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RESEARCH**

*APPLICATION NUMBER:*  
**200327**

**MICROBIOLOGY REVIEW(S)**

# Product Quality Microbiology Review

SEPTEMBER 29, 2010

**NDA:** 200327

**Drug Product Name**

**Proprietary:**

(b) (4)

**Non-proprietary:** ceftaroline fosamil

**Review Number:** 1

## Dates of Submission(s) Covered by this Review

<u>Submit</u>	<u>Received</u>	<u>Review Request</u>	<u>Assigned to Reviewer</u>
December 31, 2009	December 31, 2009	January 13, 2010	January 14, 2010

**Submission History (for amendments only) – N/A**

### **Applicant/Sponsor**

**Name:**

Cerexa Inc.

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**Name of Reviewer:**

Vinayak B. Pawar, Ph.D.

**Conclusion:**

The application is recommended for approval from product quality microbiology standpoint.

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## Product Quality Microbiology Data Sheet

- A. 1. **TYPE OF SUBMISSION:** Original NDA
2. **SUBMISSION PROVIDES FOR:** (b) (4) drug product developed for the treatment of complicated skin and skin structure infection and community-acquired bacterial pneumonia.
3. **MANUFACTURING SITE:**
- ❖ Intermediate bulk is manufactured by (b) (4)
  - ❖ Ceftaroline fosamil for Injection is manufactured by Facta Farmaceutici S.p.A, Termo, Italy.
4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** The clinical dose for (b) (4) is 600 mg (adjusted to 400 mg for moderate renal impairment) every 12 hours by IV infusion administered over 1 hour in adults  $\geq 18$  years of age for 5 to 14 days for the treatment of cSSSI and 5 to 7 days for the treatment of CABP. The drug product (DP) is a sterile powder for injection containing a blend of ceftaroline fosamil and L-arginine. DP strengths per vial are 400 mg and 600 mg of ceftaroline fosamil (anhydrous, (b) (4)).
5. **METHOD(S) OF STERILIZATION:** (b) (4)
6. **PHARMACOLOGICAL CATEGORY:** (b) (4) is indicated for the treatment of complicated skin and skin structure infection (cSSSI) and community-acquired bacterial pneumonia (CABP) caused by designated susceptible bacteria.
- B. **SUPPORTING/RELATED DOCUMENTS:** DMFS  
DMF (b) (4) (OGD micro review 01, Paul Dexter, October/9/2008).  
DMF (b) (4) processes at (b) (4)  
(OGD micro review 01, Stevens-Riley, Marla, November 20, 2007).
- C. **REMARKS:** This application is being submitted for the use of (b) (4)<sup>TM</sup> (ceftaroline fosamil for injection) for intravenous (IV) administration, in accordance with Section 505 (b) (1) of the Federal Food Drug and Cosmetic Act and Section 314.50 of the United States Code of Federal Regulations.

**filename:** N200327R1

## **Executive Summary**

### **I. Recommendations**

- A. Recommendation on Approvability** – Recommended for approval.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable** – N/A

### **II. Summary of Microbiology Assessments**

#### **A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology –**

Intermediate Drug Bulk Product is manufactured at (b) (4) and the process consists of (b) (4) of (b) (4) DS and (b) (4) arginine (b) (4)

(b) (4) Final Drug product is manufactured at Facta Farmaceutica and manufacturing process merely consists of (b) (4)

(b) (4) Finished Product Ceftaroline fosamil for Injection, 400 mg/vial and 600 mg/vial.

- B. Brief Description of Microbiology Deficiencies** - None
- C. Assessment of Risk Due to Microbiology Deficiencies** – N/A

### **III. Administrative**

- A. Reviewer's Signature** \_\_\_\_\_  
Vinayak B. Pawar, Ph.D., NDMS, OPS, CDER
- B. Endorsement Block** \_\_\_\_\_  
Bryan S. Riley, Ph.D., NDMS, OPS, CDER
- C. CC Block**  
N/A

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/s/

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VINAYAK B PAWAR  
09/30/2010

BRYAN S RILEY  
10/01/2010  
I concur.



**DIVISION OF ANTI-INFECTIVE AND OPHTHALMOLOGY DRUG PRODUCTS –HFD-520  
CLINICAL MICROBIOLOGY REVIEW**

NDA: 200-327  
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**PROPOSED INDICATION:**

(b) (4)

**DISPENSED:**

Rx

**RELATED SUBMISSION REVIEWED:**

IND 71,371

**TYPE OF SUBMISSION:**

New Drug Application (NDA)

**PURPOSE OF SUBMISSION:**

The Applicant seeks the approval for the use of use of ceftaroline for the treatment of community acquired bacterial pneumonia (CABP), and complicated skin and skin structure infections (cSSSI).

**SUMMARY AND RECOMMENDATIONS:**

Based on the clinical microbiology data submitted by the Applicant, this NDA submission may be approved, provided that the Applicant makes the changes in the microbiology subsection of the proposed label recommended by the Agency.

(b) (4)

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Based on the Applicant's data which includes MIC population distribution for the target organism, animal data, and human and animal studies that include PK/PD data, the following susceptibility breakpoints are proposed by the Agency (Table 2).

**Susceptibility Test Interpretive Criteria for Ceftaroline**

Pathogen and Isolate Source	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameter in mm)		
	S	I	R	S	I	R
<i>Staphylococcus aureus</i> (includes methicillin-resistant isolates only for skin isolates) See NOTE below	≤ 1 <sup>a</sup>	—	—	≥ 24	—	—
<i>Streptococcus agalactiae</i> <sup>a</sup> (skin isolates only)	≤0.015	—	—	—	—	—
<i>Streptococcus pyogenes</i> <sup>a</sup> (skin isolates only)	≤0.004	—	—	—	—	—
<i>Streptococcus pneumoniae</i> <sup>a</sup> (lower respiratory tract isolates only)	≤ 0.008	—	—	—	—	—
<i>Enterobacteriaceae</i> <sup>b</sup>	≤ 0.25	0.5-1	≥ 2	≥ 24	20-23	≤ 19

S = susceptible, I = intermediate, R = resistant

NOTE: Clinical efficacy of ceftaroline to treat lower respiratory tract infections such as community-acquired bacterial pneumonia due to methicillin-resistant *S. aureus* has not been shown in adequate and well controlled clinical trials (see "Clinical Trials" section 14)

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

<sup>b</sup> Clinical efficacy was shown for the following *Enterobacteriaceae*: *Escherichia coli*, *Klebsiella oxytoca*, and *Klebsiella pneumoniae*

The data submitted by the Applicant supports the inclusion of the following organisms in the CLINICAL INDICATIONS section of the label:

**For cSSSI:**

*Staphylococcus aureus*<sup>a</sup> (including methicillin-resistant isolates) for cSSSI

*S. pyogenes*

*S. agalactiae*

*Enterobacteriaceae*<sup>b</sup>

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<sup>b</sup> Efficacy was shown for the following Enterobacteriaceae: *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*

***For CABP:***

*Staphylococcus aureus* (excluding methicillin-resistant isolates)

*S. pneumoniae*

*Enterobacteriaceae*<sup>b</sup>

<sup>b</sup> Efficacy was shown for the following *Enterobacteriaceae*: *Escherichia coli* and *Klebsiella pneumoniae*.

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**EXECUTIVE SUMMARY**

**Antimicrobial Spectrum of Activity**

The Applicant has submitted data from large prospective surveillance studies and other investigator studies to support the claim that ceftaroline demonstrates in vitro activity against pathogens associated with complicated skin and skin structure infections (cSSSI), and community acquired bacterial pneumonia (CABP). Surveillance studies included *S. aureus* from Europe and the USA and isolates that tested positive for the Panton-valentine leukocidin (*pvl*) gene, heterogeneous vancomycin-intermediate (hVISA), vancomycin-intermediate (VISA), vancomycin-resistant (VRSA), quinupristin/dalfopristin non-susceptible, tetracycline-resistant, mupirocin-resistant, linezolid-resistant, daptomycin nonsusceptible and fluoroquinolone-resistant isolates. The MIC<sub>90</sub> values ranged from 0.12-2µg/ml against all staphylococci tested. A comparison between USA and European isolates show that the MIC<sub>90</sub> values against European methicillin susceptible *S. aureus* isolates were 0.5 mcg/mL or 1 dilution higher than USA MSSA isolates. Against MRSA, the ceftaroline MIC<sub>90</sub> was reported to be 1 mcg/mL for US isolates. MIC<sub>90</sub> values against USA and Europe coagulase-negative staphylococci isolates were 0.5 mcg/mL and 1 mcg/mL, respectively.

Ceftaroline in vitro is active against *S. pneumoniae*, including penicillin-intermediate and –resistant isolates. MIC<sub>90</sub> values ranged from as low as 0.004 – 0.025 mcg/mL against all *S. pneumoniae* isolates. Ceftaroline MIC<sub>90</sub> values were ≤0.016 mcg/mL for some β-hemolytic streptococci isolates. Against penicillin-resistant viridans group streptococci, ceftaroline MIC<sub>90</sub> values were 1 mcg/mL. Ceftaroline activity was also assessed against bacteria belonging to the *Enterobacteriaceae* family from Europe and the USA. The Applicant's data showed that ceftaroline demonstrated activity with MICs ranging from ≤ 0.016 mcg/mL to >32 mcg/mL against all tested isolates of the *Enterobacteriaceae* family. Drastically decreased efficacy was observed against AmpC and ESBL producers and ceftazidime non-susceptible *Enterobacteriaceae* isolates such as *K. pneumoniae*, *K. oxytoca*, *E. coli*, *Enterobacter cloacae*, and *E. aerogenes*.

**Mechanism of Action**

Investigations into the activity of ceftaroline support the claim that it binds to penicillin binding proteins (PBPs) in bacteria. In *S. aureus*, there are four natural PBPs (PBP1-4) and ceftaroline was shown to bind to all, with the highest affinity to PBP2a. A principle factor of the broad-spectrum β-lactam resistance in MRSA isolates is the penicillin-binding protein 2a (PBP2a). PBP2a has low affinity for β-lactam and thus provides transpeptidase activity to allow cell wall synthesis at β-lactam concentrations that inhibit the β-lactam-sensitive PBPs normally produced by *S. aureus*. There are six known PBPs in *S. pneumoniae*; the data suggest that ceftaroline binds to PBP 3, 1A, 2X, 1B and 2A/B and are considered the primary target of ceftaroline. Ceftaroline has high affinity for PBP2x in *S. pneumoniae*.

**Mechanism of Resistance**

Mechanisms of β-lactam resistance in staphylococci may include the production of β-lactamase and modification of the PBP target by either gene acquisition of an exogenous PBP or target alteration. Streptococci resistance to β-lactams is mediated via alterations in the β-lactam-binding site of the PBP1a, PBP2b and PBP2x. Mutations resulting in changes in the active binding sites may correlate with decrease affinity for β-lactams and

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increase MIC. In Gram negative organisms, the predominant mode of  $\beta$ -lactam resistance is the production of  $\beta$ -lactam hydrolyzing enzymes such as extended spectrum  $\beta$ -lactamases (ESBLs). Ceftaroline is hydrolyzed or inactivated by isolates producing ESBLs and AmpC  $\beta$ -lactamase positive bacteria. AmpC  $\beta$ -lactamases have been frequently identified in Gram-negative organisms, of which there are two types plasmid-mediated and chromosomal or inducible AmpC.

### **Resistance Studies**

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

The Applicant has submitted additional in vitro data that show the propensity of ceftaroline to induce AmpC, a  $\beta$ -lactam hydrolyzing enzyme. The production of AmpC has been reported in a variety of *Enterobacteriaceae* and non-fermentative Gram negatives such as *Pseudomonas auregunosa*. AmpC induction may complicate the use of  $\beta$ -lactams for the treatment of infections caused by members of the *Enterobacteriaceae* group of bacteria.

### **Post Antibiotic Effect**

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

### **Effect of Testing Factors on In Vitro Antimicrobial Activity**

The Applicant has submitted data which summarizes the activity of ceftaroline under various in vitro testing conditions. Degradation studies suggest that ceftaroline is stable in Mueller-Hinton Broth (MHB); after two hours at room temperature, there was an insignificant loss of activity. However, a 30% reduction of activity was observed over 24 hours. With this in mind, it may be worthwhile to state in the label that MIC interpretation should not be made after 18 hours due to a reduction of ceftaroline activity.

Increased levels of NaCl, and low pH, correlate with a reduction in growth against the tested organisms and changes in inoculum size caused variation in ceftaroline MIC of the testing organisms. Other variables, including the presence of serum, appear to have had a small but measurable effect on MIC values; ceftaroline MIC values were generally within one doubling dilution of the reference method.

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### **Susceptibility Test Methods**

The Applicant has evaluated the activity of ceftaroline and comparator agents in accordance with Clinical and Laboratory Standards Institute (CLSI) methods. The evaluation methods included broth microdilution, disk diffusion and agar dilution. CLSI methods were used in the development of provisional interpretive criteria and proposed quality control ranges. The Applicant conducted disk content study using six organisms to determine optimal disk loading to achieve zones of inhibition that best correlated with the MIC from broth microdilution. Resistance phenotypes were determined by reference broth microdilution tests followed by confirmatory techniques. PCR screens with mechanism-specific primer sets were also performed on certain strains with unusual resistance patterns.

### **Antimicrobial Interaction Studies**

The Applicant has provided data from synergy studies that evaluated the effect of ceftaroline in combination with other antimicrobial agents against a variety of bacterial isolates, using the checkerboard technique. No antagonism was observed when ceftaroline was tested and compared with other antimicrobial agents. Ceftaroline demonstrated synergy with meropenem against *S. aureus* strain 2296 (CA-MRSA) and *K. pneumoniae* strain (1468 ESBL). Synergy was also observed with amikacin against *E. coli* strain 2273 (ESBL) and *P. aeruginosa* strain 2559. There is not enough information on the synergy of ceftaroline with other antimicrobials to include any information in the package insert. There is sufficient information to show that there was no evidence of in vitro antagonism when ceftaroline was in the presence of vancomycin, linezolid, daptomycin, levofloxacin, azithromycin, amikacin, aztreonam, tigecycline, and meropenem. However, the clinical significance of this lack of antagonism is not known.

### **Human and Animal Studies**

A number of ceftaroline-related pharmacologic studies that determined the time of maximum plasma concentrations for ceftaroline were conducted. Data show that it generally occurred near the end of the infusion; the terminal elimination half-life ( $T_{1/2}$ ) of ceftaroline was in the range of 2 to 3 hours over the dose range studied (mean of  $2.54 \pm 0.29$  hours in healthy adult subjects with normal renal function across studies). The mean  $T_{1/2}$  of ceftaroline in subjects with severe renal impairment was  $5.05 \pm 1.22$  hours compared to  $3.02 \pm 0.43$  hours in subjects with normal renal function.

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

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**Clinical Trials**

**Community-acquired bacteria pneumonia**

Data from the clinical trials indicate that ceftaroline fosamil at a dose of 600 mg administered as a 1-hour IV infusion q12h for 5 to 7 days is effective in the treatment of moderate to severe CABP caused by susceptible strains of the following organisms: *S. pneumoniae*, *S. aureus*, *H. influenzae*, *E. coli*, and *K. pneumoniae* (non-ESBL). For *S. pneumoniae*, the microbiological response rates at TOC were 87.3% for the ceftaroline treatment group compared with 72.9% for the ceftriaxone treatment group in the CABP study. For methicillin-susceptible *S. aureus*, a TOC success rate of 19/25 (76.0%) was reported for ceftaroline compared with 19/27 (70.4%) for ceftriaxone in the ME population. Please note that based on the Applicants exclusion criteria, subjects with MRSA were excluded from the clinical studies since ceftriaxone is not expected to have an effect against MRSA. Therefore, there were no studies conducted against patients infected with MRSA so the efficacy against MRSA in CABP is unknown. Against *H. influenzae*, success rates of 15/18 (83.3%) 17/20 (85.0%) were observed for ceftaroline and ceftriaxone, respectively. Ceftaroline against *Enterobacteriaceae* exhibited an overall microbiological response rate of 87% while ceftriaxone exhibited an overall microbiological response rate of 81% in the ME population.

**Complicated skin and skin structure infections**

In the cSSSI study, the overall microbiological response rates were 92.3% in the ceftaroline group and 93.7% in the vancomycin plus aztreonam group at TOC in the ME Population. The ceftaroline microbiological response rates were 93.7% and 100%, for *S. aureus* and *S. pyogenes* respectively. The response rates for methicillin-susceptible and methicillin-resistant isolates of *S. aureus* were similar 93.9% and 93.4%, respectively, among ceftaroline-treated subjects. Clinical and microbiological response rates were similar among different genotypes of *S. aureus* such as PVL-positive, PVL-negative, and USA300 isolates.

**Applicant Proposed In Vitro Susceptibility Test Interpretive Criteria**

The following table shows the Applicant's proposed interpretive criteria for ceftaroline. The values proposed by the Applicant are not in line with those proposed by the Agency. The FDA proposed values are established using in vitro susceptibility data, pharmacokinetics/pharmacodynamic analysis, clinical experience, and microbiology eradication rates. In determining the interpretive criteria for the package insert the Agency generally uses the MIC value for which there was the most clinical experience as long as this MIC is compatible with the PK parameters of the drug and the activity of the drug against the wild type bacteria associated with the treatment indications studied during clinical trials. Therefore the differences in the Applicant's proposed interpretive criteria (Table 4) and the Agency's is [REDACTED] (b) (4)

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**Applicant's Proposed In Vitro Susceptibility Test Interpretive Criteria**



**FDA Proposed In Vitro Susceptibility Test Interpretive Criteria**

Based on in vitro data, PK/PD data, and data from the ceftaroline clinical trials, the Agency recommends the following in vitro susceptibility test result interpretive criteria for the specified clinical indications (see Table 5. The PK/PD parameters of ceftaroline were supportive of choosing the MIC breakpoints for which there was the most clinical experience at a specific MIC.

The Agency at this time has not proposed disk diffusion interpretive criteria for bacteria other than *Enterobacteriaceae* and *S. aureus* because regression analysis between the proposed FDA MIC interpretive criteria and disk diffusion zone sizes shows poor correlation.

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**Table 5. Susceptibility Test Interpretive Criteria for Ceftaroline**

Pathogen and Isolate Source	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameter in mm)		
	S	I	R	S	I	R
<i>Staphylococcus aureus</i> (includes methicillin-resistant isolates only for skin isolates) See NOTE below	≤ 1 <sup>a</sup>	—	—	≥ 24	—	—
<i>Streptococcus agalactiae</i> <sup>a</sup> (skin isolates only)	≤ 0.015	—	—	—	—	—
<i>Streptococcus pyogenes</i> <sup>a</sup> (skin isolates only)	≤ 0.004	—	—	—	—	—
<i>Streptococcus pneumoniae</i> <sup>a</sup> (lower respiratory tract isolates only)	≤ 0.008	—	—	—	—	—
<i>Enterobacteriaceae</i> <sup>b</sup>	≤ 0.25	0.5-1	≥ 2	≥ 24	20-23	≤ 19

S = susceptible, I = intermediate, R = resistant

NOTE: Clinical efficacy of ceftaroline to treat lower respiratory tract infections such as community-acquired bacterial pneumonia due to methicillin-resistant *S. aureus* has not been shown in adequate and well controlled clinical trials (see “Clinical Trials” section 14)

<sup>a</sup> The current absence of resistant isolates precludes defining any results other than "Susceptible". Isolates yielding MIC results other than “Susceptible” should be submitted to a reference laboratory for further testing.

<sup>b</sup> Clinical efficacy was shown for the following *Enterobacteriaceae*: *Escherichia coli*, *Klebsiella oxytoca*, and *Klebsiella pneumoniae*

The following tables (6-17) provide information on the clinical success and the microbiological eradication rates for specific pathogens at various MICs. This information in correlation with the PK parameters of ceftaroline and the MIC<sub>90</sub> data was used to define the Agency’s MIC interpretive criteria. Complicated Skin and Skin Structure Clinical Study MIC Data from ceftaroline clinical trials are shown below.

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**Table 6: Integrated Clinical and Microbiological Response Rates by MIC for Ceftaroline against *Staphylococcus aureus* from Skin Infections in cSSSI Studies P903-06 and P903-07 Combined**

	<i>N</i>	<i>Clinical Success</i> <i>n/N (%)</i>	<i>Microbiological Success (Eradicated/Presumed Eradicated n/N (%)</i>
<b>Ceftaroline MIC (µg/mL)</b>			
0.06	3	3/3 (100%)	3/3 (100%)
0.12	79	72/79 (91.1%)	73/79 (92.4%)
0.25	156	148/156 (94.9%)	149/156 (95.5%)
0.5	109	102/109 (93.6%)	102/109 (93.6%)
1	11	11/11 (100%)	11/11 (100%)
2	4	2/4 (50.0%)	2/4 (50.0%)
Total	362	338/362 (93.4%)	340/362 (93.9%)

**Table 7. Integrated Clinical and Microbiological Response Rates for Ceftaroline against Methicillin-resistant *Staphylococcus aureus* from Skin Infections in cSSSI Studies P903-06 and P903-07 Combined**

	<i>N</i>	<i>Clinical Success</i> <i>n/N (%)</i>	<i>Microbiological Success (Eradicated/Presumed Eradicated n/N (%)</i>
<b>Ceftaroline MIC (µg/mL)</b>			
0.25	18	18/18 (100%)	18/18 (100%)
0.5	108	101/108 (93.5%)	101/108 (93.5%)
1	11	11/11 (100%)	11/11 (100%)
2	4	2/4 (50.0%)	2/4 (50.0%)
Total	141	132/141 (93.6%)	132/141 (93.6%)

**Table 8. Integrated Clinical and Microbiological Response Rates by MIC for Ceftaroline against Methicillin-susceptible *Staphylococcus aureus* from Skin Infections in cSSSI Studies P903-06 and P903-07 Combined**

	<i>N</i>	<i>Clinical Success n/N (%)</i>	<i>Microbiological Success (Eradicated/Presumed Eradicated n/N (%)</i>
<b>Ceftaroline MIC (µg/mL)</b>			
0.06	3	3/3 (100%)	3/3 (100%)
0.12	79	72/79 (91.1%)	73/79 (92.4%)
0.25	138	130/138 (94.2%)	131/138 (94.9%)
0.5	1	1/1 (100%)	1/1 (100%)
Total	221	206/221 (93.2%)	208/221 (94.1%)

While the most clinical experience with *S. aureus* was at an MIC of 0.5 mcg/mL it would not be appropriate to use  $\leq 0.5$  mcg/mL as the susceptible interpretive criteria since it would split the wild type population for *S. aureus* making a number of isolates resistant to ceftaroline when both MRSA and MSSA isolates could be considered susceptible to ceftaroline based on MIC<sub>90</sub>, PK information, and cumulative clinical study experience. Therefore an interpretive criteria of  $<1$  mcg/mL is appropriate. Information with regards to clinical and microbiological success rates for *S. pyogenes* and *S. agalactiae* in the cSSSI studies are shown in Tables 9 and 10, respectively.

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**Table 9: Clinical and Microbiological Response Rates by MIC for Ceftaroline and Vancomycin against *Streptococcus pyogenes* from Skin Infections in cSSSI Studies P903-06 and P903-07 Combined.**

	<i>N</i>	<i>Clinical Success</i> <i>n/N (%)</i>	<i>Microbiological Success</i> <i>(Eradicated/Presumed Eradicated n/N (%))</i>
<b>Ceftaroline MIC (µg/mL)</b>			
≤ 0.004	55	55/55 (100%)	55/55 (100%)
0.008	1	1/1 (100%)	1/1 (100%)
Total	56	56/56 (100%)	56/56 (100%)
<b>Vancomycin MIC (µg/mL)</b>			
0.25	45	43/45 (95.6%)	43/45 (95.6%)
0.5	11	11/11 (100%)	11/11 (100%)
1	2	2/2 (100%)	2/2 (100%)
Total	58	56/58 (96.6%)	56/58 (96.6%)

Abbreviations: cSSSI = complicated skin and skin structure infection; MIC = minimally inhibitory concentration.

**Table 10: Clinical and Microbiological Response Rates by MIC for Ceftaroline and Vancomycin against *Streptococcus agalactiae* from Skin Infections in cSSSI Studies P903-06 and P903-07 Combined**

	<i>N</i>	<i>Clinical Success</i> <i>n/N (%)</i>	<i>Microbiological Success (Eradicated/Presumed Eradicated n/N (%))</i>
<b>Ceftaroline MIC (µg/mL)</b>			
0.008	9	8/9 (88.9%)	8/9 (88.9%)
0.015	11	11/11 (100%)	10/11 (90.9%)
Total	20	19/20 (95.0%)	18/20 (90.0%)
<b>Vancomycin MIC (µg/mL)</b>			
0.25	2	2/2 (100%)	2/2 (100%)
0.5	15	15/15 (100%)	15/15 (100%)
Total	17	17/17 (100%)	17/17 (100%)

Abbreviations: cSSSI = complicated skin and skin structure infection; MIC = minimally inhibitory concentration.

In the case of *Enterobacteriaceae* associated with cSSSI infection the most clinical experience at specific ceftaroline MICs for specific bacteria is shown below (Table 11). For more information on other *Enterobacteriaceae* see Table 81 in body of review.

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**Table 11: Integrated Clinical and Microbiological Response Rates by MIC for Ceftaroline against *E. coli*, *K. oxytoca*, and *K. pneumoniae* Studies - P903-06 and P903-07 Combined**

Ceftaroline MIC	Number	Clinical Success n/N(%)	Microbiological Eradication n/N (%)
<i>Escherichia coli</i>			
0.015	1	1/1 (100)	1/1 (100)
0.03	2	2/2 (100)	2/2 (100)
0.06	8	8/8 (100)	8/8 (100)
0.12	4	4/4 (100)	4/4 (100)
0.25	1	1/1 (100)	1/1 (100)
0.5	2	2/2 (100)	2/2 (100)
1	1	1/1 (100)	1/1 (100)
2	1	0/1 (0)	0/1 (0)
>16	1	1/1 (100)	1/1 (100)
<i>Klebsiella oxytoca</i>			
0.03	1	1/1 (100)	1/1 (100)
0.06	4	3/4 (75)	4/4 (100)
0.12	1	1/1 (100)	1/1 (100)
0.25	5	5/5 (100)	5/5 (100)
<i>Klebsiella pneumoniae</i>			
0.03	2	1/2 (50)	1/2 (50)
0.06	7	7/7 (100)	7/7 (100)
0.12	6	6/6 (100)	6/6 (100)
0.25	1	1/1 (100)	1/1 (100)
>16	2	2/2 (100)	2/2 (100)

Community Acquired Bacterial Pneumonia Clinical Study MIC Data (Table 12)

**Table 12: Clinical and Microbiological Success by Ceftaroline MIC against *Streptococcus pneumoniae* from CABP Studies P903-08 and P903-09 Combined**

Ceftaroline MIC (µg/mL)	N	Clinical Success n/N (%)	Microbiological Success (Eradicated/Presumed Eradicated n/N (%))
≤ 0.004	4	4/4 (100.0%)	4/4 (100.0%)
0.008	20	16/20 (80.0%)	16/20 (80.0%)
0.015	8	6/8 (75.0%)	7/8 (87.5%)
0.03	2	2/2 (100.0%)	2/2 (100.0%)
0.06	1	1/1 (100.0%)	1/1 (100.0%)
0.25	1	1/1 (100.0%)	1/1 (100.0%)
Total	36	30/36 (83.3%)	31/36 (86.1%)

Abbreviations: CABP = community acquired bacterial pneumonia; MIC = minimal inhibitory concentration.

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**Table 13: Integrated Clinical and Microbiological Response Rates by MIC for Ceftaroline and Ceftriaxone Against MDR *Streptococcus pneumoniae* in CABP Studies P903-08 and P903-09**

	<i>N</i>	<i>Clinical Success</i> <i>n/N (%)</i>	<i>Microbiological Success</i> <i>(Eradicated/Presumed</i> <i>Eradicated n/N (%)</i>
<b>Ceftaroline MIC (µg/mL)</b>			
≤ 0.015	2	2/2 (100%)	2/2 (100%)
0.03	1	1/1 (100%)	1/1 (100%)
0.12	1	1/1 (100%)	1/1 (100%)
Total	4	4/4 (100%)	4/4 (100%)
<b>Ceftriaxone MIC (µg/mL)</b>			
0.12	1	0/1 (0%)	1/1 (100%)
0.5	1	0/1 (0%)	0/1 (0%)
1	1	1/1 (100%)	1/1 (100%)
2	1	0/1 (0%)	0/1 (0%)
Total	4	1/4 (25.0%)	2/4 (50.0%)

Abbreviations: CABP = community acquired bacterial pneumonia; MIC = minimal inhibitory concentration.  
Source: Table 2.1.3a and Table 2.2.3a.

**Table 14: Integrated Clinical and Microbiological Response Rates by MIC for Ceftaroline Against Penicillin-intermediate *Streptococcus pneumoniae* in CABP Studies P903-08 and P903-09**

<i>Ceftaroline MIC (µg/mL)</i>	<i>N</i>	<i>Clinical Success</i> <i>n/N (%)</i>	<i>Microbiological Success</i> <i>(Eradicated/Presumed</i> <i>Eradicated n/N (%)</i>
0.12	1	1/1 (100%)	1/1 (100%)
Total	1	1/1 (100%)	1/1 (100%)

Abbreviations: CABP = community acquired bacterial pneumonia; MIC = minimal inhibitory concentration.  
Source: Table 2.1.3a and Table 2.2.3a.

Since there was very limited experience during clinical trials using ceftaroline to treat CABP due to penicillin-resistant *S. pneumoniae* (PRSP) it would not be appropriate to indicate in the package insert that ceftaroline can be used to treat CABP due to PRSP. Table 15 shows the clinical and microbiological success rates for MSSA isolates in the CABP studies. Two MRSA isolates were observed in the ceftriaxone treatment group (Table 16)

**Table 15: Integrated Clinical and Microbiological Response Rates by MIC for Ceftaroline and Ceftriaxone Against Methicillin-susceptible *Staphylococcus aureus* in CABP Studies P903-08 and P903-09**

	<i>N</i>	<i>Clinical Success</i> <i>n/N (%)</i>	<i>Microbiological Success</i> <i>(Eradicated/Presumed</i> <i>Eradicated n/N (%)</i>
<b>Ceftaroline MIC (µg/mL)</b>			
0.12	3	2/3 (66.7%)	2/3 (66.7%)
0.25	21	16/21(76.2%)	16/21(76.2%)
0.5	1	0/1 (0.0%)	1/1 (100%)
Total	25	18/25 (72.0%)	19/25 (76.0%)
<b>Ceftriaxone MIC (µg/mL)</b>			
2	3	2/3 (66.7%)	2/3 (66.7%)
4	21	12/21(57.1%)	16/21 (76.2%)
Total	24	14/24 (58.3%)	18/24 (75.0%)

Abbreviations: CABP = community acquired bacterial pneumonia; MIC = minimal inhibitory concentration.  
Source: Table 2.1.3a and Table 2.2.3a.

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**Table 16: Integrated Clinical and Microbiological Response Rates by MIC for Ceftriaxone against Methicillin-Resistant *Staphylococcus aureus* in CABP Studies P903-8 and P903-9**

<i>Ceftriaxone MIC (µg/mL)</i>	<i>N</i>	<i>Clinical Success n/N (%)</i>	<i>Microbiological Success (Eradicated/Presumed Eradicated n/N (%)</i>
8	1	0/1 (0%)	0/1 (0%)
32	1	1/1 (100%)	1/1 (100%)
Total	2	1/2 (50.0%)	1/2 (50.0%)

Abbreviations: CABP = community acquired bacterial pneumonia; MIC = minimal inhibitory concentration.

Source: Table 2.1.3a and Table 2.2.3a.

Based on the Applicants inclusion/exclusion criteria, there were no MRSA isolates in the ceftaroline-treated CABP subjects. Two isolates in the ceftriaxone-treated group were reported with a clinical and microbiological success of 50%. One microbiological failure occurred at a ceftriaxone MIC of 8 mcg/mL. Table 17 shows the clinical and microbiological success rates for *H. influenzae* in both CABP studies.

**Table 17: Clinical and Microbiological Success by Ceftaroline MIC against *Haemophilus influenzae* from CABP Studies P903-08 and P903-09**

<i>Ceftaroline MIC (µg/mL)</i>	<i>N</i>	<i>Clinical Success n/N (%)</i>	<i>Microbiological Success (Eradicated/Presumed Eradicated n/N (%)</i>
≤ 0.008	8	5/8 (62.5%)	5/8 (62.5%)
0.015	5	5/5 (100.0%)	5/5 (100.0%)
0.03	3	3/3 (100.0%)	3/3 (100.0%)
Total	16	13/16 (81.2%)	13/16 (81.2%)

Abbreviations: CABP = community acquired bacterial pneumonia; MIC = minimal inhibitory concentration.

In the case of *Enterobacteriaceae* associated with CABP infection the most clinical experience at specific ceftaroline MICs for specific bacteria is shown below (Table 18). For more information on other *Enterobacteriaceae* associated with CABP see Table 97 in body of review.

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**Table 18: Integrated Clinical and Microbiological Response Rates by MIC for Ceftaroline against *E. coli*, *K. oxytoca*, and *K. pneumoniae* – Studies P903-08 and P903-08 Combined**

Ceftaroline MIC	Number	Clinical Success n/N(%)	Microbiological Eradication n/N (%)
<i>Escherichia coli</i>			
0.03	4	3/4 (75)	3/4 (75)
0.06	5	5/5 (100)	5/5 (100)
0.12	1	0/1 (0)	0/1 (0)
0.5	1	1/1 (100)	1/1 (100)
1	1	1/1 (100)	1/1 (100)
<i>Klebsiella oxytoca</i>			
0.03	1	0/1 (0)	0/1 (0)
0.06	3	3/3 (100)	3/3 (100)
0.25	2	2/2 (100)	2/2 (100)
<i>Klebsiella pneumoniae</i>			
0.06	3	73/3(100)	3/3 100)
0.12	3	3/3 (100)	3/3 (100)
0.25	3	3/3 (100)	3/3 (100)
0.5	3	3/3 (100)	3/3 (100)

Table 19 shows the acceptable quality control ranges for ceftaroline susceptibility testing against the specified American Type Culture Collection (ATCC) strains.

**Table 19: Acceptable quality control ranges for susceptibility testing**

Quality Control Organism	Minimum Inhibitory Concentrations (µg/mL)	Disk Diffusion (zone diameters in mm)
<i>Staphylococcus aureus</i> ATCC 25923	Not Applicable	26-35
<i>Staphylococcus aureus</i> ATCC 22913	0.12 - 0.5	NA
<i>Escherichia coli</i> ATCC 25922	0.03 - 0.12	26-34
<i>Haemophilus influenzae</i> ATCC 49247	0.03 - 0.12	29-39
<i>Streptococcus pneumoniae</i> ATCC 49619	0.008 - 0.03	31-41

Abbreviations: ATCC = American Type Culture Collection.

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**AGENCY’S PROPOSED MICROBIOLOGY SUBSECTION OF THE CEFTAROLINE PACKAGE  
INSERT**

(b) (4)



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**INTRODUCTION**

**β-LACTAMS (PENICILLINS AND CEPHALOSPORINS)**

The discovery of antibiotics in the 20<sup>th</sup> century represented a significant medical evolution in the treatment and management of patients with bacterial associated infections. Before the discovery of drugs to treat bacterial infections, it was not uncommon to observe high mortality rates associated with blood stream infections caused by *Staphylococcus aureus*<sup>1</sup>. *Staphylococcus aureus* is commonly associated with a variety of invasive diseases such as community acquired pneumonia, skin and soft tissue infections, and bacteremia.

The introduction of antibiotics, such as penicillin, has dramatically reduced mortality rates. Penicillin, first discovered in 1928 by Sir Alexander Fleming, was isolated from the fungus *Penicillium chrysogenum* (formally *Penicillium notatum*)<sup>2</sup>. However, it was not until the 1940's that the methods for mass producing large quantities of penicillin became available. Penicillin belongs to a class of antibiotics which is characterized by the β-lactam ring structure. Since its discovery, penicillin has been used to treat a wide variety of bacterial associated infections. With wide spread use, resistance to penicillin mediated by the production of β-lactamase, was reported. There is a strong association with the emergence of resistance and the widespread clinical use of penicillin and other antimicrobial agents.

Resistance to β-lactam antibiotics is mediated by the production of a bacterial enzyme that hydrolyzes the β-lactam ring structure thereby inactivating it. The β-lactam antibiotics target penicillin-binding proteins (PBPs) thereby inhibiting the late stages of peptidoglycan biosynthesis<sup>3</sup>. Peptidoglycan is composed of long polysaccharide chains and pentapeptide which consist of amino acids. The reaction joining of the pentapeptide with the polysaccharide chain is catalyzed by transpeptidases that forms an amide bond within the structure of the cell wall<sup>2</sup>. It is this transpeptidase reaction that is sensitive to β-lactam antibiotics. Moreover, it is this emergence of resistance that has been the driving force for the development and modification to drugs based around the β-lactam ring structure. As a result, a number of antibiotics based on the β-lactam ring have increased significantly. Antibiotics such as methicillin and ampicillin were all developed with medication to the chemical structure protecting it from bacterial penicillinase enzymes. Following the development of new β-lactam antibiotics new mechanism of resistance emerged. In the late 1950's resistance to methicillin by *S. aureus* was first observed and this resistance resulted from the genetic acquisition of the *mecA* gene that encodes PBP2a whose enzymatic activity is resistant to methicillin.

Clinically, β-lactams are considered to have a time dependent activity against bacteria and show little in terms of concentration dependent activity. Published studies have shown that serum levels are required to be approximately 4-times over the MIC of the infecting bacteria and be maintained 50% of the time between dosing<sup>4</sup>. This level maybe maintained by continuous infusion of the β-lactam thereby avoiding subinhibitory concentrations which promote the emergence of resistance. Therefore, to achieve continuous β-lactam concentrations when treating severe infections, the MIC of the infecting organisms and the site of infection must be determined.

The cephalosporins were first produced by fermentation of *Cephalosporium acremonium* in 1945. However, it was not until 1964 that the first cephalosporin was introduced for clinical use by Eli Lilly<sup>5</sup>. The mechanism of activity is similar to that of other β-lactam antibiotics. Cephalosporin act by binding to PBPs and interfere with

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bacterial growth by affecting cell wall synthesis. The structural backbone includes a  $\beta$ -lactam ring fused to sulfur containing 6-member dihydrothiazine ring. These compounds are chemically engineered by various substitutions of the dihydrothiazine ring thereby creating novel compounds capable of inhibiting the PBP2a enzyme. Modifications to cephalosporin result in changes to the microbiologic and pharmacologic differences and serves as a basis for classification. There are currently 4 generations of cephalosporin based on varying substitution on the dihydrothiazine ring. These compounds have demonstrated antimicrobial activity against both Gram-negative and –positive organisms. Newly designed cephalosporins, such as ceftobiprole and ceftaroline, that demonstrate activity against MRSA, penicillin-resistant *Streptococcus pneumoniae*, and some enterococci while retaining some Gram-negative coverage (e.g. activity against *Pseudomonas aeruginosa*) are considered next generation (generation 5) cephalosporins due to their enhance coverage<sup>6</sup>. However, as with all antimicrobials in clinical use today, the growing medical concern has been the emergence of resistance among bacterial isolates by the acquisition of novel resistant mechanisms. Resistance mechanisms to cephalosporin include hydrolyzing of the  $\beta$ -lactamase enzyme, alteration of the PBP target, and increased efflux of the drug.

The Applicant has elected to develop Ceftaroline (b) (4) for Complicated Skin and Skin Structure Infection (cSSSI) and Community-Acquired Pneumonia (CAP). Ceftaroline is said to be a sterile, synthetic, prodrug belonging to the cephalosporin class of antibiotics that has bactericidal activity against (b) (4) Gram-positive bacteria such as *Streptococcus pneumoniae*, and Gram-negatives.

### **COMPLICATED SKIN AND SKIN STRUCTURE INFECTIONS (cSSSI)**

Skin and skin structure infections represent one of the most common indications for antibiotic therapy and skin infections. They are common and range from minor skin infections to severe necrotizing infections which may require surgical intervention such wound drainage<sup>7,8</sup>. Skin and skin structure infection are considered complicated when they involves deeper layers of soft tissue such as fascia and muscle tissue. Complicated infections including extensive cellulitis, abscess, traumatic or surgical wound infections, and foot infections in diabetic patients are both severe and complex to treat. Therefore, one of the most important aspects of treating complicated skin infection is the clinical assessment of the severity of infection<sup>7,9</sup>. The etiological agent associated with complicated skin and skin-structure infections (cSSSI) are predominantly *S. aureus* and streptococci, including Group A and Group B  $\beta$ -hemolytic streptococci (*S. pyogenes* and *S. agalactiae*, respectively). It is also not uncommon to find mix Gram-positive and –negative aerobic and anaerobic bacteria in cSSSI<sup>10,11</sup>.

To complicate matters, a growing concern in the medical community has been the widespread emergence of multidrug-resistance among bacterial pathogens including hospitalized and community acquired MRSA. It is not uncommon for community-acquired MRSA to harbor the novel type IV staphylococcal cassette chromosome (SCC)mec element<sup>12</sup>. This cassette typically confers resistance to  $\beta$ -lactam antibiotics, and sometimes contains the Panton–Valentine virulence gene (*pvl*), which may be involved in the pathogenesis of necrotizing skin or lung infections. In some communities within the United States The USA300 clone has been associated with community associated *Staphylococcus aureus* (CA-MRSA) infections. USA300 clones are characterized by the presence of SCCmec IV that confers resistance to methicillin, the Panton-Valentine leukocidin (PVL), and the arginine catabolic mobile element (ACME)<sup>12,13</sup>.

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### **COMMUNITY ACQUIRED BACTERIAL PNEUMONIA (CABP)**

Reports of community-onset skin infections, outbreaks of furunculosis, and severe pneumoniae associated with MRSA harboring the *pvl* gene and the type IV staphylococcal cassette chromosome (SCC) *mec* element have indicated that MRSA infections are evolving into a community-related dilemma<sup>13</sup>. Community acquired pneumonia (CAP) is a leading cause of death from an infectious disease in the USA<sup>14</sup>. Approximately 6 million cases occur each year, with persons 65 years or older accounting for 30% of those cases. The mortality rate of individuals who are admitted to the hospital is estimated at 12% but increases to 30-40% for those with severe CAP who require admission to the intensive care unit<sup>15</sup>.

Bacterial etiology may differ slightly in accordance to the severity of CAP. *Streptococcus pneumoniae* remains the most common pathogen associated with all severity, including ambulatory patients, hospitalized (non-ICU) patients and severe (ICU) patients. However, *Mycoplasma pneumoniae*, *Haemophilus influenzae*, and *Chlamydomphila pneumoniae* *Staphylococcus aureus*, *Legionella species*, and gram-negative pathogens, including *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, are associated with some form of CAP, ranging from mild to severe. *Staphylococcus aureus* (MRSA) has also been observed as a cause of severe CAP<sup>16,17</sup>.

### **FACTORS INFLUENCING THE MANAGEMENT OF INFECTIONS**

The routes of administration, the pharmacokinetic-pharmacodynamic profile of the antimicrobial agent and the dosing of the drug are some of the factors that must be considered in the treatment and management of infections. Studies have shown that the majority of bacterial infections are present in the extracellular compartment of tissues rather than in the plasma, and the interstitial fluid of tissues and other body fluids. Therefore, antibiotic penetration into fluids and tissues at infection sites is valuable in predicting therapeutic outcomes and that successful therapy often relies on the unbound antibiotic concentration at the site of action<sup>18</sup>.

For an antimicrobial to be effective it is important that the drug is present at the site of the bacterial infection. In some instances, treatment failures have been attributed to antimicrobials characterized as being highly protein bound in serum despite achieving concentrations in serum that are above the MIC for the target pathogens<sup>19</sup>. For bacterial pneumoniae, the delivery of treatment agent depends on the availability of the unbound concentrations of antibiotic to the infection area. The availability of unbound drug concentrations may also depend on the molecular size, drug diffusion, and a myriad of host factors. Therefore it is also important to measure the concentration of drug from sites including sputum, bronchial secretions, and whole tissue homogenates to determine drug penetration or accessibility<sup>18</sup>. In the case of cSSSI, it is important to obtain culture specimens for documentation of bacteria and for susceptibility testing to guide treatment<sup>20</sup>.

## **ACTIVITY IN VITRO**

### **ANTIMICROBIAL SPECTRUM OF ACTIVITY:**

The Applicant submitted in vitro data from large surveillance and independent studies to support the claim that ceftaroline is active against pathogens associated with complicated skin and skin structure infections and community acquired pneumonia. Ceftaroline has demonstrated activity against a wide range of Gram positive

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organisms associated with skin infections and community acquired pneumonias and Gram- negative bacteria including those sought after in the proposed indication. The Applicant has also submitted in vitro data from a number of centers across the world and the results are summarized and tabulated below. The MICs were determined by referenced broth and agar dilution methods with the appropriate quality control using Clinical Laboratory Standard Institute (CLSI) approved guidelines.

**Activity against Gram-positive Organisms:**

The in vitro activity of ceftaroline was evaluated against 14,000 staphylococci isolates. Organisms tested included those isolated from hospital-associated infections (HA-MRSA), community-associated infections (CA-MRSA), coagulase-negative staphylococci (CoNS), including those resistant to methicillin. In addition to testing methicillin resistant isolates, the Applicant included isolates with other resistant phenotype including heterogeneous vancomycin-intermediate (hVISA), vancomycin-intermediate (VISA), vancomycin-resistant (VRSA), quinupristin/dalfopristin non-susceptible, tetracycline-resistant, mupirocin-resistant, linezolid-resistant, daptomycin nonsusceptible and fluoroquinolone-resistant isolates. Included in the data were surveillance of clinical isolates of *S. aureus* from the United States and Europe. Surveillance studies also included isolates that tested positive for the Panton-valentine leukocidin (*pvl*) gene. Susceptibility testing of the isolates was conducted using Clinical Laboratory Standard Institute (CLSI) approved guidelines (Table 1).

**Table 1: Summary of In Vitro Studies to Evaluate the Activity of Ceftaroline Against *Staphylococcus* Species**

Pathogen	N	Range	Ceftaroline MIC, µg/mL		Method	Pathogen	N	Range	Ceftaroline MIC, µg/mL		Method	
			50%	90%					50%	90%		
<b><i>Staphylococcus aureus</i></b>						<b><i>Staphylococcus aureus</i></b>						
All	94	0.12-2	0.5	1	Broth microdilution (CLSI)	methicillin-resistant (CA-MRSA)	152	0.25 - 1	0.5	0.5	Broth microdilution (CLSI)	
methicillin-susceptible	32	0.12-0.25	0.25	0.25		<b><i>Staphylococcus aureus</i></b>	All	1009	≤ 0.03 - 2	0.5	1	Broth microdilution (CLSI)
methicillin-resistant	62	0.25-2	0.5	1			methicillin-susceptible	348	≤ 0.03 - 1	0.25	0.25	
mupirocin-resistant	2	0.25-0.5	NA	NA			methicillin-resistant	661	0.12 - 2	0.5	1	
tetracycline-resistant MSSA	3	0.12-0.25	NA	NA		<b>Coagulase-negative staphylococci</b>						
tetracycline-resistant gentamicin-resistant MSSA	1	0.25	NA	NA		All	500	≤ 0.03 - 2	0.25	0.25	Broth microdilution (CLSI)	
linezolid-NS	4	0.5-1	NA	NA		methicillin-susceptible	201	≤ 0.03 - 0.5	0.06	0.12		
ciprofloxacin-resistant MSSA	18	0.12-0.25	0.25	0.25		methicillin-resistant	299	0.06 - 2	0.5	0.5		
hVISA / VISA	26	0.25-2	0.5	2		<b><i>Staphylococcus aureus</i></b>						
<b><i>Staphylococcus epidermidis</i></b>						<b><i>Staphylococcus aureus</i></b>						
All	21	0.06-1	0.25	0.5		Broth microdilution (CLSI)	methicillin-susceptible	25	0.125-0.25	0.25	0.25	Broth microdilution (CLSI)
methicillin-susceptible	9	0.06-0.12	0.06	NA			methicillin-resistant	25	0.5-2	1	2	
methicillin-resistant	12	0.25-1	0.5	1			<b>Coagulase-negative staphylococci</b>					
mupirocin-resistant	1	0.06	NA	NA	methicillin-susceptible		24	≤ 0.015-0.125	0.06	0.125	Broth microdilution (CLSI)	
<b><i>Staphylococcus aureus</i></b>							methicillin-resistant	25	0.06-2	0.5		2
methicillin-susceptible	18	0.25-1	0.5	0.5	<b><i>Staphylococcus aureus</i></b>							
methicillin-resistant	47	0.5-4	1	2	All		111	0.25 - 2	0.5	1	Agar dilution (CLSI)	
hVISA / VISA	19	0.5-2	1	2	methicillin-susceptible		29	0.25 - 0.5	0.25	0.25		
vancomycin-resistant	2	1-1	NA	NA	methicillin-resistant		55	0.5 - 1	0.5	1		
fluoroquinolone-resistant MRSA	10	0.5-4	1	2	vancomycin-intermediate		24	0.25 - 2	1	1		
linezolid-NS	7	0.5-2	2	NA	vancomycin-resistant		3	0.5 - 1	NA	NA		
quinupristin-dalfopristin-NS	5	0.5-4	2	NA	<b>Coagulase-negative staphylococci</b>							
<b>Coagulase-negative staphylococci</b>							All	103	0.03 - 1	0.25	0.5	Broth microdilution (CLSI)
methicillin-susceptible	11	≤ 0.06-0.12	0.12	0.12	methicillin-susceptible	35	0.03 - 0.25	0.06	0.25			
methicillin-resistant	23	0.25-2	0.5	2	methicillin-resistant	68	0.12 - 1	0.25	0.5			
hVISA / VISA	11	0.5-2	1	2	<b><i>Staphylococcus aureus</i></b>							
fluoroquinolone-resistant MRSA	7	0.25-2	0.5	NA	methicillin-susceptible	53	≤ 0.015 - 0.25	0.25	0.25	Broth microdilution (CLSI)		
<b>Coagulase-negative staphylococci</b>						methicillin-resistant	44	0.5 - 2	0.5		2	
methicillin-susceptible	33	≤ 0.015 - 0.25	0.06	0.12	<b>Coagulase-negative staphylococci</b>							
methicillin-resistant	50	0.12 - 2	0.25	1	methicillin-susceptible	33	≤ 0.015 - 0.25	0.06	0.12	Broth microdilution (CLSI)		
<b><i>Staphylococcus aureus</i></b>						methicillin-resistant	50	0.12 - 2	0.25		1	
methicillin-susceptible	136	0.06 - 1	0.12	0.25	<b><i>Staphylococcus aureus</i></b>							
methicillin-resistant	28	0.25 - 2	1	2	methicillin-susceptible	136	0.06 - 1	0.12	0.25	Broth microdilution (CLSI)		
<b>Coagulase-negative staphylococci</b>						methicillin-resistant	28	0.25 - 2	1		2	

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Pathogen	N	Range	Ceftaroline MIC, µg/mL		Method	
			50%	90%		
<b>Staphylococcus aureus</b>						
methicillin-susceptible	60	0.13 - 0.5	0.25	0.5	Broth microdilution (Japanese Standards)	
methicillin-resistant	81	0.25 - 2	1	2		
<b>Staphylococcus epidermidis</b>						
methicillin-susceptible	20	0.06 - 0.5	0.13	0.25	Broth microdilution (Japanese Standards)	
methicillin-resistant	21	0.25 - 1	0.5	1		
<b>Staphylococcus aureus vancomycin-intermediate</b>						
	5	0.5-2	1	NA		
<b>Staphylococcus aureus</b>						
All - USA	3965	≤ 0.008 - 2	0.5	1	Broth microdilution (CLSI)	
All - Europe	2700	0.03 - 4	0.25	1		
methicillin susceptible - USA	1711	≤ 0.008 - 0.5	0.25	0.25		
methicillin-susceptible - Europe	1966	0.03 - 1	0.25	0.5		
methicillin resistant - USA	2254	0.12 - 2	1	1		
methicillin-resistant - Europe	734	0.25 - 4	1	2		
<b>Coagulase-negative staphylococci</b>						
All - USA	638	≤ 0.008 - 2	0.25	0.5		Broth microdilution (CLSI)
All - Europe	434	0.015 - 4	0.25	1		
methicillin susceptible - USA	184	≤ 0.008 - 1	0.06	0.25		
methicillin-susceptible - Europe	104	0.015 - 0.5	0.06	0.12		
methicillin resistant - USA	454	≤ 0.008 - 2	0.5	1		
methicillin-resistant - Europe	330	0.03 - 4	0.5	2		
<b>Staphylococcus aureus</b>						
CA-MRSA	92	0.25-1	0.5	1	Broth microdilution (CLSI)	
VISA and hVISA	23	0.25-1	0.5	1		
DNSSA	7	0.25-1	0.5	NA		
VRSA	10	0.12-1	0.5	1		
<b>Staphylococcus aureus (HA-MRSA)</b>						
	200	0.125-2	1	1	Broth microdilution (CLSI)	

Pathogen	N	Range	Ceftaroline MIC, µg/mL		Method	
			50%	90%		
<b>Staphylococcus aureus</b>						
All	633	0.12-2	0.5	1	Broth microdilution (CLSI)	
<b>Methicillin-susceptible</b>						
HA-MSSA	14	0.12-0.5	0.25	0.5		
CA-MSSA	86	0.12-0.5	0.25	0.25		
VISA	5	0.25-0.25	0.25	NA		
<b>Methicillin-resistant</b>						
HA-MRSA	275	0.25-2	0.5	1		
CA-MRSA	214	0.25-2	0.5	1		
VISA	39	0.25-2	1	1		
<b>Staphylococcus aureus</b>						
All	453	0.12-2	0.25	1	Agar dilution (BSAC)	
methicillin-susceptible	334	0.12-1	0.25	0.5		
methicillin-resistant	119	0.25-2	1	1		
<b>Coagulase-negative staphylococci</b>						
All	179	≤ 0.002-4	0.25	1	Agar dilution (BSAC)	
methicillin-susceptible	45	0.015-0.5	0.125	0.25		
methicillin-resistant	134	≤ 0.002-4	0.25	1		
<b>Staphylococcus aureus</b>						
methicillin-susceptible	37	0.12-0.25	0.25	0.25	Broth microdilution (CLSI)	
methicillin-resistant	43	0.25-1	0.5	0.5		
VISA	3	0.5-1	NA	NA		
VRSA	2	0.12-0.5	NA	NA		
<b>Staphylococcus epidermidis</b>						
methicillin-susceptible	8	0.06-0.06	0.06	NA	Broth microdilution (CLSI)	
methicillin-resistant	12	0.25-0.5	0.5	0.5		

Abbreviations: h = heterogeneous; CA = community-associated; CLSI = Clinical and Laboratory Standards Institute; HA = hospital-associated; DNSSA = daptomycin-non-susceptible *S. aureus*; hVISA = heterogeneous vancomycin intermediate *S. aureus*; NA = not applicable (for MIC50, fewer than 5 isolates; for MIC90, fewer than 10 isolates); MRSA = methicillin-resistant

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(oxacillin-resistant) *S. aureus*; NS = nonsusceptible; SSCmec I-IV = Staphylococcal cassette chromosome *mec* type I-IV; VISA = vancomycin-intermediate *S. aureus*; VRSA = vancomycin-resistant *S. aureus*.

For all isolates tested, the highest ceftaroline MIC observed for *S. aureus* was 4 µg/ml. This was recorded against some isolates of hVISA, VISA, MRSA, fluoroquinolone-resistant MRSA, and quinupristin-dalfopristin non-susceptible. The MIC<sub>90</sub> values ranged from 0.12 - 2µg/ml against all staphylococci tested. The MIC<sub>90</sub> values for *Staphylococcus aureus* isolates obtained from Europe and the USA were 1 µg/ml, respectively. However, the MIC<sub>90</sub> value against European methicillin susceptible *S. aureus* isolates were 0.5 µg/mL or 1 dilution higher than what was observed against USA MSSA isolates. Against European and USA MRSA isolates, an MIC<sub>90</sub> of 2 µg/mL and 1 µg/mL, respectively, was observed. Generally, MIC<sub>90</sub> values from USA and Europe were within 1 dilution factor of each other, with USA isolates having lower MIC<sub>90</sub> values. Moreover, similar trends were observed for coagulase-negative staphylococci; MIC<sub>90</sub> values against USA and Europe coagulase-negative staphylococci isolates were 0.5 µg/ml and 1 µg/mL, respectively, or within 1 dilution factor.

Data on the activity of ceftaroline against heteroresistant vancomycin-intermediate *S. aureus* (hVISA) and VISA were also submitted. The highest MIC<sub>90</sub> values recorded for hVISA/VISA were 2 µg/mL for *S. aureus* and CoNS, respectively. Table 2 summarizes the in vitro activity of ceftaroline and comparator agents against a panel of *S. aureus* and CoNS isolates from the United States and Europe from a 2008 surveillance study. The ceftaroline MIC<sub>90</sub> value of 0.25 mcg/mL for US isolates of MSSA was lower than all other β-lactam comparators except imipenem (0.12 mcg/mL) and was equal to all tested comparators of other antibiotic classes.

Against MRSA, the ceftaroline MIC<sub>90</sub> of 1 mcg/mL for US isolates was equal to or lower than those for all agents tested except trimethoprim/sulfamethoxazole (≤ 0.5 mcg/mL), daptomycin (0.5 mcg/mL) and tigecycline (0.25 mcg/mL). Against the methicillin-susceptible CoNS US isolates, the MIC<sub>90</sub> of ceftaroline (0.25 mcg/mL) was equal to or lower than all agents except oxacillin (≤ 0.25 mcg/mL) and imipenem (≤ 0.12 mcg/mL). Against the methicillin-resistant CoNS US isolates, the MIC<sub>90</sub> for ceftaroline (1 mcg/mL) was lower than all agents except daptomycin (0.5 mcg/mL) and tigecycline (0.25 mcg/mL).

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**Table 2: In Vitro Activity of Ceftaroline and Selected Antimicrobial Agents against *Staphylococcus aureus* Isolates from the US and Europe (*S. aureus* and broken down by MSSA, MRSA and CoNS)**

Organism Group & Agent	US Isolates				European Isolates			
	MIC, µg/mL			% S <sup>a</sup>	MIC, µg/mL			% S <sup>a</sup>
	Range	MIC <sub>50</sub>	MIC <sub>90</sub>		Range	MIC <sub>50</sub>	MIC <sub>90</sub>	
<i>Staphylococcus aureus</i> - All	3965 isolates				2700 isolates			
Ceftaroline	≤ 0.008 - 2	0.5	1	NA	0.03 - 4	0.25	1	NA
Oxacillin	≤ 0.25 - > 2	> 2	> 2	43.2	≤ 0.25 - > 2	0.5	> 2	72.8
Ceftriaxone	≤ 0.25 - > 32	32	> 32	43.2	1 - > 32	4	> 32	72.8
Cefepime	0.25 - > 16	8	> 16	43.2	≤ 0.12 - > 16	2	> 16	72.8
Imipenem	≤ 0.12 - > 8	≤ 0.12	8	43.2	≤ 0.12 - > 8	≤ 0.12	4	72.8
P/T	≤ 0.5 - > 64	16	> 64	43.2	≤ 0.5 - > 64	1	64	72.8
Erythromycin	≤ 0.25 - > 2	> 2	> 2	31.3	≤ 0.25 - > 2	≤ 0.25	> 2	70.0
Clindamycin	≤ 0.25 - > 2	≤ 0.25	> 2	76.8	≤ 0.25 - > 2	≤ 0.25	> 2	88.0
Levofloxacin	≤ 0.5 - > 4	≤ 0.5	> 4	54.7	≤ 0.5 - > 4	≤ 0.5	> 4	72.5
SXT	≤ 0.5 - > 2	≤ 0.5	≤ 0.5	98.5	≤ 0.5 - > 2	≤ 0.5	≤ 0.5	99.3
Linezolid	0.25 - > 8	2	2	99.9	0.25 - 4	2	2	100
Vancomycin	≤ 0.12 - 2	1	1	100	0.25 - 2	1	1	100
Daptomycin	≤ 0.06 - 4	0.25	0.5	99.8	≤ 0.06 - 1	0.25	0.5	100
Tigecycline	≤ 0.03 - 1	0.12	0.25	> 99.9	≤ 0.03 - 1	0.12	0.25	> 99.9

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Organism Group & Agent	US Isolates				European Isolates				Organism Group & Agent	US Isolates				European Isolates			
	MIC, µg/mL			% S <sup>a</sup>	MIC, µg/mL			% S <sup>a</sup>		MIC, µg/mL			% S <sup>a</sup>	MIC, µg/mL			% S <sup>a</sup>
	Range	MIC <sub>50</sub>	MIC <sub>90</sub>		Range	MIC <sub>50</sub>	MIC <sub>90</sub>			Range	MIC <sub>50</sub>	MIC <sub>90</sub>		Range	MIC <sub>50</sub>	MIC <sub>90</sub>	
MSSA	1711 isolates				1966 isolates				CoNS - All	638 isolates				434 isolates			
Ceftaroline	≤0.008 - 0.5	0.25	0.25	NA	0.03 - 1	0.25	0.5	NA	Ceftaroline	≤0.008 - 2	0.25	0.5	NA	0.015 - 4	0.25	1	NA
Oxacillin	≤0.25 - 2	0.5	0.5	100	≤0.25 - 2	0.5	0.5	100	Oxacillin	≤0.25 - >2	>2	>2	28.8	≤0.25 - >2	>2	>2	24.0
Ceftriaxone	0.5 - 16	4	4	99.6	1 - 32	4	4	99.8	Ceftriaxone	≤0.25 - >32	8	>32	28.8	≤0.25 - >32	16	>32	24.0
Cefepime	0.25 - 8	2	4	100	0.25 - 8	2	4	100	Cefepime	≤0.12 - >16	2	>16	28.8	0.25 - >16	4	>16	24.0
Imipenem	≤0.12 - 4	≤0.12	≤0.12	100	≤0.12 - 1	≤0.12	≤0.12	100	Imipenem	≤0.12 - >8	≤0.12	>8	28.8	≤0.12 - >8	0.25	>8	24.0
P/T	≤0.5 - 16	1	2	99.9	≤0.5 - 8	1	2	100	P/T	≤0.5 - >64	1	16	28.8	≤0.5 - >64	2	>64	24.0
Erythromycin	≤0.25 - >2	≤0.25	>2	64.1	≤0.25 - >2	≤0.25	>2	84.2	Erythromycin	≤0.25 - >2	>2	>2	32.6	≤0.25 - >2	>2	>2	35.5
Clindamycin	≤0.25 - >2	≤0.25	≤0.25	92.7	≤0.25 - >2	≤0.25	≤0.25	98.0	Clindamycin	≤0.25 - >2	≤0.25	>2	64.9	≤0.25 - >2	≤0.25	>2	67.1
Levofloxacin	≤0.5 - >4	≤0.5	4	88.4	≤0.5 - >4	≤0.5	≤0.5	94.0	Levofloxacin	≤0.5 - >4	4	>4	43.6	≤0.5 - >4	4	>4	45.4
SXT	≤0.5 - >2	≤0.5	≤0.5	98.4	≤0.5 - >2	≤0.5	≤0.5	99.5	SXT	≤0.5 - >2	≤0.5	>2	59.4	≤0.5 - >2	≤0.5	>2	63.6
Linezolid	0.25 - 2	2	2	100	0.5 - 2	2	2	100	Linezolid	0.25 - >8	1	1	98.4	0.12 - >8	1	1	99.5
Vancomycin	≤0.12 - 2	1	1	100	0.25 - 2	1	1	100	Vancomycin	0.25 - 4	1	2	100	≤0.12 - 4	1	2	100
Daptomycin	≤0.06 - 1	0.25	0.5	100	≤0.06 - 1	0.25	0.5	100	Daptomycin	≤0.06 - 4	0.25	0.5	99.5	≤0.06 - 2	0.25	0.5	99.8
Tigecycline	≤0.03 - 0.5	0.12	0.25	100	≤0.03 - 0.5	0.12	0.25	100	Tigecycline	≤0.03 - 0.5	0.12	0.25	NA	≤0.03 - 0.5	0.12	0.25	NA
MRSA	2254 isolates				734 isolates				MS CoNS	184 isolates				104 isolates			
Ceftaroline	0.12 - 2	1	1	NA	0.25 - 4	1	2	NA	Ceftaroline	≤0.008 - 1	0.06	0.25	NA	0.015 - 0.5	0.06	0.12	NA
Oxacillin	>2 - >2	>2	>2	0.0	>2 - >2	>2	>2	0.0	Oxacillin	≤0.25 - ≤0.25	≤0.25	≤0.25	100	≤0.25 - ≤0.25	≤0.25	≤0.25	100
Ceftriaxone	≤0.25 - >32	>32	>32	0.0	4 - >32	>32	>32	0.0	Ceftriaxone	≤0.25 - 16	2	4	99.5	0.5 - 8	2	4	100
Cefepime	1 - >16	16	>16	0.0	≤0.12 - >16	>16	>16	0.0	Cefepime	≤0.12 - 4	0.5	2	100	0.25 - 4	0.5	1	100
Imipenem	≤0.12 - >8	0.5	>8	0.0	≤0.12 - >8	2	>8	0.0	Imipenem	≤0.12 - 1	≤0.12	≤0.12	100	≤0.12 - ≤0.12	≤0.12	≤0.12	100
P/T	≤0.5 - >64	64	>64	0.0	≤0.5 - >64	64	>64	0.0	P/T	≤0.5 - 2	≤0.5	≤0.5	100	≤0.5 - 2	≤0.5	≤0.5	100
Erythromycin	≤0.25 - >2	>2	>2	6.5	≤0.25 - >2	>2	>2	32.0	Erythromycin	≤0.25 - >2	≤0.25	>2	55.4	≤0.25 - >2	≤0.25	>2	65.4
Clindamycin	≤0.25 - >2	≤0.25	>2	64.7	≤0.25 - >2	≤0.25	>2	61.2	Clindamycin	≤0.25 - >2	≤0.25	1	89.7	≤0.25 - >2	≤0.25	≤0.25	92.3
Levofloxacin	≤0.5 - >4	>4	>4	29.1	≤0.5 - >4	>4	>4	15.0	Levofloxacin	≤0.5 - >4	≤0.5	>4	79.9	≤0.5 - >4	≤0.5	>4	89.4
SXT	≤0.5 - >2	≤0.5	≤0.5	98.5	≤0.5 - >2	≤0.5	1	98.9	SXT	≤0.5 - >2	≤0.5	>2	84.8	≤0.5 - >2	≤0.5	>2	89.4
Linezolid	0.25 - >8	2	2	99.9	0.25 - 4	2	2	100	Linezolid	0.25 - >8	1	1	99.5	0.25 - 2	1	1	100
Vancomycin	0.25 - 2	1	1	100	0.25 - 2	1	1	100	Vancomycin	0.25 - 4	1	2	100	0.5 - 2	1	2	100
Daptomycin	0.12 - 4	0.25	0.5	99.7	0.12 - 1	0.25	0.5	100	Daptomycin	≤0.06 - 4	0.25	0.5	98.9	≤0.06 - 1	0.25	0.5	100
Tigecycline	≤0.03 - 1	0.12	0.25	>99.9	≤0.03 - 1	0.12	0.25	99.9	Tigecycline	≤0.03 - 0.5	0.12	0.25	NA	≤0.03 - 0.5	0.12	0.25	NA

<sup>a</sup> % susceptible according to CLSI M100-S19 (2009) or Tygacil Product Insert (2005)

Abbreviations: CoNS = coagulase negative staphylococci; MIC<sub>50</sub> = minimum inhibitory concentration required to inhibit the growth of 50% of organisms; MIC<sub>90</sub> = minimum inhibitory concentration required to inhibit the growth of 90% of organisms; MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*; MS = methicillin susceptible, MR = methicillin resistant; NA = not applicable (breakpoints not defined); P/T = piperacillin-tazobactam; SXT = trimethoprim/sulfamethoxazole; US = United States. Source: Study P0903-M-035, 2009

The Applicant also determined the activity against a number of streptococci isolates. The streptococci addressed were *S. pneumoniae*, β-hemolytic streptococci and viridans group streptococci. *S. pneumoniae* is commonly associated with acute, community-acquired bacterial respiratory infections, including pneumonia and otitis media. *S. pyogenes* (Lancefield group A) is associated with skin infections, endocarditis and necrotizing fasciitis. *S. agalactiae* (Lancefield group B) is commonly associated with neonatal bacteremia and meningitis. Lancefield group C, F and G β-hemolytic streptococci are associated with a variety of infections including endocarditis. Viridans group streptococci such as *S. anginosus* are commonly associated with abscesses<sup>21</sup>. A review of the literature show that viridans group streptococci have decreased susceptibility to β-lactams compares with β-hemolytic species. The in vitro activity of ceftaroline was evaluated against more than 6300 isolates of pneumococci. Ceftaroline was tested against penicillin-intermediate and -resistant isolates,

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fluoroquinolone-resistant strains, and multidrug-resistant strains of various serotypes. Susceptibility testing of the isolates was conducted using Clinical Laboratory Standard Institute (CLSI) approved guidelines.

Table 3 summarizes the activity of ceftaroline against pneumococci isolates. The data shows that ceftaroline is active against *S. pneumoniae*, including penicillin-intermediate and –resistant isolates. The highest MIC to ceftaroline reported for *S. pneumoniae* is 2 µg/ml. It was reported that this was from a single isolate from a study of 120 highly cefotaxime-resistant isolates from the CDC (Study P903-M-022). Additionally, MIC<sub>90</sub> values ranged from as low as 0.004 – 0.025 µg/ml against all *S. pneumoniae* isolates. The Applicant also evaluated the efficacy of ceftaroline against different *S. pneumoniae* serotypes. It is reported that of the 891 *S. pneumoniae* isolates examined from the US in 2008, 42 serotypes were represented and 11 serotypes accounted for 72.1% of all isolates (Table 3). Serotype 19A was the most common isolate and accounted for 21% of the total. Serotype 19A and 19F isolates were the most resistant serotypes, with many isolates being multidrug-resistant. The highest MIC for ceftaroline among serotype 19A and 19F isolates was 0.5 mcg/mL, with MIC<sub>90</sub> values for both of 0.25 mcg/mL.

**Table 3: Summary of In Vitro Studies to Evaluate the Activity of Ceftaroline against *Streptococcus pneumoniae***

Pathogen / phenotype	N	Range	Ceftaroline MIC, µg/ml		Method	Pathogen / phenotype	N	Range	Ceftaroline MIC, µg/ml		Method	
			50%	90%					50%	90%		
<i>Streptococcus pneumoniae</i> <sup>a</sup>						<i>Streptococcus pneumoniae</i> <sup>a</sup>						
All	601	≤ 0.008 - 0.5	0.06	0.12	Broth microdilution (CLSI)	All	655	≤ 0.0035 - 1	0.12	0.25	Agar dilution (CLSI)	
Penicillin-susceptible	202	≤ 0.008 - 0.12	≤ 0.008	0.015		Penicillin-susceptible	161	≤ 0.0035 - 0.06	0.007	0.03		
Penicillin-intermediate	103	≤ 0.008 - 0.5	0.015	0.06		Penicillin-intermediate	156	0.007 - 0.25	0.06	0.12		
Penicillin-resistant	296	≤ 0.008 - 0.5	0.12	0.12		Penicillin-resistant	338	0.03 - 1	0.12	0.25		
<i>Streptococcus pneumoniae</i> <sup>b</sup>						Amoxicillin-resistant	165	0.06 - 1	0.12	0.25		
Penicillin-susceptible	42	≤ 0.008 - 0.13	≤ 0.008	0.06	Broth microdilution (Japanese standards)	Cefotaxime-resistant	16	0.12 - 1	0.25	0.25		
Penicillin-intermediate	44	0.03 - 0.25	0.13	0.13		Erythromycin-resistant	339	≤ 0.0035 - 0.5	0.12	0.25		
Penicillin-resistant	29	0.06 - 0.5	0.13	0.25		Levofloxacin-resistant	152	≤ 0.0035 - 0.25	0.03	0.12		
<i>Streptococcus pneumoniae</i> <sup>c</sup>						<i>Streptococcus pneumoniae</i> <sup>b</sup>						
All	30	≤ 0.008 - 0.12	0.06	0.12	Broth microdilution (CLSI)	Penicillin-susceptible	27	0.004 - 0.06	0.004	0.015		Agar dilution (verified by broth dilution)
Penicillin-susceptible	10	≤ 0.008 - ≤ 0.008	≤ 0.008	≤ 0.008		Penicillin-intermediate	20	0.03 - 0.06	0.06	0.06		
Penicillin-intermediate	7	0.03 - 0.12	NA	NA		Penicillin-resistant	12	0.06 - 0.25	0.125	0.125		
Penicillin-resistant	13	0.06 - 0.12	0.06	0.12		<i>Streptococcus pneumoniae</i> <sup>b</sup>						
<i>Streptococcus pneumoniae</i> <sup>d</sup>						Penicillin-susceptible	11	0.008 - 0.015	0.008	0.015	Broth microdilution (CLSI)	
Penicillin-susceptible	11	≤ 0.06 - ≤ 0.06	≤ 0.06	≤ 0.06	Broth microdilution (CLSI)	Penicillin-intermediate	12	0.008 - 0.12	0.03	0.06		
Penicillin-resistant	11	0.12 - 1	0.25	0.5		Penicillin-resistant	50	0.06 - 0.5	0.12	0.25		
All	125	0.015 - 0.5	0.06	0.25		<i>Streptococcus pneumoniae</i> <sup>e</sup>						
Penicillin-susceptible	22	0.015 - 0.12	0.015	0.015		Penicillin-susceptible	762	≤ 0.008 - 0.25	≤ 0.008	0.015		
Penicillin-intermediate	26	0.015 - 0.12	0.03	0.06		Penicillin-intermediate	97	≤ 0.008 - 0.12	0.03	0.06		
Penicillin-resistant	29	0.015 - 0.5	0.25	0.5		Penicillin-resistant	148	≤ 0.008 - 0.5	0.12	0.25		
Levofloxacin-NS	23	0.015 - 0.25	0.03	0.25	<i>Streptococcus pneumoniae</i> <sup>e</sup>							
Multidrug-resistant	25	0.12 - 0.5	0.12	0.25	<i>Streptococcus pneumoniae</i> <sup>e</sup>							
<i>Streptococcus pneumoniae</i> <sup>e</sup>						<i>Streptococcus pneumoniae</i> <sup>e</sup>						
All	8	≤ 0.015 - 0.12	≤ 0.015	NA	Broth microdilution (CLSI)	<i>Streptococcus pneumoniae</i> <sup>e</sup>						
<i>Streptococcus pneumoniae</i> <sup>e</sup>						<i>Streptococcus pneumoniae</i> <sup>e</sup>						
Penicillin-susceptible	762	≤ 0.008 - 0.25	≤ 0.008	0.015		<i>Streptococcus pneumoniae</i> <sup>e</sup>						
Penicillin-intermediate	97	≤ 0.008 - 0.12	0.03	0.06	<i>Streptococcus pneumoniae</i> <sup>e</sup>							
Penicillin-resistant	148	≤ 0.008 - 0.5	0.12	0.25	<i>Streptococcus pneumoniae</i> <sup>e</sup>							

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Date Review Completed: 09/27/2010

Pathogen / phenotype	N	Range	Ceftaroline MIC, µg/ml		Method	Pathogen / phenotype	N	Range	Ceftaroline MIC, µg/ml		Method
			50%	90%					50%	90%	
<i>Streptococcus pneumoniae</i> <sup>a</sup> cefotaxime-resistant	120	0.125 - 2	0.5	0.5	Broth microdilution (CLSD)	<i>Streptococcus pneumoniae</i> - USA - 11 most common serotypes					
						All	891	≤ 0.008 - 0.5	≤ 0.008	0.12	Broth microdilution (CLSD)
					Serotype 19A	189	≤ 0.008 - 0.5	0.12	0.25		
					Serotype 3	82	≤ 0.008 - 0.12	≤ 0.008	≤ 0.008		
					Serotype 35B	59	≤ 0.008 - 0.25	0.12	0.12		
					Serotype 7F	52	≤ 0.008 - 0.03	≤ 0.008	0.015		
					Serotype 11A	49	≤ 0.008 - 0.12	0.06	0.06		
					Serotype 6C	43	≤ 0.008 - 0.12	0.015	0.06		
					Serotype 15A	38	≤ 0.008 - 0.12	≤ 0.008	0.03		
					Serotype 22F	35	≤ 0.008 - 0.03	≤ 0.008	0.015		
					Serotype 23A	33	≤ 0.008 - 0.12	0.12	0.25		
					Serotype 23B	33	≤ 0.008 - 0.03	0.015	0.06		
					Serotype 19F	29	≤ 0.008 - 0.5	0.12	0.25		
					<i>Streptococcus pneumoniae</i> <sup>b</sup>						
					All	201	≤ 0.004 - 0.125	0.008	0.015	Agar dilution (BSAC)	
					Penicillin-susceptible	200	≤ 0.004 - 0.125	0.008	0.015		
					Penicillin-intermediate	1	0.06	NA	NA		
					Erythromycin-resistant	13	≤ 0.004 - 0.125	0.008	0.125		
					<i>Streptococcus pneumoniae</i> <sup>c</sup>						
					Penicillin-susceptible	102	≤ 0.008 - 0.06	≤ 0.008	0.03	Broth microdilution (CLSD)	
					Penicillin-intermediate	102	≤ 0.008 - 0.12	0.03	0.06		
					Penicillin-resistant (MIC ≥ 2 µg/mL)	100	0.03 - 0.5	0.12	0.25		
					Penicillin-resistant <sup>b</sup> (MIC ≥ 8 µg/mL)	40	0.06 - 0.5	0.25	0.5		
					Levofloxacin-NS	53	≤ 0.008 - 0.5	0.015	0.12		
					Multidrug-resistant	127	≤ 0.008 - 0.5	0.12	0.25		
					<i>Streptococcus pneumoniae</i> <sup>a</sup>						
					Penicillin-susceptible	50	≤ 0.0005 - 0.008	0.004	0.008	Broth microdilution (CLSD)	
					Penicillin-intermediate	50	≤ 0.0005 - 0.25	0.03	0.12		
					Penicillin-resistant	10	0.12 - 0.5	0.25	0.25		
					MDR: macrolide & SXT-resistant	50	0.001 - 0.25	0.03	0.25		
					MDR: macrolide & doxycycline-resistant	25	≤ 0.0005 - 0.5	0.004	0.12		
					MDR: macrolide & ciprofloxacin-resistant	25	0.004 - 0.5	0.25	0.5		
					<i>Streptococcus pneumoniae</i> <sup>b</sup>						
					All	492	≤ 0.06 - 0.5	≤ 0.06	0.12	Broth microdilution (CLSD)	
					Penicillin-NS	36	0.12 - 0.5	0.25	0.25		
					Ceftriaxone-resistant	38	0.12 - 0.5	0.25	0.25		
					Erythromycin-resistant	144	≤ 0.06 - 0.5	≤ 0.06	0.25		
					Levofloxacin-NS	19	≤ 0.06 - 0.12	≤ 0.06	0.12		
					SXT-resistant	104	≤ 0.06 - 0.5	0.12	0.25		
					Tetracycline-resistant	79	≤ 0.06 - 0.5	0.12	0.25		
					Multidrug-resistant	121	≤ 0.06 - 0.5	0.12	0.25		
					Multidrug-resistant serotype 19A/19F	53	≤ 0.06 - 0.5	0.12	0.25		
					<i>Streptococcus pneumoniae</i> <sup>b</sup>						
					All	259	0.12 - 0.5	0.12	0.25	Broth microdilution (CLSD)	
					Penicillin-NS	221	0.12 - 0.5	0.25	0.25		
					Erythromycin-NS	246	0.12 - 0.5	0.12	0.25		
					Serotype 19A	60	0.12 - 0.5	0.25	0.25		

a CLSI M100-S17, 2007 penicillin breakpoints (mcg/mL): S: ≤ 0.06, I: 0.12-1, R: ≥ 2

b CLSI M100-S19, 2009 penicillin parenteral nonmeningitis breakpoints (mcg/mL): S: ≤ 2, I: 4, R: ≥ 8 Abbreviations: CLSI = Clinical and Laboratory Standards Institute; NS: non-susceptible; MIC = minimum inhibitory concentration; MDR: multidrug-resistant; NA: not applicable (for MIC<sub>50</sub>, fewer than 5 isolates; for MIC<sub>90</sub>, fewer than 10 isolates); NS = nonsusceptible; SXT = trimethoprim/sulfamethoxazole; USA = United States of America.

