenon may be related to increased virulence of community-acquired strains of MRSA (Davis et al, 2007). Similarly, nosocomial MRSA cSSSIs, such as surgical site infections, tend to be associated with relatively high morbidity and mortality rates (Cosgrove, 2006; Engemann et al, 2003).

Increasing antimicrobial resistance to the available antibiotics for cSSSI poses substantial treatment challenges. In addition, toxicities and substantial treatment-limiting AEs are of additional concern regarding the currently available antibiotic agents for cSSSI. Finally, one of the most striking limitations of the approved antibiotics for cSSSI is that most cannot be utilized as monotherapy for the infection when broad spectrum antimicrobial coverage is required, which includes coverage of gram-positive bacteria (including MRSA) and gram-negative bacteria.

Ceftaroline offers a unique advantage over the available broad spectrum beta-lactam antibiotics for the treatment of cSSSI (ie, cefotaxime, ceftriaxone, ertapenem, meropenem, and piperacillin/tazobactam) in that it provides coverage against highly resistant gram-positive organisms such as CA-MRSA, VISA, and VRSA in addition to community-acquired gram-positive and gram-negative pathogens.

The efficacy of ceftaroline in the treatment of cSSSI is summarized in Section 7.0. There is substantial evidence that ceftaroline fosamil administered as monotherapy at a dose of 600 mg (400 mg in subjects with moderate renal impairment) IV q12h for 5 to 14 days is effective for the treatment of cSSSI caused by susceptible gram-positive and gram-negative pathogens based on the results of the 2 adequate and well controlled, Phase 3, multicenter, randomized, double-blind, active-controlled studies in adult subjects (Study P903-06 and Study P903-07). Each Phase 3 cSSSI study met the primary objective of demonstrating that ceftaroline monotherapy was noninferior to the combination regimen of vancomycin plus aztreonam in clinical cure rates at TOC.

Results of an additional post-hoc sensitivity analysis in an FDA-defined population and using an FDA-defined key endpoint of clinical response based on signs and symptoms at Study Day 3 (Section 7.9.2) were consistent with results from the protocol-planned analyses, confirming the robustness of the study results.

#### **9.4 LIMITATIONS AND RISKS**

The risk of emergence of resistant bacterial strains due to widespread or inappropriate use of ceftaroline (eg, for minor illnesses) is limited by the parenteral route of administration and the fact that subjects receiving ceftaroline for treatment of cSSSI or CABP will likely be in a medical facility and/or under the direct supervision of a healthcare provider. In addition, ceftaroline shows low propensity for resistance development against key pathogens, as was demonstrated in both the spontaneous mutation and serial passage studies mentioned above.

The favorable safety profile of ceftaroline has been well characterized in all clinical studies to date. As summarized in the Overview of Safety (Section 8.0), ceftaroline is well tolerated when used in accordance with the proposed labeling. The pooled Phase 3 CABP and cSSSI studies, the core of the clinical database, consisted of 1305 adult subjects treated with the proposed recommended dose of ceftaroline. The most frequent TEAEs in the ceftaroline group were diarrhea, headache, nausea, and insomnia. These events were generally mild to moderate in severity. No TEAE had an incidence of > 5% in ceftaroline treated subjects in the pooled Phase 3 studies.

Serious and occasionally fatal hypersensitivity reactions and serious skin reactions have been reported in patients receiving antibiotics, including beta-lactams such as cephalosporins. Hypersensitivity and skin reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens. Similarly, *C. difficile*-associated diarrhea has been reported for nearly all antibacterial agents and may range in severity from mild diarrhea to fatal colitis. In the pooled Phase 3 CABP and cSSSI studies, the incidences of TEAEs representing potential allergic reactions (including hypersensitivity) were similar in the ceftaroline (5.4%) and comparator (8.5%) groups and TEAEs of potential anaphylaxis were rare. In addition, diarrhea was observed in the ceftaroline group with a low and similar incidence to comparator (4.6% vs 3.2%, respectively). The majority of the TEAEs of diarrhea were mild with 1 TEAE of diarrhea being considered severe. There were no SAEs of diarrhea and 1 TEAE of diarrhea in each treatment group led to study drug discontinuation. An additional 2 subjects in the pooled ceftaroline group and 1 subject in the pooled comparators group had TEAEs of *C. difficile* colitis (1 in the ceftaroline group was assessed as serious due to prolongation of hospitalization and 1 in each group led to study drug discontinuation). While allergic reactions and antibiotic-associated diarrhea can be associated with any antibiotic, the risk of these events with ceftaroline appears to be similar to that of the comparators studied.

Nephrotoxicity, hepatotoxicity, positive direct Coombs seroconversion (approximately 3% - 16%), and hemolytic anemia have also been reported infrequently in patients receiving beta-lactam antibiotics such as cephalosporins. In the pooled Phase 3 CABP and cSSSI studies, the incidences of subjects in the pooled ceftaroline group and the pooled comparators group with any renal event (2.7% vs 2.5%, respectively), TEAEs representing potential renal impairment (ie, renal failure, renal impairment, blood creatinine increased, CrCl decreased, and glomerular filtration rate decreased) (1.5% vs 0.8%, respectively), or subjects with PCS renal chemistry values for serum creatinine (1.4% vs 1.9%, respectively) or creatinine clearance (0.7% vs 1.3%, respectively) were low and similar. Furthermore, an independent blinded review of the renal events by 2 nephrologists revealed that a relationship to study drug was unlikely for the majority of the observed renal SAEs, TEAEs, PCS increases in creatinine and PCS decreases in CrCl values. The results of the clinical studies reveal a renal safety profile similar to the profiles of the comparators studied and do not indicate any adverse renal effects beyond those expected for the cephalosporin class. The incidences of subjects in the pooled ceftaroline group and the pooled comparators group with TEAEs representing potential liver injury were similar (2.5% vs 3.6%, respectively) and there were no cases of Hy's Law on ceftaroline therapy. Lastly, rates of seroconversion from a negative to a positive direct Coombs test in the pooled Phase 3 CABP and cSSSI studies were higher in the pooled ceftaroline group compared with the pooled comparators group (10.7% vs 4.4%, respectively). However, no cases of hemolytic anemia were identified upon an extensive review of the clinical database.

In summary, the safety results suggest that ceftaroline is well tolerated with a safety profile similar to that observed for the comparator agents studied. In addition, ceftaroline does not appear to have any unusual safety risks beyond those expected for other members of the cephalosporin drug class, such as the known cephalosporin risks of hypersensitivity or *C. difficile*-associated diarrhea.

## 9.5 CONCLUSIONS

A persistent and growing unmet medical need remains for new antibiotics that provide efficacy with a therapeutic advancement compared to the current antibiotic armamentarium. Complicated skin and skin structure infections that require hospitalization or medical attention are increasing in incidence, and, despite advances in medical care and antimicrobial therapy, CABP remains an important cause of mortality and hospitalization in the United States. New antimicrobials with enhanced spectrum of activity are needed for such serious infections, especially given the rising incidence of highly resistant and highly virulent pathogens such as MRSA, VISA, VRSA, and MDRSP. The limited spectrum of activity and toxicity profiles of currently available antibiotics that are indicated for the treatment of CABP and cSSSI contribute to the challenges of treating these infections.

Ceftaroline ameliorates this medical need as evidenced by the microbiological spectrum of activity, and efficacy and safety shown in Phase 3 trials. Specifically, monotherapy with ceftaroline may have increased effectiveness compared with ceftriaxone in the treatment of CABP (especially with regard to gram-positive infections, eg *S. pneumoniae*) at both early and late time points, is associated with high success rates in cSSSI compared with standard combination antibiotic regimens (eg, vancomycin plus aztreonam) at both early and late time points, and is associated with safety characteristics similar to the available cephalosporins for the treatment of CABP and cSSSI.

Microbiologically and pharmacologically, ceftaroline offers many benefits over other available antibiotics. Its broader spectrum of activity and enhanced bactericidal activity against highly resistant and highly virulent gram-positive organisms offer clear advantages over other available cephalosporins. This activity, due to its uniquely strong affinity for specific microbial PBPs (eg, PBP2a and PBP2x), allows for ceftaroline to be administered as a monotherapy for CABP as defined by the FDA, in covering both sensitive and resistant community-acquired typical pathogens. In vitro studies suggest that ceftaroline has a low propensity for resistance development against key pathogens involved in CABP and cSSSI. Ceftaroline is not metabolized by the liver and is not an inhibitor or inducer of major cytochrome P450 enzymes. Clinically relevant drug-drug interactions through hepatic mechanisms are therefore unlikely. Ceftaroline has no known antagonism with other commonly used antibacterial agents and has little to no adverse effect on the fecal microflora.

Clinically, the results of 4 large, multinational, randomized, well controlled pivotal trials demonstrated that ceftaroline is an effective antibiotic for the treatment of CABP and cSSSI. Specifically, when the two Phase 3 CABP studies were pooled the lower limit of the 95% CI around the treatment difference (ceftaroline – ceftriaxone) was greater than zero in both coprimary populations. This finding was driven by large treatment differences between the ceftaroline and ceftriaxone groups among subjects with CABP due to gram-positive cocci, and specifically CABP due to *S. pneumoniae* (for which the treatment difference was more than 16% in favor of ceftaroline). Ceftaroline was also associated with higher cure rates among subjects with bacteremia and subjects with CABP due to MDRSP. High clinical cure rates were observed among subjects infected with *E. coli* and *K. pneumoniae* in both the CABP and cSSSI indications. In the pooled Phase 3 cSSSI studies, ceftaroline monotherapy was noninferior to vancomycin plus aztreonam at an early time point in the treatment course (Study Day 3) in the FDA-defined endpoint of clinical response (cessation of spread and afebrile) and the lower limit of the 95% CI around the treatment difference (ceftaroline-vancomycin plus aztreonam) was greater than zero.

Finally, ceftaroline is well tolerated with a favorable safety profile in subjects diagnosed with CABP and cSSSI. In this large multinational clinical development program, which included 1745 subjects treated with ceftaroline, no adverse reaction had an incidence of > 5% in subjects receiving ceftaroline. The percentages of subjects who experienced 1 or more TEAEs assessed to be possibly or probably related to study drug were similar between treatment groups for each indication.

The totality of the safety and efficacy data supports a positive benefit/risk assessment for the use of ceftaroline in the current and future evolving environment of microbial resistance in CABP and cSSSI. Ceftaroline addresses these distinct areas of unmet medical need and has the potential to improve the treatment of CABP and cSSSI compared with currently available products, as evidenced by its effectiveness in treatment of CABP and cSSSI.

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**11.0**            **APPENDICES**

**11.1**            **SELECTION OF NONINFERIORITY MARGINS FOR  
COMMUNITY-ACQUIRED BACTERIAL PNEUMONIA STUDIES**

**1.0**

**TITLE PAGE**



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**Selection of Noninferiority Margins for Treatment of Study Subjects with  
Community-acquired Bacterial Pneumonia**

**Ceftaroline fosamil for Injection**

## **TABLE OF CONTENTS**

1.0	TITLE PAGE .....	1
2.0	History of the Noninferiority margin Determination for the Ceftriaxone Phase 3 Community-acquired Bacterial Pneumonia Studies .....	4
2.1	Method for Selecting the Noninferiority Margin .....	4
2.1.1	Estimate of the Effect Size for Subjects with Predominantly Bacterial Community-acquired Pneumonia .....	5
2.1.2	Estimate of the Effect Size for Subjects with Predominantly Community-acquired Pneumonia of Unspecified Microbial Etiology .....	7
2.1.3	Estimation of Smallest Effect Size for a Population With Bacterial and Predominantly Community-acquired Pneumonia of Unspecified Microbial Etiology and Supported Noninferiority Margin .....	7
2.2	Choice of Comparator in Ceftriaxone Trials for the Indication of Community-acquired Pneumonia .....	10
2.3	Assay Sensitivity .....	11
2.4	Evaluation of constancy assumption .....	13
2.5	Conclusions .....	18
3.0	References .....	19

## **LIST OF IN-TEXT TABLES**

Table 2.1.1–1.	Historical Studies Demonstrating Antibiotic-Mediated Reduction in Mortality Among Subjects With Bacterial Community-acquired Pneumonia Predominantly Due to <i>Streptococcus pneumoniae</i> .....	6
Table 2.1.2–1.	Historical Studies Demonstrating Antibiotic-mediated Reduction in Mortality Among Subjects With Predominantly Community-acquired Pneumonia of Unspecified Microbial Etiology .....	7
Table 2.2–1.	Clinical Cure Rates Associated With Daptomycin Versus Ceftriaxone for Community-acquired Pneumonia .....	10
Table 2.4–1.	Clinical Cure Rates Associated With Ceftriaxone From Published Community-acquired Pneumonia Studies .....	14
Table 2.4–2.	Clinical Cure Rates at Test of Cure, Study P903-08 .....	14
Table 2.4–3.	Clinical Cure Rates at Test of Cure, Study P903-09 .....	15
Table 2.4–4.	Clinical Cure Rates at Test of Cure by Pneumonia Outcomes Research Team Risk Class—CE Population .....	16
Table 2.4–5.	Clinical Cure Rates at Test of Cure in the Phase 3 Trials—mMITTE, ME, and mMITT Populations .....	18

**LIST OF ABBREVIATIONS**

CABP	community-acquired bacterial pneumonia
CAP	community-acquired pneumonia
CE	Clinically Evaluable
EOT	end of therapy
FDA	Food and Drug Administration
LFU	Late Follow-up
IDSA	Infectious Diseases Society of America
ITT	Intent-to-Treat
IV	intravenous
MITT	Modified Intent-to-Treat
MITTE	Modified Intent-to-Treat Efficacy
mMITT	microbiological Modified Intent-to-Treat
mMITTE	microbiological Modified Intent-to-Treat Efficacy
PORT	Pneumonia Outcomes Research Team
SPA	Special Protocol Assessment
TOC	Test-of-Cure
US	United States



## **2.0** **HISTORY OF THE NONINFERIORITY MARGIN** **DETERMINATION FOR THE CEFTAROLINE PHASE 3** **COMMUNITY-ACQUIRED BACTERIAL PNEUMONIA STUDIES**

In the Phase 3 community-acquired bacterial pneumonia (CABP) Studies (P903-08 and P903-09) of intravenous (IV) ceftaroline fosamil compared to IV ceftriaxone in the treatment of CABP, a noninferiority margin of 10% was prespecified for analysis of the primary outcome measure of clinical response in the coprimary populations (ie, the microbiological Modified Intent-to-Treat Efficacy [mMITTE] and the Clinically Evaluable [CE] Populations).

