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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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	Acute bacterial skin and skin structure infections in pediatrics
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Biometrics Division:	Division of Biometrics IV
Statistical Reviewer:	Daniel Rubin, PhD
Concurring Reviewers:	Statistical team leader: Karen Higgins, ScD
Medical Division:	Division of Anti-Infective Products
Clinical Team:	Clinical reviewer: Sheral Patel, MD
	Clinical team leader: Hala Shamsuddin, MD
Project Manager:	Carmen DeBellas, RPh, PharmD

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1. EXECUTIVE SUMMARY

In this submission the Applicant, Cerexa Inc., seeks to provide evidence that the intravenously administered cephalosporin antibacterial drug ceftaroline is safe and effective for treating acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP) in pediatric patients aged 2 months to <18 years. Ceftaroline was previously FDA-approved for adult ABSSSI and CABP.

Three randomized trials were reviewed that together enrolled approximately 350 pediatric patients. Study P903-23 evaluated ceftaroline in pediatric ABSSSI and Studies P903-24 and P903-31 evaluated pediatric CABP. The difference between the CABP trials was that Study P903-24 enriched for complicated pneumonia and MRSA infection, but the CABP trials were pooled for purposes of review.

The randomized comparator group received intravenous vancomycin or cefazolin in ABSSSI Study P903-23, ceftriaxone with vancomycin in CABP Study P903-24, and ceftriaxone in CABP Study P903-31. After initial intravenous treatment with ceftaroline or the comparator regimen, all three reviewed trials allowed subjects in either randomized group to have an optional switch to oral antibacterial therapy.

The primary objective of each reviewed trial was to evaluate safety and tolerability. Safety results did not identify any statistical trends warranting follow-up investigation.

None of the trials specified a primary efficacy endpoint or primary analysis, and none used formal inferential statistical hypothesis testing to evaluate efficacy. The protocols did, however, pre-specify several endpoint definitions. For ABSSSI the protocols gave three definitions for Day 3 response depending on lesion size and/or body temperature. The CABP trials defined Day 4 clinical response as improvement and no worsening on two of seven symptoms and Day 4 clinical stability as no symptom worsening with stability of temperature, pulse, respiratory rate, and oxygen saturation. All trials defined clinical cure at end of intravenous therapy (EOIV), and of therapy (EOT), and a test of cure (TOC) visit (8-15 days following the end of oral and intravenous therapy) as requiring resolution or improvement of the infection to the extent that additional antibacterial therapy was not required. The protocols specified that efficacy would be assessed in the modified intent-to-treat (MITT) population comprised of randomized subjects who received any dose of study drug and met clinical disease criteria at baseline.

Baseline characteristics were generally well balanced between the ceftaroline and comparator groups, and lack of protocol adherence did not appear to compromise results.

As shown in the subsequent tables, although confidence intervals for treatment effects did not guarantee that ceftaroline tightly preserved the efficacy of the comparator drug in all cases, numerical trends did not raise any alarms with respect to the efficacy of ceftaroline. Given the clinical judgment that efficacy and safety in ABSSSI and CABP can generally be extrapolated from adults to pediatrics, statistical evidence in this application is consistent with the safety and efficacy of ceftaroline for pediatric patients.

Table 1: Outcomes in ABSSSI Study P903-23, MITT Population

	Ceftaroline (n = 107)	Comparator (n = 52)	Difference (95% CI)
Day 3: ≥20% reduction from baseline infection area			
Responder	91/107 (85%)	44/52 (85%)	0% (-11% to 14%)
Non-responder	11/107 (10%)	4/52 (8%)	
Incomplete data	5/107 (5%)	4/52 (8%)	
Day 3: Cessation of spread by total infection area			
Responder	98/107 (92%)	47/52 (91%)	1% (-8% to 13%)
Non-responder	4/107 (4%)	1/52 (2%)	
Incomplete data	5/107 (5%)	4/52 (8%)	
Day 3: Cessation of spread by infection length and width and temperature <37.6°C			
Responder	86/107 (81%)	39/52 (75%)	5% (-8% to 20%)
Non-responder	16/107 (15%)	9/52 (18%)	
Incomplete data	5/107 (5%)	4/52 (8%)	
Clinical Outcome			
Clinical Cure at TOC	101/107 (94%)	45/52 (87%)	8% (-1% to 20%)
Observed Failure at EOIV	0/107 (0%)	1/52 (2%)	
Observed Failure at EOT	0/107 (0%)	0/52 (0%)	
Observed Failure at TOC	0/107 (0%)	0/52 (0%)	
Indeterminate	6/107 (6%)	6/52 (12%)	

Source: Study P903-23 Clinical Study Report, Table 11.4.1.1-1, Table 11.4.1.2-3, and Table 11.4.1.2-3.

Table 2: Outcomes in pooled CABP Studies P903-24 and P903-31, MITT Population

	Ceftaroline (n = 136)	Comparator (n = 45)	Difference (95% CI)
Day 4 Clinical Response			
Responder	89/136 (65%)	30/45 (67%)	-1% (-16% to 15%)
Non-responder	35/136 (26%)	14/45 (31%)	
Incomplete data	12/136 (9%)	1/45 (2%)	
Day 4 Clinical Stability			
Stability	43/136 (31%)	15/45 (33%)	-2% (-18% to 13%)
No stability	82/136 (60%)	30/45 (67%)	
Incomplete data	11/136 (8%)	0/45 (0%)	
Clinical Outcome			
Clinical Cure at TOC	120/136 (88%)	41/45 (91%)	-3% (-12% to 10%)
Observed Failure at EOIV	10/136 (7%)	3/45 (7%)	
Observed Failure at EOT	0/136 (0%)	1/45 (2%)	
Observed Failure at TOC	1/136 (1%)	0/45 (0%)	
Indeterminate	5/136 (4%)	0/136 (0%)	

Source: The Applicant's Summary of Clinical Efficacy – CABP, Table 6.2.2-1 and Table 6.2.3.1-1.