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Table 4 shows the activity of ceftaroline and comparator agents against a panel of *S. pneumoniae* isolates that were obtained from across the US and Europe from a 2008 ceftaroline surveillance study. Against penicillin susceptible *S. pneumoniae* (PSSP) from the US, ceftaroline MIC<sub>90</sub> (0.12 mcg/mL) was lower than all other β-lactams, as well as all other comparators except for tigecycline (MIC<sub>90</sub> 0.06 mcg/mL). Similar results were observed for penicillin intermediate *S. pneumoniae* (PISP) isolates where the MIC<sub>90</sub> for ceftaroline was 0.25 mcg/mL. Against a collection of penicillin resistant *S. pneumoniae* (PRSP) isolates the maximum MIC observed for ceftaroline was 0.5 mcg/mL, which was lower than all comparators except tigecycline (0.06 mcg/mL) and possibly vancomycin (≤ 1 mcg/mL). Ceftaroline also demonstrated activity against a selected number of *S. pneumoniae* serotypes including serotypes 19A, 19F, 3, and 15A. The highest MIC reported was 0.5 mcg/mL (Table 4). Please note that the highest MIC<sub>90</sub> for ceftaroline for any serotype was 0.25 mcg/mL, which was at least 8-fold lower than ceftriaxone; this value is lower than all comparators tested with the exception of tigecycline.

**Table 4: In Vitro Activity of Ceftaroline and Selected Antimicrobial Agents Against *Streptococcus pneumoniae* Isolates from the US and Europe**

Organism Group & Agent	US Isolates				European Isolates				Organism Group & Agent	US Isolates				European Isolates			
	MIC, µg/mL			% S <sup>a</sup>	MIC, µg/mL			% S <sup>a</sup>		MIC, µg/mL			% S <sup>a</sup>	MIC, µg/mL			% S <sup>a</sup>
	Range	MIC <sub>50</sub>	MIC <sub>90</sub>		Range	MIC <sub>50</sub>	MIC <sub>90</sub>			Range	MIC <sub>50</sub>	MIC <sub>90</sub>		Range	MIC <sub>50</sub>	MIC <sub>90</sub>	
<i>Streptococcus pneumoniae</i> - All	894 isolates				446 isolates				PISP <sup>b</sup>	112 isolates				36 isolates			
Ceftaroline	≤ 0.008 - 0.5	0.015	0.12	NA	≤ 0.008 - 0.5	≤ 0.008	0.12	NA	Ceftaroline	0.06 - 0.5	0.25	0.25	NA	0.12 - 0.5	0.12	0.25	NA
Penicillin <sup>b</sup>	≤ 0.03 - > 4	≤ 0.03	4	86.5	≤ 0.03 - 4	≤ 0.03	2	91.9	Penicillin <sup>b</sup>	4 - 4	4	4	0.0	4 - 4	4	4	0.0
Amox/clav	≤ 1 - 16	≤ 1	8	83.3	≤ 1 - 16	≤ 1	2	93.3	Amox/clav	2 - 16	8	8	3.6	2 - 16	4	8	47.2
Ceftriaxone	≤ 0.25 - 8	≤ 0.25	1	90.8	≤ 0.25 - 4	≤ 0.25	1	90.8	Ceftriaxone	1 - 8	2	4	41.1	1 - 4	2	2	38.9
Cefuroxime	≤ 1 - > 8	≤ 1	8	70.3	≤ 1 - > 8	≤ 1	4	79.8	Cefuroxime	4 - > 8	8	> 8	0.0	4 - > 8	8	> 8	0.0
Erythromycin	≤ 0.25 - > 2	≤ 0.25	> 2	61.6	≤ 0.25 - > 2	≤ 0.25	> 2	66.4	Erythromycin	≤ 0.25 - > 2	> 2	> 2	1.8	≤ 0.06 - > 8	4	> 8	8.3
Azithromycin	≤ 0.5 - > 4	≤ 0.5	> 4	59.2	≤ 0.5 - > 4	≤ 0.5	> 4	66.0	Azithromycin	≤ 0.5 - > 4	> 4	> 4	1.0	≤ 0.5 - > 4	> 4	> 4	8.3
Clarithromycin	≤ 0.25 - > 32	≤ 0.25	> 32	59.7	≤ 0.25 - > 32	≤ 0.25	> 32	66.4	Clarithromycin	≤ 0.25 - > 32	> 32	> 32	1.0	≤ 0.25 - > 32	2	> 32	8.3
Clindamycin	≤ 0.25 - > 2	≤ 0.25	> 2	79.3	≤ 0.25 - > 2	≤ 0.25	> 2	77.6	Clindamycin	≤ 0.25 - > 2	> 2	> 2	7.1	≤ 0.25 - > 2	≤ 0.25	> 2	63.9
Levofloxacin	≤ 0.5 - > 4	1	1	99.4	≤ 0.5 - > 4	1	1	97.1	Levofloxacin	≤ 0.5 - > 4	1	1	99.1	≤ 0.5 - 2	1	1	100
SXT	≤ 0.5 - > 2	≤ 0.5	> 2	66.3	≤ 0.5 - > 2	≤ 0.5	> 2	71.1	SXT	≤ 0.5 - > 2	> 2	> 2	1.8	≤ 0.5 - > 2	1	> 2	11.1
Vancomycin	≤ 1 - 1	1	1	100	≤ 1 - ≤ 1	≤ 1	≤ 1	100	Vancomycin	≤ 1 - ≤ 1	≤ 1	≤ 1	100	≤ 1 - ≤ 1	≤ 1	≤ 1	100
Tigecycline	≤ 0.03 - 0.25	≤ 0.03	0.06	NA	≤ 0.03 - 0.25	≤ 0.03	0.12	NA	Tigecycline	≤ 0.03 - 0.12	0.06	0.12	NA	≤ 0.03 - 0.25	≤ 0.03	0.06	NA
PSSP <sup>b</sup>	773 isolates				410 isolates				PRSP <sup>b</sup>	9 isolates				0 isolates			
Ceftaroline	≤ 0.008 - 0.5	≤ 0.008	0.12	NA	≤ 0.008 - 0.25	≤ 0.008	0.12	NA	Ceftaroline	0.25 - 0.5	0.5	-	NA	-	-	-	-
Penicillin <sup>b</sup>	≤ 0.03 - 2	≤ 0.03	1	100	≤ 0.03 - 2	≤ 0.03	2	100	Penicillin <sup>b</sup>	> 4 - > 4	> 4	-	0.0	-	-	-	-
Amox/clav	≤ 1 - 8	≤ 1	2	95.9	≤ 1 - 8	≤ 1	≤ 1	97.3	Amox/clav	8 - 16	16	-	0.0	-	-	-	-
Ceftriaxone	≤ 0.25 - 4	≤ 0.25	1	99.1	≤ 0.25 - 4	≤ 0.25	1	95.4	Ceftriaxone	2 - 8	4	-	0.0	-	-	-	-
Cefuroxime	≤ 1 - > 8	≤ 1	4	82.4	≤ 1 - > 8	≤ 1	4	86.8	Cefuroxime	> 8 - > 8	> 8	-	0.0	-	-	-	-
Erythromycin	≤ 0.25 - > 2	≤ 0.25	> 2	70.9	≤ 0.25 - > 2	≤ 0.25	> 2	71.5	Erythromycin	≤ 0.06 - > 2	> 2	-	11.1	-	-	-	-
Azithromycin	≤ 0.5 - > 4	≤ 0.5	> 4	69.1	≤ 0.5 - > 4	≤ 0.5	> 4	71.1	Azithromycin	≤ 0.5 - > 4	> 4	-	14.3	-	-	-	-
Clarithromycin	≤ 0.25 - > 32	≤ 0.25	> 32	69.5	≤ 0.25 - > 32	≤ 0.25	> 32	71.6	Clarithromycin	≤ 0.25 - > 32	> 32	-	14.3	-	-	-	-
Clindamycin	≤ 0.25 - > 2	≤ 0.25	≤ 0.25	90.3	≤ 0.25 - > 2	≤ 0.25	> 2	78.8	Clindamycin	≤ 0.25 - > 2	> 2	-	33.3	-	-	-	-
Levofloxacin	≤ 0.5 - > 4	1	1	99.5	≤ 0.5 - > 4	1	1	96.8	Levofloxacin	≤ 0.5 - 1	1	-	100	-	-	-	-
SXT	≤ 0.5 - > 2	≤ 0.5	> 2	76.5	≤ 0.5 - > 2	≤ 0.5	> 2	76.3	SXT	2 - > 2	> 2	-	0.0	-	-	-	-
Vancomycin	≤ 1 - 1	1	1	100	≤ 1 - ≤ 1	≤ 1	≤ 1	100	Vancomycin	≤ 1 - ≤ 1	≤ 1	-	100	-	-	-	-
Tigecycline	≤ 0.03 - 0.25	≤ 0.03	0.06	NA	≤ 0.03 - 0.25	≤ 0.03	0.12	NA	Tigecycline	≤ 0.03 - 0.06	≤ 0.03	-	NA	-	-	-	-

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Organism Group & Agent	US Isolates				European Isolates				Organism Group & Agent	US Isolates				European Isolates			
	MIC, µg/mL			% S <sup>a</sup>	MIC, µg/mL			% S <sup>a</sup>		MIC, µg/mL			% S <sup>a</sup>	MIC, µg/mL			% S <sup>a</sup>
	Range	MIC <sub>50</sub>	MIC <sub>90</sub>		Range	MIC <sub>50</sub>	MIC <sub>90</sub>			Range	MIC <sub>50</sub>	MIC <sub>90</sub>		Range	MIC <sub>50</sub>	MIC <sub>90</sub>	
Selected serotypes -All	891 isolates								Serotype 15A	38 isolates							
Ceftaroline	≤ 0.008 - 0.5	≤ 0.008	0.12	NA	-	-	-	-	Ceftaroline	≤ 0.008 - 0.12	≤ 0.008	0.03	NA	-	-	-	-
Penicillin <sup>b</sup>	≤ 0.03 - >4	≤ 0.03	4	86.2	-	-	-	-	Penicillin <sup>b</sup>	≤ 0.03 - 0.5	0.25	0.25	100	-	-	-	-
Ceftriaxone	≤ 0.25 - 8	≤ 0.25	1	90.7	-	-	-	-	Ceftriaxone	≤ 0.25 - 1	0.25	0.25	100	-	-	-	-
Amox/clav	≤ 1 - 16	≤ 1	8	83.1	-	-	-	-	Amox/clav	≤ 1 - ≤ 1	≤ 1	≤ 1	100	-	-	-	-
Cefuroxime	≤ 1 - ≥ 8	≤ 1	8	70.1	-	-	-	-	Cefuroxime	≤ 1 - 4	≤ 1	≤ 1	91.4	-	-	-	-
Erythromycin	≤ 0.25 - >2	≤ 0.25	> 2	61.6	-	-	-	-	Erythromycin	≤ 0.25 - >2	>2	>2	5.3	-	-	-	-
Clindamycin	≤ 0.25 - >2	0.25	> 2	79.2	-	-	-	-	Clindamycin	≤ 0.25 - >2	>2	>2	10.5	-	-	-	-
Levofloxacin	≤ 0.5 - >2	1	1	99.4	-	-	-	-	Levofloxacin	≤ 0.5 - >2	1	2	100	-	-	-	-
SXT	≤ 0.5 - >2	≤ 0.5	>2	66.2	-	-	-	-	SXT	≤ 0.5 - >2	≤ 0.5	>2	55.3	-	-	-	-
Serotype 19A	189 isolates								Serotype 19F	29 isolates							
Ceftaroline	≤ 0.008 - 0.5	0.12	0.25	NA	-	-	-	-	Ceftaroline	≤ 0.008 - 0.5	0.12	0.25	NA	-	-	-	-
Penicillin <sup>b</sup>	≤ 0.03 - >4	4	4	46.6	-	-	-	-	Penicillin <sup>b</sup>	≤ 0.03 - >4	4	4	37.9	-	-	-	-
Ceftriaxone	≤ 0.25 - 8	1	2	65.6	-	-	-	-	Ceftriaxone	≤ 0.25 - 8	1	8	65.5	-	-	-	-
Amox/clav	≤ 1 - 16	8	8	45	-	-	-	-	Amox/clav	≤ 1 - 16	8	8	37.9	-	-	-	-
Cefuroxime	≤ 1 - >8	8	> 8	36.1	-	-	-	-	Cefuroxime	≤ 1 - >8	8	>8	20.7	-	-	-	-
Erythromycin	≤ 0.25 - >2	> 2	> 2	26.5	-	-	-	-	Erythromycin	≤ 0.25 - >2	>2	>2	17.2	-	-	-	-
Clindamycin	≤ 0.25 - >2	> 2	> 2	43.4	-	-	-	-	Clindamycin	≤ 0.25 - >2	>2	>2	31.0	-	-	-	-
Levofloxacin	≤ 0.5 - >2	1	1	100	-	-	-	-	Levofloxacin	≤ 0.5 - >4	1	1	96.6	-	-	-	-
SXT	≤ 0.5 - >2	> 2	> 2	97.6	-	-	-	-	SXT	≤ 0.5 - >2	>2	>2	17.2	-	-	-	-
Serotype 3	82 isolates																
Ceftaroline	≤ 0.008 - 0.12	≤ 0.008	≤ 0.008	NA	-	-	-	-									
Penicillin <sup>b</sup>	≤ 0.03 - 4	≤ 0.03	≤ 0.03	98.8	-	-	-	-									
Ceftriaxone	≤ 0.25 - 2	≤ 0.25	≤ 0.25	98.8	-	-	-	-									
Amox/clav	≤ 1 - 8	≤ 1	≤ 1	98.8	-	-	-	-									
Cefuroxime	≤ 1 - 8	≤ 1	≤ 1	98.6	-	-	-	-									
Erythromycin	≤ 0.25 - >2	≤ 0.25	≤ 0.25	93.9	-	-	-	-									
Clindamycin	≤ 0.25 - >2	≤ 0.25	≤ 0.25	98.7	-	-	-	-									
Levofloxacin	≤ 0.5 - >2	1	1	100	-	-	-	-									
SXT	≤ 0.5 - >2	≤ 0.5	≤ 0.5	100	-	-	-	-									

a % susceptible according to CLSI M100-S19 (2009) or Tygacil Product Insert (2005)

b CLSI M100-S19, 2009 penicillin parenteral nonmeningitis breakpoints (µg/mL): S: ≤2, I: 4, R: ≥ 8

Abbreviations: Amox/clav = amoxicillin/clavulanate; MIC<sub>50</sub> = minimum inhibitory concentration required to inhibit the growth of 50% of organisms; MIC<sub>90</sub> = minimum inhibitory concentration required to inhibit the growth of 90% of organisms; PSSP = penicillin-susceptible *S. pneumoniae*; PISP = penicillin-intermediate *S. pneumoniae*; PRSP = penicillin-resistant *S. pneumoniae*; NA = not applicable (breakpoints not defined); - = not determined for fewer than 10 isolates; SXT = trimethoprim/sulfamethoxazole; US = United States. Source: Study P0903-M-035, 2009; serotype analysis from Study P903-M-069, 2009.

Data from studies investigating the activity of ceftaroline against 2700 non-pneumococcal streptococci isolates, including β-hemolytic Group A, B, C, F and G streptococci, and viridans streptococci, penicillin-intermediate and –resistant isolates, fluoroquinolone-resistant and macrolide-resistant isolates are shown in Table 5. Susceptibility testing of the isolates was conducted using Clinical Laboratory Standard Institute (CLSI) approved guidelines. Ceftaroline MIC<sub>90</sub> values were ≤0.016 µg/ml for some β-hemolytic streptococci isolates tested. Ceftaroline MIC<sub>90</sub> values were 1 µg/ml was reported against some penicillin-resistant viridans group streptococci.

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NDA: 200-327  
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Date Review Completed: 09/27/2010

**Table 5: Summary of In Vitro Studies to Evaluate the Activity of Ceftaroline against Non-pneumococcal Streptococci**

Pathogen / phenotype	N	Range	Ceftaroline MIC, µg/ml		Method	Pathogen / phenotype	N	Range	Ceftaroline MIC, µg/ml		Method
			50%	90%					50%	90%	
β-Hemolytic Group A streptococci	22	≤ 0.016	≤ 0.016	≤ 0.016	Broth microdilution (CLSI)	<i>Streptococcus pyogenes</i>	54	≤ 0.008 - 0.03	≤ 0.008	≤ 0.008	Broth microdilution (Japanese standards)
β-Hemolytic Group B streptococci	26	≤ 0.016	≤ 0.016	≤ 0.016		<i>Streptococcus agalactiae</i>	30	≤ 0.016 - 0.06	0.016	0.03	
Other β-Hemolytic streptococci	20	≤ 0.016 - 0.03	≤ 0.016	≤ 0.016		<b>Streptococcus Group C</b>	15	≤ 0.015 - 0.03	≤ 0.015	0.03	Broth microdilution (CLSI)
β-Hemolytic streptococci - levofloxacin-resistant	10	≤ 0.016 - 0.03	≤ 0.016	≤ 0.016		<b>Streptococcus Group F</b>	14	≤ 0.015 - 0.03	≤ 0.03	0.03	
<b>Viridans group streptococci</b>						<i>Streptococcus Group G</i>	2	≤ 0.015 - ≤ 0.015	NA	NA	
Penicillin-susceptible	32	≤ 0.016 - 1	≤ 0.016	0.03		<i>Streptococcus agalactiae</i>	18	≤ 0.015 - ≤ 0.015	≤ 0.015	≤ 0.015	
Penicillin-intermediate	53	≤ 0.016 - 0.5	0.03	0.12		<i>Streptococcus pyogenes</i>	2	≤ 0.015 - ≤ 0.015	NA	NA	
Penicillin-resistant	52	0.03 - 8	0.25	1		<b>Viridans group streptococci</b>					
Levofloxacin-NS	20	≤ 0.016 - 1	0.06	0.25		<i>Streptococcus acidominimus</i>	2	≤ 0.015 - ≤ 0.015	NA	NA	
<b>Viridans group streptococci</b>						<i>Streptococcus anginosus</i>	3	≤ 0.015 - 0.03	NA	NA	
Penicillin-susceptible	11	≤ 0.06-≤ 0.06	≤ 0.06	≤ 0.06	<i>Streptococcus consteallatus</i>	10	≤ 0.015 - 0.06	≤ 0.015	0.06		
Penicillin-intermediate	2	≤ 0.06-2	NA	NA	<i>Streptococcus intermedius</i>	43	≤ 0.015 - 0.06	≤ 0.015	0.03		
Penicillin-resistant	9	0.25-1	0.5	NA	<i>Streptococcus mitis</i>	4	≤ 0.015 - 0.25	NA	NA		
<i>Streptococcus pyogenes</i>					<i>Streptococcus oralis</i>	6	≤ 0.015 - 0.03	≤ 0.015	NA		
Erythromycin-susceptible	91	≤ 0.008 - 0.03	≤ 0.008	≤ 0.008	<i>Streptococcus salivarius</i>	4	≤ 0.015	NA	NA		
Erythromycin-NS	10	≤ 0.008 - 0.03	≤ 0.008	0.015	<i>Streptococcus sanguis</i>	1	0.12	NA	NA		
<i>Streptococcus agalactiae</i>					<b>α-Hemolytic streptococci</b>	3	≤ 0.015	NA	NA		
Erythromycin-susceptible	59	≤ 0.008 - 0.06	0.015	0.015	Viridans not including above	40	≤ 0.015 - 0.06	≤ 0.015	0.03		
Erythromycin-NS	42	≤ 0.008 - 0.12	0.015	0.015	Penicillin-susceptible	105	≤ 0.015 - 0.06	≤ 0.015	0.03		
<b>Viridans group streptococci</b>					<b>β-Hemolytic streptococci</b>	3	0.03	NA	NA		
Penicillin-susceptible	87	≤ 0.008 - 0.03	≤ 0.008	0.03	<i>Streptococcus spp.</i>	2	≤ 0.015	NA	NA		
Penicillin-NS	14	0.015 - 1	0.12	0.5	<i>Streptococcus pyogenes</i>	38	≤ 0.008	≤ 0.008	≤ 0.008	Broth microdilution (CLSI)	

Pathogen / phenotype	N	Range	Ceftaroline MIC, µg/ml		Method
			50%	90%	
<i>Streptococcus pyogenes</i> (pan-susceptible)	50	0.001 - 0.008	0.008	0.008	Broth microdilution (CLSI)
<i>Streptococcus pyogenes</i> - macrolide-resistant	10	0.004 - 0.008	0.004	0.008	
<i>Streptococcus dysgalactiae</i> Group C	10	0.008 - 0.015	0.008	0.015	
<i>Streptococcus dysgalactiae</i> Group G	25	0.002 - 0.015	0.008	0.008	
<i>Streptococcus anginosus</i>	10	0.004 - 0.06	0.008	0.06	
<i>Streptococcus mitis</i>	10	0.004 - 1	0.008	0.12	
<i>Streptococcus pyogenes</i>	13	≤ 0.008 - ≤ 0.008	≤ 0.008	≤ 0.008	Broth microdilution (CLSI)
<i>Streptococcus agalactiae</i>	15	0.015 - 0.015	0.015	0.015	

Table 6 shows the in vitro activities of ceftaroline and comparator agents against non-pneumococcal streptococci. The data was obtained from US and European isolates from a 2008 ceftaroline surveillance study. The MIC<sub>90</sub> for ceftaroline against the β-hemolytic streptococci was 0.03 mcg/mL for US isolates and 0.015 mcg/mL against European isolates. Against US isolates of viridans streptococci, the MIC<sub>90</sub> for ceftaroline of 0.12 mcg/mL this is compared against the European isolates which was 1 dilution higher at 0.25 mcg/mL.

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NDA: 200-327

Date Review Completed: 09/27/2010

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Cerexa Inc.

**Table 6: In Vitro Activity of Ceftaroline and Selected Antimicrobial Agents against Non-pneumococcal Streptococci from the US and Europe**

Organism Group & Agent	US Isolates				European Isolates			
	MIC, µg/mL			% S <sup>a</sup>	MIC, µg/mL			% S <sup>a</sup>
	Range	MIC <sub>50</sub>	MIC <sub>90</sub>		Range	MIC <sub>50</sub>	MIC <sub>90</sub>	
<i>β-Hemolytic streptococci</i>	327 isolates				179 isolates			
Ceftaroline	≤ 0.008 – 0.06	≤ 0.008	0.03	NA	≤ 0.008 – 0.06	≤ 0.008	0.015	NA
Ceftriaxone	≤ 0.25 – 0.5	≤ 0.25	≤ 0.25	100	≤ 0.25 – ≤ 0.25	≤ 0.25	≤ 0.25	100
Cefepime	≤ 0.12 – 0.5	≤ 0.12	≤ 0.12	100	≤ 0.12 – 0.25	≤ 0.12	≤ 0.12	100
Imipenem	≤ 0.12	≤ 0.12	≤ 0.12	NA	≤ 0.12 – ≤ 0.12	≤ 0.12	≤ 0.12	NA
Penicillin	≤ 0.015 – 0.12	≤ 0.015	0.06	100	≤ 0.015 – ≤ 0.015	≤ 0.015	0.06	100
P/T	≤ 0.5 – 1	≤ 0.5	≤ 0.5	NA	≤ 0.5 – ≤ 0.5	≤ 0.5	≤ 0.5	NA
Erythromycin	≤ 0.25 – > 2	≤ 0.25	> 2	73.4	≤ 0.25 – > 2	≤ 0.25	> 2	79.3
Clindamycin	≤ 0.25 – > 2	≤ 0.25	> 2	86.2	≤ 0.25 – > 2	≤ 0.25	≤ 0.25	91.1
Levofloxacin	≤ 0.5 – > 4	≤ 0.5	1	98.8	≤ 0.5 – 2	≤ 0.5	1	100
SXT	≤ 0.5 – > 2	≤ 0.5	≤ 0.5	NA	≤ 0.5 – 2	≤ 0.5	≤ 0.5	NA
Linezolid	0.12 – 2	1	1	100	0.25 – 2	1	1	100
Vancomycin	0.25 – 1	0.5	0.5	100	0.5 – 0.5	0.5	0.5	100
Daptomycin	≤ 0.06 – 0.5	0.12	0.25	100	≤ 0.06 – 0.5	≤ 0.06	0.25	100
Tigecycline	≤ 0.03 – 0.12	≤ 0.03	0.06	100	≤ 0.03 – 0.12	≤ 0.03	0.06	100
<i>viridans group streptococci</i>	110 isolates				88 isolates			
Ceftaroline	≤ 0.008 – 1	0.03	0.12	NA	≤ 0.008 – 16	0.015	0.25	NA
Ceftriaxone	≤ 0.25 – 16	≤ 0.25	1	90.0	≤ 0.25 – > 32	≤ 0.25	2	89.8
Cefepime	≤ 0.12 – 4	≤ 0.12	2	88.2	≤ 0.12 – > 16	0.25	1	92.0
Imipenem	≤ 0.12 – 4	≤ 0.12	0.25	NA	≤ 0.12 – > 8	≤ 0.12	0.25	NA
Penicillin	≤ 0.015 – 8	0.12	1	71.8	≤ 0.015 – > 32	0.06	2	78.4
P/T	≤ 0.5 – 32	≤ 0.5	8	NA	≤ 0.5 – > 64	≤ 0.5	4	NA
Erythromycin	≤ 0.25 – > 2	1	> 2	41.8	≤ 0.25 – > 2	≤ 0.25	> 2	58.0
Clindamycin	≤ 0.25 – > 2	≤ 0.25	≤ 0.25	91.8	≤ 0.25 – > 2	≤ 0.25	> 2	88.6
Levofloxacin	≤ 0.5 – > 4	1	> 4	85.5	≤ 0.5 – > 4	1	1	97.7
SXT	≤ 0.5 – > 2	≤ 0.5	2	NA	≤ 0.5 – > 2	≤ 0.5	2	NA
Linezolid	0.25 – 2	1	1	100	0.12 – 2	1	1	100
Vancomycin	≤ 0.12 – 1	0.5	0.5	100	0.25 – 1	0.5	1	100
Daptomycin	≤ 0.06 – 2	0.25	0.5	99.1	≤ 0.06 – 1	0.25	0.5	100
Tigecycline	≤ 0.03 – 0.25	≤ 0.03	0.12	100	≤ 0.03 – 0.12	≤ 0.03	0.06	100

a % susceptible according to CLSI M100-S19 (2009) or Tygacil Product Insert (2005). Abbreviations: MIC<sub>50</sub> = minimum inhibitory concentration required to inhibit the growth of 50% of organisms; MIC<sub>90</sub> = minimum inhibitory concentration required to inhibit the growth of 90% of organisms; NA = not applicable (breakpoints not defined); P/T = piperacillin-tazobactam; SXT = trimethoprim/sulfamethoxazole; US = United States. Source: Study P0903-M-035, 2009

Table 7 shows the activity of ceftaroline against vancomycin-susceptible and vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium*. Generally, ceftaroline demonstrated low activity against the majority of the isolates tested. Test using CLSI approved guidelines showed ceftaroline MIC<sub>90</sub> values that ranged from 4 µg/ml to >32 µg/ml for *E. faecium*. Against *E. faecalis*, ceftaroline demonstrated MIC<sub>90</sub> values that ranged from 4 µg/ml to >16 µg/ml.

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Date Review Completed: 09/27/2010

**Table 7: Summary of In Vitro Studies to Evaluate the Activity of Ceftaroline against *Enterococcus* spp.**

Pathogen / phenotype	N	Range	Ceftaroline MIC, µg/ml		Method	Pathogen / phenotype	N	Range	Ceftaroline MIC, µg/ml		Method
			50%	90%					50%	90%	
<b>All enterococci</b>	105	0.015 - > 32	2	32	Broth microdilution (CLSI)	<b>Enterococcus spp. - USA</b>	<b>1202</b>	<b>0.06 - &gt; 16</b>	<b>4</b>	<b>&gt; 16</b>	Broth microdilution (CLSI)
<i>Enterococcus faecalis</i>						<i>Enterococcus</i> spp. - Europe	652	0.03 - 16	4	> 16	
Vancomycin-susceptible	27	1 - 4	1	4		<i>Enterococcus faecalis</i>					
Vancomycin-NS	26	0.12 - 8	2	4		All - USA	733	0.12 - >16	2	8	
<i>Enterococcus faecium</i>						All - Europe	415	0.03 - > 16	2	8	
Vancomycin-susceptible	25	0.015 - 16	1	16		Vancomycin-susceptible - USA	686	0.12 - > 16	2	8	
Vancomycin-NS	27	2 - > 32	32	> 32		Vancomycin-susceptible - Europe	410	0.03 - > 16	2	8	
<i>Enterococcus faecalis</i>	83	≤ 0.015 - > 32	1	8		Vancomycin-NS - USA	47	0.5 - 16	4	8	
<i>Enterococcus faecium</i>	31	≤ 0.015 - > 32	1	> 32		Vancomycin-NS - Europe	5	4 - 8	8	NA	
<i>Enterococcus faecalis</i>	33	0.25 - 32	4	8		<i>Enterococcus faecium</i>					
<i>Enterococcus faecium</i>	55	0.5 - > 128	32	128	All - USA	431	0.06 - > 16	> 16	> 16	Agar dilution (BSAC)	
<b>Enterococcus spp.</b>					All - Europe	222	0.25 - > 16	> 16	> 16		
All	209	0.06 - > 16	2	16	Vancomycin-susceptible - USA	97	0.06 - > 16	> 16	> 16		
Vancomycin-susceptible	158	0.06 - 8	2	4	Vancomycin-susceptible - Europe	160	0.25 - > 16	> 16	> 16		
Vancomycin-resistant	51	1 - > 16	8	> 16	Vancomycin-NS - USA	334	16 - > 16	> 16	> 16		
<i>Enterococcus faecalis</i>					Vancomycin-NS - Europe	62	16 - > 16	> 16	> 16		
All	182	0.5 - 8	2	4	<b>Enterococcus spp.</b>	206	<0.015 - > 64	4	> 64		
Vancomycin-susceptible	157	0.5 - 8	2	4	<i>Enterococcus faecalis</i>	117	0.06 - > 64	1	8		
Vancomycin-resistant	25	1 - 8	4	4	<i>Enterococcus faecium</i>	73	0.5 - > 64	> 64	> 64		
<i>Enterococcus faecium</i>					<i>Enterococcus faecalis</i>						
All	27	0.06 - > 16	> 16	> 16	Vancomycin-susceptible	102	0.25 - 16	2	4	Broth microdilution (CLSI)	
Vancomycin-susceptible	1	0.06 - 0.06	NA	NA	Vancomycin-resistant	108	0.5 - 16	4	8		
Vancomycin-resistant	26	4 - > 16	> 16	> 16	<i>Enterococcus faecalis</i>	50	0.12 - 32	1	4	Broth microdilution (CLSI)	
					<i>Enterococcus faecium</i>	25	0.5 - > 64	32	> 64		

Abbreviations: BSAC = British Society of Antimicrobial Chemotherapy; CLSI = Clinical and Laboratory Standards Institute; MIC = minimum inhibitory concentration; NS: nonsusceptible; NA: not applicable (for MIC50, fewer than 5 isolates; for MIC90, fewer than 10 isolates); USA = United States of America.

Table 8 shows the in vitro activity of ceftaroline and comparator agents against enterococci isolates from surveillance studies for the United States and Europe. The MIC<sub>90</sub> for ceftaroline of 8 mcg/mL against the US isolates of *E. faecalis* was more than 4-fold lower than that for ceftriaxone but was 4-fold higher than ampicillin and imipenem, and was also 4-fold higher than the gram-positive agents linezolid, vancomycin and daptomycin. Similar to the other β-lactams tested, ceftaroline was inactive against most isolates of *E. faecium* (MIC<sub>90</sub> > 16 mcg/mL).

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Date Review Completed: 09/27/2010

**Table 8: In Vitro Activity of Ceftaroline and Selected Antimicrobial Agents against *Enterococcus* spp. from the US and Europe**

Organism Group & Agent	US Isolates				European Isolates			
	MIC, µg/mL			% S <sup>a</sup>	MIC, µg/mL			% S <sup>a</sup>
	Range	MIC <sub>50</sub>	MIC <sub>90</sub>		Range	MIC <sub>50</sub>	MIC <sub>90</sub>	
<i>Enterococcus</i> spp. - All	1202 isolates				652 isolates			
Ceftaroline	0.06 - > 16	4	> 16	NA	0.03 - > 16	4	> 16	NA
Ampicillin	≤ 1 - > 16	2	> 16	65.6	≤ 1 - > 16	2	> 16	67.3
Ceftriaxone	2 - > 32	> 32	> 32	NA	0.5 - > 32	> 32	> 32	NA
Cefepime	2 - > 16	> 16	> 16	NA	0.25 - > 16	> 16	> 16	NA
Imipenem	≤ 0.12 - > 8	2	> 8	NA	≤ 0.25 - > 8	2	> 8	NA
P/T	1 - > 64	8	> 64	65.6	1 - > 64	8	> 64	67.3
Erythromycin	≤ 0.25 - > 2	> 2	> 2	7.7	≤ 0.25 - > 2	> 2	> 2	3.8
Clindamycin	≤ 0.25 - > 2	> 2	> 2	NA	≤ 0.25 - > 2	> 2	> 2	NA
Levofloxacin	≤ 0.5 - > 4	> 4	> 4	42.4	≤ 0.5 - > 4	2	> 4	50.2
SXT	≤ 0.5 - > 2	≤ 0.5	> 2	NA	≤ 0.5 - > 2	≤ 0.5	> 2	NA
Linezolid	0.25 - > 8	1	2	99.6	0.25 - 2	1	2	100
Vancomycin	0.25 - > 16	1	> 16	67.9	0.25 - > 16	1	> 16	89.7
Daptomycin	≤ 0.06 - 8	1	2	99.6	≤ 0.12 - 4	1	2	100
Tigecycline	≤ 0.03 - 1	0.12	0.25	99.5	≤ 0.03 - 0.25	0.12	0.25	100

The activity of ceftaroline was also assessed against a broad selection of bacterial isolates belonging to the *Enterobacteriaceae* family (Table 9). Isolates from the US and Europe were assessed and MIC determinations were done using both broth microdilution and agar dilution methods. The Applicant's data showed that ceftaroline demonstrated activity with MICs ranging from ≤ 0.016 mcg/ml to >32 µg/ml against all isolates. Generally, ceftaroline showed increased efficacy against most wild type isolates of the *Enterobacteriaceae*, including *Escherichia coli*, *Morganella morganni*, *Klebsiella* spp., and *Enterobacter cloacae*. Against isolates expressing extended spectrum β-lactamase (ESBL) or hyper-producers of AmpC β-lactamase, ceftaroline demonstrated substantially little activity. Isolates of *Proteus* spp., *Providencia* spp., and *Serratia* spp. generally exhibit higher MICs to ceftaroline than other members of the *Enterobacteriaceae*, with MIC<sub>90</sub> values typically ≥ 4 mcg/mL.

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**Table 9 Summary of In Vitro Studies to Evaluate the Activity of Ceftaroline against *Enterobacteriaceae***

Pathogen	N	Range	Ceftaroline MIC, µg/ml		Method
			50%	90%	
<i>Citrobacter freundii</i>	20	0.06 - > 32	0.12	2	Broth microdilution (CLSI)
<i>Enterobacter cloacae</i>					
Wild type	20	0.03 - 0.5	0.12	0.25	
ESBL-producing strains	15	4 - > 32	> 32	> 32	
AmpC	3	32 - > 32	NA	NA	
<i>Escherichia coli</i>					
Wild type	20	≤ 0.016 - 0.25	0.06	0.12	
ESBL-producing strains	15	0.5 - > 32	> 32	> 32	
<i>Klebsiella pneumoniae</i>					
Wild type	21	0.03 - 4	0.06	.5	
ESBL-producing strains	15	32 - > 32	> 32	> 32	
<i>Morganella morganii</i> - WT	20	0.03 - 0.5	0.06	0.12	
<i>Proteus mirabilis</i>					
Wild type	20	0.03 - 4	0.12	0.12	
ESBL-producing strains	10	4 - > 32	> 32	> 32	
<i>Proteus vulgaris</i> - WT	10	0.06 - >32	2	> 32	
<i>Providencia stuartii</i> - WT	8	0.5 - > 32	2	NA	
<i>Providencia retgeri</i> - WT	4	0.03-0.12	0.03	NA	
<i>Serratia marcescens</i> - WT	20	0.12 - 8	0.5	2	

Table 10 shows the activity of ceftaroline against ceftazidime-susceptible and –non susceptible *Enterobacteriaceae*. Ceftaroline MIC<sub>90</sub> values for the majority of ceftazidime non-susceptible *Enterobacteriaceae* isolates were reported to be >16mcg/ml or 1-64 folds higher than those reported for ceftazidime susceptible isolates. Against isolates expressing extended spectrum β-lactamase (ESBL) or hyperproducers of AmpC β-lactamase, ceftaroline has very little activity since these enzymes are known to inactivate this class of drugs. Isolates of *M. morganii*, *Proteus spp.*, *Providencia spp.*, and *Serratia spp.* exhibited higher MICs to ceftaroline with MIC<sub>90</sub>s values ≥ 8 mcg/mL. There were obvious differences with MIC<sub>90</sub> data between European and USA *E. coli* isolates. Ceftaroline demonstrated MIC<sub>90</sub> values of 0.5mcg/ml compared to the European *E. coli* isolates which had an MIC<sub>90</sub> value of 16 mcg/ml. Similar trends were observed for *P. mirabilis*, and *Serratia spp.*

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**Table 10 Summary of In Vitro Studies to Evaluate the Activity of Ceftaroline against Ceftazidime Susceptible and Resistant *Enterobacteriaceae***

Pathogen	N	Range	Ceftaroline MIC, µg/ml		Method	
			50%	90%		
<i>Enterobacteriaceae</i>						
Ceftazidime-susceptible	833	≤ 0.03 - > 16	0.06	1	Broth microdilution (CLSI)	
Ceftazidime-NS	220	0.12 - > 16	> 16	> 16		
<i>Citrobacter freundii</i>						
Ceftazidime-susceptible	50	0.06 - 16	0.12	0.25		
Ceftazidime-NS	33	4 - > 16	> 16	> 16		
<i>Enterobacter cloacae</i>						
Ceftazidime-susceptible	50	≤ 0.03 - > 16	0.12	1		
Ceftazidime-NS	35	0.12 - > 16	> 16	> 16		
<i>Escherichia coli</i>						
Ceftazidime-susceptible	345	≤ 0.03 - > 16	0.06	0.5		
Ceftazidime-NS	63	2 - > 16	> 16	> 16		
<i>Klebsiella pneumoniae</i>						
Ceftazidime-susceptible	210	≤ 0.03 - > 16	0.06	0.25		
Ceftazidime-NS	66	1 - > 16	> 16	> 16		
<i>Morganella morganii</i>						
Ceftazidime-susceptible	34	≤ 0.03 - > 16	0.06	16		
Ceftazidime-NS	2	8 - > 16	NA	NA		
<i>Proteus mirabilis</i>						
Ceftazidime susceptible	58	≤ 0.03 - > 16	0.06	4		
Ceftazidime-NS	8	8 - > 16	> 16	NA		
<i>Providencia spp.</i>						
Ceftazidime-susceptible	27	≤ 0.03 - > 16	1	> 16		
Ceftazidime-NS	4	8 - >16	NA	NA		
<i>Serratia marcescens</i>						
Ceftazidime-susceptible	59	0.12 - > 16	0.5	16		
Ceftazidime-NS	9	8 - >16	>16	NA		
<i>Enterobacter cloacae</i>	10	0.06 - > 4	0.12	0.25	Broth microdilution (CLSI)	
<i>Escherichia coli</i>	10	0.03 - > 1	0.06	0.5		
<i>Klebsiella pneumoniae</i>	10	0.06 - > 0.5	0.06	0.06		
<i>Proteus mirabilis</i>	10	0.06 - > 0.5	0.06	0.06		

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**Table 10 Summary of In Vitro Studies to Evaluate the Activity of Ceftaroline against Ceftazidime Susceptible and Resistant *Enterobacteriaceae* (continued)**

Pathogen	N	Range	Ceftaroline MIC, µg/ml		Method	Pathogen	N	Range	Ceftaroline MIC, µg/ml		Method	
			50%	90%					50%	90%		
<i>Escherichia coli</i>					Agar dilution (CLSI)	<i>Citrobacter freundii</i>					Broth microdilution (CLSI)	
ESBL-negative	25	0.015 - 2	0.06	0.5		Ceftazidime- susceptible	6	0.25 - 0.5	0.25	NA		
ESBP-producing	10	2 - > 128	16	> 128		Ceftazidime-resistant	6	> 8 - > 8	> 8	NA		
<i>Klebsiella pneumoniae</i>						<i>Enterobacter cloacae</i>						
ESBL-negative	12	0.06 - 2	0.125	0.5		Ceftazidime-susceptible	11	≤ 0.06 - 1	0.25	1		
<i>Klebsiella oxytoca</i>						Ceftazidime-resistant	10	> 8 - > 8	> 8	> 8		
ESBL-negative	13	0.06 - 1	0.25	1		<i>Escherichia coli</i>						
<i>Klebsiella spp.</i>						ESBL Negative	5	≤ 0.06 - 1	0.12	NA		
ESBL-producing	10	2 - 16	4	8		ESBL Positive	10	> 8 - > 8	> 8	> 8		
<i>Enterobacter cloacae</i>						Putative Amp C	6	> 8 - > 8	> 8	NA		
ESBL-negative, non-derepressed AmpC	25	0.125 - 8	0.25	1		<i>Klebsiella pneumoniae</i>						
AmpC-derepressed	10	8 - > 128	32	> 128		ESBL negative	6	0.12 - 1	0.25	NA		
<i>Proteus mirabilis</i>	25	0.03 - 0.5	0.06	0.25		ESBL positive	11	0.12 - > 8	> 8	> 8		
<i>Proteus vulgaris</i>	25	0.015 - 1	0.25	0.5		Putative Amp C	6	> 8 - > 8	> 8	NA		
<i>Morganella morganii</i>						<i>Morganella morganii</i>						
non-derepressed AmpC	23	≤ 0.008 - 16	0.03	1		Ceftazidime-susceptible	10	≤ 0.06 - > 8	0.12	4		
AmpC-derepressed	2	32 - 64	NA	NA		Ceftazidime-intermediate	1	> 8	NA	NA		
<i>Serratia liquifaciens</i>	10	0.25 - 2	0.5	1		Ceftazidime-resistant	1	> 8	NA	NA		
<i>Serratia ficaria</i>	1	0.125	NA	NA		<i>Proteus mirabilis</i>						
<i>Serratia marcescens</i>						Ceftazidime-susceptible	15	≤ 0.06 - > 8	0.12	0.25		
non-derepressed AmpC	6	0.5 - 1	0.5	NA	Ceftazidime-resistant	10	2 - > 8	> 8	> 8			
AmpC-derepressed	10	16 - 64	32	64	<i>Providencia spp.</i>							
<i>Citrobacter freundii</i>					Ceftazidime-susceptible	6	≤ 0.06 - > 8	1	NA			
34	0.13 - 128	0.25	64	Broth microdilution (Japanese standards)	Ceftazidime-intermediate	1	2	NA	NA			
<i>Enterobacter cloacae</i>					Ceftazidime-resistant	3	> 8 - > 8	NA	NA			
32	0.06 - > 128	0.5	> 128		<i>Serratia marcescens</i>							
<i>Escherichia coli</i>					Ceftazidime-susceptible	5	1 - > 8	1	NA			
77	0.016 - > 128	0.06	25		Ceftazidime-resistant	5	> 8 - > 8	> 8	NA			
<i>Klebsiella oxytoca</i>												
19	0.03 - > 128	.25	2									
<i>Klebsiella pneumoniae</i>												
59	0.03 - 128	0.06	.25									
<i>Morganella morganii</i>												
13	0.03 - 16	0.13	8									
<i>Proteus mirabilis</i>												
42	0.03 - > 128	0.13	> 128									
<i>Proteus vulgaris</i>												
12	0.25 - 64	8	64									
<i>Salmonella spp.</i>												
46	0.13 - 2	0.13	.25									
<i>Serratia marcescens</i>												
43	0.5 - > 128	1	32									

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**Table 10 Summary of In Vitro Studies to Evaluate the Activity of Ceftaroline against Ceftazidime Susceptible and Resistant *Enterobacteriaceae* (continued)**

Pathogen	N	Range	Ceftaroline MIC, µg/ml		Method	Pathogen	N	Range	Ceftaroline MIC, µg/ml		Method
			50%	90%					50%	90%	
<i>Citrobacter amalonaticus</i>	2	0.12 - > 32	NA	NA	Broth microdilution (CLSI)	<i>Klebsiella pneumoniae</i>					Broth microdilution (CLSI)
<i>Citrobacter braakii</i>	5	0.12 - 0.25	0.12	NA		All	121	0.03 - > 32	0.12	> 32	
<i>Citrobacter farmeri</i>	1	2	NA	NA		Ceftazidime-susceptible	108	0.03 - > 32	0.12	0.5	
<i>Citrobacter freundii</i>	14	0.12 - > 32	0.25	> 32		Ceftazidime-resistant	12	2 - > 32	> 32	> 32	
Ceftazidime-susceptible	10	0.12 - 0.5	0.25	0.25		<i>Morganella morganii</i>					
Ceftazidime-resistant	4	> 32 - > 32	NA	NA		All	12	0.03 - > 32	0.06	> 32	
<i>Citrobacter koseri (diversus)</i>						Ceftazidime-susceptible	11	0.03 - > 32	0.06	0.5	
Ceftazidime-susceptible	10	0.06 - 0.05	0.12	0.25		Ceftazidime-resistant	1	> 32	NA	NA	
<i>Citrobacter youngae</i>	2	0.12 - 0.12	NA	NA		<i>Proteus mirabilis</i>					
<i>Enterobacter agglomerans</i>	2	0.06 - 0.06	NA	NA		All	57	0.03 - > 32	0.12	> 32	
<i>Enterobacter aerogenes</i>						Ceftazidime-susceptible	53	0.03 - > 32	0.06	4	
Ceftazidime-susceptible	10	0.06 - 0.5	0.12	0.25		Ceftazidime-resistant	4	> 32	NA	NA	
<i>Enterobacter cloacae</i>	43	≤ 0.015 - > 32	> 32	> 32		<i>Proteus penneri</i>	2	0.12 - 0.5	NA	NA	
Ceftazidime-susceptible	22	≤ 0.015 - > 32	0.5	8		<i>Proteus vulgaris</i>	7	0.25 - > 32	0.5	NA	
Ceftazidime-resistant	21	> 32 - > 32	> 32	> 32		<i>Providencia rettgeri</i>	2	0.06 - 0.12	NA	NA	
<i>Enterobacter hormaechei</i>	1	> 32	NA	NA		<i>Providencia stuartii</i>	2	8 - > 32	NA	NA	
<i>Enterobacter sakazaki</i>	1	0.06	NA	NA		<i>Salmonella typhi</i>	1	0.12	NA	NA	
<i>Escherichia coli</i>	721	≤ 0.015 - > 32	0.06	0.5		<i>Salmonella spp.</i>	1	0.25	NA	NA	
Ceftazidime-susceptible	715	≤ 0.015 - > 32	0.06	0.5		<i>Serratia liquefaciens</i>	1	0.5	NA	NA	
Ceftazidime-resistant	3	16 - > 32	NA	NA		<i>Serratia marcescens</i>					
<i>Escherichia spp</i>	1	1	NA	NA		All	18	0.5 - > 32	1	> 32	
<i>Hafnia alvei</i>	4	0.5 - 16	NA	NA	Ceftazidime-susceptible	17	0.5 - > 32	1	> 32		
<i>Klebsiella oxytoca</i>					Ceftazidime-resistant	1	> 32	NA	NA		
Ceftazidime-susceptible	29	0.06 - > 32	0.25	2	<i>Serratia plymuthica</i>	1	0.12	NA	NA		
<i>Klebsiella ozaenae</i>	2	0.12 - 4	NA	NA	<i>Enterobacteriaceae</i>						
					Ceftazidime-susceptible	1010	≤ 0.015 - > 32	0.12	0.5		
					Ceftazidime-resistant	49	2 - > 32	> 32	> 32		
Pathogen	N	Range	Ceftaroline MIC, µg/ml		Method	Pathogen	N	Range	Ceftaroline MIC, µg/ml		Method
			50%	90%					50%	90%	
<i>All Enterobacteriaceae</i>	368	0.015 - > 32	0.25	> 32	Broth microdilution (CLSI)	<i>Escherichia coli - USA</i>	1076	0.015 - > 16	0.12	0.5	Broth microdilution (CLSI)
<i>Enterobacter aerogenes</i>						<i>Escherichia coli - Europe</i>	1143	≤ 0.008 - > 16	0.12	16	
ESBL negative	42	0.03 - > 32	0.12	≥ 32		<i>Klebsiella spp. - USA</i>	706	≤ 0.008 - > 16	0.12	> 16	
<i>Enterobacter cloacae</i>						<i>Klebsiella spp. - Europe</i>	436	≤ 0.008 - > 16	0.12	> 16	
ESBL negative	41	0.06 - 2	0.12	0.5		<i>Enterobacter spp. - USA</i>	403	≤ 0.008 - > 16	0.25	> 16	
<i>Escherichia coli</i>						<i>Enterobacter spp. - Europe</i>	226	≤ 0.008 - > 16	0.5	> 16	
ESBL negative	51	0.015 - 16	0.06	1		<i>Citrobacter spp. - USA</i>	79	0.06 - > 16	0.25	> 16	
ESBL positive	26	0.06 - > 32	> 32	> 32		<i>Citrobacter spp. - Europe</i>	49	0.06 - > 16	0.12	> 16	
<i>Klebsiella pneumoniae</i>						<i>Proteus mirabilis - USA</i>	120	0.03 - 16	0.12	0.25	
ESBL negative	50	0.03 - 1	0.06	0.25		<i>Proteus mirabilis - Europe</i>	88	0.03 - > 16	0.12	4	
ESBL positive	43	0.5 - > 32	32	> 32		<i>Indole-positive Proteus spp. - USA</i>	48	0.03 - > 16	0.5	> 16	
<i>Morganella morganii</i>	21	0.06 - > 32	> 32	> 32		<i>Indole-positive Proteus spp. - Europe</i>	47	0.03 - > 16	0.25	> 16	
<i>Proteus mirabilis</i>	16	0.03 - 32	0.06	4		<i>Serratia spp. - USA</i>	182	0.25 - > 16	1	4	
<i>Providencia rettgeri / stuartii</i>	15	0.06 - > 32	1	4		<i>Serratia spp. - Europe</i>	108	0.12 - > 16	1	> 16	
<i>Proteus vulgaris</i>	16	0.03 - > 32	16	> 32		<i>Salmonella spp. - USA</i>	28	0.06 - 0.25	0.12	0.25	
<i>Serratia marcescens</i>	16	0.5 - 16	0.5	8		<i>Salmonella spp. - Europe</i>	15	0.12 - 0.25	0.12	0.25	
<i>Shigella species</i>	15	0.015 - 0.25	0.03	0.12		<i>Escherichia coli</i>					
<i>Salmonella species</i>	16	0.06 - > 32	0.12	> 32		All	467	<0.015 - > 128	0.12	16	
						Ceftazidime-susceptible	441	<0.015 - > 128	0.12	0.5	
						Ceftazidime-NS	26	0.5 - > 128	> 128	> 128	
						<i>Enterobacter cloacae</i>					
					All	123	0.06 - > 128	0.5	128		
					Ceftazidime-susceptible	98	0.06 - 128	0.5	2		
					Ceftazidime-NS	25	4 - > 128	64	> 128		
					<i>Enterobacter aerogenes</i>						
					All	14	0.125 - 32	0.5	16		
					Ceftazidime-susceptible	12	0.125 - 8	0.25	4		
					Ceftazidime-NS	2	16 - 32	NA	NA		

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**Table 10 Summary of In Vitro Studies to Evaluate the Activity of Ceftaroline against Ceftazidime Susceptible and Resistant *Enterobacteriaceae* (continued)**

Pathogen	N	Range	Ceftaroline MIC, µg/ml		Method	
			50%	90%		
<b>Other <i>Enterobacter</i> spp.</b>						
All	20	0.06 - 128	0.25	16	Agar dilution (BSAC)	
Ceftazidime-susceptible	16	0.06 - 2	0.25	1		
Ceftazidime-NS	4	8 - 128	NA	NA		
<b><i>Klebsiella pneumoniae</i></b>						
All	142	0.06 - > 128	0.25	16		
Ceftazidime-susceptible	129	0.06 - 32	0.25	1		
Ceftazidime-NS	13	16 - > 128	> 128	> 128		
<b><i>Klebsiella oxytoca</i></b>						
All	51	0.03 - > 128	0.5	128		
Ceftazidime-susceptible	48	0.03 - > 128	0.25	> 128		
Ceftazidime-NS	3	2 - 128	NA	NA		
<b>Other <i>Klebsiella</i> spp.</b>						
All	13	0.06 - 4	0.25	2		
Ceftazidime-susceptible	13	0.06 - 4	0.25	2		
<b><i>Serratia marcescens</i></b>						
All	109	0.5 - >128	1	32		
Ceftazidime-susceptible	109	0.5 - > 128	1	32		
<b>Other <i>Serratia</i> species</b>						
All	10	0.06 - 2	0.5	2		
<b><i>Proteus</i></b>						
<i>Proteus mirabilis</i>	157	0.03 - 8	0.06	0.5		
<i>Proteus vulgaris</i>	7	0.06 - 4	0.25	NA		
<i>Proteus penneri</i>	1	1	NA	NA		
<b><i>Morganella morganii</i></b>						
All	22	≤ 0.015 - 16	0.06	0.5		
Wild type	20	≤ 0.015 - 0.5	0.06	0.5		
AmpC	2	2 - 16	NA	NA		
<i>Providencia</i> spp.	2	0.03 - 2	NA	NA		
Pathogen	N	Range	Ceftaroline MIC, µg/ml		Method	
			50%	90%		
<i>Citrobacter koseri</i> (CAZ-S)	104	0.015 - 2	0.12	0.5	Broth microdilution (CLSI)	
<i>Citrobacter freundii</i> (CAZ-S)	107	0.06 - > 16	0.25	0.5		
<i>Enterobacter cloacae</i> (CAZ-S)	103	0.015 - 2	0.25	0.5		
<i>Enterobacter aerogenes</i> (CAZ-S)	103	0.03 - > 16	0.12	0.5		
<i>Escherichia coli</i> (CAZ-S)	102	0.015 - 8	0.12	0.25		
<i>Klebsiella pneumoniae</i> (CAZ-S)	102	0.015 - 1	0.06	0.5		
<i>Klebsiella oxytoca</i> (CAZ-S)	102	0.03 - 8	0.12	0.5		
<i>Morganella morganii</i> (CAZ-S)	101	0.03 - > 16	0.12	> 16		
<i>Proteus vulgaris</i> (CAZ-S)	100	0.06 - > 16	1	> 16		
<i>Providencia rettgeri</i> (CAZ-S)	102	0.03 - > 16	0.06	1		
<i>Providencia smartii</i> (CAZ-S)	105	0.03 - > 16	2	16		
<i>Proteus mirabilis</i> (CAZ-S)	105	0.03 - 1	0.12	0.25		
<i>Serratia marcescens</i> (CAZ-S)	106	0.25 - > 16	1	2		
<i>Salmonella</i> spp. (CAZ-S)	104	0.06 - 16	0.12	0.25		
<i>Shigella</i> spp. (CAZ-S)	104	0.03 - 2	0.12	0.25		

Surveillance data that evaluated the in vitro activities of ceftaroline and comparator agents against isolates of *Enterobacteriaceae* from the US and Europe from a 2008 ceftaroline surveillance study are shown in Table 11. Here the Applicant reports that the activity of ceftaroline and ceftriaxone against US isolates of *E. coli* (MIC<sub>90</sub> 0.5 mcg/mL and ≤ 0.25 mcg/mL, respectively) was lower than for the European isolates (MIC<sub>90</sub> 16 mcg/mL); a

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phenomenon reflected by the fact that a greater proportion of ESBL producers were located in the European subset. In the collection of US surveillance isolates that included ceftazidime-resistant subsets, the MIC<sub>90</sub>s of ceftaroline and ceftriaxone were generally similar and both were high ( $\geq 16$  mcg/mL) against *Klebsiella spp.*, *Enterobacter spp.*, and *Citrobacter spp.* Against the US indole-positive *Proteus spp.*, the MIC<sub>90</sub> for ceftaroline also was higher ( $>16$  mcg/mL), while that for ceftriaxone was 4 mcg/mL. The MICs for ceftaroline and ceftriaxone were lower against *Proteus mirabilis* (MIC<sub>90</sub> for ceftaroline and ceftriaxone of 0.25 and  $\leq 0.25$  mcg/mL respectively), *Serratia spp.* (MIC<sub>90</sub> for ceftaroline and ceftriaxone of 4 and 2 mcg/mL respectively), and *Salmonella spp.* (MIC<sub>90</sub> for ceftaroline and ceftriaxone of 0.25 and  $\leq 0.25$  mcg/mL, respectively).

**Table 11 In Vitro Activity of Ceftaroline and Selected Antimicrobial Agents against *Enterobacteriaceae* from the US and Europe**

Organism Group & Agent	US Isolates				European Isolates				Organism Group & Agent	US Isolates				European Isolates			
	MIC, $\mu\text{g/mL}$			% S <sup>a</sup>	MIC, $\mu\text{g/mL}$			% S <sup>a</sup>		MIC, $\mu\text{g/mL}$			% S <sup>a</sup>	MIC, $\mu\text{g/mL}$			% S <sup>a</sup>
	Range	MIC <sub>50</sub>	MIC <sub>90</sub>		Range	MIC <sub>50</sub>	MIC <sub>90</sub>			Range	MIC <sub>50</sub>	MIC <sub>90</sub>		Range	MIC <sub>50</sub>	MIC <sub>90</sub>	
<i>Escherichia coli</i>	1076 isolates				1143 isolates				<i>Enterobacter spp.</i>	403 isolates				226 isolates			
Ceftaroline	0.015 – > 16	0.12	0.5	NA	$\leq 0.008$ – > 16	0.12	16	NA	Ceftaroline	$\leq 0.008$ – > 16	0.25	> 16	NA	$\leq 0.008$ – > 16	0.5	> 16	NA
Ceftriaxone	$\leq 0.25$ – > 32	$\leq 0.25$	$\leq 0.25$	96.0	$\leq 0.25$ – > 32	$\leq 0.25$	16	89.9	Ceftriaxone	$\leq 0.25$ – > 32	$\leq 0.25$	32	81.4	$\leq 0.25$ – > 32	0.5	> 32	69.0
Cefepime	$\leq 0.12$ – > 16	$\leq 0.12$	$\leq 0.12$	98.1	$\leq 0.12$ – > 16	$\leq 0.12$	2	93.7	Cefepime	$\leq 0.12$ – > 16	$\leq 0.12$	2	97.0	$\leq 0.12$ – > 16	$\leq 0.12$	4	97.3
Ceftazidime	$\leq 1$ – > 16	$\leq 1$	$\leq 1$	96.8	$\leq 1$ – > 16	$\leq 1$	2	93.1	Ceftazidime	$\leq 1$ – > 16	$\leq 1$	> 16	79.4	$\leq 1$ – > 16	$\leq 1$	> 16	66.4
Cefuroxime	$\leq 2$ – > 16	4	16	88.8	$\leq 2$ – > 16	4	> 16	83.8	Cefuroxime	$\leq 2$ – > 16	8	> 16	51.6	$\leq 2$ – > 16	> 16	> 16	35.8
Cefazolin	$\leq 2$ – > 16	$\leq 2$	> 16	84.9	$\leq 2$ – > 16	$\leq 2$	> 16	79.9	Cefazolin	$\leq 2$ – > 16	> 16	> 16	3.7	$\leq 2$ – > 16	> 16	> 16	5.8
Imipenem	$\leq 0.12$ – 4	$\leq 0.12$	0.25	100	$\leq 0.12$ – 4	$\leq 0.12$	0.25	100	Imipenem	$\leq 0.12$ – > 8	0.5	1	99.0	$\leq 0.12$ – > 8	0.5	1	98.7
Ertapenem	$\leq 0.06$ – 1	$\leq 0.06$	$\leq 0.06$	100	$\leq 0.06$ – 1	$\leq 0.06$	$\leq 0.06$	100	Ertapenem	$\leq 0.06$ – > 8	$\leq 0.06$	0.5	97.0	$\leq 0.06$ – > 8	$\leq 0.06$	0.5	97.3
Ampicillin	$\leq 1$ – > 16	> 16	> 16	46.4	$\leq 1$ – > 16	> 16	> 16	41.1	Ampicillin	$\leq 1$ – > 16	> 16	> 16	9.4	2 – > 16	> 16	> 16	7.1
P/T	$\leq 0.5$ – > 64	2	4	95.5	$\leq 0.5$ – > 64	2	16	91.3	P/T	$\leq 0.5$ – > 64	2	64	83.6	$\leq 0.5$ – > 64	4	> 64	73.9
Levofloxacin	$\leq 0.5$ – > 4	$\leq 0.5$	> 4	74.3	$\leq 0.5$ – > 4	$\leq 0.5$	> 4	76.5	Levofloxacin	$\leq 0.5$ – > 4	$\leq 0.5$	1	93.3	$\leq 0.5$ – > 4	$\leq 0.5$	> 4	86.7
Amikacin	0.5 – 32	2	4	99.7	$\leq 0.25$ – > 32	2	4	99.6	Amikacin	$\leq 0.25$ – > 32	1	2	99.0	0.5 – > 32	1	4	97.8
Tigecycline	$\leq 0.03$ – 2	0.12	0.25	100	0.06 – 1	0.12	0.25	100	Tigecycline	0.06 – > 4	0.25	1	98.5	0.12 – 4	0.25	1	99.6
<i>Klebsiella spp.</i>	706 isolates				436 isolates				<i>Citrobacter spp.</i>	79 isolates				49 isolates			
Ceftaroline	$\leq 0.008$ – > 16	0.12	> 16	NA	$\leq 0.008$ – > 16	0.12	> 16	NA	Ceftaroline	0.06 – > 16	0.25	> 16	NA	0.06 – > 16	0.12	> 16	NA
Ceftriaxone	$\leq 0.25$ – > 32	$\leq 0.25$	16	89.4	$\leq 0.25$ – > 32	$\leq 0.25$	> 32	77.8	Ceftriaxone	$\leq 0.25$ – > 32	$\leq 0.25$	32	84.8	$\leq 0.25$ – > 32	$\leq 0.25$	> 32	81.6
Cefepime	$\leq 0.12$ – > 16	$\leq 0.12$	2	92.5	$\leq 0.12$ – > 16	$\leq 0.12$	> 16	83.0	Cefepime	$\leq 0.12$ – 16	$\leq 0.12$	2	98.7	$\leq 0.12$ – > 16	$\leq 0.12$	1	95.9
Ceftazidime	$\leq 1$ – > 16	$\leq 1$	16	89.1	$\leq 1$ – > 16	$\leq 1$	> 16	82.6	Ceftazidime	$\leq 1$ – > 16	$\leq 1$	> 16	82.3	$\leq 1$ – > 16	$\leq 1$	> 16	83.7
Cefuroxime	$\leq 2$ – > 16	$\leq 2$	> 16	80.9	$\leq 2$ – > 16	$\leq 2$	> 16	71.1	Cefuroxime	$\leq 2$ – > 16	4	> 16	73.4	$\leq 2$ – > 16	4	> 16	75.5
Cefazolin	$\leq 2$ – > 16	$\leq 2$	> 16	80.3	$\leq 2$ – > 16	$\leq 2$	> 16	67.2	Cefazolin	$\leq 2$ – > 16	> 16	> 16	25.3	$\leq 2$ – > 16	> 16	> 16	46.9
Imipenem	$\leq 0.12$ – > 8	0.25	0.5	95.8	$\leq 0.12$ – > 8	0.25	0.5	96.3	Imipenem	$\leq 0.12$ – 4	0.5	1	100	$\leq 0.12$ – 2	0.25	1	100
Ertapenem	$\leq 0.06$ – > 8	$\leq 0.06$	$\leq 0.06$	95.0	$\leq 0.06$ – > 8	$\leq 0.06$	0.25	96.3	Ertapenem	$\leq 0.06$ – 8	$\leq 0.06$	0.25	98.7	$\leq 0.06$ – 1	$\leq 0.06$	0.12	100
Ampicillin	$\leq 1$ – > 16	> 16	> 16	4.1	$\leq 1$ – > 16	> 16	> 16	4.6	Ampicillin	4 – > 16	> 16	> 16	12.7	2 – > 16	> 16	> 16	14.3
P/T	$\leq 0.5$ – > 64	2	32	89.5	$\leq 0.5$ – > 64	2	> 64	81.0	P/T	1 – > 64	2	64	86.1	1 – > 64	2	64	85.7
Levofloxacin	$\leq 0.5$ – > 4	$\leq 0.5$	> 4	88.1	$\leq 0.5$ – > 4	$\leq 0.5$	> 4	83.7	Levofloxacin	$\leq 0.5$ – > 4	$\leq 0.5$	4	89.9	$\leq 0.5$ – > 4	$\leq 0.5$	1	93.9
Amikacin	$\leq 0.25$ – > 32	1	4	94.6	0.5 – > 32	1	16	95.6	Amikacin	$\leq 0.25$ – 16	1	2	100	0.5 – > 32	1	2	98.0
Tigecycline	0.06 – 4	0.25	1	99.2	0.12 – 2	0.25	0.5	100	Tigecycline	0.12 – 1	0.25	0.5	100	0.12 – 1	0.25	0.5	100

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NDA: 200-327

Date Review Completed: 09/27/2010

Ceftaroline for Injection  
Cerexa Inc.

Organism Group & Agent	US Isolates				European Isolates			
	MIC, µg/mL			% 5 <sup>a</sup>	MIC, µg/mL			% 5 <sup>a</sup>
	Range	MIC <sub>50</sub>	MIC <sub>90</sub>		Range	MIC <sub>50</sub>	MIC <sub>90</sub>	
<i>Proteus mirabilis</i>	120 isolates				88 isolates			
Ceftaroline	0.03 – 16	0.12	0.25	NA	0.03 – 16	0.12	4	NA
Ceftriaxone	≤ 0.25 – 4	≤ 0.25	≤ 0.25	100	≤ 0.25 – 32	≤ 0.25	≤ 0.25	94.3
Cefepime	≤ 0.12 – 1	≤ 0.12	≤ 0.12	100	≤ 0.12 – 16	≤ 0.12	0.25	96.6
Ceftazidime	≤ 1 – 4	≤ 1	≤ 1	100	≤ 1 – 16	≤ 1	≤ 1	97.7
Cefuroxime	≤ 2 – 16	≤ 2	4	99.2	≤ 2 – 16	≤ 2	4	93.2
Cefazolin	≤ 2 – 16	4	16	84.2	≤ 2 – 16	4	> 16	78.4
Imipenem	≤ 0.12 – 4	1	2	100	≤ 0.12 – 4	1	2	100
Ertapenem	≤ 0.06	≤ 0.06	≤ 0.06	100	≤ 0.06 – 0.12	≤ 0.06	≤ 0.06	100
Ampicillin	≤ 1 – 16	≤ 1	> 16	79.2	≤ 1 – 16	≤ 1	> 16	63.6
P/T	≤ 0.5 – 4	≤ 0.5	1	100	≤ 0.5 – 32	≤ 0.5	1	98.9
Levofloxacin	≤ 0.5 – 4	≤ 0.5	> 4	73.3	≤ 0.5 – 4	≤ 0.5	4	88.6
Amikacin	1 – 16	2	8	100	1 – 32	4	8	93.2
Tigecycline	0.25 – 4	2	4	80	0.5 – 4	2	4	72.7
<b>Indole-positive <i>Proteus</i> spp.</b>	48 isolates				47 isolates			
Ceftaroline	0.03 – 16	0.5	> 16	NA	0.03 – 16	0.25	> 16	NA
Ceftriaxone	≤ 0.25 – 32	≤ 0.25	4	93.8	≤ 0.25 – 32	≤ 0.25	2	97.9
Cefepime	≤ 0.12 – 16	≤ 0.12	0.25	97.9	≤ 0.12 – 8	≤ 0.12	0.25	100
Ceftazidime	≤ 1 – 16	≤ 1	16	89.6	≤ 1 – 16	≤ 1	8	93.6
Cefuroxime	≤ 2 – 16	> 16	> 16	20.8	≤ 2 – 16	> 16	> 16	23.4
Cefazolin	≤ 2 – 16	> 16	> 16	6.3	4 – 16	> 16	> 16	8.5
Imipenem	0.5 – 4	2	4	100	0.5 – 8	2	4	97.9
Ertapenem	≤ 0.06 – 0.12	≤ 0.06	≤ 0.06	100	≤ 0.06	≤ 0.06	≤ 0.06	100
Ampicillin	≤ 1 – 16	> 16	> 16	10.4	≤ 1 – 16	> 16	> 16	8.5
P/T	≤ 0.5 – 16	≤ 0.5	4	100	≤ 0.5 – 64	≤ 0.5	2	97.9
Levofloxacin	≤ 0.5 – 4	≤ 0.5	> 4	77.1	≤ 0.5 – 4	≤ 0.5	2	91.5
Amikacin	≤ 0.25 – 8	2	4	100	≤ 0.25 – 8	2	4	100
Tigecycline	0.25 – 4	0.5	2	91.7	0.25 – 4	1	2	97.9
<i>Serratia</i> spp.	182 isolates				108 isolates			
Ceftaroline	0.25 – 16	1	4	NA	0.12 – 16	1	> 16	NA
Ceftriaxone	≤ 0.25 – 32	≤ 0.25	2	95.6	≤ 0.25 – 32	≤ 0.25	16	87.0
Cefepime	≤ 0.12 – 16	≤ 0.12	0.25	99.5	≤ 0.12 – 16	≤ 0.12	1	99.1
Ceftazidime	≤ 1 – 16	≤ 1	≤ 1	96.7	≤ 1 – 16	≤ 1	≤ 1	98.1
Cefuroxime	8 – 16	> 16	> 16	1.1	16 – 16	> 16	> 16	0.0
Cefazolin	8 – 16	> 16	> 16	0.5	> 16	> 16	> 16	0.0
Imipenem	0.25 – 8	1	2	99.5	≤ 0.12 – 4	1	2	100
Ertapenem	≤ 0.06 – 4	≤ 0.06	≤ 0.06	99.5	≤ 0.06 – 8	≤ 0.06	0.12	99.1
Ampicillin	2 – 16	> 16	> 16	3.8	4 – 16	> 16	> 16	9.3
P/T	≤ 0.5 – 64	2	4	94.5	≤ 0.5 – 64	2	32	85.2
Levofloxacin	≤ 0.5 – 4	≤ 0.5	1	97.8	≤ 0.5 – 4	≤ 0.5	4	88.9
Amikacin	0.5 – 16	2	4	100	0.5 – 32	2	4	99.1
Tigecycline	0.12 – 4	1	1	99.5	0.12 – 4	1	1	97.2
<i>Salmonella</i> spp.	28 isolates				15 isolates			
Ceftaroline	0.06 – 0.25	0.12	0.25	NA	0.12 – 0.25	0.12	0.25	NA
Ceftriaxone	≤ 0.25	≤ 0.25	≤ 0.25	100	≤ 0.25	≤ 0.25	≤ 0.25	100
Cefepime	≤ 0.12	≤ 0.12	≤ 0.12	100	≤ 0.12	≤ 0.12	≤ 0.12	100
Ceftazidime	≤ 1	≤ 1	≤ 1	100	≤ 1	≤ 1	≤ 1	100
Cefuroxime	≤ 2 – 16	4	8	92.9	≤ 2 – 16	4	8	93.3
Cefazolin	≤ 2 – 4	≤ 2	≤ 2	100	≤ 2 – 4	≤ 2	4	100
Imipenem	≤ 0.12 – 0.5	0.25	0.5	100	0.25 – 0.5	0.25	0.5	100
Ertapenem	≤ 0.06 – 0.12	≤ 0.06	≤ 0.06	100	≤ 0.06	≤ 0.06	≤ 0.06	100
Ampicillin	≤ 1 – 16	≤ 1	2	96.4	≤ 1 – 4	≤ 1	4	100
P/T	1 – 4	2	4	100	1 – 4	2	4	100
Levofloxacin	≤ 0.5 – 1	≤ 0.5	≤ 0.5	100	≤ 0.5 – 1	≤ 0.5	≤ 0.5	100
Amikacin	≤ 0.25 – 8	1	2	100	0.5 – 2	1	1	100
Tigecycline	0.06 – 0.5	0.25	0.5	100	0.12 – 0.5	0.25	0.5	100

<sup>a</sup> % susceptible according to CLSI M100-S19 (2009) or Tygacil Product Insert (2005)  
Abbreviations: MIC<sub>50</sub> = minimum inhibitory concentration required to inhibit the growth of 50% of organisms;  
MIC<sub>90</sub> = minimum inhibitory concentration required to inhibit the growth of 90% of organisms; NA = not applicable (breakpoints not defined); P/T = piperacillin/tazobactam; US = United States.  
Source: Study P0903-M-035, 2009.