The prespecified noninferiority margin of 10% was presented in the Special Protocol Assessment (SPA; 2007) for Studies P903-08 and P903-09. On March 15, 2007, in a response to the SPA, the US FDA stated that further discussion regarding the noninferiority design of the Phase 3 CABP studies was necessary in order to determine whether the studies would fulfill the requirements to support an indication for CABP. The first subject was enrolled in Study P903-09 on July 4, 2007. On September 11, 2007, the US FDA acknowledged and accepted the use of a noninferiority margin of 10% in evaluating clinical efficacy in subjects with moderate to severe CABP as defined by Pneumonia Outcomes Research Team (PORT) Risk Class of III or more. As a result, on October 12, 2007 the protocol for Study P903-09 was amended to exclude subjects in PORT Risk Class II, and include only subjects in PORT Risk Class III or IV. The protocol for Study P903-08 was similarly amended on November 13, 2007. The prespecified noninferiority margin of 10% was acknowledged and accepted by the US FDA in comments to the P903-08 and P903-09 Statistical Analysis Plan dated January 8, 2009.

In this document the justification of the prespecified noninferiority margin is updated to include relevant information in the public domain as it pertains to the historical effect of the drug on the study endpoints, and the applicability to the populations that were assessed for noninferiority in Study P903-08 (2009) and Study P903-09 (2009).

### **2.1** **METHOD FOR SELECTING THE NONINFERIORITY MARGIN**

The International Conference on Harmonisation (ICH) E10 guidance (2000) stipulates that, "In practice, the noninferiority margin chosen usually will be smaller than that suggested by the smallest expected effect size of the active control because of interest in ensuring that some clinically acceptable effect size (or fraction of the control drug effect) was maintained".

Ideally, estimates of the treatment effect size are obtained from placebo-controlled studies for the comparator arm. However, for anti-infective drugs in the treatment of serious infections such as CABP, such studies are generally not available and considered unethical for moderate to severe disease. In fact, the historical medical literature on antibiotic treatment of CABP (cited below) indicates that, in the absence of effective antimicrobial therapy, a majority of moderate-to-severe community-acquired pneumonia (CAP) cases would result in unfavorable patient outcomes, including death, overwhelming systemic infection and sepsis, prolonged recovery, and pulmonary complications (eg, bronchiectasis, chronic empyema).

Therefore, to show that the prespecified margin for the ceftaroline Phase 3 CABP studies meets the requirements of ICH E10 (2000), we proceeded heuristically as follows:

1. Point estimates, variability, and 95% corresponding CI of the effect size of antibiotics versus no treatment among subjects with CAP of bacterial etiology, predominantly due to *Streptococcus pneumoniae*, were obtained using available historical data. These consisted of literature on historical controlled studies for subjects with confirmed CABP.
2. Point estimates, variability, and 95% corresponding CI of the effect size of antibiotics versus no treatment among subjects with CAP of predominantly unspecified etiology were obtained using available historical data. These consisted of literature on concurrent controlled studies for subjects with predominantly lobar CAP for whom specific microbiological etiology was not determined.
3. The point estimates and estimates of variation in the preceding Steps 1 and 2 were then used to obtain the “smallest effect size that the active drug would be expected to have” (ICH E10, 2000) using the relationship:  $0.30 \times [\text{effect size in CABP}] + 0.70 \times [\text{effect size in CAP of unspecified etiology}]$ , where the weights of 0.30 and 0.70 correspond to the relative frequency in the coprimary populations of the ceftaroline Phase 3 CABP trials of subjects with CABP of proven bacterial etiology and CAP of unspecified etiology, respectively.
4. Comparison of the value obtained in Step 3 to the prespecified noninferiority margin of 10% is used to show conformance to ICH E10 (2000).
5. Lastly, the historical evidence was also examined to show that the prespecified margin also preserves a significant fraction of the effect size.

### **2.1.1 Estimate of the Effect Size for Subjects with Predominantly Bacterial Community-acquired Pneumonia**

Convincing evidence exists for an effect of antibiotics in reducing both mortality and morbidity due to CAP.

Based in part on a jointly-sponsored Infectious Diseases Society of America (IDSA) and US FDA workshop on the appropriate design of clinical trials of antibiotics for the treatment of CAP (January 17-18, 2008), the IDSA conducted a systematic literature review on the treatment of CABP in the pre-antibiotic era (1920s -1940s) (Spellberg et al., 2008). A total of six studies were identified that compared antibiotic treatment with no treatment for CAP in patients with a confirmed microbial etiology. These six “historical control” studies compared the outcomes for subjects given antibiotics with the outcomes of historical untreated control subjects before the availability of antibiotics (Table 2.1.1–1). Most of the subjects in these studies had CAP due to *S. pneumoniae*. In the historical control studies, the weighted average mortality rate was 38% without antibiotic treatment and 12% with antibiotic treatment, indicating a 26% (95% CI, 24% - 28%) absolute reduction in mortality with antibiotic therapy.

**Table 2.1.1–1. Historical Studies Demonstrating Antibiotic-Mediated Reduction in Mortality Among Subjects With Bacterial Community-acquired Pneumonia Predominantly Due to *Streptococcus pneumoniae***

<i>Study</i>	<i>Mortality</i>		
	<i>No Treatment N (%)</i>	<i>Antibiotic Treatment N (%)</i>	<i>Absolute Mortality Reduction<sup>a</sup> %, (95% CI)</i>
<b>Historical control studies</b>			
Finland and Tilghman, 1936	1161/2832 (41)	207/1220 (17)	
Dowling and Lepper, 1951	331/1087 (31)	47/920 (5)	
Austrian and Gold, 1964	405/480 (84)	90/527 (17)	
Heinzelman, et al., 1937	8/10 (80)	2/9 (22)	
Anderson and Cairns, 1940	86/462 (19)	26/217 (12)	
Gaisford, 1939	193/876 (22)	26/400 (7)	
<b>Total (weighted average)</b>	<b>2184/5747 (38)</b>	<b>398/3293 (12)</b>	<b>26 (24 - 28)</b>

Note: Reproduced from Spellberg et al. (2008).

- a The reduction in mortality is summarized as the difference between the group receiving antibiotics and the group not receiving antibiotics, weighted by the numbers of patients. The 95% CIs were calculated using a standard linear combination variance formula technique, which allows for inclusion of one-arm studies and nonrandomized two-arm studies, which is not possible with meta-analytic techniques.

The data in Table 2.1.1–1 clearly indicate a reduction in mortality as a result of antibiotic treatment of CABP. In the pre-antibiotic era, there were greatly higher mortality rates among subjects with CABP, regardless of disease severity or age, and an immediate decline in mortality due to CAP was observed within 1 year after the introduction of sulfa antibiotics for the treatment of CAP. Without exception, lower mortality rates were associated with antibiotics versus no antibiotic therapy in every historical clinical study of CAP.

### 2.1.2 Estimate of the Effect Size for Subjects with Predominantly Community-acquired Pneumonia of Unspecified Microbial Etiology

The IDSA (2008) also reported the results of five “concurrent control” studies, which compared the outcomes for subjects with predominantly CAP of unspecified microbial etiology given antibiotics with the outcomes of concurrent control subjects given no specific antibiotic therapy (Spellberg et al., 2008) (Table 2.1.2–1).

In these studies, the weighted average mortality rate was 23% without antibiotic treatment and 7% with antibiotic treatment, indicating a 16% (95% CI, 10% - 22%) absolute reduction in mortality with antibiotic therapy.

**Table 2.1.2–1. Historical Studies Demonstrating Antibiotic-mediated Reduction in Mortality Among Subjects With Predominantly Community-acquired Pneumonia of Unspecified Microbial Etiology**

<i>Study</i>	<i>Mortality</i>		
	<i>No Treatment</i>	<i>Antibiotic Treatment</i>	<i>Absolute Mortality Reduction<sup>a</sup> %, (95% CI)</i>
Concurrent control studies			
Evans and Gaisford, 1938	27/100 (27)	8/100 (8)	
Graham, et al, 1939	7/30 (23)	4/80 (5)	
Agranat, et al (Population 1), 1939	16/86 (19)	6/71 (8)	
Agranat, et al (Population 2), 1939	6/27 (22)	2/27 (7)	
Ormiston, et al., 1942	2/11 (18)	1/30 (3)	
Total (weighted average)	58/254 (23)	21/308 (7)	16 (10-22)

Note: Reproduced from Spellberg et al. (2008).

### 2.1.3 Estimation of Smallest Effect Size for a Population With Bacterial and Predominantly Community-acquired Pneumonia of Unspecified Microbial Etiology and Supported Noninferiority Margin

The coprimary populations in the ceftriaxone trials included subjects with confirmed CABP (approximately 30% of subjects) and subjects with CAP without confirmed typical bacterial etiology (approximately 70% of subjects). Using the approach described above, the point estimate of the effect size is obtained from the weighted average of the individual point estimates in Table 2.1.1–1 and Table 2.1.2–1. This is given by  $0.30 \times 0.26 + 0.70 \times 0.16 = 0.189$  or 18.9%. The corresponding variance of this estimate is  $0.30^2 \times 0.000007 + 0.70^2 \times 0.000899 = 0.00045$ . The standard error is equal to the square root of this value or 0.0212. The minimum effect size is given by the corresponding lower limit of the resulting CI for the weighted estimate of 0.148 ( $= 0.189 - 1.96 \times 0.0212$ ) or 14.8%. Since the preplanned noninferiority margin of 10% is below this value, the criterion defined in the ICH E10 (2000) is satisfied.

The ICH E10 guidance (2000) also stipulates that “In practice, the noninferiority margin chosen usually will be smaller than that suggested by the smallest expected effect size of the active control because of interest in ensuring that some clinically acceptable effect size (or fraction of the control drug effect) was maintained.” The prespecified margin in the ceftaroline trials also meets this criterion. This can be noted not only because its magnitude is smaller than the estimated minimum effect size, but also by further consideration of the subject population enrolled in the ceftaroline trials which consisted of subjects with PORT Risk Class III or IV. As the PORT score is predominantly based on age, a majority of subjects in PORT Risk Classes III and IV would be expected to be of at least 50 years of age (Fine et al., 1997). Indeed, approximately 80% of subjects were older than 50 years of age in the ceftaroline Phase 3 CABP trials.

The IDSA (2008) stratified historical mortality data by age and severity, in order to provide point estimates of efficacy to be used in justifying noninferiority margins in CABP studies (Tilghman and Finland, 1937; Bullowa, 1937; Heinztelman, et al., 1937; Evans and Gaisford, 1938; Dowling and Lepper, 1951). In general, the absolute reduction in mortality associated with antibiotic treatment increased as either disease severity or age increased. Among the historical studies analyzed by the IDSA (2008), the weighted average mortality reduction was 11% (95% CI, 8% - 13%) among subjects with “good” baseline status or age under 30 years, 27% (95% CI, 25% - 30%) among subjects with “fair” status or age of 30 through 59 years, and 45% (95% CI, 39% - 54%) among subjects with “poor” status or age greater than or equal to 60 years. The baseline status of the severity of illness was correlated with the PORT severity score that is used in contemporary studies (Fine et al., 1997). Good baseline status was deemed equivalent to PORT Risk Classes II and III, fair status to PORT Risk Classes III and IV, and poor status to PORT Risk Classes IV and V (Spellberg et al., 2008). The concurrent control study by Evans and Gaisford (1938) cited above provides an example that is relevant to the ceftaroline Phase 3 studies, as this historical trial included subjects with lobar CAP, whether the etiological pathogen was *S. pneumoniae* (22% of cases) or not (78% of cases) (Evans and Gaisford, 1938). The sulfa antibiotic therapy used in this study led to a 16% reduction in mortality among subjects less than 30 years old, a 21% reduction among subjects aged 30 through 59 years, and a 55% reduction among subjects greater than or equal to 60 years old.

These data suggest that the noninferiority margin used in the population included in the ceftaroline trials would preserve a significant fraction (> 50%) of the effect size given the larger effect size noted above among older subjects with CAP and the characteristics of the subjects enrolled in the ceftaroline studies (eg, subjects with moderate to severe disease requiring hospitalization and IV antibiotic therapy).

It should be noted that the estimated effect size obtained above is most likely an underestimate of the true effect size due to limitations of the historical data based on a mortality endpoint. For example, the studies for subjects with lobar pneumonia largely included a younger population treated with suboptimal doses of oral sulfonamides. Nevertheless, this approach still shows that a significant fraction of the effect size is maintained in the population of older subjects who are more likely to have a PORT Risk Class of III or IV.