2 INTRODUCTION

2.1 Overview

Ceftaroline fosamil (henceforth referred to as ceftaroline in this review) is an antibacterial drug that has been developed by the Applicant Cerexa, Inc. Ceftaroline belongs to the cephalosporin class of β-lactam antibacterial drugs. Cephalosporins are bactericidal rather than bacteriostatic, and operate by inhibiting bacterial cell wall synthesis. Ceftaroline has shown *in vitro* activity against a variety of Gram-positive and Gram-negative bacterial pathogens, including *S. aureus* (including both methicillin-susceptible and methicillin-resistant strains), *Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus agalactiae, Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca*, and *Haemophilus influenzae*.

Ceftaroline was FDA-approved in 2010 for the treatment of both acute bacterial skin and skin structure infections (ABSSSI[1]) and community-acquired bacterial pneumonia (CABP) in adults, due to selected susceptible pathogens. These approvals were based on replicated Phase 3 trials in each indication that were randomized, controlled, double-blinded, multinational, non-inferiority studies. A total of 1396 subjects were enrolled in the Phase 3 ABSSSI program, while 1231 subjects were enrolled in the Phase 3 CABP program. All adult Phase 3 trials restricted enrollment to subjects ≥18 years of age.

In this submission the Applicant seeks to indicate ceftaroline for the treatment of ABSSSI and CABP in both adult and pediatric patients, and to place results of pediatric studies in the Clinical Studies section of the resulting label.

The evidence submitted by the Applicant includes one pediatric clinical trial in ABSSSI, two pediatric clinical trials in CABP, two pharmacokinetic studies, an updated population pharmacokinetic model for ceftaroline and a modeling and simulation report on pediatric dosing, and two juvenile rat toxicity studies. This review focuses on evidence of safety and efficacy from the three pediatric clinical trials, which are summarized in subsequent tables. These studies were conducted to fulfill post-marketing requirements under the Pediatric Research Equity Act. The ABSSSI trial (Study P903-23) and CABP trials (Study P903-24 and Study P903-31) together enrolled approximately 350 subjects. The difference between the CABP studies was that Study P903-24 enriched for subjects with complicated pneumonia at greater risk for MRSA infection.

The primary objective of these trials was to evaluate safety and tolerability. Although several efficacy endpoints were pre-specified for analysis, none were specified as primary, and formal inferential statistical testing was not used. The Applicant's rationale was that efficacy in ABSSSI and CABP can be largely extrapolated from adults to pediatrics, and therefore that full confirmatory trials in pediatrics were not necessary.

[1] At the time the trials were conducted the Agency term for this indication was "complicated skin and skin structure infections" (cSSSI). For consistency the term "acute bacterial skin and skin structure infections" (ABSSSI) is used throughout this review.

Table 3: Reviewed pediatric clinical trials

Study	Patient population	Design	Active comparator	Sample size in modified intent-to-treat population
P903-23	ABSSSI, ages 2 months to 18 years	Randomized, observer blinded, descriptive efficacy statistics	Vancomycin or cefazolin with or without aztreonam	2:1 randomized Ceftaroline: N = 107 Comparator: N = 52
P903-24	CABP, ages 2 months to 18 years (enriched for complicated cases and MRSA risk)		Ceftriaxone with vancomycin	3:1 randomized Ceftaroline: N = 29 Comparator: N = 9
P903-31	CABP, ages 2 months to 18 years		Ceftriaxone	3:1 randomized Ceftaroline: N = 107 Comparator: N = 36

Source: Clinical Study Reports for the respective studies.

Table 4: Ceftaroline dosing in reviewed trials

Study	Ceftaroline dose and mode of administration
P903-23	Intravenous infusion over 60 (±10) minutes every 8 (±1) hours Children ≥6 months weighing ≤33 kg: 12 mg/kg Children ≥6 months weighing >33 kg: 400 mg Children <6 months: 8 mg/kg
P903-24	Intravenous infusion over 120 (±10) minutes every 8 (±1) hours Children ≥6 months weighing ≤40 kg: 15 mg/kg Children ≥6 months weighing >40 kg: 600 mg Children <6 months: 10 mg/kg
P903-31	Intravenous infusion over 60 (±10) minutes every 8 (±1) hours Children ≥6 months weighing ≤33 kg: 12 mg/kg Children ≥6 months weighing >33 kg: 400 mg Children <6 months: 8 mg/kg

Source: Clinical Study Reports for the respective studies.

2.2 Data sources

The patient-level datasets analyzed by this reviewer can be found at the following link in the Electronic Document Room: \\CDSESUB1\evsprod\NDA200327\0137\m5\datasets

3 STATISTICAL EVALUATION

3.1 Data and analysis quality

Patient-level data were available for all three of the reviewed trials. The data quality was sufficient, and it was straightforward to reproduce the Applicant's main efficacy results and baseline tables from the submitted datasets. The statistical analysis plans were finalized before study completion, and the Applicant appeared to faithfully executive the planned analyses.