Another study examined the effect of ceftaroline on the activity of *Haemophilus influenzae*, including isolates expressing β-lactamase as well as β-lactamase-negative ampicillin-resistant (BLNAR) isolates with mutations affecting penicillin binding protein 3 (PP3) (Table 12). MIC values determined by broth microdilution were higher for β-lactamase-positive isolates (N = 448) compared to those lacking β-lactamase (N = 923) (Table 11); however, MIC<sub>90</sub>s for both were ≤ 0.06 mcg/mL in 7 out of 8 studies. (In study 1563-102, the MIC<sub>90</sub> for 10 β-lactamase-positive isolates was 0.25 mcg/mL.) The highest MIC observed among the BLNAR isolates (N = 160) was 0.25 mcg/mL. Against *H. parainfluenzae*, with an MIC<sub>90</sub> of 0.06 mcg/mL from a single study of 24 isolates was reported.

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Date Review Completed: 09/27/2010

**Table 12 Summary of In Vitro Studies to Evaluate the Activity of Ceftaroline against *Haemophilus***

Pathogen / Phenotype	N	Range	Ceftaroline MIC, µg/mL		Method	Reference	Pathogen / Phenotype	N	Range	Ceftaroline MIC, µg/mL		Method	Reference			
			50%	90%						50%	90%					
<i>Haemophilus influenzae</i>						Study P0903-M-001, 2004; Sader et al, 2005	<i>Haemophilus influenzae</i>						Broth microdilution (CLSI)	Study P0903-M-012, 2006; Brown and Treczewski, 2009		
β-lactamase negative	23	≤ 0.016	≤ 0.016	≤ 0.016	Broth microdilution (CLSI)		All	105	0.015 - 0.25	0.015	0.12	Broth microdilution (CLSI)				
β-lactamase positive	24	≤ 0.016 - 0.25	≤ 0.016	≤ 0.016			β-lactamase negative	27	0.015 - 0.015	0.015	0.015					
BLNAR	30	≤ 0.016 - 0.03	≤ 0.016	0.03			β-lactamase positive	52	0.015 - 0.06	0.015	0.06					
						BLNAR	26	0.015 - 0.25	0.12	0.25						
<i>Haemophilus influenzae</i>						Study TAK-599/00053, 2003	<i>Haemophilus influenzae</i>						Broth microdilution (CLSI)	Study P0903-M-018, 2007; Ge et al, 2009		
	71	≤ 0.008 - 0.25	≤ 0.008	0.06	Broth microdilution (Japanese standards)		All	119	≤ 0.008 - 0.06	≤ 0.008	0.015					
							β-lactamase negative	94	≤ 0.008 - 0.03	≤ 0.008	0.03					
<i>Haemophilus influenzae</i> β-lactamase negative						Study P0903-M-002, 2003	<i>Haemophilus influenzae</i>						Broth microdilution (CLSI)	Study P0903-M-035, 2009		
	10	≤ 0.015 - 0.12	≤ 0.015	≤ 0.015	Broth microdilution (CLSI)		All - USA	381	≤ 0.008 - 0.12	≤ 0.008	0.015					
<i>Haemophilus influenzae</i>						Study 1563-102, 2004	All - Europe	203	≤ 0.008 - 0.06	≤ 0.008	0.015					
β-lactamase negative	11	≤ 0.06 - 0.12	≤ 0.06	≤ 0.06	Broth microdilution (CLSI)		β-lactamase negative - USA	275	≤ 0.008 - 0.06	≤ 0.008	0.015					
β-lactamase positive	10	≤ 0.06 - > 8	≤ 0.06	0.25			β-lactamase negative - Europe	174	≤ 0.008 - 0.06	≤ 0.008	0.015					
BLNAR	5	≤ 0.06 - ≤ 0.06	≤ 0.06	NA			β-lactamase positive - USA	106	≤ 0.008 - 0.12	≤ 0.008	0.03					
<i>Haemophilus influenzae</i>						Study P0903-M-004/011, 2006	<i>Haemophilus influenzae</i>								Broth microdilution (CLSI)	Study P903-M-053, 2009
ampicillin-susceptible	26	≤ 0.015 - 0.06	≤ 0.015	0.03	Agar dilution (not CLSI)		β-lactamase positive - Europe	29	≤ 0.008 - 0.03	≤ 0.008	0.015					
β-lactamase positive	22	≤ 0.015 - 0.125	≤ 0.015	0.03			<i>Haemophilus influenzae</i>									
impermeability/efflux	9	0.015 - 0.125	0.03	NA		β-lactamase negative	110	≤ 0.008 - 0.25	≤ 0.008	0.015						
<i>Haemophilus influenzae</i>						Study P0903-M-010, 2006; Ge et al, 2008	<i>Haemophilus influenzae</i>						Broth microdilution (CLSI)			
All	300	≤ 0.008 - 2	≤ 0.008	0.03	Broth microdilution (CLSI)		β-lactamase positive	101	≤ 0.008 - 0.12	≤ 0.008	0.03					
β-lactamase negative	199	≤ 0.008 - 1	≤ 0.008	0.015			BLNAR	104	≤ 0.008 - 0.25	0.06	0.12					
β-lactamase positive	101	≤ 0.008 - 2	≤ 0.008	0.015		<i>Haemophilus parainfluenzae</i>										
							24	≤ 0.008 - 0.06	0.015	0.06						

Abbreviations: BLNAR = β-lactamase-negative ampicillin-resistant; CLSI = Clinical and Laboratory Standards Institute; MIC = minimum inhibitory concentration; N = number of isolates; USA = United States of America.

Table 13 shows the in vitro activities of ceftaroline and comparator agents against *Haemophilus influenzae* for US and European isolates from a 2008 ceftaroline surveillance study. Ceftaroline had lower MICs than those of the comparators. The highest MIC for ceftaroline against any isolates, including those producing β-lactamase, was 0.12 mcg/mL, which was 4-fold lower than for ceftriaxone. Against 104 BLNAR isolates, whose ampicillin resistance is the result of mutations in PBPs, the MIC<sub>90</sub> of ceftaroline of 0.12 mcg/mL and the highest MIC observed for ceftaroline of 0.25 mcg/mL was lower than all comparators.

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NDA: 200-327

Date Review Completed: 09/27/2010

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**Table 13 In Vitro Activity of Ceftaroline and Selected Antimicrobial Agents against *Haemophilus influenzae* from the US and Europe**

Organism Group & Agent	US Isolates				European Isolates			
	MIC, µg/mL			% S <sup>a</sup>	MIC, µg/mL			% S <sup>a</sup>
	Range	MIC <sub>50</sub>	MIC <sub>90</sub>		Range	MIC <sub>50</sub>	MIC <sub>90</sub>	
<i>Haemophilus influenzae</i> - All	381 isolates				203 isolates			
Ceftaroline	≤ 0.008 – 0.12	≤ 0.008	0.015	N	≤ 0.008 – 0.06	≤ 0.008	0.015	NA
Ampicillin	≤ 1 – > 16	≤ 1	> 16	71.7	≤ 1 – > 16	≤ 1	8	85.2
Amoxi/clav	≤ 1 – 8	≤ 1	≤ 1	99.7	≤ 1 – 4	≤ 1	≤ 1	100
Ceftriaxone	≤ 0.25 – 0.5	≤ 0.25	≤ 0.25	100	≤ 0.25 – 0.5	≤ 0.25	≤ 0.25	100
Cefuroxime	≤ 1 – > 8	≤ 1	2	98.4	≤ 1 – 8	≤ 1	2	99.5
Erythromycin	0.25 – > 8	4	8	NA	1 – > 8	4	8	NA
Azithromycin	≤ 0.5 – > 4	1	2	99.2	≤ 0.5 – > 4	1	2	98.5
Clarithromycin	≤ 0.25 – > 32	8	16	76.9	2 – > 32	8	16	88.7
Clindamycin	1 – > 2	> 2	> 2	NA	0.5 – > 2	> 2	> 2	NA
Levofloxacin	≤ 0.5 – ≤ 0.5	≤ 0.5	≤ 0.5	100	≤ 0.5	≤ 0.5	≤ 0.5	100
SXT	≤ 0.5 – > 2	≤ 0.5	> 2	80.6	≤ 0.5 – > 2	≤ 0.5	> 2	81.8
Tigecycline	0.25 – 2	0.5	1	NA	0.25 – 2	1	1	NA
<i>Haemophilus influenzae</i> - β-lactamase pos.	106 isolates				29 isolates			
Ceftaroline	≤ 0.008 – 0.12	≤ 0.008	0.03	NA	≤ 0.008 – 0.03	≤ 0.008	0.015	NA
Ampicillin	2 – > 16	16	> 16	0.0	2 – > 16	16	> 16	0.0
Amoxi/clav	≤ 1 – 4	≤ 1	≤ 1	100	≤ 1 – 2	≤ 1	≤ 1	100
Ceftriaxone	≤ 0.25 – 0.5	≤ 0.25	≤ 0.25	100	≤ 0.25 – 0.5	≤ 0.25	≤ 0.25	100
Cefuroxime	≤ 1 – 8	≤ 1	2	98.1	≤ 1 – 2	≤ 1	≤ 1	100
Erythromycin	0.25 – > 8	4	8	0.0	1 – 8	4	8	NA
Azithromycin	≤ 0.5 – 4	1	2	100	≤ 0.5 – 2	1	2	100
Clarithromycin	≤ 0.25 – 32	8	16	76.4	2 – 16	4	8	93.1
Clindamycin	1 – > 2	> 2	> 2	NA	0.5 – > 2	> 2	> 2	NA
Levofloxacin	≤ 0.5 – ≤ 0.5	≤ 0.5	≤ 0.5	100	≤ 0.5	≤ 0.5	≤ 0.5	100
SXT	≤ 0.5 – > 2	≤ 0.5	> 2	83.0	≤ 0.5 – > 2	≤ 0.5	> 2	79.3
Tigecycline	0.25 – 1	0.5	1	NA	0.25 – 2	1	1	NA
<i>Haemophilus influenzae</i> - β-lactamase neg.	275 isolates				174 isolates			
Ceftaroline	≤ 0.008 – 0.06	≤ 0.008	0.015	NA	≤ 0.008 – 0.06	≤ 0.008	0.015	NA
Ampicillin	≤ 1 – 4	≤ 1	≤ 1	99.3	≤ 1 – 2	≤ 1	≤ 1	99.4
Amoxi/clav	≤ 1 – 8	≤ 1	≤ 1	99.6	≤ 1 – 4	≤ 1	≤ 1	100
Ceftriaxone	≤ 0.25 – 0.5	≤ 0.25	≤ 0.25	100	≤ 0.25	≤ 0.25	≤ 0.25	100
Cefuroxime	≤ 1 – > 8	≤ 1	2	98.5	≤ 1 – 8	≤ 1	2	99.4
Erythromycin	0.5 – > 8	4	8	NA	1 – > 8	4	8	NA
Azithromycin	≤ 0.5 – > 4	1	2	98.9	≤ 0.5 – > 4	1	2	98.3
Clarithromycin	1 – > 32	8	16	77.1	2 – > 32	8	16	87.9
Clindamycin	1 – > 2	> 2	> 2	NA	2 – > 2	> 2	> 2	NA
Levofloxacin	≤ 0.5 – ≤ 0.5	≤ 0.5	≤ 0.5	100	≤ 0.5	≤ 0.5	≤ 0.5	100
SXT	≤ 0.5 – > 2	≤ 0.5	> 2	79.6	≤ 0.5 – > 2	≤ 0.5	> 2	82.2
Tigecycline	0.25 – 2	0.5	1	NA	0.25 – 2	1	1	NA

<sup>a</sup> % susceptible according to CLSI M100-S19 (2009) or Tygacil Product Insert (2005)

Abbreviations: MIC<sub>50</sub> = minimum inhibitory concentration required to inhibit the growth of 50% of organisms;

MIC<sub>90</sub> = minimum inhibitory concentration required to inhibit the growth of 90% of organisms; NA = not applicable (breakpoints not defined); Amoxi/clav = amoxicillin/clavulanate;

SXT = trimethoprim/sulfamethoxazole; US = United States.

Source: Study P0903-M-035, 2009.

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Table 14 shows the activity of ceftaroline is active against *Moraxella catarrhalis*, with all MIC<sub>90</sub> ≤ 1 mcg/mL including β-lactamase-positive isolates (N = 452). Please note that *Moraxella catarrhalis* β-lactamases are of two types (BRO-1 and BRO-2) distinguished by isoelectric focusing and are quite different from β-lactamases from other bacteria genus. The two enzymes are phenotypically similar with BRO-1 being the most abundant (some estimates have it at 90% in all β-lactamase-positive isolates)<sup>22</sup>. The MIC<sub>90</sub> values from nine studies performed with broth microdilution were all ≤ 0.5 mcg/mL (Table 14). In one study performed with the agar dilution method the MIC<sub>90</sub> was 1 mcg/mL. The Applicant states that many of the *M. catarrhalis* isolates contained β-lactamase BRO-1 or BRO-2 based on their resistance to ampicillin and susceptibility to amoxicillin/clavulanic acid and ceftaroline has activity against these resistant organisms.

**Table 14 Summary of In Vitro Studies to Evaluate the Activity of Ceftaroline against *Moraxella catarrhalis***

Pathogen / Phenotype	N	Range	Ceftaroline MIC, µg/mL		Method	Reference
			50%	90%		
<i>Moraxella catarrhalis</i>	25	≤ 0.016 - 0.12	0.06	0.12	Broth microdilution (CLSI)	Study P0903-M-001, 2004; Sader et al, 2005
<i>Moraxella catarrhalis</i>						
All	102	≤ 0.03 - 0.5	0.06	0.12	Broth microdilution (CLSI)	Study P0903-M-010, 2006; Ge et al, 2008
β-lactamase negative	9	≤ 0.03 - ≤ 0.03	≤ 0.03	NA		
β-lactamase positive	93	≤ 0.03 - 0.5	0.06	0.25		
<i>Moraxella catarrhalis</i>	50	≤ 0.08 - 0.5	0.25	0.5	Broth microdilution (Japanese standards)	Study TAK-599/00053, 2003
<i>Moraxella catarrhalis</i>						
β-lactamase negative	6	≤ 0.06 - ≤ 0.06	≤ 0.06	NA	Broth microdilution (CLSI)	Study 1563-102, 2004
β-lactamase positive	5	0.12 - 0.5	0.25	NA		
<i>Moraxella catarrhalis</i>	27	≤ 0.004 - 1	0.25	1	Agar dilution (CLSI)	Study P0903-M-004/011, 2006; Mushtaq et al, 2007
<i>Moraxella catarrhalis</i>	101	≤ 0.015 - 1	0.125	0.25	Broth microdilution (CLSI)	Study P0903-M-012, 2006
<i>Moraxella catarrhalis</i>	1	0.25	NA	NA	Broth microdilution (CLSI)	Study P0903-M-013, 2006
<i>Moraxella catarrhalis</i>	9	0.015 - 0.5	0.12	0.5	Broth microdilution (CLSI)	Study P0903-M-018, 2007; Ge et al, 2009
<i>Moraxella catarrhalis</i>	101	≤ 0.008 - 0.5	0.06	0.12	Broth microdilution (CLSI)	Study P903-M-053, 2009
<i>Moraxella catarrhalis</i>	25	0.001 - 0.06	0.03	0.06	Broth microdilution (CLSI)	Study P903-M-057, 2008

Abbreviations: CLSI = Clinical and Laboratory Standards Institute; MIC = minimum inhibitory concentration; NA: not applicable (for MIC<sub>50</sub>, fewer than 5 isolates; for MIC<sub>90</sub>, fewer than 10 isolates).

Table 15 shows the in vitro activity of ceftaroline and comparator agents against *Moraxella catarrhalis*. Most of the data for *M. catarrhalis* were taken from a study performed to support ceftaroline Tier 2 label claims (Study P903-M-053, 2009). The isolates in study P903-M-053 were primarily US isolates collected during 2007 and 2008 as a part of the SENTRY Surveillance program by JMI Laboratories. The MIC<sub>90</sub> of 0.12 mcg/mL for ceftaroline was 8-fold lower than ceftriaxone, and lower than the other comparators tested except for levofloxacin (MIC<sub>90</sub> ≤ 0.03 mcg/mL) and possibly the macrolides (erythromycin ≤ 0.25 mcg/mL; azithromycin ≤ 0.5 mcg/mL; clarithromycin ≤ 0.25 mcg/mL), and trimethoprim/sulfamethoxazole (< 0.5 mcg/mL).

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**Table 15 In Vitro Activity of Ceftaroline and Selected Antimicrobial Agents against *Moraxella catarrhalis***

Agent	101 isolates (US) <sup>a</sup>			% S <sup>b</sup>
	MIC, µg/mL			
	Range	MIC <sub>50</sub>	MIC <sub>90</sub>	
Ceftaroline	≤ 0.008 – 0.5	0.06	0.12	NA
Ampicillin	≤ 0.5 – > 4	1	> 4	NA
Amox/clav	≤ 0.06 – 0.5	0.12	0.25	100
Ceftriaxone	≤ 0.008 – 2	0.25	1	100
Cefuroxime	0.25 – 2	1	2	100
Erythromycin	≤ 0.25 – 1	≤ 0.25	≤ 0.25	100
Azithromycin	≤ 0.5 – ≤ 0.5	≤ 0.5	≤ 0.5	100
Clarithromycin	≤ 0.25 – 0.5	≤ 0.25	≤ 0.25	100
Clindamycin	1 – > 2	2	> 2	0.0
Levofloxacin	≤ 0.03 – 0.06	≤ 0.03	≤ 0.03	100
SXT	≤ 0.5 – 1	≤ 0.5	≤ 0.5	99
Tigecycline	≤ 0.12 – 0.5	≤ 0.12	0.25	NA

a includes isolates from prior to 2007

b % susceptible according to CLSI M45-A (2006) or Tygacil Product Insert (2005)

Abbreviations: MIC<sub>50</sub> = minimum inhibitory concentration required to inhibit the growth of 50% of organisms;

MIC<sub>90</sub> = minimum inhibitory concentration required to inhibit the growth of 90% of organisms; NA = not applicable (breakpoints not defined); Amox/clav = amoxicillin/clavulanate;

SXT = trimethoprim/sulfamethoxazole; US = United States.

Source: Study P903-M-053, 2009

Table 16 shows the activity of ceftaroline against *Neisseria meningitidis*. In studies involving 510 isolates, the highest MIC observed was 1 mcg/mL including those isolates resistance to penicillin (β-lactamase positive and -negative), tetracycline, and ciprofloxacin.

**Table 16 Summary of In Vitro Studies to Evaluate the Activity of Ceftaroline against *Neisseria* spp.**

Pathogen / Phenotype	N	Range	Ceftaroline MIC, µg/mL		Method	Reference	
			50%	90%			
<i>Neisseria meningitidis</i>	10	≤ 0.016 - ≤ 0.016	≤ 0.016	≤ 0.016	Broth microdilution (CLSI)	Study P0903-M-001, 2004; Sader et al, 2005	
<i>Neisseria gonorrhoeae</i>							
All	403	0.002 - 1	0.125	0.25	Agar dilution (CLSI)	Study P0903-M-036, 2008	
Wild type	255	0.004 - 0.5	0.06	0.25			
TET-R, PEN-R (chromosomal)	73	0.06 - 1	0.25	0.5			
TET-R (plasmid)	29	0.008 - 0.25	0.06	0.25			
TET-R (chromosomal)	14	0.002 - 0.5	0.25	0.5			
PEN-R (chromosomal)	21	0.008 - 0.5	0.25	0.25			
Penicillinase producing	11	0.008 - 0.125	0.125	0.125			
<i>Neisseria meningitidis</i>	20	≤ 0.008 - ≤ 0.008	≤ 0.008	≤ 0.008	Broth microdilution (CLSI)	Study P903-M-053, 2009	
<i>Neisseria gonorrhoeae</i>							
All	107	0.004 - 1	0.25	0.5	Agar dilution (CLSI)		
Penicillin-susceptible	8	0.004 - 0.06	0.015	NA			
Penicillin-intermediate	61	0.008 - 1	0.25	0.5			
Penicillin-resistant	38	0.03 - 1	0.5	1			
Ciprofloxacin-susceptible	44	0.004 - 1	0.06	0.5			
Ciprofloxacin-intermediate	20	0.06 - 1	0.5	0.5			
Ciprofloxacin-resistant	43	0.008 - 1	0.25	0.5			

Abbreviations: CLSI = Clinical and Laboratory Standards Institute; TET-R: tetracycline resistant; PEN-R: penicillin resistant; MIC - minimum inhibitory concentration; NA: not applicable (for MIC<sub>50</sub>, fewer than 5 isolates; for MIC<sub>90</sub>, fewer than 10 isolates).

Source: Study P0903-M-001 (Part I), 2004; Study P0903-M-036, 2008; Study P903-M-053, 2009

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Table 17 shows the activity of ceftaroline and comparator agents against *Neisseria meningitidis* and *M. gonorrhoeae*; the in vitro activities of ceftaroline and comparator agents were from study P903-M-053 (2009). Ceftaroline demonstrated activity against *N. meningitidis*, as did all the comparators, Against *N. gonorrhoeae*, the MIC<sub>90</sub> of 0.5 mcg/mL for ceftaroline was equal to that of azithromycin and lower than all other comparators except ceftriaxone (MIC<sub>90</sub> 0.12 mcg/mL).

**Table 17 In Vitro Activity of Ceftaroline and Selected Antimicrobial Agents Against *Neisseria* spp.**

<i>Organism &amp; Agent</i>	<i>Range</i>	<i>MIC<sub>50</sub></i>	<i>MIC<sub>90</sub></i>	<i>% S<sup>a</sup></i>
<i>Neisseria meningitidis</i> 20 isolates (US)				
Ceftaroline	≤ 0.008 - ≤ 0.008	≤ 0.008	≤ 0.008	NA
Ceftriaxone	≤ 0.25 - ≤ 0.25	≤ 0.25	≤ 0.25	NA
Cefepime	≤ 0.12 - ≤ 0.12	≤ 0.12	≤ 0.12	NA
Penicillin	≤ 0.03 - 0.12	≤ 0.03	0.06	95.0
Meropenem	≤ 0.12 - ≤ 0.12	≤ 0.12	≤ 0.12	100
Levofloxacin	≤ 0.5 - ≤ 0.5	≤ 0.5	≤ 0.5	NA
<i>Neisseria gonorrhoeae</i> 107 isolates (US)				
Ceftaroline	0.004 - 1	0.25	0.5	NA
Ceftriaxone	≤ 0.001 - 0.12	0.015	0.12	100
Penicillin	0.015 - > 4	1	> 4	7.5
Tetracycline	0.06 - > 4	1	2	15.0
Ciprofloxacin	≤ 0.008 - > 4	0.25	> 4	41.1
Azithromycin	0.03 - 2	0.25	0.5	NA
Cefuroxime	≤ 0.008 - 2	0.25	1	94.4

<sup>a</sup> % susceptible according to CLSI M100-S18 (2008)

Abbreviations: MIC<sub>50</sub> = minimum inhibitory concentration required to inhibit the growth of 50% of organisms;  
MIC<sub>90</sub> = minimum inhibitory concentration required to inhibit the growth of 90% of organisms; NA = not applicable (breakpoints not defined).

Source: Study P903-M-053, 2009

The Applicant also tested ceftaroline against *Pasteurella multocida*. A total of 73 isolates were tested in two separate studies (Table 18). MIC<sub>90</sub> values for ceftaroline ranged from 0.03 to 0.06 mcg/ml.

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**Table 18 Summary of In Vitro Studies to Evaluate the Activity of Ceftaroline Against *Pasteurella multocida***

Pathogen	Range	MIC, µg/mL		Method	Reference
		50%	90%		
<i>Pasteurella multocida</i>	22 isolates <sup>a</sup>			Broth microdilution (CLSI)	Study P0903-M-010, 2006; Ge et al., 2008
Ceftaroline	≤ 0.008 - 0.06	≤ 0.008	0.06		
Ceftazidime	≤ 1 - ≤ 1	≤ 1	≤ 1		
Ceftriaxone	≤ 0.015 - 0.06	≤ 0.015	≤ 0.015		
Penicillin	≤ 0.12 - > 8	≤ 0.12	0.25		
Imipenem	0.06 - 4	0.25	2		
Erythromycin	0.25 - > 16	2	4		
Levofloxacin	≤ 0.015 - > 8	≤ 0.015	0.03		
<i>Pasteurella multocida</i>	51 isolates <sup>b</sup>			Broth microdilution (CLSI)	Study P903-M-053, 2009
Ceftaroline	≤ 0.008-0.12	≤ 0.008	0.03		
Ceftriaxone	≤ 0.25 - 0.5	≤ 0.25	≤ 0.25		
Ceftazidime	≤ 2 - 4	≤ 2	≤ 2		
Cefepime	≤ 0.12 - 2	≤ 0.12	0.5		
Cefuroxime	≤ 2 - ≤ 2	≤ 2	≤ 2		
Cefazolin	≤ 2 - ≤ 2	≤ 2	≤ 2		
Ampicillin	≤ 2 - 16	≤ 2	≤ 2		
Piperacillin/tazobactam	≤ 8 - ≤ 8	≤ 8	≤ 8		
Ertapenem	≤ 0.06 - ≤ 0.06	≤ 0.06	≤ 0.06		
Imipenem	≤ 0.5 - 1	≤ 0.5	≤ 0.5		
Levofloxacin	≤ 0.5 - ≤ 0.5	≤ 0.5	≤ 0.5		
Amikacin	≤ 4 - 16	8	16		
Tigecycline	≤ 0.03 - ≤ 0.12	0.06	0.06		

a includes isolates from 2004-2006

b includes isolates from earlier than 2007 and/or from outside the US

Abbreviations: CLSI = Clinical and Laboratory Standards Institute; MIC = minimum inhibitory concentration.

Source: Study P0903-M-010, 2006; Ge et al, 2008; Study P903-M-053, 2009

Table 19 shows the activity of ceftaroline against non-fermenting Gram-negative bacteria such as *Pseudomonas spp.*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia*. Generally, all had MIC<sub>90</sub> values that were >16mcg/ml.

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**Table 19 Summary of In Vitro Studies to Evaluate the Activity of Ceftaroline against Non-Fermenting Gram-negative Bacilli**

Pathogen / phenotype	N	Range	Ceftaroline MIC, µg/mL		Method	Reference
			50%	90%		
<i>Acinetobacter baumannii</i>	20	2 - > 32	16	> 32	Broth microdilution (CLSI)	Study P0903-M-001, 2004; Sader et al, 2005
<i>Alcaligenes spp.</i>	10	16 - > 32	> 32	> 32		
<i>Pseudomonas aeruginosa</i>	20	4 - > 32	16	> 32		
<i>Stenotrophomonas maltophilia</i>	10	32 - > 32	> 32	> 32		
<i>Acinetobacter baumannii</i>	10	1 - 32	4	8	Broth microdilution (CLSI)	Study TAK-599/00053, 2003
<i>Pseudomonas aeruginosa</i>	58	1 - >128	16	128		
<i>Acinetobacter baumannii</i>					Broth microdilution (CLSI)	Study 1563-102, 2004
Ceftazidime-susceptible	5	2 - > 8	2	NA		
Ceftazidime-intermediate	3	8 - > 8	NA	NA		
Ceftazidime-resistant	5	> 8 - > 8	> 8	NA		
<i>Pseudomonas aeruginosa</i>						
Ceftazidime-resistant	6	> 8 - > 8	> 8	NA		
<i>Acinetobacter baumannii</i>	10	1 - 8	2	8	Broth microdilution (CLSI)	Study P0903-M-002, 2003
<i>Acinetobacter baumannii</i>	3	8 - 128	NA	NA	Agar dilution (CLSI)	Study P0903-M-004/011, 2006; Mushtaq et al, 2007
<i>Acinetobacter spp.</i>	7	2 - 128	4	NA		
Pathogen / phenotype	N	Range	Ceftaroline MIC, µg/mL		Method	Reference
			50%	90%		
<i>Acinetobacter baumannii</i>	26	2 - > 32	> 32	> 32	Broth microdilution (CLSI)	Study P0903-M-013, 2006
<i>Pseudomonas aeruginosa</i>						
Ceftazidime-susceptible	80	2 - > 32	16	> 32		
Ceftazidime-resistant	15	> 32 - > 32	> 32	> 32		
<i>Burkholderia cepacia</i>	28	0.03 - > 32	> 32	> 32	Broth microdilution (CLSI)	Study P0903-M-012, 2006; Brown and Treczewski, 2009
<i>Pseudomonas aeruginosa</i>						
All	25	0.5 - >32	16	> 32		
MDR	10	4 - >32	16	> 32		
<i>Pseudomonas fluorescens/putida</i>	28	0.25 - 32	1	16		
<i>Stenotrophomonas maltophilia</i>	27	0.12 - >32	> 32	> 32		
<i>Acinetobacter spp.</i>					Broth microdilution (CLSI)	Study P0903-M-010, 2006; Ge et al, 2008
All	52	≤ 0.03 - >16	4	≥ 16		
MDR	16	8 - >16	> 16	≥ 16		
Imipenem-susceptible	47	≤ 0.03 - >16	4	≥ 16		
Imipenem-resistant	5	>16 - > 16	32	NA		
<i>Pseudomonas aeruginosa</i>	305	1 - > 16	16	> 16	Broth microdilution (CLSI)	Study P0903-M-035, 2009
<i>Pseudomonas aeruginosa</i>					Agar dilution (BSAC)	Study P903-M-052 Amendment1, 2009
Ceftazidime-susceptible	184	0.125-64	2	16		
Ceftazidime-NS	6	64 - > 64	> 64	ND		
<i>Pseudomonas fluorescens</i>	2	1 - 2	ND	ND		
<i>Acinetobacter baumannii</i>	101	2 - > 16	> 16	> 16	Broth microdilution (CLSI)	Study P903-M-053, 2009
<i>Pseudomonas aeruginosa</i>	101	4 - > 16	> 16	> 16		
<i>Acinetobacter baumannii</i>	25	1 - > 64	2	8	Broth microdilution (CLSI)	Study P903-M-057, 2008
<i>Pseudomonas aeruginosa</i>	50	4 - > 64	16	> 64		
<i>Stenotrophomonas maltophilia</i>	25	1 - > 64	> 64	> 64		

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Pathogen / phenotype	N	Range	Ceftaroline MIC, µg/mL		Method	Reference
			50%	90%		
<i>Pseudomonas aeruginosa</i>						
Wild type	5	8 - 32	16	NA	Broth microdilution (CLSI)	Study P903-M-084, 2009
AmpC or OMP alteration	5	16 - > 128	128	NA		
Class B β-lactamase	5	> 128 - > 128	> 128	NA		
<i>Acinetobacter baumannii</i>						
wild type	5	2 - 4	4	NA	Broth microdilution (CLSI)	Study P903-M-085, 2009
OXA β-lactamase	10	128 - > 128	> 128	> 128		
<i>Acinetobacter baumannii</i>	10	1 - > 64	> 64	> 64		
<i>Pseudomonas aeruginosa</i>	10	8 - > 64	> 64	> 64		

Abbreviations: AmpC = AmpC β-lactamase; BSAC = British Society for Antimicrobial Chemotherapy; Ceftazidime-NS = ceftazidime-nonsusceptible; CLSI = Clinical and Laboratory Standards Institute; MIC = minimum inhibitory concentration; MDR = multi-drug resistant; OMP = outer membrane protein; OXA = oxacillin; NA = not applicable (for MIC<sub>50</sub>, fewer than 5 isolates; for MIC<sub>90</sub>, fewer than 10 isolates); NS = not susceptible

Ceftaroline demonstrated no activity against *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae* (MIC values were >64 mcg/mL) (Table 20). Ceftaroline has in vitro activity against the extracellular form of *Legionella pneumophila* (MIC<sub>90</sub> 0.25 mcg/mL; 10 isolates) as measured by an agar dilution method; however, ceftaroline fails to demonstrate activity against intracellular *L. pneumophila*, which supports the idea that ceftaroline, like other cephalosporins, fails to accumulate to significant levels intracellularly in mammalian cells. Levofloxacin served as a positive control for these studies, and it exhibited activity against all three of these respiratory pathogens (levofloxacin MIC ranges: *M. pneumoniae* 0.25-1 mcg/mL; *C. pneumoniae* 0.25 - 0.5 mcg/mL; extracellular *L. pneumophila* 0.008-0.015 mcg/mL). Against intracellular *L. pneumophila*, levofloxacin was also active, although the MIC<sub>90</sub> increased 30-fold to 0.5 mcg/mL (Study P903-M-061, 2009).

**Table 20 Summary of In Vitro Studies to Evaluate the Activity of Ceftaroline against Atypical Respiratory Pathogens**

Pathogen	N	Range	Ceftaroline MIC, µg/mL		Method	Reference
			50%	90%		
<i>Mycoplasma pneumoniae</i>	10	64- > 64	64	> 64	Broth dilution with phenol red color change (in vitro)	Study P903-M-061, 2009
<i>Chlamydia pneumoniae</i>	5	> 64- > 64	> 64	NA	Inclusion formation in McCoy cell culture monolayers	
<i>Legionella pneumophila</i>	10	0.015-1	0.12	0.25	Agar dilution (in vitro)	
<i>Legionella pneumophila</i>	10	> 32- > 32	> 32	> 32	Cell killing in Hep-2 cell monolayers	

Abbreviations: N = number of isolates; NA = not applicable (for MIC<sub>50</sub>, fewer than 5 isolates; for MIC<sub>90</sub>, fewer than 10 isolates).

Source: Study P903-M-061, 2009

Ceftaroline was also tested for its activity against Gram-positive anaerobes such as *Clostridium spp.*, (Table 21). Overall, MIC<sub>90</sub> values were ≤ 2 mcg/mL for all non *C. difficile* isolates. However, for *C. difficile*, the ceftaroline MIC<sub>90</sub>s are typically in the range of 4-8 mcg/mL.

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**Table 21 Summary of In Vitro Studies to Evaluate the Activity of Ceftaroline against Gram-positive Anaerobes**

Pathogen	N	Range	Ceftaroline MIC, µg/mL		Method	Reference		
			50%	90%				
<i>Clostridium</i> spp.	25	≤ 0.016 - 8	0.12	2	Broth microdilution (CLSI)	Study P0903-M-001, 2004; Sader et al, 2005		
<i>Propionibacterium</i> spp. and <i>Peptostreptococcus</i> spp.	15	0.03 - 0.12	0.06	0.12				
Pathogen	N	Range	Ceftaroline MIC, µg/mL		Method	Reference		
			50%	90%				
<i>Parvimonas micra</i>	22	0.015-0.5	0.06	0.25	Agar dilution (CLSI)	Study P903-M-058, 2009		
<i>Finegoldia magna</i>	19	0.03-1	0.25	0.5				
<i>Peptoniphilus azaccharolytica</i>	21	≤ 0.008-0.25	0.06	0.25				
<i>Anaerococcus tetradius</i>	20	≤ 0.008-2	0.03	0.125				
<i>Peptostreptococcus anaerobius</i>	23	0.125-8	0.5	4				
Other Gram-positive cocci spp.	22	≤ 0.008-8	0.06	1				
<i>Clostridium</i>								
<i>Clostridium perfringens</i>	20	≤ 0.008-0.5	0.125	0.25				
<i>Clostridium ramosum</i>	21	1-2	1	1				
<i>Clostridium inocuum</i>	21	0.5-4	1	2				
<i>Clostridium clostridioforme</i> group	20	0.25-2	1	2				
other <i>Clostridium</i> spp.	24	0.015-16	0.5	16				
<i>Actinomyces</i> spp.	13	≤ 0.008-0.25	0.015	0.25				
<i>Eggerthella lenta</i>	17	2-16	8	8				
" <i>Eubacterium</i> " group	25	0.015-0.25	0.125	0.25				
<i>Lactobacillus casei-ramosus</i> group	10	0.25-8	0.5	1				
<i>Propionibacterium acnes</i>	20	≤ 0.008-0.125	≤ 0.008	0.06				
<i>Propionibacterium avidum</i>	11	0.015-0.25	0.25	0.25				
<i>Clostridium difficile</i>								
All	26	≤ 0.015-8	2	8	Agar dilution (CLSI)	Study P903-M-060, 2009		
Quinolone-susceptible	13	0.015-8	2	8				
Quinolone-resistant	13	0.5-8	2	4				
<i>Clostridium perfringens</i>	7	≤ 0.015-0.12	0.06	NA				
<i>Clostridium</i> spp.	16	0.06-64	1	4				
<i>Peptostreptococcus</i> spp.	39	≤ 0.015-8	0.03	0.5				
<i>Propionibacterium acnes</i>	15	≤ 0.015-0.06	0.03	0.06				
<i>Propionibacterium</i> spp.	13	≤ 0.015-0.06	0.03	0.03				
other Gram-positive non-spore-forming bacilli	11	≤ 0.015-1	0.12	0.5				

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Pathogen	N	Range	Ceftaroline MIC, µg/mL		Method	Reference
			50%	90%		
<i>Clostridium butyricum</i>	1	≤ 0.06	NA	NA	Broth microdilution (CLSI)	Study P0903-M-013, 2006
<i>Clostridium cadaveris</i>	1	0.25	NA	NA		
<i>Clostridium clostridioforme</i>	3	0.12 - 0.25	0.25	NA		
<i>Clostridium difficile</i>	1	0.12	NA	NA		
<i>Clostridium histolyticum</i>	1	1	NA	NA		
<i>Clostridium perfringens</i>	6	≤ 0.06 - ≤ 0.06	≤ 0.06	NA		
<i>Clostridium septicum</i>	2	1 - 16	NA	NA		
<i>Clostridium species</i>	4	≤ 0.06 - 0.05	NA	NA		
<i>Actinomyces odontolyticus</i>	1	0.12	NA	NA		
<i>Actinomyces turicensis</i>	1	≤ 0.06	NA	NA		
<i>Eubacterium lentum</i>	2	≤ 0.06 - ≤ 0.06	NA	NA		
<i>Peptostreptococcus anaerobius</i>	1	≤ 0.06	NA	NA		
<i>Peptostreptococcus asaccharolyticus</i>	1	≤ 0.06	NA	NA		
<i>Peptostreptococcus micros</i>	2	≤ 0.06 - ≤ 0.06	NA	NA		
<i>Peptostreptococcus prevotii</i>	1	≤ 0.06	NA	NA		
<i>Propionibacterium acnes</i>	4	≤ 0.06 - ≤ 0.06	NA	NA		

Pathogen	N	Range	Ceftaroline MIC, µg/mL		Method	Reference
			50%	90%		
<i>Clostridium difficile</i>					Agar dilution	Study P903-M-050, 2009
All	60	0.125-16	4	4		
Genotypically distinct ribotypes	30	1-16	4	8		
3 most common ribotypes	30	0.25-4	4	4		
Ribotype 001	10	0.25-4	2	4		
Ribotype 027	10	0.25-4	4	4		
Ribotype 106	10	0.25-4	4	4		

Abbreviations: CLSI = Clinical and Laboratory Standards Institute; MIC = minimum inhibitory concentration; N = number of isolates; NA = not applicable (for MIC<sub>90</sub>, fewer than 5 isolates; for MIC<sub>50</sub>, fewer than 10 isolates).

Against *Peptostreptococcus* spp. and other Gram-negative anaerobes, ceftaroline demonstrated MIC<sub>90</sub> of 4 mcg/mL (Table 22). Against *Propionibacterium acnes* the MIC<sub>90</sub> for ceftaroline (0.06 mcg/mL) was equal to that for ceftriaxone and lower than clindamycin and metronidazole. The same pattern held for *Peptoniphilus asaccharolytica* (ceftaroline and ceftriaxone MIC<sub>90</sub>s of 0.25 mcg/mL). Ceftaroline MIC<sub>90</sub> of 0.5 mcg/mL against *Finexgoldia magna* was lower than those of ceftriaxone, clindamycin and metronidazole. Ceftaroline had in vitro activity against *Clostridium perfringens*, with an MIC<sub>90</sub> of 0.25 mcg/mL; a value that was lower than ceftriaxone, clindamycin and metronidazole. Against other *Clostridium* spp., except *C. difficile*, the MIC<sub>90</sub>s for ceftaroline ranged from 1-2 mcg/mL, lower than for ceftriaxone, clindamycin and metronidazole (Study P903-M-058, 2009).

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**Table 22 In Vitro Activity of Ceftaroline and Selected Antimicrobial Agents against Gram-positive Anaerobes**

Organism Group & Agent	Study P903-M-058, 2009			Study P903-M-060, 2009		
	MIC, µg/mL			MIC, µg/mL		
	Range	MIC <sub>50</sub>	MIC <sub>90</sub>	Range	MIC <sub>50</sub>	MIC <sub>90</sub>
<i>Peptostreptococcus</i> spp.	23 isolates			39 isolates		
Ceftaroline	0.125 - 8	0.5	4	≤ 0.015 - 8	0.03	0.5
Ceftriaxone	0.5 - 16	2	8	≤ 0.015 - 64	0.5	4
Clindamycin	≤ 0.03 - 32	≤ 0.03	0.25	≤ 0.06 - 16	0.06	1
Metronidazole	0.125 - 1	0.5	1	≤ 0.12 - > 32	1	> 32
<i>Propionibacterium acnes</i>	20 isolates			15 isolates		
Ceftaroline	≤ 0.008 - 0.125	≤ 0.008	0.06	≤ 0.015 - 0.06	0.03	0.06
Ceftriaxone	≤ 0.008 - 0.125	0.015	0.06	0.03 - 0.5	0.03	0.06
Clindamycin	0.125 - > 128	0.125	0.25	≤ 0.06 - 0.12	≤ 0.06	0.125
Metronidazole	> 32 - > 32	> 32	> 32	32 - > 32	32	> 32
<i>Finegoldia magna</i>	19 isolates					
Ceftaroline	0.03 - 1	0.25	0.5			
Ceftriaxone	2 - 8	4	8			
Clindamycin	0.06 - > 128	2	> 128			
Metronidazole	0.06 - 1	0.5	1			
<i>Peptoniphilus asaccharolytica</i>	21 isolates					
Ceftaroline	≤ 0.008 - 0.25	0.06	0.25			
Ceftriaxone	0.03 - 1	0.125	0.25			
Clindamycin	≤ 0.03 - > 128	0.125	> 128			
Metronidazole	0.125 - 2	1	1			
<i>Clostridium difficile</i>	4 isolates			26 isolates		
Ceftaroline	8 - 16	NA	NA	≤ 0.015 - 8	2	8
Ceftriaxone	32 - > 64	NA	NA	≤ 0.015 - > 64	32	64
Clindamycin	4 - > 128	NA	NA	≤ 0.06 - 16	2	16
Metronidazole	0.25 - 2	NA	NA	≤ 0.12 - > 32	16	32
<i>Clostridium perfringens</i>	20 isolates			7 isolates		
Ceftaroline	≤ 0.008 - 0.5	0.125	0.25	≤ 0.015 - 0.12	0.06	NA
Ceftriaxone	≤ 0.008 - 4	0.5	2	≤ 0.015 - 0.12	0.06	NA
Clindamycin	≤ 0.03 - 2	0.25	1	0.5 - 16	0.5	NA
Metronidazole	0.5 - 4	2	4	≤ 0.5 - 8	1	NA

Abbreviations: MIC<sub>50</sub> = minimum inhibitory concentration required to inhibit the growth of 50% of organisms;  
MIC<sub>90</sub> = minimum inhibitory concentration required to inhibit the growth of 90% of organisms; NA = not applicable (for MIC<sub>50</sub>, fewer than 5 isolates; for MIC<sub>90</sub>, fewer than 10 isolates).  
Source: Study P903-M-058, 2009; P903-M-060, 2009

The activity of ceftaroline against gram-negative anaerobes varies according to species. Against anaerobic species where β-lactamases are common its activity is limited. Against *Bacteroides fragilis* and other *Bacteroides* spp. the MIC<sub>90</sub>s for ceftaroline were ≥ 32 mcg/mL (with the exception of *B. uniformis*, which was 16 mcg/mL) (Table 22). Ceftaroline also had no relevant activity against most isolates of *Prevotella* spp. (MIC<sub>90</sub>s 32 - 64 mcg/mL). Activity was observed against *Fusobacterium* spp. (MIC<sub>90</sub>s ≤ 0.5 mcg/mL), except for *F. mortiferum* (MIC<sub>90</sub> 32 mcg/mL). It is active against most isolates of *Veillonella* spp. (MIC<sub>90</sub> 0.5 mcg/mL) and *Porphyromonas asaccharolytica* (MIC<sub>90</sub> 0.03 mcg/mL), but not β-lactamase-producing *P. somerae* (MIC<sub>90</sub> 16 mcg/mL) Table 23.

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**Table 23 Summary of In Vitro Studies to Evaluate the Activity of Ceftaroline against Gram-Negative Anaerobes**

Pathogen	N	Range	Ceftaroline MIC, µg/ml		Method	Reference
			50%	90%		
<i>Bacteroides fragilis</i>	20	4 - > 32	32	> 32	Broth microdilution (CLSI)	Study P0903-M-001, 2004, Sader et al, 2005
<i>Prevotella</i> spp.	16	0.03 - > 16	8	> 32		
<i>Bacteroides fragilis</i>	14	8 - > 8	> 8	> 8	Agar dilution (CLSI)	Study 1563-102, 2004
<i>Prevotella</i> spp.	11	≤ 0.06 - > 8	2	> 8		
<i>Eubacterium limosum</i>	1	0.03	NA	NA	Agar dilution (Japanese method)	Study TAK599/00023, 2003
<i>Bacteroides fragilis</i>	8	2 - > 128	4	NA		
<i>Bacteroides vulgatus</i>	1	8	NA	NA		
<i>Bacteroides hypermegas</i>	1	1	NA	NA		
<i>Tissierella praeacuta</i>	1	0.03	NA	NA		
<i>Fusobacterium nucleatum</i>	2	0.016 - 0.06	NA	NA		
<i>Fusobacterium ruzsii</i>	1	0.016	NA	NA		
<i>Fusobacterium varium</i>	2	0.25 - 0.5	NA	NA		
<i>Fusobacterium mortiferum</i>	1	2	NA	NA		

Pathogen	N	Range	Ceftaroline MIC, µg/ml		Method	Reference
			50%	90%		
<i>Bacteroides caccae</i>	9	0.25 - 16	2	NA	Broth Microdilution (CLSI)	Study P0903-M-013, 2006
<i>Bacteroides capillozus</i>	1	0.25	NA	NA		
<i>Bacteroides distanzosii</i>	8	0.12 - > 32	16	NA		
<i>Bacteroides egerthii</i>	2	≤ 0.06 - > 32	NA	NA		
<i>Bacteroides fragilis</i>	47	0.25 - > 32	2	> 32		
<i>Bacteroides fragilis</i> group	14	0.12 - > 32	16	> 32		
<i>Bacteroides ovatus</i>	3	1 - 4	2	NA		
<i>Bacteroides splanchnicus</i>	1	0.12	NA	NA		
<i>Bacteroides stercoris</i>	1	8	NA	NA		
<i>Bacteroides thetaioamicron</i>	27	4 - > 32	16	> 32		
<i>Bacteroides uniformis</i>	11	1 - > 32	8	32		
<i>Bacteroides vulgatus</i>	4	32 - > 32	> 32	NA		
<i>Bacteroides</i> species	1	8	NA	NA		
<i>Fusobacterium nucleatum</i>	2	≤ 0.06 - ≤ 0.06	≤ 0.06	NA		
<i>Fusobacterium varium</i>	1	0.25	NA	NA		
<i>Porphyromonas asaccharolytica</i>	2	≤ 0.06 - ≤ 0.06	≤ 0.06	NA		
<i>Porphyromonas gingivalis</i>	2	≤ 0.06 - ≤ 0.06	≤ 0.06	NA		
<i>Prevotella bivia</i>	2	8 - > 32	NA	NA		
<i>Prevotella buccae</i>	3	0.12 - 16	0.25	NA		
<i>Prevotella corporis</i>	1	1	NA	NA		
<i>Prevotella denticola</i>	3	≤ 0.06 - 16	4	NA		
<i>Prevotella intermedia</i>	2	≤ 0.06 - 8	NA	NA		
<i>Prevotella loeschii</i>	3	1 > 32	> 32	NA		
<i>Prevotella melaninogenica</i>	3	≤ 0.06 - 1	≤ 0.06	NA		
<i>Prevotella oralis</i> group	2	0.5 - 2	0.5	NA		
<i>Prevotella oralis</i>	3	> 32	> 32	NA		

In Study P903-M-058, 2009 and Study P903-M-060, 2009, ceftaroline demonstrated little to no activity against *Bacteroides fragilis* and other members of the *Bacteroides* group, with MIC<sub>90s</sub> that are typically > 64 mcg/mL and are similar to those of ceftriaxone and clindamycin, but much higher than metronidazole (MIC<sub>90s</sub> ≤ 2 mcg/mL). Ceftaroline also has low activity against most isolates of *Prevotella* spp., similar to ceftriaxone and clindamycin but unlike metronidazole. Ceftaroline demonstrated activity against *Porphyromonas asaccharolytica* (MIC<sub>90</sub> 0.03 mcg/mL), *Fusobacterium nucleatum* (MIC<sub>90</sub> 0.125 mcg/mL) and most other

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*Fusobacterium* spp., and *Veillonella* spp. (Study P903-M-058, 2009), the MICs for which are generally equal to or lower than those for ceftriaxone, clindamycin, and metronidazole (Table 24).

**Table 24 In Vitro Activity of Ceftaroline and Selected Antimicrobial Agents against Gram-negative Anaerobes**

Organism Group & Agent	Study P903-M-058, 2009			Study P903-M-060, 2009			Organism Group & Agent	Study P903-M-058, 2009			Study P903-M-060, 2009			
	MIC, µg/mL			MIC, µg/mL				MIC, µg/mL			MIC, µg/mL			
	Range	MIC <sub>50</sub>	MIC <sub>90</sub>	Range	MIC <sub>50</sub>	MIC <sub>90</sub>		Range	MIC <sub>50</sub>	MIC <sub>90</sub>	Range	MIC <sub>50</sub>	MIC <sub>90</sub>	
<i>Bacteroides fragilis</i>	30 isolates			205 isolates			<i>Porphyromonas asaccharolytica</i>	21 isolates			0 isolates			
Ceftaroline	4 - > 64	16	> 64	0.5 - > 64	8	64		Ceftaroline	≤ 0.008 - 0.5	0.015	0.03			
Ceftriaxone	4 - > 64	32	> 64	0.12 - > 64	32	> 64		Ceftriaxone	≤ 0.008 - 0.1	0.06	0.06			
Clindamycin	0.06 - > 128	1	> 128	≤ 0.5 - > 64	≤ 0.5	> 64		Clindamycin	≤ 0.03 - > 128	≤ 0.03	> 128			
Metronidazole	0.25 - 2	1	2	1 - 8	1	4		Metronidazole	≤ 0.03 - 0.25	0.06	0.125			
<i>Bacteroides thetaiotaomicron</i>	20 isolates			69 isolates			<i>Fusobacterium nucleatum</i>	22 isolates			0 isolates			
Ceftaroline	32 - > 64	64	> 64	2 - 64	32	64		Ceftaroline	≤ 0.008 - 0.125	≤ 0.008	0.125			
Ceftriaxone	64 - > 64	> 64	> 64	0.12 - > 64	> 64	> 64		Ceftriaxone	0.015 - 1	0.125	0.5			
Clindamycin	0.06 - > 128	4	> 128	≤ 0.5 - 64	2	64		Clindamycin	< 0.03 - 0.5	0.06	0.06			
Metronidazole	0.5 - 2	1	1	1 - 8	2	4		Metronidazole	< 0.03 - 0.25	< 0.03	0.25			
<i>Prevotella melaninogenica</i>	18 isolates			0 isolates			<i>Veillonella</i> spp.	19 isolates			0 isolates			
Ceftaroline	≤ 0.008 - 32	2	32					Ceftaroline	0.015 - 1	0.125	0.5			
Ceftriaxone	0.03 - 32	2	32					Ceftriaxone	0.03 - 8	4	8			
Clindamycin	≤ 0.03 - > 128	≤ 0.03	> 128					Clindamycin	≤ 0.03 - 128	0.125	128			
Metronidazole	.06 - 2	0.5	1					Metronidazole	1 - 8	2	8			
<i>Prevotella intermedia</i>	20 isolates			0 isolates										
Ceftaroline	≤ 0.008 - 64	1	16											
Ceftriaxone	0.03 - 64	1	16											
Clindamycin	≤ 0.03 - > 128	≤ 0.03	16											
Metronidazole	0.125 - 2	0.25	1											

Abbreviations: MIC<sub>50</sub> = minimum inhibitory concentration required to inhibit the growth of 50% of organisms; MIC<sub>90</sub> = minimum inhibitory concentration required to inhibit the growth of 90% of organisms. Source: Study P903-M-058, 2009; P903-M-060, 2009

Pathogen	N	Range	Ceftaroline MIC, µg/ml		Method	Reference		
			50%	90%				
<b>Bacteroides</b>								
<i>B. fragilis</i>	30	4- > 64	16	> 64	Agar dilution (CLSI)	Study P903-M-058, 2009		
<i>B. thetaiotaomicron</i>	20	32- > 64	64	> 64				
<i>B. fragilis</i> group (others)	26	2- > 64	64	> 64				
<b>Prevotella</b>								
<i>P. melaninogenica</i>	18	≤ 0.008-32	2	32				
<i>P. intermedia</i>	20	≤ 0.008-64	1	16				
<i>P. buccae</i>	20	0.125- > 64	0.5	64				
<b>Porphyromonas</b>								
<i>P. asaccharolytica</i>	21	≤ 0.008-0.5	0.015	0.03				
<i>P. somerae</i>	10	≤ 0.008-16	0.015	16				
<b>Fusobacterium</b>								
<i>F. nucleatum</i>	22	≤ 0.008-0.125	≤ 0.008	0.125				
<i>F. necrophorum</i>	22	0.015-0.06	0.03	0.06				
<i>F. mortiferum</i>	10	1-64	8	32				
<i>F. varium</i>	10	0.015-0.5	0.25	0.5				
<i>Veillonella</i> spp.	19	0.015-1	0.125	0.5				
<b>Bacteroides</b>								
<i>B. fragilis</i>	205	0.5- > 64	8	64	Agar dilution (CLSI)	Study P903-M-060, 2009		
<i>B. distazonis</i>	22	1- > 64	16	64				
<i>B. ovatus</i>	36	8-64	16	64				
<i>B. thetaiotaomicron</i>	69	2-64	32	64				
<i>B. uniformis</i>	11	0.03-64	8	16				
<i>B. vulgatus</i>	20	1-64	64	64				
other <i>Bacteroides</i> spp.	7	4-64	16	NA				
<i>Prevotella</i> spp.	14	0.015-32	1	8				
<i>Fusobacterium</i> spp.	3	≤ 0.015- ≤ 0.015	NA	NA				

Abbreviations: CLSI = Clinical and Laboratory Standards Institute; MIC = minimum inhibitory concentration NA = not applicable (for MIC<sub>90</sub>, fewer than 5 isolates; for MIC<sub>50</sub>, fewer than 10 isolates).

**Activity against Select Bio-Threat Bacteria**

Ceftaroline was tested subset of bio-diverse set of isolates including *Yesinia pestis*, *Burkholderia mallei*, *Burkholderia pseudomallei*, and *Francisella tularensis* were tested according to CLSI guidelines (M7-A7, 2006) using broth microdilution (Table 25). The results in Table 24 indicate that ceftaroline has activity against

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*Y. pestis* (highest MIC 0.06 mcg/mL) that was nearly equivalent to that of the comparator ciprofloxacin. Ceftaroline had good activity against most isolates of *F. tularensis* (MIC<sub>90</sub> 1 mcg/mL), although its activity was less than that of ciprofloxacin (MIC<sub>90</sub> 0.6 mcg/mL). It has moderate activity against both *B. mallei* and *B. pseudomallei* (MIC<sub>90</sub> 4 mcg/mL), which was two-fold lower than the comparator azithromycin for *B. mallei* but was equal to that for ceftazidime against *B. pseudomallei*. Ceftaroline had little if any activity against *B. anthracis* (all isolates with MICs > 8 mcg/mL).

**Table 25 Activity of Ceftaroline and Antimicrobial Agents Against some bio-threat agents**

Organism & Agent	MIC, µg/mL		
	Range	MIC <sub>50</sub>	MIC <sub>90</sub>
<i>Bacillus anthracis</i>	30 isolates		
Ceftaroline	> 8 - > 8	> 8	> 8
Ciprofloxacin	0.06 - 0.25	0.06	0.12
<i>Burkholderia mallei</i>	30 isolates		
Ceftaroline	0.25 - 8	2	4
Azithromycin	0.12 - 2	0.5	1
<i>Burkholderia pseudomallei</i>	30 isolates		
Ceftaroline	0.5 - 4	4	4
Ceftazidime	0.25 - 32	2	4
<i>Francisella tularensis</i>	27 isolates		
Ceftaroline	0.06 - > 8	0.25	1
Ciprofloxacin	0.008 - 0.5	0.015	0.06
<i>Yersinia pestis</i>	30 isolates		
Ceftaroline	0.008 - 0.06	0.015	0.03
Ciprofloxacin	0.008 - 0.03	0.015	0.03

Abbreviations: MIC<sub>50</sub> = minimum inhibitory concentration required to inhibit the growth of 50% of organisms;

MIC<sub>90</sub> = minimum inhibitory concentration required to inhibit the growth of 90% of organisms.

Source: Study P903-M-070, 2009

The Applicant has provided data from a surveillance study for ceftaroline that was carried out by JMI Laboratories in 2008. All studies were conducted in accordance to the CLSI M23 document<sup>23</sup>. The study involved the collection and testing of 17,326 organisms. A total of 10,496 clinical isolates were collected from 27 medical centers in 19 states across the US. An additional 6,830 isolates were collected from 28 medical centers in 12 countries in Europe (and Israel) (Study P0903-M-035, 2009). Organisms (one per subject) were from bloodstream infections, community-acquired respiratory tract infections, pneumonia in hospitalized subjects, skin and skin structure infections, and gram-positive infections of any site. All isolates underwent identification and susceptibility testing (using lyophilized microdilution panels) at the same central laboratory. The QC results for the MIC testing of the surveillance isolates are summarized in Table 26. Of 370 MIC tests for QC organisms for which ranges have been established (does not include *E. faecalis* ATCC 29212 and *P. aeruginosa* ATCC 27853), 368 (99.5%) were within the CLSI ranges.

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**Table 26 Ceftaroline MIC Values for Quality Control Strains Tested in the 2008 Ceftaroline Surveillance Study**

QC Organism (# tests)	Number of Occurrences (% of Total) at MIC, µg/mL <sup>a</sup>											
	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	> 16
<i>S. aureus</i> ATCC 29213 (142)	-	-	-	-	142 (100)	-	-	-	-	-	-	-
<i>E. faecalis</i> ATCC 29212 (143)	-	-	-	-	1 (0.7)	3 (2.1)	132 (92.3)	7 (4.9)	-	-	-	-
<i>S. pneumoniae</i> ATCC 49619 (68)	57 (83.8)	10 (14.7)	1 (1.5)	-	-	-	-	-	-	-	-	-
<i>P. aeruginosa</i> ATCC 27853 (11)	-	-	-	-	-	-	-	-	1 (9.1)	8 (72.7)	2 (18.2)	-
<i>E. coli</i> ATCC 25922 (131)	-	-	62 (47.3)	68 (51.9)	1 (0.8)	-	-	-	-	-	-	-
<i>H. influenzae</i> ATCC 49247 (29)	-	-	27 (93.1)	2 (6.9)	-	-	-	-	-	-	-	-

<sup>a</sup> Boxed areas indicate acceptable ranges for quality control strains according to CLSI M100-S18, 2008  
Abbreviations: ATCC = American Type Culture Collection; MIC = minimum inhibitory concentration; QC = Quality Control.  
Source: Study P0903-M-035, 2009

**Conclusions: Antimicrobial Spectrum of Activity:**

The information submitted by the Applicant from the large prospective surveillance studies and other investigations of the in vitro activity of ceftaroline supports the Applicant’s claim of activity against some of the pathogens shown to be associated with complicated skin and skin structure infections, and community acquired pneumoniae. Ceftaroline had low activity against vancomycin-susceptible and vancomycin resistant *E. faecalis* and generally inactive against all *E. faecium* isolates tested. MIC values for all tested isolates of *S. aureus* (including strains resistant to other classes of antimicrobials, and stains with specific virulence profiles), *S. pyogenes*, Data comparing the US and European studies yielded similar results in some cases there was a tendency towards 1-dilution higher MICs from the European countries. Among the *S. aureus* isolates tested. Serotyping was performed on the *S. pneumoniae* isolates from the 2008 US surveillance study and the predominant serotype was 19A. Serotype 19A isolates are often resistant to antibiotics and of the MDR *S. pneumoniae* isolates from the ceftaroline US surveillance study, 80.8% were serotype 19A and 15% were serotype 19F, and the ceftaroline MIC<sub>90</sub> for both 19A and 19F was 0.25 mcg/mL (maximum ceftaroline MIC was 0.5 mcg/mL).

**MECHANISM OF ACTION:**

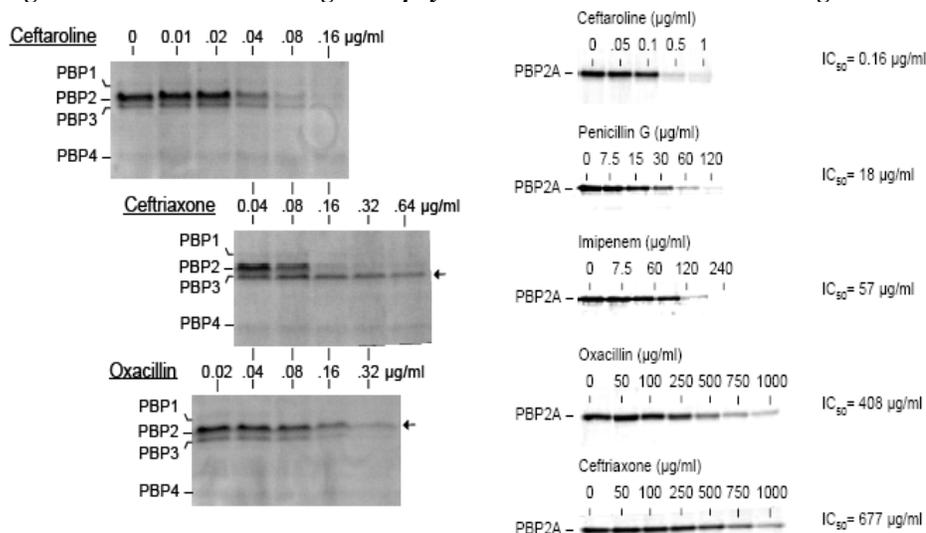
Cephalosporins, like other β-lactam antibiotic, inhibit bacterial cell growth by binding to the active site of bacterial transpeptidase enzyme. The Applicant conducted a number of studies to characterize the mechanism of action of ceftaroline. Ceftaroline was investigated for its binding affinities to penicillin binding protein PBP and compared with other comparator agents. Figure 1 shows the binding to *Staphylococcus aureus* PBP by ceftaroline, penicillin, imipenem oxacillin and ceftriaxone. The Applicant report the IC<sub>50</sub> values of the agents tested. The IC<sub>50</sub> is the concentration of the inhibitor (β-lactam) at which 50% inhibition of enzyme activity is seen. The IC<sub>50</sub> values show that ceftaroline demonstrated the lowest inhibitory concentration of 0.16 mcg/mL.

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**Figure 1. Ceftaroline Binding to *Staphylococcus aureus* Penicillin Binding Proteins**



In another experiment, the affinity of ceftaroline for PBPs in methicillin-sensitive *S. aureus* was determined. Ceftaroline bound with higher affinity than its comparators (ceftriaxone or oxacillin/cefotaxime) to PBP1-3. However, oxacillin had a two-fold higher affinity than ceftaroline for PBP1. There were also differences in the absolute values for the IC<sub>50</sub>s for PBPs from ATCC 29213 in these two studies, although in each ceftaroline exhibited potent binding to *S. aureus* PBP1-3 with IC<sub>50</sub> values less than 0.5 mcg/mL (Table 26). The affinity of ceftaroline for PBP4, like that of ceftriaxone or oxacillin/cefotaxime, was low relative to those for PBP1-3.

**Table 26 Affinity of Ceftaroline and Comparators for PBPs from Methicillin-susceptible *Staphylococcus aureus***

Phenotype	Strain Number	PBP IC <sub>50</sub> or MIC	IC <sub>50</sub> <sup>a</sup> or MIC, µg/mL				Study
			CPT	CRO	OXA	CTX	
MSSA	ATCC 29213	MIC	0.12-0.25	2	0.12-0.25		Study P0903-M-024, 2008
		PBP1	0.10	0.16	0.045		
		PBP2	0.034	0.065	0.125		
		PBP3	0.049	0.71	0.11		
		PBP4	> 1	> 1	> 1		
MSSA	ATCC 29213	MIC	0.5	2		2	Study P0903-M-041, 2009
		PBP1	0.01	2.49		0.49	
		PBP2	0.25	0.64		1.27	
		PBP3	0.06	0.14		0.74	
		PBP4	8.89	5.69		10.0	

<sup>a</sup> indicated as mean ± standard deviation where available

Abbreviations: ATCC = American Type Culture Collection; CPT = ceftaroline; CRO = ceftriaxone; MIC = minimum inhibitory concentration; OXA = oxacillin; CTX = cefotaxime; MSSA = methicillin-susceptible *Staphylococcus aureus*; PBP = penicillin-binding protein.

Source: Study P0903-M-024, 2008; Study P0903-M-041, 2009

Table 27 shows the affinities of ceftaroline and comparators for PBP2a of methicillin-resistant *S. aureus* along with the MICs for the corresponding strains. The PBP2a is sometimes referred to as an inducible PBP that have a weak affinity to the penicillins M and other β-lactams. The PBP2a is encoded by a conserved gene which is part of a conserved region of the *S. aureus* genome (*mecA*) which is also part of a mobile genetic element called the Staphylococcal cassette chromosome (*SCCmec*). PBP2a is not inhibited by β-lactams lacking MRSA

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activity, the transpeptidase activity of PBP2a allows growth of MRSA even in the presence of  $\beta$ -lactams that inhibit PBP1-3.

**Table 27 Affinity of Ceftaroline and Comparators for PBP2a from Methicillin-resistant *Staphylococcus aureus***

Strain Number	PBP IC50 or MIC	IC <sub>50</sub> <sup>a</sup> or MIC, $\mu\text{g/mL}$					Study #
		CPT	CRO	CTX	PEN-G	IMP	
N200P	MIC	0.5	128			16	Study TAK-599/00055, 2003
	PBP2a	0.9	910			270	
67-0	MIC	0.25-0.5	16			0.25-0.5	Study P0903-M-024, 2008
	PBP2a	0.16 $\pm$ 0.04	677 $\pm$ 53		18	57	
2149 (LNZ-R)	MIC	0.5	64	32	64		Study P0903-M-041, 2009
	PBP2a	0.37	> 128	> 128	1.63		
873 (hVISA)	MIC	0.5	> 64	> 64	8		
	PBP2a	0.25	> 128	14.1	22.2		
1287 (VISA)	MIC	0.5	8	4	32		
	PBP2a	0.36	0.88	1.95	1.99		
25 (VISA, DAP-R)	MIC	0.5	> 64	> 64	64		
	PBP2a	0.01	0.24	0.45	2.83		
510 (VRS2) (VISA)	MIC	1	> 64	> 64	32		
	PBP2a	0.29	0.29	> 128	14.2		

<sup>a</sup> indicated as mean  $\pm$  standard deviation where available

Abbreviations: CPT = ceftaroline; CRO = ceftriaxone; CTX = cefotaxime; DAP-R = daptomycin resistant; IMP = imipenem; hVISA = hetero-vancomycin intermediate *S. aureus*; IC50 = concentration at which 50% of activity is inhibited; LNZ-R = linezolid resistant; MIC = minimum inhibitory concentration; PBP = penicillin-binding protein; PEN-G = penicillin G; VISA = vancomycin intermediate *S. aureus*; VISA = vancomycin-resistant *S. aureus*.

Table 28 shows the binding of ceftaroline PBPs of *Streptococcus pneumoniae*. The highest ceftaroline MICs against *S. pneumoniae* studied was 0.25 mcg/mL for penicillin-resistant (PRSP) isolate 24. The MICs for comparator agents ceftriaxone and cefotaxime were  $\geq 1$  for all PRSP isolates with the exception of isolate 2527 (penicillin MIC = 2 mcg/mL), for which the MICs were 0.015 and 0.03 mcg/mL for cefotaxime and ceftriaxone, respectively. *S. pneumoniae* resistance to  $\beta$ -lactams is usually associated with mutations in PBPs 2X, 2B and/or 1A, and the degree of resistance conferred reflects the constellation of PBP mutations present in these isolates.

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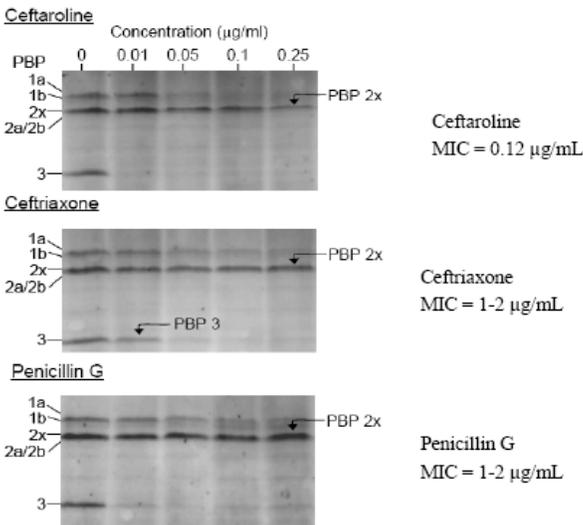
**Table 28 Affinity of Ceftaroline and Comparators for PBPs from *Streptococcus pneumoniae***

Phenotype	Strain Number	PBP IC50 or MIC	IC50 <sup>a</sup> or MIC, µg/mL				Study #	Phenotype	Strain Number	PBP IC50 or MIC	IC50 <sup>a</sup> or MIC, µg/mL				Study #
			CPT	CRO	CTX	PEN-G					CPT	CRO	CTX	PEN-G	
PEN-S	R6	MIC	0.008	0.03-0.06		0.06-0.12	Study P0903-M-024, 2008	PEN-R	24	MIC	0.25	2	1	4	Study P0903-M-041, 2009
		PBP 1A	0.019 ± 0.01	0.017 ± 0.008		0.019 ± 0.008				PBP 1A	0.10	0.38	0.08		
		PBP 1B	0.039 ± 0.028	0.017 ± 0.013		0.027 ± 0.001				PBP 1B	0.21	0.41	5.41		
		PBP 2A/B	0.053 ± 0.018	0.044 ± 0.016		0.053 ± 0.015				PBP 2A	0.23	0.74	0.34		
		PBP 2X	0.025 ± 0.015	0.054 ± 0.007		0.028 ± 0.008				PBP 2B	0.39	10.9	0.61		
		PBP 3	0.009 ± 0.007	0.016 ± 0.006		0.003 ± 0.002				PBP 2X	0.30	0.09	0.71		
PEN-R	2039	MIC	0.12	1-2		1-2	Study P0903-M-041, 2009	PEN-R	3413	MIC	0.125	2	2	4	Study P0903-M-041, 2009
		PBP1A	0.019 ± 0.002	0.045 ± 0.009		0.025 ± 0.015				PBP 1A	0.29	0.16	0.13		
		PBP 2X	0.17 ± 0.06	0.64 ± 0.07		0.79 ± 0.22				PBP 1B	0.35	2.08	1.64		
		PBP 3	0.001 ± 0.0001	0.011 ± 0.007		0.001 ± 0.0006				PBP 2A	0.16	0.40	0.30		
PEN-S	1076	MIC	0.015	0.03	0.03	0.03	Study P0903-M-041, 2009	PEN-R	2527	MIC	0.015	0.03	0.015	2	Study P0903-M-041, 2009
		PBP 1A	0.13	0.03	0.11					PBP 2B	1.48	4.24	6.68		
		PBP 1B	0.12	0.06	0.20					PBP 2X	0.16	5.06	2.85		
		PBP 2A	0.12	0.15	0.24					PBP 3	0.16	0.19	0.12		
		PBP 2B	2.55	60.24	9.61										
		PBP 2X	0.04	0.04	0.03										
		PBP 3	0.24	0.11	0.08										

<sup>a</sup> indicated as mean ± standard deviation where available  
Abbreviations: CPT = ceftaroline; CRO = ceftriaxone; CTX = cefotaxime; IC50 = ; MIC = minimum inhibitory concentration; PBP = penicillin binding protein; PEN-G = penicillin G; Pen-R = penicillin resistant; Pen S = penicillin susceptible.  
Source: Study P0903-M-024, 2008; P0903-M-041, 2009

Figure 2 shows the binding assessment of ceftaroline and its comparators (ceftriaxone and penicillin) for PBPs from the penicillin resistant *S. pneumoniae* strain 2039. The Applicant submitted data showing the binding affinity to *S. pneumoniae* PBPs. PBP 1A, 2A and 2X and 2B are transpeptidase that allows for the formation of the peptide bridges and are similar in molecular weights. PBPs 1A, 2B and 2X are considered the primary targets of β-lactams and once the β-lactam binds to the PBP, peptidoglycan synthesis ceases, leading to cell lysis and death. The data suggest that ceftaroline binds to PBPs 3, 1A, 2X, 1B and 2A/B.

**Figure 2. Binding of Ceftaroline, Ceftriaxone, and Penicillin to PBPs from the Penicillin-resistant *Streptococcus pneumoniae* Strain 2039**



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**MECANISMS OF RESISTANCE:**

Resistance to cephalosporins can be mediated through a variety of mechanisms including the alterations of PBPs, formation of cephalosporinases that inactivate the drug, a decrease in the ability of the drug to penetrate the cell wall and reach the drug target, or efflux of the drug thereby preventing the drug from reaching its target. Streptococci resistance to  $\beta$ -lactams is mediated via alterations in the  $\beta$ -lactam-binding site of the PBP1a, PBP2b and PBP2x. Mutations resulting in changes in the active binding sites correlate with decrease affinity for  $\beta$ -lactams and increase MIC. In some Gram positive organisms, most notably staphylococci, resistance to cephalosporins is due to the reduced binding affinity of PBPs and these enzymes are located between the outer membrane and the inner cell membrane in a location referred to as the periplasmic space. In Gram negative organisms, the predominant mode of resistance is the production of  $\beta$ -lactamase hydrolyzing enzyme such as extended spectrum  $\beta$ -lactamases (ESBLs). At least 400 different types of  $\beta$ -lactamases, originating from clinical isolates, have been described and a web site has been created to monitor the latest developments among the newer types of  $\beta$ -lactamases (web site at <http://www.lahey.org/studies/webt.htm>)<sup>24</sup>. AmpC  $\beta$ -lactamases have been frequently identified in Gram-negative organisms and there are of two types plasmid-mediated and chromosomal or inducible AmpC. Chromosomal AmpC enzymes are seen in organisms such as *Citrobacter freundii*, *Enterobacter cloacae*, *Morganella morganii*, *Hafnia alvei* and *Serratia marcescens* and are typically inducible by some  $\beta$ -lactam antibiotics<sup>25</sup>.

ESBLs were first described in 1983, and have the ability to hydrolyse oxyimino-cephalosporins, and monobactams, but not cephamycins or carbapenems. Although ESBLs have been described in a range of *Enterobacteriaceae* and *Pseudomonadaceae* from different parts of the world, they are most often identified in *Klebsiella pneumoniae* and *Escherichia coli*<sup>26</sup>. The majority of ESBLs identified in clinical isolates to date, have been SHV or TEM types, which have evolved from narrow-spectrum  $\beta$ -lactamases such as TEM-1, -2 and SHV-1<sup>25</sup>. The CTX-M enzymes have originated from *Kluyvera* spp., and recently gained prominence in *Enterobacteriaceae* with reports from Europe, Africa, Asia, South America and North America<sup>27</sup>.

The Applicant conducted a series of experiments to detect resistant organisms. Study P0903-M-024, 2008 evaluated the propensity for the development of spontaneous mutations by exposing bacteria to concentrations of ceftaroline that are higher than the MIC and determining whether any bacteria grew. Large numbers of bacteria are exposed to high doses of the antibiotic (at 4, 8, and 16  $\times$  the MIC); and only very small numbers are capable of growing in the presence of antibiotic. The spontaneous mutation frequencies for resistance to ceftaroline versus other antibiotic comparators are given in Table 29. The data show that plating very high inocula ( $14 \times 10^9$  CFU) of *S. aureus* strains of MSSA, CA-MRSA, MRSA, or VISA on agar plates containing ceftaroline did not produce a single spontaneous mutant colony on even the 4-fold MIC plates. Low spontaneous mutation frequency values for ceftaroline on the order of less than  $10^{-10}$  to  $10^{-11}$  were reported for the various phenotypes. This was unlike the case for spontaneous rifampin resistance, which was readily detected at frequencies of  $10^{-6}$  to  $10^{-8}$ .