The primary endpoint of interest in the ceftaroline trials is the cure rate at Test-of-Cure (TOC). The cure rate is a composite endpoint of clinical signs and symptoms and mortality. The evidence of the efficacy of ceftriaxone versus a putative placebo treatment and the corresponding effect size on the cure rates are inferred from the historical controlled studies of antibiotics discussed above using a mortality endpoint. Antibiotic clinical trials have demonstrated significantly shorter times to resolution of signs and symptoms of CAP than those observed in the pre-antibiotic era. Multiple studies have shown a shorter time to defervescence associated with antibiotics (Flippin 1939; Raycraft 1941; Agranat 1939). Clinical improvement, using a composite endpoint of resolution of fever, chest pain, and cough, among symptoms, also occurs faster with antibiotic therapy (Petersdorf 1967). Multiple placebo-controlled studies involving military recruits with mild CAP have revealed significantly shorter times to defervescence and clinical response rates among subjects receiving either macrolide or tetracycline therapy than for those receiving placebo (Kingston 1961; Smilack 1974; Shames 1970; Rasch 1965; Gooch and Mogabgab, 1970). Finally, contemporary antibiotic trials utilizing active comparators have demonstrated superiority with regard to time to resolution of signs and symptoms of CAP of any severity (ie, PORT Risk Classes I - IV) (Welte et al., 2005; Dunbar et al., 2003). Specifically, Welte and colleagues (2005) showed that moxifloxacin therapy was equivalent to ceftriaxone +/- erythromycin therapy in subjects with hospitalized CAP with respect to clinical cure; however, moxifloxacin was associated with faster resolution of fever and clinical signs and symptoms (Welte et al., 2005). Dunbar and colleagues (2003) showed that a short 5-day course of levofloxacin 750 mg qd was equivalent to 500 mg qd for 10 days with respect to clinical success; however, subjects randomized to the short course of high-dose levofloxacin were more likely to defervesce by Study Day 3 (Dunbar et al., 2003). This finding may have been related to the higher peak plasma concentrations of levofloxacin achieved with the higher dose. Among all clinical trial data assessed by the IDSA (2008), the antibiotic treatment effect for time to defervescence or clinical improvement at 72 hours after initiation of antibiotic therapy ranged from 35% to 95%, depending on disease severity and etiological agent (Spellberg et al., 2008). These data suggest that a strong correlation exists between antibiotic exposure and clinical cure rates. Therefore, an antibiotic effect on this composite endpoint is expected to be at least as large as an antibiotic effect based on mortality data only.

## 2.2 CHOICE OF COMPARATOR IN CEFTAROLINE TRIALS FOR THE INDICATION OF COMMUNITY-ACQUIRED PNEUMONIA

Ceftriaxone was chosen as the active comparator agent best suited for the Phase 3 CABP studies because it is an approved and globally accepted therapy for the treatment of CABP. Recent CABP studies investigating daptomycin (Pertel et al, 2008), ertapenem (Ortiz-Ruiz et al, 2004; Vetter et al., 2002), ceftobiprole (Nicholson et al, 2008), amoxicillin-clavulanate (Rosón et al, 2001), gemifloxacin (Lode et al, 2002), and clinafloxacin (Petermann et al, 2001) used ceftriaxone as an active comparator and were generally of similar design (eg, global, randomized, often double-blinded studies and typically using a noninferiority design), with similar duration of therapy and timing of clinical assessments. The predictability, reproducibility, and consistency of efficacy results for ceftriaxone, as well as its global therapeutic acceptance for the treatment of CABP caused by gram-positive pathogens (Mandell et al, 2007), further support the sensitivity-to-drug effect requirement for an active control agent used in a noninferiority study. Finally, the dose and dosing regimen of ceftriaxone chosen for the ceftaroline Phase 3 CABP studies ensured an adequate comparison with the investigational agent. The dosage regimen for ceftriaxone in both Phase 3 CABP studies was 1 g q24 hours, consistent with the approved label recommendations for use in adults. Given the global nature of these trials, and the acceptance and availability of ceftriaxone, it was considered a suitable comparator.

Ceftriaxone was first approved by the US FDA in 1985. Clinical studies involving ceftriaxone that were conducted in the 1980s enrolled subjects with lower respiratory infection of varying types and disease severity, with relatively small numbers of subjects with each infection type enrolled into any given clinical study, and were open-label in design.

Table 2.2–1 presents data from two Phase 3 randomized, double-blind, active-controlled studies of IV daptomycin vs IV ceftriaxone. These data provide evidence for a treatment effect of ceftriaxone in the indication of CAP that is directly relevant to the ceftaroline Phase 3 CABP studies, and specifically to the choice of coprimary populations. The daptomycin studies included CAP due to various bacterial etiologies, including non-*S. pneumoniae* pathogens (Pertel et al, 2008). Of the 834 subjects in the Intent-to-Treat (ITT) Population, only 24% had microbiological confirmation of *S. pneumoniae* as the etiological agent. The enrollment of subjects into the second Phase 3 study was terminated after it was discovered that daptomycin was inactivated by pulmonary surfactant, resulting in loss of activity in lung tissue (Silverman et al, 2005).

**Table 2.2–1. Clinical Cure Rates Associated With Daptomycin Versus Ceftriaxone for Community-acquired Pneumonia**

<i>Population</i>	<i>Daptomycin</i>	<i>Ceftriaxone</i>	<i>95% CI</i>	<i>p-value<sup>a</sup></i>
ITT Population	293/413 (70.9)	326/421 (77.4)	-12.4%, -0.6%	.0322
CE	293/369 (79.4)	326/371 (87.9)	-13.8, -3.2%	.0018

Abbreviations: CE = clinically evaluable; ITT = intent-to-treat.

<sup>a</sup> Two sided p-values not included in original publication. These have been added by the Sponsor.

In these trials, ceftriaxone was associated with statistically significantly higher cure rates compared with daptomycin in both the ITT and CE Populations. In these populations, subjects with CAP were diagnosed using clinical and radiographic criteria and represented a range of disease severity (PORT Risk Classes II - IV) and a variety of etiological pathogens. Nevertheless, standard therapy with ceftriaxone was superior to a drug partially deactivated by pulmonary surfactant. As the benefit of a partially inactivated drug should still be greater than a placebo, it follows that even greater benefit would be measured for ceftriaxone in a placebo-controlled trial. Therefore, these trials provide evidence of an antibiotic effect for ceftriaxone whether or not a bacterial etiology of disease is confirmed among subjects who have otherwise met clinical and radiographic diagnostic criteria for CAP. These results therefore support the choice of ceftriaxone as an efficacious drug for the treatment of CAP in the coprimary populations in the ceftaroline trials.

### **2.3 ASSAY SENSITIVITY**

Assay sensitivity (or the ability of a study to detect clinically important differences between treatment groups, if they exist) is of particular importance in noninferiority trials lacking a concurrent placebo treatment group.

Study design and conduct are critical factors in ensuring that a noninferiority study attains accurate results without false-positive conclusions. Important elements include choice of the control regimen, definition of eligible subjects, permissible concomitant treatments, outcome measures, and timing of assessments. Of particular importance is the rigor of study conduct since a poorly-conducted study will bias the conclusion towards the noninferiority hypothesis.

The design of the ceftaroline Phase 3 CABP studies, including the choice of the comparator regimen and selection of the noninferiority margin, was generally comparable to, or more conservative than, most contemporary CABP studies (see Section 5 for relevant contemporary trials). Ceftriaxone was chosen as the active comparator agent for the ceftaroline Phase 3 CABP studies because of its effectiveness in treating CABP and its global acceptance in clinical practice. Recent CABP studies that involved ceftriaxone as the active comparator were of similar construct (eg, noninferiority design, duration of therapy, and timing of clinical assessments). Finally, the dosing regimen of ceftriaxone in the ceftaroline Phase 3 CABP studies ensures a fair comparison with the investigational agent.



Patient selection criteria were defined rigorously in the ceftaroline Phase 3 CABP protocols. The protocols were designed to ensure that subjects were enrolled only with radiographically-confirmed CABP and disease of sufficient severity (ie, moderate-to-severe disease in PORT Risk Class III or IV) to warrant hospitalization in a general medical ward and administration of IV antimicrobial therapy. Subjects with mild CABP (ie, PORT Risk Class I or II) were excluded, as were subjects who did not require hospitalization or oral antibiotic therapy in an outpatient setting; no oral switch therapy was allowed in either Phase 3 CABP study. Severe CABP that required intensive care management at baseline and subjects in PORT Risk Class V were excluded, as most of these subjects would require combination antimicrobial therapy (eg,  $\beta$ -lactam plus a fluoroquinolone) per local standards of care. Based on the CABP disease definitions and severity criteria, the subjects enrolled in the Phase 3 CABP studies had moderate-to-severe disease that required IV antimicrobial therapy and hospitalization for appropriate care and prevention of morbidity and mortality.

In accordance with the previous US FDA Guidance for Industry for CABP (US FDA, 1998), the ceftaroline Phase 3 CABP studies did *not* exclude subjects without cough or production of sputum, nor did they exclude subjects without a pre-enrollment or pretreatment bacterial etiology for disease. Within a population of subjects with CAP requiring hospitalization, a minority of subjects (approximately 30%) would be expected to have a confirmed microbiological etiology using standard diagnostic methods. In fact, among all subjects with CAP, blood and sputum cultures collected at the time of CAP presentation are usually negative; pretreatment blood cultures yield a pathogen in only 5% to 14% of hospitalized patients with CAP (Mandell et al, 2007). In addition, among the subset of CABP patients with productive sputum, an adequate Gram's stain with a predominant bacterial morphotype is observed in only 14% of hospitalized patients with CAP. Subjects without microbiological confirmation of disease using conventional tests (eg, blood and sputum cultures and serological tests) comprise up to 50% of subjects diagnosed with CAP (File, 2003).

Subjects with suspected or confirmed nontypical bacterial CAP were excluded from the ceftaroline Phase 3 CABP studies, such as atypical bacterial pneumonia (eg, due to *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, or *Legionella* spp.), mycobacterial pneumonia (eg, tuberculosis), or nonbacterial CAP (eg, viral or fungal pneumonia). Although nontypical bacterial CAP cannot be distinguished reliably from typical bacterial CABP based on clinical presentation or radiographic findings alone, the likelihood of these etiologies can be estimated based on clinical characteristics (eg, the presence of upper respiratory tract signs and symptoms or extrapulmonary findings), radiographic abnormalities, seasonality, and case clustering in outbreak scenarios (Falsey 2007, Cunha 2008). However, the possibility of enrollment of nontypical bacterial etiologies among subjects included in clinical trials cannot be eliminated with certainty.

Neither prior nor concomitant potentially-effective antibacterial therapies were permitted during the studies. However, a single dose of a single short-acting antibiotic for the treatment of CABP was permissible within 96 hours before the first dose of study drug to allow for rapid administration of antimicrobial therapy in cases where enrollment into the Phase 3 studies was delayed by several hours. Subjects were permitted to take any necessary nonantimicrobial medications, with the exception of probenecid, which has the potential to alter the plasma and tissue exposure of ceftaroline.

Outcome measures typically used in assessment of CABP in clinical trials of new antimicrobial therapies were employed in the ceftaroline Phase 3 CABP studies. For example, the primary outcome measure was clinical cure at TOC and secondary outcome measures included microbiological assessment at TOC and clinical and microbiological assessments at End of Therapy (EOT) and Late Follow-up (LFU). The timing of these assessments was consistent with regulatory guidance and standard practice in clinical trials of investigational antimicrobial agents. Specifically, TOC was timed such that the study drugs were no longer present in plasma or tissue and that complete spontaneous resolution of CABP would likely not have occurred in the absence of effective intervention.

In summary, the ceftaroline Phase 3 CABP studies were developed in accordance with guidance documents from regulatory agencies (US FDA, 1998) and professional societies and in accordance with GCP requirements. Introduction of potential bias was minimized by the use of a double-blind, randomized design. Rigorous study conduct was ensured throughout the studies and included pre-enrollment due diligence to assess site quality, strict site selection procedures, and close monitoring of sites during and after active enrollment to ensure excellent protocol adherence.

## **2.4 EVALUATION OF CONSTANCY ASSUMPTION**

As previously mentioned, the effect size of ceftriaxone is inferred from the historical studies discussed in this appendix. That is, the effect size provides an estimate of the difference in cure rate between ceftriaxone and a putative placebo arm.

To evaluate the constancy of the effect of ceftriaxone in the ceftaroline Phase 3 trials, Cerexa conducted a search of the published medical literature in order to identify the highest quality studies whose design was consistent with that of the ceftaroline fosamil Phase 3 CABP studies. The objective of this search was to estimate the cure rates for ceftriaxone observed in contemporary trials and to assess how they compared to those observed in the ceftaroline trials.

The National Center for Biotechnology Information at the US National Library of Medicine was used as the search database. Search terms included: “natural history and community-acquired pneumonia,” “community-acquired pneumonia and placebo,” “community-acquired pneumonia and antibiotic,” and “lower respiratory infection and ceftriaxone” (search limits included: English, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, and Review). Publications excluded from analysis included those in which ceftriaxone was used in combination with other antimicrobial agents, including oral switch studies; studies in which atypical pathogens were allowed; publications evaluating health outcomes such as duration of hospital stay and cost effectiveness; studies with very few subjects (< 100); and pediatric studies.