3.2 Evaluation of efficacy

This review separately discusses efficacy for ABSSSI Study P903-23 and CABP Studies P903-24 and P903-31.

3.2.1 ABSSSI Study P903-23

The primary objective of Study P903-23 was to evaluate safety and tolerability of ceftaroline in pediatric subjects with ABSSSI, but evaluation of efficacy was a secondary objective.

The first subject was enrolled in August 2012 and the last subject visit was in May 2014.

Subjects were randomized to a ceftaroline group or comparator group in a 2:1 ratio, with the randomization stratified by age and region. Age cohorts were defined as follows:

- Cohort 1: children from 12 years to <18 years.
- Cohort 2: children from 6 years to <12 years.
- Cohort 3: children from 24 months to <6 years.
- Cohort 4: young infants/toddlers from 2 months to <24 months.

Subjects in the ceftaroline group were assigned intravenous ceftaroline infused over 60 (±10) minutes every 8 (±1) hours. Children at least 6 months old received ceftaroline 12 mg/kg if weighing ≤33 kg and 400 mg if weighing >33 kg. Children under 6 months old received ceftaroline 8 mg/kg.

Subjects in the comparator group received intravenous vancomycin 15 mg/kg every 6 (±1) hours or intravenous cefazolin 75 mg/kg/day every 8 hours. The comparator group also allowed optional intravenous aztreonam 30 mg/kg every 8 (±1) hours at any time during intravenous therapy if a Gram-negative infection was identified or suspected.

The trial included an optional switch to oral therapy. On or after Day 4 subjects could switch to oral cephalexin 25 mg/kg q6h (the preferred switch), clindamycin 10 mg/kg q8h, or linezolid (600 mg q12h for Cohort 1, 10 mg/kg q8h for Cohorts 2-4).

The total duration of intravenous and oral therapy was 5 to 14 days, with a minimum of 3 days of intravenous therapy (7 infusions for subjects randomized to ceftaroline).

Inclusion criteria required the presence of ABSSSI with measureable margins of erythema, edema, or induration that was an abscess, wound infection, or cellulitis/erysipelas. In addition to erythema the subject had to have at least one local sign or symptom of acute infection present for <10 days (among purulent or seropurulent drainage or discharge, induration/edema, fluctuance, or heat or localized warmth) and one additional sign (fever or hypothermia, white blood cell count >12,000/mm^3, >10% immature neutrophils, or lymphangitic spread).

Exclusion criteria disallowed subjects with uncomplicated skin and soft tissue infections (such as simple abscesses or impetigo), infections with a high expected cure rate after surgical incision alone or aggressive local skin care, more than 24 hours of prior systemic antibacterial therapy within 96 hours before randomization (except in cases of prior clinical or microbiological treatment failure), requirement for potentially effective concomitant therapy, a variety of conditions specific to safety profiles of the study drugs (e.g., history of hypersensitivity or allergic reactions), abnormal renal function (creatinine clearance < 50 mL/min/1.73 m^2), and a variety of serious co-morbid conditions (e.g., burn wounds, necrotizing fasciitis, need for amputation, osteomyelitis, meningitis, significant hepatic, hematologic, or immunocompromising conditions, septic shock).

Post-baseline study visits included an end of intravenous (EOIV) visit within 24 hours of the last dose of intravenous study drug, an end of therapy (EOT) visit within 48 hours of the last dose of oral study drug (for subjects who switched to oral therapy), a test of cure (TOC) visit 8-15 days after the last dose of any study drug (intravenous or oral), and a late follow-up (LFU) visit 21-35 days after the last dose of any study drug. While on study drug and at scheduled study visits the subjects were assessed for vital signs, prior and concomitant medications, pain, ABSSSI site examination, and safety events.

Efficacy was analyzed in the modified intent-to-treat analysis population (MITT Population), comprised in all subjects who were randomized, received any dose of study drug, and had a clinically confirmed diagnosis of ABSSSI.

No efficacy endpoint was specified as primary, but the protocol did define several endpoints. These included three different definitions for Day 3 response, and a clinical cure definition for EOIV, TOC, and EOT visits.

The three definitions for clinical response at Day 3 were as follows:

- Definition 1: Had a ≥20% reduction from baseline in total infection area.
- Definition 2: Had cessation of spread relative to baseline as measured by total infection area.
- Definition 3: Had cession of spread relative to baseline as measured by both length and width, and temperature <37.6°C.

At the EOIV, EOT, TOC, and LFU visits, clinical cure was defined as total resolution of all signs and symptoms of the primary ABSSSI, or improvement of the primary ABSSSI to such an extent that no further antimicrobial therapy was necessary. Subjects removed

from therapy due to insufficient therapeutic effect or adverse events were deemed clinical failures.

This was an observed-blinded study, in that at each study center one investigator was blinded to subject treatment assignments and conducted efficacy and safety assessments.

This trial did not assess efficacy using formal inferential statistics. The statistical analysis plan did specify that confidence intervals for treatment effects on the risk difference scale were to be formed using the method[2] of Miettinen and Nurminen This method is used throughout the review, except for the use of exact confidence intervals in Section 4.

Because the sample size was not chosen to power the trial for hypothesis testing, the Applicant calculated that assuming an underlying incidence rate of 2% for a specific adverse event, the sample size of 180 ceftaroline-treated subjects would yield an approximately 97% chance of observing the event. Thus, using 2:1 randomization the planned sample size was 270 total pediatric subjects with 180 in the ceftaroline group and 90 in the comparator group. However, the trial only randomized 163 subjects. The difference between planned and actual sample size was due to completing the study in accordance with timelines in the FDA pediatric post-marketing requirement. Of the 163 randomized subjects, 159 subjects were in the MITT Population used for efficacy analysis, while 4 subjects were excluded because did not take any study drug.