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**Table 29 Spontaneous Mutation Frequencies for Ceftaroline and Comparators**

Strain	Drug	MIC, µg/mL	Inoculum CFU, ×10 <sup>8</sup>	Spontaneous Mutation Frequency (MIC Multiple of 4 to 16)	Strain	Drug	MIC, µg/mL	Inoculum CFU, ×10 <sup>8</sup>	Spontaneous Mutation Frequency (MIC Multiple of 4 to 16)					
Study P0903-M-028, 2008														
Staphylococcus aureus 2053 HA-MRSA	Ceftaroline	4	6.67	< 1.5 × 10 <sup>-10</sup>	Haemophilus influenzae 1224	Ceftaroline	0.12	0.20	< 4.98 × 10 <sup>-9</sup>					
	Levofloxacin	32	ND	ND (Resistant)		Levofloxacin	0.015	0.20	< 4.98 × 10 <sup>-9</sup>					
	Linezolid	4	6.67	< 1.5 × 10 <sup>-10</sup>		Rifampin	0.25	0.20	1.49 - 9.95 × 10 <sup>-9</sup>					
	Rifampin	0.008	6.67	1.29 - 2.25 × 10 <sup>-7</sup>	Haemophilus influenzae 2797 BLNAR	Ceftaroline	0.25	0.233	< 1.43 × 10 <sup>-9</sup>					
Staphylococcus aureus 2202 CA-MRSA	Ceftaroline	1	9.09	< 1.1 × 10 <sup>-10</sup>		Levofloxacin	0.03	0.233	< 1.43 × 10 <sup>-9</sup>					
	Levofloxacin	0.25	9.09	< 1.1 × 10 <sup>-10</sup>		Rifampin	0.5	0.233	< 1.43 - 1.43 × 10 <sup>-9</sup>					
	Linezolid	4	9.09	< 1.1 × 10 <sup>-10</sup>	Moraxella catarrhalis 0555	Ceftaroline	0.12	2.27	< 1.47 × 10 <sup>-10</sup>					
	Rifampin	0.015	9.09	5.98 - 8.7 × 10 <sup>-8</sup>		Levofloxacin	0.06	2.27	3.99 × 10 <sup>-8</sup> - 1.47 × 10 <sup>-10</sup>					
Ceftaroline	0.5	14.3	< 7 × 10 <sup>-11</sup>	Rifampin		0.06	2.27	1.1 - 1.25 × 10 <sup>-7</sup>						
Staphylococcus aureus 0753 MSSA	Levofloxacin	0.12	14.3	5.31 × 10 <sup>-8</sup> - 7 × 10 <sup>-11</sup>	Study P0903-M-004/011, 2006									
	Linezolid	4	14.3	< 7.0 × 10 <sup>-11</sup>	MSSA ST751	Ceftaroline	0.25	0.5	< 2.82 × 10 <sup>-8</sup>					
	Rifampin	0.015	14.3	2.81 - 8.88 × 10 <sup>-8</sup>		Cefotaxime	2	0.5	< 2.82 × 10 <sup>-10</sup>					
Staphylococcus aureus 2012 VISA	Ceftaroline	2	3.09	< 3.24 × 10 <sup>-10</sup>	MRSA H044340161	Ceftaroline	1	0.5	< 2.74 × 10 <sup>-10</sup>					
	Levofloxacin	> 8	ND	ND (Resistant)		Cefotaxime	NT	0.5	NT					
	Linezolid	2	3.09	< 3.24 × 10 <sup>-10</sup>	VISA Mu50	Ceftaroline	1	0.5	5.88 × 10 <sup>-10</sup>					
	Rifampin	0.015	3.09	1.19 × 10 <sup>-7</sup> - 6.44 × 10 <sup>-8</sup>		Cefotaxime	> 256	0.5	NT					
Enterococcus faecalis 0796 VSE	Ceftaroline	2	1.42	1.25 × 10 <sup>-7</sup> - < 7.04 × 10 <sup>-10</sup>	E. cloacae AmpC- inducible 684	Ceftaroline	2	0.5	5.47 × 10 <sup>-8</sup>					
	Levofloxacin	1	1.42	< 7.04 × 10 <sup>-10</sup>		Cefotaxime	1	0.5	7.47 × 10 <sup>-8</sup>					
	Linezolid	4	1.42	< 7.04 × 10 <sup>-10</sup>	E. cloacae AmpC-Cinducible E827	Ceftaroline	0.5	0.5	9.95 × 10 <sup>-8</sup>					
	Rifampin	2	1.42	4.37 × 10 <sup>-7</sup> - 5.85 × 10 <sup>-8</sup>		Cefotaxime	0.5	0.5	2.89 × 10 <sup>-7</sup>					
Enterococcus faecalis 0847 VRE	Ceftaroline	2	0.589	< 1.7 × 10 <sup>-9</sup>	E. coli TEM-negative LN01QC06	Ceftaroline	0.06	0.5	< 2.91 × 10 <sup>-8</sup>					
	Levofloxacin	1	0.589	< 1.7 × 10 <sup>-9</sup>		Cefotaxime	0.06	0.5	< 4.85 × 10 <sup>-8</sup>					
	Linezolid	2	0.589	< 1.7 × 10 <sup>-9</sup>	E. coli TEM-positive EO770	Ceftaroline	0.25	0.5	< 2.13 × 10 <sup>-8</sup>					
	Rifampin	0.25	0.589	4.18 - 9.19 × 10 <sup>-7</sup>		Cefotaxime	0.06	0.5	< 2.13 × 10 <sup>-8</sup>					
Streptococcus pneumoniae 0869 PSSP	Ceftaroline	0.015	0.147	< 6.8 × 10 <sup>-9</sup>	E. coli 1411 TEM-positive (pT1)	Ceftaroline	0.125	0.5	4.97 × 10 <sup>-7</sup>					
	Levofloxacin	1	0.147	< 6.8 × 10 <sup>-9</sup>		Cefotaxime	0.06	0.5	< 9.03 × 10 <sup>-9</sup>					
	Linezolid	4	0.147	< 6.8 × 10 <sup>-9</sup>	E. coli 1413 mutS TEM-positive (pT1)	Ceftaroline	0.06	0.5	1.13 × 10 <sup>-6</sup>					
	Rifampin	0.006	0.147	2.26 - 3.53 × 10 <sup>-9</sup>		Cefotaxime	0.06	0.5	< 3.07 × 10 <sup>-9</sup>					
Streptococcus pneumoniae 0884 PRSP	Ceftaroline	0.25	0.14	< 7.14 × 10 <sup>-9</sup>	S. pneumoniae PEN-R H045040101	Ceftaroline	0.12	0.5	< 3.6 × 10 <sup>-7</sup>					
	Levofloxacin	1	0.14	< 7.14 × 10 <sup>-9</sup>		Cefotaxime	4	0.5	< 3.6 × 10 <sup>-7</sup>					
	Linezolid	4	0.14	< 7.14 × 10 <sup>-9</sup>	S. pneumoniae PEN-S H051360048	Ceftaroline	0.06	0.5	< 1.08 × 10 <sup>-8</sup>					
	Rifampin	0.015	0.14	≥ 1.83 × 10 <sup>-6</sup> - 5.71 × 10 <sup>-8</sup>		Cefotaxime	0.12	0.5	< 1.08 × 10 <sup>-8</sup>					
H. influenzae TEM-positive 02/A_H/00106	Ceftaroline	0.03	0.5	< 3.3 × 10 <sup>-9</sup>										
	Cefotaxime	5	0.5	< 3.3 × 10 <sup>-9</sup>										
H. influenzae AmpS 02/A_H/00128	Ceftaroline	0.03	0.5	< 4.0 × 10 <sup>-9</sup>										
	Cefotaxime	0.06	0.5	< 4.0 × 10 <sup>-9</sup>										

Abbreviations: AmpC = ampC β-lactamase; BLNAR = β-lactamase-negative ampicillin-resistant; CA-MRSA = community-acquired MRSA; CFU = colony forming unit; HA-MRSA = hospital-acquired MRSA; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*; ND = not determined; NT = not tested; PEN-S = penicillin susceptible; PEN-R = penicillin resistant; PSSP = penicillin-susceptible *S. pneumoniae*; PRSP = penicillin-resistant *S. pneumoniae*; VISA = vancomycin-intermediate *S. aureus*; VSE = vancomycin-susceptible enterococci; VRE = vancomycin-resistant enterococci.

Source: Study P0903-M-028, 2008; Study P0903-M-004/011, 2006.

For the enterococcal strains tested, the frequency of resistance mutations was  $1.7 \times 10^{-9}$ . For *E. faecalis* 0796, the Applicant stated that colonies were observed on  $4 \times \text{MIC}$  plates resulting in a mutation frequency value  $1.25 \times 10^{-7}$ . However, no colonies were observed on the 8 or  $16 \times \text{MIC}$  plates, resulting in a mutation frequency was  $< 7.04 \times 10^{-10}$ . Furthermore, the MIC of these colonies from the  $4 \times \text{MIC}$  plate was the same as that of the parental strain (1-2 mcg/mL), suggesting that many of these apparent spontaneous mutants did not maintain stable resistance to ceftaroline.

There were no spontaneous mutants generated for either the *S. pneumoniae* PSSP or PRSP isolates tested against ceftaroline, linezolid, or levofloxacin. *H. influenzae* 1224 (amoxicillin-susceptible) and the BLNAR isolate 2797 did produce spontaneous mutants on plates containing either ceftaroline or levofloxacin at 4, 8, or  $16 \times$  the MIC value. For *M. catarrhalis*, a single isolate was tested and there were no ceftaroline-resistant colonies isolated, yielding a spontaneous mutation frequency of  $< 1.47 \times 10^{-10}$ . In contrast, levofloxacin at  $8 \times$

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MIC yielded a value of  $3.99 \times 10^{-8}$  and rifampin produced an even higher spontaneous mutation frequency of  $1 \times 10^{-7}$  on plates at 4 to  $16 \times$  MIC.

For *E. coli*, the hypermutator derivative, 1413 pT1 was obtained under selection with ceftaroline but not cefotaxime. Only the mutants of *E. coli* 1413 pT1 retained increased MICs on retesting and these increases affected ceftaroline only. Since MICs of ceftaroline + clavulanate were not raised, the mechanism likely involved some change to TEM  $\beta$ -lactamase quantity or specificity. It did not involve selection of a true ESBL, as the MICs of cefotaxime, ceftriaxone, and ceftazidime were not raised.

**Summary and conclusion:**

This Reviewer thinks that the spontaneous mutation frequency for ceftaroline was very low for all staphylococci and streptococci isolates tested; these include isolates for which  $\beta$ -lactamase was not the primary mechanism of resistance. However, *E. faecalis* resistant colonies were isolated and on further analysis, the MICs from these colonies were equivalent to the MIC from the initial inocula prior to selective pressure from ceftaroline. This suggests that within the population of cells tested, there are cells that express resistance to ceftaroline and resistance occurred at lower concentrations of ceftaroline and showed the typical heterogeneous resistance. The data show that *H. influenzae* 1224 (amoxicillin-susceptible) and the BLNAR isolate 2797 did produce spontaneous mutants on plates containing either ceftaroline or levofloxacin. Beta-lactamase production is the most common mechanism of resistance in *H. influenzae*. Published studies have shown that two enzymes TEM-1 and ROB-1 account for almost all  $\beta$ -lactamase-mediated resistance in *H. influenzae*. Both are considered to be class A  $\beta$ -lactamase that confer resistance to ampicillin and are effectively inhibited by clavulanate<sup>28</sup>. TEM-1 is encoded by an identical gene that is encountered in *Enterobacteriaceae*; however, the levels of  $\beta$ -lactamase resistance in TEM-1 producing isolate of *H. influenzae* are lower than what's observed in the *Enterobacteriaceae*. It should be noted that the potential emergence of high level resistance in *H. influenzae* due to combination of ESBL production and altered PBP3 is concerning.

**EMERGENCE OF RESISTANCE**

The emergence of resistance to ceftaroline was examined by serial passage studies using subinhibitory concentrations of ceftaroline against *S. aureus*. High-level resistance may require multiple mutations, which may potentially be revealed by serial-passage studies in which multistep mutations can accumulate during growth at subinhibitory concentrations of antibiotic. Figure 4 shows the result of the experiment; the MIC of ceftaroline for *Staphylococcus aureus* 2053 (MRSA) did not change during 10 serial passages, while the MIC of rifampin increased after 5 passages. Please note that no changes were observed for the comparator agents tested.

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**Figure 4: In Vitro Acquisition of Resistance in Serial Sub-MIC Broth Cultures of *Staphylococcus aureus* 2053 (MRSA)**

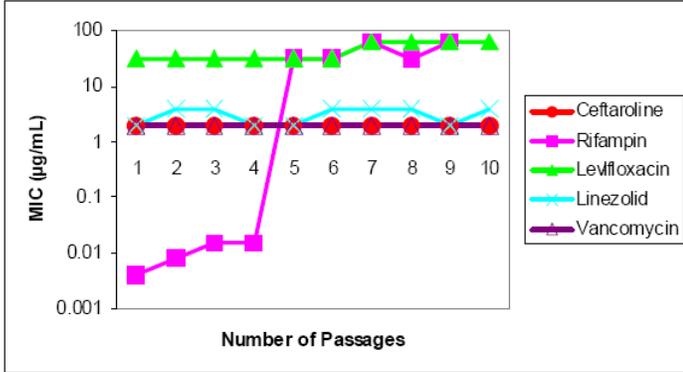


Table 30 summarize changes in MIC after serial passage in the presence of sub-MIC concentrations of ceftaroline or comparator antibiotics for a subset of the gram-positive isolates tested, while Table 31 lists the ceftaroline MICs (not comparators) for all isolates tested before and after 10-serial passages.

**Table 30 Acquisition of Resistance to Ceftaroline or Comparators in Serial Sub-MIC Broth Cultures**

Organism	Antibiotic	MIC, µg/mL	
		Passage 1	Passage 10
Study P0903-M-029, 2008			
<i>Staphylococcus aureus</i> 2053 MRSA	Ceftaroline	2	2
	Rifampin	0.004	64
	Levofloxacin	32	64
	Linezolid	2	4
	Vancomycin	2	2
<i>Streptococcus pneumoniae</i> 884 PRSP	Ceftaroline	0.12	0.25
	Rifampin	0.06	1
	Levofloxacin	1	2
	Linezolid	0.5	1
	Vancomycin	0.25	1
<i>Enterococcus faecalis</i> 847 VRE	Ceftaroline	2	8
	Rifampin	0.5	8
	Levofloxacin	64	64
	Linezolid	2	2
	Vancomycin	128	128

**Table 31 Acquisition of Resistance to Ceftaroline or Comparators in Serial Sub-MIC Broth Cultures**

Organism	Antibiotic	MIC, µg/mL	
		Passage 1	Passage 14
Study TAK-599/00057, 2003			
MRSA N315P	Ceftaroline	0.5	2
	Vancomycin	1	2
	Flomoxef	4	512
	Imipenem	0.25	256
MRSA OFU4	Ceftaroline	1	4
	Vancomycin	2	4
	Flomoxef	128	512
	Imipenem	64	512
MRSA OFU4	Ceftaroline	1	4
	Linezolid	2	16

Abbreviations: MIC = minimal inhibitory concentration; MRSA = methicillin-resistant *S. aureus*; PRSP = penicillin-resistant *S. pneumoniae*; VRE = vancomycin-resistant enterococci  
Source: Study P0903-M-029, 2008; Study TAK-599/00057, 2003.

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After 10 serial passages, a 2-fold change in ceftaroline MIC was observed for *S. aureus* and *S. pneumoniae* strains tested, with the exception of *S. pneumoniae* 884 whose MIC increased 4-fold (from 0.12 to 0.5 mcg/mL). For *E. faecalis* the ceftaroline MIC increased 4-fold (from 2 to 8 mcg/mL). For rifampin, MIC increased 16-fold for *S. pneumoniae* 884; 16-fold for *E. faecalis* 847, and 16,000-fold for MRSA 2053; for vancomycin, MIC increased 4-fold for *S. pneumoniae* 884; and for levofloxacin, MIC increased 8-fold for MRSA 2202 and *S. pneumoniae* 3130 and 128-fold for MSSA 753.

In study TAK-599/00057 (2003), two different strains of MRSA showed a 4-fold change in ceftaroline MIC over 14 serial passages (Table 32). The increases in MIC occurred at or before the seventh serial passage and did not increase upon further passage. Table 32 summarizes serial passage results for additional organisms including resistant and susceptible gram-positive and gram-negative strains. For the gram-negative species tested, neither *H. influenzae* nor *M. catarrhalis* had more than a 2-fold increase in ceftaroline MIC over 10 serial passages, including one BLNAR isolate of *H. influenzae*.

**Table 32 Summary Serial Passage at Subinhibitory Concentrations of Ceftaroline**

Organism	MIC, µg/mL	
	Passage 1	Passage 10
<i>Enterococcus faecalis</i> 796 (VSE)	2	8
<i>Enterococcus faecalis</i> 847 (VRE)	2	8
<i>Haemophilus influenzae</i> 1224	0.06	0.12
<i>Haemophilus influenzae</i> 2797 (BLNAR)	0.06	0.12
<i>Moraxella catarrhalis</i> 555	0.004	0.004

Abbreviations: BLNAR = β-lactamase negative ampicillin resistant; CA-MRSA = community acquired methicillin resistant *S. aureus*; MIC = minimal inhibitory concentration; MRSA = methicillin resistant *S. aureus*; MSSA = methicillin susceptible *S. aureus*; PSSP = penicillin susceptible *S. pneumoniae*; VISA = vancomycin intermediate *S. aureus*; VRE = vancomycin resistant enterococci; VSE = vancomycin susceptible enterococci

Source: Study P0903-M-029, 2008.

In another experiment, the potential of resistance to develop following long-term serial passage was examined. Isolates of *S. pneumoniae* and *S. pyogenes* were serially passaged up to 50 times in sub-MIC concentrations of ceftaroline, or comparators azithromycin and amoxicillin/clavulanate. The isolates of *S. pneumoniae* had MICs to penicillin ranging from 0.03 to 4 mcg/mL. Following 50 passages, the ceftaroline MICs for the *S. pneumoniae* isolates increased by no more than 4-fold. MICs for two isolates of *S. pneumoniae* increased 2-fold (one was multidrug-resistant serotype 19A) and the other two isolates increased only 4-fold over 50 generations. For the three *S. pyogenes* isolates, no increase in ceftaroline MIC was observed over 50 generations. The highest ceftaroline MIC following serial passage was only 0.5 mcg/mL (Table 33).

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**Table 33 Multistep Selection for Resistance with *S. pneumoniae* and *S. pyogenes***

Strain	Phenotype <sup>a</sup>	Antibiotic	Initial MIC, µg/mL	Final MIC, µg/mL	# Passages	MIC Fold-Increase
<i>S. pneumoniae</i> 3665	PEN-S (PEN G MIC 0.125 µg/mL), Macrolide-R	Ceftaroline	0.016	0.03	50	2X
		Azithromycin	8	16	50	2X
		Amox/clav	0.25	1	50	4X
<i>S. pneumoniae</i> 2686	PEN-S (PEN G MIC 2 µg/mL), Macrolide-R	Ceftaroline	0.125	0.5	50	4X
		Azithromycin	> 64	NT	NT	NT
		Amox/clav	8	16	50	2X
<i>S. pneumoniae</i> 1077	PEN-S (PEN G MIC 0.03 µg/mL), Macrolide-S, Quinolone-R	Ceftaroline	0.008	0.03	50	4X
		Azithromycin	0.03	> 64	29	> 2100X
		Amox/clav	0.03	0.03	50	no change
<i>S. pneumoniae</i> 7599	PEN-I (PEN G MIC 4 µg/mL), Macrolide-R, MDR	Ceftaroline	0.125	0.25	50	2X
		Azithromycin	> 64	NT	NT	NT
		Amox/clav	8	16	50	2X
<i>S. pyogenes</i> 2132	PEN-S, Macrolide-R	Ceftaroline	0.004	0.004	50	no change
		Azithromycin	0.06	1	28	16
		Amox/clav	0.016	0.016	50	no change
<i>S. pyogenes</i> 2368	PEN-S, Macrolide-R	Ceftaroline	0.004	0.004	50	no change
		Azithromycin	> 64	NT	NT	NT
		Amox/clav	0.016	0.016	50	no change
<i>S. pyogenes</i> 2011	PEN-S, Macrolide-R	Ceftaroline	0.004	0.004	50	no change
		Azithromycin	4	32	35	8X
		Amox/clav	0.016	0.016	50	no change

<sup>a</sup> Penicillin breakpoints from CLSI M100-S19, 2009.

Abbreviations: Amox/clav = amoxicillin/clavulanate; MIC = minimum inhibitory concentration; NT = not tested; PEN G = penicillin G; PEN-I = penicillin-intermediate; PEN-R = penicillin resistant; PEN-S = penicillin susceptible; -R = resistant.

Source: Clark et al, 2009.

Another study examined the serial passage of *E. coli*, a Gram-negative pathogen. The ceftaroline MIC for the TEM-β-lactamase-negative strain U went up 16-fold, from 0.06 to 1 mcg/mL, and from 0.25 to 64/128 mcg/mL for the TEM-producer strain V. The mutants with increased ceftaroline MIC derived from the TEM-negative strain also showed increases in MICs of other cephalosporins and levofloxacin (Table 34). However, the number of serial passages performed was not given for this study.

**Table 34 MICs (mcg/mL) for *Escherichia coli* Mutants with Increased Ceftaroline MIC Selected in Multistep Experiments**

Strain*	Species	Selective agent	CPT	CPT/Clav	CTX	CAZ	FEP	CRO	DOR	P/T	LVX	Resistance type
LN01QC06 (U)	<i>E. coli</i> R-		0.06	0.06	0.06	0.125	0.03	0.06	0.015	2	0.03	parent
U/multi/2X/0.125	<i>E. coli</i>	ceftaroline	0.25	0.25	0.25	1	0.25	0.06	0.015	2	0.125	Permeability/efflux
U/multi/4X/0.25	<i>E. coli</i>	ceftaroline	1	0.5	1	4	2	0.25	0.03	4	0.125	Permeability/efflux
EO770 (V)	<i>E. coli</i> TEM +		0.25	0.06	0.06	0.25	0.03	0.06	0.015	2	0.03	parent
V/multi/2X/0.5	<i>E. coli</i>	ceftaroline	64	0.06	0.125	4	1	0.25	0.015	> 128	0.03	ESBL
V/multi/16X/4	<i>E. coli</i>	ceftaroline	128	0.06	0.125	8	1	0.25	0.015	> 128	0.03	ESBL
V/multi/128X/32	<i>E. coli</i>	ceftaroline	8	0.125	0.125	4	0.5	0.125	0.015	> 128	0.06	ESBL
V/multi/1024X/256	<i>E. coli</i>	ceftaroline	64	0.125	0.125	4	1	0.25	0.015	> 128	0.06	ESBL

\*Codes indicate: Strain number/multistep/MIC multiple at which selected/actual selective concentration in µg/mL.

Abbreviations: Clav = clavulanate; CAZ = ceftazidime; CPT = ceftaroline; CRO = ceftroxone; CTX = cefotaxime; DOR = doripenem; FEP = cefepime; P/T = Piperacillin/Tazobactam; and LVX = levofloxacin.

Source: Study P0903-M-004/011, 2006.

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**Activity against isolates with different resistant mechanisms**

The Applicant determined the in vitro activity of ceftaroline against *S. aureus* isolates possessing the *mec* type resistance determinant (Table 35). The data showed that with SCC*mec* type IV showed ceftaroline MIC values slightly lower (0.5–1 mcg/mL) than strains with SCC*mec* types I, II and III. The highest ceftaroline MIC values were observed among strains with SCC*mec* type I (2–4 mcg/mL).

**Table 35 Activity of Ceftaroline against Molecularly Characterized *Staphylococcus aureus***

<i>S. aureus</i> Methicillin-resistance Status and <i>mec</i> Type	N	Ceftaroline MIC, µg/mL		
		Range	MIC <sub>50</sub>	MIC <sub>90</sub>
<b>Study P903-M-084, 2009</b>				
Methicillin-resistant <i>S. aureus</i>	50	0.5 - 4	1	2
Methicillin-susceptible <i>S. aureus</i>	10	.25	0.25	0.25
<i>S. aureus</i> SCC <i>mec</i> type I	10	2 - 4	2	4
<i>S. aureus</i> SCC <i>mec</i> type II	10	0.5 - 2	1	2
<i>S. aureus</i> SCC <i>mec</i> type III	10	1-2	2	2
<i>S. aureus</i> SCC <i>mec</i> type IV	10	0.5 - 1	1	1
<i>S. aureus</i> SCC <i>mec</i> type IV special set of dominant USA clonal types and variants	10	0.5 - 1	1	1
<b>Study P903-M-085, 2009</b>				
MRSA	50	0.5 - 2	1	2
<i>S. aureus</i> SCC <i>mec</i> type I	9	1 - 2	2	2
<i>S. aureus</i> SCC <i>mec</i> type II	10	0.5 - 1	1	1
<i>S. aureus</i> SCC <i>mec</i> type III	10	0.5 - 2	1	2
<i>S. aureus</i> SCC <i>mec</i> type IV	21	0.5 - 1	0.5	1
<b>Study P0903-M-038, 2009</b>				
CA-MRSA	92	0.25 - 1	0.5	1
<i>S. aureus</i> (VISA and hVISA)	23	0.25 - 1	0.5	1
<i>S. aureus</i> (DNSSA)	7	0.25 - 1	0.5	NA
<i>S. aureus</i> (VRSA)	10	0.12 - 1	0.5	1
<i>S. aureus</i> SCC <i>mec</i> type II (PVL Neg and ACME Neg)	38	-	1	1
<i>S. aureus</i> SCC <i>mec</i> type IV (USA 100 - PVL Neg and ACME Neg)	13	-	0.25	0.5
<i>S. aureus</i> SCC <i>mec</i> type IV (USA 300 - PVL Pos and ACME Pos)	40	-	0.5	0.5

Abbreviations: CA-MRSA = community-acquired methicillin-resistant *S. aureus*; DNSS = daptomycin-nonsusceptible *S. aureus*; hVISA = heterogeneous vancomycin intermediate *S. aureus*; MIC = minimal inhibitory concentration; N = number of isolates; Neg = negative; Pos = positive; PVL = Panton-Valentine Leukocidin toxin; SCC*mec* = Staphylococcal cassette chromosome *mec* type; VISA = vancomycin-intermediate *S. aureus*; VRSA = vancomycin-resistant *S. aureus*.

Source: Study P903-M-038, 2009; P903-M-084, 2009; P903-M-085, 2009.

In another study, the activity of ceftaroline against a collection of molecularly characterized ESBL, AmpC, and KPC isolates was assessed in Study P903-M-084 (2009) and the results are shown in Table 36 through Table 38. As expected, all the MICs and minimal bactericidal concentrations (MBC) from these isolates were high,

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with an MIC<sub>90</sub> ≥ 128. Ceftaroline also had very limited or insignificant activity against *P. aeruginosa* in these studies.

**Table 36 Activity of Ceftaroline against Characterized Clinical Isolates of Gram Negative Bacteria with Characterized β-lactamases**

Organism	Enzyme Type	N	MIC range, µg/mL	MBC range, µg/mL
<i>E. coli</i>	ESBL	10	2 - 512	4 -1024
<i>K. pneumoniae</i>	ESBL	10	8 - 1024	32 - 1024
<i>E. cloacae</i>	AmpC - derepressed	10	0.125 - 512	0.125 - 1024
<i>P. aeruginosa</i>	MDR	20	8 - 256	16 -256

Abbreviations: ESBL = extended-spectrum β-lactamase, MBC = minimal bactericidal concentration, MDR = multidrug resistant, MIC = minimal inhibitory concentration.

Source: Study P903-M-084, 2009.

**Table 37 Activities of Ceftaroline against Selected β-lactamase-Producing Isolates of Enterobacteriaceae**

β-lactamase Enzyme Type	N	Ceftaroline MIC, µg/mL		
		Range	MIC <sub>50</sub>	MIC <sub>90</sub>
KPC	20	64 - > 128	> 128	> 128
CTX-M	22	64 - > 128	> 128	> 128
Plasmidic AmpC	15	8 - > 128	16	> 128
SME	5	1-2	-	-
MBL	5	32 - > 128	-	-

Abbreviations: MBL = metallo-β-lactamase; MIC = minimum inhibitory concentration; MIC<sub>50</sub> = minimum inhibitory concentration required to inhibit growth of 50% of organisms; MIC<sub>90</sub> = minimum inhibitory concentration required to inhibit growth of 90% of organisms; N = number of isolates.

Source: Study P903-M-084, 2009.

**Table 38 Activity of Ceftaroline against Class A and C β-lactamase-Producing Escherichia coli and Klebsiella pneumoniae**

Organism and Enzyme Class	No. of Isolates	Ceftaroline MIC, µg/mL		
		Range	MIC <sub>50</sub>	MIC <sub>90</sub>
<i>E. coli</i> Class A and C	22	8 - 128	128	128
<i>K. pneumoniae</i> Class A and C	24	8 - 128	128	128

Abbreviations: MIC = minimum inhibitory concentration; MIC<sub>50</sub> = minimum inhibitory concentration required to inhibit growth of 50% of organisms; MIC<sub>90</sub> = minimum inhibitory concentration required to inhibit growth of 90% of organisms.

Source: Study P903-M-084, 2009.

### **Beta-lactamase Hydrolysis Studies on Ceftaroline**

In another study, the kinetics of ceftaroline hydrolysis in the presence of various ESBL and cephalosporinase enzymes was determined. The highest rates of ceftaroline hydrolysis were obtained for CTX-M-15 and KPC-2, followed by TEM-1, SHV-4 and P99. P99 enzyme demonstrated the highest affinity for ceftaroline, followed by SHV-4, CTX-M-15, TEM-1, and KPC-2 (Table 39). This suggests that ceftaroline is readily hydrolyzed by all of these enzymes, and thus isolates producing these enzymes would be expected to be resistant to ceftaroline.

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**Table 39  $\beta$ -lactamase Hydrolysis Parameters for Ceftaroline and Benzylpenicillin as Comparator**

Enzyme	Final Enzyme Concentration	Substrate	Mean kcat, s <sup>-1</sup>	Mean Km, $\mu$ M	Mean kcat/Km, $\mu$ M <sup>-1</sup> s <sup>-1</sup>
P99	200 nM	CPT	0.74	2.1	0.3
P99	20 nM	BZP	20.8	4.9	4.2
Tem-1	10.4 nM	CPT	31.2	201	0.2
Tem-1	1 nM	BZP	859	30.6	28.1
CTX-M-15	5.6 nM	CPT	150	40.9	3.6
CTX-M-15	11.2 nM	BZP	49	10	4.9
KPC-2	8.6 nM	CPT	73	342	0.2
KPC-2	8.6 nM	BZP	33.0	33.4	1.0
SHV-4	12 nM	CPT	20.7	15.5	1.3
SHV-4	30 nM	BZP	28.6	11.4	2.5

Abbreviations: CPT = ceftaroline; BZP = benzylpenicillin; kcat = turnover number; Km = half-maximal activity concentration.

Source: Study CXL-M-002, 2009.

### ***$\beta$ -lactamase Induction in Gram-Negative Bacteria***

AmpC is either chromosomally or plasmid based cephalosporinase and contributes to resistance. Inducible AmpC is capable of inactivating most penicillins and cephalosporins. AmpC induction is mediated by a repressor system that is under the control of the AmpR. This system is commonly found in *Enterobacteriaceae* such as *E. cloacae*, *M. morgani*, *S. marcescens*, *P. aeruginosa* and *C. freundii*, and mutations in the regulatory system causing high level production of Amp C affects the activity of penicillin and cephalosporins. Overexpression of AmpC in *Enterobacteriaceae* correlates with a decrease in susceptibility, or resistance, to penicillin and cephalosporins. Moreover, phenotypic variations in the bacterial expression of the enzymes make the task of laboratory detection more complicated.

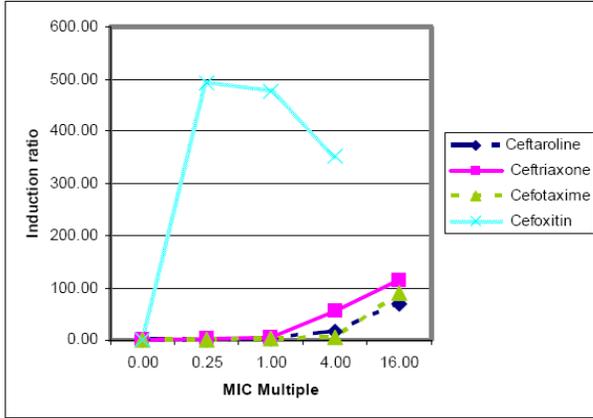
Fourth generation cephalosporins, although more stable against hydrolysis from cephalosporinases, are ineffective against *Enterobacteriaceae* that overexpress AmpC. To determine if ceftaroline induces AmpC, the Applicant examined the effect of  $\beta$ -lactamase induction in some *Enterobacteriaceae*. Figure 5 shows ceftaroline induction of AmpC with comparator agents. Two inducible isolates and their basal mutant derivatives were studied for each of the following species: *E. cloacae*, *C. freundii*, *M. morgani*, *S. marcescens*, *P. vulgaris*, and *P. aeruginosa*. All strains studied were characterized using isoelectric focusing and were shown to produce no other  $\beta$ -lactamases than AmpC. All the reference strains had low  $\beta$ -lactamase activity in the absence of inducers but showed strong induction by cefoxitin, with high induction ratios. Ceftaroline, cefotaxime, and ceftriaxone were weaker inducers of Amp C.

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**Figure 5. Induction Ratios ( $\beta$ -lactamase Specific Activity with Inducer/ $\beta$ -lactamase-Specific Activity without Inducer) for *Enterobacter cloacae* 684C**



In Table 40, the results of studies with one isolate of *E. cloacae* are shown. *E. cloacae* 684 had an induction ratio of 475 for cefoxitin at 1 × MIC, which was the largest induction ratio of all isolates tested, which compared to a ratio of only 2.31 for ceftaroline at 1 × MIC.

**Table 40 Induction Ratios ( $\beta$ -lactamase-specific Activity with Inducer/ $\beta$ -lactamase-Specific Activity without Inducer) for *Enterobacter cloacae* 684**

Sample	Inducer, $\mu\text{g/mL}$	$\Delta\text{OD}/\text{min}$ with 20 $\mu\text{l}$ Extract	Protein, $\text{mg/mL}$	Specific activity (nmoles nitrocefin hydrolysed/min/mg protein)	Induction Ratio
None	0	0.015	0.885	0.0533	1.00
Ceftaroline 0.25 × MIC	0.5	0.014	0.767	0.0574	1.08
Ceftaroline 1 × MIC	2	0.032	0.816	0.1233	2.31
Ceftaroline 4 × MIC	8	0.07	0.263	0.8370	15.70
Ceftaroline 16 × MIC	32	0.304	0.257	3.7197	69.79
Ceftriaxone 0.25 × MIC	0.5	0.034	0.844	0.1267	2.38
Ceftriaxone 1 × MIC	2	0.046	0.577	0.2507	4.70
Ceftriaxone 4 × MIC	8	0.143	0.153	2.9391	55.14
Ceftriaxone 16 × MIC	32	0.337	0.174	6.0905	114.27
Cefotaxime 0.25 × MIC	0.25	0.017	0.915	0.0584	1.10
Cefotaxime 1 × MIC	1	0.022	0.932	0.0742	1.39
Cefotaxime 4 × MIC	4	0.018	0.292	0.1938	3.64
Cefotaxime 16 × MIC	16	0.18	0.118	4.7969	90.00
Cefoxitin 0.25 × MIC	64	0.858	0.103	26.1953	491.47
Cefoxitin 1 × MIC	256	1.119	0.139	25.3156	474.96
Cefoxitin 4 × MIC	1024	1.297	0.217	18.7955	352.64

Abbreviations: MIC = minimal inhibitory concentration; OD = optical density.  
Source: Study P903-M-059, 2009.

**Summary and conclusion:**

The in vitro studies described within this review, indicate a lower propensity for the development of ceftaroline resistance following serial passage experimental studies compared with comparator agents. Additional data

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presented by the Applicant show that ceftaroline is an inducer of AmpC. The production of AmpC has been reported in a variety of *Enterobacteriaceae* and non-fermentative Gram negatives. AmpC induction may complicate the use of  $\beta$ -lactams for the treatment of infections caused by these organisms. AmpC  $\beta$ -lactamase confers resistance to a variety of penicillin and cephalosporin antibiotics and poses diagnostic and therapeutic challenges as their presence may go undetected in the presence of ESBLs. The detection of AmpC is clinically important since they are usually not inhibited by  $\beta$ -lactamase inhibitors.

**EFFECT OF TESTING DYNAMICS ON CEFRAROLINE ACTIVITY:**

***Effect of medium on the in vitro activity:***

Table 41 summarizes ceftaroline activity using variations from the CLSI broth microdilution method (CLSI M7-A7, 2006) including Ca<sup>2+</sup>, percent NaCl, medium, atmosphere during incubation, presence of serum, and agar dilution. Five percent (5%) NaCl inhibited growth and/or reduced MICs for *E. coli* and *K. pneumoniae* and completely inhibited the growth of *M. catarrhalis*, *H. influenzae*, and all streptococci. At pH 5.0, the MIC decreased for an isolate of *P. aeruginosa* and for most tested isolates of staphylococci and enterococci (Study P0903-M-001). At pH 6.0 the MICs were usually within 2-fold of the reference values, except for isolates of *H. influenzae* and *M. catarrhalis* which failed to grow at this pH (Study P0903-M-046, 2008). Variable such as the presence of serum had a small but measurable effect; the MICs were generally within one dilution of the reference method.

**Table 41 Effect of Medium and Incubation on the In Vitro Activity of Ceftaroline Compared with CLSI CAMHB Broth**

Organism	Strain #	REF	Ca <sup>++</sup>	% NaCl	Medium		Incubation Atmosphere		% Serum		Agar Dilution			pH		
			50mg/L	5	LHB	HTM	CO <sub>2</sub>	anaerobic	10	50	MHA	MHA / LHB	HTMA	5	6	8
MIC, $\mu$ g/ml																
Study P0903-M-046, 2008																
<i>E. coli</i>	25922	0.06	0.06	0.008	0.125	0.125	0.125	0.03	0.06	0.125	0.06	0.25	0.25	nr	0.125	0.06
	19089	0.06	0.125	0.015	0.125	0.06	0.125	0.125	0.06	0.06	0.125	0.25	0.25	nr	0.06	0.06
	19090	0.03	0.125	0.008	0.125	0.125	0.125	0.125	0.06	0.03	0.03	0.25	0.25	nr	0.06	0.03
<i>K. pneumoniae</i>	19091	0.25	0.25	0.015	0.25	0.5	0.5	0.25	0.25	0.125	0.125	0.25	0.5	nr	0.5	0.25
	19092	0.03	0.125	0.015	0.125	0.06	0.125	0.06	0.06	0.06	0.125	0.25	0.25	nr	0.06	0.06
	19093	0.06	0.125	0.015	0.125	0.06	0.125	0.06	0.03	0.06	0.06	0.125	0.25	nr	0.06	0.06
<i>H. influenzae</i>	49247	0.015	0.015	ng	0.06	nr	0.06	0.03	0.06	0.06	ng	0.06	0.125	nr	ng	0.06
	16081	0.008	0.008	ng	0.008	nr	0.008	0.008	0.008	0.008	ng	0.06	0.015	nr	ng	0.008
	18520	0.015	0.015	ng	0.03	nr	0.015	0.03	0.06	0.03	ng	0.015	0.06	nr	ng	0.03
<i>M. catarrhalis</i>	11940	0.125	0.06	ng	0.125	0.125	0.06	ng	0.06	0.125	0.06	0.03	ng	nr	ng	0.125
	14032	0.06	0.06	ng	0.125	0.125	0.25	ng	0.125	0.25	0.06	0.03	0.03	nr	ng	0.25
	18861	0.03	0.03	ng	0.125	0.006	0.25	ng	0.25	0.25	0.03	0.015	0.06	nr	0.03	0.06
<i>S. aureus</i> MSSA	29213	0.125	0.125	0.125	0.25	0.25	0.125	0.125	0.125	0.125	0.25	0.25	0.5	nr	0.25	0.25
	18488	0.125	0.125	0.25	0.25	0.25	0.125	0.125	0.125	0.125	0.25	0.25	0.5	nr	0.25	0.25
	18401	0.125	0.125	0.125	0.25	0.25	0.125	0.125	0.125	0.125	0.25	0.25	0.5	nr	0.25	0.125
<i>S. aureus</i> MRSA	18483	0.25	0.5	0.25	0.5	0.5	0.25	0.25	0.25	0.5	0.5	0.5	1	nr	0.5	0.5
	18504	0.25	0.5	0.25	0.5	0.25	0.25	0.25	0.25	0.5	0.5	0.5	1	nr	0.25	0.5
	18526	0.25	0.5	0.25	0.5	0.5	0.25	0.25	0.25	0.5	0.5	0.5	1	nr	0.25	0.25

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Organism	Strain #	REF	Ca++	% NaCl	Medium		Incubation Atmosphere		% Serum		Agar Dilution			pH		
			50mg/L	5	LHB	HTM	CO <sub>2</sub>	anaerobic	10	50	MHA	MHA / LHB	HTMA	5	6	8
MIC, µg/ml																
<i>E. faecalis</i>	29212	0.5	0.5	1	0.5	1	0.5	0.5	1	1	1	0.5	2	nt	0.5	1
	18284	1	1	2	2	2	1	1	1	2	2	2	4	nt	2	2
	18877	1	1	0.06	1	2	0.5	0.5	2	2	2	0.5	4	nt	0.5	2
<i>S. pyogenes</i>	17018	0.002	0.002	ng	n/t	0.004	0.004	0.004	0.002	0.002	0.008	0.008	0.015	nt	0.002	0.002
	17019	0.004	0.004	ng	n/t	0.004	0.004	0.004	0.002	0.002	0.008	0.008	0.015	nt	0.004	0.004
	19047	0.004	0.004	ng	n/t	0.008	0.004	0.004	0.004	0.004	0.008	0.008	0.015	nt	0.004	0.004
<i>S. pneumoniae</i>	49619	0.015	0.015	ng	n/t	0.015	0.015	0.015	0.015	0.008	0.008	0.015	0.008	nt	0.015	0.008
	19094	0.004	0.004	ng	n/t	0.008	0.004	0.004	0.004	0.004	0.008	0.008	0.008	nt	0.004	0.004
	19095	0.004	0.004	ng	n/t	0.004	0.004	0.004	0.004	0.004	0.008	0.008	0.008	nt	0.004	0.004
	13345	0.125	0.125	ng	n/t	0.06	0.06	0.125	0.125	0.06	0.06	0.125	0.125	nt	0.125	.06
	13385	0.125	0.125	ng	n/t	0.125	0.125	0.125	0.125	0.125	0.06	0.125	0.125	nt	0.125	.06
	18876	0.25	0.25	ng	n/t	0.25	0.25	0.125	0.25	0.25	0.125	0.25	0.25	nt	0.125	0.25

**Study P0903-M-001 (Part II), 2004**

<i>E. coli</i> 0.06	25922	0.06	0.06	nt	0.06	0.06	0.06	0.06	0.06	0.03	nt	nt	nt	0.12	0.06	0.06
<i>E. cloacae</i>	32-43A	0.5	0.5	nt	0.25	0.25	0.5	0.5	nt	nt	nt	nt	nt	0.5	0.12	0.25
<i>P. aeruginosa</i>	27853	8	16	nt	32	8	4	4	16	32	nt	nt	nt	0.5	2	32
<i>A. baumannii</i>	25-755A	2	2	nt	2	1	2	2	nt	nt	nt	nt	nt	4	2	2
<i>S. aureus</i>	25923	0.12	0.06	nt	0.12	0.06	0.12	0.06	nt	nt	nt	nt	nt	≤0.016	0.12	0.12
<i>S. aureus</i>	29213	0.25	0.12	nt	0.12	0.12	0.25	0.25	nt	nt	nt	nt	nt	0.03	0.12	0.25
<i>S. aureus</i>	VISA12	1	1	nt	2	1	1	1	nt	nt	nt	nt	nt	0.03	0.5	2

Organism	Strain #	REF	Ca++	% NaCl	Medium		Incubation Atmosphere		% Serum		Agar Dilution			pH		
			50mg/L	5	LHB	HTM	CO <sub>2</sub>	anaerobic	10	50	MHA	MHA / LHB	HTMA	5	6	8
MIC, µg/ml																
<i>S. aureus</i>	30-100A	0.5	0.25	nt	0.5	0.5	0.5	0.5	nt	nt	nt	nt	nt	0.03	0.5	0.5
CoNS	51-81A	0.5	0.5	nt	0.5	0.5	0.5	0.5	nt	nt	nt	nt	nt	0.03	0.25	0.5
CoNS	57-353A	0.06		nt					nt	nt	nt	nt	nt	0.06	0.12	≤0.016
<i>E. faecalis</i>	29212	1	0.5	nt	0.5	0.25	1	1	nt	nt	nt	nt	nt	1	2	0.06
<i>E. faecalis</i>	33-16A	8	4	nt	4	0.5	4	4	nt	nt	nt	nt	nt	0.12	1	4
<i>E. faecium</i>	78-464A	4	4	nt	2	1	4	4	nt	nt	nt	nt	nt	0.12	1	4
<i>S. pneumoniae</i>	49619	0.016	0.016	nt	nt	nt	0.08	nt	nt	nt	nt	nt	nt	0.016	0.016	ng
Viridans group streptococcus	35-329A	0.016	0.016	0.016	nt	nt	0.08	nt	nt	nt	nt	nt	nt	0.016	0.016	Ng

Abbreviations: CAMHB = cation adjusted Mueller Hinton broth; CLSI = Clinical Laboratories Standards Institute; CO<sub>2</sub> = carbon dioxide; CoNS = coagulase-negative staphylococci; HTM = Haemophilus test medium; HTMA = Haemophilus test medium agar; LHB = lysed horse blood; MHA = Mueller Hinton agar; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*; REF = CLSI reference conditions; ng = no growth; nt = not tested.

Source: Study P0903-M-001 (Part II), 2004; Jones et al, 2005; Study P0903-M-046, 2008.

**Effect of inoculum size on activity:**

The impact of inocula was evaluated using broth microdilution. In Table 42, the MIC increased greater than 32-fold with an inoculum of  $1 \times 10^6$  CFU/mL compared to  $1 \times 10^4$  CFU/mL (or to the reference at  $10^5$  CFU/mL), for 1 of 3 *E. coli* strains that were also resistant to ampicillin (MIC > 32 mcg/mL) and 1 of 3 *K. pneumoniae* strains. Higher inocula also increased MICs by 16- to 66-fold for *M. catarrhalis*. With an inoculum of  $5 \times 10^7$  CFU/mL, a tested isolate of both *E. cloacae* and *P. aeruginosa* had increased MIC.

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**Table 42 Effect of Inoculum Size on the In Vitro Activity of Ceftaroline in Broth Microdilution**

Organism	Strain #	MIC, ug/mL, as a Function of Inoculum, CFU/mL		
		REF	1 × 10 <sup>4</sup>	1 × 10 <sup>6</sup>
<b>Study P0903-M-046, 2008</b>				
<i>E. coli</i>	25922	0.06	0.06	0.125
	19089	0.06	0.03	0.125
	19090	0.03	0.03	2
<i>K. pneumoniae</i>	19091	0.25	0.25	> 8
	19092	0.03	0.03	0.125
	19093	0.06	0.03	0.25
<i>H. influenzae</i>	49247	0.015	ng	0.06
	16081	0.008	ng	0.008
	18520	0.015	0.015	0.06
<i>M. catarrhalis</i>	11940	0.125	0.03	2
	14032	0.06	0.03	1
	18861	0.03	0.015	2
<i>S. aureus</i> MSSA	29213	0.125	0.125	0.25
	18488	0.125	0.125	0.25
	18401	0.125	0.125	0.25
<i>S. aureus</i> MRSA	18483	0.25	0.25	0.5
	18504	0.25	0.25	0.5
	18526	0.25	0.25	0.5
<i>E. faecalis</i>	29212	0.5	0.5	1
	18284	1	1	2
	18877	1	1	2
<b>Study P0903-M-001 (Part II), 2004</b>				
MIC, ug/mL, as a Function of Inoculum, CFU/mL				
<i>S. pyogenes</i>	17018	0.002	0.002	0.004
	17019	0.004	0.004	0.004
	19047	0.004	0.004	0.004
<i>S. pneumoniae</i>	49619	0.015	0.008	0.015
	19094	0.004	0.004	0.004
	19095	0.004	0.004	0.004
	13345	0.125	.06	0.125
	13385	0.125	0.125	0.125
	18876	0.25	0.25	0.25
<b>Study P0903-M-001 (Part II), 2004</b>				
<i>E. coli</i>	25922	0.06	0.06	0.25
<i>E. cloacae</i>	32-43A	0.5	0.25	> 32
<i>P. aeruginosa</i>	27853	8	4	> 32
<i>A. baumannii</i>	25-755A	2	2	4
<i>S. aureus</i>	25923	0.12	0.12	0.12
<i>S. aureus</i>	29213	0.25	0.12	0.25
<i>S. aureus</i>	VISA12	1	1	2
<i>S. aureus</i>	30-100A	0.5	0.5	1
CoNS	51-81A	0.5	0.5	1
CoNS	57-353A	0.06	0.06	0.12
<i>E. faecalis</i>	29212	1	1	2
<i>E. faecalis</i>	33-16A	8	4	8
<i>E. faecium</i>	78-464A	4	4	4
<i>S. pneumoniae</i>	49619	0.016	0.016	0.016
viridans group streptococcus	35-329A	0.016	0.016	0.016

Abbreviations: CFU = colony-forming unit; MIC = minimum inhibitory concentration; REF = CLSI reference conditions (ie, inocula 5 × 10<sup>7</sup> CFU/mL); ng = no growth.

Source: Study P0903-M-046, 2008; Study P0903-M-001 (Part II), 2004.

In another study, the inoculum effects on ceftaroline MICs were also studied for 96 *Enterobacteriaceae* using agar dilutions and an inoculum of 10<sup>4</sup> or 10<sup>6</sup> CFU/spot using the oxyimino-cephalosporin, cefotaxime, as a comparator (Table 43). All β-lactamase-producing isolates from this study were characterized using isoelectric focusing and by PCR (Study P0903-M-004/011, 2006). Geometric mean (geomean) MICs and the ratio of the geomean MICs between the two inocula (106/104) for all the MICs for each organism group were used to

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evaluate the impact of inoculum cell number on the MIC (Table 42). Overall, higher MICs were observed for all isolates containing  $\beta$ -lactamases at higher inoculum cell numbers.

**Table 43 Impact of Inocula Cell Number on Ceftaroline and Cefotaxime Agar Dilution MIC Using Molecularly Characterized *Enterobacteriaceae***

Organism Type		MIC, $\mu\text{g/mL}$ , as a Function of Inoculum CFU/mL				MIC Ratio ( $10^6/10^4$ )		Organism Type		MIC, $\mu\text{g/mL}$ , as a Function of Inoculum CFU/mL				MIC Ratio ( $10^6/10^4$ )	
		Ceftaroline		Cefotaxime		Ceftaroline	Cefotaxime			Ceftaroline		Cefotaxime		Ceftaroline	Cefotaxime
		$10^4$	$10^6$	$10^4$	$10^6$					$10^4$	$10^6$	$10^4$	$10^6$		
<b><i>Escherichia coli</i> AmpR</b>								<b><i>Proteus mirabilis</i> AmpR</b>							
<i>E. coli</i>	TEM-1	0.06	0.06	0.06	0.125	1.0	2.08	<i>P. mirabilis</i>	TEM-1	0.25	256	0.015	0.5	1024	33.33
<i>E. coli</i>	TEM-1	0.25	128	0.03	2	512.00	66.67	<i>P. mirabilis</i>	TEM-PCR only	0.125	0.125	0.015	0.25	1	16.67
<i>E. coli</i>	TEM-1	0.5	4	0.06	0.25	8.00	4.17	<i>P. mirabilis</i>	TEM-2	0.5	256	0.015	2	512	133.33
<i>E. coli</i>	TEM-1	0.125	2	0.06	2	16.00	33.33	<i>P. mirabilis</i>	TEM-1	0.125	0.25	0.015	0.06	2	4
<i>E. coli</i>	TEM-1	0.06	0.5	0.06	0.25	8.33	4.17	<i>P. mirabilis</i>	TEM-2	0.25	4	0.015	0.25	16	16.67
<i>E. coli</i>	TEM-1	0.06	0.25	0.06	0.25	4.17	4.17	<i>P. mirabilis</i>	TEM-3	0.125	128	0.015	0.25	1024	16.67
<i>E. coli</i>	TEM-1	0.125	0.05	0.06	0.125	4.00	2.08	<i>P. mirabilis</i>	TEM-2	0.5	256	0.015	0.5	512	33.33
<i>E. coli</i>	TEM-1 + OXA-1	0.25	2	0.06	0.25	8.00	4.17	<i>P. mirabilis</i>	TEM-1	0.06	2	0.015	0.5	33.33	33.33
<i>E. coli</i>	TEM-1	0.125	0.25	0.06	0.125	2.00	2.08	<i>P. mirabilis</i>	TEM-2	0.125	1	0.015	0.5	8	33.33
<i>E. coli</i>	TEM-1	0.125	4	0.06	0.125	32.00	2.08	<i>P. mirabilis</i>	TEM-PCR only	0.06	2	0.015	0.5	33.33	33.33
<i>E. coli</i>	TEM-1	0.25	64	0.06	0.125	256.00	2.08	<i>P. mirabilis</i>	TEM-2	0.5	256	0.03	2	512	66.67
<i>E. coli</i>	TEM-1	0.06	0.25	0.03	0.06	4.17	2.00	<i>P. mirabilis</i>	TEM-1	0.5	64	0.03	0.5	128	16.67
<i>E. coli</i>	TEM-1	0.125	1	0.06	0.125	8.00	2.08	<i>P. mirabilis</i>	TEM-2	0.5	32	0.015	0.06	64	4
<i>E. coli</i>	TEM-1	0.25	1	0.06	0.25	4.00	4.17	<i>P. mirabilis</i>	TEM-1	0.5	32	0.015	0.5	64	33.33
<i>E. coli</i>	TEM-1	1	4	0.06	0.25	4.00	4.17	<b><i>Proteus mirabilis</i> AmpS</b>							
<i>E. coli</i>	TEM-1	0.125	0.25	0.06	0.125	2.00	2.08	<i>P. mirabilis</i>	none	0.03	1	0.015	1	33.33	66.67
<i>E. coli</i>	TEM-1	4	256	0.06	0.125	64.00	2.08	<i>P. mirabilis</i>	none	0.06	0.5	0.015	0.25	8.33	16.67
<b><i>Escherichia coli</i> AmpS</b>								<i>P. mirabilis</i>	none	0.125	4	0.03	0.5	32	16.67
<i>E. coli</i>	none	0.06	0.125	0.06	0.125	2.08	2.08	<i>P. mirabilis</i>	none	0.06	2	0.015	1	33.33	66.67
<i>E. coli</i>	none	0.125	0.06	0.125	0.25	0.48	2.00	<i>P. mirabilis</i>	none	0.125	4	0.015	0.5	32	33.33
<i>E. coli</i>	none	0.03	0.06	0.06	0.125	2.00	2.08	<i>P. mirabilis</i>	none	0.06	2	0.015	1	33.33	66.67
<i>E. coli</i>	none	0.06	0.125	0.06	0.25	2.08	4.17	<i>P. mirabilis</i>	none	0.03	1	0.015	0.25	33.33	16.67
<i>E. coli</i>	none	0.03	0.06	0.03	0.06	2.00	2.00	<i>P. mirabilis</i>	none	0.03	0.5	0.015	0.125	16.67	8.33
<i>E. coli</i>	none	0.06	0.06	0.06	0.25	1.00	4.17	<i>P. mirabilis</i>	none	0.03	1	0.015	0.5	33.33	33.33
<i>E. coli</i>	none	0.06	0.06	0.06	0.125	1.00	2.08	<i>P. mirabilis</i>	none	0.06	0.125	0.015	0.5	2.08	33.33
<i>E. coli</i>	none	0.06	0.06	0.06	0.125	1.00	2.08	<i>P. mirabilis</i>	none	0.06	1	0.008	0.25	16.67	31.25

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Organism Type		MIC, µg/mL, as a Function of Inoculum CFU/mL				MIC Ratio (10 <sup>6</sup> 10 <sup>4</sup> )	
		Ceftaroline		Cefotaxime		Ceftaroline	Cefotaxime
		10 <sup>4</sup>	10 <sup>6</sup>	10 <sup>4</sup>	10 <sup>6</sup>		
<b>ESBL producers</b>							
<i>E. coli</i>	ESBL	8	> 128	16	> 128	> 16	> 8
<i>E. coli</i>	ESBL	16	> 128	0.125	1	> 8	8
<i>E. coli</i>	ESBL	8	> 128	0.125	1	> 16	8
<i>E. coli</i>	ESBL	8	> 128	16	> 128	> 16	> 8
<i>E. coli</i>	ESBL	2	> 128	8	128	> 64	> 16
<i>E. coli</i>	ESBL	2	128	2	> 128	> 32	> 64
<i>Klebsiella</i>	ESBL	4	> 128	16	> 128	> 32	> 8
<i>Klebsiella</i>	ESBL	4	> 128	16	> 128	> 16	> 8
<i>Klebsiella</i>	ESBL	8	> 128	32	> 128	> 16	> 4
<i>Klebsiella</i>	ESBL	4	> 128	8	> 128	> 32	> 16
<i>Klebsiella</i>	ESBL	32	> 128	32	> 128	> 4	> 4
<i>Klebsiella</i>	ESBL	4	> 128	32	> 128	> 32	> 4
<i>Klebsiella</i>	ESBL	32	> 128	64	> 128	> 4	> 2
<i>Klebsiella</i>	ESBL	8	> 128	16	> 128	> 16	> 8
<i>Klebsiella</i>	ESBL	4	> 128	16	> 128	> 32	> 8
<i>Klebsiella</i>	ESBL	32	> 128	16	> 128	> 4	> 8
<b>Reference strains</b>							
<i>E. coli</i>	none	0.06	0.06	0.06	0.06	1	1
<i>E. coli</i>	TEM-1	2	256	0.06	0.06	128	1
<i>E. coli</i>	TEM-2	0.5	256	0.06	0.25	512	4.17
<i>E. coli</i>	SHV-1	0.5	32	0.06	0.125	64	2.08
<i>E. coli</i>	none	0.03	0.06	0.03	0.125	2	4.17

Abbreviations: AmpS = ampicillin susceptible; AmpR = ampicillin resistant; CFU = colony-forming unit;  
ESBL = extended-spectrum β-lactamase; Geomean = geometric mean; MIC = minimum inhibitory concentration;  
NC = not calculated; PipS = piperacillin susceptible; PipR = piperacillin resistant.  
Source: Study P0903-M-004/011, 2006.

***Effect of Broth Micro Dilution Panel Storage at -70°C on the In Vitro Activity of Ceftaroline***

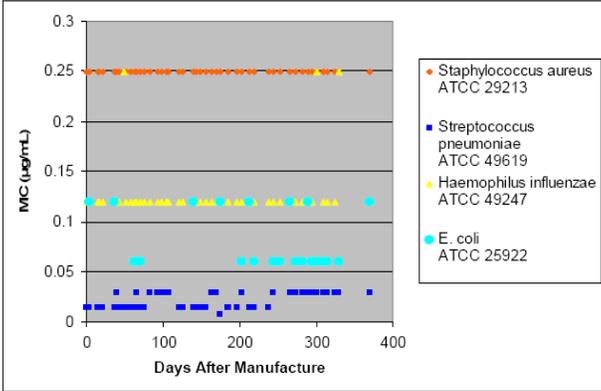
The Applicant investigated shifts in MIC over time course of storage of MIC panels. If degradation of ceftaroline were to occur over time, it is expected that MIC values would increase with panel storage as the active concentration of the drug decreases and a shift in MIC would occur from the early time point measurement versus the MIC of the same QC isolate after panel aging. The data in Figure 6 using *E. coli* ATCC 25922, *H. influenzae* ATCC 49247, *S. aureus* ATCC 29213, and *S. pneumoniae* ATCC 49619 demonstrate that no systematic changes occurred in the MIC for ceftaroline when CLSI reference panels were stored at -70°C, thawed, inoculated, and then MIC determinations carried out. No systematic changes to MIC were observed for up to 400 days for two gram-positive QC isolates and two gram-negative QC isolates (Figure 6). This indicates that ceftaroline in MIC panels stored frozen at -70°C is stable, and the panels can be used routinely for at least one year after manufacture.

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**Figure 6. Gram-Positive and Gram-Negative CLSI Frozen Panel QC Stability of Ceftaroline Stored After Freezing at -70°C**



***Effect of Disc Storage on the In Vitro Activity of Ceftaroline***

In another study, the Applicant determined whether degradation of ceftaroline occurs during disk storage thus impacting the zone size. Performance was analyzed at the beginning, middle, and end of the storage time: T = 0 weeks (Baseline test), T = 26 weeks, and T = 52 weeks. Test discs were tested against a control freshly made on the day of testing. Overall, the performance of the product stored between -20°C and 8°C at the 64-week time point was found to be comparable to the Baseline test (Table 44 and Table 45). The stability is therefore satisfactory and the microbiological adequacy reached.

**Table 44 Determination of Ceftaroline Concentration of 30-µg Disk - Stability after Storage at -20°C, by Bioassay**

Date of Test (dd/mm/yy)	Test Period / Average Zone Size, mm							
	03/07/2007		08/11/2007		15/04/2008		01/07/2008	
Age of disks, months	3		6		12		15	
Days in use	1	1	7	1	7	1	7	
<i>S. aureus</i> ATCC 25293	29.29	32.75	32.71	36.68	29.88	32.53	32.48	
<i>E. coli</i> ATCC 25922	29.34	29.62	31.38	31.91	31.54	29.34	30.35	
<i>P. aeruginosa</i> ATCC 27853	23.45	22.1	21.97	21.77	22.51	21.86	20.72	
<i>K. pneumoniae</i> ATCC 29665	28.78	34.48	34.8	35.37	35.9	33.34	33.18	
<i>H. influenzae</i> ATCC 49247	39.81	37.63	38.56	33.34	33.04	31.64	32.02	
<i>S. pneumoniae</i> ATCC 49619	36.68	37.26	38.93	36.61	36.7	34.68	35.35	
Plate Assay	-	30.89	-	35.54	-	34.87	-	

Abbreviations: ATCC = American Type Culture Collection  
Source: P903-M-087, 2009

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**Table 45 Determination of Ceftaroline Concentration of 30-µg Disk - Stability after Storage at 8°C, by Bioassay**

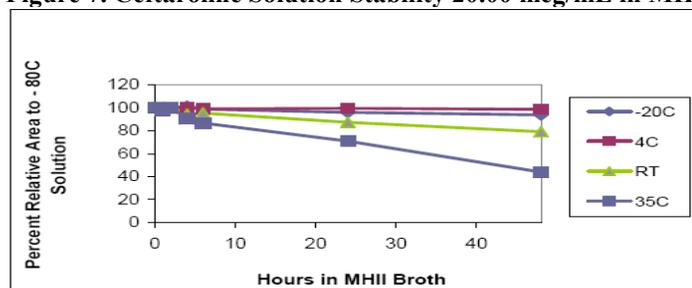
Date of Test (dd/mm/yy)	Test Period / Average Zone Size, mm						
	03/07/2007	08/11/2007		15/04/2008		01/07/2008	
Age of disks, months	3	6		12		15	
Days in use	1	1	7	1	7	1	7
<i>S. aureus</i> ATCC 25293	29.5	33.32	33.58	36.55	36.17	32.02	32.97
<i>E. coli</i> ATCC 25922	28.82	31.15	30.88	32.76	32.48	30.06	29.26
<i>P. aeruginosa</i> ATCC 27853	23.42	21.6	21.47	22.04	22.81	21.56	20.73
<i>K. pneumoniae</i> ATCC 29665	29.45	35.98	35.23	35.07	36.46	32.38	31.53
<i>H. influenzae</i> ATCC 49247	38.95	38.54	38.27	32.23	32.67	31.67	31.46
<i>S. pneumoniae</i> ATCC 49619	35.5	38.5	38.00	36.19	35.76	34.86	34.26
Plate Assay	-	33.83	-	35.5	-	35.94	-

Abbreviations: ATCC = American Type Culture Collection.  
Source: Study P0903-M-087, 2009.

**Stability of Ceftaroline in Mueller-Hinton Broth (MHB)**

Another study examined the stability of ceftaroline in MHB by high-performance liquid chromatography/mass spectroscopy (HPLC/MS) analysis to measure ceftaroline concentrations over a period of 48 hours in MHB (Study P903-BDM-01, 2009) at different temperatures (Figure 7 and Table 46). After two hours at room temperature there was an approximate 1.5% degradation of ceftaroline. This suggests that storage time on the bench prior to inoculation is relatively robust at room temperature and should have little impact on the MIC. At 35°C, the presumed panel incubation temperature after inoculation, an approximate 15% decrease in concentration of ceftaroline after 6.5 hours occurred, and an approximate 30% decrease occurred over 24 hours.

**Figure 7. Ceftaroline Solution Stability 20.00 mcg/mL in MH Broth**



**Table 46 Ceftaroline Stability in Mueller-Hinton Broth: Percentage Initial Ceftaroline Area at Time 0 Hours Using HPLC/MS Analysis**

Hours	-20°C	4°C	RT	35°C
0	100%	100%	100%	100%
1	100%	100%	99.2%	97.2%
2	99%	99%	99.6%	100%
4	100%	100%	94.1%	90.3%
6	98.6%	98.9%	95.2%	86.6%
24	95.7%	99.4%	87.1%	70.9%
48	93.7%	98.5%	79%	43.9%

Abbreviations: HPLC/MS = high-performance liquid chromatography/mass spectroscopy; RT = room temperature.  
Source: Study P903-BDM-01, 2009.

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Ceftaroline for Injection

Cerexa Inc.

**EFFECT OF MISCELLANEOUS FACTORS ON CEFTAROLINE ACTIVITY**

***Effect of Protein-Binding***

The activity of  $\beta$ -lactams has been shown to be dependent upon the time the serum concentration exceeds the MIC of the drug. Clinical success usually occurs when the unbound serum concentration of the  $\beta$ -lactam exceeds the MIC of an infecting agent for more than 20-50% of the dosing interval<sup>24</sup>. This dosing interval varies by the  $\beta$ -lactam class. For instance, 20-25% is generally required for carbapenems, 30-40% for penicillins, and 40-50% for cephalosporins<sup>4, 24</sup>. Therefore, the Applicant conducted protein binding studies to investigate the extent at which ceftaroline binds to plasma protein.

A summary of the protein binding that were conducted in mice, rats, rabbits, monkeys, and humans using different ultrafiltration and MIC methods is presented in Table 47. The effect of 50% human serum (heat-inactivated or not) and serum albumin (45 mcg/mL) on in vitro MICs of ceftaroline was assessed against a set of gram-positive and gram-negative pathogens. Serum-resistant isolates were employed in order to obviate the killing effects of complement. In one study (TAK-599/00069 2003), protein binding in mouse ranged from 32.1 - 35.6%, rat from 36.8 - 40.7%, monkey 14.2 - 20% and human from 23.4 - 26.4%. In another study (P0903-P-001, 2006) binding to proteins in mouse serum ranged from 34.5%-37.5%, while binding to plasma proteins in rabbit was 4.6%-17.0%, monkey was 16.8%-22%, and human was 0.9%-19.3% (0.9% at 50 mcg/mL, 7.4% at 150 mcg/mL, and 19% at 5 mcg/mL). MIC testing using standard broth microdilution methods with 2-fold serial dilutions of ceftaroline revealed no significant differences (greater than  $\pm 1 \log_2$  dilution) in MICs from the CLSI reference conditions by the addition of up to 50% inactivated human serum for the vast majority of the isolates tested. The only exceptions were for some isolates of *H. influenzae* and *M. catarrhalis* that showed a greater than 2 or more-dilution increase in MIC in the presence of serum.

**Table 47 Summary Table of Studies on Protein-Binding of Ceftaroline**

Method	Protein Source	Assay or Organisms	Protein-Binding, or Outcome	Reference
Ultrafiltration	mouse plasma rat plasma monkey plasma human plasma	Scintillation counting; <sup>14</sup> C-ceftaroline at 0.5, 5.0, 50 $\mu$ g/mL	32.1 - 35.6% 36.8 - 40.7% 14.2 - 20% 23.4 - 26.4%	Study TAK-599/00069, 2003
Ultrafiltration	mouse plasma rabbit plasma monkey plasma human plasma	HPLC/MS; ceftaroline at 5, 50, and 150 $\mu$ g/mL	34.5 - 37.5% 4.6 - 17.0% 16.8 - 22.2% 0.9 - 19.3%	Study P0903-P-001, 2006
Ultrafiltration	human plasma	LC/MS; ceftaroline at 1, 5, 20 50 $\mu$ g/mL	14.5 - 28%	Study P0903-P-003, 2006
Ultrafiltration	neutropenic mouse serum	ceftaroline at 10 and 100 $\mu$ g/mL	63 - 66%	Study P0903-M-003, 2004; Andes and Craig, 2006
Effect on MICs (broth microdilution)	inactivated human serum at 5, 10 and 50%	MICs vs <i>S. aureus</i> (4), <i>S. pneumoniae</i> (2), <i>E. coli</i> , <i>K. pneumoniae</i> , <i>P. aeruginosa</i>	No changes in MIC greater than $\pm 1 \log_2$ dilution	Study P0903-M-001 (Part II), 2004; Jones et al, 2005
Effect on MICs (broth microdilution)	inactivated pooled human serum at 10 and 50%	MICs vs <i>S. aureus</i> (5), <i>S. pyogenes</i> (3), <i>E. faecalis</i> (3), <i>S. pneumoniae</i> (6), <i>H. influenzae</i> (3), <i>M. catarrhalis</i> (3), <i>K. pneumoniae</i> (3), <i>E. coli</i> (3)	No changes in MIC greater than $\pm 1 \log_2$ dilution, except for 2-dilution differences for 2 isolates of <i>H. influenzae</i> and <i>M. catarrhalis</i>	Study P0903-M-046, 2008
Effect on MICs (broth microdilution)	active pooled human serum at 50%; inactivated pooled human serum at 50%; human serum albumin at 45 $\mu$ g/mL	MICs vs serum resistant isolates of <i>S. aureus</i> (6), <i>S. pneumoniae</i> (2), <i>E. faecalis</i> (3), <i>E. faecium</i> (2), <i>E. coli</i> (2), <i>K. pneumoniae</i> (1), <i>H. influenzae</i> (2)	No changes in MIC in presence of serum (active or inactive) or albumin; except for some enterococci MICs increased 2- to 8-fold	Study P903-M-062, 2009

Abbreviations: MIC = minimum inhibitory concentration.

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Table 48 shows the effect of serum protein on MIC, the test was conducted against a panel of characterized serum-resistant isolates of *S. aureus* (6), *S. pneumoniae* (2), *E. faecalis* (3), *E. faecium* (2), *E. coli* (2), *K. pneumoniae* (1), and *H. influenzae* (2). The genotype/phenotype data given show that many of these isolates had known resistances to other agents. MICs were determined by broth dilution according to CLSI methods in cation-adjusted Mueller-Hinton broth (CAMHB), and CAMHB containing 50% active pooled human serum, 50% heat-inactivated pooled human serum, and 45 mg/L albumin. Ceftriaxone served as a comparator for all species except *S. aureus*, for which vancomycin was the comparator. With the exception of some enterococci, the MICs of ceftaroline for all strains ranged from < 0.06 to 2 mcg/mL. This range occurred for isolates that were susceptible or resistant to methicillin, vancomycin, daptomycin, quinupristin/dalfopristin, or quinolones, or whether they were a  $\beta$ -lactamase producer (*H. influenzae*). The presence of inactive or active serum or albumin appear to have little to no effect on ceftaroline MICs except for the enterococci, for which the MICs were increased 2- to 8-fold by serum (active or inactive) or albumin. In this Reviewer's opinion, conclusive data was not submitted for *S. pneumoniae* isolates. The Applicant stated that *S. pneumoniae* could not be evaluated in the presence of serum, as a result of frequent phase variation that influences their serum resistance properties. Additionally, *H. influenzae* isolates grew poorly in active serum. Increases in MIC were also observed for *K. pneumoniae* ATCC 13182 in the presence of serum.

**Table 48 Effect of Serum Proteins on MICs for Ceftaroline against a Panel of Serum-Resistant Gram-Positive and Gram-Negative Isolates**

Strain	Phenotype/ Genotype	Ceftaroline MIC, $\mu\text{g/mL}^a$			
		No Serum	+ 50% Active Serum	+ 50% Inactive Serum	+ 45 $\mu\text{g/mL}$ Albumin
<i>S. aureus</i> ATCC 29213	MSSA	0.25	0.125	0.125	0.25
<i>S. aureus</i> ATCC 33593	MRSA	2	2	1	1
<i>S. aureus</i> Mu-50	VISA	1	1	0.5	0.5
<i>S. aureus</i> ST247	MRSA, quinu/dalfo-R ( <i>vatB ygbA</i> )	2	2	2	2, 1
<i>S. aureus</i> ST225	MRSA, DAP-R	1	1	1	1
<i>S. aureus</i> ST8	MSSA	0.25	0.25	0.25	0.25
<i>S. pneumoniae</i> ATCC 49619	susceptible	< 0.06	ND	ND	0.125
<i>S. pneumoniae</i> BAY 19397	PEN-R, macrolide-R, quinolone-R ( <i>gyrA parC</i> )	0.125	ND	ND	0.125
<i>E. faecalis</i> ATCC 29212	VAN-S	0.5	2	2	2
<i>E. faecalis</i> ATCC 51299	VAN-R	0.25, 0.5	4	8	4
<i>E. faecalis</i> UW 6940	TGC-R	4	16	32	32
<i>E. faecium</i> UW 3695	Van-S, LNZ-R, quinolone-R	16	32	32	32
<i>E. coli</i> WT	susceptible	$\leq 0.06$	0.125	$\leq 0.06$	0.125, $\leq 0.06$
<i>E. coli</i> WT 3-1-M4	quinolone-R ( <i>gyrA parC</i> )	$\leq 0.06, 0.125$	0.125, 0.06	0.125	0.125
<i>K. pneumoniae</i> ATCC 13182	susceptible	$\leq 0.06$	$\leq 0.06$	1	0.5
<i>K. pneumoniae</i> ATCC 13182 <sup>b</sup>	susceptible	1	1	1	1
<i>H. influenzae</i> ATCC 33391	$\beta$ -lactamase negative	$\leq 0.06$	NG	$\leq 0.06$	$\leq 0.06$
<i>H. influenzae</i> England 1	$\beta$ -lactamase positive	$\leq 0.06$	NG	$\leq 0.06$	0.25

a MIC tests were performed in duplicate, and where the results were identical, only one value is listed.

b Results of a duplicate test performed on a separate day.

Abbreviations: ATCC = American Type Culture Collection; DAP = daptomycin; MIC = minimal inhibitory concentration; MSSA = methicillin-sensitive *S. aureus*; MRSA = methicillin-resistant *S. aureus*; quinu/dalfo-R = quinupristin/dalfopristin resistant; VISA: vancomycin-intermediate *S. aureus*; R = resistant; S = susceptible; PEN = penicillin; VAN = vancomycin; WT = wild type; TGC = tigecycline; LNZ = linezolid; ND = not determined; NG = no growth.

Source: Study P903-M-062, 2009.

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**Post Antibiotic effect**

The PAE describes the suppression of bacterial growth that occurs after short exposure to an antibiotic. The PAE is a consequence of the initial exposure to high concentrations of antibiotics rather than to persistent sub-inhibitory levels. The PAE was determined for ceftaroline against the list of organisms in Table 49.