Three similarly-designed studies were identified that compared ceftriaxone 1 g q24h with either ertapenem (Ortiz-Ruiz et al., 2004; Vetter et al., 2002) or amoxicillin-clavulanate (Rosón et al., 2001) for the treatment of CAP. The clinical cure rates associated with the ceftriaxone groups in the CE Populations were similar, ranging from 88% to 93% (Table 2.4–1). For Modified Intent-to-Treat (MITT) Populations, these ranged from 74% to 86.8%. Patients enrolled had the expected range of CAP severity, and patient evaluability was typically over 75%. The Ortiz-Ruiz and colleagues (2004) study was sufficiently powered to demonstrate noninferiority with an observed noninferiority margin of 10%.

**Table 2.4–1. Clinical Cure Rates Associated With Ceftriaxone From Published Community-acquired Pneumonia Studies**

<i>Study</i>	<i>Clinical Cure Rates in the CE Population</i>	<i>Clinical Cure Rates in the MITT Population</i>
Ortiz-Ruiz, et al., 2004	270/294 (92.0%)	318/371 (85.7%)
Vetter, et al., 2002	87/93 (93.5%)	105/121 (86.8%)
Rosón, et al., 2001	137/155 (88.4%)	144/194 (74.2%)
Overall (CI) <sup>a</sup>	91.5% (88.9%, 93.9%)	82.5% (75.3%, 89.6%)

Abbreviations: CE = clinically evaluable, MITT= modified intent-to-treat.

a Overall cure rate and CI obtained using DerSimonian-Laird weighted noniterative estimates.

The cure rates at TOC in the coprimary populations in the ceftaroline Phase 3 studies are shown in Table 2.4–2 and Table 2.4–3.

**Table 2.4–2. Clinical Cure Rates at Test of Cure, Study P903-08**

<i>Population</i>	<i>Ceftaroline</i>	<i>Ceftriaxone</i>	<i>95% CI</i>
MITTE	244/291 (83.8)	233/300 (77.7)	(-0.2, 12.6)
CE	194/224 (86.6)	183/234 (78.2)	(1.4, 15.4)

Abbreviations: CE = clinically evaluable; MITTE = modified intent-to-treat efficacy.

Source: Study P903-08, 2009, Table 14.4.1.2A.

**Table 2.4–3. Clinical Cure Rates at Test of Cure, Study P903-09**

<i>Population</i>	<i>Ceftaroline</i>	<i>Ceftriaxone</i>	<i>95% CI</i>
MITTE	235/289 (81.3)	206/273 (75.5)	(-1.0, 12.7)
CE	193/285 (82.1)	166/215 (77.2)	(-2.5, 12.5)

Abbreviations: CE = clinically evaluable; MITTE = modified intent-to-treat efficacy.  
Source: Study P903-09, 2009, Table 14.4.1.2A.

The observed cure rates for ceftriaxone in the Phase 3 CABP studies are somewhat lower than expected based on the contemporary historical studies. In addition, the results were fairly consistent between the two coprimary populations as compared to the historical studies in which lower cure rates were typically noted in the MITT Populations. These results are not surprising given that the ceftaroline Phase 3 CABP studies included only subjects with moderate to severe CABP requiring hospitalization and IV therapy in PORT Risk Class III or IV, and are unique in this respect (as previously discussed, a PORT Risk Class of at least III is correlated with poorer outcomes).

For example, among CE subjects, Ortiz-Ruiz and colleagues reported cure rates of 87% (74/85) among subjects with PORT Risk Class greater than III, with a 95% CI of 79.9% to 94.2%. The cure rate in the subgroup of CE subjects with PORT Risk Class of III or less was 93.8 % with a 95% CI of 90.5% to 97.1%. Cure rates for subjects with a PORT Risk Class of III were not reported. These subjects comprised 29.2% (61/209) of CE subjects with a PORT Risk Class of III or less.

Vetter and colleagues (2002) reported cure rates of 89.3% (25/28) with a 95% CI of 77.6% to 100% for subjects with a PORT Risk Class greater than III. The cure rate in the subgroup of subjects with a PORT Risk Class of III or less was 95.4 % (62/65) with a CI of 90.2% to 100%. Cure rates for subjects with a PORT score of III were not reported. These subjects comprised 35% (23/65) of CE subjects with a PORT Risk Class of III or less.

Rosón and colleagues did not report outcomes by PORT Risk Class, but 58% of all randomized subjects were in PORT Risk Class IV and V, and the clinical cure rates in the MITT Population closely matched the cure rates in the ceftaroline Phase 3 CABP studies.

Therefore, all three contemporary studies reported lower cure rates for subjects with a PORT Risk Class greater than III. Of interest, Rosón and colleagues had the highest relative frequency of subjects with PORT Risk Class greater than III, and this study also reported the lowest cure rate at TOC among the contemporary trials.

The cure rates at TOC by PORT Risk Class in the ceftaroline trials are shown in Table 2.4–4. The results for the ceftaroline trials are in alignment with the contemporary trials when results are evaluated by PORT Risk Class and the greater relative frequency of subjects with more severe disease in the ceftaroline trials versus the historical trials is considered.

**Table 2.4–4. Clinical Cure Rates at Test of Cure by Pneumonia Outcomes Research Team Risk Class—CE Population**

PORT Risk Class	P903-08		P903-09		Pooled Phase 3 Studies (08, 09)	
	Ceftaroline n (%)	Ceftriaxone n (%)	Ceftaroline n (%)	Ceftriaxone n (%)	Ceftaroline n (%)	Ceftriaxone n (%)
III						
Clinical Cure (%)	136/150 (90.7)	113/142 (79.6)	113/137 (82.5)	104/132 (78.8)	249/287 (86.8)	217/274 (79.2)
Difference (CI)	11.1 (3.0, 19.5)		3.7 (-5.8, 13.3)		7.6	
Weighted Difference (CI)					7.5 (1.3, 13.8)	
IV						
Clinical Cure (%)	58/74 (78.4)	70/92 (76.1)	80/98 (81.6)	62/83 (74.7)	138/172 (80.2)	132/175 (75.4)
Difference (CI)	2.3 (-10.9, 15.0)		6.9 (-5.1, 19.3)		4.8	
Weighted Difference (CI)					4.7 (-4.1, 13.5)	

Abbreviation: CE = clinically evaluable

Source: ISE CABP Table 4.1.7

The constancy of the mortality rate in the ceftaroline trials versus the contemporary trials was also evaluated. Ortiz-Ruiz and colleagues reported a mortality rate (defined as death up to 14 days after EOT) of 2.1% (8/379) for subjects treated with ceftriaxone. One death was reported among subjects treated with ceftriaxone by Vetter and colleagues (2004). The overall mortality (defined as death from any cause up to 30 days after hospitalization) for ceftriaxone-treated subjects was 8.8% (17/194, ITT Population) and 9.6% (16/166, CE Population) in the study by Rosón and colleagues (2001). Mortality rates in these contemporary studies parallel closely the mortality rates reported in historical trials (eg, the Fine and colleagues [1997] PORT study). For example, the observed mortality rates among subjects from historical trials who were treated with antibiotics and who had “fair” baseline status or ages of 30 to 59 years (which according to the IDSA [2008] approximates PORT Risk Classes III to IV [Spellberg et al., 2008]) was 5%. This approximates the predicted mortality of antibiotic-treated subjects in PORT Risk Classes III and IV from contemporary studies, ie, the average of 0.9% mortality for PORT Risk Class III and 9.5% for PORT Risk Class IV is 5.3% (Fine et al., 1997).

In the ceftaroline trials, a total mortality (defined as any death up to the LFU visit or up to 30 days after last dose for subjects missing the LFU visit ) of 1.7% (4/234) and 2.3% (5/215) was observed in Studies P903-08 and P903-09, respectively, among ceftriaxone subjects. Although these results parallel those reported above for the contemporary trials, they seemed lower than expected given the greater severity of subjects enrolled in the ceftaroline trials. As previously mentioned, based on the predicted mortality rates from the PORT scoring system and proportion of subjects in the ceftaroline Phase 3 CABP studies with PORT Risk Class III versus IV, the 30-day all-cause mortality would be expected to be approximately 4% if 60% of the subjects were in PORT Risk Class III (average 0.9% predicted mortality) and 40% were in PORT Risk Class IV (average 9.3% predicted mortality) (Fine et al., 1997). The lower mortality rate of 2.5% observed in this study can be explained by a number of factors including the exclusion of subjects who require admission to an ICU, subjects with PORT Risk Class V disease, subjects with life-threatening disease (eg, respiratory failure, sepsis, acute cardiac events, unstable arrhythmias, acute hepatic failure, acute renal failure, active gastrointestinal bleeding, profound metabolic abnormalities, acute cerebrovascular events), subjects with progressively fatal disease (eg, neoplastic lung disease, cystic fibrosis), and subjects with evidence of significant hepatic, hematological, or immunological disease. Therefore, when these factors are taken into consideration, the mortality observed in the ceftaroline trials is consistent with what would be expected given the study enrollment criteria.

#### Recent Regulatory Developments

Since the initiation and completion of the ceftaroline Phase 3 CABP studies, the US FDA has re-evaluated the design elements of a noninferiority study for CABP (US FDA CAP, 2009). In the 2009 Draft CABP Guidance, the US FDA recommended that a noninferiority margin of 15% is appropriate in registration-seeking trials using the clinical cure rate as the endpoint of interest in a population of subjects with microbiological confirmation of disease (denoted the mMITTE and microbiologically evaluable Populations in the ceftaroline Phase 3 CABP studies), given the established treatment effect observed among subjects with a bacteriological diagnosis in the historical studies and the relative paucity of data to establish a treatment effect among subjects without bacterial confirmation of CABP.

The results for the microbiological populations in the ceftaroline trials are shown in Table 2.4–5. The results in these populations clearly show that ceftaroline is noninferior to ceftriaxone in the populations recommended as primary in the recent regulatory guidance using a noninferiority margin of 15%. Indeed, these results indicate that ceftaroline would have met noninferiority criteria in the microbiologically confirmed populations even if the noninferiority margin for these populations was 10%. It should also be noted that the preplanned analyses for these studies included testing for the noninferiority of the per-subject microbiological favorable outcome rate at the TOC in the microbiological Modified Intent-to-Treat (mMITT) Population (results not shown here) using a noninferiority margin of 15%.

**Table 2.4–5. Clinical Cure Rates at Test of Cure in the Phase 3 Trials—mMITTE, ME, and mMITT Populations**

Population	P903-08		P903-09		Pooled Phase 3 Studies (08, 09)	
	Ceftaroline n (%)	Ceftriaxone n (%)	Ceftaroline n (%)	Ceftriaxone n (%)	Ceftaroline n (%)	Ceftriaxone n (%)
mMITTE						
Clinical Cure	66/75 (88.0)	60/80 (75.0)	72/90 (80.0)	66/88 (75.0)	138/165 (83.6)	126/168 (75.0)
Difference (CI) <sup>a</sup>	13.0 (0.7, 25.2)		5.0 (-7.4, 17.4)		8.6	
Weighted Difference (CI)					8.7 (-0.0, 17.4)	
ME						
Clinical Cure	62/69 (89.9)	54/71 (76.1)	69/85 (81.2)	57/76 (75.0)	131/154 (85.1)	111/147 (75.5)
Difference (CI)	13.8 (1.3, 26.4)		6.2 (-6.7, 19.2)		9.6	
Weighted Difference (CI)					9.7 (0.7, 18.8)	
mMITT						
Clinical Cure	66/75 (88.0)	62/82 (75.6)	79/99 (79.8)	78/102 (76.5)	145/174 (83.3)	140/184 (76.1)
Difference (CI)	12.4 (0.2, 24.4)		3.3 (-8.2, 14.8)		7.2	
Weighted Difference (CI)					7.3 (-1.1, 15.6)	

Abbreviations: ME = microbiologically evaluable; mMITT = microbiological modified intent-to-treat;  
mMITTE = microbiological modified intent-to-treat efficacy.

a Difference ceftaroline minus ceftriaxone.

Source: ISE CABP Table 4.1.5.

## 2.5 CONCLUSIONS

In this document the justification for the pre-specified noninferiority boundary of 10% in the ceftaroline trials for the indication of CABP has been presented.

Relevant information available in the public domain as it pertains to the historical effect of the comparator drug on the study endpoints, as well as its applicability to the study populations, have been discussed.

The rigor of study design and conduct of the ceftaroline CABP trials has been described. These ensured that subjects who would actually benefit from antibiotic therapy were enrolled in these trials. This was also shown to be supported by study results consistent with the historical evidence of a treatment effect in a population of subjects with more severe disease.

Furthermore, recent regulatory developments regarding the choice of study populations in this indication and the magnitude of the applicable margin have also been considered and similar observations noted.

In conclusion, all the important considerations for establishing the validity of noninferiority trials in the indication of CABP were discussed and shown to be established.