The Clinically Evaluable (CE) Population was comprised of all subjects in the MITT Population who met sufficient evaluability criteria with respect to outcome measurements and protocol compliance. Within the MITT Population, 141/159 (89%) subjects were in the CE Population. Most non-evaluable cases were due to subjects having the TOC visit outside the window specified in the protocol (17 subjects). In general, compliance issues or exclusions from efficacy analysis population did not compromise the integrity of the results or the integrity of randomized comparisons.

No interim analysis of efficacy was planned for the trial, but an external data safety monitoring board met periodically at pre-specified intervals to evaluate safety signals.

The subsequent table shows baseline characteristics of subjects in the trial. The randomized ceftaroline and comparator groups were comparable with respect to baseline factors. Each of the four age cohorts had 23-36 MITT ceftaroline subjects and 12-15 MITT comparator subjects. The pediatric trial population was predominately White, male, and enrolled outside the United States. Approximately two thirds of subjects received some degree of prior therapy in the 96 hours before randomization. Most infections were cases of cellulitis, although there were 39 MITT subjects with an abscess, which in many cases was drained. Approximately one half of subjects had no bacterial pathogen identified. The most common identified pathogen was *Staphylococcus aureus*. Gram-negative infections were extremely rare in this trial.

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

Table 5: Baseline characteristics in ABSSSI Study P903-23, MITT Population

	Ceftaroline (n = 107)	Comparator (n = 52)
Age cohort		
12 years to < 18 years	23/107 (22%)	13/52 (25%)
6 years to <12 years	36/107 (34%)	15/52 (29%)
24 months to <6 years	23/107 (22%)	12/52 (23%)
2 months to <24 months	25/107 (23%)	12/52 (23%)
Male	57/107 (53%)	31/52 (60%)
White	91/107 (85%)	48/52 (92%)
Enrolled in United States	22/107 (21%)	8/52 (15%)
Creatinine clearance		
≥80 mL/min/1.73 m^2	99/107 (93%)	45/52 (87%)
≥50 to <80 mL/min/1.73 m^2	6/107 (6%)	6/52 (12%)
<50 mL/min/1.73 m^2	1/107 (1%)	0/52 (0%)
Prior therapy in 96 hours before randomization	71/107 (66%)	35/52 (67%)
Procedure on infection site prior to randomization	31/107 (29%)	16/52 (31%)
Drainage of abscess	20/107 (19%)	12/52 (23%)
Debridement	2/107 (2%)	0/52 (0%)
Other procedure	9/107 (8%)	6/52 (12%)
Infection description		
Wound infection	11/107 (10%)	4/52 (8%)
Cellulitis or erysipelas	69/107 (65%)	36/52 (69%)
Major abscess	27/107 (25%)	12/52 (23%)
Median infection length	12 cm	12 cm
Median infection width	9 cm	9 cm
Median infection area	108 cm^2	112 cm^2
Bacteremia	1/107 (1%)	0/52 (0%)
No pathogen identified	55/107 (51%)	30/52 (58%)
S. aureus (MRSA)	18/107 (17%)	7/52 (14%)
S. aureus (MSSA)	25/107 (23%)	15/52 (29%)
Streptococcus pyogenes	13/107 (12%)	1/52 (2%)
Gram-negative pathogen	3/107 (3%)	1/52 (2%)

Source: Study P903-23 Clinical Study Report, Section 11.2.

The table below shows results for clinical outcomes using the three different definitions of Day 3 response, and clinical cure rates at the TOC visit. For the three response definitions used at Day 3, numerical trends for treatment effects were favorable for ceftaroline and the lower bound of nominal confidence intervals ruled out deficits in response rates of approximately 10% compared to the control group.

At the TOC visit the reported clinical cure rates were high in both groups, with numerical trends favoring ceftaroline. Only one subject in either treatment group was classified as a clinical failure at or before the TOC visit. The remaining 12 subjects who did not achieve clinical cure were classified as having indeterminate outcomes. The Applicant's Clinical Study Report states that these subjects with indeterminate responses were either lost to follow-up (5 cases) or had extenuating circumstances precluding classification (7 cases).

Table 6: Outcomes in ABSSSI Study P903-23, MITT Population

	Ceftaroline (n = 107)	Comparator (n = 52)	Difference (95% CI)
Day 3: ≥20% reduction from baseline infection area			
Responder	91/107 (85%)	44/52 (85%)	0% (-11% to 14%)
Non-responder	11/107 (10%)	4/52 (8%)	
Incomplete data	5/107 (5%)	4/52 (8%)	
Day 3: Cessation of spread by total infection area			
Responder	98/107 (92%)	47/52 (91%)	1% (-8% to 13%)
Non-responder	4/107 (4%)	1/52 (2%)	
Incomplete data	5/107 (5%)	4/52 (8%)	
Day 3: Cessation of spread by infection length and width and temperature <37.6°C			
Responder	86/107 (81%)	39/52 (75%)	5% (-8% to 20%)
Non-responder	16/107 (15%)	9/52 (18%)	
Incomplete data	5/107 (5%)	4/52 (8%)	
Clinical Outcome			
Clinical Cure at TOC	101/107 (94%)	45/52 (87%)	8% (-1% to 20%)
Observed Failure at EOIV	0/107 (0%)	1/52 (2%)	
Observed Failure at EOT	0/107 (0%)	0/52 (0%)	
Observed Failure at TOC	0/107 (0%)	0/52 (0%)	
Indeterminate	6/107 (6%)	6/52 (12%)	

Source: Study P903-23 Clinical Study Report, Table 11.4.1.1-1, Table 11.4.1.2-3, and Table 11.4.1.2-3.