**Table 49 Postantibiotic and Sub-MIC Studies with Ceftaroline**

<i>Organism (Number of isolates)</i>	<i>Resistance Phenotypes</i>	<i>Test</i>	<i>Study Number</i>
<i>S. aureus</i> (2)	MSSA, MRSA,	in vitro PAE	Study P0903-M-030, 2008
<i>E. faecalis</i> (2)	VSE, VRE,		
<i>S. pneumoniae</i> (2)	PSSP, PRSP,		
<i>M. catarrhalis</i> (2)	β-lac neg, β-lac pos		
<i>H. influenzae</i> (2)	ampS, BLNAR		
<i>K. pneumoniae</i> (1)	non-ESBL		
<i>E. coli</i> (1)	non-ESBL		
<i>Organism (Number of isolates)</i>	<i>Resistance Phenotypes</i>	<i>Test</i>	<i>Study Number</i>
<i>S. aureus</i> (2)	MSSA, MRSA,	in vitro PAE	Study P903-M-055, 2009
<i>E. faecalis</i> (2)	VSE, VRE,		
<i>S. pneumoniae</i> (2)	PSSP, PRSP,		
<i>M. catarrhalis</i> (2)	β-lac neg, β-lac pos		
<i>H. influenzae</i> (2)	ampS, BLNAR		
<i>K. pneumoniae</i> (1)	non-ESBL		
<i>E. coli</i> (1)	non-ESBL		
<i>S. aureus</i> (6)	MSSA, MRSA (VAN-S), hVISA, VISA, VRSA	in vitro PAE	Study P903-M-056, 2009
<i>S. pneumoniae</i> (4)	PSSP, PISP, PRSP		
<i>E. faecalis</i> (2)	VAN-S		
<i>E. faecium</i> (3)	VAN-S, VAN-R	in vivo PAE, various doses in neutropenic mouse thigh infection model	Study P0903-M-003, 2004; Andes and Craig, 2006
<i>S. aureus</i> (1)	MSSA,		
<i>S. pneumoniae</i> (2)			
<i>E. coli</i> (1)	PSSP		

Abbreviations: ampS = ampicillin susceptible; β-lac neg = β-lactamase negative; β-lac pos = β-lactamase positive; BLNAR = β-lactamase-negative ampicillin-resistant; ESBL = extended-spectrum β-lactamase; MSSA = methicillin-susceptible *S. aureus*; MRSA = methicillin-resistant *S. aureus*; hVISA = heterogeneous vancomycin-intermediate *S. aureus*; PAE = postantibiotic effect; PSSP = penicillin-susceptible *S. pneumoniae*; PISP = penicillin-intermediate *S. pneumoniae*; PRSP = penicillin-resistant *S. pneumoniae*; VAN-S = vancomycin susceptible, VAN-R = vancomycin resistant, VISA = vancomycin-intermediate *S. aureus*; VRSA = vancomycin-resistant *S. aureus*; VSE = vancomycin-susceptible enterococci, VRE = vancomycin-resistant enterococci.

PAEs were determined following a 1 hour treatment with 10x MIC ceftaroline and 1000-fold dilution into fresh media. Table 50 shows the PAE of ceftaroline against selected isolates.

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**Table 50 PAE of ceftaroline against selected isolates**

Isolates	PAE (hours) at 10x MIC
<i>S. aureus</i> (including MSSA, MRSA, VISA, hVISA)	0.8-1.8
<i>S. pneumoniae</i> (including PSSP, PISP, PRSP)	0.75-2.2
<i>E. faecalis</i> (Van-S and Van-R)	0.6-1.1
<i>E. faecium</i> (Van-S)	0.55-0.7
<i>M. catarrhalis</i>	1.7
<i>H. influenzae</i>	0.6
<i>E. coli</i>	-0.2

***In vivo Post antibiotic effects***

The Applicant examined the in vivo post antibiotic effect of ceftaroline in a neutropenic mouse thigh-infection model. The isolates studied were *S. pneumoniae* ATCC 10813 (ceftaroline MIC 0.008 mcg/mL, penicillin susceptible), *S. aureus* ATCC 29213 (ceftaroline MIC 0.25 mcg/mL, MSSA), and *E. coli* ATCC 25922 (ceftaroline MIC 0.12 mcg/mL). Two hours after infection, mice were treated with single subcutaneous doses of ceftaroline fosamil (the prodrug form of ceftaroline) of 1.56, 6.25, 25, and 100 mg/kg. Treated and control mice had their thighs removed and colony counts performed at times 0, 1, 2, 4, 6, 9, 12, 18, and 24 h. Serum concentrations of ceftaroline were determined in two groups of three mice at 0.25- to 1-h intervals over 6 h (sample times included 0.25, 0.5, 1, 2, 4, and 6 h), using a microbiologic assay. From the time course, it was possible to estimate when the serum concentration dropped below the MIC for the test organisms. The protein binding was determined in order that free drug concentrations could be estimated. Following doses of 1.56, 6.25, 25, and 100 mg/kg, free-drug serum levels of ceftaroline were estimated to remain above the MIC for (1) *S. pneumoniae*: 4.3, 5.9, 8.0, and 8.2 h, respectively; (2) *S. aureus*: 0.17, 0.84, 4.2, and 4.6 h, respectively and (3) *E. coli*: 2.3, 3.4, 4.8, and 5.4 h, respectively (P0903-M-003, 2004). The PAE was calculated by determining the time required for the cell counts to increase by 1-log<sub>10</sub> after the free ceftaroline concentration dropped below the MIC, less the time required for the saline-treated control group to reach the same 1-log<sub>10</sub> increase in counts. Depending on the dose administered, free-drug PAEs were found to range from:

- *S. pneumoniae*: -1.9 to 1.5 h
- *S. aureus*: 0.8 to 7.2 h
- *E. coli*: -0.31 to 4.2 h

***In vivo post antibiotic effect comment***

Cephalosporins are time-dependent bactericidal antibiotics and generally act on the bacteria during the growth phase. The duration of the PAE is species specific and dependent on the drug used. The PAE observed here appear very minimal. Theoretically, an agent with a long PAE can be dosed less frequently than one having a shorter PAE. Based on the data provide, ceftaroline would be expected to have activity ranging from 0.8 to 7.2 hours for *S. aureus* and lower for *S. pneumoniae* and *E. coli*.

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***Synergy between comparator agents***

Antimicrobial combination and synergy are important for treating pathogens in mixed infection, to enhance the killing of specific pathogens, and to prevent or delay the emergence of drug-resistant populations. The Applicant evaluated synergy of ceftaroline in combination with different antibiotics using the checkerboard technique against a variety of bacterial isolates. The MIC and fractional inhibitory concentrations (FIC) and FIC indices (FICI) was used to assess drug interaction for ceftaroline in combination with other antimicrobials. A “synergistic interaction” is evidenced by inhibition of organism growth by combinations that are at concentrations significantly below the MIC of either compound alone, resulting in a low FICI value ( $\leq 0.50$ ). The interpretation of “no interaction” results in growth inhibition at concentrations below the MICs of the individual compounds, but the effect is not significantly different from the additive effects of the two compounds, resulting in an FICI value of  $> 0.50$  but  $\leq 4.0$ . (The interpretation “no interaction” has previously been referred to as “additivity” or “indifference.”) An “antagonistic interaction” results when the concentrations of the compounds in combination that are required to inhibit organism growth are greater than those for the compounds individually, resulting in an FIC value of  $> 4.0$ . While there is no officially sanctioned set of FICI criteria,  $\leq 0.50$  was used to define synergism in this study. The MIC and FICI results for selected antibiotic combinations are detailed in Table 51.

**Table 51 Drug Interaction with Selected Gram-Positive and Gram-Negative Bacteria Using Fractional Inhibitory Combination Analysis**

<i>Organism</i>	<i>Ceftaroline MIC Alone, <math>\mu\text{g/mL}</math></i>	<i>Test Compound</i>	<i>Test Compound MIC Alone, <math>\mu\text{g/mL}</math></i>	<i>FICI</i>	<i>Interpretation</i>
<i>S. aureus</i> 0753 (MSSA)	0.5	Daptomycin	0.5	0.93	No Interaction
<i>S. aureus</i> 2063 (MSSA)	0.5		1	0.70	No Interaction
<i>S. aureus</i> 0765 (MRSA)	1		0.5	0.96	No Interaction
<i>S. aureus</i> 2053 (MRSA)	2		0.5	0.72	No Interaction
<i>E. faecalis</i> 795 (VSE)	8		1	0.57	No Interaction
<i>E. faecalis</i> 796 (VSE)	2		2	0.63	No Interaction
<i>S. pyogenes</i> 717	0.008		0.06	0.75	No Interaction
<i>S. pyogenes</i> 722	0.008		0.06	1.17	No Interaction

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<i>Organism</i>	<i>Ceftaroline MIC Alone, µg/mL</i>	<i>Test Compound</i>	<i>Test Compound MIC Alone, µg/mL</i>	<i>FICI</i>	<i>Interpretation</i>
<i>S. aureus</i> 0765 (MRSA)	2	Tigecycline	0.25	1.05	No Interaction
<i>S. aureus</i> 2053 (MRSA)	2		0.5	1.10	No Interaction
<i>S. pneumoniae</i> 880 (PRSP)	0.12		0.03	1.42	No Interaction
<i>S. pneumoniae</i> 884 (PRSP)	0.12		0.03	1.26	No Interaction
<i>K. pneumoniae</i> 1468 (ESBL)	32		0.25	1.36	No Interaction
<i>A. baumannii</i> 2601	2		0.06	1.42	No Interaction
<i>A. baumannii</i> 2602	2		0.06	1.42	No Interaction
<i>S. aureus</i> 2296 (CA-MRSA)	1	Meropenem	> 16 <sup>a</sup>	0.62	No Interaction
<i>S. aureus</i> 2202 (CA-MRSA)	1		4	0.44	Synergy
<i>K. pneumoniae</i> 1468 (ESBL)	32		0.06	0.49	Synergy
<i>P. aeruginosa</i> 2555	32		4	0.60	No Interaction
<i>P. aeruginosa</i> 2559	16		0.12	1.65	No Interaction
<i>S. pneumoniae</i> 866 (PSSP)	0.008	Levofloxacin	1	1.14	No Interaction
<i>S. pneumoniae</i> 869 (PSSP)	0.008		1	1.04	No Interaction
<i>S. pneumoniae</i> 880 (PRSP)	0.12		> 4 <sup>a</sup>	1.19	No Interaction
<i>S. pneumoniae</i> 884 (PRSP)	0.12		1	1.13	No Interaction
<i>S. pyogenes</i> 717	0.008		0.5	1.15	No Interaction
<i>S. pyogenes</i> 722	0.008		0.5	0.90	No Interaction
<i>K. pneumoniae</i> 1461	0.25		> 4 <sup>a</sup>	1.75	No Interaction
<i>K. pneumoniae</i> 1340	0.12		0.06	1.14	No Interaction

<i>Organism</i>	<i>Ceftaroline MIC Alone, µg/mL</i>	<i>Test Compound</i>	<i>Test Compound MIC Alone, µg/mL</i>	<i>FICI</i>	<i>Interpretation</i>
<i>E. coli</i> 2273 (ESBL)	2	Levofloxacin	> 4 <sup>a</sup>	1.86	No Interaction
<i>E. coli</i> 1587	0.12	Levofloxacin	0.06	1.05	No Interaction
<i>H. influenzae</i> 1224	0.06		0.015	1.76	No Interaction
<i>H. influenzae</i> 2797 (BLNAR)	0.06		0.015	1.43	No Interaction
<i>H. influenzae</i> 2798 (BLNAR)	0.03		0.015	1.52	No Interaction
<i>H. influenzae</i> 2799 (BLNAR)	0.03		0.015	1.52	No Interaction
<i>K. pneumoniae</i> 1461	0.5	Amikacin	1	0.79	No Interaction
<i>K. pneumoniae</i> 1340	0.12		1	0.96	No interaction
<i>E. coli</i> 2273 (ESBL)	2		8	0.50	Synergy
<i>E. coli</i> 1587	0.12		4	0.96	No interaction
<i>P. aeruginosa</i> 2555	32		8	0.83	No Interaction
<i>P. aeruginosa</i> 2559	16	4	0.42	Synergy	
<i>K. pneumoniae</i> 1461	0.25	Aztreonam	0.25	1.27	No interaction
<i>K. pneumoniae</i> 1340	0.12		0.12	0.83	No Interaction
<i>E. coli</i> 2273 (ESBL)	2		16	0.64	No Interaction
<i>E. coli</i> 1587	0.12	0.25	0.60	No Interaction	
<i>S. pneumoniae</i> 866 (PSSP)	0.008	Azithromycin	0.06	1.16	No Interaction
<i>S. pneumoniae</i> 869 (PSSP)	0.008		0.06	1.16	No Interaction
<i>S. pneumoniae</i> 876 (PRSP)	0.12		2	1.11	No Interaction
<i>S. pneumoniae</i> 877 (PRSP)	0.12		> 32 <sup>a</sup>	0.99	No Interaction

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Organism	Ceftaroline MIC Alone, µg/mL	Test Compound	Test Compound MIC Alone, µg/mL	FICI	Interpretation
<i>H. influenzae</i> 1224	0.12	Azithromycin	1	1.26	No Interaction
<i>H. influenzae</i> 2797 (BLNAR)	0.12		1	1.13	No Interaction
<i>H. influenzae</i> 2798 (BLNAR)	0.03		2	1.24	No Interaction
<i>H. influenzae</i> 2799 (BLNAR)	0.03		0.25	1.11	No Interaction

Abbreviations: BLNAR = β-lactamase-negative ampicillin-resistant; CA-MRSA = community-acquired methicillin-resistant *Staphylococcus aureus*; ESBL = extended-spectrum β-lactamase; FICI = fractional inhibitory concentration indices; MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*; PRSP = penicillin-resistant *Streptococcus pneumoniae*; PSSP = penicillin-susceptible *Streptococcus pneumoniae*; VSE = vancomycin-susceptible enterococci.

Source: Study P0903-M-020, 2007.

Further studies were conducted with the aminoglycoside tobramycin compared with vancomycin against four strains of hospital-acquired methicillin-resistant *S. aureus* (HA-MRSA) including isolates with reduced susceptibility to vancomycin (Study P0903-M-043 Amendment 1, 2009). No synergy, or antagonism, was found with combinations of both agents at ¼ MIC and ½ MIC. Vancomycin or tobramycin alone at ½ MIC were not bactericidal against any tested isolates. In contrast, ceftaroline at ½ MIC was bactericidal against the hVISA (R1629) and the time to achieve 99.9% of the kill was 5.1 hours. A combination of antimicrobials at ½ MIC led to various outcomes depending on the isolate tested. Against the two vancomycin-susceptible MRSA, ceftaroline plus tobramycin was synergistic and the time to achieve bactericidal activity was 6.1 and 4.8 hours for R3804 and R4039, respectively. In contrast, vancomycin plus tobramycin was indifferent, and the difference of activity compared with ceftaroline plus tobramycin was statistically significant, with p-values of 0.001 for R3804 and 0.006 for R4039.

**Summary:**

Ceftaroline tested in combination with other antibacterial agents against individual representative bacterial strains using the checkerboard method demonstrated synergy (with meropenem and amikacin) and no observed interaction for all of the other organisms tested. Ceftaroline demonstrated synergy with meropenem against *S. aureus* strain 2296 (CA-MRSA) and *K. pneumoniae* strain (1468 ESBL). Synergy was also observed with amikacin against *E. coli* strain 2273 (ESBL) and *P. aeruginosa* strain 2559. It is important to note that no evidence of antagonism was observed between ceftaroline and the tested antimicrobial drug combinations with the strains tested.

**BACTERICIDAL ACTIVITY**

***Minimum Bactericidal Concentration (MBC)***

The bactericidal activities of ceftaroline were determined against Gram-negative and –positive bacteria. Studies were conducted in several independent laboratories and for the purpose of this review; the Minimum Bactericidal Concentration (MBC) was defined as the lowest concentration of antimicrobial agent that killed ≥ 99.9 % of the starting inoculum. The term “bactericidal” was defined as an MBC/MIC ratio of ≤ 4. A total of 172 Gram–negative and –positive isolates were tested by CLSI broth microdilution methods. The MBC for each organism was assessed by plating the broth from the MIC well, and from those wells up to three log<sub>2</sub> dilutions above the MIC, onto appropriate growth media and colony counts were compared to the starting inoculum. Table 52 compares the MBC to MIC. Of the isolates tested, 95% had a MBC/MIC ratio of ≤ 4.

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**Table 52 Ceftaroline Minimum Bactericidal Concentration Compared to Minimum Inhibitory Concentration**

Organism group (Number of isolates)	Occurrences at MBC/MIC ratio of:			
	1	2	4	> 4
<b>Staphylococcus aureus</b>				
MRSA (10)	6	3	0	1
MSSA (10)	9	1	0	0
hVISA (10)	7	2	0	1
<b>CoNS</b>				
MR (10)	8	2	0	0
MS (10)	8	2	0	0
<b>Streptococcus pneumoniae</b>				
PEN-S (21)	17	3	1	0
PEN-I (11)	7	2	1	1
PEN-R (50)	35	11	1	3
<b>viridans group streptococci</b>				
PEN-S (5)	5	0	0	0
PEN-R (5)	3	2	0	0
Enterobacteriaceae	12	3	3	2
QC strains (10)	6	2	1	1
Total (172)	123	33	7	9
Cumulative %	72	91	95	100

a *S. pneumoniae* penicillin breakpoints (µg/mL): ≤ 0.06 (PEN-S), 0.12-1 (PEN-I) and ≥ 2 (PEN-R), according to CLSI M100-S17, 2007

Abbreviations: CoNS = coagulase-negative staphylococci; hVISA = heterogeneous vancomycin-intermediate *S. aureus*; MBC = minimum bactericidal concentration; MIC = minimum inhibitory concentration; MR-CoNS = methicillin-resistant coagulase-negative staphylococcus; MRSA = methicillin-resistant *S. aureus*; MS-CoNS = methicillin-susceptible coagulase-negative staphylococcus; MSSA = methicillin-susceptible *S. aureus*; PEN-I = penicillin intermediate; PEN-R = penicillin resistant; PEN-S = penicillin susceptible. QC = quality control.

Source: Study P0903-M-001 Part II, 2004; Study P0903-M-005, 2006.

The result of the MIC<sub>90</sub> and the MBC<sub>90</sub> values for the isolates tested are summarized in Table 53.

**Table 53 MIC<sub>90</sub> and MBC<sub>90</sub> Values for Common Skin and Respiratory Pathogens**

Organism	Resistance	Number of isolates	MIC <sub>90</sub> (geometric mean)	MBC <sub>90</sub> (geometric mean)
<i>Staphylococcus aureus</i>	MSSA	10	0.25	0.25
	MRSA	10	2	2
	hVISA	10	1	2
CoNS	MS-CoNS	10	0.12	0.12
	MR-CoNS	10	0.5	0.5
<i>Streptococcus pneumoniae</i>	PSSP	11	0.015	0.015
	PISP	12	0.06	0.12
	PRSP	50	0.25	0.5
<i>Escherichia coli</i>	WT	5	(0.13)	(0.61)
<i>Klebsiella pneumoniae</i>	WT	5	(0.25)	(0.25)

Abbreviations: CoNS = coagulase-negative staphylococci; hVISA = heterogeneous vancomycin-intermediate *S. aureus*;

MBC<sub>90</sub> = minimum bacterial concentration to kill (≥ 3-log<sub>10</sub> decrease in viable counts) 90% of organisms;

MIC<sub>90</sub> = minimum inhibitory concentration to inhibit growth of 90% of organisms; MR-CoNS = methicillin-resistant coagulase-negative staphylococcus; MRSA = methicillin resistant *S. aureus*; MS-CoNS = methicillin-susceptible coagulase-negative staphylococcus; MSSA = methicillin-susceptible *S. aureus*; PISP = penicillin-intermediate *S. pneumoniae*; PRSP = penicillin-resistant *S. pneumoniae*; PSSP = penicillin-susceptible *S. pneumoniae*; WT = wild type.

Source: Study P0903-M-001 Part II, 2004; Study P0903-M-005, 2006.

Isolates with MBC/MIC ratios of > 4 included two of 30 isolates of *S. aureus*, two of 20 *Enterobacteriaceae* (The Applicant stated that isolates were one *E. coli* and one *S. marcescens*), three of 50 isolates of *S. pneumoniae* (all were PRSP) and one of 11 penicillin intermediate *S. pneumoniae*.

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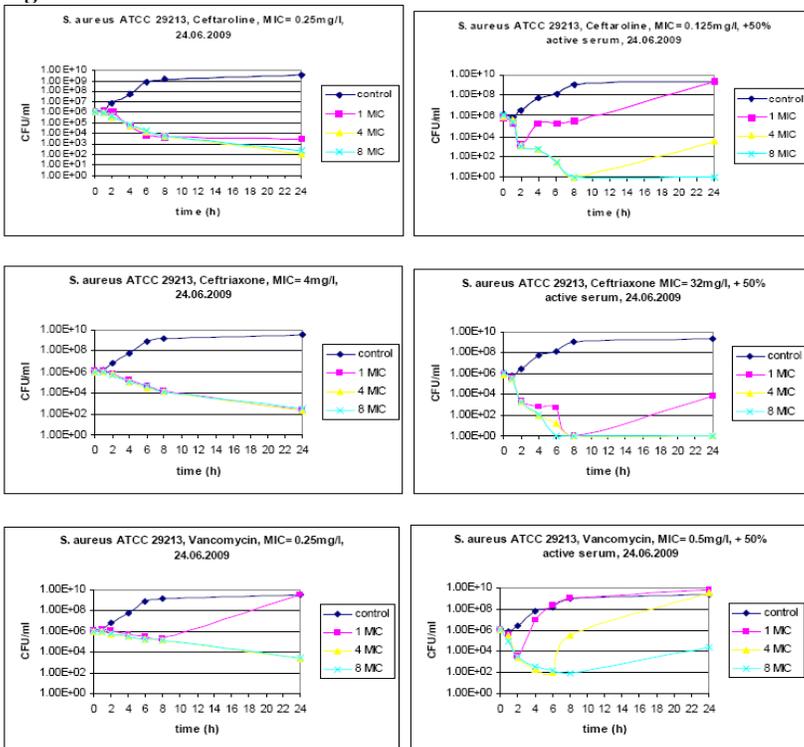
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***Time-kill Studies***

Ceftaroline demonstrated bactericidal activity against pathogens included in the proposed indication. In time-kill studies performed at multiples of MIC, ceftaroline was bactericidal versus *S. aureus*; *S. pneumoniae*; *E. coli* and *H. influenzae*. The bactericidal activity was not concentration dependent, and higher concentrations did not affect the speed or degree of killing effect. Moreover, ceftaroline was shown to demonstrate time-dependent killing, inline with what is expected for an antibiotic of the  $\beta$ -lactam class in which %T > MIC is the most important PK/PD parameter. Maximal rates of killing were generally seen at greater than or equal to two-times the MIC, with bactericidal effects ( $\geq 3$ -log<sub>10</sub> killing) occurring within 8 to 24 hours.

Additional studies were performed with isolates of *S. aureus*, *S. pneumoniae*, *H. influenzae*, *E. coli* and *K. pneumoniae* in the presence of human serum to determine if serum proteins affected the killing kinetics of ceftaroline. Tested isolates of *S. pneumoniae* and *H. influenzae* were not able to be grown in serum, possibly owing to serum sensitivity as a result of phase variation. Vancomycin and ceftriaxone were used as comparators. The presence of active serum enhanced the bactericidal activities of ceftaroline, vancomycin and to a lesser extent ceftriaxone, against staphylococcal isolates. Against *E. coli*, the effects of serum on killing by ceftaroline and ceftriaxone were not as pronounced. For *Klebsiella pneumoniae* ATCC 13182, which neither ceftaroline nor ceftriaxone were bactericidal in the absence of serum; however, the presence of serum increased the killing effect notably (Figure 8).

**Figure 8: Time-kill Curves for MSSA ATCC 29213 in 50% Active Serum**



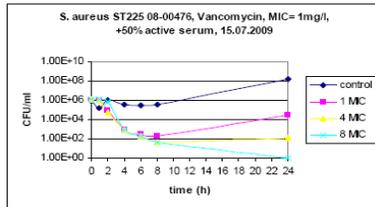
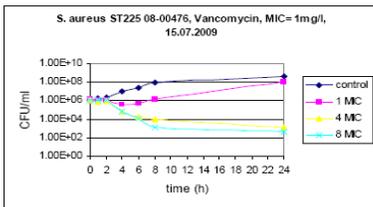
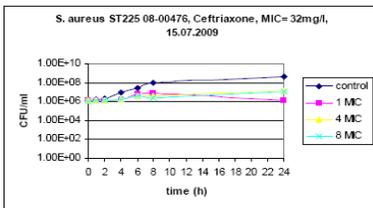
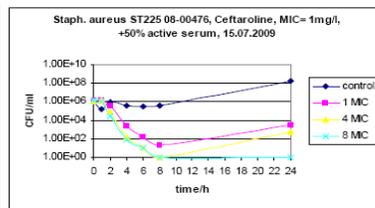
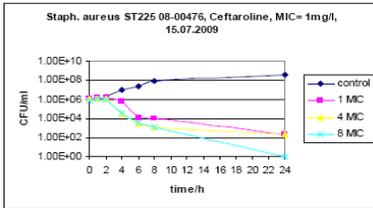
Abbreviations: ATCC = American Type Culture Collection; MIC = minimum inhibitory concentration; MSSA = methicillin-susceptible *S. aureus*.

Source: Study P903-M-062, 2009.

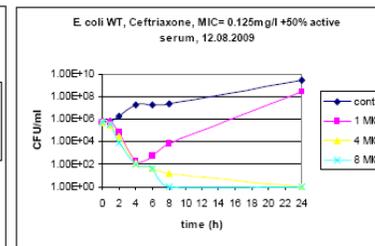
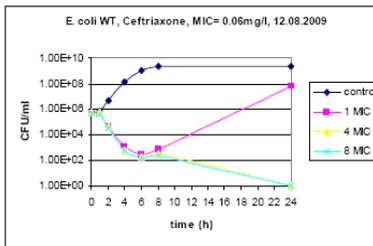
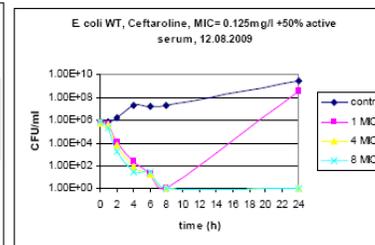
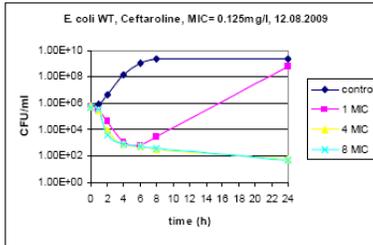
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Abbreviations: MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *S. aureus*.  
Source: Study P903-M-062, 2009.

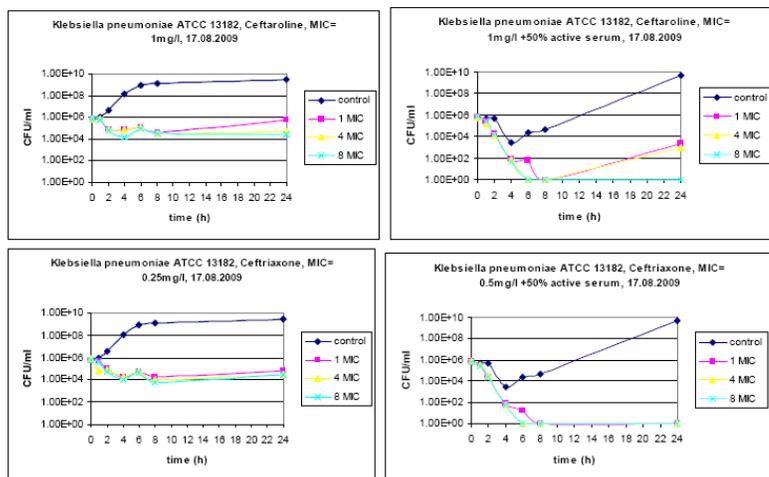


Abbreviations: MIC = minimum inhibitory concentration; WT = wild type.  
Source: Study P903-M-062, 2009

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Abbreviations: ATCC = American Type Culture Collection; MIC = minimum inhibitory concentration.  
Source: Study P903-M-062, 2009

## Summary and conclusion:

A common method for the estimation of the potential activity of an antibiotic is to compare the MICs of the bacteria with the achievable antibiotic concentration. Factors such as inoculum size, test medium, pharmacologic response, post antibiotic effect and pharmacokinetic properties of the antibiotic can affect the achievable antibiotic concentrations. Moreover, highly protein bound antibiotics may have minimal bactericidal activity despite good MICs or MBCs. Therefore, the measurement of bacterial activity in the presence of serum against becomes a useful predictor of antibacterial effect in vitro. Generally, ceftaroline demonstrated low protein binding and would theoretically be more efficacious than a drug with higher protein binding affinity. Time-kill and post-antibiotic effect studies are used to predict in vivo efficacy. The time kill studies were used to analyze the effects of fixed concentrations of ceftaroline on the killing of clinically relevant isolates over time. Ceftaroline displayed time dependent killing where the rate of killing was not significantly affected by concentration.

The data from the time-kill kinetic studies support a claim of bactericidal activity of ceftaroline against a variety of Gram negative and Gram positive isolates. Ceftaroline was bactericidal at greater than or equal to two-times the MIC values with bactericidal effects ( $\geq 3\text{-log}_{10}$  killing) occurring within 8-24 hours.

## SUSCEPTIBILITY TEST METHODS

### CEFTAROLINE TESTING PROCEDURES:

The Applicant evaluated the activity of ceftaroline by a variety of CLSI antimicrobial susceptibility test methods including broth microdilution, disk diffusion and agar dilution. Inoculum were prepared for MRSA by microdilution broth or by dilution in agar supplemented by 2% NaCl with 24 hour incubation at 35°C. Isolates with a MIC  $\geq$  are therefore considered resistant or probably possess a *mecA* gene. *Streptococcus pneumoniae* and other *Streptococcus* spp. were tested using the broth dilution method with cation-adjusted Mueller-Hinton broth (CA-MHB) and lysed horse blood (LHB) (2% to 5% v/v). The inoculum was prepared by direct colony

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suspension, equivalent to a 0.5 McFarland Standard. The microtiter plates were incubated at  $35^{\circ}\text{C} \pm 2^{\circ}\text{C}$  in ambient air for 20 to 24 hours. *Haemophilus* species were tested for their susceptibility to ceftaroline in *Haemophilus* Test Medium (HTM) broth.

The inoculum was prepared by direct colony suspension, equivalent to a 0.5 McFarland Standard. The plates were incubated at  $35^{\circ}\text{C} \pm 2^{\circ}\text{C}$  in ambient air for 20 to 24 hours. *Staphylococcus* species were tested for their susceptibility to ceftaroline in CAMHB. The inoculum was prepared by direct colony suspension, equivalent to a 0.5 McFarland Standard. The plates were incubated at  $35^{\circ}\text{C} \pm 2^{\circ}\text{C}$  in ambient air for 16 to 24 hours. *Enterobacteriaceae* were tested for their susceptibility to ceftaroline in CA-MHB. The inoculum was prepared by direct colony suspension, equivalent to a 0.5 McFarland Standard. The plates were incubated at  $35^{\circ}\text{C} \pm 2^{\circ}\text{C}$  in ambient air for 16 to 24 hours. Anaerobic isolates were tested for their susceptibility to ceftaroline in accordance with CLSI document M11-A7 (CLSI M11-A7, 2007) using agar dilution.

Before carrying out disk diffusion determinations, the Applicant would perform a disk content study using six organisms to determine optimal disk loading to achieve zones of inhibition that best correlate with the MIC from broth microdilution. It was determined that the 10- $\mu\text{g}$  disk would provide ideal test conditions for susceptible and intermediate MIC breakpoints of 1 to 4 mcg/mL/mL, while the 30- $\mu\text{g}$  disk could be used for breakpoints over the 1 to 16 mcg/mL/mL interval. However, a disk content of 30- $\mu\text{g}$  disk was selected to account for all breakpoints over 1 mcg/mL. All disk diffusion testing methods were conducted in accordance with CLSI guidelines (CLSI M2-A9, 2006) using 30- $\mu\text{g}$  disks from various commercial vendors. Growth media used were un-supplemented MHA for aerobic and facultative anaerobes, MHA+ 5% sheep blood for *Streptococci* or HTM agar for *Haemophilus*.

#### **METHODS FOR DETECTING RESISTANT ORGANISMS:**

Table 54 compares ceftaroline activity tracked in US and international surveillance isolates from 2004 to 2008 to detect if resistance patterns changed during this time. MICs from 1,478 strains, isolated from human infections from 2002 to 2004 from an international surveillance program, were used as baseline. Recent clinical isolates were obtained for comparison from patients (primarily in the US) from surveillance during 2007 to 2008. Sources of infection were bloodstream, skin and soft tissue, respiratory and patients hospitalized from pneumonia. Resistance phenotypes were determined by reference broth microdilution tests followed by confirmatory techniques that included CLSI M100-S18 criteria. PCR screens with mechanism-specific primer sets were also performed on certain strains with unusual resistance patterns.

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**Table 54 Ceftaroline Activity Tracked in USA and International Surveillance Isolates from 2004 to 2008 for Changes in Resistance**

Pathogen	Study P0903-M-001(Part I), 2004				Study P903-M-053, 2009			
	N	Range	Ceftaroline MIC, $\mu\text{g}/\text{mL}$		N	Range	Ceftaroline MIC, $\mu\text{g}/\text{mL}$	
			MIC <sub>20</sub>	MIC <sub>90</sub>			MIC <sub>20</sub>	MIC <sub>90</sub>
<i>Staphylococcus aureus</i>								
methicillin-susceptible	73	0.03 - 0.5	0.25	0.25	102	0.03 - 0.5	0.25	0.25
methicillin-resistant	102	0.12 - 2	1	2	105	0.5 - 2	0.5	1
Coagulase-negative staphylococci								
<i>S. epidermidis</i> methicillin-susceptible	50	$\leq 0.016 - 0.5$	0.06	0.25	100	$\leq 0.008 - 1$	0.06	0.12
<i>S. epidermidis</i> methicillin-resistant	80	$\leq 0.016 - 2$	0.25	0.5	100	0.12 - 1	0.5	0.5
<i>Streptococcus pneumoniae</i>								
Penicillin-susceptible (MIC $\leq 0.06 \mu\text{g}/\text{mL}$ )	33	$\leq 0.016 - 0.06$	$\leq 0.016$	$\leq 0.016$	102	$\leq 0.008 - 0.06$	$\leq 0.008$	0.03
Penicillin-intermediate (MIC 0.12 - 1 $\mu\text{g}/\text{mL}$ )	53	$\leq 0.016 - 0.12$	0.03	0.06	102	$\leq 0.008 - 0.12$	0.03	0.06
Penicillin-resistant (MIC $\geq 2 \mu\text{g}/\text{mL}$ )	50	0.06 - 0.5	0.12	0.25	100	0.03 - 0.5	0.12	0.25
Penicillin-resistant (MIC $\geq 8 \mu\text{g}/\text{mL}$ )	ND	ND	ND	ND	40	0.06 - 0.5	0.25	0.5
Multidrug-resistant	23	0.12 - 0.5	0.12	0.25	127	$\leq 0.008 - 0.5$	0.12	0.25
<i>Escherichia coli</i> (not ESBL)	20	$\leq 0.016 - 0.25$	0.06	0.12	102	0.015 - 8	0.12	0.25
<i>Klebsiella pneumoniae</i>	21	0.03 - 4	0.06	0.5	102	0.015 - 1	0.06	0.5
<i>Haemophilus influenzae</i>								
$\beta$ -lactamase negative	23	$\leq 0.016$	$\leq 0.016$	$\leq 0.016$	110	$\leq 0.008 - 0.25$	$\leq 0.008$	0.015
$\beta$ -lactamase positive	24	$\leq 0.016 - 0.25$	$\leq 0.016$	$\leq 0.016$	101	$\leq 0.008 - 0.12$	$\leq 0.008$	0.03
BLNAR	30	$\leq 0.016 - 0.03$	$\leq 0.016$	0.03	104	$\leq 0.008 - 0.25$	0.06	0.12

Abbreviations: BLNAR =  $\beta$ -lactamase-negative ampicillin-resistant; ESBL = extended-spectrum  $\beta$ -lactamase; MIC = minimum inhibitory concentration; MIC<sub>50</sub> = minimum inhibitory concentration required to inhibit 50% of the organisms; MIC<sub>90</sub> = minimum inhibitory concentration required to inhibit 90% of the organisms; ND = not determined.

Source: Study P0903-M-001 (Part I), 2004; P903-M-053, 2009.

**COMPARISON OF AGAR AND BROTH DILUTION METHODS:**

The Applicant compared ceftaroline broth microdilution MICs to those of agar dilution, the distribution of MICs and the cumulative percent inhibited was very similar when testing the same isolates. The results are in Table 55.

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**Table 55: MIC Broth Dilution versus Agar Dilution Cumulative Percent Inhibited**

Species	MIC, µg/ml	MIC Broth		Agar Dilution	
		MIC Frequency	Cumulative % inhibited	MIC Frequency	Cumulative % inhibited
All Staphylococcal Strains Combined	0.03	-	-	1	1
	0.06	8	7.6	7	7.7
	0.12	9	16.2	8	15.4
	0.25	34	48.6	43	56.7
	0.5	51	97.1	45	100
	1	3	100		
<i>S. aureus</i>	0.12	9	10.6	7	8.2
	0.25	31	47.1	33	47.1
	0.5	42	96.5	45	100
	1	3	100	-	-
	≤ 0.008	25	24.5	25	24.2
All Streptococcal Strains Combined	0.15	23	47.1	22	46.5
	0.3	7	53.9	14	60.6
	0.6	15	68.6	9	69.7
	0.12	11	79.4	14	83.8
	0.25	19	98.0	15	99
	0.5	2	100	1	100
	≤ 0.008	12	16.2	14	18.9
<i>S. pneumoniae</i>	0.15	8	27	7	28.4
	0.3	7	36.5	14	47.3
	0.6	15	56.8	9	59.5
	0.12	11	71.6	14	78.4
	0.25	19	97.3	15	98.6
	0.5	2	100	1	100
	≤ 0.008	61	52.1	55	46.6
<i>H. influenzae</i>	0.015	20	70.9	36	77.1
	0.03	10	79.5	9	84.7
	0.06	8	86.3	18	100
	0.12	14	98.3	-	-
	0.25	2	100	1	100
Species	MIC, µg/ml	MIC Broth		Agar Dilution	
		MIC Frequency	Cumulative % inhibited	MIC Frequency	Cumulative % inhibited
<i>Enterobacteriaceae</i>	0.25	2	100		
	0.03	2	1.3	2	1.3
	0.06	23	16.6	27	19.3
	0.12	25	33.1	23	34.7
	0.25	18	45.0	20	48.0
	0.5	10	51.7	10	54.7
	1	13	60.3	7	59.3
	2	3	62.3	9	65.3
	4	2	63.6	4	68.0
	8	3	65.6	4	70.7
	16	3	67.5	4	73.3
	32	3	69.5	12	81.3
	64	6	73.5	13	90.0
	> 64	40	100	15	100

Abbreviations: MIC = minimum inhibitory concentration  
Source: Study P903-M-075, 2009.

Figure 9 shows the direct comparisons of individual MICs and the correlation between broth microdilution and agar dilution against all staphylococci isolates tested (Study P903-M-075, 2009). For all isolates tested, the agreement of individual MICs between the two methods was in excess of 98%.

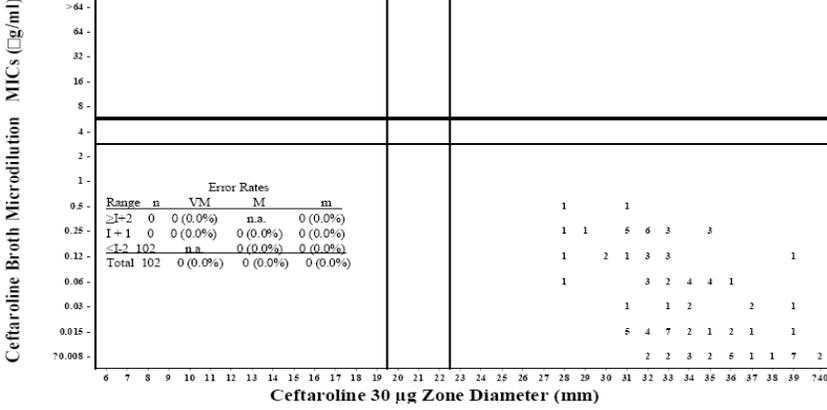


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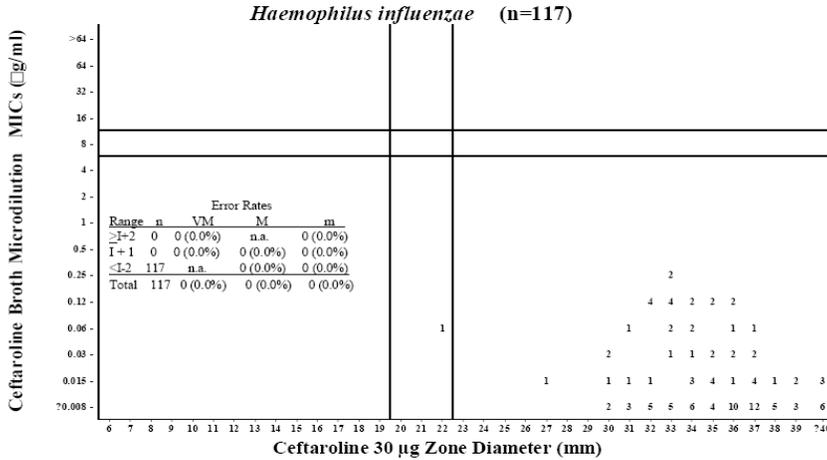
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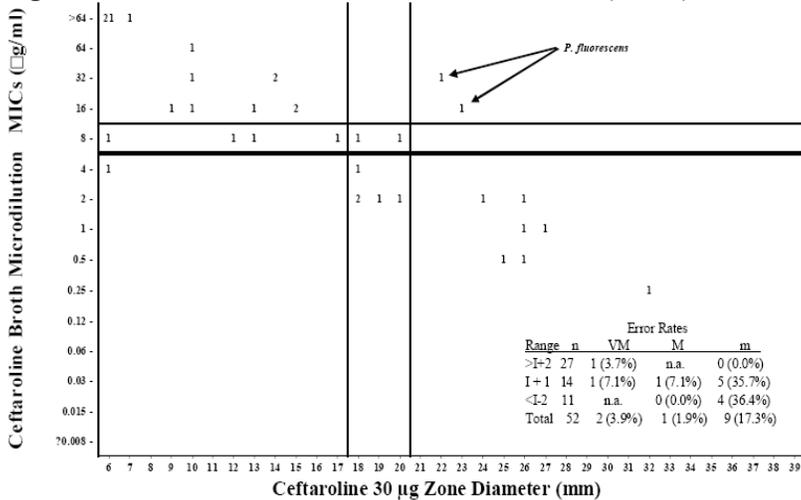
**Figure 10b: All Streptococcal Strains Combined (n = 102)**



**Figure 10c: Haemophilus influenzae**



**Figure 10d: All Non-fermentative Strains Combined (n = 52)**

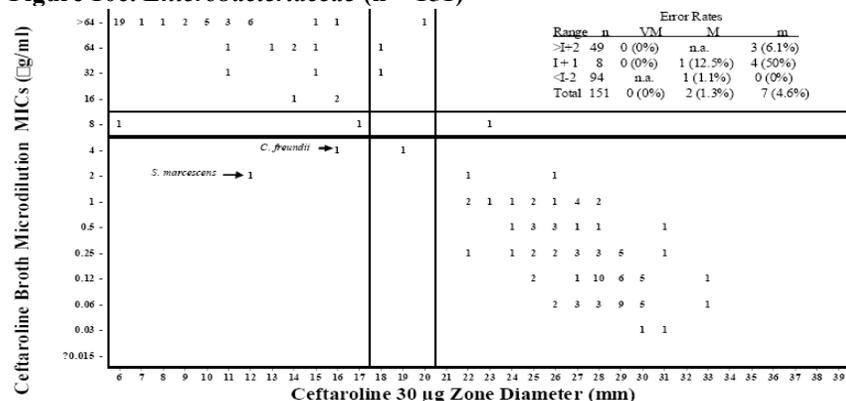


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**Figure 10c: *Enterobacteriaceae* (n = 151)**



**Summary and conclusion:**

The data presented above were analyzed by the error bounded method and indicate good correlation between MIC and zone diameters for staphylococcal, streptococcal, and *Haemophilus influenzae*.

A false susceptible rate of 3.9% was observed against non-fermentative organisms, and the Applicant alluded that this high rate was due primarily to the low number of organisms tested and the fact that pseudomonas isolates (other than *P. aeruginosa*) were tested by the disk method. Please note that the CLSI recommend testing at least 100 or more clinical isolates, and in this case, only 52 isolates were tested.

Proposing breakpoints for ceftaroline versus *Enterobacteriaceae* can be problematic due to the presence of ESBLs and AmpC. This may lead to high error rates for cephalosporin and ceftaroline is no exception. For the *Enterobacteriaceae* the false-susceptible rate (very major discrepancies) was kept to a minimum at 0%. All intermediate areas (minor errors) with the exception of moderately susceptible amounted to a sum of 4.6%, which is below the CLSI limit of  $\leq 5\%$ . However, the false-resistant, or major discrepancies, was at 12.5%; the CLSI allowable limit is  $< 10\%$ . These were the percentage of isolates with MICs in the range of one two-fold concentration above the intermediate MIC (I+1). The minor discrepancies, where one of the test results is intermediate and the other is susceptible were also above the CLSI allowable limit. A value of 6.1% was obtained for MICs that were more than two-fold concentrations above ( $>I+2$ ) the intermediate MIC. The Applicant stated that this high discrepancy was a result of ESBL producing isolates, which are recognized by CLSI as being a problem for MIC testing.

***Equivalency between Commercially Prepared Dried MIC plate Compared to CLSI broth microdilution reference method***

The Applicant performed equivalency test between TREK dried Sensititre 18- to 24-hour susceptibility to the CLSI broth microdilution reference method (CLSI M7-A7, 2006) using 200 challenge and clinical isolates (Table 56). Standard ATCC QC strains were used daily for testing.

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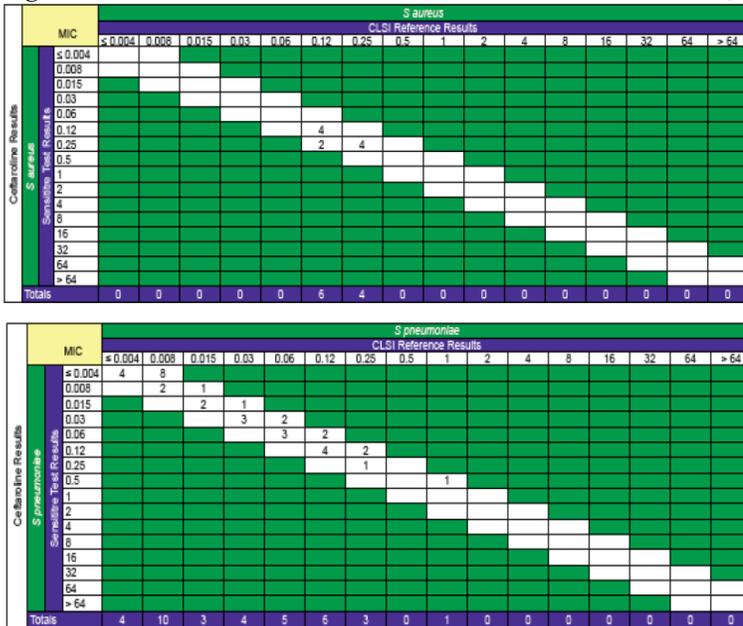
**Table 56: 200 Clinical and Challenge Isolates Tested in TREK Dried Sensititre Plates**

Organisms	Number Tested
<i>Streptococcus pneumoniae</i>	36
Groups A and B β-hemolytic streptococci	22
<i>Staphylococcus aureus</i>	10
<i>Staphylococcus epidermidis</i>	4
<i>Staphylococcus saprophyticus</i>	1
<i>Enterococcus faecalis</i>	8
<i>Haemophilus influenzae</i>	23
<i>Escherichia coli</i>	23
<i>Enterobacter aerogenes</i>	11
<i>Enterobacter agglomerans</i>	1
<i>Enterobacter cloacae</i>	11
<i>Proteus mirabilis</i>	10
<i>Proteus vulgaris</i>	5
<i>Serratia marcescens</i>	4
<i>Klebsiella pneumoniae</i>	24
<i>Klebsiella oxytoca</i>	4
<i>Morganella morganii</i>	1
<i>Providencia rettgeri</i>	1
<i>Providencia stuartii</i>	1

Source: Study P0903-M-048, 2007

Figure 11 shows the MIC distribution using both methods on the same isolates plotted for *S. aureus*, and *S. pneumoniae*. Figure 12 shows *E. coli* and *H. influenzae*, For *S. aureus*, 8 out of 10 isolates were in agreement. For *S. pneumoniae*, 51.4% (18/36) of the MICs were in absolute agreement and 48.6% (17/36) of the MICs were one dilution lower for the dried panel relative to the CLSI reference panel. For *E. coli*, 56.5% (13/23) of the MICs were in agreement and 43.4% (10/23) of the MICs were one dilution higher. For *H. influenzae*, 26% (6/23) of the MICs were in absolute agreement, and 74% (17/23) were one dilution higher.

**Figure 11: MIC Distribution for Ceftaroline vs. Gram Positive QC Isolates for Trek Dried Panels vs. Frozen Reference Panels**

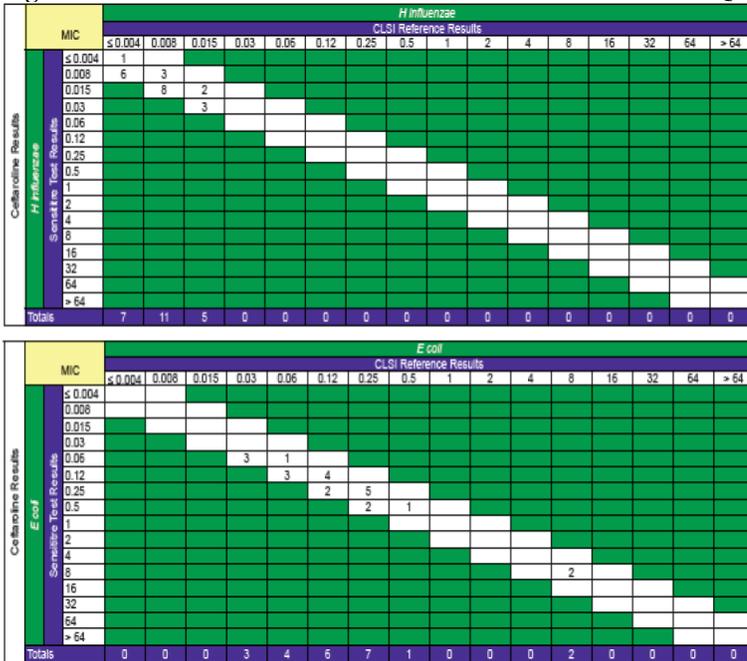


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**Figure 12: MIC Distribution for Ceftaroline vs. Gram Positive QC Isolates for Trek Dried Panels vs. Frozen Reference Panels**



Reproducibility testing on 10 strains, including the CLSI, ATCC, and QC isolates, was performed in triplicate on 3 separate days (Table 57). This testing generated 90 values that did not demonstrate greater than  $\pm 1$  well variation ( $\le 10\%$ ).

**Table 57: Reproducibility; TREK Sensititre Test Results for Ceftaroline in Triplicate on 3 Days**

Organism	Day 1			Day 2			Day 3			Mode
	A	B	C	A	B	C	A	B	C	
<i>S. aureus</i>	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
<i>E. coli</i>	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12
<i>H. influenzae</i>	0.06	0.12	0.06	0.06	0.06	0.06	0.12	0.12	0.12	0.06
<i>S. pneumoniae</i>	0.03	0.03	0.03	0.03	0.015	0.015	0.015	0.03	0.03	0.03
<i>S. aureus</i>	0.12	0.25	0.12	0.25	0.25	0.25	0.25	0.25	0.25	0.25
<i>S. epidermidis</i>	0.25	0.25	0.25	0.25	0.25	0.25	0.5	0.5	0.5	0.5
<i>E. coli</i>	0.25	0.25	0.25	0.5	0.5	0.5	0.25	0.5	0.25	0.25
<i>H. influenzae</i>	0.008	0.008	0.008	0.008	0.008	0.008	0.008	0.008	0.008	0.008
<i>S. pneumoniae</i>	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Group B streptococci	0.03	0.015	0.015	0.015	0.015	0.03	0.015	0.015	0.015	0.015

Source: Study P0903-M-048, 2007.

**Quality Control Parameters**

The Applicant developed QC limits for aerobic microdilution and disk diffusion susceptibility tests of ceftaroline. Studies conducted at the (b) (4) (Study P0903-M-007/008, 2006). The aerobic QC limits were reviewed and approved by the CLSI in June 2006. The study was conducted across 8 laboratories in accordance with CLSI document M23-A2 (CLSI M23-A2, 2001). A collaborative study was

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undertaken to define QC parameters for broth microdilution and disk diffusion susceptibility tests. Cefotaxime was used as the control drug for the MIC portion of the study.

Broth microdilution trays were prepared to contain log<sub>2</sub> dilutions of ceftaroline diluted in each of three (3) different lots of CAMHB, CAMHB + 3% LHB, or HTM. Serial dilutions of cefotaxime were prepared in one lot of the same media. The following lots of dehydrated MHB base were selected and prepared at a common source as CAMHB, CAMHB + LHB, or HTM. All laboratories studied all three manufacturer lots: (b) (4). The primary control drug, cefotaxime, and two additional control drugs were used for testing *Haemophilus* only: Quinupristin/dalfopristin and cefuroxime.

Disk diffusion plates containing plain MHA, MHA + 5% sheep blood or HTM were purchased as prepared media from three different plate manufacturers and distributed to each laboratory for use. All lots of media were tested in all laboratories for each phase of testing. Two lots of 30-µg ceftaroline disks (b) (4) Lot#441796 and (b) (4) Lot#191110), and one lot of 30-µg cefotaxime disks (b) (4) Lot#5239329) were tested at each site.

On each of ten separate days, each of the control strains was inoculated into microbroth dilution MIC trays, providing 3 ceftaroline MICs, and 1 control drug MIC. Three lots of agar disk diffusion media were also tested at each site. Control limits for ceftaroline disk tests were estimated. MIC limits were selected to include the mode ±1 doubling concentration. Samples from broth microdilution trays were tested for colony counts by all participants throughout the study and are listed in Table 58.

**Table 58 Broth Microdilution Colony Counts**

Control Strain/ (No. of Determinations)	CFU/mL (Min - Max)	Median CFU/mL
<i>Escherichia coli</i> ATCC 25922 (23)	2.0 × 10 <sup>4</sup> - 7.9 × 10 <sup>5</sup>	3.7 × 10 <sup>5</sup>
<i>Staphylococcus aureus</i> ATCC 29213 (35)	5.8 × 10 <sup>4</sup> - 2.0 × 10 <sup>6</sup>	4.6 × 10 <sup>5</sup>
<i>Streptococcus pneumoniae</i> ATCC 49619 (25)	1.0 × 10 <sup>4</sup> - 1.0 × 10 <sup>6</sup>	3.0 × 10 <sup>5</sup>
<i>Haemophilus influenzae</i> ATCC 49247 (24)	3.0 × 10 <sup>4</sup> - 1.0 × 10 <sup>6</sup>	6.5 × 10 <sup>5</sup>
<i>Haemophilus influenzae</i> ATCC 49766 (22)	2.4 × 10 <sup>4</sup> - 1.4 × 10 <sup>6</sup>	7.0 × 10 <sup>5</sup>

Abbreviations: ATCC = American Type Culture Collection; Min = minimum; Max = maximum.  
Source: Study P0903-M-007/008, 2006

Table 59 shows the QC limits for susceptibility test for ceftaroline MIC (in CAMHB, CAMHB+LHB, or HTM and 30-µg disks on either plain MHA or MHA+ 5% sheep blood, or HTM agar).

**Table 59 Quality Control Limits (% Included)**

Control Strain	MIC QC Ranges, µg/mL, (% in Range) <sup>a</sup>	Zone Diameter QC Ranges, mm, (% in Range) <sup>a</sup>
<i>Escherichia coli</i> ATCC 25922	0.03 - 0.12 (100%)	26 - 34 (96.6%)
<i>Staphylococcus aureus</i> ATCC 29213	0.12 - 0.5 (100%)	NA
<i>Staphylococcus aureus</i> ATCC 25923	NA	26 - 35 (95.2%) or 26 - 36% (97.5%)
<i>Streptococcus pneumoniae</i> ATCC 49619	0.008 - 0.03 (100%)	31 - 41 (97.7%)
<i>Haemophilus influenzae</i> ATCC 49247	0.03 - 0.12 (100%)	29 - 39 (95.1%)
<i>Haemophilus influenzae</i> ATCC 49766	≤ 0.008 (94.6%) or No Range Recommended	ND

a (%) denotes the % MICs or Zones within the proposed quality control ranges.  
Abbreviations: ATCC = American Type Culture Collection; MIC = minimum inhibitory concentration; Min = minimum; Max = maximum; NA = not applicable; ND = not done; QC = quality control.  
Source: Study P0903-M-007/008, 2006

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***Quality Control Parameters for Anaerobic Microdilution and Agar Dilution Susceptibility Tests***

The Applicant presented broth microdilution and agar dilution QC parameters for anaerobic susceptibility tests. Cefoxitin and meropenem were used as controls. Studies were conducted across 8 laboratories using CLSI guidelines. Colony counts from broth microdilution trays were tested for colony counts by all participants throughout the study and are listed in Table 60.

**Table 60 Anaerobic Broth Microdilution Colony Counts**

<i>Control Strain/ (No. of Determinations)</i>	<i>CFU/mL (Min - Max)</i>	<i>Median CFU/mL</i>
<i>Bacteroides fragilis ATCC 25285 (52)</i>	$1.1 \times 10^2 - 5.9 \times 10^8$	$1.4 \times 10^8$
<i>Bacteroides thetaiotaomicron ATCC 29741 (49)</i>	$1.2 \times 10^2 - 9.4 \times 10^9$	$1.1 \times 10^8$
<i>Eubacterium lentum ATCC 43055 (49)</i>	$6.1 \times 10^1 - 4.0 \times 10^6$	$3.2 \times 10^7$
<i>Clostridium difficile ATCC 700057 (49)</i>	$3.0 \times 10^4 - 1.0 \times 10^8$	$7.6 \times 10^6$

Abbreviations: ATCC = American Type Culture Collection; CFU = colony-forming units; Max = maximum; Min = minimum.  
Source: Study P0903-M-040, 2008.

QC limits for anaerobic susceptibility tests of ceftaroline MICs in supplemented Brucella broth microdilution and agar dilution are listed in Table 61. The Applicant noted that significant lot-to-lot variability in MIC determinations in MHB media was not observed with any of the broth media or agar media. The mode for each lot was essentially the same.

**Table 61 Tentative Anaerobic Quality Control Limits (% Included)**

<i>Quality Control Strain</i>	<i>Broth Microdilution MIC Range, µg/mL, (% in Range)<sup>a</sup></i>	<i>Agar Dilution MIC Range, µg/mL, (% in Range)<sup>a</sup></i>
<i>Bacteroides fragilis ATCC 25285</i>	2 - 16 (96.9%)	4 - 32 (96.0%)
<i>Bacteroides thetaiotaomicron ATCC 29741</i>	8 - 64 (97.6%)	16 - 128 (100%)
<i>Eubacterium lentum ATCC 43055</i>	NR	8 - 32 (100%)
<i>Clostridium difficile ATCC 700057</i>	0.5 - 4 (99.1%)	2 - 16 (99.8%)

<sup>a</sup> (%) denotes the % of MICs included within the proposed quality control ranges  
Abbreviations: ATCC = American Type Culture Collection; NR = no range.  
Source: Study P0903-M-040, 2008.

**HUMAN AND ANIMAL STUDIES**

**Human Pharmacokinetics:**

Single and multiple dose phase 1 studies demonstrated that ceftaroline fosamil (prodrug) is rapidly converted in plasma to active ceftaroline following IV infusion. Maximum plasma concentration (C<sub>max</sub>) and area under the plasma concentration-time curve (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 every 24 hours (q24h) multiple-dose regimens. A summary of the pharmacokinetic parameters in single and multiple dose studies in healthy subjects is presented in Table 62.

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**Table 62: Summary (Mean ± SD) of Ceftaroline Pharmacokinetic Parameters in Single- and Multiple-Dose Studies in Healthy Subjects**

Study Report No.	Objective	Study Design	Route of Administration	Ceftaroline Fosamil Dose <sup>a</sup>	No. of Subjects (M/F) Mean Age (Range)	C <sub>max</sub> , ng/mL	T <sub>max</sub> <sup>b</sup> , h	AUC <sub>0-24</sub> or AUC <sub>0-12</sub> , ng•h/mL	T <sub>1/2</sub> , h	CL/F <sub>m</sub> <sup>c</sup> , mL/h	CL <sub>R</sub> , mL/h	Report Location
P903-01	To determine the safety and PK profile of ceftaroline when administered IV to healthy adult subjects for up to 14 days	Single- and multiple-ascending dose, placebo-controlled	IV infusion over 1 hour	50 mg	72 healthy male subjects 26.2 years (19-54)	1509.7 ± 251.1	0.92 (0.90-1.08)	3953.6 ± 733.9	2.03 ± 0.15	11528.0 ± 2332.7	5618.0 ± 1502.0	5.3.3.1
				100 mg		3078.8 ± 963.6	0.92 (0.92-1.10)	6724.0 ± 1674.3	2.23 ± 0.42	13733.0 ± 2944.5	5772.0 ± 1777.9	
				250 mg		10046.7 ± 1677.3	0.92 (0.92-1.25)	23406.3 ± 5379.9	2.33 ± 0.26	9874.0 ± 2349.4	4645.0 ± 1664.7	
				500 mg		16639.3 ± 2107.3	1.08 (0.92-1.08)	44821.4 ± 2858.5	2.53 ± 0.28	9886.0 ± 633.1	5611.0 ± 862.8	
				750 mg		23383.0 ± 4917.9	1.0 (0.92-1.08)	57600.2 ± 9752.9	2.62 ± 0.29	11787.0 ± 2067.0	6453.0 ± 1609.8	
				1000 mg		30494.5 ± 4318.0	0.92 (0.92-1.02)	80888.82 ± 8631.9	2.90 ± 0.14	11022.0 ± 1173.3	7842.0 ± 1278.0	
				300 mg q12h, 14 days		8548.5 ± 1853.2	0.92 (0.92-1.08)	24318.4 ± 3660.2	2.62 ± 0.41	11096.0 ± 1615.1	4520.0 ± 1192.7	
				600 mg q12h, 14 days		21329.8 ± 4104.5	0.92 (0.92-1.08)	56246.8 ± 8901.5	2.66 ± 0.40	9604.0 ± 1396.8	7133.0 ± 4366.9	
				800 mg q24h, 7 days		31508.3 ± 2392.14	1.08 (0.92-1.08)	74151.4 ± 14223.6	2.63 ± 0.24	9860.0 ± 2110.5	3967 ± 1211.6	
P903-05	Assess the effects of a single supratherapeutic IV dose of ceftaroline fosamil versus placebo on the QTc interval in healthy adult subjects	Randomized (stratified by gender), double-blind, placebo-controlled, 3-period crossover study	IV infusion over 1 hour	1500 mg	54 healthy subjects (53 in PK population) 27M/27F 27.3 years (18-45)	81391.2 ± 12456.9	0.98 (0.98-1.30)	204639.6 ± 28233.1	2.59 ± 0.31	6592.88 ± 908.15	NA	5.3.4.1
P903-13	To determine the rates and routes of elimination of radioactivity after IV administration of [ <sup>14</sup> C] ceftaroline fosamil and to characterize and identify the metabolites of ceftaroline fosamil in plasma and excreta	Open-label, single-dose study	IV infusion over 1 hour	600 mg	6 healthy male subjects 31.3 years (23-45)	27352.2 ± 2845.2	0.98 (0.95-1.08)	64217.7 ± 6379.1	2.60 ± 0.46	8679.5 ± 875.5	5555.6 ± 198.0	5.3.3.1
P903-14	To assess the effect of ceftaroline on the intestinal microflora of healthy subjects	Open-label, multiple-dose study	IV infusion over 1 hour	600 mg q12h for 7 days	12 healthy subjects 6M/6F 24.7 years (20-41)	22674.1 ± 3668.3	1.03 (0.98-1.10)	61332.6 ± 9163.3	2.00 ± 0.21	8679.9 ± 1326.1	NA	5.3.4.1
P903-17	To determine the safety, tolerability, and PK profile of single and multiple doses of ceftaroline fosamil administered by IM injection in healthy adult subjects.	This study was a 2-part, randomized, parallel-group study. Part A was an open-label, single dose study. Part B was a double-blind, multiple-dose study	Intramuscular (IM) injection or IV infusion over 1 hour	400 mg IM (228 mg/mL)	24 healthy subjects 17M/7F 27.4 years (19-44)	6971.16 ± 1616.26	1.5 (1.0-2.0)	35610.50 ± 6130.81	2.36 ± 0.22	NA	6636.45 ± 1414.73	5.3.3.1
				600 mg IM (165 mg/mL)		14650.55 ± 3299.18	2.0 (1.0-2.0)	73826.02 ± 12030.89	2.27 ± 0.16	NA	5092.32 ± 761.35	
				600 mg IM (228 mg/mL)		8509.95 ± 1691.20	2.0 (1.0-2.0)	48108.15 ± 3845.96	2.55 ± 0.49	NA	6851.64 ± 1621.38	
				600 mg IV		19684.69 ± 2263.84	0.98 (0.98-0.98)	44987.13 ± 5041.33	2.13 ± 0.31	11895.14 ± 1269.71	6460.11 ± 1977.65	
				1000 mg IM (228 mg/mL)		15996.94 ± 3738.82	2.0 (1.0-2.0)	110265.36 ± 31,282.80	2.68 ± 0.31	NA	5380.87 ± 1258.15	
				600 mg IM (228 mg/mL) q12h, 5 days		12960.27 ± 1360.85	2.0 (1.0-2.02)	65407.4 ± 11807.4	2.51 ± 0.45	NA	5711.9 ± 1257.7	

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Study Report No.	Objective	Study Design	Route of Administration	Ceftaroline Fosamil Dose <sup>a</sup>	No. of Subjects (M/F) Mean Age (Range)	C <sub>max</sub> ng/mL	T <sub>max</sub> <sup>b</sup> , h	AUC <sub>0-∞</sub> or AUC <sub>0-t</sub> ng·h/mL	T <sub>1/2</sub> , h	CL/F <sub>m</sub> <sup>c</sup> , mL/h	CL <sub>R</sub> , mL/h	Report Location
P903-20	To determine the safety, tolerability, and PK profile of single (Part A) and multiple (Part B) doses of IV ceftaroline fosamil in healthy adult subjects	Two-part, randomized, double-blind, placebo-controlled study	IV infusion over 1 hour	1500 mg	20 healthy subjects (16 received ceftaroline fosamil)	80671.5 ± 10848.1	1.0 (0.98-1.13)	191203.8 ± 24749.6	2.68 ± 0.28	7031.5 ± 927.5	4234.5 ± 731.2	5.3.3.1
				2000 mg	8M/12F 29.5 years (18-41)	105584.9 ± 21114.1	1.03 (0.98-1.08)	247599.4 ± 40977.9	2.45 ± 0.40	6933.8 ± 1146.9	4286.5 ± 858.2	
				600 mg q8h, 10 days	10 healthy subjects (8 received ceftaroline fosamil) 5M/5F 30.6 years (18-44)	29936.0 ± 5424.0	1.07 (1.02-1.13)	84202.5 ± 19042.6	2.78 ± 0.65	6548.3 ± 1539	4387.6 ± 900	

a For multiple-dose cohorts, PK parameters following the last dose are reported.

b Median (minimum-maximum).

c Reported as CL in study reports for studies P903-05, P903-13, P903-14, P903-17, and P903-20.

AUC<sub>0-∞</sub> = area under the plasma concentration versus time curve from time 0 to infinity; AUC<sub>0-t</sub> = area under the plasma concentration versus time curve during the dosing interval; CL = total clearance of drug from plasma; CL<sub>R</sub> = renal clearance of the drug from plasma; C<sub>max</sub> = maximum plasma drug concentration; F<sub>m</sub> = fraction metabolized; IM = intramuscular; IV = intravenous; PK = pharmacokinetic; q8h = every 8 hours; q12h = every 12 hours; q24h = every 24 hours; QTc = QT interval corrected for heart rate; T<sub>1/2</sub> = terminal elimination half-life; T<sub>max</sub> = time of maximum plasma drug concentration.

The Applicant conducted a number of ceftaroline-related pharmacologic studies. They determined that the time of maximum plasma concentrations for ceftaroline generally occurred near the end of the infusion, and the terminal elimination half-life (T<sub>1/2</sub>) of ceftaroline was typically in the range of 2 to 3 hours over the dose range studied (mean of 2.54 ± 0.29 hours in healthy adult subjects with normal renal function across studies). It was also determined that a significant percentage of the ceftaroline fosamil dose was excreted in the urine as ceftaroline (approximately 40% - 70%). Additionally, ceftaroline renal clearance was generally independent of dose and approximately equal to or less than glomerular filtration rate.

The plasma protein binding of ceftaroline in vitro was generally low (average of 20% bound) and concentration-independent in human plasma over the clinically relevant concentration range.

Following IV infusion of [<sup>14</sup>C] ceftaroline fosamil, a mean of 87.5% ± 3.9% of the dose of radioactivity was excreted in urine and 5.95% ± 2.93% was excreted in feces through the last collection interval, confirming that urinary excretion is the principal route of elimination for ceftaroline and its metabolites. Most of the administered radioactivity was recovered in the first 48 hours (approximately 90%). The overall mean recovery of radioactivity in urine and feces was 93.4% ± 3.1%.

The Applicant presented data indicating that the PK parameters of ceftaroline were modestly altered in subjects with mild (50 mL/min < CrCl ≤ 80 mL/min) or moderate (30 mL/min < CrCl ≤ 50 mL/min) renal impairment. The mean T<sub>1/2</sub> of ceftaroline was increased by 27% and 58% in subjects with mild and moderate renal impairment, respectively, from an average of 2.87 ± 0.43 hours in subjects with normal renal function (CrCl > 80 mL/min). Systemic exposure (AUC) to ceftaroline increased by 19% and 52% in subjects with mild and moderate renal impairment, respectively, compared to subjects with normal renal function; however, C<sub>max</sub> values in subjects with mild and moderate renal impairment and subjects with normal renal function were similar.

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Subjects with severe renal impairment ( $CrCl \leq 30$  mL/min) also had a longer  $T_{1/2}$  and greater systemic exposure for ceftaroline compared to subjects with normal renal function. Following a single IV infusion of 400 mg ceftaroline fosamil over 1 hour to both groups, mean values for ceftaroline AUC were about 115% greater and  $C_{max}$  was about 21% greater in subjects with severe renal impairment compared to subjects with normal renal function. The mean  $T_{1/2}$  of ceftaroline in subjects with severe renal impairment was  $5.05 \pm 1.22$  hours compared to  $3.02 \pm 0.43$  hours in subjects with normal renal function. Table 63 depicts the pharmacokinetic parameters of ceftaroline in subjects with renal impairment.

**Table 63 Summary (Mean  $\pm$  SD) of Ceftaroline Pharmacokinetic Parameters in Special Populations**

Study Report No.	Objective	Study Design	Route of Administration	Ceftaroline Fosamil Dose	No. of Subjects (M/F) Mean Age (Range)	$C_{max}$ , ng/mL	$T_{max}$ , h	$AUC_{0-\infty}$ , ng•h/mL	$T_{1/2}$ , h	$CL/F_{cr}$ , mL/h	$CL_{cr}$ , mL/h	Report Location
P903-02	Primary: Evaluate the PK of single IV doses of ceftaroline fosamil in subjects with normal renal function, or mild or moderate renal impairment. Secondary: Evaluate the PK of single IV doses of ceftaroline fosamil administered over 30 minutes	Open-label, single-dose, parallel-group study	IV infusion over 1 hour and IV infusion over 30 minutes	500 mg infused over 30 min	Normal renal function: 5 subjects 4M/1F 44 years (35.1-62.1)	27822.0 $\pm$ 8355.05	0.42 (0.42-0.62)	54042.0 $\pm$ 14207.0	2.65 $\pm$ 0.13	8644.8 $\pm$ 2290.3	3903.6 $\pm$ 1424.5	5.3.3.3
				600 mg infused over 1 h	Normal renal function: 6 subjects 3M/3F 34.7 years (24.2-47.2)	28351.7 $\pm$ 6950.5	1.00 (0.67-1.25)	75563.3 $\pm$ 9661.9	2.87 $\pm$ 0.43	7107.0 $\pm$ 887.5	3360.0 $\pm$ 831.7	
				600 mg infused over 1 h	Mild renal impairment: 6 subjects 2M/4F 69.8 years (58.8-74)	28168.3 $\pm$ 5416.0	0.92 (0.92-1.25)	92270.0 $\pm$ 25289.4	3.67 $\pm$ 0.74	6120.0 $\pm$ 1688.3	1872.0 $\pm$ 322.9	
				600 mg infused over 1 h	Moderate renal impairment: 6 subjects 4M/2F 49.6 years (30.7-75.9)	30825.0 $\pm$ 4857.0	1.13 (0.92-1.27)	114838.3 $\pm$ 14094.4	4.60 $\pm$ 1.11	4681.0 $\pm$ 661.1	1198.0 $\pm$ 375.7	
P903-04	Evaluate the PK profile of a single IV dose of ceftaroline fosamil in subjects with normal renal function or severe renal impairment	Open-label, single-dose, parallel-group study	IV infusion over 1 hour	400 mg	Normal renal function: 6 subjects 5M/1F 63.5 years (51-79)	14751.82 $\pm$ 1815.00	1.08 (0.33-1.25)	52811.1 $\pm$ 10507.02	3.02 $\pm$ 0.43	6896.27 $\pm$ 1440.66	4381.69 $\pm$ 1127.79	5.3.3.3
					Severe renal impairment: 6 subjects 5M/1F 65.2 years (52-74)	17866.16 $\pm$ 2856.47	1.25 (0.92-1.58)	113317.06 $\pm$ 20482.02	5.05 $\pm$ 1.22	3216.87 $\pm$ 673.93	713.15 $\pm$ 258.68	
P903-11	To compare PK profiles of healthy elderly subjects ( $\geq 65$ years of age) with those of healthy young adult subjects (18 - 45 years of age) who received a single IV dose of ceftaroline fosamil	Open-label, parallel-group, single-dose study	IV infusion over 1 hour	600 mg	Young subjects: 16 subjects 6M/10F 30.6 years (19-44)	31003.1 $\pm$ 3789.1	1.02 (0.88 - 1.1)	70492.2 $\pm$ 10089.1	2.2 $\pm$ 0.4	7635.4 $\pm$ 900.9	4858.6 $\pm$ 1404.4	5.3.3.3
				600 mg	Elderly subjects: 17 subjects (16 in PK population) 10M/7F 72.2 years (65-81)	31816.4 $\pm$ 4583.7	1.01 (0.93 - 1.1)	94062.5 $\pm$ 13603.3	3.1 $\pm$ 0.4	5740.5 $\pm$ 806.4	3292.8 $\pm$ 763.2	

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Study Report No.	Objective	Study Design	Route of Administration	Ceftaroline Fosamil Dose	No. of Subjects (M/F) Mean Age (Range)	$C_{max}$ , ng/mL	$T_{max}$ , h	$AUC_{0-24}$ , ng•h/mL	$T_{1/2}$ , h	$CL/F_m^b$ , mL/h	$CL_R$ , mL/h	Report Location
P903-15 <sup>c</sup>	To evaluate the single-dose PK profile of ceftaroline fosamil administered by IV infusion in subjects 12 to 17 years of age who were hospitalized and receiving antibiotic therapy for treatment of infections of any type	Open-label, single-dose study	IV infusion over 1 hour	8 mg/kg if < 75 kg; 600 mg if ≥ 75 kg	9 adolescent subjects 5M:4F 13.7 years (12-16)	17031.49 ± 3632.80	0.95 (0.48-1.00)	43569.02 ± 10110.04	1.86 ± 0.17	9357.06 ± 2151.11	4954.76 ± 1693.33	5.3.3.3

**Human Gastrointestinal effects:**

Ceftaroline was evaluated in an open-label, multiple-dose study of ceftaroline fosamil in 12 healthy subjects (6 males and 6 females) 18 to 45 years of age. Subjects received 600 mg ceftaroline fosamil by IV infusion over 1 hour q12h on study Days 1 through 6, and once on Day 7. In order to assess the effects of ceftaroline on the intestinal microflora, fecal samples were obtained for bacterial culture and ceftaroline susceptibility tests on Days –1, 2, 5, 7, and 9 and at the follow-up and end-of-study visits on Days 14 and 21, respectively. Plasma samples for PK analysis were collected before the first ceftaroline infusion on Day 1, before and at the end of the first infusions on Days 2 and 5, over 48 hours after the start of the infusion on Day 7, and at the follow-up and end-of-study visits.

The Applicant stated that no measurable fecal concentrations of ceftaroline were found, using a bioassay, at baseline (Day –1) or at any subsequent time point. No new colonizing aerobic or anaerobic bacteria with 4-fold or more increased MIC to ceftaroline were found. Ceftaroline effects on aerobic intestinal microflora included no effect on the numbers of enterococci or *Candida albicans*, no significant change in the median value for *Enterobacteriaceae* from baseline (Day –1) to Day 14, and a nonsignificant decrease in the median *Escherichia coli* counts from baseline (Day –1) to Day 7 followed by recovery on Day 14.