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**11.2           SELECTION OF NONINFERIORITY MARGINS FOR  
COMPLICATED SKIN AND SKIN STRUCTURE INFECTION  
STUDIES**

**1.0**

**TITLE PAGE**



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**Selection of Noninferiority Margins for Treatment of Study Subjects with  
Complicated Skin and Skin Structure Infections**

**Ceftaroline fosamil for Injection**

## **TABLE OF CONTENTS**

1.0	TITLE PAGE .....	1
2.0	INTRODUCTION .....	3
3.0	METHODS FOR SELECTING THE NONINFERIORITY MARGINS .....	4
3.1	Estimate of the Cure Rate for Untreated Subjects with Complicated Skin and Skin Structure Infections.....	4
3.2	Estimate of the Cure Rate for Subjects Treated with Vancomycin with Aztreonam .....	6
3.2.1	Treatment Effect Size for Vancomycin with Aztreonam .....	7
3.2.2	Assay Sensitivity .....	7
4.0	Evaluation of Constancy Assumption .....	10
5.0	REFERENCES .....	12

## **LIST OF TABLES**

Table 3-1.	Historical Data For Untreated Subjects with Complicated Skin and Skin Structure Infections .....	5
Table 3-2.	Historical Cure Rates for Vancomycin plus Aztreonam from Published Complicated Skin and Skin Structure Studies .....	6
Table 3-3.	Cure Rates for Vancomycin plus Aztreonam with Two-sided 95% Confidence Intervals from Historical Data. ....	7
Table 3-4.	Noninferiority Margin Based on 50% Preservation of Benefit Over Placebo .....	7
Table 4-1.	Clinical Cure Rates at Test of Cure, Study P903-06.....	10
Table 4-2.	Clinical Cure Rates at Test of Cure, Study P903-07.....	10
Table 4-3.	Relative Frequency of Types of Infections in the Vancomycin plus Aztreonam Treatment Group (MITT Populations).....	11

## **2.0**                    **INTRODUCTION**

In the Phase 3 cSSSI studies of ceftaroline compared to IV vancomycin plus aztreonam in the treatment of cSSSI, a noninferiority margin of 10% was prespecified.

Current regulatory requirements stipulate that the magnitude of the noninferiority margin in registration-seeking studies must be shown to preserve an acceptable fraction of the effect size (versus placebo) of the comparator arm.

In this section we show that the prespecified 10% margin preserves at least 50% of the effect size of the vancomycin plus aztreonam treatment group. This fraction of 50% was recommended by the US FDA in correspondence provided to Cerexa regarding the Ceftaroline End-of-Phase-2 Meeting Briefing Book (2006).

### **3.0** **METHODS FOR SELECTING THE NONINFERIORITY MARGINS**

Ideally, estimates of the treatment effect size are obtained from placebo-controlled studies for the comparator arm. However, for anti-infective drugs in the treatment of serious infections such as cSSSI, such studies are generally not available and considered unethical. In fact, the historical medical literature on antibiotic treatment of cSSSI (Keefer et al, 1938; Keefer et al, 1937; Skinner and Keefer et al, 1941; Keefer et al, 1943; Kirby et al 1958-59; Kirby et al, 1960) indicates that, in the absence of effective antimicrobial therapy, a majority of severe cSSSI would result in unfavorable patient outcomes including death from overwhelming infection (including bacteremia) or local extension (eg, intracranial, contiguous bone), chronic suppurative infection, delayed resolution potentially for weeks or months, disability, pain, or impaired quality of life.

Therefore, in order to estimate the effect size for the comparator arm, we proceeded heuristically as follows:

1. Estimates and corresponding CI of the cure rate for untreated subjects with cSSSI (ie, putative placebo cure rate) were obtained using available historical data.
2. Estimates and corresponding CI of the cure rate for subjects with cSSSI treated with vancomycin plus aztreonam were obtained using available historical data.
3. The difference between the lower limit of the CI for the treated group and the upper limit for the putative placebo group was used as a conservative estimate of the effect size for the vancomycin plus aztreonam treatment group.
4. One-half of the difference amount defined above was used as the largest acceptable magnitude of the noninferiority margin to preserve 50% of the effect size.

#### **3.1 ESTIMATE OF THE CURE RATE FOR UNTREATED SUBJECTS WITH COMPLICATED SKIN AND SKIN STRUCTURE INFECTIONS**

Spellberg et al (2009) conducted a systematic literature review on the treatment of cSSSI in the pre-antibiotic era (1900-1950). Skin infections were classified as cellulitis/erysipelas; infection due to trauma, surgical, or combat wounds or ulcers; and major abscess. The cure rates among the “untreated subjects” are provided in Table 3–1.



**Table 3–1. Historical Data For Untreated Subjects with Complicated Skin and Skin Structure Infections**

<i>Description of Infection</i>	<i>Cure Rate</i>	<i>95% CI</i>
Trauma, surgical or combat wounds or ulcers	160/449 (36%)	32%-39%
Cellulitis/erysipelas	1520/2294 (66%)	64%-68%
Major abscess	254/336 (76%)	71%-80%

Abbreviation: CI = confidence interval.

Untreated subjects may have received non-antimicrobial therapies, including topical creams, blood transfusion, injection of anti-streptococcal serum into lesions, x-ray therapy (not ultraviolet), or bacteriophage therapy.

The data in Table 3–1 indicate clear trends in the cure rates among untreated subjects with cSSSI depending on the type of infection. Trauma, surgical or combat wounds, or ulcers had the worst outcome.

Extrapolating the results from Table 3–1 to the current Phase 3 cSSSI studies, in which approximately equal proportions of the three types of infections were observed, a conservative estimate of the putative placebo cure rate of 59.3% was calculated  $[(1/3 \times 0.36) + (1/3 \times 0.66) + (1/3 \times 0.76)] \times 100$ . This estimate has a variance of  $(1/9) \times [(0.36 \times 0.64)/449 + (0.66 \times 0.34)/2294 + (0.76 \times 0.24)/336]$ , resulting in a standard error of 0.0113. The upper bound of the 95% CI for the overall placebo cure rate would then be 61.5% (obtained as  $59.3\% + 1.96 \times (0.0113 \times 100) = 59.3\% + 2.2\% = 61.5\%$ ).

The relevance of these results to modern standards of care is discussed by Spellberg et al (2009). The authors present contemporary results for a dose-escalation study using dalbavancin for cSSSI (Seltzer et al, 2003). In this study, eligible types of skin and soft-tissue infections were those that involved deep soft tissue and/or required surgical intervention such as major abscess, infected ulcer, major burns, or deep and extensive cellulitis. Sixty-two subjects were randomly assigned to receive either one or two doses of IV dalbavancin or a comparator regimen. At TOC in the CE Population, clinical cure rates of 62%, 94% and 76% were observed for the one-dose, two-dose, and comparator regimens, respectively. Similar differences in clinical cure rates were observed in the ITT Population (60% for the one-dose group and 91% for the two-dose group). Although this was a small study, the difference in clinical cure rates between the two-dose and one-dose dalbavancin groups (ie, the two-dose regimen was 31%- 32% more effective than the one-dose regimen) suggests that the conservative estimate of 61.5% for the putative placebo group, based on historical data, remains applicable even by modern standards of care. Other supportive evidence to this statement is presented by Spellberg et al (2009) in the context of mortality data among subjects with cSSSI, which have remained virtually unchanged since the introduction of penicillin to modern times.

### 3.2 ESTIMATE OF THE CURE RATE FOR SUBJECTS TREATED WITH VANCOMYCIN WITH AZTREONAM

Vancomycin and aztreonam were chosen as the active comparative agents best suited for the Phase 3 cSSSI studies because of their acceptance in clinical practice worldwide as highly effective, standard-of-care therapies for cSSSI (Stevens et al, 2005). Aztreonam has selective activity against aerobic gram-negative bacteria involved in the pathogenesis of cSSSI, and its spectrum does not overlap with the gram-positive activity of vancomycin. In the Phase 3 cSSSI studies, aztreonam was administered with vancomycin in the comparator group because gram-negative bacilli are significant etiologies of cSSSI and their pathogenic role in any given subject with cSSSI cannot be excluded until culture results are available. Furthermore, since ceftaroline has clinically meaningful activity against common aerobic gram-negative pathogens, a bias against the comparator regimen could be introduced by not allowing such adjunctive therapy.

The combination of vancomycin plus aztreonam has also been used in several recent cSSSI studies, which investigated the efficacy of tigecycline (Breedt et al, 2005, Saccchidanand et al, 2005) and telavancin (Corey et al, 2006). These studies were of similar construct (eg, disease definition and severity, noninferiority design, duration of therapy, timing of clinical assessments) to the Phase 3 cSSSI ceftaroline studies. The clinical cure rates that were associated with the vancomycin plus aztreonam comparator regimen in these studies are provided in Table 3–2.

**Table 3–2. Historical Cure Rates for Vancomycin plus Aztreonam from Published Complicated Skin and Skin Structure Studies**

<i><b>Study ID</b></i>	<i><b>Number Cured/Total</b></i>	<i><b>Percentage Cured</b></i>
Saccchidanand et al, 2005	163/198	82%
Breedt et al, 2005	201/213	94%
Corey et al, 2006 (ATLAS 1)	302/349	87%
Corey et al, 2006 (ATLAS 2)	346/395	88%

Based on the clinical cure rates associated with vancomycin plus aztreonam shown in Table 3–2, the estimated cure rate and corresponding confidence interval were determined (Table 3–3). Specifically, an estimated cure rate of 88.0% was obtained for vancomycin plus aztreonam, with a 95% CI lower limit of 83.2%

**Table 3–3. Cure Rates for Vancomycin plus Aztreonam with Two-sided 95% Confidence Intervals from Historical Data.**

<i>Estimates (Cure rate %)</i>	<i>DerSimonian-Laird Weighted Non-iterative Estimates</i>
<i>Percentage Cured (<math>P_C</math>)</i>	88.0%
Standard error of $P_C$	2.4%
95% CI ( $P_C$ )	83.2%, 92.7%

In view of the similar designs of these contemporary studies with the Phase 3 cSSSI ceftaroline studies, the above estimates are considered appropriate for the estimation of the treatment effect of vancomycin plus aztreonam.

### 3.2.1 Treatment Effect Size for Vancomycin with Aztreonam

For the estimation of the treatment effect of vancomycin plus aztreonam, we apply the methods described in Section 3.0 and obtain the results in Table 3–4.

**Table 3–4. Noninferiority Margin Based on 50% Preservation of Benefit Over Placebo**

<i>95% CI Lower Limit for Cure Rate for Vancomycin plus Aztreonam</i>	<i>95% CI Upper Limit for Putative Placebo Cure Rate</i>	<i>Difference<sup>a</sup> (Estimated Effect Size)</i>	<i>Noninferiority Margin for 50% Preservation of Effect Size</i>
83.2%	61.5 %	21.7%	10.9%

a Difference is (95% CI lower limit for vancomycin plus aztreonam - 95% CI upper limit for putative placebo cure rate).

The conservative estimated upper limit of the noninferiority margin obtained from historical data is 10.9%. The prespecified margin of 10% is slightly lower than suggested by the historical data, indicating that the prespecified margin of 10% meets the regulatory requirement of preservation of at least 50% of the estimated effect size.

### 3.2.2 Assay Sensitivity

Assay sensitivity (or the ability of a study to detect clinically important differences between treatment groups, if they exist) is of particular importance in noninferiority trials lacking a concurrent placebo treatment group.

Study design and conduct are critical factors in ensuring that a noninferiority study attains accurate results without false-positive conclusions. Important elements include choice of the control regimen, definition of eligible subjects, permissible concomitant treatments, outcome measures, and timing of assessments. Of particular importance is the rigor of study conduct since a poorly conducted study will bias the conclusion towards the noninferiority hypothesis.

The design of the Phase 3 cSSSI ceftaroline studies, including the choice of the comparator regimen and selection of the noninferiority margin, was generally comparable to, or more conservative than, most contemporary cSSSI studies.

As detailed above, vancomycin and aztreonam were chosen as the active comparator agents for the ceftaroline Phase 3 cSSSI studies because of their effectiveness for cSSSI and their global acceptance in clinical practice. Recent cSSSI studies that investigated the clinical efficacy of tigecycline and telavancin involved vancomycin and aztreonam as active comparators (Table 3–2) and were of similar construct (eg, noninferiority design, duration of therapy, timing of clinical assessments). Finally, the dosing regimen of vancomycin plus aztreonam in the ceftaroline Phase 3 cSSSI studies ensures a fair comparison with the investigational agent.

Patient selection criteria were defined rigorously in the Phase 3 cSSSI protocols. The protocols were designed to ensure that subjects were enrolled only if their skin or skin structure infection was complicated (ie, met predefined cSSSI criteria), clinically relevant, and of sufficient severity to warrant hospitalization and/or intravenous antimicrobial therapy. The protocols provided a detailed definition of each type of cSSSI and ensured that the infection was severe enough that antimicrobial therapy was not only advisable, but essential, for optimal care of the subject. Based on these cSSSI disease definitions and severity criteria, the subjects enrolled in the Phase 3 cSSSI studies required intravenous antimicrobial therapy for appropriate care.

Concomitant potentially effective antibacterial therapies were not permitted during the studies. Subjects were permitted to take any necessary non-antimicrobial medications, with the exception of probenecid, which could alter the plasma and tissue exposure of ceftaroline. Appropriate surgical interventions and local wound care were permitted with the exception of those that, in themselves, would be expected to cure the infection (eg, amputation).

Outcome measures typically used in assessment of cSSSI in clinical trials of new antimicrobial therapies were employed in the Phase 3 cSSSI studies. For example, the primary outcome measure was clinical cure at TOC and secondary outcome measures included microbiological assessment at TOC and clinical and microbiological assessments at EOT and LFU. The timing of these assessments was consistent with regulatory guidance and standard practice in clinical trials of investigational antimicrobial agents. Specifically, TOC was timed such that the study drugs were no longer present in plasma or tissue and that complete spontaneous resolution of cSSSI would likely not have occurred in the absence of effective intervention.

In summary, the Phase 3 cSSSI studies were developed in accordance with guidance documents from regulatory agencies and professional societies and in accordance with Good Clinical Practice requirements. Introduction of potential bias was minimized by the use of a double-blind, randomized design. Rigorous study conduct was ensured throughout the studies and included pre-enrollment due diligence to assess site quality, strict site initiation procedures, and close monitoring of sites during and after active enrollment to ensure excellent protocol adherence.