Limitations of the efficacy results included lack of a pre-specified primary analysis and a nontrivial number of subjects with incomplete or indeterminate responses. In addition, the degree of possible measurement error is unknown for skin lesion area in pediatric patients, as is the meaningfulness of cessation of lesion spread or 20% reduction in area. Nevertheless, ceftaroline efficacy results in this trial did not raise any alarms.

3.2.2 CABP Studies P903-24 and P903-31

As in the ABSSSI trial discussed in the previous subsection, evaluation of efficacy was a secondary objective in CABP Studies P903-24 and P903-31, with the primary objective being to evaluate safety and tolerability.

Except where otherwise noted, analyses in this review pool the two CABP trials even though Study P903-24 enriched for subjects with complicated pneumonia at greater risk for MRSA infection. The reason for pooling was to increase sample size given that the Applicant's efficacy analysis was largely descriptive. Furthermore, Study P903-24 was too small to provide interpretable independent evidence, having only 9 subjects in the comparator group. Pooling was justified given that these were studies of the same disease and had similar designs, procedures, and endpoint definitions, and there was no obvious heterogeneity in results. Despite enrichment strategies used in Study P903-24 that potentially differentiated patient populations, almost no subjects with MRSA infections were enrolled in either trial. Both studies also used the same randomization ratio, which is needed with naïve pooling to prevent Simpson's paradox phenomena. Efficacy outcomes for the separate CABP trials will be documented in Section 4 of this review.

The pediatric CABP trials enrolled subjects between January 2013 and May 2014.

Both pediatric CABP trials enrolled subjects ages 2 months to <18 years. Randomization was stratified by the same age cohorts as used in the ABSSSI trial, and was also stratified by region for Study P903-31. Recall that the four age cohorts were 12 years to <18 years, 6 years to <12 years, 24 months to <6 years, and 2 months to <24 months.

The ceftaroline age-dependent dosing and infusion times were as described in Section 2.

The active comparator group in Study P903-24 was to be initially administered intravenous ceftriaxone (75 mg/kg/day up to 4 g/day infused over 30 minutes q12h) and vancomycin (15 mg/kg q6h infused over at least 60 minutes, or a maximum of 10 mg/min). Vancomycin may have been discontinued on or after Day 4 depending on confirmed or suspected microbiological findings. The comparator arm in Study P903-31 was to receive intravenous ceftriaxone infusions at the same dose as in Study P903-24, but without use of vancomycin.

In both trials, an optional switch was allowed to an open-label oral study drug on or after Day 4. Both trials allowed amoxicillin clavulanate as the oral switch, and Study P903-24 also allowed use of clindamycin and linezolid.

The total duration of therapy, including both intravenous and oral therapy, was to be 5 to 21 days in Study P903-24 and 5 to 14 days in Study P903-31.

Post-baseline visits in both trials included an end of intravenous (EOIV) visit, an end of therapy (EOT) visit following completion of both intravenous and optional oral therapy, a

test of cure (TOC) visit 8 to 15 days after the last dose of any intravenous or oral study drug, and a late follow-up (LFU) visit 21 to 35 days after last dose of study drug.

The inclusion criteria in both trials required a clinical CABP diagnosis with fever or hypothermia, a new infiltrate compatible with bacterial pneumonia based on imaging results or diagnostic testing, acute onset or worsening within 5 days before randomization of at least 2 clinical signs or symptoms (among cough, tachypnea, dyspnea, grunting, sputum production, chest pain, cyanosis, parenchymal consolidation, increased work of breathing) and at least 1 other marker (among a pathogenic organism from a respiratory or blood culture, leukocytosis, >15% immature white blood cells, leukopenia, or hypoxemia).

Study P903-24 inclusion criteria additionally enriched for complicated CABP or staphylococcal pneumonia by requiring at least one of empyema, pulmonary abscess, necrotizing pneumonia, pulmonary pneumatocele, pleural effusion needing chest tube drainage, Gram-positive cocci in clusters on a Gram stain from a respiratory specimen, requirement for positive pressure assisted ventilation, previous influenza-like illness, or requirement for treatment in an intensive care unit.

Exclusion criteria in both trials disallowed respiratory infection confirmed or suspected to be of non-bacterial origin, noninfectious causes of pulmonary infiltrates (e.g., cystic fibrosis), subjects with infecting pathogens that ceftaroline or ceftriaxone were unlikely to treat (e.g., *Pseudomonas aeruginosa*), subjects with a variety of conditions specific to the safety profiles of the study drugs (e.g., history of hypersensitivity to study drugs), receipt of more than 24 hours of potentially effective systemic antibacterial therapy within the 96 hours before randomization (except in cases of prior treatment failures), abnormal renal function (creatinine clearance <50 mL/min/1.73 m^2), or a variety of co-morbid conditions (e.g., meningitis, hepatic, hematologic, or immunocompromising conditions, evidence of immediately life-threatening disease).

The efficacy analysis population emphasized in the study protocols and this review was the MITT Population comprised of all randomized subjects who received any dose of study drug and had a clinically confirmed diagnosis of CABP.