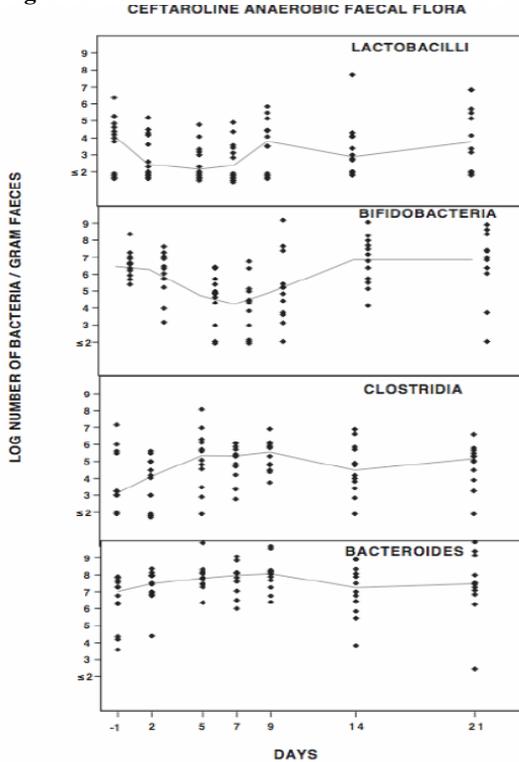
The effects on anaerobic intestinal microflora are shown in Figure 13. The data show that ceftaroline had an effect at decreasing in the numbers of bifidobacteria (bifidobacteria—a genera of bacteria Gram positive non-motile anaerobic bacteria that make up the gut microflora) and lactobacilli during the first 7 days, an increase in the numbers of *Clostridia* during the same period; a small increase on the numbers of *Bacteroides* were also noted at Day 2-9.

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Figure 13. Effects of Ceftaroline on Anaerobic Intestinal Microflora



Animal Disease Models

The Applicant has submitted data from a variety of animal models, including the mouse neutropenic thigh (MNT) model, murine subcutaneous infection (MSI) model, endocarditis infection model, pneumonia infection model, bacteremia infection model, and meningitis infection model. Efficacy has been demonstrated in mouse lung, thigh, and peritonitis infection models against Gram-positive and –negative organism. Efficacy has also been demonstrated in endocarditis modes in rat against MSSA and MRSA, and *E. faecalis*; in a rabbit pneumoniae model against *S. pneumoniae* including PRSP and in a rabbit model of MRSA osteomyelitis. Ceftaroline was also studied in a rabbit model of meningitis against *E. coli* and *K. pneumoniae* and the in vivo activity of ceftaroline was better than or similar to cefepime. Table 64 lists a summary of efficacy studies performed with ceftaroline in animal models of infection.

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**Table 64 Summary Listing of Ceftaroline Efficacy Studies in Animal Models of Infection**

<i>Model</i>	<i>Organism</i>	<i>Resistance Phenotypes</i>	<i>Efficacy Measure</i>	<i>Comparators</i>	<i>Study #</i>
Mouse (healthy and neutropenic) peritonitis	<i>S. aureus</i>	MRSA	ED <sub>50</sub>	VAN, TEC, ABK	Study TAK-599/00058, 2003
Mouse peritonitis	<i>S. aureus</i>	MRSA	ED <sub>50</sub>	VAN, TEC, ABK, LNZ	Study TAK-599/00059, 2003
Mouse peritonitis	<i>S. aureus</i> <i>S. pneumoniae</i> <i>S. pyogenes</i>	MSSA	ED <sub>50</sub>	VAN, CRO, CAZ, IMP/CS	Study TAK-599/00060, 2003
Mouse (neutropenic) peritonitis	<i>S. aureus</i>	VISA, MRSA	ED <sub>50</sub>	VAN	Study TAK-599/00061, 2003
Mouse peritonitis	<i>E. coli</i> <i>E. cloacae</i> <i>S. marcescens</i> <i>P. aeruginosa</i> <i>H. influenzae</i>		ED <sub>50</sub>	CRO, CAZ, IMP/CS	Study TAK-599/00062, 2003
Mouse (neutropenic) pneumonia	<i>S. aureus</i>	MRSA	CFU/g lung	VAN, LNZ	Study TAK-599/00063, 2003
<i>Model</i>	<i>Organism</i>	<i>Resistance Phenotypes</i>	<i>Efficacy Measure</i>	<i>Comparators</i>	<i>Study #</i>
Mouse (neutropenic) pneumonia	<i>S. pneumoniae</i>	PSSP	CFU/g lung	CRO	Study P0903-M-033, 2008
Mouse thigh (healthy & neutropenic)	<i>S. aureus</i> <i>S. pneumoniae</i> <i>E. coli</i> <i>K. pneumoniae</i>	MSSA PSSP, PISP, PRSP WT	CFU/g thigh	None	Study P0903-M-003, 2004
Mouse (neutropenic) pneumonia	<i>K. pneumoniae</i>		CFU/g lung	None	
Mouse thigh infection	<i>S. aureus</i>	MRSA	CFU/g	VAN, LNZ	Study TAK-599/00064, 2003
Rat endocarditis	<i>S. aureus</i>	MSSA	CFU/g spleen, lung (and bio-luminescence)	DAP, VAN	Study P0903-M-021, 2008
Rabbit endocarditis (simulated human dosing)	<i>S. aureus</i>	MRSA, GISA	CFU/g vegetation	VAN, LNZ	Study P0903-M-006, 2006; Jacqueline et al, 2007
Rabbit endocarditis (IM administration)	<i>S. aureus</i>	MRSA	CFU/g vegetation	TEC	Study P0903-M-016, 2007
Rabbit endocarditis (simulated human dosing)	<i>E. faecalis</i>	VAN-S, VAN-R	CFU/g vegetation	VAN, LNZ	Study P0903-M-023, 2009; Jacqueline et al, 2009
Rabbit endocarditis (simulated human dosing)	<i>S. aureus</i>	MRSA	CFU/g vegetation	DAP, TGC	Jacqueline et al, ICAAC, 2009
Rabbit osteomyelitis (simulated human dosing)	<i>S. aureus</i>	MRSA, GISA	CFU/g bone, marrow, joint fluid	VAN, LNZ	Study P0903-M-025, 2008
Rabbit osteomyelitis (IM administration)	<i>S. aureus</i>	MRSA	CFU/g bone, marrow, joint fluid; & resistance development	None	Study P0903-M-034, 2008

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<i>Model</i>	<i>Organism</i>	<i>Resistance Phenotypes</i>	<i>Efficacy Measure</i>	<i>Comparators</i>	<i>Study #</i>
Rabbit pneumonia (simulated human dosing)	<i>S. pneumoniae</i>	PSSP, PISP, PRSP	CFU/g lung	CRO	Study P0903-M-019, 2008
Rabbit meningitis	<i>E. coli</i> , <i>K. pneumoniae</i>		CFU/mL CSF	FEP	Study P903-M-086, 2009

Abbreviations: ABK = arbekacin; CAZ = ceftazidime; CFU = colony-forming unit; CRO = ceftriaxone; CSF = cerebrospinal fluid; DAP = daptomycin; ED<sub>50</sub> = dose demonstrating efficacy in 50% of animals; FEP = cefepime; GISA = glycopeptide-intermediate *S. aureus*; IM = intramuscular; IMP/CS = Imipenem/cilastatin; LNZ = linezolid; MRSA = methicillin-resistant *Staphylococcus aureus*; PISP = penicillin-intermediate *Streptococcus pneumoniae*; PRSP = penicillin-resistant *Streptococcus pneumoniae*; PSSP = penicillin-susceptible *Streptococcus pneumoniae*; TEC = teicoplanin; TGC = tigecycline; VAN = vancomycin; VAN-R = vancomycin-resistant; VAN-S = vancomycin-susceptible; VISA = vancomycin-intermediate-susceptible *S. aureus*; WT = wild type.

### Pharmacokinetics and Pharmacodynamics

Pharmacokinetic and measurements that quantify antimicrobial susceptibilities have been incorporated using PK/PD models to estimate clinical and microbiological outcomes in the treatment of bacterial infections. In vitro antimicrobial activity can be described as a function of drug concentration at the site of infection and the duration of time the pathogen is exposed to the drug. This phenomenon applies to in vitro and in vivo antimicrobial effects. For cephalosporins and other β-lactam antibiotics, the percentage of time during the dosing interval that the plasma free-drug concentration exceeds the MIC for the target organism (represented as %T > MIC) has been established as the PK/PD index that correlates with the therapeutic efficacy. To confirm that this relationship is applicable for ceftaroline, the Applicant conducted a neutropenic mouse thigh infection study using multiple isolates of *S. pneumoniae*, *S. aureus*, and *Enterobacteriaceae*. The objectives for this study were to characterize the in vivo time course of antimicrobial activity of ceftaroline and to determine the PK/PD parameters and magnitudes predictive of efficacy to provide a guideline for dosing regimen design in human studies.

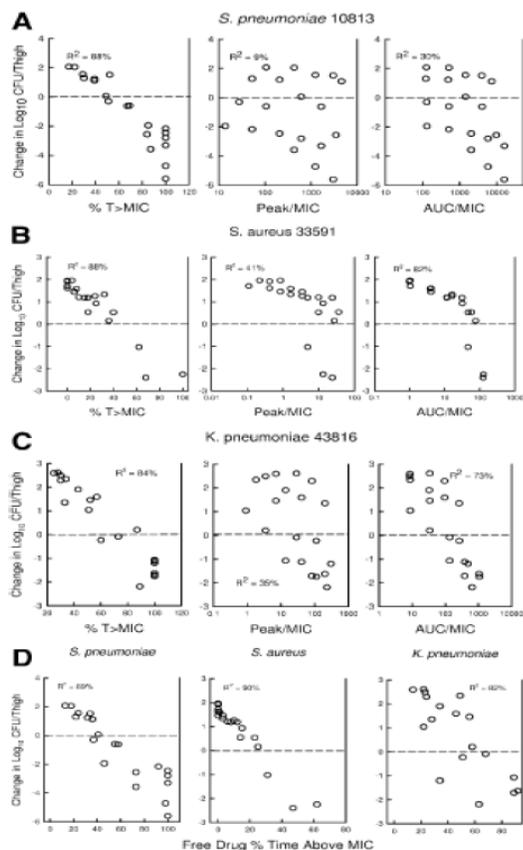
Figure 14 shows the relationships between microbiological effect and each of the pharmacodynamic indices (%T > MIC, 24h AUC/MIC and peak/MIC) against *S. pneumoniae* ATCC 10813, *S. aureus* ATCC 33591, and *K. pneumoniae* ATCC 43816. The strongest relationship was observed when the microbiological effect was correlated with the %T > MIC, with R<sup>2</sup> values of 82%-90%. In addition, bound drug %T > MIC values were only slightly larger than corresponding free drug %T > MIC values.

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**Figure 14. The Relationship of Microbiological Effect with Ceftaroline %T > MIC, Peak/MIC, and 24 Hours AUC/MIC**



Abbreviations: AUC = area under the concentration time curve; CFU = colony-forming units; MIC = minimum inhibitory concentration; %T = percentage of time during dosing interval that plasma free-drug concentration exceeds MIC for target organism.

Note: Each symbol represents the mean data from two mice (four thighs). The dashed horizontal line represents no net change in the burden of organisms present at the start of therapy (bacteriostatic effect). Data below and above the line represent growth and killing, respectively. R<sup>2</sup> is the coefficient of determination. Figure D represents %T > MIC against the three organisms using free-drug concentrations.

Source: Andes & Craig, 2006

Table 65 shows the doses calculated to achieve a bacteriostatic effect, as well as 1- and 2-log<sub>10</sub> reductions against multiple organisms. The mean free-drug %T > MIC corresponding with these bacteriostatic doses varied from 26% to 39% for the gram-positive species and was 60% for the gram-negatives. Penicillin and methicillin resistance did not alter the magnitude of the %T > MIC necessary for efficacy.

**Table 65 Ceftaroline in Vivo Activity in Murine Thigh and Lung Infection Models against Multiple Organisms**

Organisms (Number)	%T > MIC at the Dose Interval (24 h)		
	Static Dose	1-Log Kill	2-Log Kill
<i>Staphylococcus aureus</i> (4)	26 ± 8	33 ± 9	45 ± 13
<i>Streptococcus pneumoniae</i> (6)	39 ± 9	43 ± 9	50 ± 10
Gram-negative bacilli (5) <sup>1</sup>	60 ± 23	72 ± 18	88 ± 12

Abbreviation: MIC = minimum inhibitory concentration; %T = percentage of time during dosing interval that plasma free-drug concentration exceeds MIC for target organism.

<sup>1</sup> includes one *Klebsiella pneumoniae* isolate from pneumonia model.

Source: Study P0903-M-003, 2004

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The Applicant examined the impact of infection site and host immunity on the magnitude of the PK/PD parameter associated with efficacy. In the animal thigh model infected with *S. pneumoniae* ATCC 10813, ceftaroline therapy was examined in both neutropenic and non-neutropenic mice. Although the dose-response relationship for the non-neutropenic group was shifted, suggesting less drug was needed for efficacy, the differences in the amount of drug necessary to produce a bacteriostatic effect, 1- and 2-log reduction in organisms, were not statistically significant. In a second study, *K. pneumoniae* ATCC 43816 was used in both the thigh and pneumonia model to determine if a similar ceftaroline %T > MIC would be necessary to achieve various therapeutic end points. The dose-response curves are similar for both infection models. However, the %T > MIC associated with a net bacteriostatic effect and 1 log<sub>10</sub> organism reductions was lower in the lung infection model.

**Summary and conclusion**

Cephalosporin %T > MIC target to produce a net bacteriostatic effect for gram-positive bacteria occur in the range of 30% to 40% provided that free-drug concentrations are considered, consistent with the results obtained for ceftaroline. Data from the current multiple dosing regimen studies confirmed that (1) the %T > MIC is the best PK/PD predictor of efficacy of ceftaroline. In addition, although the dose response curves were similar in the thigh and lung infection model, the %T > MIC associated with a net bacteriostatic effect and 1 log<sub>10</sub> organism reductions was lower in the lung infection model. Therefore, the PK/PD parameter appears to be dependent on the site of infection.

**Proposed Susceptibility Interpretive Criteria:**

In a previous submission, the Applicant has proposed MIC in vitro susceptibility interpretive criteria against the target pathogens before they conducted the Phase 3 clinical trials. Ceftaroline MIC and disk diffusion provisional breakpoints were proposed based upon the population distribution analysis and are given in Table 66. Interpretive breakpoints for ceftaroline were determined according to CLSI guidelines

**Table 66. Pre-Phase III Proposed Broth Microdilution and Disk Diffusion Provisional Breakpoints**

Bacterial Group	MIC Breakpoints (µg/ml)			Disk Diffusion Breakpoints (mm)		
	S	I	R	S	I	R
Staphylococcus species	(b) (4)					
Enterococcus species						
<i>M. catarrhalis</i>						
Enterobacteriaceae						
Pseudomonas species						
<i>S. pneumoniae</i>						
Streptococcus other than <i>S. pneumoniae</i>						
<i>H. influenzae</i>						

Abbreviations: MIC = minimum inhibitory concentration.  
Source: Study P0903-M-012, 2006

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**HUMAN CLINICAL TRIALS**

Ceftaroline was evaluated in a global, multicenter, randomized, double-blinded, well-controlled Phase 3 clinical trial in patients with complicated skin structure infections (cSSSI) and in a separate study in patients with community acquired pneumonia (CABP) as defined in 21CFR 314.126. The cSSSI trial comprised of two pivotal clinical studies: Study P903-06, 2009 (also known as CANVAS 1) and P903-07, 2009 (also known as CANVAS 2); the CABP trial also comprised of two clinical studies: Study P903-08, 2009, (also known as FOCUS 1), and Study P903-09, 2009 (also known as FOCUS 2).

**Complicated skin structure infections (cSSSI) Studies:**

For the cSSSI evaluation, there were 1378 adult patients with cSSSI enrolled in studies P903-06 and P903-07. The dosage regimen for ceftaroline fosamil in both Phase 3 cSSSI studies was 600 mg was administered intravenously (IV) over 60 minutes every 12 hours (q12h) for a treatment duration of 5 - 14 days. For both studies the primary efficacy variable was clinical cure rate assessed at test of cure (TOC) visit, which was scheduled to occur 8-15 days post-therapy. The comparator agents were 5 to 14 day combination regimen of vancomycin 1 g IV q12h plus aztreonam 1 g IV q12h) for the treatment of cSSSI. As previously mentioned this was a global. There were three study centers in Romania, seven in Russia, and four in the Ukraine. In South America, there were six study centers in Argentina, four in Chile, and four in Peru. In the United States, there were 12 study centers and one study center in Mexico. In Western and Central Europe, there were seven study centers in Germany and seven in Poland.

*Inclusion and Exclusion Criteria*

**Inclusion criteria** included the following: Adults aged 18 years or older; skin and skin structure infection (SSSI) that involved deeper soft tissue or required significant surgical intervention and that was a wound infection, abscess, or cellulitis, or was cellulitis or abscess of a lower extremity in patients with diabetes mellitus or peripheral vascular disease (PVD); three or more clinical signs (local, systemic, or both) of SSSI; need for hospitalization or for treatment in an emergency room or urgent care setting; and that the subject's infection was expected to require at least 5 days of IV antimicrobial therapy.

**Exclusion criteria** included the following: 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; uncomplicated SSSI; requirement for concomitant antimicrobial therapy (including systemic antifungal therapy); severely impaired renal function ( $CrCl \leq 30$  mL/min) estimated by the Cockcroft-Gault formula; or evidence of significant hepatic, hematologic, or immunologic disease.

*Microbiology and Laboratory Testing*

Microbiological assessment of the cSSSI site required a specimen from all patients at baseline for Gram stain and culture. The method used to obtain a specimen was dependent on the cSSSI disease entity:

- For cellulitis, specimens were obtained by leading-edge needle aspiration or punch biopsy and were submitted for aerobic culture only.

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- For other cSSSIs, a deep-site specimen was obtained via biopsy or needle aspiration or from surgically obtained tissue, fluid, or pus that was physically contiguous with the ulcer or wound. The sample was submitted for both aerobic and anaerobic cultures, using recommended anaerobic transport techniques.
- Superficial swabs of infected area were NOT acceptable, because of the high probability that such specimens could be contaminated with clinically insignificant and therefore misleading isolates. However, deep swabs taken during significant surgical interventions were acceptable

If a focus of infection was present, microbiological assessments were repeated when medically appropriate and at the end of therapy if the subject was considered to be a clinical failure or had prematurely discontinued from study drug during therapy. Microbiological assessments were also performed at Test-of-Cure (TOC) if a focus of infection was present.

All specimens were cultured, and Gram staining, organism identification, and initial antimicrobial susceptibility testing were conducted at the local or regional laboratory, as appropriate. However, certain sites in Eastern Europe and South America were instructed to submit specimens directly to a regional central laboratory. Isolates from all local or regional laboratories were then sent on to the central laboratory (b) (4) (b) (4) for identification confirmation (genus and species) and antimicrobial susceptibility testing.

Antimicrobial susceptibility testing was conducted using the Clinical and Laboratory Standards Institute (CLSI) reference broth microdilution method using frozen Sensititre minimal inhibitory concentration (MIC) panels manufactured by TREK Diagnostics (Cleveland, OH). All isolates were also tested simultaneously for their susceptibility to ceftaroline and comparator agents (ceftriaxone and ceftazidime) using the Kirby Bauer disk diffusion method in accordance with CLSI guidelines.

Blood for culture was also obtained at baseline and as medically indicated during the period of study drug treatment (Study Days 1 to 14), extension of study drug treatment (Study Days 15 to 21), and at End-of-Treatment (EOT) and TOC. Blood cultures were repeated on receipt of a positive result until sterilization was confirmed in those patients with a positive result at baseline (ie, the baseline blood culture grew an organism other than those judged to be transient or resident skin flora. Blood for cultures was obtained at long-term follow-up only if medically indicated or if the subject was experiencing clinical relapse. When blood cultures were required, one aerobic and one anaerobic bottle were obtained from two separate infection sites, for a total of four bottles.

Clinical and Microbiological Outcome Categories and the definitions of the various clinical outcome categories are provided in Table 67.

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**Table 67 Clinical Outcome Categories Definitions**

<i>Outcome</i>	<i>Definition</i>
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 Note: for patients with an underlying skin ulcer or wound, healing of the ulcer or wound is not required for an outcome of cure.
Clinical failure	<ul style="list-style-type: none"> <li>• Any of the following:</li> <li>• Persistence, incomplete resolution, or worsening in signs and symptoms of the cSSSI that requires alternative antimicrobial therapy.</li> <li>• 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 do not constitute evidence of study drug failure.</li> <li>• New signs and symptoms associated with the original cSSSI or a new cSSSI at the same anatomical site.</li> <li>• Subject required alternative, antimicrobial therapy to treat the cSSSI, including oral step-down therapy. Extension of study drug therapy to 21 days is allowed with prior approval of the Medical Monitor and does not constitute evidence of study drug failure.</li> <li>• 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>• Diagnosis of osteomyelitis 8 or more days after randomization.</li> <li>• Death wherein cSSSI is considered causative.</li> </ul>
Indeterminate	Study data are not available for evaluation of efficacy, for any reason including: treatment change prior to completing at least 48 hours of study drug therapy, death wherein cSSSI is clearly noncontributory, lost to follow-up, or extenuating circumstances that preclude 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 infections

<i>Outcome</i>	<i>Definition</i>
Eradication	An adequate source specimen demonstrates absence of the original baseline pathogen.
Presumed eradication	An adequate source specimen was not available to culture and the subject was assessed as a clinical cure.
Persistence	Source specimen demonstrates continued presence of the original baseline pathogen.
Presumed persistence	An adequate source specimen was not available to culture and the subject was assessed as a clinical failure.
Indeterminate	An adequate source specimen was not available to culture and the subject's clinical response was assessed as indeterminate.

Abbreviations: AE = adverse event; cSSSI = complicated skin and skin structure infections

For by-pathogen microbiological response analyses, a microbiological outcome at TOC was derived using electronic microbiology data from the central laboratory and from pathogen information determined by the Sponsor for each baseline isolate. Microbiological outcome categories were eradication, presumed eradication, persistence, presumed persistence, and indeterminate (mMITT Population only). Favorable microbiological outcomes were eradication or presumed eradication. Unfavorable microbiological outcomes were persistence, presumed persistence, or indeterminate (mMITT Population only).

By-subject microbiological response at TOC in the mMITT and ME Populations were categorized as favorable or unfavorable. For a subject to have an overall favorable microbiological response, the outcome for each baseline pathogen had to be favorable. If the outcome for any pathogen was unfavorable, the subject was considered to have an unfavorable microbiological response.

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***cSSSI Study P903-06 and P903-07 Subject Populations:***

For the purpose of this review, both cSSSI Study P903-06 and P903-07 subject population analysis will be integrated and analyzed for clinical microbiology efficacy. Table 62 shows the number and percentage of patients in each population for Study P903-06.

**Table 68 Summary of Integrated Clinical and Microbiological Success of Ceftaroline and Vancomycin plus Aztreonam in Adults with Skin and Skin Structure Infections in cSSSI Studies P903-06 and P903-07**

<i>Subject Populations</i>	<i>Ceftaroline (N = 353)</i>	<i>Vancomycin plus Aztreonam (N = 349) n (%)</i>	<i>Total (N = 702) n (%)</i>
MITT Population	351 (99.4)	347 (99.4)	698 (99.4)
mMITT Population	271 (76.8)	263 (75.4)	534 (76.1)
CE Population	316 (89.5)	300 (86.0)	616 (87.7)
ME Population	244 (69.1)	227 (65.0)	471 (67.1)

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

Source: Clinical Study Report P903-06, 2009, Table 10.1-2.

***Efficacy in Study Populations:***

Table 69 shows the summary of the clinical and microbiological success rates of ceftaroline and comparator agents in the cSSSI study P903-06 and P903-06 at test of cure (TOC). In the ME Population, the integrated clinical success rate for ceftaroline was 92.7% (434/468) compared with 94.4% (421/446) for vancomycin plus aztreonam for all subjects. The microbiological success rates were similar, with a 92.3% (432/468) success rate for ceftaroline and 93.7% (418/446) for vancomycin plus aztreonam.

**Table 69 Clinical and Microbiological Success of Ceftaroline and Vancomycin plus Aztreonam in Adults with cSSSI for All Patients with Either Monomicrobial or Polymicrobial Infections at Baseline (ME Population) in Studies P903-06 and P903-07.**

<i>Population</i>	<i>Clinical Success at TOC (ME Population)</i>		<i>Microbiological Success at TOC (ME Population)</i>	
	<i>Ceftaroline n/N (%)</i>	<i>Vancomycin plus Aztreonam n/N (%)</i>	<i>Ceftaroline n/N (%)</i>	<i>Vancomycin plus Aztreonam n/N (%)</i>
All Subjects (ME Population)	434/468 (92.7%)	421/446 (94.4%)	432/468 (92.3%)	418/446 (93.7%)
Subjects with monomicrobial infections at baseline (ME Population)	309/332 (93.1%)	287/307 (93.5%)	308/332 (92.8%)	289/307 (94.1%)
Subjects with polymicrobial infections at baseline (ME Population)	125/136 (91.9%)	134/139 (96.4%)	124/136 (91.2%)	129/139 (92.8%)

Abbreviations: cSSSI = complicated skin and skin structure infection; ME = microbiologically evaluable; TOC = test-of-cure.

Table 70 shows the clinical and microbiological response rate by pathogen from the primary infection site or blood in the ME population for some skin pathogens. The microbiological response rates are as follows: *Staphylococcus aureus* were 93.7%; for *S. pyogenes* a response rate of 100% was observed. Among *S. aureus*, the clinical and microbiological response rates were similar for both methicillin-susceptible and methicillin-resistant isolates. For ceftaroline-treated patients, the clinical success rates for methicillin-resistant *S. aureus* (MRSA) and methicillin-susceptible *S. aureus* (MSSA) were both 95.1%. Ceftaroline and vancomycin plus

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aztreonam both demonstrated similar clinical and microbiological response rates against other  $\beta$ -hemolytic streptococci, including *S. agalactiae* and *S. dysgalactiae*. Among gram-negative pathogens such as *E. coli* and *K. pneumoniae*, the microbiological response rates for ceftaroline were 90.5% and 92.9%, respectively.

**Table 70 Clinical and Microbiological Success by Baseline Pathogen from the Primary Infection Site or Blood at TOC (ME Population).**

Baseline Pathogen	Clinical Success at TOC by Baseline Pathogen from the Primary Infection Site or Blood (ME Population)		Microbiological Success at TOC by Baseline Pathogen from the Primary Infection Site or Blood (ME Population)	
	Ceftaroline n/N (%)	Vancomycin plus Aztreonam n/N (%)	Ceftaroline n/N (%)	Vancomycin plus Aztreonam n/N (%)
<b>Gram-positive aerobes</b>				
<b>Staphylococcus spp.</b>				
<i>Staphylococcus aureus</i>	352/378 (93.1%)	336/356 (94.4%)	357/381 (93.7%)	338/360 (93.9%)
MRSA	142/152 (93.4%)	115/122 (94.3%)	142/152 (93.4%)	113/122 (92.6%)
MSSA	212/228 (93.0%)	225/238 (94.5%)	214/228 (93.9%)	225/238 (94.5%)
<i>Staphylococcus lugdunensis</i>	2/2 (100%)	2/3 (66.7%)	2/2 (100%)	2/3 (66.7%)
<b>Enterococcus spp.</b>				
<i>Enterococcus faecalis</i>	20/25 (80.0%)	22/24 (91.7%)	21/25 (84.0%)	23/24 (95.8%)
<i>Enterococcus faecium</i>		3/3 (100%)		3/3 (100%)
<b>Streptococcus spp. (<math>\beta</math>-hemolytic group)</b>				
<i>Streptococcus pyogenes</i>	56/56 (100%)	56/58 (96.6%)	56/56 (100%)	56/58 (96.6%)
<i>Streptococcus agalactiae</i>	21/22 (95.5%)	18/18 (100%)	20/22 (90.9%)	18/18 (100%)
<i>Streptococcus dysgalactiae</i>	13/13 (100%)	15/16 (93.8%)	13/13 (100%)	15/16 (93.8%)
<i>Streptococcus equisimilis</i>	1/1 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)
Group G $\beta$ -hemolytic streptococci	1/1 (100%)		1/1 (100%)	
B-hemolytic streptococci	1/1 (100%)		1/1 (100%)	
<b>Streptococcus spp. (viridans group)</b>				
<i>Streptococcus anginosus group</i>	12/13 (92.3%)	15/16 (93.8%)	12/13 (92.3%)	15/16 (93.8%)
<i>Streptococcus mitis group</i>		1/1 (100%)		1/1 (100%)
<i>Streptococcus oralis</i>	1/1 (100%)	1/2 (50.0%)	1/1 (100%)	2/2 (100%)
<i>Streptococcus parasanguis</i>		1/1 (100%)		1/1 (100%)
<i>Streptococcus sanguis</i>	1/1 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)
<b>Other gram-positive aerobes</b>				
<i>Arcanobacterium haemolyticum</i>		1/1 (100%)		1/1 (100%)

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<i>Baseline Pathogen</i>	<i>Clinical Success at TOC by Baseline Pathogen from the Primary Infection Site or Blood (ME Population)</i>		<i>Microbiological Success at TOC by Baseline Pathogen from the Primary Infection Site or Blood (ME Population)</i>	
	<i>Ceftaroline n/N (%)</i>	<i>Vancomycin plus Aztreonam n/N (%)</i>	<i>Ceftaroline n/N (%)</i>	<i>Vancomycin plus Aztreonam n/N (%)</i>
<b>Gram-positive anaerobes</b>				
<i>Clostridium perfringens</i>		1/1 (100%)		1/1 (100%)
<i>Finegoldia magna</i>	2/2 (100%)		2/2 (100%)	
<i>Peptostreptococcus anaerobius</i>		1/1 (100%)		1/1 (100%)
<i>Peptostreptococcus micros</i>	2/2 (100%)	1/1 (100%)	2/2 (100%)	1/1 (100%)
<i>Propionibacterium spp.</i>		1/1 (100%)		1/1 (100%)
<b>Gram-negative aerobes</b>				
<i>Enterobacteriaceae</i>				
<i>Citrobacter freundii complex</i>	3/3 (100%)	4/4 (100%)	3/3 (100%)	4/4 (100%)
<i>Citrobacter koseri</i>	1/1 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)
<i>Enterobacter aerogenes</i>	1/1 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)
<i>Enterobacter cloacae</i>	4/5 (80.0%)	11/12 (91.7%)	3/5 (60.0%)	12/12 (100%)
<i>Escherichia coli</i>	20/21 (95.2%)	19/21 (90.5%)	20/21 (95.2%)	19/21 (90.5%)
<i>Klebsiella oxytoca</i>	10/12 (83.3%)	6/6 (100%)	11/12 (91.7%)	5/6 (83.3%)
<i>Klebsiella pneumoniae</i>	17/18 (94.4%)	13/14 (92.9%)	17/18 (94.4%)	13/14 (92.9%)
<i>Morganella morganii</i>	11/12 (91.7%)	5/6 (83.3%)	11/12 (91.7%)	6/6 (100%)
<i>Proteus mirabilis</i>	10/15 (66.7%)	20/21 (95.2%)	11/15 (73.3%)	19/21 (90.5%)
<i>Proteus penneri</i>	1/1 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)
<i>Proteus vulgaris group</i>	3/5 (60.0%)	1/1 (100%)	3/5 (60.0%)	1/1 (100%)
<i>Providencia rettgeri</i>		1/1 (100%)		1/1 (100%)
<i>Providencia stuartii</i>	2/2 (100%)		2/2 (100%)	
<i>Salmonella group D</i>		1/1 (100%)		1/1 (100%)
<i>Serratia liquefaciens</i>	1/1 (100%)		1/1 (100%)	
<i>Serratia marcescens</i>	3/3 (100%)	3/3 (100%)	2/3 (66.7%)	3/3 (100%)
<b>Nonfermenting gram-negative bacilli</b>				
<i>Acinetobacter calcoaceticus - A. baumannii complex</i>	3/3 (100%)	7/7 (100%)	2/3 (66.7%)	5/7 (71.4%)
<i>Pseudomonas aeruginosa</i>	14/16 (87.5%)	17/18 (94.4%)	13/16 (81.3%)	17/18 (94.4%)
<i>Pseudomonas stutzeri</i>	1/1 (100%)		1/1 (100%)	
<i>Pseudomonas spp.</i>		2/2 (100%)		2/2 (100%)

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<i>Baseline Pathogen</i>	<i>Clinical Success at TOC by Baseline Pathogen from the Primary Infection Site or Blood (ME Population)</i>		<i>Microbiological Success at TOC by Baseline Pathogen from the Primary Infection Site or Blood (ME Population)</i>	
	<i>Ceftaroline n/N (%)</i>	<i>Vancomycin plus Aztreonam n/N (%)</i>	<i>Ceftaroline n/N (%)</i>	<i>Vancomycin plus Aztreonam n/N (%)</i>
<b>Other gram-negatives</b>				
<i>Aeromonas hydrophila</i>		2/2 (100%)		2/2 (100%)
<i>Alcaligenes faecalis</i>		2/2 (100%)		2/2 (100%)
<i>Eikenella corrodens</i>	1/1 (100%)		1/1 (100%)	
<i>Moraxella osloensis</i>	1/1 (100%)		1/1 (100%)	
<i>Haemophilus parainfluenzae</i>	1/1 (100%)		1/1 (100%)	
<i>Ralstonia pickettii</i>		1/1 (100%)		1/1 (100%)
<b>Gram-negative anaerobes</b>				
<i>Bacteroides capillosus</i>	1/1 (100%)		1/1 (100%)	
<i>Bacteroides fragilis</i>	2/3 (66.7%)	1/1 (100%)	2/3 (66.7%)	1/1 (100%)
<i>Bacteroides thetaiotaomicron</i>		1/1 (100%)		1/1 (100%)
<i>Capnocytophaga spp.</i>	1/1 (100%)		1/1 (100%)	
<i>Fusobacterium varium</i>		1/1 (100%)		1/1 (100%)
<i>Prevotella bivia</i>		1/1 (100%)		1/1 (100%)
<i>Prevotella loeschii</i>		1/1 (100%)		1/1 (100%)

Abbreviations: cSSSI = complicated skin and skin structure infection; ME = microbiologically evaluable;  
MRSA = methicillin resistant *Staphylococcus aureus*; MSSA = methicillin susceptible *Staphylococcus aureus*;  
TOC = test-of-cure.

Table 71 shows the activity of ceftaroline against *S. aureus* that were characterized by genotyping. Please note that this genotype characterization technique is informative for the surveillance of epidemics caused by resistant bacteria and may detect both the gene and the genetic element that carries the gene. The genotyping method may confirm the presence or absence of resistance in isolates for which the MIC of ceftaroline is close to the upper critical concentration.

The data show that presence or absence of pvl appears to have had no significant effect on ceftaroline eradication rates. The most prevalent PFGE type was USA300 from subjects in the U.S. and the microbiological success rates for ceftaroline and vancomycin plus aztreonam were 91.40% and 91.1%, respectively. The most prevalent SCCmec type was type IV, and ceftaroline and vancomycin plus aztreonam both exhibited clinical and microbiological success rates against SCCmecIV isolates of *S. aureus* of 96.6% and 89.5%, respectively.

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**Table 71 Clinical and Microbiological Success by Baseline *Staphylococcus aureus* Genotypes from Primary Infection Site or Blood at TOC (ME Population) in cSSSI Study P903-06 and P903-07.**

<i>Baseline Pathogen</i>	<i>Clinical Success at TOC by Baseline Pathogen from the Primary Infection Site or Blood (ME Population)</i>		<i>Microbiological Success at TOC by Baseline Pathogen from the Primary Infection Site or Blood (ME Population)</i>	
	<i>Ceftaroline n/N (%)</i>	<i>Vancomycin plus Aztreonam n/N (%)</i>	<i>Ceftaroline n/N (%)</i>	<i>Vancomycin plus Aztreonam n/N (%)</i>
PVL-positive	149/161 (92.5%)	136/145 (93.8%)	149/161 (92.5%)	135/145 (93.1%)
PVL-negative	188/200 (94.0%)	180/190 (94.7%)	190/200 (95.0%)	178/190 (93.7%)
USA100	4/4 (100%)	2/3 (66.7%)	4/4 (100%)	2/3 (66.7%)
USA200	15/16 (93.8%)	17/19 (89.4%)	16/16 (100%)	17/19 (89.4%)
USA300	96/105 (91.4%)	72/79 (91.1%)	96/105 (91.4%)	72/79 (91.1%)
USA400	12/12 (100%)	7/8 (87.5%)	12/12 (100%)	7/8 (87.5%)
USA600	20/22 (90.9%)	22/22 (100%)	20/22 (90.9%)	22/22 (100%)
USA700	1/1 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)
USA800	3/3 (100%)	1/1 (100%)	3/3 (100%)	1/1 (100%)
SCC <i>mecI</i>	2/2 (100%)	NA	2/2 (100%)	NA
SCC <i>mecII</i>	5/5 (100%)	6/7 (85.7%)	5/5 (100%)	6/7 (85.7%)
SCC <i>mecIII</i>	8/8 (100%)	7/7 (100%)	8/8 (100%)	6/7 (85.7%)
SCC <i>mecIV</i>	111/118 (94.1%)	80/86 (93.0%)	111/118 (94.1%)	79/86 (91.9%)

Abbreviations: cSSSI = complicated skin and skin structure infection; ME = microbiologically evaluable;  
PVL = Pantón-Valentine leukocidin toxin; SCC*mec* = staphylococcal cassette chromosome *mec* type;  
TOC = test-of-cure; USA = United States of America.

The clinical and microbiological response rates for ceftaroline and vancomycin plus aztreonam against baseline pathogens from patients with monomicrobial infections are shown in Table 72. For *S. aureus* and *S. pyogenes*, the microbiological success rates were 93.4% and 100%, respectively. Although the numbers of individual species within the *Enterobacteriaceae* was low, 100% success rates were observed for *E. coli* (8/8) and *K. oxytoca* (4/4).

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**Table 72. Clinical and Microbiological Success by Baseline Pathogen from Subjects with Monomicrobial Infections at TOC (ME Population) in cSSSI Study P903-06 and P903-07**

Baseline Pathogen	Clinical Success at TOC by Baseline Pathogen from Subjects with Monomicrobial Infections (ME Population)		By Pathogen Microbiological Success at TOC by Baseline Pathogen from Subjects with Monomicrobial Infections (ME Population)	
	Ceftaroline n/N (%)	Vancomycin plus Aztreonam n/N (%)	Ceftaroline n/N (%)	Vancomycin plus Aztreonam n/N (%)
<b>Gram-positive aerobes</b>				
<b>Staphylococcus spp.</b>				
<i>Staphylococcus aureus</i>	252/271 (93.0%)	224/240 (93.3%)	253/271 (93.4%)	225/240 (93.8%)
MRSA	118/124 (95.2%)	90/96 (93.8%)	118/124 (95.2%)	90/96 (93.8%)
MSSA	134/147 (91.2%)	134/144 (93.1%)	135/147 (91.8%)	135/144 (93.8%)
<i>Staphylococcus lugdunensis</i>	1/1 (100%)	1/2 (50.0%)	1/1 (100%)	1/2 (50.0%)
<b>Enterococcus spp.</b>				
<i>Enterococcus faecalis</i>	2/2 (100%)	1/2 (50.0%)	2/2 (100%)	2/2 (100%)
<i>Enterococcus faecium</i>		1/1 (100%)		1/1 (100%)
<b>Streptococcus spp. (B-hemolytic group)</b>				
<i>Streptococcus pyogenes</i>	15/15 (100%)	24/25 (96.0%)	15/15 (100%)	24/25 (96.0%)
<i>Streptococcus agalactiae</i>	4/4 (100%)	7/7 (100%)	3/4 (75.0%)	7/7 (100%)
<i>Streptococcus dysgalactiae</i>	5/5 (100%)	3/3 (100%)	5/5 (100%)	3/3 (100%)
β-hemolytic streptococci	1/1 (100%)		1/1 (100%)	
<b>Streptococcus spp. (viridans group)</b>				
<i>Streptococcus anginosus</i> group	5/5 (100%)	6/7 (85.7%)	5/5 (100%)	6/7 (85.7%)
<b>Nonfermenting gram-negative bacilli</b>				
<i>Pseudomonas</i> spp.	NA	1/1 (100%)	NA	1/1 (100%)

Abbreviations: cSSSI = complicated skin and skin structure infections; ME = microbiologically evaluable;  
MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*;  
TOC = test-of-cure.

Source: Table 1.1.2b and Table 1.2.2b

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Baseline Pathogen	Clinical Success at TOC by Baseline Pathogen from Subjects with Monomicrobial Infections (ME Population)		By Pathogen Microbiological Success at TOC by Baseline Pathogen from Subjects with Monomicrobial Infections (ME Population)	
	Ceftaroline n/N (%)	Vancomycin plus Aztreonam n/N (%)	Ceftaroline n/N (%)	Vancomycin plus Aztreonam n/N (%)
<b>Gram-negative aerobes</b>				
<b>Enterobacteriaceae</b>				
<i>Citrobacter freundii</i> complex	1/1 (100%)	3/3 (100%)	1/1 (100%)	3/3 (100%)
<i>Enterobacter cloacae</i>	1/1 (100%)	2/2 (100%)	0/1 (0%)	2/2 (100%)
<i>Escherichia coli</i>	8/8 (100%)	7/7 (100%)	8/8 (100%)	7/7 (100%)
<i>Klebsiella oxytoca</i>	4/4 (100%)		4/4 (100%)	
<i>Klebsiella pneumoniae</i>	1/1 (100%)	2/2 (100%)	1/1 (100%)	2/2 (100%)
<i>Morganella morganii</i>	2/2 (100%)		2/2 (100%)	
<i>Proteus mirabilis</i>	1/3 (33.3%)	2/2 (100%)	2/3 (66.7%)	2/2 (100%)
<i>Proteus vulgaris</i> group	3/5 (60.0%)		3/5 (60.0%)	
<i>Providencia rettgeri</i>		1/1 (100%)		1/1 (100%)
<i>Salmonella</i> group D		1/1 (100%)		1/1 (100%)
<i>Serratia marcescens</i>	3/3 (100%)	1/1 (100%)	2/3 (66.7%)	1/1 (100%)
<b>Nonfermenting gram-negative bacilli</b>				
<i>Pseudomonas</i> spp.		1/1 (100%)		1/1 (100%)

Abbreviations: cSSSI = complicated skin and skin structure infection; ME = microbiologically evaluable; MRSA = methicillin resistant *Staphylococcus aureus*; MSSA = methicillin susceptible *Staphylococcus aureus*; TOC = test-of-cure

Table 73 shows the clinical and microbiological outcome for baseline pathogens from patients with polymicrobial infections. The microbiological success rates for ceftaroline and *S. aureus* was 94.5% and for *S. pyogenes* was 100%.

**Table 73 Clinical and Microbiological Success by Baseline Pathogen from Subjects with Polymicrobial Infections at TOC (ME Population) in cSSSI Study P903-06 and P903-07,**

Baseline Pathogen	Clinical Success at TOC by Baseline Pathogen from Subjects with Polymicrobial Infections (ME Population)		Microbiological Success at TOC by Baseline Pathogen from Subjects with Polymicrobial Infections (ME Population)	
	Ceftaroline n/N (%)	Vancomycin plus Aztreonam n/N (%)	Ceftaroline n/N (%)	Vancomycin plus Aztreonam n/N (%)
<b>Gram-positive aerobes</b>				
<b>Staphylococcus spp.</b>				
<i>Staphylococcus aureus</i>	100/107 (93.5%)	112/116 (96.6%)	104/110 (94.5%)	113/120(94.2%)
MRSA	24/28 (85.7%)	25/26 (96.2%)	24/28 (85.7%)	23/26 (88.5%)
MSSA	78/81 (96.3%)	91/94 (96.8%)	79/81 (97.5%)	90/94 (95.7%)
<i>Staphylococcus lugdunensis</i>	1/1 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)
<b>Enterococcus spp.</b>				
<i>Enterococcus faecalis</i>	18/23 (78.3%)	21/22 (95.5%)	19/23 (82.6%)	21/22 (95.5%)
<b>Streptococcus spp. (β-hemolytic group)</b>				
<i>Streptococcus pyogenes</i>	41/41 (100%)	32/33 (97%)	41/41 (100%)	32/33 (100%)
<i>Streptococcus agalactiae</i>	17/18 (94.4%)	11/11 (100%)	17/18 (94.4%)	11/11 (100%)
<i>Streptococcus dysgalactiae</i>	8/8 (100%)	12/13 (92.3%)	8/8 (100%)	12/13 (92.3%)
<i>Streptococcus equisimilis</i>	1/1 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)
Group G β-hemolytic streptococci	1/1 (100%)	-	1/1 (100%)	-
<b>Streptococcus spp. (viridans group)</b>				
<i>Streptococcus anginosus</i> group	7/8 (87.5%)	9/9 (100%)	7/8 (87.5%)	9/9 (100%)
<b>Gram-negative aerobes</b>				
<b>Enterobacteriaceae</b>				
<i>Escherichia coli</i>	12/13 (92.3%)	12/14 (85.7%)	12/13 (92.3%)	12/14 (85.7%)
<i>Klebsiella oxytoca</i>	6/8 (75%)	6/6 (100%)	7/8 (87.5%)	5/6 (83.3%)
<i>Klebsiella pneumoniae</i>	16/17 (94.1%)	11/12 (91.7%)	16/17 (94.1%)	11/12 (91.7%)
<i>Morganella morganii</i>	9/10 (90%)	5/6 (83.3%)	9/10 (90.0%)	6/6 (100%)
<i>Proteus mirabilis</i>	9/12 (75%)	18/19 (94.7%)	9/12 (75%)	17/19 (89.5%)
<i>Proteus penneri</i>	1/1 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)
<i>Proteus vulgaris</i> group	-	1/1 (100%)	-	1/1 (100%)

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Baseline Pathogen	Clinical Success at TOC by Baseline Pathogen from Subjects with Polymicrobial Infections (ME Population)		Microbiological Success at TOC by Baseline Pathogen from Subjects with Polymicrobial Infections (ME Population)	
	Ceftaroline n/N (%)	Vancomycin plus Aztreonam n/N (%)	Ceftaroline n/N (%)	Vancomycin plus Aztreonam n/N (%)
<b>Nonfermenting gram-negative bacilli</b>				
<i>Acinetobacter calcoaceticus</i> - <i>A. baumannii</i> complex	3/3 (100%)	7/7 (100%)	2/3 (66.7%)	5/7 (71.4%)
<i>Pseudomonas aeruginosa</i>	14/16 (87.5%)	17/18 (94.4%)	13/16 (81.3%)	17/18 (94.4%)

Abbreviations: cSSSI = complicated skin and skin structure infection; ME = microbiologically evaluable; MRSA = methicillin resistant *Staphylococcus aureus*; MSSA = methicillin susceptible *Staphylococcus aureus*; TOC = test-of-cure.

**Correlation of clinical and microbiological response with in vitro susceptibility rates for Studies P903-06 and P903-07:**

MIC values and response rates for ceftaroline and vancomycin for all baseline pathogens identified are summarized in Table 74. MIC values for all listed pathogens are similar to the data seen in the large surveillance studies. The MIC<sub>90</sub>s of ceftaroline for methicillin-susceptible and methicillin-resistant strains were 0.25 and 1 mcg/mL, respectively. Among the 362 isolates of *S. aureus* from ceftaroline-treated subjects, the ceftaroline MICs ranged from 0.06 to 2 mcg/mL. There were 24 clinical and microbiological failures that were associated with 7 isolates with a ceftaroline MIC of 0.12 mcg/mL, 8 isolates with a MIC of 0.25 mcg/mL, 7 isolates with a MIC of 0.5 mcg/mL, and 2 isolates with a MIC of 2 mcg/mL.

**Table 74 Clinical and Microbiological Response Rates by MIC for Ceftaroline and Vancomycin against *Staphylococcus aureus* from Skin Infections in cSSSI Studies P903-06 and P903-07 Combined**

	N	Clinical Success n/N (%)	Microbiological Success (Eradicated/Presumed Eradicated) n/N (%)
<b>Ceftaroline MIC (µg/mL)</b>			
0.06	3	3/3 (100%)	3/3 (100%)
0.12	79	72/79 (91.1%)	73/79 (92.4%)
0.25	156	148/156 (94.9%)	149/156 (95.5%)
0.5	109	102/109 (93.6%)	102/109 (93.6%)
1	11	11/11 (100%)	11/11 (100%)
2	4	2/4 (50.0%)	2/4 (50.0%)
Total	362	338/362 (93.4%)	340/362 (93.9%)
<b>Vancomycin MIC (µg/mL)</b>			
≤ 0.25	1	1/1 (100%)	1/1 (100%)
0.5	151	144/151 (95.4%)	145/151 (96%)
1	184	172/184 (93.5%)	169/184 (91.8%)
2	2	2/2 (100%)	1/2 (50.0%)
Total	338	319/338 (94.4%)	316/338 (93.5%)

Abbreviations: cSSSI = complicated skin and skin structure infection; MIC = minimally inhibitory concentration

Table 75 shows the analysis based on pvl status of the isolates. There were 167 pvl positive isolates. The MIC<sub>90</sub> values for both pvl positive and pvl negative isolates were 0.5 mcg/mL.

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**Table 75 Antibacterial Activity of Ceftaroline against Different Genotypes of *Staphylococcus aureus* from Ceftaroline-treated Subjects in cSSSI Studies P903-06 and P903-07 Combined**

Organism	N	Ceftaroline MIC (µg/ml)		
		Range	50%	90%
<i>S. aureus</i> PVL-positive	167	0.12 - 2	0.5	0.5
<i>S. aureus</i> PVL-negative	209	0.06 - 2	0.25	0.5
<i>S. aureus</i> (PFGE type) USA100	4	0.5 - 1	NA	NA
<i>S. aureus</i> (PFGE type) USA200	16	0.12 - 0.25	0.12	0.25
<i>S. aureus</i> (PFGE type) USA300	112	0.12 - 0.5	0.5	0.5
<i>S. aureus</i> (PFGE type) USA400	14	0.12 - 0.25	0.25	0.25
<i>S. aureus</i> (PFGE type) USA600	23	0.06 - 0.25	0.12	0.25
<i>S. aureus</i> (PFGE type) USA700	1	0.25	NA	NA
<i>S. aureus</i> (PFGE type) USA800	3	0.25 - 0.5	NA	NA
<i>S. aureus</i> SCCmecI	3	2	NA	NA
<i>S. aureus</i> SCCmecII	5	0.5 - 2	NA	NA
<i>S. aureus</i> SCCmecIII	8	0.5 - 2	NA	NA
<i>S. aureus</i> SCCmecIV	122	0.25 - 1	0.5	0.5

Abbreviations: cSSSI = complicated skin and skin structure infection; MIC = minimally inhibitory concentration; PFGE = pulsed-field gel electrophoresis; PVL = Pantone-Valentine leukocidin toxin; USA = United States of America.

There were no significant differences in terms of rates of eradication with respect to the pvl status of the isolates. An eradication rate of 94.5% was observed for the 91 pvl negative isolates in the ceftaroline treatment group in Study P903-06 (Table 76). Table 77 shows the eradication rates by pvl status for Study P903-07.

**Table 76 Clinical and Microbiological Success Rates for Ceftaroline and Vancomycin by MIC for PVL-negative *Staphylococcus aureus* from Skin Infections in cSSSI Study P903-06**

	N	Clinical Success n/N (%)	Microbiological Success (Eradicated/Presumed Eradicated n/N (%))
<b>Ceftaroline MIC (µg/mL)</b>			
0.06	2	2/2 (100%)	2/2 (100%)
0.12	24	22/24 (91.7%)	23/24 (95.8%)
0.25	40	37/40 (92.5%)	37/40 (92.5%)
0.5	17	17/17 (100%)	17/17 (100%)
1	6	6/6 (100%)	6/6 (100%)
2	2	1/2 (50.0%)	1/2 (50.0%)
<b>Total</b>	<b>91</b>	<b>85/91 (93.4%)</b>	<b>86/91 (94.5%)</b>

**Table 77 Clinical and Microbiological Success Rates for Ceftaroline and Vancomycin by MIC for PVL-negative *Staphylococcus aureus* from Skin Infections in cSSSI Study P903-07**

	N	Clinical Success n/N (%)	Microbiological Success (Eradicated/Presumed Eradicated n/N (%))
<b>Ceftaroline MIC (µg/mL)</b>			
0.06	1	1/1 (100%)	1/1 (100%)
0.12	41	37/41 (90.3%)	37/41 (90.3%)
0.25	59	58/59 (98.3%)	58/59 (98.3%)
0.5	8	7/8 (87.5%)	7/8 (87.5%)
1	2	2/2 (100%)	2/2 (100%)
2	1	0/1 (0%)	0/1 (0%)
<b>Total</b>	<b>112</b>	<b>105/112 (93.8%)</b>	<b>105/112 (93.8%)</b>
<b>Vancomycin MIC (µg/mL)</b>			
0.5	56	53/56 (94.6%)	54/56 (96.4%)
1	50	45/50 (90.0%)	45/50 (90.0%)
<b>Total</b>	<b>106</b>	<b>98/106 (92.5%)</b>	<b>99/106 (93.4%)</b>

Abbreviations: cSSSI = complicated skin and skin structure infection; MIC = minimum inhibitory concentration; PVL = Pantone-Valentine leukocidin toxin.

Source: Table 4.3 and Table 4.4

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Table 78 shows the clinical and microbiological eradication rates my MIC values for ceftaroline and vancomycin for USA 300 isolates for the Study P903-06 and P903-07.

**Table 78 Integrated Clinical and Microbiological Success Rates for Ceftaroline and Vancomycin by MIC for *Staphylococcus aureus* USA300 from Skin Infections in cSSSI Studies P903-06 and P903-07 Combined**

	<i>N</i>	<i>Clinical Success</i> <i>n/N (%)</i>	<i>Microbiological Success</i> <i>(Eradicated/Presumed Eradicated n/N (%))</i>
<b>Ceftaroline MIC (µg/mL)</b>			
0.12	5	5/5 (100%)	5/5 (100%)
0.25	27	25/27 (92.6%)	24/27 (88.9%)
0.5	75	68/75 (90.7%)	68/75 (90.7%)
Total	107	98/107 (91.5%)	97/107 (90.7%)
<b>Vancomycin MIC (µg/mL)</b>			
0.5	39	38/39 (97.4%)	38/39 (97.4%)
1	41	35/41 (85.4%)	35/41 (85.4%)
Total	80	73/80 (91.3%)	73/80 (91.3%)

Abbreviations: cSSSI = complicated skin and skin structure infection; MIC = minimally inhibitory concentration;  
USA = United States of America.

Table 79 shows the success rates for ceftaroline and vancomycin against *S. pyogenes*. The Applicant reported a success rate of 100% among the 56 baseline isolates among the ceftaroline treated subjects. However, there were two clinical and microbiological failures associated with isolates with vancomycin MICs of 0.25 mcg/mL.

**Table 79 Clinical and Microbiological Response Rates by MIC for Ceftaroline and Vancomycin against *Streptococcus pyogenes* from Skin Infections in cSSSI Studies P903-06 and P903-07 Combined.**

	<i>N</i>	<i>Clinical Success</i> <i>n/N (%)</i>	<i>Microbiological Success</i> <i>(Eradicated/Presumed Eradicated n/N (%))</i>
<b>Ceftaroline MIC (µg/mL)</b>			
≤ 0.004	55	55/55 (100%)	55/55 (100%)
0.008	1	1/1 (100%)	1/1 (100%)
Total	56	56/56 (100%)	56/56 (100%)
<b>Vancomycin MIC (µg/mL)</b>			
0.25	45	43/45 (95.6%)	43/45 (95.6%)
0.5	11	11/11 (100%)	11/11 (100%)
1	2	2/2 (100%)	2/2 (100%)
Total	58	56/58 (96.6%)	56/58 (96.6%)

Abbreviations: cSSSI = complicated skin and skin structure infection; MIC = minimally inhibitory concentration.

Ceftaroline demonstrated antibacterial activity against *S. pyogenes* with MICs that ranged from ≤ 0.004 to 0.008 mcg/mL and a MIC<sub>90</sub> of ≤ 0.004 mcg/mL. All other *Streptococcus* species were also susceptible to ceftaroline with all isolates being inhibited by concentrations that were ≤ 0.03 mcg/mL (Table 80-85).

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**Table 80 Clinical and Microbiological Response Rates by MIC for Ceftaroline and Vancomycin against *Streptococcus agalactiae* from Skin Infections in cSSSI Studies P903-06 and P903-07 Combined**

	<i>N</i>	<i>Clinical Success</i> <i>n/N (%)</i>	<i>Microbiological Success (Eradicated/Presumed Eradicated n/N (%)</i>
<b>Ceftaroline MIC (µg/mL)</b>			
0.008	9	8/9 (88.9%)	8/9 (88.9%)
0.015	11	11/11 (100%)	10/11 (90.9%)
Total	20	19/20 (95.0%)	18/20 (90.0%)
<b>Vancomycin MIC (µg/mL)</b>			
0.25	2	2/2 (100%)	2/2 (100%)
0.5	15	15/15 (100%)	15/15 (100%)
Total	17	17/17 (100%)	17/17 (100%)

Abbreviations: cSSSI = complicated skin and skin structure infection; MIC = minimally inhibitory concentration.

**Table 81 Integrated Clinical and Microbiological Response Rates by MIC for Ceftaroline and Vancomycin against *Streptococcus dysgalactiae* Clinical Isolates from Skin Infections in cSSSI Studies P903-06 and P903-07 Combined**

	<i>N</i>	<i>Clinical Success</i> <i>n/N (%)</i>	<i>Microbiological Success (Eradicated/Presumed Eradicated n/N (%)</i>
<b>Ceftaroline MIC (µg/mL)</b>			
≤ 0.004	6	6/6 (100%)	6/6 (100%)
0.008	6	6/6 (100%)	6/6 (100%)
Total	12	12/12 (100%)	12/12 (100%)
<b>Vancomycin MIC (µg/mL)</b>			
0.25	15	14/15 (93.3%)	14/15 (93.3%)
0.5	1	1/1 (100%)	1/1 (100%)
Total	16	15/16 (93.8%)	15/16 (93.8%)

Abbreviations: cSSSI = complicated skin and skin structure infection; MIC = minimally inhibitory concentration.

**Table 82 Integrated Clinical and Microbiological Response Rates by MIC for Ceftaroline and Vancomycin Against *Streptococcus anginosus* Group Clinical Isolates from Skin Infections in cSSSI Studies P903-06 and P903-07 Combined**

	<i>N</i>	<i>Clinical Success</i> <i>n/N (%)</i>	<i>Microbiological Success (Eradicated/Presumed Eradicated n/N (%)</i>
<b>Ceftaroline MIC (µg/mL)</b>			
≤ 0.004	3	3/3 (100%)	3/3 (100.0%)
0.008	3	3/3 (100%)	3/3 (100%)
0.015	1	1/1 (100%)	1/1 (100%)
0.03	5	5/5 (100%)	5/5 (100%)
Total	12	12/12 (100%)	12/12 (100%)

**Table 83 Integrated Clinical and Microbiological Response Rates by MIC for Ceftaroline and Vancomycin against *Streptococcus anginosus* Group Clinical Isolates from Skin Infections in cSSSI Studies P903-06 and P903-07 Combined**

	<i>N</i>	<i>Clinical Success</i> <i>n/N (%)</i>	<i>Microbiological Success (Eradicated/Presumed Eradicated n/N (%)</i>
<b>Vancomycin MIC (µg/mL)</b>			
0.5	10	10/10 (100%)	10/10 (100%)
1	6	5/6 (83.3%)	5/6 (83.3%)
Total	16	15/16 (93.8%)	15/16 (93.8%)

Abbreviations: cSSSI = complicated skin and skin structure infection; MIC = minimally inhibitory concentration.

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**Table 84 Integrated Clinical and Microbiological Response Rates by MIC for Ceftaroline and Vancomycin Against Other Streptococci from Skin Infections in cSSSI Studies P903-06 and P903-07 Combined**

	N	Clinical Success n/N (%)	Microbiological Success (Eradicated/Presumed Eradicated n/N (%)
<b>Ceftaroline MIC (µg/mL)</b>			
Group G β-hemolytic streptococci			
≤ 0.004	1	1/1 (100%)	1/1 (100%)
<i>Streptococcus equisimilis</i>			
≤ 0.004	1	1/1 (100%)	1/1 (100%)
<i>Streptococcus mitis</i>			
0.03	1	1/1 (100%)	1/1 (100%)
<i>Streptococcus oralis</i>			
0.015	1	1/1 (100%)	1/1 (100%)
<i>Streptococcus sanguis</i>			
0.008	1	1/1 (100%)	1/1 (100%)

**Table 85 Integrated Clinical and Microbiological Response Rates by MIC for Ceftaroline and Vancomycin Against Other Streptococci from Skin Infections in cSSSI Studies P903-06 and P903-07 Combined**

	N	Clinical Success n/N (%)	Microbiological Success (Eradicated/Presumed Eradicated n/N (%)
<b>Vancomycin MIC (µg/mL)</b>			
<i>Streptococcus mitis</i> group			
0.5	1	1/1 (100%)	1/1 (100%)
<i>Streptococcus equisimilis</i>			
0.5	1	1/1 (100%)	1/1 (100%)
<i>Streptococcus oralis</i>			
0.5	2	1/2 (50.0%)	2/2 (100%)
<i>Streptococcus parasanguis</i>			
0.25	1	1/1 (100%)	1/1 (100%)
<i>Streptococcus sanguis</i>			
0.5	1	1/1 (100%)	1/1 (100%)

Abbreviations: cSSSI = complicated skin and skin structure infection; MIC = minimally inhibitory concentration.

Ceftaroline and vancomycin success rates for *E. faecalis* are shown in Table 86. Among the 25 baseline isolates from ceftaroline-treated subjects, the ceftaroline MICs ranged from 0.25 to 16 mcg/mL. The clinical success rate was 80% and the microbiological success rate was 84%. One microbiological failure occurred at 0.5 mcg/mL and 3 at 1 mcg/mL. Among the *E. faecalis* from vancomycin-treated subjects, the vancomycin MICs ranged from 0.5 to 2 mcg/mL. The clinical success rate and the microbiological success rate were 91.7 %.

**Table 86 Integrated Clinical and Microbiological Response Rates by MIC for Ceftaroline and Vancomycin against *Enterococcus faecalis* Clinical Isolates from Skin Infections in cSSSI Studies P903-06 and P903-07 Combined**

	N	Clinical Success n/N (%)	Microbiological Success (Eradicated/Presumed Eradicated n/N (%)
<b>Ceftaroline MIC (µg/mL)</b>			
0.25	1	1/1 (100%)	1/1 (100%)
0.5	7	6/7 (85.7%)	6/7 (85.7%)
1	14	10/14 (71.4%)	11/14 (78.6%)
4	1	1/1 (100%)	1/1 (100%)
8	1	1/1 (100%)	1/1 (100%)
16	1	1/1 (100%)	1/1 (100%)
Total	25	20/25 (80.0%)	21/25 (84.0%)

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	<i>N</i>	<i>Clinical Success</i> <i>n/N (%)</i>	<i>Microbiological Success (Eradicated/Presumed Eradicated n/N (%)</i>
<b>Vancomycin MIC (µg/mL)</b>			
0.5	5	4/5 (80.0%)	4/5 (80.0%)
1	12	11/12 (91.7%)	12/12 (100%)
2	7	7/7 (100%)	7/7 (100%)
Total	24	22/24 (91.7%)	23/24 (95.8%)

Abbreviations: cSSSI = complicated skin and skin structure infection; MIC = minimally inhibitory concentration.

Among the Gram-negative pathogens, ceftaroline MIC<sub>90s</sub> for *E. coli*, *K. oxytoca*, and *K. pneumoniae* were 1, 0.25 and > 16 mcg/mL, respectively (Table 87). Among the 21 isolates of *E. coli*, the ceftaroline MICs ranged from 0.015 to > 16 mcg/mL, with 1 clinical and microbiological failure at 2 mcg/mL. There were 18 baseline isolates of *K. pneumoniae* with ceftaroline MICs that ranged from 0.03 to > 16 mcg/mL with 1 clinical and microbiological failure at 0.03 mcg/mL. There were 15 baseline isolates of *P. mirabilis* with ceftaroline MICs that ranged from ≤ 0.008 to > 16 mcg/mL and 4 total microbiological failures being associated with 2 isolates with MICs of 0.06 mcg/mL, 1 isolate at 0.12 mcg/mL, and 1 isolate at > 16 mcg/mL. The MIC<sub>90s</sub> for aztreonam and *E. coli* and *K. pneumoniae* were 0.12 mcg/mL and > 32 mcg/mL, respectively.

**Table 87 Integrated Clinical and Microbiological Response Rates by MIC for Ceftaroline against Gram-negative Organisms from Skin Infections in cSSSI Studies P903-06 and P903-07 Combined**

<i>Ceftaroline MIC</i> <i>(µg/mL)</i>	<i>N</i>	<i>Clinical Success</i> <i>n/N (%)</i>	<i>Microbiological Success</i> <i>(Eradicated/Presumed Eradicated n/N (%)</i>
<i>Citrobacter freundii complex</i>			
0.06	1	1/1 (100%)	1/1 (100%)
0.25	1	1/1 (100%)	1/1 (100%)
> 16	1	1/1 (100%)	1/1 (100%)
<i>Citrobacter koseri</i>			
0.12	1	1/1 (100%)	1/1 (100%)
<i>Enterobacter aerogenes</i>			
0.12	1	1/1 (100%)	1/1 (100%)
<i>Enterobacter cloacae</i>			
0.06	1	1/1 (100%)	1/1 (100%)
0.12	1	1/1 (100%)	1/1 (100%)
0.25	1	1/1 (100%)	0/1 (0%)
1	2	1/2 (50.0%)	1/2 (50.0%)

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<i>Ceftaroline MIC (µg/mL)</i>	<i>N</i>	<i>Clinical Success n/N (%)</i>	<i>Microbiological Success (Eradicated/Presumed Eradicated n/N (%))</i>
<i>Escherichia coli</i>			
0.015	1	1/1 (100%)	1/1 (100%)
0.03	2	2/2 (100%)	2/2 (100%)
0.06	8	8/8 (100%)	8/8 (100%)
0.12	4	4/4 (100%)	4/4 (100%)
0.25	1	1/1 (100%)	1/1 (100%)
0.5	2	2/2 (100%)	2/2 (100%)
1	1	1/1 (100%)	1/1 (100%)
2	1	0/1 (0%)	0/1 (0%)
> 16	1	1/1 (100%)	1/1 (100%)
<i>Klebsiella oxytoca</i>			
0.03	1	1/1 (100%)	1/1 (100%)
0.06	4	3/4 (75.0%)	4/4 (100%)
0.12	1	1/1 (100%)	1/1 (100%)
0.25	5	5/5 (100%)	5/5 (100%)
<i>Klebsiella pneumoniae</i>			
0.03	2	1/2 (50.0%)	1/2 (50.0%)
0.06	7	7/7 (100%)	7/7 (100%)
0.12	6	6/6 (100%)	6/6 (100%)
0.25	1	1/1 (100%)	1/1 (100%)
> 16	2	2/2 (100%)	2/2 (100%)
<i>Morganella morganii</i>			
0.06	2	2/2 (100%)	2/2 (100%)
0.25	2	2/2 (100%)	2/2 (100%)
0.5	1	1/1 (100%)	1/1 (100%)
1	1	0/1 (0%)	0/1 (0%)
4	1	1/1 (100%)	1/1 (100%)
16	1	1/1 (100%)	1/1 (100%)
> 16	3	3/3 (100%)	3/3 (100%)
<i>Ceftaroline MIC (µg/mL)</i>	<i>N</i>	<i>Clinical Success n/N (%)</i>	<i>Microbiological Success (Eradicated/Presumed Eradicated n/N (%))</i>
<i>Proteus mirabilis</i>			
≤ 0.008	1	1/1 (100%)	1/1 (100%)
0.06	6	3/6 (50.0%)	4/6 (66.7%)
0.12	4	3/4 (75.0%)	3/4 (75.0%)
0.5	1	1/1 (100%)	1/1 (100%)
> 16	3	2/3 (66.7%)	2/3 (66.7%)
<i>Proteus penneri</i>			
16	1	1/1 (100%)	1/1 (100%)
<i>Proteus vulgaris group</i>			
0.12	1	1/1 (100%)	1/1 (100%)
0.5	1	1/1 (100%)	1/1 (100%)
4	1	1/1 (100%)	1/1 (100%)
<i>Providencia stuartii</i>			
0.5	1	1/1 (100%)	1/1 (100%)
> 16	1	1/1 (100%)	1/1 (100%)
<i>Serratia liquefaciens</i>			
0.25	1	1/1 (100%)	1/1 (100%)
<i>Serratia marcescens</i>			
0.25	1	1/1 (100%)	1/1 (100%)
0.5	2	2/2 (100%)	1/2 (50.0%)
<b>Total</b>	<b>96</b>	<b>86/96 (89.6%)</b>	<b>86/96 (89.6%)</b>

Abbreviations: cSSSI = complicated skin and skin structure infection; MIC = minimally inhibitory concentration.

The clinical and microbiological success rates as a function of ceftaroline or aztreonam MIC is shown in Table 88.

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**Table 88 Integrated Clinical and Microbiological Response Rates by MIC for Aztreonam against Gram-negative Organisms from Skin Infections in cSSSI Studies P903-06 and P903-07 Combined**

<i>Aztreonam MIC (µg/mL)</i>	<i>N</i>	<i>Clinical Success n/N (%)</i>	<i>Microbiological Success (Eradicated/Presumed Eradicated n/N (%))</i>
<i>Citrobacter freundii complex</i>			
0.06	1	1/1 (100%)	1/1 (100%)
0.12	3	3/3 (100%)	3/3 (100%)
<i>Citrobacter koseri</i>			
≤ 0.03	1	1/1 (100%)	1/1 (100%)
<i>Enterobacter aerogenes</i>			
0.06	1	1/1 (100%)	1/1 (100%)
<i>Enterobacter cloacae</i>			
≤ 0.03	2	2/2 (100%)	2/2 (100%)
0.06	3	3/3 (100%)	3/3 (100%)
0.12	2	2/2 (100%)	2/2 (100%)
0.25	1	1/1 (100%)	1/1 (100%)
0.5	1	1/1 (100%)	1/1 (100%)
16	1	0/1 (0%)	1/1 (100%)
> 32	1	1/1 (100%)	1/1 (100%)
<i>Escherichia coli</i>			
≤ 0.03	7	5/7 (71.4%)	5/7 (71.4%)
0.06	8	8/8 (100%)	8/8 (100%)
0.12	3	3/3 (100%)	3/3 (100%)
0.25	1	1/1 (100%)	1/1 (100%)
0.5	1	1/1 (100%)	1/1 (100%)
<i>Klebsiella oxytoca</i>			
≤ 0.03	1	1/1 (100%)	0/1 (0%)
0.06	1	1/1 (100%)	1/1 (100%)
0.12	2	2/2 (100%)	2/2 (100%)
0.25	2	2/2 (100%)	2/2 (100%)
<i>Aztreonam MIC (µg/mL)</i>			
<i>Klebsiella pneumoniae</i>			
≤ 0.03	3	3/3 (100%)	3/3 (100%)
0.06	3	2/3 (66.7%)	2/3 (66.7%)
0.25	2	2/2 (100%)	2/2 (100%)
8	1	1/1 (100%)	1/1 (100%)
16	1	1/1 (100%)	1/1 (100%)
32	1	1/1 (100%)	1/1 (100%)
> 32	3	3/3 (100%)	3/3 (100%)
<i>Morganella morganii</i>			
≤ 0.03	4	3/4 (75.0%)	4/4 (100%)
1	1	1/1 (100%)	1/1 (100%)
4	1	1/1 (100%)	1/1 (100%)
<i>Proteus mirabilis</i>			
≤ 0.03	17	16/17 (94.1%)	15/17 (88.2%)
0.06	2	2/2 (100%)	2/2 (100%)
0.25	1	1/1 (100%)	1/1 (100%)
16	1	1/1 (100%)	1/1 (100%)
<i>Proteus penneri</i>			
≤ 0.03	1	1/1 (100%)	1/1 (100%)
<i>Providencia rettgeri</i>			
≤ 0.03	1	1/1 (100%)	1/1 (100%)
<i>Proteus vulgaris group</i>			
≤ 0.03	1	1/1 (100%)	1/1 (100%)
<i>Salmonella group D</i>			
	1	1/1 (100%)	1/1 (100%)
<i>Serratia marcescens</i>			
0.06	1	1/1 (100%)	1/1 (100%)
0.12	1	1/1 (100%)	1/1 (100%)
0.25	1	1/1 (100%)	1/1 (100%)
<b>Total</b>	<b>91</b>	<b>85/91 (93.4%)</b>	<b>85/91 (93.4%)</b>

Abbreviations: cSSSI = complicated skin and skin structure infection; MIC = minimally inhibitory concentration.

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The activity of ceftaroline against *P. aeruginosa* is shown in Table 89.

**Table 89 Integrated Clinical and Microbiological Response Rates by MIC for Ceftaroline and Aztreonam against *Pseudomonas aeruginosa* Clinical Isolates from Skin Infections in cSSSI Studies P903-06 and P903-07 Combined**

<i>Ceftaroline</i> MIC (µg/mL)	N	Clinical Success ( <i>ceftaroline</i> -treated) n/N (%)	Microbiological Success (Eradicated/Presumed Eradicated) n/N (%)
4	4	3/4 (75.0%)	3/4 (75.0%)
8	7	7/7 (100%)	6/7 (85.7%)
16	2	2/2 (100%)	2/2 (100%)
> 16	3	2/3 (66.7%)	2/3 (66.7%)
Total	16	14/16 (87.5%)	13/16 (81.3%)
<i>Aztreonam</i> MIC (µg/mL)	N	Clinical Success ( <i>vancomycin plus aztreonam</i> -treated) n/N (%)	Microbiological Success (Eradicated/Presumed Eradicated) n/N (%)
1	1	0/1 (0%)	0/1 (0%)
4	6	6/6 (100%)	6/6 (100%)
8	3	3/3 (100%)	3/3 (100%)
16	3	3/3 (100%)	3/3 (100%)
32	2	2/2 (100%)	2/2 (100%)
> 32	2	2/2 (100%)	2/2 (100%)
Total	17	16/17 (94.1%)	16/17 (94.1%)

Abbreviations: cSSSI = complicated skin and skin structure infection; MIC = minimally inhibitory concentration.

There were very few anaerobes encountered in Study P903-06 and P903-07, the clinical and microbiological success rates are shown in Table 90. However, due to the small numbers, no conclusions can be made.

**Table 90 Integrated Clinical and Microbiological Response Rates by MIC for Ceftaroline against Anaerobes from Skin Infections in cSSSI Studies P903-06 and P903-07 Combined**

<i>Ceftaroline</i> MIC (µg/mL)	N	Clinical Success n/N (%)	Microbiological Success (Eradicated/Presumed Eradicated) n/N (%)
<b>Gram-positive</b>			
<i>Finegoldia magna</i>			
0.25	2	2/2 (100%)	2/2 (100%)
<i>Peptostreptococcus micros</i>			
0.12	1	1/1 (100%)	1/1 (100%)
0.25	1	1/1 (100%)	1/1 (100%)
<b>Gram-negative</b>			
<i>Bacteriodes fragilis</i>			
8	1	1/1 (100%)	1/1 (100%)
16	1	1/1 (100%)	1/1 (100%)
> 32	1	0/1 (0%)	0/1 (0%)

Abbreviations: cSSSI = complicated skin and skin structure infection; MIC = minimally inhibitory concentration.

**Community Acquired Pneumoniae (Study P903-08 and P903-09)**

Along with the cSSSI studies, ceftaroline was evaluated in two pivotal studies P903-08 (Study P903-08, 2009) and P903-09 (Study P903-09, 2009) conducted in 1240 subjects with community-acquired bacterial pneumonia (CABP). The dosage regimen for ceftaroline fosamil in both Phase 3 CABP studies was 600 mg q12h as a 1-hour IV infusion for treatment duration of 5 to 7 days. TOC was scheduled to occur 8 to 15 days after the last dose of study medication in the Phase 3 CABP Studies.

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These two pivotal studies are global, multicenter, randomized, double-blinded, well-controlled studies conducted using identical protocols, with the exception of the use of, and criteria related to the use of, adjunctive clarithromycin therapy. The visit schedule, subject population, length of therapy, efficacy endpoints, and statistical considerations in each study are consistent with the US FDA Guidance for Industry for CABP (US FDA, 1998 July). For both studies, the primary efficacy parameter used was the clinical cure rate at TOC. The investigator using prospective definitions in the protocols did by-subject clinical outcome assessment.

***Treatment Administered***

In the ceftaroline group, ceftaroline fosamil 600 mg was administered by IV infusion over 60 minutes q12h. The dose was split into two consecutive 30-minute infusions to maintain the blind. The dose, on occasion, was adjusted to 400 mg q12h for subjects with moderate renal impairment as defined by a CrCl of greater than 30 mL/min but less than or equal to 50 mL/min.