#### **4.0** **EVALUATION OF CONSTANCY ASSUMPTION**

To evaluate the constancy of the effect of vancomycin plus aztreonam in the ceftaroline cSSSI Phase 3 trials, the study results were compared to historical cure rates for the comparator regimen used in the estimation of the effect size. In addition, the relative frequency of the types of infections (abscess, cellulitis, and infected wounds/burn/ulcer) was evaluated among the various studies.

As discussed in Section 3.2, four studies were identified as being similar in design to the Phase 3 cSSSI studies. The clinical cure rates (and 95% CIs) associated with the vancomycin plus aztreonam comparator regimen in these studies are provided in Table 3–2 and Table 3–3. The corresponding cure rates at TOC for the cSSSI Phase 3 studies are shown in Table 4–1 and Table 4–2 for Study P903-06 and P903-07, respectively.

The cure rates for the vancomycin plus aztreonam group in the Phase 3 cSSSI studies were comparable between the two Phase 3 cSSSI studies and were within the range of values observed in the historical trials. However, the 95% CI indicates that the cure rates in the Phase 3 cSSSI studies were also in the upper portion of the distribution of values.

**Table 4–1. Clinical Cure Rates at Test of Cure, Study P903-06**

<i>Population</i>	<i>Ceftaroline</i>	<i>Vancomycin plus Aztreonam</i>	<i>Diff (95% CI)</i>
CE	288/316 (91.1)	280/300 (93.3)	-2.2 (-6.6, 2.1)
MITT	304/351 (86.6)	297/347 (85.6)	1.0 (-4.2, 6.2)

Source: Study P903-06, 2009, Table 4.4.1.2

**Table 4–2. Clinical Cure Rates at Test of Cure, Study P903-07**

<i>Population</i>	<i>Ceftaroline</i>	<i>Vancomycin plus Aztreonam</i>	<i>Diff (95% CI)</i>
CE	271/294 (92.2)	269/292 (92.1)	0.1 (-4.4, 4.5)
MITT	291/342 (85.1)	289/338 (85.5)	-0.4 (-5.8, 5.0)

Source: Study P903-07, 2009, Table 4.4.1.2

The relative frequencies of the most common types of skin and skin structure infections (abscess, cellulitis, and infected wounds/burns/ulcer) in the four historical studies using a vancomycin plus aztreonam treatment group are shown in Table 4–3.

**Table 4–3. Relative Frequency of Types of Infections in the Vancomycin plus Aztreonam Treatment Group (MITT Populations)**

<i>Study ID</i>	<i>Abscess</i>	<i>Cellulitis</i>	<i>Infected Wounds/Burn/Ulcer</i>
Sacchidanand et al, 2005	27.0%	60.1%	11.0%
Breedt et al, 2005	31.2%	55.0%	10.0% <sup>a</sup>
Corey et al, 2006 (ATLAS 1)	NA	NA	NA
Corey et al, 2006 (ATLAS 2)	NA	NA	NA
Corey et al, 2006 (pooled) <sup>b</sup>	42%	38%	20%
Ceftaroline Study P903-06 <sup>c</sup>	29.4%	40.1%	27.1%
Ceftaroline Study P903-07 <sup>c</sup>	39.6%	39.7%	18.3%

Abbreviations: MITT = modified intent-to-treat.

a Wound infections were included under cellulitis in this study.

b Individual treatment groups were not reported. Data are for the clinically evaluable (CE) Population.

c Source: Study P903-06, 2009, Table 14.2.19; Study P903-07, 2009, Table 14.2.19.

The distribution of the types of infections was somewhat variable among the historical trials, yet this variation does not appear to explain the variation in the cure rates. For example, the relative frequency of the types of infections was most comparable between Sacchidanand et al (2005) and Breedt et al (2005), yet these two studies had the lowest and had highest cure rates observed, respectively.

The distribution of the types of infections in the Phase 3 cSSSI studies had a somewhat higher proportion of infected wounds/burn/ulcer and for Study P903-07 a higher proportion of abscesses. However, these proportions were comparable to results reported by Corey et al (2006) for the pooled ATLAS studies.

To conclude, the cure rates for the comparator treatment group in the Phase 3 cSSSI studies, although being somewhat higher than other historical studies, were not markedly so and were also within the range of observed cure rates when all studies were considered. The variation in the distribution of the types of infections among the various studies did not appear to be correlated with the variability in cure rates.

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### **11.3           END OF TEXT TABLES**

**Table 11.3–1. Incidence of Serious Adverse Events, Phase 3 Studies for cSSSI and CABP—Safety Population**

<b>System Organ Class/ Preferred Term</b>	<b>cSSSI (06, 07)</b>		<b>CABP (08, 09)</b>		<b>Pooled Phase 3 Studies (06, 07, 08, 09)</b>	
	<i>Ceftriaxone (N = 692) n(%)</i>	<i>Vancomycin plus Aztreonam (N = 686) n(%)</i>	<i>Ceftriaxone (N = 613) n(%)</i>	<i>Ceftriaxone (N = 615) n(%)</i>	<i>Ceftriaxone (N = 1305) n(%)</i>	<i>Pooled Comparators (N = 1301) n(%)</i>
Subjects with at Least One SAE	30 (4.3)	28 (4.1)	69 (11.3)	72 (11.7)	99 (7.6)	100 (7.7)
Blood and lymphatic system disorders	0	2 (0.3)	3 (0.5)	0	3 (0.2)	2 (0.2)
Anaemia	0	1 (0.1)	1 (0.2)	0	1 (0.1)	1 (0.1)
Disseminated intravascular coagulation	0	0	1 (0.2)	0	1 (0.1)	0
Lymphadenitis	0	0	1 (0.2)	0	1 (0.1)	0
Hypocoagulable state	0	1 (0.1)	0	0	0	1 (0.1)
Cardiac disorders	4 (0.6)	5 (0.7)	7 (1.1)	11 (1.8)	11 (0.8)	16 (1.2)
Cardiac failure congestive	1 (0.1)	1 (0.1)	1 (0.2)	1 (0.2)	2 (0.2)	2 (0.2)
Cardiopulmonary failure	1 (0.1)	0	1 (0.2)	1 (0.2)	2 (0.2)	1 (0.1)
Bradycardia	1 (0.1)	1 (0.1)	0	0	1 (0.1)	1 (0.1)
Cardiac arrest	0	0	1 (0.2)	0	1 (0.1)	0
Cardiac failure	0	0	1 (0.2)	0	1 (0.1)	0
Ischaemic cardiomyopathy	0	0	1 (0.2)	0	1 (0.1)	0
Left ventricular failure	0	0	1 (0.2)	0	1 (0.1)	0
Myocardial infarction	1 (0.1)	1 (0.1)	0	2 (0.3)	1 (0.1)	3 (0.2)
Ventricular tachycardia	0	0	1 (0.2)	0	1 (0.1)	0
Acute myocardial infarction	0	0	0	1 (0.2)	0	1 (0.1)
Atrioventricular block complete	0	0	0	1 (0.2)	0	1 (0.1)

**Table 11.3–1. Incidence of Serious Adverse Events, Phase 3 Studies for cSSSI and CABP—Safety Population**

<b>System Organ Class/ Preferred Term</b>	<b>cSSSI (06, 07)</b>		<b>CABP (08, 09)</b>		<b>Pooled Phase 3 Studies (06, 07, 08, 09)</b>	
	<i>Ceftriaxone (N = 692) n(%)</i>	<i>Vancomycin plus Aztreonam (N = 686) n(%)</i>	<i>Ceftriaxone (N = 613) n(%)</i>	<i>Ceftriaxone (N = 615) n(%)</i>	<i>Ceftriaxone (N = 1305) n(%)</i>	<i>Pooled Comparators (N = 1301) n(%)</i>
Cardiac failure acute	0	0	0	1 (0.2)	0	1 (0.1)
Cardio-respiratory arrest	0	0	0	2 (0.3)	0	2 (0.2)
Cardiomyopathy	0	0	0	1 (0.2)	0	1 (0.1)
Coronary artery disease	0	1 (0.1)	0	1 (0.2)	0	2 (0.2)
Postinfarction angina	0	0	0	1 (0.2)	0	1 (0.1)
Sinoatrial block	0	1 (0.1)	0	0	0	1 (0.1)
Endocrine disorders	0	0	1 (0.2)	0	1 (0.1)	0
Hypothyroidism	0	0	1 (0.2)	0	1 (0.1)	0
Gastrointestinal disorders	4 (0.6)	2 (0.3)	3 (0.5)	2 (0.3)	7 (0.5)	4 (0.3)
Abdominal pain	1 (0.1)	0	0	0	1 (0.1)	0
Duodenal ulcer	0	0	1 (0.2)	0	1 (0.1)	0
Gastritis	0	0	1 (0.2)	0	1 (0.1)	0
Gastrointestinal perforation	0	0	1 (0.2)	0	1 (0.1)	0
Haematochezia	1 (0.1)	0	0	0	1 (0.1)	0
Intestinal ischaemia	1 (0.1)	0	0	0	1 (0.1)	0
Peptic ulcer haemorrhage	1 (0.1)	0	0	0	1 (0.1)	0
Constipation	0	1 (0.1)	0	0	0	1 (0.1)
Gastric ulcer	0	0	0	1 (0.2)	0	1 (0.1)
Ileus	0	1 (0.1)	0	0	0	1 (0.1)
Volvulus	0	0	0	1 (0.2)	0	1 (0.1)

**Table 11.3–1. Incidence of Serious Adverse Events, Phase 3 Studies for cSSSI and CABP—Safety Population**

<b>System Organ Class/ Preferred Term</b>	<b>cSSSI (06, 07)</b>		<b>CABP (08, 09)</b>		<b>Pooled Phase 3 Studies (06, 07, 08, 09)</b>	
	<i>Ceftriaxone (N = 692) n(%)</i>	<i>Vancomycin plus Aztreonam (N = 686) n(%)</i>	<i>Ceftriaxone (N = 613) n(%)</i>	<i>Ceftriaxone (N = 615) n(%)</i>	<i>Ceftriaxone (N = 1305) n(%)</i>	<i>Pooled Comparators (N = 1301) n(%)</i>
General disorders and administration site conditions	1 (0.1)	2 (0.3)	2 (0.3)	1 (0.2)	3 (0.2)	3 (0.2)
Sudden death	0	0	2 (0.3)	0	2 (0.2)	0
Multi-organ failure	1 (0.1)	0	0	0	1 (0.1)	0
General physical health deterioration	0	1 (0.1)	0	0	0	1 (0.1)
Generalised oedema	0	1 (0.1)	0	0	0	1 (0.1)
Multi-organ disorder	0	0	0	1 (0.2)	0	1 (0.1)
Hepatobiliary disorders	0	1 (0.1)	1 (0.2)	4 (0.7)	1 (0.1)	5 (0.4)
Hepatic failure	0	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Acute hepatic failure	0	0	0	1 (0.2)	0	1 (0.1)
Cholecystitis acute	0	0	0	2 (0.3)	0	2 (0.2)
Hepatitis	0	1 (0.1)	0	0	0	1 (0.1)
Immune system disorders	3 (0.4)	1 (0.1)	0	1 (0.2)	3 (0.2)	2 (0.2)
Anaphylactic shock	1 (0.1)	0	0	0	1 (0.1)	0
Anaphylactoid reaction	1 (0.1)	0	0	0	1 (0.1)	0
Hypersensitivity	1 (0.1)	1 (0.1)	0	1 (0.2)	1 (0.1)	2 (0.2)

**Table 11.3–1. Incidence of Serious Adverse Events, Phase 3 Studies for cSSSI and CABP—Safety Population**

<b>System Organ Class/ Preferred Term</b>	<b>cSSSI (06, 07)</b>		<b>CABP (08, 09)</b>		<b>Pooled Phase 3 Studies (06, 07, 08, 09)</b>	
	<i>Ceftriaxone (N = 692) n(%)</i>	<i>Vancomycin plus Aztreonam (N = 686) n(%)</i>	<i>Ceftriaxone (N = 613) n(%)</i>	<i>Ceftriaxone (N = 615) n(%)</i>	<i>Ceftriaxone (N = 1305) n(%)</i>	<i>Pooled Comparators (N = 1301) n(%)</i>
Infections and infestations	8 (1.2)	6 (0.9)	23 (3.8)	26 (4.2)	31 (2.4)	32 (2.5)
Pneumonia	0	1 (0.1)	9 (1.5)	9 (1.5)	9 (0.7)	10 (0.8)
Pyothorax	0	0	4 (0.7)	0	4 (0.3)	0
Cellulitis	2 (0.3)	1 (0.1)	1 (0.2)	1 (0.2)	3 (0.2)	2 (0.2)
Lung abscess	0	0	2 (0.3)	4 (0.7)	2 (0.2)	4 (0.3)
Sepsis	0	1 (0.1)	2 (0.3)	1 (0.2)	2 (0.2)	2 (0.2)
Urinary tract infection	0	0	2 (0.3)	1 (0.2)	2 (0.2)	1 (0.1)
Bacteraemia	1 (0.1)	0	0	0	1 (0.1)	0
Bronchitis	0	0	1 (0.2)	0	1 (0.1)	0
Catheter related infection	1 (0.1)	0	0	0	1 (0.1)	0
Central line infection	1 (0.1)	0	0	0	1 (0.1)	0
Clostridium difficile colitis	1 (0.1)	0	0	0	1 (0.1)	0
Empyema	0	0	1 (0.2)	2 (0.3)	1 (0.1)	2 (0.2)
Osteomyelitis	1 (0.1)	1 (0.1)	0	0	1 (0.1)	1 (0.1)
Renal abscess	1 (0.1)	0	0	0	1 (0.1)	0
Septic shock	0	0	1 (0.2)	0	1 (0.1)	0
Tuberculosis	0	0	1 (0.2)	0	1 (0.1)	0
Wound infection	1 (0.1)	1 (0.1)	0	0	1 (0.1)	1 (0.1)
Endocarditis	0	0	0	2 (0.3)	0	2 (0.2)
Gastroenteritis	0	0	0	2 (0.3)	0	2 (0.2)