The CABP trials did not specify any efficacy endpoint as a primary endpoint. However, the protocols defined a clinical response at Day 4 endpoint, a clinical stability at Day 4 endpoint, and clinical outcomes at the EOIV, EOT, and TOC visits. These endpoints will be emphasized in this review.

Clinical response at Day 4 was defined by improvement from baseline in at least 2 of the following 7 symptoms, and worsening from baseline in none of the symptoms. Each of the symptoms was measured at different study visits as absent, mild, moderate, or severe:

- Cough
- Dyspnea
- Chest pain
- Sputum production

- Chills or rigors
- Feeling feverish
- Exercise intolerance or lethargy

Clinical stability at Day 4 was defined by worsening in none of the above 7 symptoms, being afebrile (temperature ≤38.0°C), having an age-appropriate normal pulse and respiratory rate, and oxygen saturation ≥92% on room air.

Clinical cure at the EOIV, EOT, TOC, and LFU visits was defined by resolution of all acute signs and symptoms of CABP or improvement to such an extent that no further antimicrobial therapy was required. Subjects were defined as having clinical failure if treatment was discontinued due to insufficient therapeutic effect or adverse events.

As in the ABSSSI trial, the CABP trials were observer-blinded studies in which one investigator per center was blinded to treatment assignments and performed assessments for safety and efficacy.

Formal inferential statistics were not used, but the Applicant did pre-specify use of the Miettinen and Nurminen method for reporting confidence intervals for treatment effects on the risk difference scale.

There was no interim efficacy analysis for either CABP trial, but an external data safety monitoring board met periodically to assess any safety signals.

Both trials used 3:1 randomization. The MITT Population of Study P903-24 contained 29 subjects in the ceftaroline group and 9 subjects in the control group, while the MITT Population of Study P903-31 contained 107 ceftaroline subjects and 36 control subjects. Sample sizes were consistent with the respective protocols, and were not chosen to power for statistical hypothesis testing.

The Clinically Evaluable (CE) Population was comprised of subjects in the MITT Population who sufficiently adhered to the protocol and met evaluability criteria. In the pooled trials 124/136 (91%) ceftaroline subjects and 45/45 (100%) comparator subjects were in the CE Population. Thus, lack of compliance or protocol adherence did not appear to compromise efficacy results of these studies.

The table below shows baseline characteristics of subjects in the CABP trials. The ceftaroline and control groups appeared relatively well balanced on baseline factors. About 80% of subjects in the pooled trials were enrolled in Study P903-31, which did not enrich of complicated pneumonia or MRSA. There was variation in the size of age cohorts, with over half of subjects being in the 24 month to <6 years cohort and under 10% of subjects being in the 12 years to <18 years cohort. Subjects were predominately White and were enrolled outside the United States. Approximately one half of subjects received some degree of prior antibacterial therapy within 96 hours before randomization. With the exception of positive urinary antigen tests for *Streptococcus pneumoniae*, few subjects had microbiologically confirmed bacterial pneumonia.

Table 7: Baseline characteristics in CABP Studies P903-24 and P903-31, MITT Population

	Ceftaroline (n = 136)	Comparator (n = 45)
Study		
P903-24	29/136 (21%)	9/45 (20%)
P903-31	107/136 (79%)	36/45 (80%)
Age cohort		
12 years to < 18 years	11/136 (8%)	4/45 (9%)
6 years to <12 years	26/136 (19%)	8/45 (18%)
24 months to <6 years	70/136 (52%)	25/45 (56%)
2 months to <24 months	29/136 (21%)	8/45 (18%)
Male	77/136 (57%)	24/45 (53%)
White	132/136 (97%)	43/45 (96%)
Enrolled in United States	20/136 (15%)	7/45 (16%)
Creatinine clearance		
≥80 mL/min/1.73 m^2	108/136 (79%)	32/45 (71%)
≥50 to <80 mL/min/1.73 m^2	28/136 (21%)	13/45 (29%)
<50 mL/min/1.73 m^2	0/136 (0%)	0/45 (0%)
Prior antibacterial therapy in 96 hours before study drug	65/136 (48%)	22/45 (49%)
Pleural effusion	26/136 (19%)	16/45 (36%)
Multilobar pneumonia	49/136 (36%)	19/45 (42%)
Pneumococcal vaccine	59/136 (43%)	20/45 (44%)
Chest wall retractions	63/136 (46%)	23/45 (51%)
Nasal flaring	53/136 (39%)	22/45 (49%)
Cyanosis	30/136 (22%)	8/45 (18%)
Dullness or percussion	79/136 (58%)	32/45 (71%)
Rales and/or crackles	118/136 (87%)	36/45 (80%)
Positive urinary antigen test for *S. pneumoniae*	29/136 (21%)	11/45 (24%)
Respiratory culture with at least one typical pathogen	9/136 (7%)	3/45 (7%)
Positive blood culture	6/136 (4%)	2/45 (4%)

Source: The Applicant's Summary of Clinical Efficacy – CABP.

The table below shows outcomes in the pooled CABP trials for the previously described Day 4 clinical response endpoint, Day 4 clinical stability endpoint, and clinical outcome endpoint at the TOC visit. Point estimates for success rates were roughly similar between the ceftaroline group and comparator group for all three endpoints, although nominal confidence intervals did not allow these analyses to rule out absolute losses of 10%.