In the active-comparator group, ceftriaxone was administered based on the approved Rocephin label recommendation (Rocephin [ceftriaxone sodium] package insert, 2004), which was 1 g IV infused over 30 minutes q24h. A 30-minute IV saline placebo to maintain the blind followed the dose.

The duration of study treatment was 5 to 7 days. During the initial 24 hours on study, all subjects in both treatment groups received adjunctive therapy which consisted of two oral doses of clarithromycin, at 500 mg each. Subjects were evaluated for efficacy at EOT, at TOC and, for those who were clinically cured at TOC, for persistence of clinical efficacy at LFU. For the purpose of analysis, TOC was defined as 8 to 15 days after EOT, and LFU was defined as 21 to 35 days after EOT.

**Key Inclusion and Exclusion Criteria**

***Key inclusion criteria included:***

- Adults aged 18 years or older with acute onset (= 7 days' duration) of CABP confirmed by radiograph or computed tomography (CT) scan
- At least three of seven predefined clinical signs or symptoms consistent with lower respiratory tract infection
- PORT Risk Class III or IV, thus requiring treatment with IV antimicrobials in a hospital, emergency room, or urgent care setting.

PORT scores were determined and the scores were used to classify subjects into five PORT Risk Classes. PORT Risk Class I represents subjects with the lowest risk for mortality and PORT Risk Class V represents subjects with the highest risk for mortality. Subjects with a PORT Risk Class of I or V were excluded in the original Phase 3 CABP protocols; this criterion was expanded to also exclude subjects in PORT Risk Class II at protocol Amendment 2. Randomization was stratified according to PORT Risk Class; subjects in PORT Risk Class III comprised one stratum and subjects in PORT Risk Class IV comprised the other stratum.

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***Key exclusion criteria included:***

- Respiratory infection with confirmed or suspected to be attributable to sources other than community-acquired bacterial pathogens including ventilator-associated, hospital-acquired, healthcare-associated
- Noninfectious causes (eg, cancer, aspiration)
- Pathogens that ceftaroline or ceftriaxone were unlikely to effectively treat such as *P. aeruginosa*, MRSA, or atypical organisms alone (eg, *M. pneumoniae*, *C. pneumoniae*, *Legionella spp.*)
- CABP that required treatment in an ICU setting
- 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.

***Microbiology and Laboratory Testing***

Sputum specimens (and pleural fluid if medically indicated) were collected by deep expectoration at baseline and study Days 1 - 6, and at End-of-Therapy (EOT) and Test-of-Cure (TOC) if the subject was deemed a clinical failure. Sputum induction (eg, via nebulization) was performed by appropriately trained personnel. Sputum samples were considered adequate and acceptable for processing if the sputum Gram stain revealed the presence of WBCs and is less than or equal to 10 squamous epithelial cells under low-power magnification. If the sputum Gram stain revealed greater than or equal to 11 squamous epithelial cells under low-power magnification, regardless of whether WBCs were present, the investigator was asked to obtain an additional specimen. All sputum specimens were transported to a local or regional laboratory for culture and antimicrobial susceptibility testing. All cultured isolates were then shipped to the central laboratory for identification confirmation (genus and species) and antimicrobial susceptibility testing.

The following organisms were considered sputum contaminants, rather than primary pathogens of CABP, and were not sent to the central laboratory for confirmation of organism identity and susceptibility: Fungi (yeast and molds, e.g., *Candida spp.* and *Aspergillus spp.*); however, these isolates were sent if there was evidence of a secondary fungal infection, *Enterococcus spp.* or Group D streptococci, Viridans streptococci, Coagulase-negative staphylococci, *Micrococcus spp.*, *Neisseria spp.* other than *N. meningitidis* or *N. gonorrhoeae*, *Corynebacterium spp.* and other coryneforms, *Lactobacillus spp.*, *Vibrio spp.*, *Capnocytophaga spp.*, *Cardiobacterium spp.*, *Flavobacterium spp.*

Pleural fluid samples for culture, Gram stain, and susceptibility testing were obtained as medically indicated during the study (from baseline to EOT). When pleural fluid cultures were required, fluid was collected on one aerobic blood culture bottle and one anaerobic blood culture bottle, for a total of two bottles. Culture and susceptibility testing were performed at the local or regional laboratory, as applicable, and all isolates were sent on to the central laboratory of identification confirmation and antimicrobial susceptibility testing. The microbiological procedures in this study were performed in concordance with the recommendations of the

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IDSA/ATS Guidelines for hospitalized subjects with CAP (Mandell et al, 2007). All baseline sputum samples were evaluated from white blood cells and squamous epithelial cells (Table 2.5B and 2.6B).

Antimicrobial susceptibility testing was conducted using the CLSI reference broth microdilution method using dried Sensititre MIC panels manufactured by Trek Diagnostics (Cleveland, OH). All isolates were tested for their susceptibility to ceftaroline and comparator agents (ceftriaxone) using the Kirby Bauer disk diffusion method in accordance with CLSI guidelines.

Blood for culture was also obtained at baseline and as medically indicated during the period of study drug treatment (Day 1 to TOC). Blood cultures were repeated on receipt of a positive result until sterilization was confirmed in those subjects with a positive result at baseline (i.e., the baseline blood culture grew an organism other than those judged to be transient or resident flora). When blood cultures were required, one aerobic bottle and one anaerobic bottle were obtained from two separate infection sites, for four bottles.

All blood culture specimens were transported to a local or regional laboratory for culture and antimicrobial susceptibility testing. All cultured isolates were then shipped to the central laboratory for identification confirmation (genus and species) and antimicrobial susceptibility testing. Antimicrobial susceptibility testing was conducted using the CLSI reference broth microdilution method using dried Sensititre MIC panels manufactured by Trek Diagnostics (Cleveland, OH). All isolates were tested for their susceptibility to ceftaroline and comparator agents (ceftriaxone) using the Kirby Bauer disk diffusion method in accordance with CLSI guidelines.

Blood samples were also collected at baseline and at Late Follow-up (LFU) for serology testing for atypical respiratory pathogens. Urine samples were also collected at baseline for Legionella pneumophila serogroup 1 and Streptococcus pneumoniae antigen detection. All results for the Legionella antigen test were available prior to enrollment since all subjects with a positive Legionella antigen test at baseline were excluded from enrollment.

***Efficacy Results Study P903-09 and -09:***

The individual and pooled results of these two pivotal studies show that ceftaroline fosamil administered IV at a dose of 600 mg every 12 hours (q12h) for 5 to 7 days is noninferior to ceftriaxone administered IV at a dose of 1 g (q24h) for 5 to 7 days for the treatment of CABP. The combined efficacy results for ceftaroline and ceftriaxone for Study CABP P903-08 and -09 are shown in Table 91. 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; in the Microbiological Evaluable Population, the clinical cure rate was 87.0% in the ceftaroline group and 81.0% in the ceftriaxone group.

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**Table 91 Summary of Integrated Clinical and Microbiological Success of Ceftaroline and Ceftriaxone in Adults with Pneumonia in Studies CABP P903-08 and P903-09**

Population	Clinical Success at Test-of-Cure- Noninferiority (CE and MITT Populations)			
	Ceftaroline n/N (%)	Ceftriaxone n/N (%)	Difference <sup>a</sup>	95% CI <sup>b</sup>
CE	387/459 (84.3%)	349/449 (77.7%)	6.6	1.6, 11.8
MITTE	479/580 (82.6%)	439/573 (76.6%)	6.0	1.4, 10.7
	Favorable <sup>c</sup> Microbiological Success at Test-of-Cure (ME and mMITT Populations)			
ME	134/154 (87.0%)	119/147 (81.0%)	6.1	-2.3, 14.6

a Difference = % cures in the ceftaroline group minus % cures in the ceftriaxone group.

b CIs were calculated using the Miettinen and Nurimen method without adjustment.

c Favorable responses included eradication and presumed eradication.

Abbreviations: CABP = community acquired bacterial pneumonia; CE = clinically evaluable; ME = microbiologically evaluable; MITT = modified intent-to-treat; mMITT = microbiological modified intent-to-treat;

MITTE = modified intent-to-treat efficacy; mMITTE = microbiological modified intent-to-treat efficacy

The combined clinical and microbiological success rates by baseline pathogen from the primary infection site or blood at TOC are shown in Table 92. For *S. pneumoniae*, the microbiological success rates were 87.3% and 72.9% for ceftaroline and ceftriaxone, respectively. For MDRSP, the clinical success for ceftaroline was 100% (4/4) and 25% (1/4) for ceftriaxone. For *S. aureus*, the clinical success rates were 72% (18/25) for ceftaroline and 55.6% (15/27) for ceftriaxone with microbiological success rates of 76% for ceftaroline and 70.4% for ceftriaxone.

For the *Enterobacteriaceae*, the microbiological success rates for ceftaroline for key pathogens were *E. coli* (83.3%), *K. oxytoca* (83.3%), and *K. pneumoniae* (100%). Overall, the success rates for ceftaroline were similar to those observed for ceftriaxone, suggesting that ceftaroline offers potential as a monotherapy for treating CABP caused by both gram-positive and gram-negative pathogens. The clinical success rates for ceftaroline and the nonfermenting gram-negative bacilli were low, 33.3%, for *P. aeruginosa* with a microbiological success rate of 66.7%. For *H. influenzae*, both rates were 83.3% (15/18) for ceftaroline and 85% (17/20) for ceftriaxone. For *Moraxella catarrhalis*, the clinical and microbiological success rates were 66.7% (2/3) for ceftaroline and 100% (2/2) for ceftriaxone.

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**Table 92 Clinical and Microbiological Success by Baseline Pathogen at TOC (ME Population) in CABP Studies P903-08 and P903-09**

Baseline Pathogen	Clinical Success at TOC Visit by Baseline Pathogen (ME Population)		Microbiological Success at TOC Visit by Baseline Pathogen (ME Population)	
	Ceftaroline n/N (%)	Ceftriaxone n/N (%)	Ceftaroline n/N (%)	Ceftriaxone n/N (%)
<b>Gram-positive aerobes</b>				
<i>Streptococcus pneumoniae</i>	54/63 (85.7%)	41/59 (69.5%)	55/63 (87.3%)	43/59 (72.9%)
MDRSP	4/4 (100%)	1/4 (25.0%)	4/4 (100%)	2/4 (50.0%)
Non-MDRSP	28/34 (82.4%)	18/24 (75.0%)	30/34 (88.2%)	18/24 (75.0%)
Penicillin-susceptible	31/37 (83.3%)	19/28 (67.9%)	33/37 (89.2%)	20/28 (71.4%)
Penicillin-intermediate	1/1 (100%)		1/1 (100%)	
<i>Streptococcus agalactiae</i>	1/1 (100%)		1/1 (100%)	
<i>Staphylococcus aureus</i>	18/25 (72.0%)	15/27 (55.6%)	19/25 (76.0%)	19/27 (70.4%)
MRSA		1/2 (50.0%)		1/2 (50.0%)
MSSA	18/25 (72.0%)	14/25 (56.0%)	19/25 (76.0%)	18/25 (72.0%)
<b>Gram-negative aerobes</b>				
<b>Enterobacteriaceae</b>				
<i>Citrobacter freundii</i> complex		1/1 (100%)		1/1 (100%)
<i>Citrobacter koseri</i>	2/2 (100%)	1/1 (100%)	2/2 (100%)	1/1 (100%)
<i>Enterobacter aerogenes</i>	1/2 (50.0%)	2/2 (100%)	2/2 (100%)	2/2 (100%)
<i>Enterobacter cloacae</i>	7/7 (100%)	9/12 (75.0%)	7/7 (100%)	10/12 (83.3%)
<i>Escherichia coli</i>	10/12 (83.3%)	9/12 (75.0%)	10/12 (83.3%)	11/12 (91.7%)
<i>Klebsiella oxytoca</i>	5/6 (83.3%)	7/8 (87.5%)	5/6 (83.3%)	8/8 (100%)
<i>Klebsiella pneumoniae</i>	13/13 (100%)	10/12 (83.3%)	13/13 (100%)	10/12 (83.3%)
<i>Proteus mirabilis</i>	2/3 (66.7%)		2/3 (66.7%)	
<i>Serratia liquefaciens</i>	1/1 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)
<i>Serratia marcescens</i>	3/3 (100%)	2/3 (66.7%)	3/3 (100%)	2/3 (66.7%)
<b>Nonfermenting gram-negative bacilli</b>				
<i>Pseudomonas aeruginosa</i>	1/3 (33.3%)	0/2 (0%)	2/3 (66.7%)	0/2 (0%)
Baseline Pathogen	Clinical Success at TOC Visit by Baseline Pathogen (ME Population)		Microbiological Success at TOC Visit by Baseline Pathogen (ME Population)	
	Ceftaroline n/N (%)	Ceftriaxone n/N (%)	Ceftaroline n/N (%)	Ceftriaxone n/N (%)
<b>Other gram-negatives</b>				
<i>Haemophilus influenzae</i>	15/18 (83.3%)	17/20 (85.0%)	15/18 (83.3%)	17/20 (85.0%)
<i>Haemophilus haemolyticus</i>	1/1 (100%)		1/1 (100%)	
<i>Haemophilus parahaemolyticus</i>	2/3 (66.7%)	2/2 (100%)	2/3 (66.7%)	2/2 (100%)
<i>Haemophilus parainfluenzae</i>	16/16 (100%)	15/17 (88.2%)	16/16 (100%)	16/17 (94.1%)
<i>Moraxella catarrhalis</i>	2/3 (66.7%)	2/2 (100%)	2/3 (66.7%)	2/2 (100%)

Abbreviations: CABP = community acquired bacterial pneumonia; MDRSP = Multi Drug Resistant *S. pneumoniae*; ME = Microbiologically Evaluable; MRSA = Methicillin Resistant *S. aureus*; MSSA =Methicillin Susceptible *S. aureus*; TOC = Test-of-cure.

The integrated clinical and microbiological success by baseline pathogen from subjects with monomicrobial infections at TOC in the ME population is shown in Table 93. For *S. pneumoniae* and *S. aureus*, the ceftaroline microbiological success rates were 88.6% and 80%, respectively. Among the limited numbers of *Enterobacteriaceae*, a 100% ceftaroline success rates were observed for *E. coli* (8/8) and *K. pneumoniae* (6/6) and 75% (3/4) for *K. oxytoca*. The ceftaroline microbiological success rate was 77.8% (7/9) for *H. influenzae* and 100% (10/10) for *H. parainfluenzae*.

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**Table 93 Clinical and Microbiological Success by Baseline Pathogen from Subjects with Monomicrobial Infections at TOC (ME Population) in CABP Studies P903-08 and P903-09**

Baseline Pathogen	Clinical Success at TOC Visit by Baseline Pathogen (ME Population)		Microbiological Success at TOC Visit by Baseline Pathogen (ME Population)	
	Ceftaroline n/N (%)	Ceftriaxone n/N (%)	Ceftaroline n/N (%)	Ceftriaxone n/N (%)
<b>Gram-positive aerobes</b>				
<i>Streptococcus pneumoniae</i>	39/44 (86.6%)	27/38 (71.1%)	39/44 (88.6%)	28/38 (73.7%)
MDRSP	3/3 (100%)	1/2 (50.0%)	3/3 (100%)	2/2 (100%)
Non-MDRSP	18/20 (90.0%)	13/17 (76.5%)	19/20 (95.0%)	13/17 (76.5%)
Penicillin-susceptible	21/23 (91.3%)	14/19 (73.7%)	22/23 (95.7%)	15/19 (78.9%)
<i>Streptococcus agalactiae</i>	1/1 (100%)		1/1 (100%)	
<i>Staphylococcus aureus</i>	11/15 (73.3%)	5/12 (41.7%)	12/15 (80.0%)	7/12 (58.3%)
MRSA		1/2 (50.0%)		1/2 (50.0%)
MSSA	11/15 (73.3%)	4/10 (40.0%)	12/15 (80.0%)	6/10 (60.0%)
<b>Gram-negative aerobes</b>				
<b>Enterobacteriaceae</b>				
<i>Citrobacter koseri</i>	1/1 (100%)		1/1 (100%)	
<i>Enterobacter aerogenes</i>	0/1 (0%)	1/1 (100%)	1/1 (100%)	1/1 (100%)
<i>Enterobacter cloacae</i>	4/4 (100%)	4/4 (100%)	4/4 (100%)	4/4 (100%)
<i>Escherichia coli</i>	8/8 (100%)	6/6 (100%)	8/8 (100%)	6/6 (100%)
<i>Klebsiella oxytoca</i>	3/4 (75.0%)	5/5 (100%)	3/4 (75.0%)	5/5 (100%)
<i>Klebsiella pneumoniae</i>	6/6 (100%)	5/6 (83.3%)	6/6 (100%)	5/6 (83.3%)
<i>Proteus mirabilis</i>	1/1 (100%)		1/1 (100%)	
<i>Serratia marcescens</i>	2/2 (100%)		2/2 (100%)	
<b>Nonfermenting gram-negative bacilli</b>				
<i>Pseudomonas aeruginosa</i>	2/2 (100%)	1/1 (100%)	1/2 (50.0%)	0/1 (0%)
<b>Other gram-negatives</b>				
<i>Haemophilus influenzae</i>	7/9 (77.8%)	14/15 (93.3%)	7/9 (77.8%)	14/15 (93.3%)
<i>Haemophilus haemolyticus</i>	1/1 (100%)		1/1 (100%)	
<i>Haemophilus parahaemolyticus</i>	1/1 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)
<i>Haemophilus parainfluenzae</i>	10/10 (100%)	10/11 (90.9%)	10/10 (100%)	10/11 (90.9%)
<i>Moraxella catarrhalis</i>	1/1 (100%)	2/2 (100%)	1/1 (100%)	2/2 (100%)

Abbreviations: CABP = community acquired bacterial pneumonia; MIC = minimal inhibitory concentration; TOC = test-of-cure.

Combined success rates by baseline pathogens from subjects with polymicrobial infections are shown in Table 94. The microbiological success rates for *S. pneumoniae* were 84.2% (16/19) for ceftaroline and 71.4% (15/21) for ceftriaxone and for *S. aureus* was 70.0% (7/10) for ceftaroline and 80% (12/15) for ceftriaxone.

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**Table 94 Clinical and Microbiological Success by Baseline Pathogen from Subjects with Polymicrobial Infections at TOC (ME Population) in CABP Studies P903-08 and P903-09**

Baseline Pathogen	Clinical Success at TOC Visit by Baseline Pathogen (ME Population)		Microbiological Success at TOC Visit by Baseline Pathogen (ME Population)	
	Ceftaroline n/N (%)	Ceftriaxone n/N (%)	Ceftaroline n/N (%)	Ceftriaxone n/N (%)
<b>Gram-positive aerobes</b>				
<i>Streptococcus pneumoniae</i>	15/19 (78.9%)	14/21 (66.7%)	16/19 (84.2%)	15/21 (71.4%)
MDRSP	1/1 (100%)	0/2 (0%)	1/1 (100%)	0/2 (0%)
Non-MDRSP	10/14 (71.4%)	5/7 (71.4%)	11/14 (78.6%)	5/7 (71.4%)
Penicillin-susceptible	10/14 (71.4%)	5/9 (55.6%)	11/14 (78.6%)	5/9 (55.6%)
<i>Staphylococcus aureus</i>	7/10 (70.0%)	10/15 (66.7%)	7/10 (70.0%)	12/15 (80.0%)
MSSA	7/10 (70.0%)	10/15 (66.7%)	7/10 (70.0%)	12/15 (80.0%)
<b>Gram-negative aerobes</b>				
<i>Enterobacteriaceae</i>				
<i>Citrobacter freundii</i> complex		1/1 (100%)		1/1 (100%)
<i>Citrobacter koseri</i>	1/1 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)
<i>Enterobacter aerogenes</i>	1/1 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)
<i>Enterobacter cloacae</i>	3/3 (100%)	5/8 (62.5%)	3/3 (100%)	6/8 (75.0%)
<i>Escherichia coli</i>	2/4 (50.0%)	3/6 (50.0%)	2/4 (50%)	5/6 (83.3%)
<i>Klebsiella oxytoca</i>	2/2 (100%)	2/3 (66.7%)	2/2 (100%)	3/3 (100%)
<i>Klebsiella pneumoniae</i>	7/7 (100%)	5/6 (83.3%)	7/7 (100%)	5/6 (83.3%)
<i>Proteus mirabilis</i>	2/2 (100%)		2/2 (100%)	
<i>Serratia liquefaciens</i>	1/1 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)
<i>Serratia marcescens</i>	1/1 (100%)	2/3 (66.7%)	1/1 (100%)	1/1 (100%)
<b>Nonfermenting gram-negative bacilli</b>				
<i>Pseudomonas aeruginosa</i>	1/1 (100%)	0/1 (0%)	1/1 (100%)	0/1 (0%)
<b>Other gram-negatives</b>				
<i>Haemophilus influenzae</i>	8/9 (88.9%)	3/5 (60.0%)	8/9 (88.9%)	3/5 (60.0%)
<i>Haemophilus parahaemolyticus</i>	1/2 (50.0%)	1/1 (100%)	1/2 (50.0%)	1/1 (100%)
<i>Haemophilus parainfluenzae</i>	6/6 (100%)	5/6 (83.3%)	6/6 (100%)	5/6 (83.3%)
<i>Moraxella catarrhalis</i>	1/2 (50%)		1/2 (50%)	

Abbreviations: CABP = community acquired bacterial pneumonia; MDRSP = multidrug-resistant *Streptococcus pneumoniae*; Non-MDRSP = non multidrug-resistant *Streptococcus pneumoniae*; ME = microbiologically evaluable; MSSA = methicillin susceptible *Staphylococcus aureus*; TOC = test-of-cure.

***Correlation of Microbiological and Clinical Response with In Vitro Susceptibility Test Results***

The combined clinical and microbiological eradication rates for ceftaroline and ceftriaxone against *S. pneumoniae* as a function of MIC are shown in Table 95. There were 36 *S. pneumoniae* isolates in the ceftaroline treatment arm that had a range in MIC from  $\leq 0.015$  to 0.12 mcg/mL. The Applicant reported 6 clinical and 5 microbiological failures associated with  $\leq 0.015$  mcg/mL. There were 4 failures associated with a MIC of 0.008 mcg/mL and 1 at 0.015 mcg/ml in the ceftriaxone treatment arm, MIC values for *S. pneumoniae* ranged from  $\leq 0.015$  to 2 mcg/mL for the 28 ceftriaxone-treated subjects. There were 9 clinical and 8 microbiological failures, where 5 microbiological failures were associated with  $\leq 0.015$  mcg/mL, 1 at 0.03 mcg/mL, 1 at 0.06 mcg/mL, and 1 at 0.5 mcg/mL.

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**Table 95 Integrated Clinical and Microbiological Response Rates by MIC for Ceftaroline and Ceftriaxone against *Streptococcus pneumoniae* in CABP Studies P903-08 and P903-09**

<i>Ceftaroline</i> MIC (µg/mL)	<i>N</i>	<i>Clinical Success</i> n/N (%)	<i>Microbiological Success</i> ( <i>Eradicated/Presumed Eradicated</i> n/N (%))
≤ 0.004	4	4/4 (100.0%)	4/4 (100.0%)
0.008	20	16/20 (80.0%)	16/20 (80.0%)
0.015	8	6/8 (75.0%)	7/8 (87.5%)
0.03	2	2/2 (100.0%)	2/2 (100.0%)
0.06	1	1/1 (100.0%)	1/1 (100.0%)
0.25	1	1/1 (100.0%)	1/1 (100.0%)
<b>Total</b>	<b>36</b>	<b>30/36 (83.3%)</b>	<b>31/36 (86.1%)</b>
<b><i>Ceftriaxone</i> MIC (µg/mL)</b>			
≤ 0.015	17	12/17 (70.6%)	12/17 (70.6%)
0.03	3	2/3 (66.7%)	2/3 (66.7%)
0.06	2	2/2 (100%)	2/2 (100%)
0.12	2	1/2 (50.0%)	2/2 (100%)
0.25	1	1/1 (100%)	1/1 (100%)
0.5	1	0/1 (0%)	0/1 (0%)
1	1	1/1 (100%)	1/1 (100%)
2	1	0/1 (0%)	0/1 (0%)
<b>Total</b>	<b>28</b>	<b>19/28 (67.9%)</b>	<b>20/28 (71.4%)</b>

There were 4 isolates that were identified as multi-drug resistant *S. pneumoniae* (MDRSP). The designation MDRSP applied to isolates resistant to two or more of the following antibiotics: penicillin (MIC > 2 µg/mL); second-generation cephalosporins, eg, cefuroxime; macrolides, tetracyclines, chloramphenicol, fluoroquinolones, and trimethoprim/sulfamethoxazole). Additional information with respect to resistance concerning these organisms was not found. The MIC ranged from ≤0.015-0.12 mcg/mL and following treatment, all were successfully treated with ceftaroline and presumed eradicated. Among the 4 MDR *S. pneumoniae* isolates in the ceftriaxone treatment group, only 2 were presumed eradicated (Table 96).

**Table 96 Integrated Clinical and Microbiological Response Rates by MIC for Ceftaroline and Ceftriaxone against MDR *Streptococcus pneumoniae* in CABP Studies P903-08 and P903-09**

	<i>N</i>	<i>Clinical Success</i> n/N (%)	<i>Microbiological Success</i> ( <i>Eradicated/Presumed Eradicated</i> n/N (%))
<b><i>Ceftaroline</i> MIC (µg/mL)</b>			
≤ 0.015	2	2/2 (100%)	2/2 (100%)
0.03	1	1/1 (100%)	1/1 (100%)
0.12	1	1/1 (100%)	1/1 (100%)
<b>Total</b>	<b>4</b>	<b>4/4 (100%)</b>	<b>4/4 (100%)</b>
<b><i>Ceftriaxone</i> MIC (µg/mL)</b>			
0.12	1	0/1 (0%)	1/1 (100%)
0.5	1	0/1 (0%)	0/1 (0%)
1	1	1/1 (100%)	1/1 (100%)
2	1	0/1 (0%)	0/1 (0%)
<b>Total</b>	<b>4</b>	<b>1/4 (25.0%)</b>	<b>2/4 (50.0%)</b>

Abbreviations: CABP = community acquired bacterial pneumonia; MIC = minimal inhibitory concentration.

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Table 97 shows the combined clinical and microbiological response rate by MIC for ceftaroline and ceftriaxone against non-MDR *S. pneumoniae*. There were a total of 32 isolates for the ceftaroline-treated group, all with 81.3% (26/32) clinical and 87.5% (28/32) microbiological success. All 4 clinical and microbiological failures occurred at an MIC  $\leq$  0.015 mcg/mL. There were 24 isolates for the ceftriaxone-treated group with a clinical and microbiology success of 75% (18/24). Five ceftriaxone microbiological failures occurred at an MIC of  $\leq$  0.015 mcg/mL and 1 occurred at 0.03 mcg/mL.

**Table 97 Integrated Clinical and Microbiological Response Rates by MIC for Ceftaroline and Ceftriaxone against Non-MDR *Streptococcus pneumoniae* in CABP Studies P903-08 and P903-09**

	<i>N</i>	<i>Clinical Success</i> <i>n/N (%)</i>	<i>Microbiological Success</i> <i>(Eradicated/Presumed</i> <i>Eradicated n/N (%)</i>
<b>Ceftaroline MIC (<math>\mu</math>g/mL)</b>			
$\leq$ 0.015	32	26/32 (81.3%)	28/32 (87.5%)
Total	32	26/32 (81.3%)	28/32 (87.5%)
<b>Ceftriaxone MIC (<math>\mu</math>g/mL)</b>			
$\leq$ 0.015	17	12/17 (70.6%)	12/17 (70.6%)
0.03	3	2/3 (66.7%)	2/3 (66.7%)
0.06	2	2/2 (100%)	2/2 (100%)
0.12	1	1/1 (100%)	1/1 (100%)
0.25	1	1/1 (100%)	1/1 (100%)
Total	24	18/24 (75.0%)	18/24 (75.0%)

Abbreviations: CABP = community acquired bacterial pneumonia; MDR = multi-drug resistant; MIC = minimal inhibitory concentration.

Table 98 shows the integrated clinical and microbiological response rates by MIC for ceftaroline and ceftriaxone against penicillin-intermediate *S. pneumoniae* (PISP). There was only 1 isolate in the ceftaroline-treated group with a penicillin MIC of 0.12 mcg/mL and 100% clinical and microbiological success. There were no isolates from the ceftriaxone-treated group.

**Table 98 Integrated Clinical and Microbiological Response Rates by MIC for Ceftaroline against Penicillin-intermediate *Streptococcus pneumoniae* in CABP Studies P903-08 and P903-09**

<i>Ceftaroline MIC</i> ( $\mu$ g/mL)	<i>N</i>	<i>Clinical Success</i> <i>n/N (%)</i>	<i>Microbiological Success</i> <i>(Eradicated/Presumed</i> <i>Eradicated n/N (%)</i>
0.12	1	1/1 (100%)	1/1 (100%)
Total	1	1/1 (100%)	1/1 (100%)

Abbreviations: CABP = community acquired bacterial pneumonia; MIC = minimal inhibitory concentration.

Table 99 shows the activity of ceftaroline and comparator against penicillin-susceptible *S. pneumoniae* (PSSP) isolates. A microbiological success rate of 88.6% (31/35) was reported in the ceftaroline treatment arm compared with a 71.4 success rate for the comparator.

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**Table 99 Integrated Clinical and Microbiological Response Rates by MIC for Ceftaroline and Ceftriaxone against Penicillin-susceptible *Streptococcus pneumoniae* in CABP Studies P903-08 and P903-09**

	<i>N</i>	<i>Clinical Success</i> <i>n/N (%)</i>	<i>Microbiological Success</i> <i>(Eradicated/Presumed</i> <i>Eradicated n/N (%)</i>
<b>Ceftaroline MIC (µg/mL)</b>			
≤ 0.015	34	28/34 (82.4%)	30/34 (88.2%)
0.03	1	1/1 (100%)	1/1 (100%)
Total	35	29/35 (82.9%)	31/35 (88.6%)
<b>Ceftriaxone MIC (µg/mL)</b>			
≤ 0.015	17	12/17 (70.6%)	12/17 (70.6%)
0.03	3	2/3 (66.7%)	2/3 (66.7%)
0.06	2	2/2 (100%)	2/2 (100%)
0.12	2	1/2 (50.0%)	2/2 (100%)
0.25	1	1/1 (100%)	1/1 (100%)
0.5	1	0/1 (0%)	0/1 (0%)
1	1	1/1 (100%)	1/1 (100%)
2	1	0/1 (0%)	0/1 (0%)
Total	28	19/28 (67.9%)	20/28 (71.4%)

Abbreviations: CABP = community acquired bacterial pneumonia; MIC = minimal inhibitory concentration.

Table 100 shows the clinical and microbiological response by MIC for ceftaroline and ceftriaxone against *S. aureus*. Of the 25 isolates identified in the ceftaroline treatment arm, 19 were eradicated for a success rate of 76%. Please note that all isolates in the ceftaroline treatment group were MSSA; none was identified as MRSA. A similar success rate was observed in the ceftriaxone treated group.

**Table 100 Integrated Clinical and Microbiological Response Rates by MIC for Ceftaroline and Ceftriaxone against *Staphylococcus aureus* in CABP Studies P903-08 and P903-09**

	<i>N</i>	<i>Clinical Success</i> <i>n/N (%)</i>	<i>Microbiological Success</i> <i>(Eradicated/Presumed</i> <i>Eradicated n/N (%)</i>
<b>Ceftaroline MIC (µg/mL)</b>			
0.12	3	2/3 (66.7%)	2/3 (66.7%)
0.25	21	16/21 (76.2%)	16/21 (76.2%)
0.5	1	0/1 (0%)	1/1 (100%)
Total	25	18/25 (72.0%)	19/25 (76.0%)
<b>Ceftriaxone MIC (µg/mL)</b>			
2	3	2/3 (66.7%)	2/3 (66.7%)
4	21	12/21 (57.1%)	16/21 (76.2%)
8	1	0/1 (0%)	0/1 (0%)
32	1	1/1 (100%)	1/1 (100%)
Total	26	15/26 (57.7%)	19/26 (73.1%)

Abbreviations: CABP = community acquired bacterial pneumonia; MIC = minimal inhibitory concentration.

Table 101 shows the response rates by MIC for ceftaroline and ceftriaxone against MRSA. There were no isolates in the ceftaroline-treated group and 2 isolates in the ceftriaxone-treated group with a clinical and microbiological success of 50% (1/2). The microbiological failure occurred at an MIC of 8 mcg/mL.

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**Table 101 Integrated Clinical and Microbiological Response Rates by MIC for Ceftriaxone against Methicillin-resistant *Staphylococcus aureus* in CABP Studies P903-08 and P903-09**

<i>Ceftriaxone</i> MIC (µg/mL)	<i>N</i>	<i>Clinical Success</i> <i>n/N (%)</i>	<i>Microbiological Success</i> <i>(Eradicated/Presumed</i> <i>Eradicated n/N (%)</i>
8	1	0/1 (0%)	0/1 (0%)
32	1	1/1 (100%)	1/1 (100%)
Total	2	1/2 (50.0%)	1/2 (50.0%)

Abbreviations: CABP = community acquired bacterial pneumonia; MIC = minimal inhibitory concentration.

Table 102 shows the integrated clinical and microbiological response rates by MIC for ceftaroline and ceftriaxone against *Pseudomonas aeruginosa*. There were only 2 isolates in the ceftaroline-treated group with 50% (1/2) clinical and microbiological success rate. The one ceftaroline microbiological failure occurred at an MIC ≤ 4 mcg/mL. There were a total of 2 isolates for the ceftriaxone-treated group with a clinical and microbiological success of 0% (0/2). One microbiological failure occurred at 2 mcg/mL and 1 at > 32 mcg/mL.

**Table 102 Integrated Clinical and Microbiological Response Rates by MIC for Ceftaroline and Ceftriaxone against *Pseudomonas aeruginosa* in CABP Studies P903-08 and P903-09**

	<i>N</i>	<i>Clinical Success</i> <i>(ceftaroline-treated)</i> <i>n/N (%)</i>	<i>Microbiological Success</i> <i>(Eradicated/Presumed</i> <i>Eradicated n/N (%)</i>
<b>Ceftaroline MIC (µg/mL)</b>			
4	1	0/1 (0%)	0/1 (0%)
16	1	1/1 (100%)	1/1 (100%)
Total	2	1/2 (50.0%)	1/2 (50.0%)
<b>Ceftriaxone MIC (µg/mL)</b>			
4	1	0/1 (0%)	0/1 (0%)
> 32	1	0/1 (0%)	0/1 (0%)
Total	2	0/2 (0%)	0/2 (0%)

Abbreviations: CABP = community acquired bacterial pneumonia; MIC = minimal inhibitory concentration.

Table 103 and Table 104 show the combined clinical and microbiological response rates by MIC for ceftaroline and ceftriaxone against *Enterobacteriaceae*. There were a total of 46 isolates for ceftaroline-treated group with 89.1% (41/46) clinical and 91.3% (42/46) microbiological success. For *E. coli*, 1 ceftaroline microbiological failure occurred at an MIC 0.03 mcg/mL and 1 occurred at 0.12 mcg/mL. For *P. mirabilis*, 1 ceftaroline microbiological failure occurred at an MIC 0.06 mcg/mL. There were a total of 52 isolates for ceftriaxone-treated group with 80.8% (42/52) clinical and 88.5% (46/52) microbiological success. For *E. cloacae*, 1 ceftriaxone microbiological failure occurred at an MIC 0.06 mcg/mL, 1 at 0.25 mcg/mL, and 1 at 0.5 mcg/mL; for *E. coli*, 2 ceftriaxone microbiological failures occurred at an MIC 0.06 mcg/mL; for *K. pneumoniae*, 2 ceftriaxone microbiological failures occurred at 0.06 mcg/mL; and for *S. marcescens*, 1 microbiological failure occurred at 0.25 mcg/mL.

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**Table 103 Integrated Clinical and Microbiological Response Rates by MIC for Ceftaroline against *Enterobacteriaceae* in CABP Studies P903-08 and P903-09**

<i>Ceftaroline</i> MIC (µg/mL)	N	Clinical Success n/N (%)	Microbiological Success (Eradicated/Presumed Eradicated n/N (%))
<i>Citrobacter koseri</i>			
0.06	1	1/1 (100%)	1/1 (100%)
<i>Enterobacter aerogenes</i>			
0.12	1	0/1 (0%)	1/1 (100%)
0.25	1	1/1 (0%)	1/1 (0%)
<i>Enterobacter cloacae</i>			
0.25	4	4/4 (100%)	4/4 (100%)
0.5	3	3/3 (100%)	3/3 (100%)
<i>Escherichia coli</i>			
0.03	4	3/4 (75/0%)	3/4 (75/0%)
0.06	5	5/5 (100%)	5/5 (100%)
0.12	1	0/1 (0%)	0/1 (0%)
0.5	1	1/1 (100%)	1/1 (100%)
1	1	1/1 (100%)	1/1 (100%)
<i>Klebsiella oxytoca</i>			
0.03	1	0/1 (0%)	0/1 (0%)
0.06	3	3/3 (100%)	3/3 (100%)
0.25	2	2/2 (100%)	2/2 (100%)
<i>Klebsiella pneumoniae</i>			
0.06	3	3/3 (100%)	3/3 (100%)
0.12	3	3/3 (100%)	3/3 (100%)
0.25	3	3/3 (100%)	3/3 (100%)
0.5	3	3/3 (100%)	3/3 (100%)
<i>Proteus mirabilis</i>			
0.06	2	1/2 (50.0%)	1/2 (50.0%)
<i>Serratia liquefaciens</i>			
0.5	1	1/1 (100%)	1/1 (100%)
<i>Serratia marcescens</i>			
0.5	2	2/2 (100%)	2/2 (100%)
1	1	1/1 (100%)	1/1 (100%)
<b>Total</b>	<b>46</b>	<b>41/46 (89.1%)</b>	<b>42/46 (91.3%)</b>

Abbreviations: CABP = community acquired bacterial pneumonia; MIC = minimal inhibitory concentration.

**Table 104 Integrated Clinical and Microbiological Response Rates by MIC for Ceftriaxone against *Enterobacteriaceae* in CABP Studies P903-08 and P903-09**

<i>Ceftriaxone</i> MIC (µg/mL)	N	Clinical Success n/N (%)	Microbiological Success (Eradicated/Presumed Eradicated n/N (%))
<i>Citrobacter koseri</i>			
0.03	1	1/1 (100%)	1/1 (100%)
<i>Citrobacter freundii</i> complex			
0.12	1	1/1 (100%)	1/1 (100%)
<i>Enterobacter aerogenes</i>			
0.06	1	1/1 (100%)	1/1 (100%)
0.12	1	1/1 (100%)	1/1 (100%)
<i>Enterobacter cloacae</i>			
0.12	4	3/4 (75.0%)	3/4 (75.0%)
0.25	5	4/5 (80.0%)	5/5 (100%)
0.5	3	2/3 (66.7%)	2/3 (66.7%)
<i>Escherichia coli</i>			
0.03	3	3/3 (100%)	3/3 (100%)
0.06	7	5/7 (71.4%)	6/7 (85.7%)
0.12	1	0/1 (0%)	1/1 (100%)
> 32	1	1/1 (100%)	1/1 (100%)
<i>Klebsiella oxytoca</i>			
≤ 0.015	1	1/1 (100%)	1/1 (100%)
0.03	1	1/1 (100%)	1/1 (100%)
0.06	6	5/6 (83.3%)	6/6 (100%)
<i>Klebsiella pneumoniae</i>			
0.03	2	2/2 (100%)	2/2 (100%)
0.06	10	8/10 (80.0%)	8/10 (80.0%)
<i>Serratia liquefaciens</i>			
0.12	1	1/1 (100%)	1/1 (100%)
<i>Serratia marcescens</i>			
0.25	3	2/3 (66/7%)	2/3 (66/7%)
<b>Total</b>	<b>52</b>	<b>42/52 (80.8%)</b>	<b>46/52 (88.5%)</b>

Abbreviations: CABP = community acquired bacterial pneumonia; MIC = minimal inhibitory concentration.

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Date Review Completed: 09/27/2010

Table 105 and Table 106 show the combined clinical and microbiological response rates by MIC for ceftaroline and ceftriaxone against *Haemophilus spp.* The Applicant reported a total of 35 isolates in the ceftaroline-treated group with 88.6% (31/35) clinical and 88.6% (31/35) microbiological success. Table 100 shows that there were a total of 16 subjects with *H. influenzae* in the ceftaroline treatment group. Three ceftaroline microbiological failures occurred at an MIC of  $\leq 0.008$  mcg/mL for *H. influenzae* (Table 100). In the ceftriaxone-treated group, there were 36 isolates with a clinical success of 91.7% (33/36) and 94.4% (34/36) microbiological success. One microbiological failure occurred at 2 mcg/mL and 5 at 4 mcg/mL. For *Haemophilus parainfluenzae*, there were 15 isolates in both CABP study groups (P903-08 and P903-09) of those, 10 were presented as single infection with a 100% presumed eradication rate. Five *H. parainfluenzae* isolates were present as mixed infection; however, following treatment with ceftaroline, all were presumed eradicated.

**Table 105 Integrated Clinical and Microbiological Response Rates by MIC for Ceftaroline and Ceftriaxone against *Haemophilus spp.* in CABP Studies P903-08 and P903-09**

<i>Ceftaroline MIC (µg/mL)</i>	<i>N</i>	<i>Clinical Success n/N (%)</i>	<i>Microbiological Success (Eradicated/Presumed Eradicated n/N (%))</i>
<i>Haemophilus influenzae</i>			
$\leq 0.015$	13	10/13 (76.9%)	10/13 (76.9%)
0.03	3	3/3 (100%)	3/3 (100%)
<i>Haemophilus haemolyticus</i>			
$\leq 0.015$	1	1/1 (100%)	1/1 (100%)
<i>Haemophilus parahaemolyticus</i>			
$\leq 0.015$	3	2/3 (66.7%)	2/3 (66.7%)
<i>Haemophilus parainfluenzae</i>			
$\leq 0.015$	12	12/12 (100%)	12/12 (100%)
0.06	2	2/2 (100%)	2/2 (100%)
0.12	1	1/1 (100%)	1/1 (100%)
<b>Total</b>	<b>35</b>	<b>31/35 (88.6%)</b>	<b>31/35 (88.6%)</b>

Abbreviations: CABP = community acquired bacterial pneumonia; MIC = minimal inhibitory concentration.

<i>Ceftriaxone MIC (µg/mL)</i>	<i>N</i>	<i>Clinical Success n/N (%)</i>	<i>Microbiological Success (Eradicated/Presumed Eradicated n/N (%))</i>
<i>Haemophilus influenzae</i>			
$\leq 0.015$	17	15/17 (88.2%)	15/17 (88.2%)
0.03	2	2/2 (100%)	2/2 (100%)
<i>Haemophilus parahaemolyticus</i>			
$\leq 0.015$	2	2/2 (100%)	2/2 (100%)
<i>Haemophilus parainfluenzae</i>			
$\leq 0.015$	14	13/14 (92.9%)	13/14 (92.9%)
0.06	1	1/2 (50.0%)	2/2 (100%)
<b>Total</b>	<b>36</b>	<b>33/36 (91.7%)</b>	<b>34/36 (94.4%)</b>

Abbreviations: CABP = community acquired bacterial pneumonia; MIC = minimal inhibitory concentration.

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**Table 106 Clinical and Microbiological Success by Ceftaroline MIC against *Haemophilus influenzae* from CABP Studies P903-08 and P903-09 Combined**

<i>Ceftaroline</i> MIC ( $\mu\text{g/mL}$ )	<i>N</i>	<i>Clinical Success</i> n/N (%)	<i>Microbiological Success</i> ( <i>Eradicated/Presumed Eradicated</i> n/N (%))
$\leq 0.008$	8	5/8 (62.5%)	5/8 (62.5%)
0.015	5	5/5 (100.0%)	5/5 (100.0%)
0.03	3	3/3 (100.0%)	3/3 (100.0%)
Total	16	13/16 (81.2%)	13/16 (81.2%)

Abbreviations: CABP = community acquired bacterial pneumonia; MIC = minimal inhibitory concentration.

Table 107 shows the integrated clinical and microbiological response rates by MIC for ceftaroline and ceftriaxone against *M. catarrhalis*. There were 3 isolates for the ceftaroline-treated group with 66.7% (31/35) clinical and microbiological success. One ceftaroline microbiological failure occurred at an MIC  $\leq 0.06$  mcg/mL.

**Table 107 Integrated Clinical and Microbiological Response Rates by MIC for Ceftaroline and Ceftriaxone against *Moraxella catarrhalis* in CABP Studies P903-08 and P903-09**

	<i>N</i>	<i>Clinical Success</i> ( <i>ceftaroline-treated</i> ) n/N (%)	<i>Microbiological Success</i> ( <i>Eradicated/Presumed Eradicated</i> n/N (%))
<b>Ceftaroline MIC (<math>\mu\text{g/mL}</math>)</b>			
0.06	1	0/1 (0%)	0/1 (0%)
0.12	2	2/2 (100%)	2/2 (100%)
Total	3	2/3 (66.7%)	2/3 (66.7%)
<b>Ceftriaxone MIC (<math>\mu\text{g/mL}</math>)</b>			
0.5	2	2/2 (100%)	2/2 (100%)
Total	2	2/2 (100%)	2/2 (100%)

Abbreviations: CABP = community acquired bacterial pneumonia; MIC = minimal inhibitory concentration.

***Disk diffusion (Combined cSSSI and CABP studies):***

All Phase 3 clinical isolates of *S. aureus* were also tested for their susceptibility to ceftaroline using the disk diffusion method with 30- $\mu\text{g}$  disks. There were 395 isolates with available disk diffusion results; clinical and microbiological response rates by zone diameter are shown in Table 108. The zone diameters ranged from 7 mm to  $\geq 40$  mm. The single isolate with a zone diameter of 7 mm was subsequently found to be an aberrant result that did not repeat in follow-up testing. The results show that clinical and microbiological failures were associated with zone diameters that were also evenly distributed across the range. Figure 14 shows the zone diameter distribution histogram for ceftaroline and Phase 3 clinical isolates of *S. aureus*.

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**Table 108 Clinical and Microbiological Response Rates by Disk Diffusion Zone Diameter for all Phase 3 Clinical Isolates of *Staphylococcus aureus***

<i>Zone of Inhibition (mm)</i>	<i>N</i>	<i>Clinical Success n/N (%)</i>	<i>Microbiological Success: Eradicated/Presumed Eradicated (%)</i>
7	1	0/1 (0)	0/1 (0)
22	2	1/2 (50)	1/2 (50)
23	7	6/7 (85.7)	6/7 (85.7)
24	4	4/4 (100)	4/4 (100)
25	6	6/6 (100)	6/6 (100)
26	18	16/18 (88.9)	16/18 (88.9)
27	25	25/25 (100)	25/25 (100)
28	29	28/29 (96.6)	28/29 (96.6)
29	30	27/30 (90.0)	28/30 (93.3)
30	39	36/39 (92.3)	36/39 (92.3)
31	31	29/31 (93.5)	29/31 (93.5)
32	47	46/47 (97.9)	46/47 (97.9)
33	35	33/35 (94.3)	33/35 (94.3)
34	37	32/37 (86.5)	33/37 (89.2)
35	30	27/30 (90.9)	27/30 (90.0)
36	17	15/17 (88.2)	16/17 (94.1)
37	12	11/12 (91.7)	11/12 (91.7)
38	4	4/4 (100)	4/4 (100)
39	10	9/10 (90)	9/10 (90)
40	8	7/8 (87.5)	7/8 (87.5)
41	2	2/2 (100)	2/2 (100)
42	1	1/1 (100)	1/1 (100)

The disk diffusion zone diameter distributions for ceftaroline and the 37 isolates are shown in Table 109. The zone diameters ranged from 31 to  $\geq 40$  mm; clinical failures were associated with isolates with zone diameters that ranged from 37 to  $\geq 40$  mm. There were four isolates of MDR *S. pneumoniae* that were resistant to multiple antibiotic classes; [(MDRSP) was defined as resistance to two or more classes of antibiotics, including penicillin, macrolides, tetracycline, fluoroquinolones, chloramphenicol, trimethoprim/sulfamethoxazole and second-generation cephalosporins]. The ceftaroline MICs for the MDRSP isolates ranged from  $\leq 0.015$  to 0.12 mcg/mL, and all four isolates were from subjects who had successful clinical and microbiological outcomes.

**Table 109 Combined Clinical and Microbiological Response Rates by Disk Diffusion Zone Diameter for Ceftaroline and All Phase 3 Clinical Isolates of *Streptococcus pneumoniae* from Ceftaroline-treated Subjects**

<i>Zone of Inhibition (mm)</i>	<i>N</i>	<i>Clinical Success n/N (%)</i>	<i>Microbiological Success: Eradicated/Presumed Eradicated (%)</i>
31	2	2/2 (100)	2/2 (100)
32	1	1/1 (100)	1/1 (100)
34	3	3/3 (100)	3/3 (100)
36	3	3/3 (100)	3/3 (100)
37	5	4/5 (80)	4/5 (80)
38	5	3/5 (60)	3/5 (60)
39	4	3/4 (75.0)	3/4 (75.0)
40	1	1/1 (100)	1/1 (100)
41	5	4/5 (80.0)	5/5 (100)
42	3	2/3 (66.7)	2/3 (66.7)
43	2	2/2 (100)	2/2 (100)
44	2	2/2 (100)	2/2 (100)
45	1	1/1 (100)	1/1 (100)

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The ceftaroline zone diameter distributions and the 56 isolates of *S. pyogenes* from ceftaroline-treated subjects are shown in Table 110. The zone diameter for the isolates ranged from 24 to  $\geq 40$  mm.

**Table 110 Integrated Clinical and Microbiological Response Rates by Disk Diffusion Zone Diameter for Ceftaroline and all Phase 3 Clinical Isolates of *Streptococcus pyogenes* from Ceftaroline-treated Subjects**

<i>Zone of Inhibition (mm)</i>	<i>N</i>	<i>Clinical Success n/N (%)</i>	<i>Microbiological Success: Eradicated/Presumed Eradicated (%)</i>
24	1	1/1 (100)	1/1 (100)
28	2	2/2 (100)	2/2 (100)
30	2	2/2 (100)	2/2 (100)
31	2	2/2 (100)	2/2 (100)
32	2	2/2 (100)	2/2 (100)
33	7	7/7 (100)	7/7 (100)
34	6	6/6 (100)	6/6 (100)
35	10	10/10 (100)	10/10 (100)
36	8	8/8 (100)	8/8 (100)
37	5	5/5 (100)	5/5 (100)
38	7	7/7 (100)	7/7 (100)
39	1	1/1 (100)	1/1 (100)
$\geq 40$	4	4/4 (100)	4/4 (100)

The ceftaroline zone diameters for clinical isolates of *S. agalactiae* ranged from 30 to 39 mm and are shown in Table 111.

**Table 111 Integrated Clinical and Microbiological Response Rates by Disk Diffusion Zone Diameter for Ceftaroline and all Phase 3 Clinical Isolates of *Streptococcus agalactiae* from Ceftaroline-treated Subjects**

<i>Zone of Inhibition (mm)</i>	<i>N</i>	<i>Clinical Success n/N (%)</i>	<i>Microbiological Success: Eradicated/Presumed Eradicated (%)</i>
30	3	3/3 (100)	3/3 (100)
31	2	2/2 (100)	2/2 (100)
32	4	4/4 (100)	3/4 (75)
33	4	4/4 (100)	4/4 (100)
34	2	2/2 (100)	2/2 (100)
35	2	2/2 (100)	2/2 (100)
37	2	1/2 (50)	1/2 (50)
38	1	1/1 (100)	1/1 (100)
39	1	1/1 (100)	1/1 (100)

Table 112 shows the zone diameters for ceftaroline and *S. dysgalactiae*; zone diameters ranged from 25 to 35 mm.

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**Table 112 Combined Clinical and Microbiological Response Rates by Disk Diffusion Zone Diameter for Ceftaroline and all Phase 3 Clinical Isolates of *Streptococcus dysgalactiae* from Ceftaroline-treated Subjects**

<i>Zone of Inhibition (mm)</i>	<i>N</i>	<i>Clinical Success n/N (%)</i>	<i>Microbiological Success: Eradicated/Presumed Eradicated n/N (%)</i>
25	2	2/2 (100)	2/2 (100)
27	2	2/2 (100)	2/2 (100)
28	1	1/1 (100)	1/1 (100)
31	1	1/1 (100)	1/1 (100)
32	4	4/4 (100)	4/4 (100)
34	1	1/1 (100)	1/1 (100)
35	1	1/1 (100)	1/1 (100)

142 baseline isolates of *Enterobacteriaceae* with antimicrobial susceptibility test results were available from ceftaroline-treated subjects in the four Phase 3 clinical studies. However, the clinical and microbiological response rates by disk diffusion zone diameter are available for 125 *Enterobacteriaceae* from ceftaroline treated subjects (Table (113)).

**Table 113 Clinical and Microbiological Response Rates by Disk Diffusion Zone Diameter for Ceftaroline Against all Phase 3 Clinical Isolates of *Enterobacteriaceae* from Ceftaroline-treated Subjects**

<i>Ceftaroline zone diameter (mm)</i>	<i>N</i>	<i>Clinical Success n/N (%)</i>	<i>Microbiological Success: Eradicated/Presumed Eradicated n/N (%)</i>
<i>Citrobacter freundii</i> complex			
6	1	1/1 (100)	1/1 (100)
27	1	1/1 (100)	1/1 (100)
31	1	1/1 (100)	1/1 (100)
<i>Citrobacter koseri</i>			
29	1	1/1 (100)	1/1 (100)
34	1	1/1 (100)	1/1 (100)
<i>Ceftaroline zone diameter (mm)</i>	<i>N</i>	<i>Clinical Success n/N (%)</i>	<i>Microbiological Success: Eradicated/Presumed Eradicated n/N (%)</i>
<i>Enterobacter aerogenes</i>			
27	1	0/1 (0)	1/1 (100)
28	1	1/1 (100)	1/1 (100)
29	1	1/1 (100)	1/1 (100)
<i>Enterobacter cloacae</i>			
25	1	1/1 (100)	1/1 (100)
26	1	1/1 (100)	1/1 (100)
27	3	3/3 (100)	3/3 (100)
28	2	1/2 (50)	1/2 (50)
29	2	2/2 (100)	1/2 (50)
30	2	2/2 (100)	2/2 (100)
31	1	1/1 (100)	1/1 (100)
<i>Escherichia coli</i>			
6	1	1/1 (100)	1/1 (100)
25	2	1/2 (50)	1/2 (50)
26	1	1/1 (100)	1/1 (100)
27	1	1/1 (100)	1/1 (100)
28	1	1/1 (100)	1/1 (100)
29	5	4/5 (80)	4/5 (80)
30	8	8/8 (100)	8/8 (100)
31	5	5/5 (100)	5/5 (100)
32	4	3/4 (75)	3/4 (75)
33	3	3/3 (100)	3/3 (100)
35	2	2/2 (100)	2/2 (100)

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<i>Ceftaroline zone diameter (mm)</i>	<i>N</i>	<i>Clinical Success n/N (%)</i>	<i>Microbiological Success: Eradicated/Presumed Eradicated n/N (%)</i>
<i>Klebsiella oxytoca</i>			
24	1	1/1 (100)	1/1 (100)
26	1	1/1 (100)	1/1 (100)
28	1	1/1 (100)	1/1 (100)
29	2	2/2 (100)	2/2 (100)
30	3	3/3 (100)	3/3 (100)
31	4	3/4 (75)	4/4 (100)
32	2	2/2 (100)	2/2 (100)
33	2	1/2 (50)	1/2 (50)
34	1	1/1 (100)	1/1 (100)
<i>Klebsiella pneumoniae</i>			
6	1	1/1 (100)	1/1 (100)
11	1	1/1 (100)	1/1 (100)
26	2	2/2 (100)	2/2 (100)
27	4	4/4 (100)	4/4 (100)
28	5	5/5 (100)	5/5 (100)
29	8	8/8 (100)	8/8 (100)
30	7	6/7 (85.7)	6/7 (85.7)
32	2	2/2 (100)	2/2 (100)
<i>Morganella morganii</i>			
8	1	1/1 (100)	1/1 (100)
10	1	1/1 (100)	1/1 (100)
16	1	1/1 (100)	1/1 (100)
24	1	1/1 (100)	1/1 (100)
28	1	0/1 (0)	0/1 (0)
29	1	1/1 (100)	1/1 (100)
30	4	4/4 (100)	4/4 (100)
31	1	1/1 (100)	1/1 (100)
<i>Ceftaroline zone diameter (mm)</i>	<i>N</i>	<i>Clinical Success n/N (%)</i>	<i>Microbiological Success: Eradicated/Presumed Eradicated n/N (%)</i>
<i>Proteus mirabilis</i>			
10	1	0/1 (0)	0/1 (0)
12	1	1/1 (100)	1/1 (100)
13	1	1/1 (100)	1/1 (100)
20	1	0/1 (0)	0/1 (0)
21	2	1/2 (50)	1/2 (50)
24	1	1/1 (100)	1/1 (100)
28	1	0/1 (0)	0/1 (0)
29	4	3/4 (75)	3/4 (75)
31	3	2/3 (66.7)	3/3 (100)
32	1	1/1 (100)	1/1 (100)
33	2	2/2 (100)	2/2 (100)
<i>Proteus penneri</i>			
25	1	1/1 (100)	1/1 (100)
<i>Proteus vulgaris group</i>			
20	1	1/1 (100)	1/1 (100)
28	1	1/1 (100)	1/1 (100)
31	1	1/1 (100)	1/1 (100)
<i>Providencia stuartii</i>			
6	1	1/1 (100)	1/1 (100)
30	1	1/1 (100)	1/1 (100)
<i>Serratia liquefaciens</i>			
29	1	1/1 (100)	1/1 (100)
30	1	1/1 (100)	1/1 (100)
<i>Serratia marcescens</i>			
26	1	1/1 (100)	1/1 (100)
28	4	4/4 (100)	3/4 (75)
30	1	1/1 (100)	1/1 (100)
<b>Total</b>	<b>142</b>	<b>127/142 (89.4)</b>	<b>128/142 (90.1)</b>

Abbreviations: MIC = minimum inhibitory concentration.

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For *H. influenzae*, zone diameters ranged from 35 mm to  $\geq 40$  mm; however, there were three isolates of *H. influenzae* associated with clinical and microbiological failures and had ceftaroline zone diameters that were  $\geq 40$  mm. Among the *H. parainfluenzae* isolates that were all associated with successful outcomes were susceptible to ceftaroline with zone diameters ranging from 28 to  $\geq 40$  mm (Table 114).

**Table 114 Clinical and Microbiological Response Rates by Disk Diffusion Zone Diameter for Ceftaroline Against all Phase 3 Clinical Isolates of *Haemophilus* spp. from Ceftaroline-treated Subjects**

Ceftaroline MIC ( $\mu\text{g/mL}$ )	N	Clinical Success n/N (%)	Microbiological Success (Eradicated/Presumed Eradicated) n/N (%)
<i>Haemophilus influenzae</i>			
35	2	2/2 (100)	2/2 (100)
36	1	1/1 (100)	1/1 (100)
27	1	1/1 (100)	1/1 (100)
38	2	2/2 (100)	2/2 (100)
$\geq 40$	10	7/10 (70)	7/10 (70)
<i>Haemophilus parahaemolyticus</i>			
18	1	1/1 (100)	1/1 (100)
26	1	0/1 (0)	1/1 (100)
30	1	1/1 (100)	0/1 (0)
<i>Haemophilus parainfluenzae</i>			
28	2	2/2 (100)	2/2 (100)
29	3	3/3 (100)	3/3 (100)
33	1	1/1 (100)	1/1 (100)
35	1	1/1 (100)	1/1 (100)
36	1	1/1 (100)	1/1 (100)
39	1	1/1 (100)	1/1 (100)
$\geq 40$	5	5/5 (100)	5/5 (100)
Total	33	29/33 (87.8)	29/33 (87.8)

Abbreviations: MIC = minimum inhibitory concentration.

***Clinical trials conclusion:***

The Applicant presented data on two cSSSI and two CABP trials and data from these trials reveal that ceftaroline is effective against the target pathogens in the proposed indications. No development of resistance was reported by the Applicant during the clinical studies. Similar eradication rates were observed between the two cSSSI studies; likewise, similar eradication rates were observed between the two CABP studies. In addition, the Applicant presented data to show that ceftaroline is efficacious against specific Gram-positive and -negative isolates encountered in the clinical trials.

**Quality Control Analysis for Clinical Studies:**

The following QC organisms and ranges were used throughout the susceptibility testing during the Phase 3 clinical studies for ceftaroline (P903-06, P903-07, P903-08, and P903-09) at the (b) (4). Table 115 shows the number of times each QC isolate was tested and the percentage of ceftaroline QC results tested that were in range for all frozen and dried panels and disks used. Nearly all ceftaroline QC results were within the expected CLSI proposed QC range for both MIC and disk diffusion results.

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**Table 115: Percent of Clinical Study Aerobic Quality Control Results in CLSI Range**

Quality control strain	MIC		Disk diffusion	
	Number tested	% in Range	Number tested	% in Range
<i>Escherichia coli</i> ATCC 25922	97	99	43	100
<i>Staphylococcus aureus</i> ATCC 29213	194	100	NA	NA
<i>Staphylococcus aureus</i> ATCC 25923	NA	NA	36	100
<i>Streptococcus pneumoniae</i> ATCC 49619	134	100	49	98
<i>Haemophilus influenzae</i> ATCC 49247	13	100	20	100

Abbreviations: ATCC = American type culture collection; CLSI = Clinical and Laboratory Standards Institute;  
MIC = minimum inhibitory concentration; NA = not applicable.

Table 116 show the QC data that were evaluated to determine how the results compared to CLSI approved ranges. All the results were within CLSI approved ranges. Only test with panels and disks that fell within range of accepted QC results were used for MICs or zone determination.

**Table 116: Summary of Quality Control Results for Ceftaroline for Broth Micro Dilution**

QC organism	Study	Panel Type	Number Tested	Expected CLSI QC range (MIC in µg/mL)	Clinical Trial QC Range (MIC in µg/mL)	Clinical Trial QC Geomean
<i>Staphylococcus aureus</i> ATCC 29213	cSSSI P903-06 and P903-07	Frozen	31	0.12 - 0.25	0.12 - 0.25	0.19
<i>Staphylococcus aureus</i> ATCC 29213	CABP P903-08 and P903-09	Dried	138	0.12 - 0.25	0.12 - 0.25	0.19
<i>Streptococcus pneumoniae</i> ATCC 49619	cSSSI P903-06 and P903-07	Frozen	66	0.008 - 0.03	0.008 - 0.03	0.015
<i>Streptococcus pneumoniae</i> ATCC 49619	CABP P903-08 and P903-09	Dried	15	0.008 - 0.03	0.008 - 0.03	0.013
<i>Escherichia coli</i> ATCC 25922	cSSSI P903-06 and P903-07	Frozen	11	0.03 - 0.12	0.06 - 0.12	0.068
<i>Escherichia coli</i> ATCC 25922	CABP P903-08 and P903-09	Dried	37	0.03 - 0.12	0.06 - 0.12	0.0724
<i>Haemophilus influenzae</i> ATCC 49247	cSSSI P903-06 and P903-07	Frozen	6	0.03 - 0.12	0.06	0.06
<i>Haemophilus influenzae</i> ATCC 49247	CABP P903-08 and P903-09	Dried	4	0.03 - 0.12	0.06 - 0.12	0.06

Abbreviations: ATCC = American type culture collection; CABP = community acquired bacterial pneumonia;  
CLSI = Clinical and Laboratory Standards Institute; cSSSI = complicated skin and skin structure infections;  
MIC = minimum inhibitory concentration; QC = quality control.

QC testing was performed during clinical studies for ceftaroline and all comparator drugs. Only tests with panels and disks that fell within range of accepted QC results were used for determining MICs or zone sizes. Overall, few failures occurred; these are listed in Table 117 along with actions taken, suggesting that the susceptibility results obtained had few issues. No additional information was provided.

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**Table 117: Susceptibility Clinical Trial Quality Control Testing Failures and Actions Taken**

<i>Date</i>	<i>Study</i>	<i>Method</i>	<i>QC Organism</i>	<i>Ceftaroline Expected Range (µg/mL)</i>	<i>Ceftaroline MIC (µg/mL)</i>	<i>Comments</i>
04/17/07	cSSSI	Frozen BMD	<i>Streptococcus pneumoniae</i> 49619	0.008 - 0.03	0.03	No values reported, subjects reset
04/19/07	cSSSI	Disk Diffusion	<i>Streptococcus pneumoniae</i> 49619	31 -41 mm	30	Subject samples reset
05/04/07	cSSSI	Frozen BMD	<i>Escherichia coli</i> 25922	0.03 - 0.12	0.06	QC out for ceftazidime, all Subject samples reset for ceftazidime
06/05/07	cSSSI	Frozen BMD	<i>Escherichia coli</i> 25922	0.03 - 0.12	0.12	Subject samples reset
08/24/07	cSSSI	Frozen BMD	<i>Escherichia coli</i> 25922	0.03 - 0.12	0.12	Subject samples reset for ceftazidime
10/05/07	cSSSI	Frozen BMD	<i>Escherichia coli</i> 25922	0.03 - 0.12	0.06	Amox-clav out, all subject samples reset for Amox-clav
11/14/07	cSSSI	Frozen BMD	<i>Escherichia coli</i> 25922	0.03 - 0.12	0.25	All subject samples reset
11/16/07	cSSSI	Frozen BMD	<i>Escherichia coli</i> 25922	0.03 - 0.12	0.12	Subject samples reset
02/01/08	cSSSI	Frozen BMD	<i>Escherichia coli</i> 25922	0.03 - 0.12	0.06	Subject samples reset
05/04/07	cSSSI	Frozen BMD	<i>Staphylococcus aureus</i> 29213	0.06 - 0.25	0.12	Out multiple drugs, subject samples reset
05/11/07	cSSSI	Frozen BMD	<i>Staphylococcus aureus</i> 29213	0.06 - 0.25	0.12	Out multiple drugs, subject samples reset
<i>Date</i>	<i>Study</i>	<i>Method</i>	<i>QC Organism</i>	<i>Ceftaroline Expected Range (µg/mL)</i>	<i>Ceftaroline MIC (µg/mL)</i>	<i>Comments</i>
05/13/07	cSSSI	Frozen BMD	<i>Staphylococcus aureus</i> 29213	0.06 - 0.25	0.25	Imipenem out, subject samples reset for imipenem
05/15/07	cSSSI	Frozen BMD	<i>Staphylococcus aureus</i> 29213	0.06 - 0.25	0.12	Ampicillin out, subject samples reset for ampicillin
10/30/07	cSSSI	Frozen BMD	<i>Staphylococcus aureus</i> 29213	0.06 - 0.25	0.12	Ampicillin out, subject samples reset for ampicillin
11/09/07	cSSSI	Frozen BMD	<i>Staphylococcus aureus</i> 29213	0.06 - 0.25	0.12	Ampicillin out, subject samples reset for ampicillin
12/01/07	cSSSI	Frozen BMD	<i>Staphylococcus aureus</i> 29213	0.06 - 0.25	0.25	Imipenem out, subject samples reset for imipenem
12/04/07	cSSSI	Frozen BMD	<i>Staphylococcus aureus</i> 29213	0.06 - 0.25	0.25	Imipenem out, subject samples reset for imipenem
12/22/07	cSSSI	Frozen BMD	<i>Staphylococcus aureus</i> 29213	0.06 - 0.25	0.25	Imipenem out, subject samples reset for imipenem
06/04/08	CABP	Dried BMD	<i>Staphylococcus aureus</i> 29213	0.06 - 0.25	0.25	P/T QC incomplete, subject samples reset for P/T
06/06/08	CABP	Dried BMD	<i>Staphylococcus aureus</i> 29213	0.06 - 0.25	0.25	P/T QC incomplete, subject samples reset for P/T
06/06/08	CABP	Dried BMD	<i>Haemophilus influenzae</i> 49247	0.03 - 0.12	0.06	Amox/Clav QC incomplete, subject samples reset for Amox/Clav

Abbreviations: Amox-clav = amoxicillin with clavulanate potassium; BMD = broth micro-dilution; CABP = community acquired bacterial pneumonia; cSSSI = complicated skin and skin structure infections; MIC = minimum inhibitory concentration; P/T = piperacillin/tazobactam; QC = quality control.

**Correlation between Phase 3 MIC distributions with recent surveillance study**

Ceftaroline MIC distribution for all Phase 3 clinical isolates were compared with those collected in a recent surveillance study conducted in the US and Europe in 2008 (Study P0903-M-35). For *S. aureus*, the mode MIC for ceftaroline and the clinical and surveillance isolates was 0.25 mcg/mL (Figure 15). The mode was similar in both instances. However, there were 4 isolates from Greece in the surveillance with a ceftaroline MIC that was

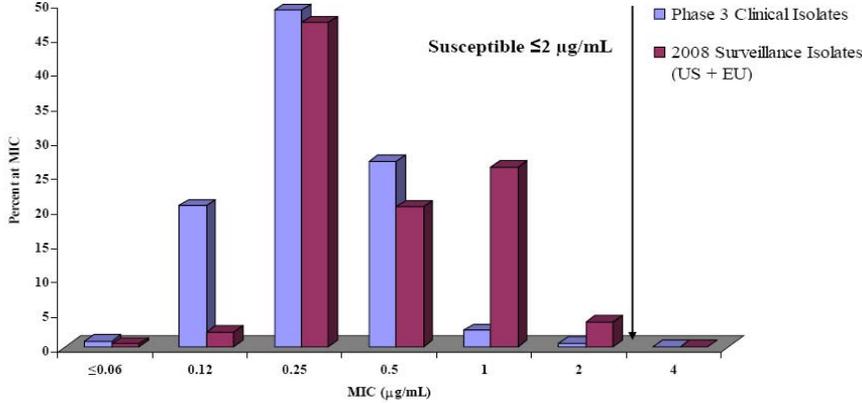
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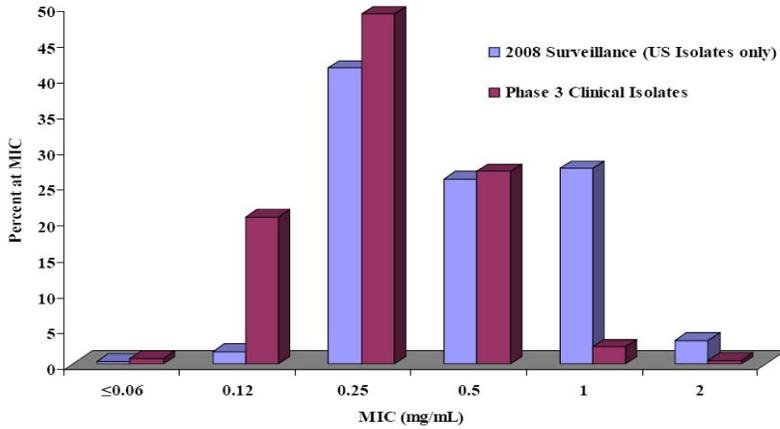
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16 fold higher than the mode and 2 fold higher than the highest MIC observed. Figure 16 shows the MIC distribution for ceftaroline and Phase 3 clinical isolates for US isolates only. The surveillance study shows that the mode for US isolates is 0.25 mcg/mL

**Figure 15. MIC Distributions for Ceftaroline and Phase 3 Clinical Isolates and 2008 Surveillance Isolates of *Staphylococcus aureus***



**Figure 16. MIC Distributions for Ceftaroline and all Phase 3 Clinical Isolates and 2008 US only Surveillance Isolates of *Staphylococcus aureus***



A comparison between MSSA and MRSA isolates from the Phase 3 clinical studies show that the difference between ceftaroline modal MIC values is within +/- 1 doubling dilution (Figure 17).

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**Figure 17. MIC Distributions for Ceftaroline and Methicillin-susceptible and Methicillin-resistant Phase 3 Isolates of *Staphylococcus aureus***

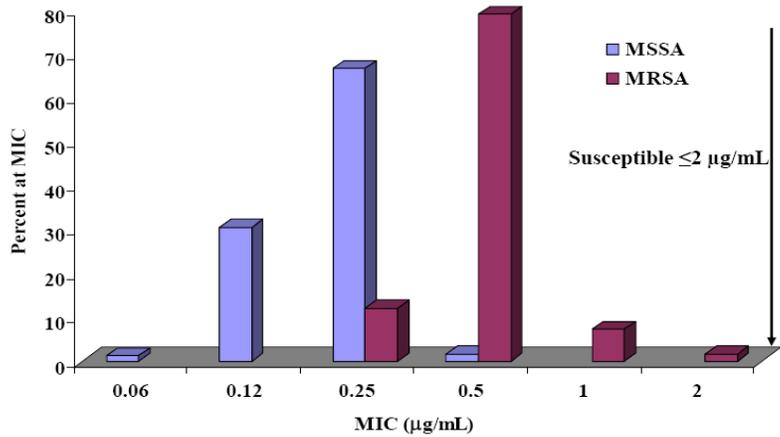
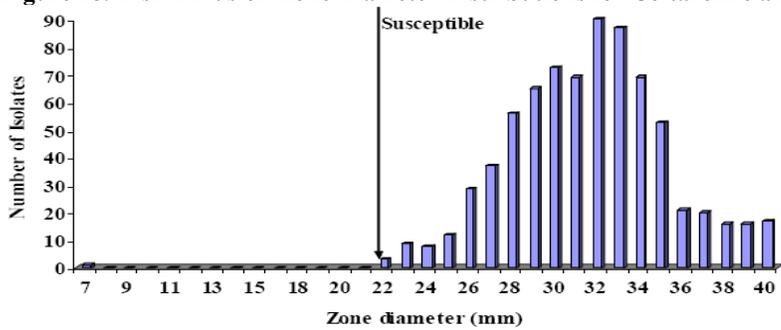


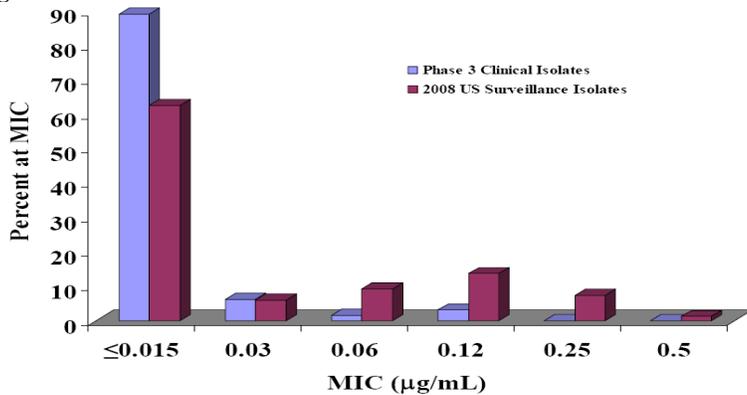
Figure 18 shows the zone diameter distribution histogram for ceftaroline and Phase 3 clinical isolates of *S. aureus*. Disk diameter ranged from 22 mm to >40 mm. The disk diffusion data has a

**Figure 18. Disk Diffusion Zone Diameter Distributions for Ceftaroline and all Phase 3 Clinical Isolates of *Staphylococcus aureus***



For *S. pneumoniae*, the ceftaroline MIC distributions for Phase 3 clinical isolates were compared with those from the 2008 US surveillance study P0903-M-035, 2009 (Figure 19). The mode MIC for ceftaroline against both clinical and US surveillance isolates was  $\leq 0.015$  mcg/mL.

**Figure 19. MIC Distributions for Ceftaroline and 2008 US Surveillance Isolates of *Streptococcus pneumoniae***



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Figure 20 shows the disk diffusion diameter for *S. pneumoniae* from the Phase 3 clinical studies. Disk diameter ranged from 28 mm to  $\geq 40$ mm.