**Table 11.3–1. Incidence of Serious Adverse Events, Phase 3 Studies for cSSSI and CABP—Safety Population**

<b>System Organ Class/ Preferred Term</b>	<b>cSSSI (06, 07)</b>		<b>CABP (08, 09)</b>		<b>Pooled Phase 3 Studies (06, 07, 08, 09)</b>	
	<i>Ceftriaxone (N = 692) n(%)</i>	<i>Vancomycin plus Aztreonam (N = 686) n(%)</i>	<i>Ceftriaxone (N = 613) n(%)</i>	<i>Ceftriaxone (N = 615) n(%)</i>	<i>Ceftriaxone (N = 1305) n(%)</i>	<i>Pooled Comparators (N = 1301) n(%)</i>
Hepatitis C	0	0	0	1 (0.2)	0	1 (0.1)
Lung infection pseudomonal	0	0	0	1 (0.2)	0	1 (0.1)
Pulmonary tuberculosis	0	0	0	1 (0.2)	0	1 (0.1)
Staphylococcal bacteraemia	0	0	0	1 (0.2)	0	1 (0.1)
Urosepsis	0	0	0	1 (0.2)	0	1 (0.1)
Viral infection	0	1 (0.1)	0	0	0	1 (0.1)
Injury, poisoning and procedural complications	2 (0.3)	1 (0.1)	0	0	2 (0.2)	1 (0.1)
Accidental overdose	1 (0.1)	0	0	0	1 (0.1)	0
Dislocation of joint prosthesis	1 (0.1)	0	0	0	1 (0.1)	0
Post procedural haemorrhage	0	1 (0.1)	0	0	0	1 (0.1)
Investigations	1 (0.1)	0	1 (0.2)	1 (0.2)	2 (0.2)	1 (0.1)
Electrocardiogram ST segment elevation	1 (0.1)	0	0	0	1 (0.1)	0
Liver function test abnormal	0	0	1 (0.2)	0	1 (0.1)	0
Hepatic enzyme increased	0	0	0	1 (0.2)	0	1 (0.1)

**Table 11.3–1. Incidence of Serious Adverse Events, Phase 3 Studies for cSSSI and CABP—Safety Population**

<i><b>System Organ Class/ Preferred Term</b></i>	<i><b>cSSSI (06, 07)</b></i>		<i><b>CABP (08, 09)</b></i>		<i><b>Pooled Phase 3 Studies (06, 07, 08, 09)</b></i>	
	<i>Ceftriaxone (N = 692) n(%)</i>	<i>Vancomycin plus Aztreonam (N = 686) n(%)</i>	<i>Ceftriaxone (N = 613) n(%)</i>	<i>Ceftriaxone (N = 615) n(%)</i>	<i>Ceftriaxone (N = 1305) n(%)</i>	<i>Pooled Comparators (N = 1301) n(%)</i>
Metabolism and nutrition disorders	1 (0.1)	1 (0.1)	3 (0.5)	4 (0.7)	4 (0.3)	5 (0.4)
Diabetes mellitus	0	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Diabetes mellitus inadequate control	0	1 (0.1)	1 (0.2)	0	1 (0.1)	1 (0.1)
Hyperglycaemia	1 (0.1)	0	0	0	1 (0.1)	0
Hypoglycaemia	0	0	1 (0.2)	0	1 (0.1)	0
Gout	0	0	0	1 (0.2)	0	1 (0.1)
Type 1 diabetes mellitus	0	0	0	1 (0.2)	0	1 (0.1)
Type 2 diabetes mellitus	0	0	0	1 (0.2)	0	1 (0.1)
Musculoskeletal and connective tissue disorders	2 (0.3)	0	0	1 (0.2)	2 (0.2)	1 (0.1)
Back pain	1 (0.1)	0	0	0	1 (0.1)	0
Osteoarthritis	1 (0.1)	0	0	0	1 (0.1)	0
Myopathy	0	0	0	1 (0.2)	0	1 (0.1)



**Table 11.3–1. Incidence of Serious Adverse Events, Phase 3 Studies for cSSSI and CABP—Safety Population**

<b>System Organ Class/ Preferred Term</b>	<b>cSSSI (06, 07)</b>		<b>CABP (08, 09)</b>		<b>Pooled Phase 3 Studies (06, 07, 08, 09)</b>	
	<i>Ceftriaxone (N = 692) n(%)</i>	<i>Vancomycin plus Aztreonam (N = 686) n(%)</i>	<i>Ceftriaxone (N = 613) n(%)</i>	<i>Ceftriaxone (N = 615) n(%)</i>	<i>Ceftriaxone (N = 1305) n(%)</i>	<i>Pooled Comparators (N = 1301) n(%)</i>
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.1)	2 (0.3)	11 (1.8)	3 (0.5)	12 (0.9)	5 (0.4)
Lung neoplasm malignant	0	0	3 (0.5)	0	3 (0.2)	0
Malignant neoplasm progression	1 (0.1)	0	1 (0.2)	0	2 (0.2)	0
Colon cancer	0	0	1 (0.2)	0	1 (0.1)	0
Lung adenocarcinoma	0	0	1 (0.2)	0	1 (0.1)	0
Lung neoplasm	0	0	1 (0.2)	0	1 (0.1)	0
Metastases to liver	0	0	1 (0.2)	0	1 (0.1)	0
Metastatic neoplasm	0	0	1 (0.2)	0	1 (0.1)	0
Pancreatic neoplasm	0	0	1 (0.2)	0	1 (0.1)	0
Renal neoplasm	0	0	1 (0.2)	0	1 (0.1)	0
Small cell lung cancer stage unspecified	0	0	1 (0.2)	0	1 (0.1)	0
Bronchial carcinoma	0	1 (0.1)	0	0	0	1 (0.1)
Chronic lymphocytic leukaemia recurrent	0	1 (0.1)	0	0	0	1 (0.1)
Lung adenocarcinoma metastatic	0	0	0	1 (0.2)	0	1 (0.1)
Multiple myeloma	0	0	0	1 (0.2)	0	1 (0.1)
Prostate cancer	0	0	0	1 (0.2)	0	1 (0.1)

**Table 11.3–1. Incidence of Serious Adverse Events, Phase 3 Studies for cSSSI and CABP—Safety Population**

<b>System Organ Class/ Preferred Term</b>	<b>cSSSI (06, 07)</b>		<b>CABP (08, 09)</b>		<b>Pooled Phase 3 Studies (06, 07, 08, 09)</b>	
	<i>Ceftriaxone (N = 692) n(%)</i>	<i>Vancomycin plus Aztreonam (N = 686) n(%)</i>	<i>Ceftriaxone (N = 613) n(%)</i>	<i>Ceftriaxone (N = 615) n(%)</i>	<i>Ceftriaxone (N = 1305) n(%)</i>	<i>Pooled Comparators (N = 1301) n(%)</i>
Nervous system disorders	2 (0.3)	3 (0.4)	3 (0.5)	1 (0.2)	5 (0.4)	4 (0.3)
Convulsion	1 (0.1)	0	1 (0.2)	0	2 (0.2)	0
Anoxic encephalopathy	0	0	1 (0.2)	0	1 (0.1)	0
Cerebrovascular accident	1 (0.1)	0	0	1 (0.2)	1 (0.1)	1 (0.1)
Thrombotic stroke	0	0	1 (0.2)	0	1 (0.1)	0
Toxic encephalopathy	0	0	1 (0.2)	0	1 (0.1)	0
Hemiplegia	0	0	0	1 (0.2)	0	1 (0.1)
Loss of consciousness	0	1 (0.1)	0	0	0	1 (0.1)
Syncope	0	1 (0.1)	0	0	0	1 (0.1)
Transient ischaemic attack	0	1 (0.1)	0	0	0	1 (0.1)
Renal and urinary disorders	2 (0.3)	1 (0.1)	2 (0.3)	2 (0.3)	4 (0.3)	3 (0.2)
Renal failure	1 (0.1)	0	2 (0.3)	0	3 (0.2)	0
Acute prerenal failure	1 (0.1)	0	0	0	1 (0.1)	0
Hydronephrosis	0	0	0	1 (0.2)	0	1 (0.1)
Renal failure acute	0	1 (0.1)	0	0	0	1 (0.1)
Urinary retention	0	0	0	1 (0.2)	0	1 (0.1)

**Table 11.3–1. Incidence of Serious Adverse Events, Phase 3 Studies for cSSSI and CABP—Safety Population**

<i><b>System Organ Class/ Preferred Term</b></i>	<i><b>cSSSI (06, 07)</b></i>		<i><b>CABP (08, 09)</b></i>		<i><b>Pooled Phase 3 Studies (06, 07, 08, 09)</b></i>	
	<i>Ceftriaxone (N = 692) n(%)</i>	<i>Vancomycin plus Aztreonam (N = 686) n(%)</i>	<i>Ceftriaxone (N = 613) n(%)</i>	<i>Ceftriaxone (N = 615) n(%)</i>	<i>Ceftriaxone (N = 1305) n(%)</i>	<i>Pooled Comparators (N = 1301) n(%)</i>
Reproductive system and breast disorders	0	0	0	1 (0.2)	0	1 (0.1)
Epididymitis	0	0	0	1 (0.2)	0	1 (0.1)
Respiratory, thoracic and mediastinal disorders	4 (0.6)	1 (0.1)	20 (3.3)	25 (4.1)	24 (1.8)	26 (2.0)
Pulmonary embolism	1 (0.1)	0	5 (0.8)	4 (0.7)	6 (0.5)	4 (0.3)
Pleural effusion	0	0	5 (0.8)	6 (1.0)	5 (0.4)	6 (0.5)
Respiratory failure	1 (0.1)	0	4 (0.7)	1 (0.2)	5 (0.4)	1 (0.1)
Chronic obstructive pulmonary disease	0	0	4 (0.7)	6 (1.0)	4 (0.3)	6 (0.5)
Pleurisy	1 (0.1)	0	1 (0.2)	2 (0.3)	2 (0.2)	2 (0.2)
Pulmonary oedema	0	0	2 (0.3)	0	2 (0.2)	0
Acute pulmonary oedema	1 (0.1)	0	0	1 (0.2)	1 (0.1)	1 (0.1)
Interstitial lung disease	0	0	1 (0.2)	0	1 (0.1)	0
Acute respiratory failure	0	1 (0.1)	0	1 (0.2)	0	2 (0.2)
Asthma	0	0	0	3 (0.5)	0	3 (0.2)
Asthmatic crisis	0	0	0	1 (0.2)	0	1 (0.1)
Atelectasis	0	0	0	1 (0.2)	0	1 (0.1)

**Table 11.3–1. Incidence of Serious Adverse Events, Phase 3 Studies for cSSSI and CABP—Safety Population**

<i><b>System Organ Class/ Preferred Term</b></i>	<i><b>cSSSI (06, 07)</b></i>		<i><b>CABP (08, 09)</b></i>		<i><b>Pooled Phase 3 Studies (06, 07, 08, 09)</b></i>	
	<i>Ceftriaxone (N = 692) n(%)</i>	<i>Vancomycin plus Aztreonam (N = 686) n(%)</i>	<i>Ceftriaxone (N = 613) n(%)</i>	<i>Ceftriaxone (N = 615) n(%)</i>	<i>Ceftriaxone (N = 1305) n(%)</i>	<i>Pooled Comparators (N = 1301) n(%)</i>
Vascular disorders	1 (0.1)	2 (0.3)	4 (0.7)	2 (0.3)	5 (0.4)	4 (0.3)
Aortic aneurysm	0	0	1 (0.2)	0	1 (0.1)	0
Aortic dissection	0	0	1 (0.2)	0	1 (0.1)	0
Cardiovascular insufficiency	0	0	1 (0.2)	0	1 (0.1)	0
Hypotension	1 (0.1)	0	0	0	1 (0.1)	0
Peripheral ischaemia	0	0	1 (0.2)	0	1 (0.1)	0
Arterial thrombosis limb	0	1 (0.1)	0	0	0	1 (0.1)
Deep vein thrombosis	0	0	0	1 (0.2)	0	1 (0.1)
Hypertensive crisis	0	0	0	1 (0.2)	0	1 (0.1)
Thrombophlebitis	0	1 (0.1)	0	0	0	1 (0.1)

**Table 11.3–2. Incidence of Adverse Events Leading to Discontinuation of Study Drug or Withdrawal from Study, Phase 3 Studies for cSSSI and CABP—Safety Population**