At Day 4, approximately two thirds of subjects in each arm met the clinical response criteria based on symptom improvement and one third of subjects in each arm met clinical stability criteria that also considered vital signs. Approximately 90% of subjects in both arms met clinical cure criteria at the TOC that required resolution or improvement to the extent that further antimicrobial therapy was not needed. Across the different endpoints the rates of incomplete or indeterminate outcomes were slightly higher in the ceftaroline group than in the comparator group.

Table 8: Outcomes in pooled CABP Studies P903-24 and P903-31, MITT Population

	Ceftaroline (n = 136)	Comparator (n = 45)	Difference (95% CI)
Day 4 Clinical Response			
Responder	89/136 (65%)	30/45 (67%)	-1% (-16% to 15%)
Non-responder	35/136 (26%)	14/45 (31%)	
Incomplete data	12/136 (9%)	1/45 (2%)	
Day 4 Clinical Stability			
Stability	43/136 (31%)	15/45 (33%)	-2% (-18% to 13%)
No stability	82/136 (60%)	30/45 (67%)	
Incomplete data	11/136 (8%)	0/45 (0%)	
Clinical Outcome			
Clinical Cure at TOC	120/136 (88%)	41/45 (91%)	-3% (-12% to 10%)
Observed Failure at EOIV	10/136 (7%)	3/45 (7%)	
Observed Failure at EOT	0/136 (0%)	1/45 (2%)	
Observed Failure at TOC	1/136 (1%)	0/45 (0%)	
Indeterminate	5/136 (4%)	0/136 (0%)	

Source: The Applicant's Summary of Clinical Efficacy – CABP, Table 6.2.2-1 and Table 6.2.3.1-1.

Limitations of the above results included lack of a pre-specified primary analysis, and confidence intervals that did not guarantee ceftaroline tightly preserved the efficacy of the control regimen.

However, as with the ABSSSI results, the efficacy results in the pediatric CABP trials did not raise any specific concerns.

3.3 Evaluation of safety

Evaluation of safety was a primary objective of the reviewed trials. Because the statistical analysis of safety was based on descriptive summaries, primary review of safety issues is deferred to the Medical Officer Sheral Patel, MD.

The Safety Population defined in the protocols of reviewed trials was comprised of all randomized subjects who received any amount of intravenous study drug. This was a superset of the MITT Population used for efficacy analysis, which also required a confirmed clinical diagnosis of ABSSSI or CABP in the respective trials. The MITT Population of ABSSSI Study P903-23 only excluded 2 subjects who were in the Safety Population, but the MITT Population of CABP Studies P903-24 and P903-31 together excluded 19 subjects who were in the Safety Population.

The following table shows the extent of study drug exposure. Although ceftaroline was used for a median of 5-7 days across trials, safety outcomes in both the ceftaroline and comparator arms may also have been influenced by extensive use of oral switch therapy.

Table 9: Extent of exposure, Safety Population

	ABSSSI Study P903-23		CABP Studies P903-24 and P903-31	
	Ceftaroline (n = 106)	Comparator (n = 53)	Ceftaroline (n = 151)	Comparator (n = 49)
Median days on study drug (IV and oral)	10 days	10 days	10 days	11 days
Median days on IV study drug	5 days	5 days	6 days	7 days
Median doses of cefaroline	12 doses		15 doses	
Switched to oral study drug	65/106 (61%)	28/53 (53%)	101/151 (67%)	35/49 (71%)
Oral study drug				
Amoxicillin clavulanate	0/106 (0%)	0/53 (0%)	87/151 (58%)	31/49 (%)
Cephalexin	41/106 (39%)	17/53 (32%)	0/151 (0%)	0/49 (0%)
Clindamycin	21/106 (20%)	8/53 (15%)	13/151 (9%)	4/49 (8%)
Linezolid	7/106 (7%)	3/53 (6%)	2/151 (1%)	0/49 (0%)
Median days on oral study drug	8 days	8 days	7 days	6 days

Source: The Applicant's Summary of Clinical Safety, Table 4.2.1-1.

The following table displays overall treatment emergent adverse events (AEs), drug-related events (as classified by investigators), serious adverse events (SAEs), and events associated with study drug discontinuations. Overall event rates were roughly comparable between ceftaroline and comparator arms. There were no deaths in the reviewed studies.

Table 10: Summary of adverse events, Safety Population

	ABSSSI Study P903-23		CABP Studies P903-24 and P903-31	
	Ceftaroline (n = 106)	Comparator (n = 53)	Ceftaroline (n = 151)	Comparator (n = 49)
Any treatment emergent AE	51/106 (48%)	23/53 (43%)	67/151 (44%)	26/49 (53%)
Any treatment emergent AE classified as drug-related	23/106 (22%)	12/53 (23%)	19/151 (13%)	6/49 (12%)
Any treatment emergent SAE	4/106 (4%)	1/53 (2%)	6/151 (4%)	2/49 (4%)
Any treatment emergent AE associated with discontinuation of study drug	4/106 (4%)	2/53 (4%)	6/151 (4%)	0/49 (0%)
Deaths	0/106 (0%)	0/53 (0%)	0/151 (0%)	0/49 (0%)

Source: The Applicant's Summary of Clinical Safety, Table 5.1-1.

Treatment emergent serious adverse events were very rare, and thus reliable statistical conclusions could not be drawn. This reviewer defers to the Medical Officer regarding review of narratives provided by the Applicant and determinations of causality.