**Figure 20. Disk Diffusion Zone Diameter Distributions for Ceftaroline and all Phase 3 Clinical Isolates of *Streptococcus pneumoniae***

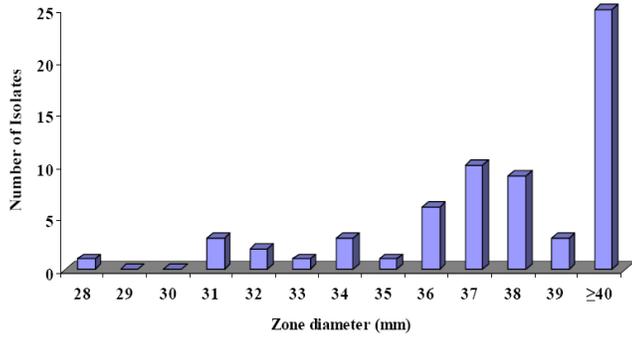
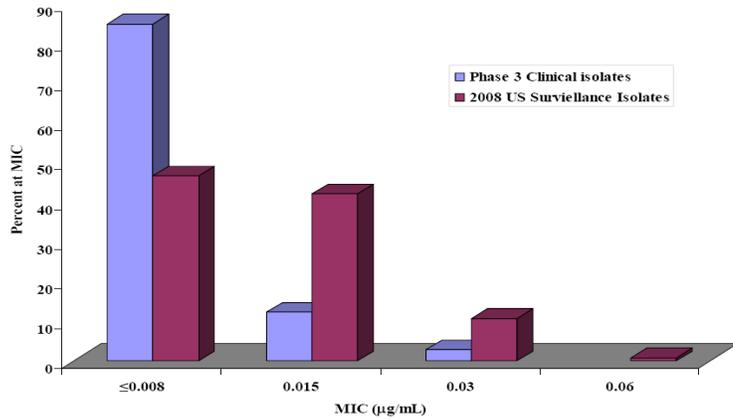
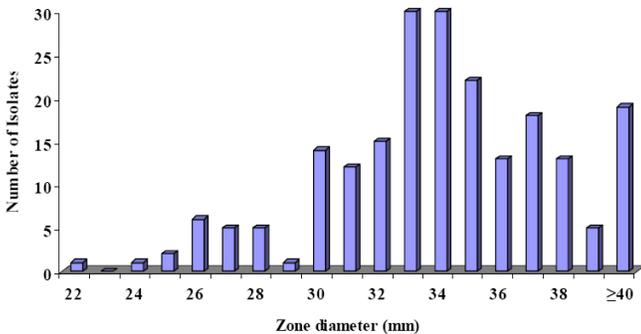


Figure 21 shows the MIC distribution for all Phase 3 clinical isolates from both treatment groups compared with 2008 US surveillance study for non-pneumococcal streptococci isolates. The mode MIC between the Phase 3 clinical isolates and the US surveillance isolates were similar. Disk diffusion zone diameters ranged from 22 mm to  $\geq 40$  mm and are shown in Figure 22.

**Figure 21. MIC Distributions for Ceftaroline and Phase 3 and 2008 US Surveillance Isolates of Non-pneumococcal Streptococci**



**Figure 22. Disk Diffusion Zone Diameter Distributions for Ceftaroline and all Phase 3 Clinical Isolates of Non-pneumococcal Streptococci**



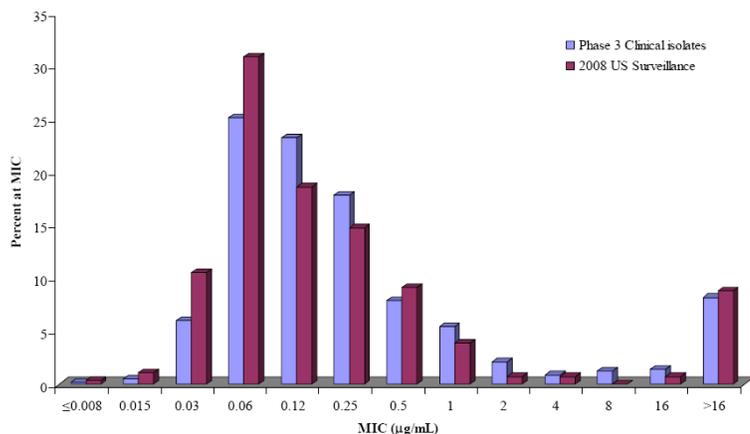
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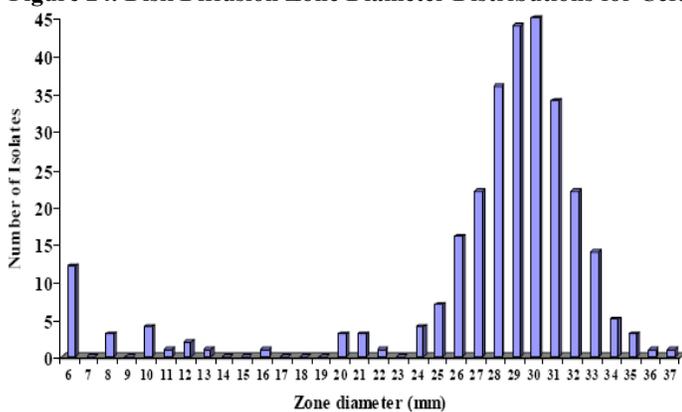
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The MIC distributions for ceftaroline and all Phase 3 clinical isolates for members of the *Enterobacteriaceae* encountered were compared to 2008 surveillance isolates are shown in Figure 23. MIC values ranged from  $\leq 0.008$  mcg/mL to  $> 16$  mcg/mL with a somewhat bimodal appearance at 0.06 mcg/mL and peaking again at 16 mcg/mL. The bimodal disk diffusion zone diameter distributions for ceftaroline and all Phase 3 clinical isolates of *Enterobacteriaceae* are shown in Figure 24.

**Figure 23. MIC Distributions for Ceftaroline and Phase 3 and 2008 US Surveillance Isolates of *Enterobacteriaceae***



**Figure 24. Disk Diffusion Zone Diameter Distributions for Ceftaroline and all Phase 3 Clinical Isolates of *Enterobacteriaceae***



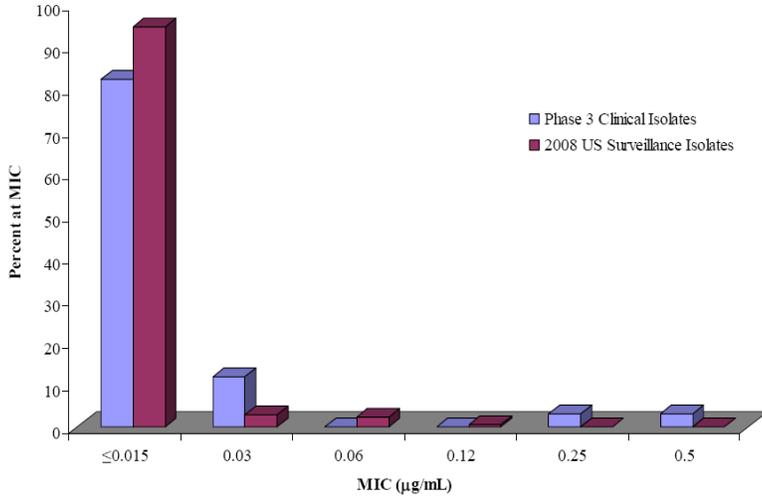
For *H. influenzae* isolates, the ceftaroline MIC distributions for Phase 3 clinical isolates were compared with those for 2008 US surveillance (Figure 25). The MICs for ceftaroline and the Phase 3 clinical isolates ranged from  $\leq 0.015$  to 0.5 mcg/mL compared to  $\leq 0.015$  to 0.12 mcg/mL for the surveillance isolates. The mode MIC for ceftaroline against both isolate collections was  $\leq 0.015$  mcg/mL. Figure 26 shows the zone diameter, which ranged from 26 to  $\geq 40$  mm with the exception of one outlier with a zone diameter of 18 mm.

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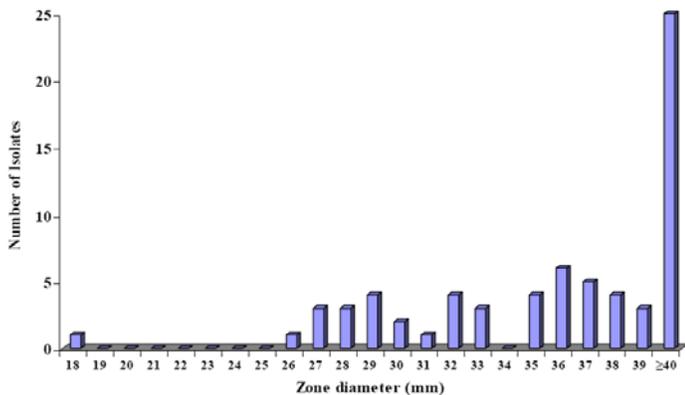
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**Figure 25. MIC Distributions for Ceftaroline and Phase 3 and 2008 US Surveillance Isolates of *Haemophilus influenzae***



**Figure 26. Disk Diffusion Zone Diameter Distributions for Ceftaroline and all Phase 3 Clinical Isolates of *Haemophilus spp.***



**Summary and Conclusion:**

The MIC data for *Enterobacteriaceae* at the wild-type distribution and some are above the wild type distribution this effect may be described as a bimodal distribution where there is a split in the susceptibility data of the wild-type population. This effect may lead to irreproducible in vitro testing, as replicating results will fall on either side of the breakpoint of the drug. Breakpoints that fall in the troughs of the bimodal MIC distribution will probably result in reproducible categorization of susceptibility, breakpoints that fall in the middle of the distribution will result in poor reproducibility, and it may be necessary to shift breakpoints slightly to reduce the impact of the problem.

**SCATTER PLOTS SHOWING MIC AND DISK DIFFUSION METHODS:**

MIC susceptibility and resistance interpretive criteria are established by using three principles. The first is the MIC distribution patterns from large surveillance studies; second, is the observation of clinical response data with respect to the prescribed drug dose; third, is the PK/PD characteristics of the drug. The in vitro

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antibacterial effect of ceftaroline has been considered to be time-dependent. Based on information submitted by the Applicant, an MIC of up to 0.5 mcg/mL is supported by PK/PD data.

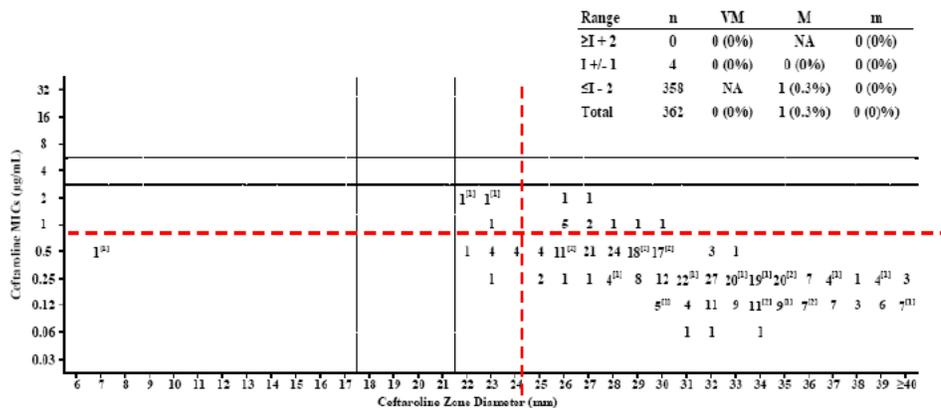
The error-rate bounded method classification is used to show a correlation between the MIC and zone diameter of bacteria encountered in the clinical trial. The zone diameters used to classify bacteria as susceptible or resistant to antibiotics depended on clinically relevant MIC breakpoints from the bacteria encountered in the clinical trials, as well as reproducible methods with adequate quality controls. Scatter plots with error rates comparing MIC and disk diffusion methods for isolates encountered in the Phase 3 studies (ME population) are presented in Figures 27-44.

**Breakpoint analysis for *Staphylococcus aureus*:**

The Scatter plots showing MICs and ceftaroline zone diameters for 386 Phase 3 isolates of *S. aureus* from ceftaroline-treated subjects, and representing isolates collected in both the skin and respiratory studies, are shown in Figure 27-31. **FDA proposed breakpoints for the Phase 3 cSSSI clinical study are shown in hashed, red lines with the appropriate discrepancy rates.** Clinical failures are shown in parenthesis. There were no isolates with a MIC higher than 2 mcg/mL. One result had a zone diameter of 7 mm that corresponded with a failure. The testing was subsequently repeated and was shown to be irregular.

Based on the data presented in clinical studies and on surveillance studies, (b) (4) There were 2/4 (50%) clinical microbiological failures associated with MRSA corresponding with an MIC of 2 mcg/mL and zone diameter of 22 mm. The failures occurred in the cSSSI studies. One patient, subject 300406679 was enrolled in Study P903-06 for treatment of a subcutaneous MRSA abscess at the hip replacement surgical site. Blood cultures also revealed MRSA. The subject began treatment with ceftaroline on Study Day 1 and received ceftaroline for 11 days but ultimately the isolate was presumed to have persisted. A second patient, subject 300707285 was enrolled in Study P903-07 for an infected wound with MRSA (with a MIC of 2 mcg/mL and a zone diameter of 23 mm) plus *E. faecalis*. This subject was a clinical failure and the organisms were presumed to have persisted.

**Figure 27. Ceftaroline MICs vs Ceftaroline Zone Diameter (30-µg disks) for *Staphylococcus aureus* Clinical Isolates from Ceftaroline-treated Subjects in cSSSI Studies P903-06 and P903-07 Combined**



<sup>[1]</sup> Denotes number of clinical failures

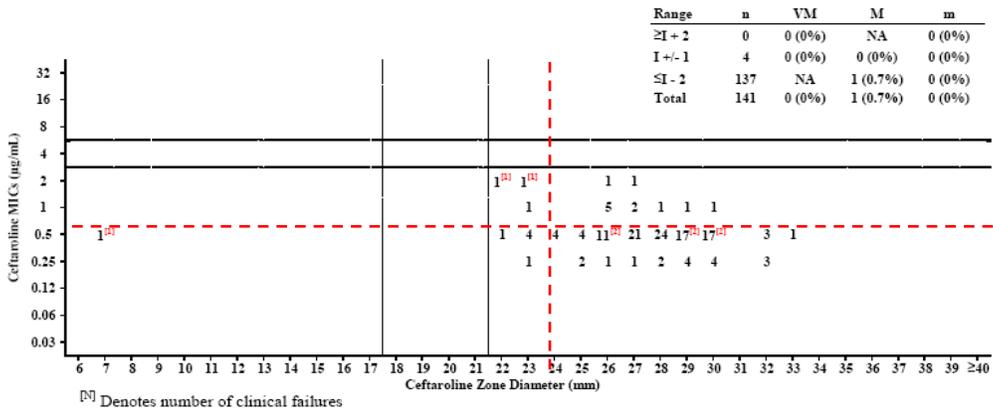
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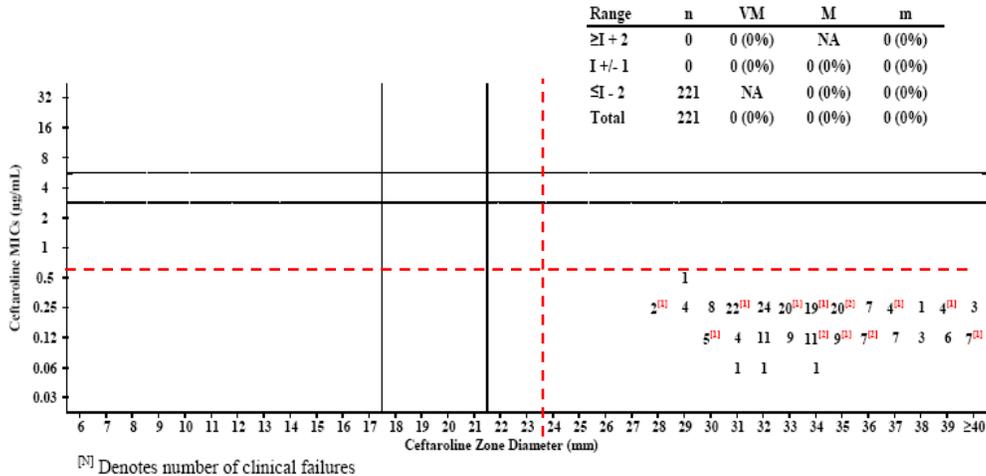
MIC Range	n	Discrepancy Rates		
		Very Major	Major	Minor
≥ I+2	0	0	0	0
I+1 to I-1	123	0	1 (1%)	20 (16%)
≤ I-2	239	NA	0	1 (0.4%)
Total	362			

**Figure 28. Ceftaroline MICs vs Ceftaroline Zone Diameter (30-µg disks) for Methicillin resistant *Staphylococcus aureus* Clinical Isolates from Ceftaroline-treated Subjects in cSSSI Studies P903-06 and P903-07 Combined**



MIC Range	n	Discrepancy Rates		
		Very Major	Major	Minor
≥ I+2	0	0	0	0
I+1 to I-1	123	0	1 (1%)	20 (16%)
≤ I-2	18	NA	0	1 (5.6%)
Total	141			

**Figure 29. Ceftaroline MICs vs. Ceftaroline Zone Diameter (30-µg disks) for Methicillin-susceptible *Staphylococcus aureus* Clinical Isolates from Ceftaroline-treated Subjects in cSSSI Studies P903-06 and P903-07 Combined**

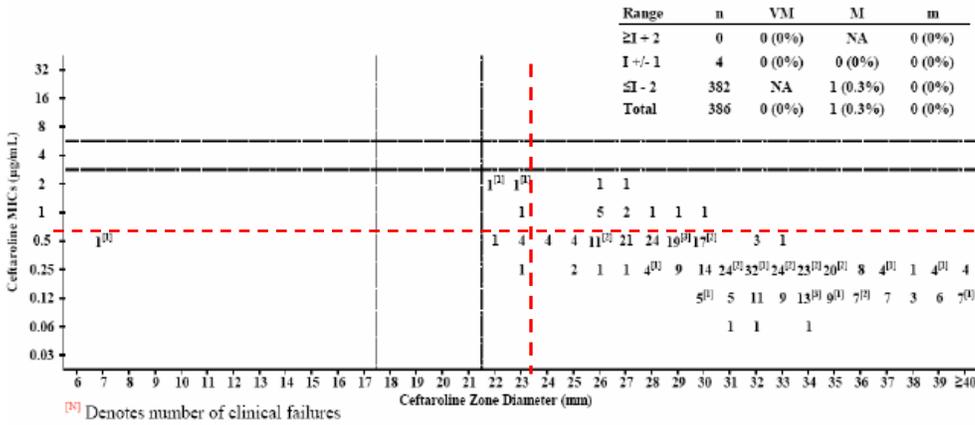


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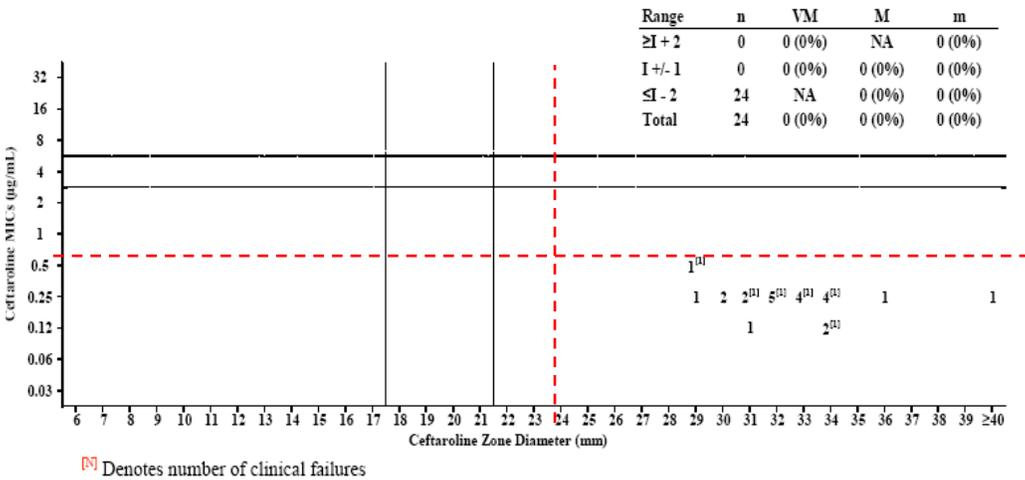
**Figure 30. Ceftaroline MICs vs. Ceftaroline Zone Diameter (30-µg disks) for all Phase 3 Clinical Isolates of *Staphylococcus aureus* from Ceftaroline-treated Subjects in the cSSSI (P903-06 and P903-07) and CABP (P903-08 and P903-09) Studies Combined**



Abbreviations: MIC = minimum inhibitory concentration; I = intermediate ; m = minor; M = major; VM = very major error.

MIC Range	n	Discrepancy Rates		
		Very Major	Major	Minor
≥ I + 2	0	0	0	0
I + 1 to I - 1	125	0	1 (1%)	20 (16%)
≤ I - 2	261	NA	1 (0.27%)	1 (0.3%)
<b>Total</b>	<b>386</b>			

**Figure 31. Ceftaroline MICs vs. Ceftaroline Zone Diameter (30-µg disks) for *Staphylococcus aureus* Clinical Isolates from CABP P903-08 and P903-09 Studies Combined (Isolates from Ceftaroline-treated Subjects)**



For cSSSI, the Agency suggests setting the MIC susceptible breakpoint at ≤ 0.5 mcg/mL for ceftaroline and a zone diameter susceptible breakpoint of ≥ 24 mm for *S. aureus* (including methicillin-resistant isolates) using the 30 µg disk diffusion methods. FDA modified breakpoint had no significant effect on the discrepancy rates for *S. aureus*; the major error rate remained at 0.27%. For CABP, the FDA proposed a MIC susceptible breakpoint at ≤ 0.5 mcg/mL for MSSA (not including MRSA) and a zone diameter susceptible breakpoint of ≥ 24 mm using the 30 µg disk diffusion methods. Please note that based on the Applicant’s exclusion criteria, the

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following pathogens were excluded *P. aeruginosa*, and MRSA since ceftriaxone is not expected to have an effect against both isolates and ceftaroline does not have activity against *P. aeruginosa*. (b) (4)

**Breakpoint analysis for *Streptococcus pneumoniae*:**

**Applicant’s Proposed Susceptibility Interpretive Criteria for Ceftaroline and *Streptococcus pneumoniae*:**

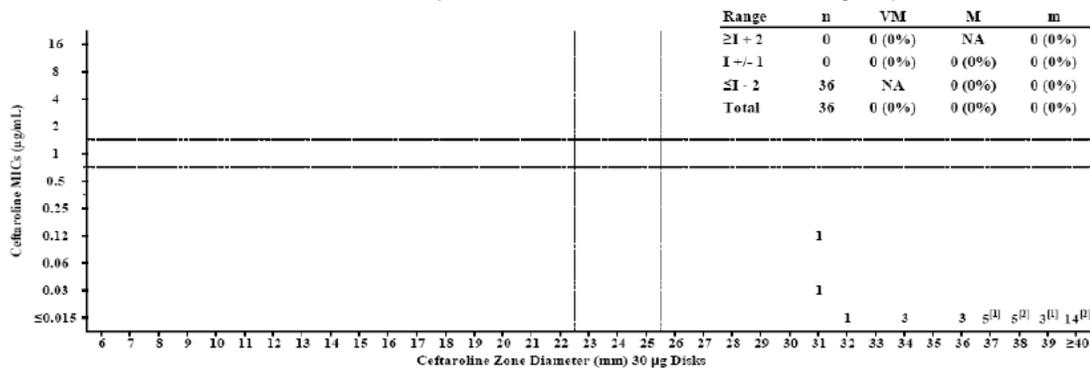
	MIC (µg/mL)			Disk diffusion zone diameter (mm)		
	S	I	R	S	I	R
<i>Streptococcus pneumoniae</i>	(b) (4)					

Abbreviations: MIC = minimum inhibitory concentration; I = intermediate; R = resistant; S = susceptible.

In the Phase 3 clinical trial, the ceftaroline MICs ranged from ≤ 0.015 mcg/mL to 0.12 mcg/mL for *S. pneumoniae*, the overall microbiological response rate was 86.1%. There were six subjects with clinical failures that were associated with isolates with ceftaroline MICs ≤ 0.015 mcg/mL which account for a response rate of 82.3% at that MIC. (b) (4)

The Scatterplot showing MICs and ceftaroline zone diameters for 36 Phase 3 isolates of *S. pneumoniae* from ceftaroline-treated subjects in the CABP studies with available antimicrobial susceptibility is shown in Figure 32 and 29. The Applicant has submitted additional data in a 26 July 2010 (NDA 200327 - SN 0026) communication to the Agency that supports setting the breakpoint ceftaroline against *S. pneumoniae* at 0.008 mcg/mL; the additional data supporting this breakpoint is shown in Table 89. The data show that there were 20 isolates at an MIC of 0.008 with a microbiological response rate of 80%. However, at a value of 0.015 mcg/mL (1 dilution higher) seven out of 8 isolates were eradicated by ceftaroline; this equates to a microbiological response rate of 87.5%. Therefore, this Reviewer thinks that it is not inconceivable to set the breakpoint at this MIC (0.015 mcg/mL). Scatterplots supporting data submitted to NDA 200327 - SN 0026 were not submitted therefore. Based on the Phase 3 clinical trial, the appropriate breakpoint should be set on the available data; therefore, the appropriate ceftaroline MIC interpretive criteria should be 0.008 mcg/mL for ceftaroline; no zone diameter is suggested due to a lack of sufficient data.

**Figure 32. Ceftaroline MICs vs. Ceftaroline Zone Diameter (30-µg disks) for *Streptococcus pneumoniae* Clinical Isolates from CABP P903-08 and P903-09 Studies Combined (Isolates from Ceftaroline-treated Subjects)**



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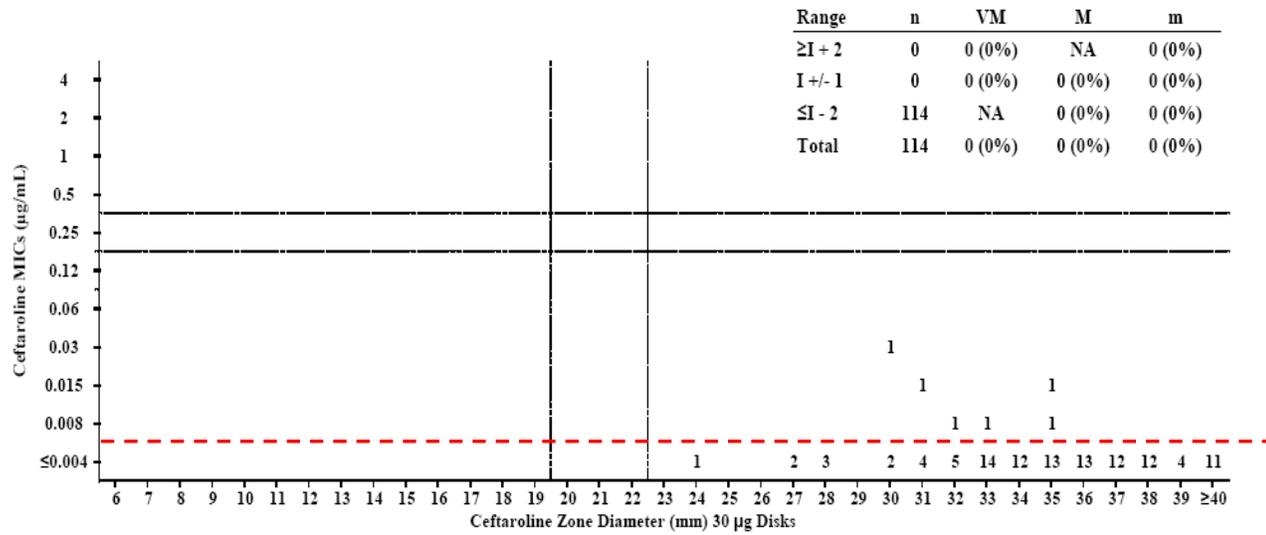
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**Breakpoint analysis for *Streptococcus spp.*:**

**Proposed Susceptibility Interpretive Criteria for Ceftaroline and Nonpneumococcal Streptococci** (b) (4)

There were 212 non-pneumococcal clinical isolates between both study groups. The MIC ranged from 0.03 to  $\leq 0.004$  mcg/mL. Figure 33 shows the scatterplots for the 114 *S. pyogenes* isolates encountered in the ceftaroline treatment group and the comparator group. Of those, 56 *Streptococcus pyogenes* isolates were identified in the ceftaroline cSSSI studies; 55/56 isolates had an MIC of  $\leq 0.004$  mcg/mL with a 100% eradication rate, and one isolate had an MIC of 0.008 mcg/mL with 100% eradication. Therefore, the antimicrobial susceptibility test results, microbiological response rates were 100% in the ceftaroline arm and all isolates were considered susceptible to ceftaroline, with MICs that ranged from  $\leq 0.004$  to 0.008 mcg/mL; zone diameter for the isolates ranged from 24 to  $\geq 40$  mm. In the vancomycin treatment group, there were a total of 58 isolates, 45 of those isolates had a MIC of 0.25 mcg/mL with a 95.6% eradication rate; 11 isolates with a MIC value of 0.5 mcg/mL were all eradicated while 2 isolates with a MIC of 1 mcg/mL were all eradicated. For comparison, Figure 34 shows ceftaroline MICs vs. Ceftaroline Zone Diameter for US Clinical Isolates of Nonpneumococcal Streptococci from study to evaluate provisional interpretive criteria.

**Figure 33. Ceftaroline MICs vs. Ceftaroline Zone Diameter for Phase 3 Clinical Isolates of *Streptococcus pyogenes* from cSSSI Studies P903-06 and P903-07 Combined (Isolates from both Treatment Groups)**

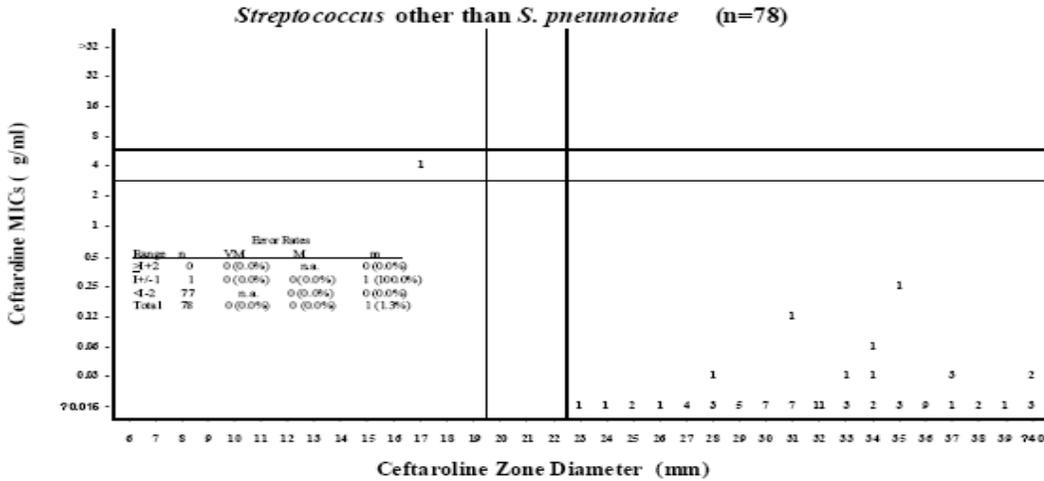


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**Figure 34. Ceftaroline MICs vs. Ceftaroline Zone Diameter for US Clinical Isolates of Nonpneumococcal Streptococci from Study to Evaluate Provisional Interpretive Criteria**

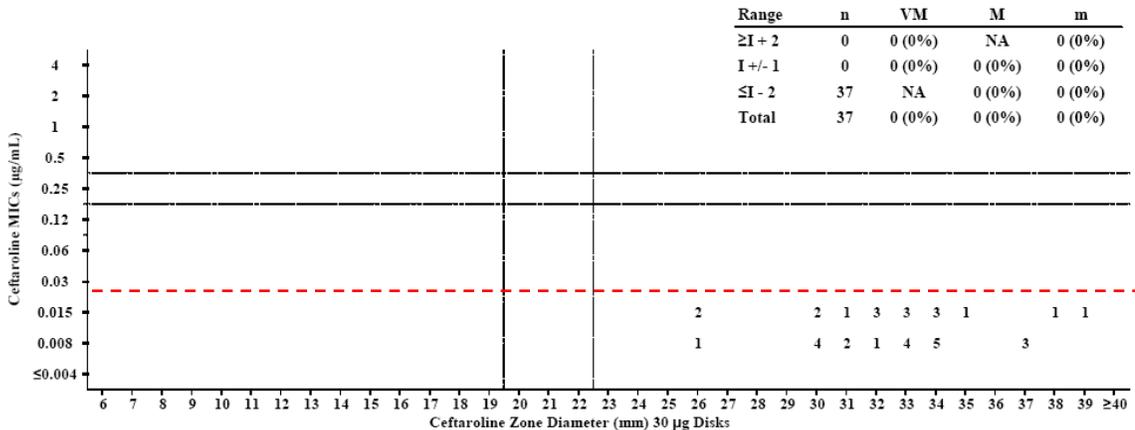


Abbreviations: cSSSI = complicated skin and skin structure infections; MIC = minimum inhibitory concentration; I = intermediate; m = minor; M = major; VM = very major error.

Based on the Phase 3 clinical trial, the appropriate breakpoint should be set on the available data; therefore, the appropriate ceftaroline MIC interpretive criteria for *S. pyogenes* should be  $\leq 0.004$  mcg/mL based on the available data. However, no ceftaroline zone diameter is suggested due to lack of sufficient data.

Scatterplots for all Phase 3 clinical isolates of *S. agalactiae* and *S. dysgalactiae* are shown in Figure 35 and 36, respectively. For *S. dysgalactiae*, one isolate had a zone diameter of 22 mm and an MIC  $\leq 0.004$  mcg/mL (Figure 36). FDA proposed breakpoints are shown in red hashed lines ceftaroline MIC  $\leq 0.015$  mcg/mL *S. agalactiae* and at this time, no breakpoint are proposed for *S. dysgalactiae* due to insufficient data information. No ceftaroline zone diameter is suggested due to lack of sufficient data.

**Figure 35. Ceftaroline MICs vs. Ceftaroline Zone Diameter for Phase 3 Clinical Isolates of *Streptococcus agalactiae* from cSSSI Studies P903-06 and P903-07 Combined (Isolates from both Treatment Groups)**



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**Figure 36. Ceftaroline MICs vs. Ceftaroline Zone Diameter for Phase 3 Clinical Isolates of *Streptococcus dysgalactiae* from cSSSI Studies P903-06 and P903-07 Combined (Isolates from both Treatment Groups)**

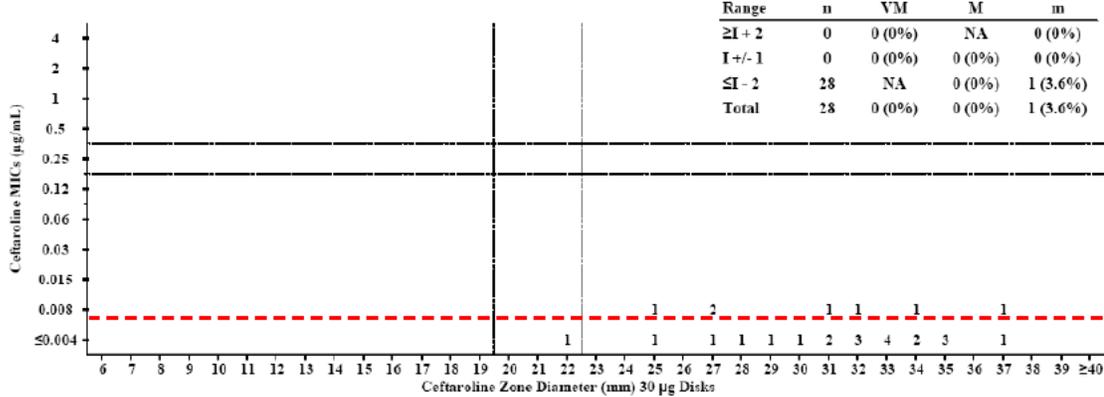
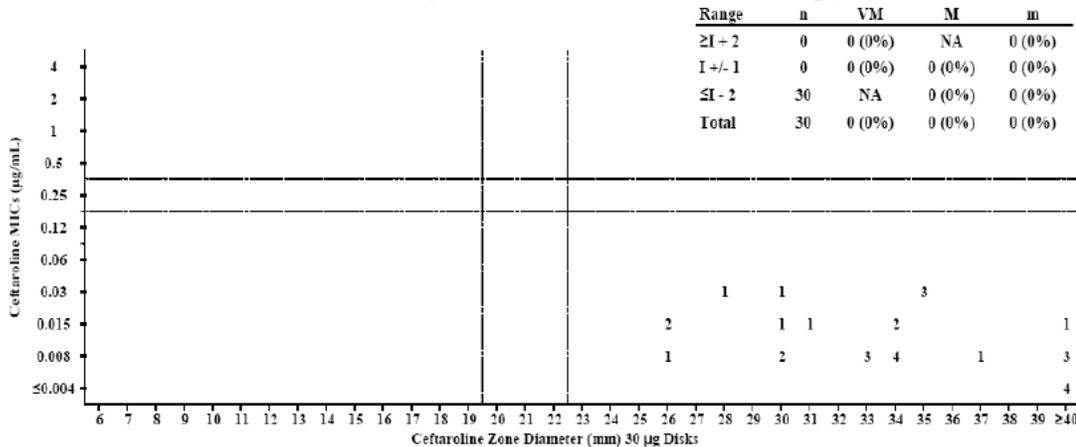


Figure 37 shows the scatterplot for *Streptococcus anginosus*, a member of the viridians streptococcal group. There were a total of 12 isolates in the study; 5 isolates with MIC of 0.03mcg/mL, 1 isolate at 0.015 mcg/mL; 3 isolates at a ceftaroline MIC of 0.008 mcg/mL and 3 at  $\le 0.004$  mcg/mL. Please note that at this time, no susceptibility breakpoint for ceftaroline is proposed for *S. anginosus* due to insufficient information.

**Figure 37. Ceftaroline MICs vs. Ceftaroline Zone Diameter for Phase 3 Clinical Isolates of *Streptococcus anginosus* group from cSSSI Studies P903-06 and P903-07 Combined (Isolates from both Treatment Groups)**



***Breakpoint analysis for Enterobacteriaceae:***

The Applicant presented scatter plots for all clinical isolates of *Enterobacteriaceae*; in addition, individual scatter plots for representative members of the group were also submitted. Figure 38-40 shows the scatterplot for all clinical isolates of *Enterobacteriaceae* from ceftaroline-treated subjects in all Phase 3 studies. Clinical failures, indicated in parentheses, show that failures are well scattered across the MIC and zone diameter ranges. (b) (4)

The Applicant submitted data which suggest that ceftaroline is an AmpC inducer, and thus, AmpC produces as well as ESBL producing organisms will potentially have reduce susceptibility to ceftaroline. AmpC resistance is known to negatively affect clinical outcome and may result in MICs that is above the breakpoint. As expected with the cephalosporin

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class of antibiotics, *Enterobacteriaceae* MIC of ceftaroline increased with the presence of AmpC induction or ESBL. The in vitro study suggest that ceftaroline MIC against the non AmpC and non-ESBL *Enterobacteriaceae* are low while the MIC<sub>90</sub> values for the AmpC and ESBL producers are higher.

Both clinical and surveillance data suggest a bimodal ceftaroline MIC distribution for the Enterobacteriaceae. The net effect is a split in the susceptibility data and breakpoints that fall in the troughs of the bimodal MIC distribution will probably result in reproducible categorization of susceptibility and breakpoints that fall in the middle of the distribution will result in poor reproducibility and it may be necessary to shift breakpoints slightly to reduce the impact of the problem. Resistance mechanisms are also known to affect clinical outcome and results in MIC above the chosen breakpoint. In the case of the *Enterobacteriaceae*, it may be necessary to adjust the breakpoints to report organisms as intermediate or resistant.

Based on PK/PD values and on the issue regarding ESBL, this Reviewer feels that the data support setting the susceptible breakpoint to  $\leq 0.25$  mcg/mL, the intermediate breakpoint to 0.5 mcg/mL and a resistant breakpoint to  $\geq 2$  mcg/mL for *Enterobacteriaceae*. The following disk diffusion zone diameters are recommended: susceptible  $\geq 24$ ; intermediate 20-23 mm; resistant  $\leq 19$  mm.

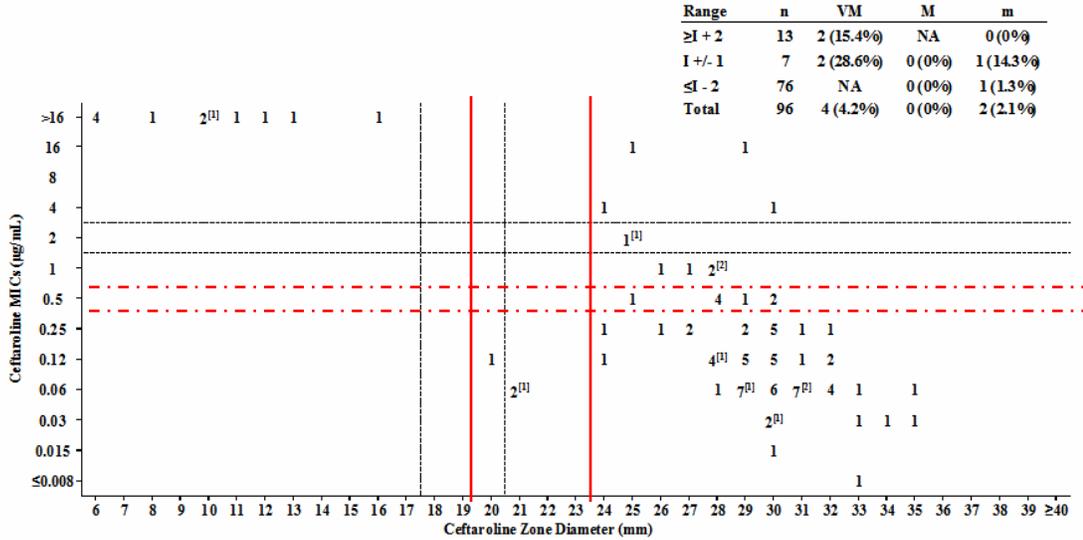
The proposed final breakpoint determinations takes into consideration interpretation of MIC data, pharmacokinetic evaluation, overall discrepancy rates, and clinical verification of breakpoints by clinical and bacteriological response rates. Proposing these breakpoints are somewhat problematic since they lead to higher error rates, however, the overall rates were kept relatively low. The CLSI disk diffusion breakpoint for a similar in class cephalosporin range from sensitive  $\geq 20$ ; intermediate 18 – 19; resistant  $\leq 17$  so the breakpoint suggested by the Agency appear to be a reasonable compromise. It is also important to note that it is plausible that higher error rates may lead to the initiation of inadequate antimicrobial therapy. The red lines in figure 38 are the FDA proposed breakpoints.

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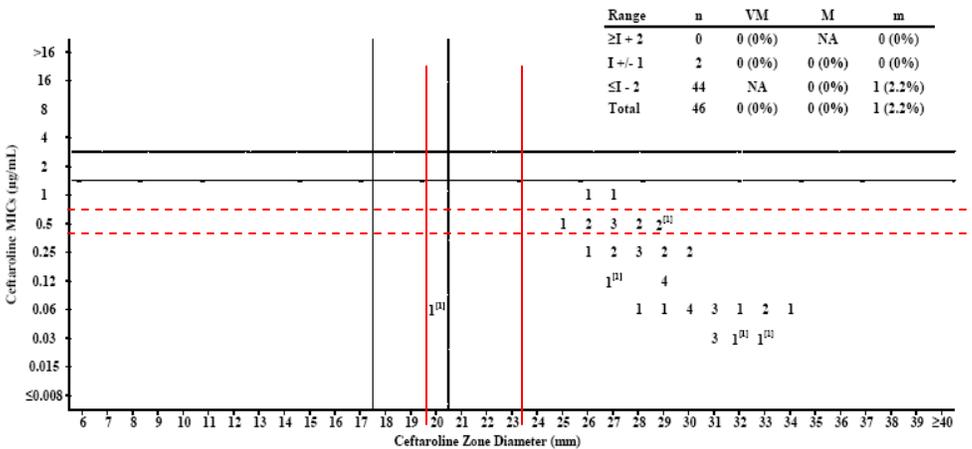
Date Review Completed: 09/27/2010

**Figure 38. Ceftaroline MICs vs. Ceftaroline Zone Diameter (30 -µg disks) for Phase 3 Clinical Isolates of *Enterobacteriaceae* from Ceftaroline-treated Subjects in cSSSI Studies P903-06 and P903-07 Combined**



MIC Range	n	Discrepancy Rates		
		Very Major	Major	Minor
$\ge I+2$	16	5	0	0
I +1 to I-1	25	4	0	8
$\le I-2$	55	NA	0	3
<b>Total</b>	<b>96</b>	<b>9</b>	<b>0</b>	<b>11</b>

**Figure 39: Ceftaroline MICs vs. Ceftaroline Zone Diameter (30-µg disks) for *Enterobacteriaceae* Clinical Isolates from CABP P903-08 and P903-09 Studies Combined (Isolates from Ceftaroline-treated Subjects)**



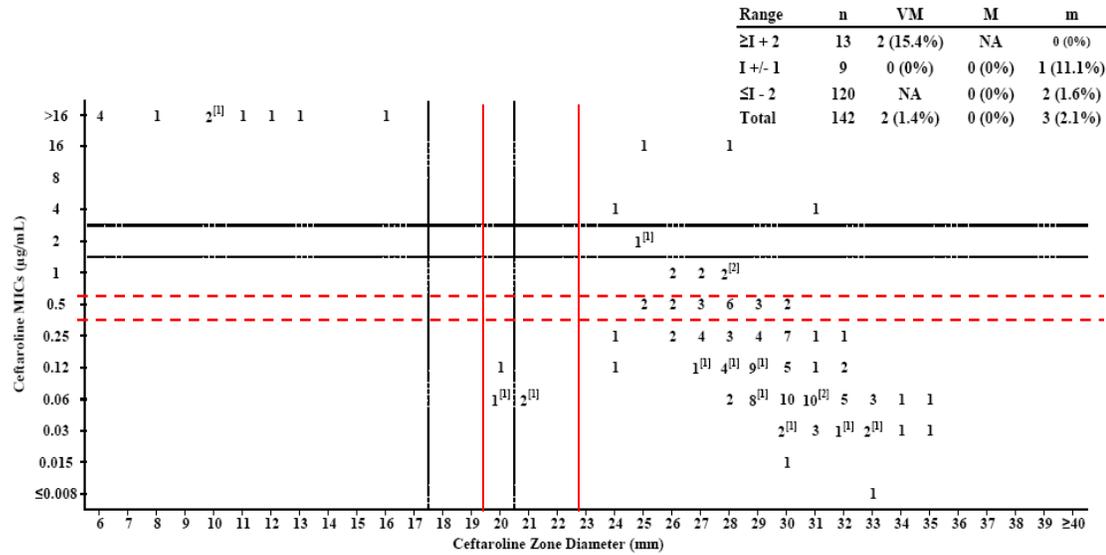
MIC Range	n	Discrepancy Rates		
		Very Major	Major	Minor
$\ge I+2$	0	0	0	0
I +1 to I-1	22	2	0	11
$\le I-2$	24	0	0	1
<b>Total</b>	<b>46</b>	<b>0</b>	<b>0</b>	<b>12</b>

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**Figure 40. Ceftaroline MICs vs. Ceftaroline Zone Diameter (30-µg disks) for all *Enterobacteriaceae* Clinical Isolates from Ceftaroline-treated Subjects in cSSSI and CABP Studies Combined**



MIC Range	n	Discrepancy Rates		
		Very Major	Major	Minor
≥ I + 2	16	4	0	0
I + 1 to I - 1	47	6	0	18
≤ I - 2	79	NA	0	4
<b>Total</b>	<b>142</b>	<b>5 (4%)</b>	<b>0</b>	<b>22</b>

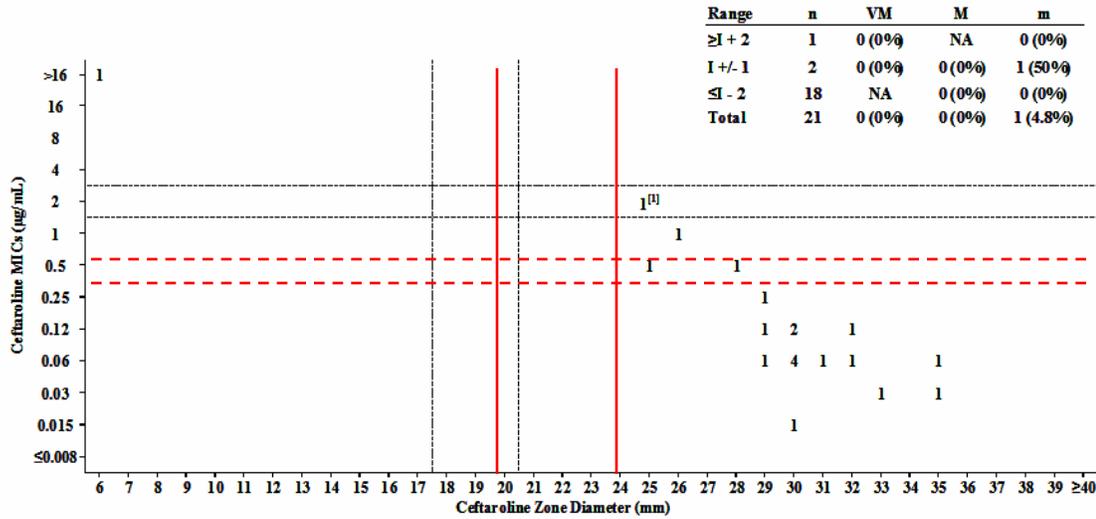
Scatterplots for individual *Enterobacteriaceae* (by pathogen) for the combined cSSSI and CABP ceftaroline-treated subjects are presented as follows: *E. coli* (Figures 41-42), *K. pneumoniae* (Figures 43-44), *K. oxytoca* (Figure 45-46), *M. morgani* (Figure 47), and *P. mirabilis* (Figure 48). The FDA proposed MIC and disk diffusion breakpoints are shown in red hatched marks. Proposing these breakpoints leads to higher error rates; even though the Very Major error rates were kept as low as possible they some were above what the CLSI considered acceptable limits. The false resistance reporting may be considered a lesser problem compared to false susceptible. Traditionally, due to the presence of ESBLs and AmpC expression, occasionally, the *Enterobacteriaceae* in combination with cephalosporin may result in consistently higher rates of false resistance and false susceptible reporting leading to higher Major, and Very Major discrepancy values, respectively. The

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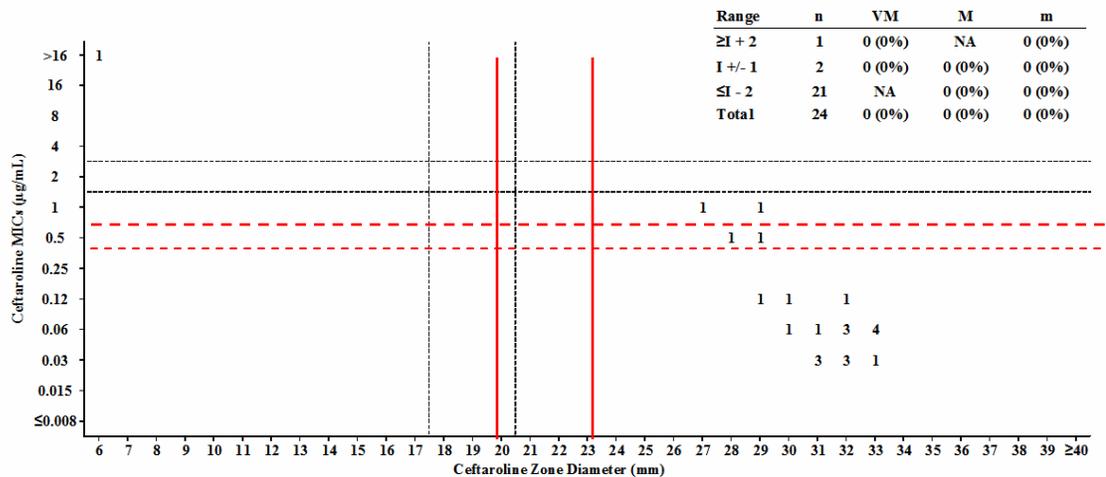
Date Review Completed: 09/27/2010

**Figure 41. Ceftaroline MICs vs. Ceftaroline Zone Diameter (30-µg disks) for *Escherichia coli* Clinical Isolates from Ceftaroline-treated Subjects in cSSSI Studies P903-06 and P903-07**



MIC Range	n	Discrepancy Rates		
		Very Major	Major	Minor
$\geq I+2$	2	1	0	0
I +1 to I-1	4	1	0	2
$\leq I-2$	15	NA	0	0
<b>Total</b>	<b>21</b>	<b>1</b>	<b>0</b>	<b>2</b>

**Figure 42. Ceftaroline MICs vs. Ceftaroline Zone Diameter (30-µg disks) for *Escherichia coli* Clinical Isolates from CABP P903-08 and P903-09 Studies Combined (Isolates from Both Treatment Groups)**



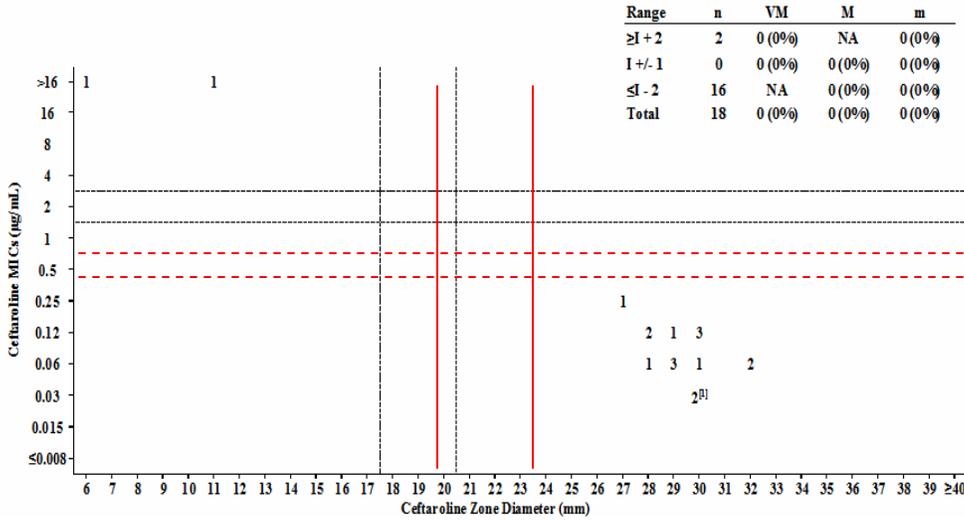
MIC Range	n	Discrepancy Rates		
		Very Major	Major	Minor
$\geq I+2$	1	0	0	0
I +1 to I-1	4	2	0	2
$\leq I-2$	19	NA	0	0
<b>Total</b>	<b>24</b>	<b>2</b>	<b>0</b>	<b>2</b>

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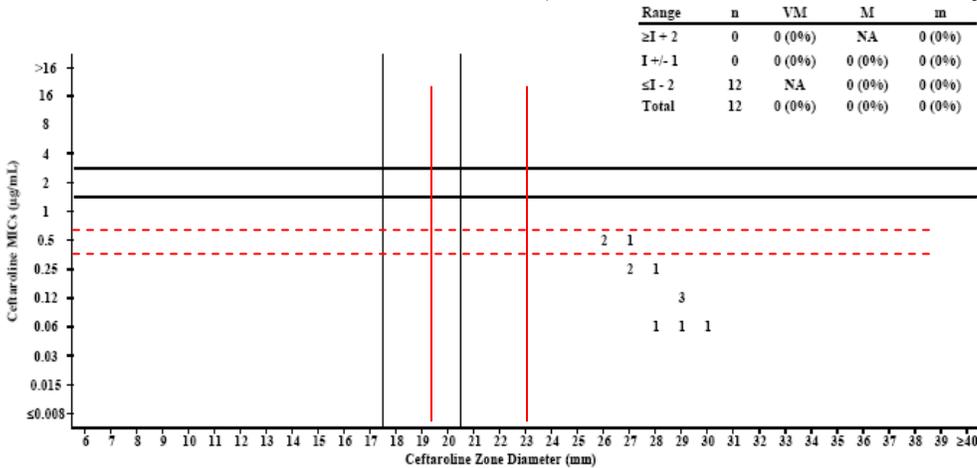
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**Figure 43. Ceftaroline MICs vs. Ceftaroline Zone Diameter (30-µg disks) for *Klebsiella pneumoniae* Clinical Isolates from Ceftaroline-treated Subjects in cSSSI Studies P903-06 and P903-07**



MIC Range	n	Discrepancy Rates		
		Very Major	Major	Minor
$\geq I+2$	2	0	0	0
I+1 to I-1	1	0	0	0
$\leq I-2$	15	0	0	0
Total	18	0	0	0

**Figure 44. Ceftaroline MICs vs. Ceftaroline Zone Diameter (30-µg disks) for *Klebsiella pneumoniae* Clinical Isolates from CABP P903-08 and P903-09 Studies Combined (Isolates from Ceftaroline-treated Subjects)**



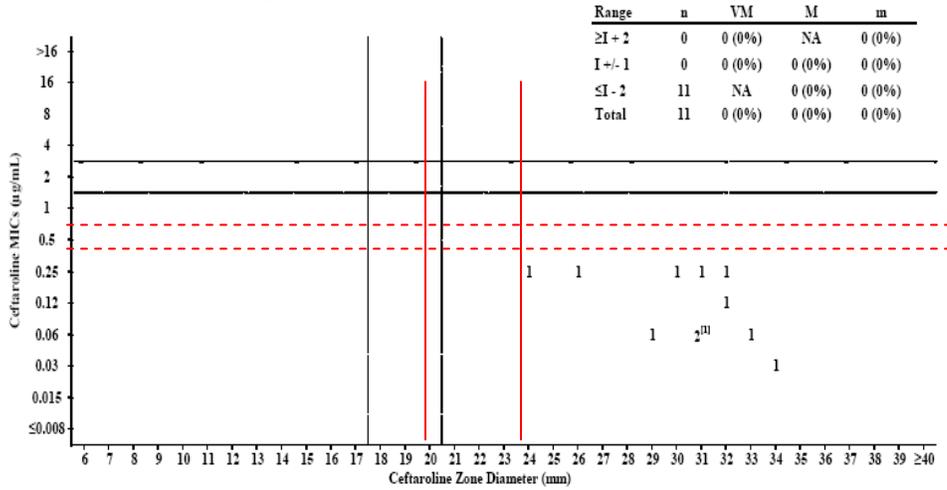
MIC Range	n	Discrepancy Rates		
		Very Major	Major	Minor
$\geq I+2$	0	0	0	0
I+1 to I-1	6	0	0	3
$\leq I-2$	6	0	0	0
Total	12	0	0	3

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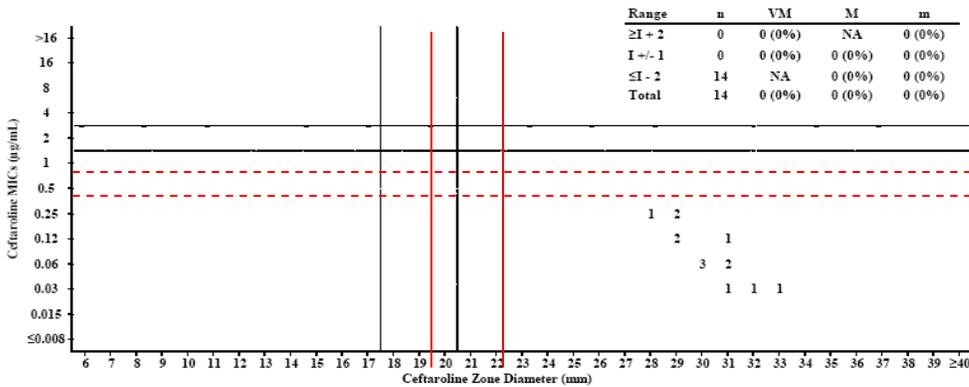
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**Figure 45. Ceftaroline MICs vs. Ceftaroline Zone Diameter (30-µg disks) for *Klebsiella oxytoca* Clinical Isolates from Ceftaroline-treated Subjects in cSSSI Studies P903-06 and P903-07**



MIC Range	n	Discrepancy Rates		
		Very Major	Major	Minor
$\geq I+2$	0	0	0	0
I +1 to I-1	5	0	0	0
$\leq I-2$	6	0	0	0
Total	11	0	0	0

**Figure 46. Ceftaroline MICs vs. Ceftaroline Zone Diameter (30-µg disks) for *Klebsiella oxytoca* clinical isolates from CABP P903-08 and P903-09 Studies Combined (Isolates from Both Treatment Groups)**



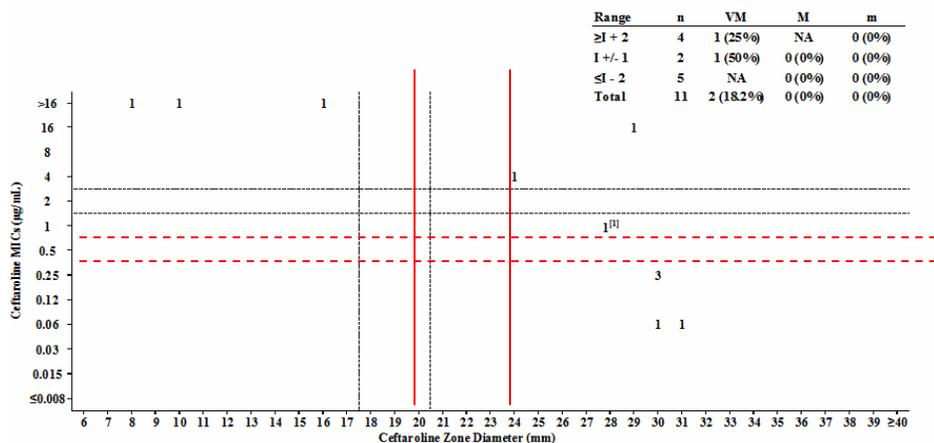
MIC Range	n	Discrepancy Rates		
		Very Major	Major	Minor
$\geq I+2$	0	0	0	0
I +1 to I-1	3	0	0	0
$\leq I-2$	11	0	0	0
Total	14	0	0	0

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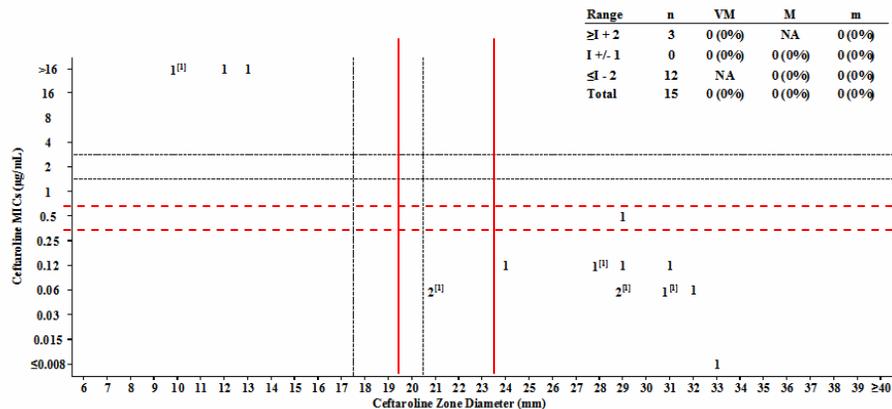
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**Figure 47. Ceftaroline MICs vs. Ceftaroline Zone Diameter (30-µg disks) for *Morganella morganii* Clinical Isolates from Ceftaroline-treated Subjects in cSSSI Studies P903-06 and P903-07**



MIC Range	n	Discrepancy Rates		
		Very Major	Major	Minor
$\ge I + 2$	5	2 (20%)	0	0
I +/- 1	4	1	0	0
$\le I - 2$	2	0	0	0
<b>Total</b>	<b>11</b>	<b>3</b>	<b>0</b>	<b>0</b>

**Figure 48. Ceftaroline MICs vs. Ceftaroline Zone Diameter (30-µg disks) for *Proteus mirabilis* Clinical Isolates from Ceftaroline-treated Subjects in cSSSI Studies P903-06 and P903-07**



MIC Range	n	Discrepancy Rates		
		Very Major	Major	Minor
$\ge I + 2$	3	0	0	0
I +/- 1	1	0	0	1
$\le I - 2$	11	0	0	2
<b>Total</b>	<b>15</b>	<b>0</b>	<b>0</b>	<b>3</b>

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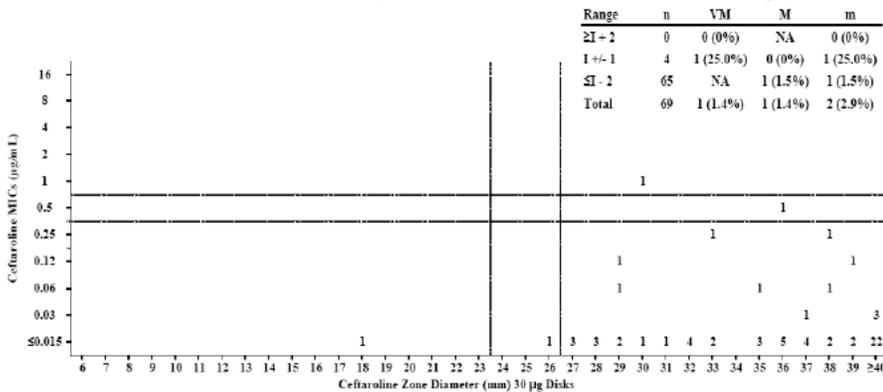
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**Breakpoint analysis for *Haemophilus* spp.**

The disk diffusion zone diameters for ceftaroline all Phase 3 isolates of *Haemophilus* spp. are shown in Figure 49. The zone diameters ranged from 18 to  $\geq 40$  mm. The Applicant stated that all isolates were tested for their ability to produce  $\beta$ -lactamase and that one isolate of *H. influenzae* was identified from a ceftaroline-treated subject from Poland in CABP P0903-09 (Pat. no. 661309500). The ceftaroline MIC for the isolate was 0.03 mcg/mL and was associated with a subject with a 100% successful clinical and microbiological outcome. (b) (4)

Scatterplots for the 69 isolates of *Haemophilus* spp. encountered in the clinical trial are shown in Figure 49. Please note that due to the limited number of isolates and the lack of clinical experience, the Agency does not recommended setting a breakpoint for *H. influenzae* at this time due to insufficient clinical experience at the Applicant’s proposed breakpoint (Table 100).

**Figure 49. Ceftaroline MICs vs. Ceftaroline Zone Diameter (30  $\mu$ g disks) for all *Haemophilus* spp. Clinical Isolates from CABP P903-08 and P903-09 Studies Combined (Isolates from Both Treatment Groups)**



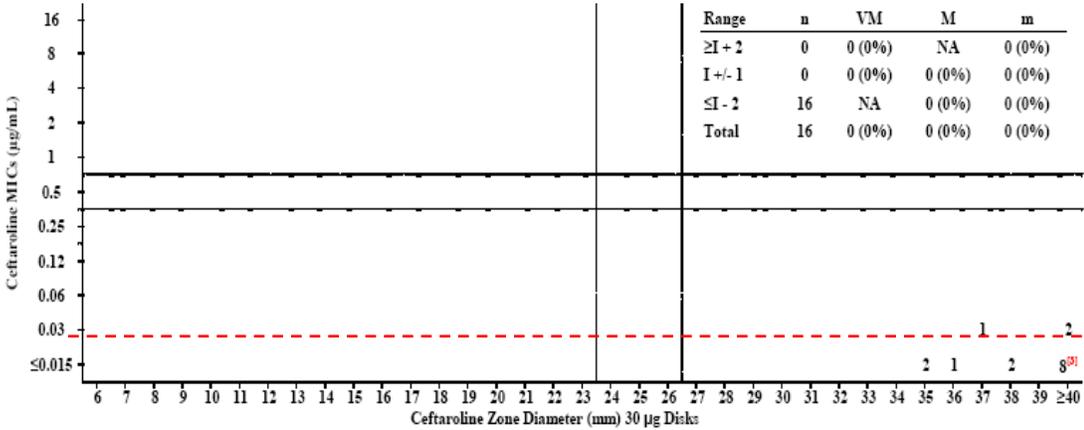
Figures 50 and 51 show scatterplots for *H. influenzae* and *H. parainfluenzae*, respectively. The combined MIC data is shown in Table 118. For *H. parainfluenzae*, out a possible 15 isolates reported in the study, only scatter plots for 14 isolates are shown. Please note that the Agency does not recommended setting a breakpoint for *Haemophilus parainfluenzae* at this time (b) (4); moreover, the Agency believes that this organism is not a true pathogen and should not be included in the first list.

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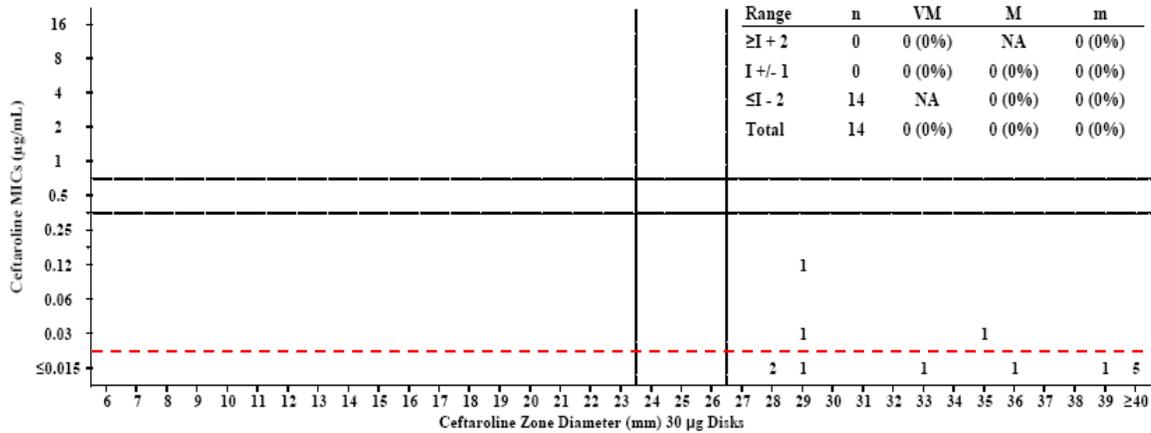
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**Figure 50. Ceftaroline MICs vs. Ceftaroline Zone Diameter (30-µg disks) for *Haemophilus influenzae* Clinical Isolates from CABP P903-08 and P903-09 Studies combined (Isolates from Ceftaroline-treated Subjects)**



**Figure 51. Ceftaroline MICs vs. Ceftaroline Zone Diameter (30-µg disks) for *Haemophilus parainfluenzae* Clinical Isolates from CABP P903-08 and P903-09 Studies Combined (Isolates from Ceftaroline-treated Subjects)**



**Table 118 Clinical and Microbiological Success by Ceftaroline MIC against *Haemophilus influenzae* from CABP Studies P903-08 and P903-09 Combined**

Ceftaroline MIC (µg/mL)	N	Clinical Success n/N (%)	Microbiological Success (Eradicated/Presumed Eradicated n/N (%))
$\leq 0.008$	8	5/8 (62.5%)	5/8 (62.5%)
0.015	5	5/5 (100.0%)	5/5 (100.0%)
0.03	3	3/3 (100.0%)	3/3 (100.0%)
Total	16	13/16 (81.2%)	13/16 (81.2%)

Abbreviations: CABP = community acquired bacterial pneumonia; MIC = minimal inhibitory concentration.

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**Summary and Conclusion:**

Based on a detailed analysis of the data which includes in vitro surveillance data, clinical outcome data, and PK/PD analysis, the Agency proposes the in vitro susceptibility test interpretation criteria as shown in the “EXECUTIVE SUMMARY” of this review.

**APPLICANT’S AND AGENCY’S PROPOSED MICROBIOLOGY SUBSECTION OF THE  
PACKAGE INSERT**

**See EXECUTIVE SUMMARY**

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Avery Goodwin, Ph.D.  
Microbiology Reviewer  
DAIOP

Fred Marsik, Ph.D.  
Microbiology Team Leader  
DAIOP  
27 Sep 10 FIN FJM

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/s/

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AVERY C GOODWIN  
09/28/2010

FREDERIC J MARSIK  
09/28/2010

# PRODUCT QUALITY MICROBIOLOGY FILING CHECKLIST

**NDA Number:** 200327

**Applicant:** Cerexa Inc.

**Letter Date:** December 30, 2010

**Drug Name:** (b) (4)<sup>TM</sup>

**NDA Type:** Original

**Stamp Date:** December 31, 2010

The following are necessary to initiate a review of the NDA application:

	Content Parameter	Yes	No	Comments
1	Is the product quality microbiology information described in the NDA and organized in a manner to allow substantive review to begin? Is it legible, indexed, and/or paginated adequately?	X		
2	Has the applicant submitted an overall description of the manufacturing processes and microbiological controls used in the manufacture of the drug product?	X		Description of Manufacturing Process & Controls is referenced in Section 3.2.P.3.3. Drug substance is a (b) (4) antibiotic & is referenced in DMF 23167.
3	Has the applicant submitted protocols and results of validation studies concerning microbiological control processes used in the manufacture of the drug product?	X		Where applicable SOP numbers were listed, e.g. page 15 section 3.2.P.3.3
4	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?		X	
5	Has the applicant submitted preservative effectiveness studies (if applicable) and container-closure integrity studies?	X		Section 3.2.P.5.4
6	Has the applicant submitted microbiological specifications for the drug product and a description of the test methods?	X		The applicant refers to DMF (b) (4) for details.
7	Has the applicant submitted the results of analytical method verification studies?	X		Stability data from production reports contained sterility and bacterial endotoxins test results.
8	Has the applicant submitted all special/critical studies/data requested during pre-submission meetings and/or discussions?			N/A
9	Is this NDA fileable? If not, then describe why.	X		

**Additional Comments:**

Based on the information provided the application is fileable from the Product Quality Microbiology standpoint.

\_\_\_\_\_  
Vinayak B. Pawar, Ph.D.

\_\_\_\_\_  
Date

\_\_\_\_\_  
Bryan S. Riley, Ph.D.

\_\_\_\_\_  
Date

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

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/s/

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VINAYAK B PAWAR  
02/17/2010

BRYAN S RILEY  
02/17/2010  
I concur.

**CLINICAL Microbiology: 45-Day Meeting NDA Checklist for Filing  
 NDA 200327 Ceftaroline Fosamil (b) (4) for Complicated Skin  
 and Skin Structure Infections and Community-Acquired Bacterial  
 Pneumonia**

**Reviewer: Avery Goodwin, Ph.D**

**Date Completed: 1/25/2010**

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

No.	Item	Yes	No	Comments
1	Is the clinical microbiology information (preclinical/nonclinical and clinical) described in different sections of the NDA organized in a manner to allow substantive review to begin?	✓		
2	Is the clinical microbiology information (preclinical/nonclinical and clinical) described in different sections of the NDA indexed, paginated, and/or linked in a manner to allow substantive review to begin?	✓		
3	Is the clinical microbiology information (preclinical/nonclinical and clinical) in different sections of the NDA legible so that substantive review can begin?	✓		
4	On its face, has the applicant <u>submitted</u> <i>in vitro</i> data in necessary quantity, using necessary clinical and non-clinical strains/ isolates, and using necessary numbers of approved current divisional standard of approvability of the submitted draft labeling?	✓		
5	Has the applicant <u>submitted</u> draft provisional breakpoint and interpretive criteria, along with quality control (QC) parameters, if applicable, in a manner consistent with contemporary standards, which attempt to correlate criteria with clinical results of NDA studies, and in a manner to allow substantive review to begin?	✓		
6	Has the applicant <u>submitted</u> any required animal model studies necessary for approvability of the product based on the submitted draft labeling?	✓		
7	Has the applicant <u>submitted</u> all special/critical studies/data requested by the Division during pre-submission discussions?	✓		
8	Has the applicant <u>submitted</u> the clinical microbiology datasets in a format which intends to correlate baseline pathogen with clinical and microbiologic outcomes exhibited by relevant pathogens isolated from test of cure or end of treatment?	✓		
9	Has the applicant <u>submitted</u> a clinical microbiology			

**CLINICAL Microbiology: 45-Day Meeting NDA Checklist for Filing  
 NDA 200327 Ceftaroline Fosamil (b) (4) for Complicated Skin  
 and Skin Structure Infections and Community-Acquired Bacterial  
 Pneumonia**

**Reviewer: Avery Goodwin, Ph.D**

**Date Completed: 1/25/2010**

	dataset in a format which intends to determine resistance development by correlating changes in the phenotype (such as <i>in vitro</i> susceptibility) and/or genotype (such as mutations) of the baseline relevant pathogen with clinical and microbiologic outcome as exhibited by relevant pathogens isolated from test of cure or end of treatment?	✓		
10	Has the applicant used standardized methods or if non-standardized methods were used has the applicant included full details of the method, the name of the laboratory where actual testing was done and performance characteristics of the assay in the laboratory where the actual testing was done?	✓		
11	Is the clinical microbiology draft labeling consistent with 21 CFR Parts 201, 314, 601 and current Divisional policy.	✓		
12	FROM A CLINICAL MICROBIOLOGY PERSPECTIVE, IS THIS NDA FILEABLE? <b>IF NO, GIVE REASONS BELOW.</b>	✓		

**Any Additional Clinical Microbiology Comments:** There are no additional comments

**Avery Goodwin, Ph.D.**  
**Reviewing Clinical Microbiologist**

**Fred Marsik, Ph.D.**  
**Team Leader Clinical Microbiology**  
**HFD-520**  
**26 Jan 10 FIN FJM**

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

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

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/s/

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AVERY C GOODWIN  
02/17/2010

FREDERIC J MARSIK  
02/17/2010