<i><b>System Organ Class/ Preferred Term</b></i>	<i><b>cSSSI (06, 07)</b></i>		<i><b>CABP (08, 09)</b></i>		<i><b>Pooled Phase 3 Studies (06, 07, 08, 09)</b></i>	
	<i>Ceftaroline (N = 692) n(%)</i>	<i>Vancomycin plus Aztreonam (N = 686) n(%)</i>	<i>Ceftaroline (N = 613) n(%)</i>	<i>Ceftriaxone (N = 615) n(%)</i>	<i>Ceftaroline (N = 1305) n(%)</i>	<i>Pooled Comparators (N = 1301) n(%)</i>
Subjects with at Least One AE Leading to Discontinuation of Study Drug or Withdrawal from Study	21 (3.0)	33 (4.8)	27 (4.4)	25 (4.1)	48 (3.7)	58 (4.5)
Cardiac disorders	0	2 (0.3)	2 (0.3)	7 (1.1)	2 (0.2)	9 (0.7)
Cardiac failure	0	0	1 (0.2)	0	1 (0.1)	0
Left ventricular failure	0	0	1 (0.2)	0	1 (0.1)	0
Cardiac failure acute	0	0	0	1 (0.2)	0	1 (0.1)
Cardiac failure congestive	0	1 (0.1)	0	0	0	1 (0.1)
Cardio-respiratory arrest	0	0	0	2 (0.3)	0	2 (0.2)
Cardiomyopathy	0	0	0	1 (0.2)	0	1 (0.1)
Cardiopulmonary failure	0	0	0	1 (0.2)	0	1 (0.1)
Coronary artery disease	0	0	0	1 (0.2)	0	1 (0.1)
Myocardial infarction	0	1 (0.1)	0	1 (0.2)	0	2 (0.2)
Eye disorders	0	1 (0.1)	0	0	0	1 (0.1)
Eye swelling	0	1 (0.1)	0	0	0	1 (0.1)

**Table 11.3–2. Incidence of Adverse Events Leading to Discontinuation of Study Drug or Withdrawal from Study, Phase 3 Studies for cSSSI and CABP—Safety Population**

<b>System Organ Class/ Preferred Term</b>	<b>cSSSI (06, 07)</b>		<b>CABP (08, 09)</b>		<b>Pooled Phase 3 Studies (06, 07, 08, 09)</b>	
	<i>Ceftaroline (N = 692) n(%)</i>	<i>Vancomycin plus Aztreonam (N = 686) n(%)</i>	<i>Ceftaroline (N = 613) n(%)</i>	<i>Ceftriaxone (N = 615) n(%)</i>	<i>Ceftaroline (N = 1305) n(%)</i>	<i>Pooled Comparators (N = 1301) n(%)</i>
Gastrointestinal disorders	0	1 (0.1)	3 (0.5)	2 (0.3)	3 (0.2)	3 (0.2)
Abdominal pain	0	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Diarrhoea	0	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Flatulence	0	0	1 (0.2)	0	1 (0.1)	0
Gastric disorder	0	0	1 (0.2)	0	1 (0.1)	0
Vomiting	0	0	1 (0.2)	0	1 (0.1)	0
Gingival pruritus	0	1 (0.1)	0	0	0	1 (0.1)
Gingival swelling	0	1 (0.1)	0	0	0	1 (0.1)
General disorders and administration site conditions	1 (0.1)	3 (0.4)	3 (0.5)	1 (0.2)	4 (0.3)	4 (0.3)
Sudden death	0	0	2 (0.3)	0	2 (0.2)	0
Chest pain	1 (0.1)	0	0	0	1 (0.1)	0
Fatigue	0	0	1 (0.2)	0	1 (0.1)	0
General physical health deterioration	0	1 (0.1)	0	0	0	1 (0.1)
Infusion site urticaria	0	1 (0.1)	0	0	0	1 (0.1)
Multi-organ disorder	0	0	0	1 (0.2)	0	1 (0.1)
Pyrexia	0	1 (0.1)	0	0	0	1 (0.1)

**Table 11.3–2. Incidence of Adverse Events Leading to Discontinuation of Study Drug or Withdrawal from Study, Phase 3 Studies for cSSSI and CABP—Safety Population**

<i><b>System Organ Class/ Preferred Term</b></i>	<i><b>cSSSI (06, 07)</b></i>		<i><b>CABP (08, 09)</b></i>		<i><b>Pooled Phase 3 Studies (06, 07, 08, 09)</b></i>	
	<i>Ceftaroline (N = 692) n(%)</i>	<i>Vancomycin plus Aztreonam (N = 686) n(%)</i>	<i>Ceftaroline (N = 613) n(%)</i>	<i>Ceftriaxone (N = 615) n(%)</i>	<i>Ceftaroline (N = 1305) n(%)</i>	<i>Pooled Comparators (N = 1301) n(%)</i>
Hepatobiliary disorders	0	0	2 (0.3)	2 (0.3)	2 (0.2)	2 (0.2)
Cytolytic hepatitis	0	0	1 (0.2)	0	1 (0.1)	0
Hepatic failure	0	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Acute hepatic failure	0	0	0	1 (0.2)	0	1 (0.1)
Immune system disorders	6 (0.9)	6 (0.9)	1 (0.2)	0	7 (0.5)	6 (0.5)
Hypersensitivity	3 (0.4)	6 (0.9)	1 (0.2)	0	4 (0.3)	6 (0.5)
Anaphylactic reaction	1 (0.1)	0	0	0	1 (0.1)	0
Anaphylactic shock	1 (0.1)	0	0	0	1 (0.1)	0
Anaphylactoid reaction	1 (0.1)	0	0	0	1 (0.1)	0
Infections and infestations	3 (0.4)	5 (0.7)	6 (1.0)	7 (1.1)	9 (0.7)	12 (0.9)
Pneumonia	0	0	2 (0.3)	3 (0.5)	2 (0.2)	3 (0.2)
Septic shock	0	0	2 (0.3)	0	2 (0.2)	0
Cellulitis	1 (0.1)	0	0	0	1 (0.1)	0
Clostridium difficile colitis	1 (0.1)	1 (0.1)	0	0	1 (0.1)	1 (0.1)
Pyothorax	0	0	1 (0.2)	0	1 (0.1)	0
Sepsis	0	1 (0.1)	1 (0.2)	0	1 (0.1)	1 (0.1)
Tuberculosis	0	0	1 (0.2)	0	1 (0.1)	0
Urinary tract infection	0	0	1 (0.2)	0	1 (0.1)	0
Wound infection	1 (0.1)	1 (0.1)	0	0	1 (0.1)	1 (0.1)

**Table 11.3–2. Incidence of Adverse Events Leading to Discontinuation of Study Drug or Withdrawal from Study, Phase 3 Studies for cSSSI and CABP—Safety Population**

<b>System Organ Class/ Preferred Term</b>	<b>cSSSI (06, 07)</b>		<b>CABP (08, 09)</b>		<b>Pooled Phase 3 Studies (06, 07, 08, 09)</b>	
	<i>Ceftaroline (N = 692) n(%)</i>	<i>Vancomycin plus Aztreonam (N = 686) n(%)</i>	<i>Ceftaroline (N = 613) n(%)</i>	<i>Ceftriaxone (N = 615) n(%)</i>	<i>Ceftaroline (N = 1305) n(%)</i>	<i>Pooled Comparators (N = 1301) n(%)</i>
Endocarditis	0	0	0	1 (0.2)	0	1 (0.1)
Lung abscess	0	0	0	2 (0.3)	0	2 (0.2)
Osteomyelitis	0	1 (0.1)	0	0	0	1 (0.1)
Pulmonary tuberculosis	0	0	0	1 (0.2)	0	1 (0.1)
Viral infection	0	1 (0.1)	0	0	0	1 (0.1)
Investigations	2 (0.3)	2 (0.3)	1 (0.2)	1 (0.2)	3 (0.2)	3 (0.2)
Blood creatinine increased	1 (0.1)	0	1 (0.2)	0	2 (0.2)	0
Blood urea increased	1 (0.1)	0	0	0	1 (0.1)	0
Electrocardiogram QRS complex prolonged	1 (0.1)	0	0	0	1 (0.1)	0
Hepatic enzyme increased	0	0	0	1 (0.2)	0	1 (0.1)
Laboratory test abnormal	0	1 (0.1)	0	0	0	1 (0.1)
Platelet count decreased	0	1 (0.1)	0	0	0	1 (0.1)
Metabolism and nutrition disorders	0	1 (0.1)	0	1 (0.2)	0	2 (0.2)
Dehydration	0	1 (0.1)	0	0	0	1 (0.1)
Type 1 diabetes mellitus	0	0	0	1 (0.2)	0	1 (0.1)



**Table 11.3–2. Incidence of Adverse Events Leading to Discontinuation of Study Drug or Withdrawal from Study, Phase 3 Studies for cSSSI and CABP—Safety Population**

<i><b>System Organ Class/ Preferred Term</b></i>	<i><b>cSSSI (06, 07)</b></i>		<i><b>CABP (08, 09)</b></i>		<i><b>Pooled Phase 3 Studies (06, 07, 08, 09)</b></i>	
	<i>Ceftaroline (N = 692) n(%)</i>	<i>Vancomycin plus Aztreonam (N = 686) n(%)</i>	<i>Ceftaroline (N = 613) n(%)</i>	<i>Ceftriaxone (N = 615) n(%)</i>	<i>Ceftaroline (N = 1305) n(%)</i>	<i>Pooled Comparators (N = 1301) n(%)</i>
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	4 (0.7)	1 (0.2)	4 (0.3)	1 (0.1)
Lung neoplasm malignant	0	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Malignant neoplasm progression	0	0	1 (0.2)	0	1 (0.1)	0
Metastases to liver	0	0	1 (0.2)	0	1 (0.1)	0
Metastatic neoplasm	0	0	1 (0.2)	0	1 (0.1)	0
Nervous system disorders	0	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Headache	0	0	1 (0.2)	0	1 (0.1)	0
Cerebrovascular accident	0	0	0	1 (0.2)	0	1 (0.1)
Renal and urinary disorders	0	1 (0.1)	1 (0.2)	0	1 (0.1)	1 (0.1)
Renal failure	0	0	1 (0.2)	0	1 (0.1)	0
Renal failure acute	0	1 (0.1)	0	0	0	1 (0.1)

**Table 11.3–2. Incidence of Adverse Events Leading to Discontinuation of Study Drug or Withdrawal from Study, Phase 3 Studies for cSSSI and CABP—Safety Population**

<i><b>System Organ Class/ Preferred Term</b></i>	<i><b>cSSSI (06, 07)</b></i>		<i><b>CABP (08, 09)</b></i>		<i><b>Pooled Phase 3 Studies (06, 07, 08, 09)</b></i>	
	<i>Ceftaroline (N = 692) n(%)</i>	<i>Vancomycin plus Aztreonam (N = 686) n(%)</i>	<i>Ceftaroline (N = 613) n(%)</i>	<i>Ceftriaxone (N = 615) n(%)</i>	<i>Ceftaroline (N = 1305) n(%)</i>	<i>Pooled Comparators (N = 1301) n(%)</i>
Respiratory, thoracic and mediastinal disorders	1 (0.1)	1 (0.1)	6 (1.0)	4 (0.7)	7 (0.5)	5 (0.4)
Pulmonary embolism	0	0	2 (0.3)	2 (0.3)	2 (0.2)	2 (0.2)
Respiratory failure	0	0	2 (0.3)	0	2 (0.2)	0
Acute pulmonary oedema	1 (0.1)	0	0	0	1 (0.1)	0
Interstitial lung disease	0	0	1 (0.2)	0	1 (0.1)	0
Pleural effusion	0	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Pulmonary oedema	0	0	1 (0.2)	0	1 (0.1)	0
Acute respiratory failure	0	0	0	1 (0.2)	0	1 (0.1)
Chronic obstructive pulmonary disease	0	0	0	1 (0.2)	0	1 (0.1)
Pharyngeal oedema	0	1 (0.1)	0	0	0	1 (0.1)
Skin and subcutaneous tissue disorders	8 (1.2)	17 (2.5)	0	1 (0.2)	8 (0.6)	18 (1.4)
Pruritus generalised	2 (0.3)	3 (0.4)	0	0	2 (0.2)	3 (0.2)
Rash	2 (0.3)	4 (0.6)	0	0	2 (0.2)	4 (0.3)
Rash generalised	2 (0.3)	1 (0.1)	0	0	2 (0.2)	1 (0.1)
Rash maculo-papular	2 (0.3)	0	0	0	2 (0.2)	0
Dermatitis allergic	1 (0.1)	2 (0.3)	0	0	1 (0.1)	2 (0.2)
Urticaria	1 (0.1)	2 (0.3)	0	1 (0.2)	1 (0.1)	3 (0.2)

**Table 11.3–2. Incidence of Adverse Events Leading to Discontinuation of Study Drug or Withdrawal from Study, Phase 3 Studies for cSSSI and CABP—Safety Population**

<b><i>System Organ Class/ Preferred Term</i></b>	<b><i>cSSSI (06, 07)</i></b>		<b><i>CABP (08, 09)</i></b>		<b><i>Pooled Phase 3 Studies (06, 07, 08, 09)</i></b>	
	<i>Ceftaroline (N = 692) n(%)</i>	<i>Vancomycin plus Aztreonam (N = 686) n(%)</i>	<i>Ceftaroline (N = 613) n(%)</i>	<i>Ceftriaxone (N = 615) n(%)</i>	<i>Ceftaroline (N = 1305) n(%)</i>	<i>Pooled Comparators (N = 1301) n(%)</i>
Erythema	0	5 (0.7)	0	0	0	5 (0.4)
Generalised erythema	0	1 (0.1)	0	0	0	1 (0.1)
Pruritus	0	3 (0.4)	0	0	0	3 (0.2)
Vascular disorders	0	2 (0.3)	3 (0.5)	1 (0.2)	3 (0.2)	3 (0.2)
Aortic dissection	0	0	1 (0.2)	0	1 (0.1)	0
Cardiovascular insufficiency	0	0	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.1)
Peripheral ischaemia	0	0	1 (0.2)	0	1 (0.1)	0
Hypotension	0	1 (0.1)	0	0	0	1 (0.1)
Thrombophlebitis superficial	0	1 (0.1)	0	0	0	1 (0.1)