Table 11: Treatment emergent serious adverse events, Safety Population

System Organ Class Preferred Term	*ABSSSI Study P903-23*		*CABP Studies P903-24 and P903-31*	
	Ceftaroline (N = 106) n (%)	*Comparators (N = 53) n (%)*	*Ceftaroline (N = 151) n (%)*	*Comparators (N = 49) n (%)*
Subjects with at least 1 SAE	*4 (3.8)*	*1 (1.9)*	*6 (4.0)*	*2 (4.1)*
Blood and lymphatic system disorders				
Lymphadenitis	0	1 (1.9)	0	0
Immune system disorders				
Hypersensitivity	1 (0.9)	0	0	0
Infections and infestations				
Gastroenteritis	0	0	2 (1.3)	0
Bronchitis	0	0	1 (0.7)	0
Clostridium difficile colitis	1 (0.9)	0	0	0
Infectious pleural effusion	0	0	1 (0.7)	0
Osteomyelitis	1 (0.9)	0	0	0
Pneumonia	0	0	1 (0.7)	0
Pneumonia respiratory syncytial viral	0	0	1 (0.7)	0
Pneumonia viral	1 (0.9)	0	0	0
Lower respiratory tract infection viral	0	0	0	1 (2.0)
Tonsillitis	0	1 (1.9)	0	0
Viral upper respiratory tract infection	0	0	0	1 (2.0)
Metabolism and nutrition disorders				
Dehydration	0	0	1 (0.7)	0
Respiratory, thoracic and mediastinal disorders				
Pulmonary thrombosis	0	0	0	1 (2.0)

Source: The Applicant's Summary of Clinical Safety, Table 5.1.4.1-1.

The table below displays treatment emergent adverse events that occurred at a frequency of ≥3% in either treatment group for ABSSSI or CABP. The most common adverse events for pediatric subjects treated with ceftaroline included diarrhea, vomiting, and rash. This reviewer did not identify any noticeable statistical trends from the table that warranted follow-up investigation.

Table 12: Incidence of common treatment emergent adverse events by system organ class and preferred term, Safety Population

System Organ Class *Preferred Term*	*ABSSSI* *Study P903-23*		*CABP* *Studies P903-24 and P903-31*	
	Ceftaroline (N = 106) n (%)	*Comparators (N = 53) n (%)*	*Ceftaroline (N = 151) n (%)*	*Comparators (N = 49) n (%)*
Subjects with at least 1 TEAE	**51 (48.1)**	**23 (43.4)**	**67 (44.4)**	**26 (53.1)**
Blood and lymphatic system disorders				
Anaemia	0	0	6 (4.0)	1 (2.0)
Eosinophilia	5 (4.7)	1 (1.9)	1 (0.7)	0
Thrombocytosis	0	0	3 (2.0)	4 (8.2)
Gastrointestinal disorders				
Diarrhoea	8 (7.5)	8 (15.1)	12 (7.9)	2 (4.1)
Vomiting	7 (6.6)	8 (15.1)	6 (4.0)	4 (8.2)
Nausea	5 (4.7)	0	3 (2.0)	1 (2.0)
General disorders and administration site conditions				
Pyrexia	4 (3.8)	0	4 (2.6)	2 (4.1)
Infections and infestations				
Upper respiratory tract infection	5 (4.7)	1 (1.9)	1 (0.7)	2 (4.1)
Otitis media	0	0	1 (0.7)	3 (6.1)
Viral upper respiratory tract infection	0	0	1 (0.7)	2 (4.2)
Injury, poisoning and procedural complications				
Arthropod bite	0	2 (3.8)	0	0
Investigations				
Alanine aminotransferase increased	1 (0.9)	1 (1.9)	3 (2.0)	2 (4.1)
Metabolism and nutrition disorders				
Hypocalcaemia	0	0	1 (0.7)	2 (4.1)
Hyperphosphataemia	0	0	0	2 (4.1)
Respiratory, thoracic and mediastinal disorders				
Cough	4 (3.8)	2 (3.8)	0	1 (2.0)
Skin and subcutaneous tissue disorders				
Rash	8 (7.5)	2 (3.8)	5 (3.3)	0
Pruritus	1 (0.9)	3 (5.7)	3 (2.0)	0
Rash macular[a]	1 (0.9)	0	2 (1.3)	0
Rash maculo-papular[a]	1 (0.9)	0	1 (0.7)	0
Rash erythematous[a]	0	0	0	1 (2.0)

Source: The Applicant's Summary of Clinical Safety, Table 5.1.2.1-1.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, race, age, and geographic region

Because ABSSSI Study P903-23 and CABP Studies P903-24 and P903-31 defined four age cohorts and stratified randomization within these pediatric cohorts, the first tables in this section display subgroup results by age cohort. Results are shown for the endpoint of Clinical Outcome at the TOC visit.

Sample sizes were small within age cohorts, and therefore nominal confidence intervals for treatment effects were quite wide. However, point estimates for Clinical Cure rates were generally ≥80% in the ceftaroline and comparator groups across all age cohorts.

Results for the Clinical Outcome at TOC visit are also shown for subgroups defined by gender, race, and geographic region for both the ABSSSI and CABP trials in this section. Descriptive analysis of the results did not reveal any numerical trends differentiating ceftaroline response rates or treatment effects between males and females.

Subgroup analysis by race was uninformative, as almost all enrolled subjects were White.

Likewise, although numerical trends did not point to any differences between US and ex-US subjects, there were a limited number of subjects enrolled in the United States.

Due to small sample sizes the tables in this section report exact confidence intervals for differences in success rates using the ExactCIdiff package for the R language. This method forms a two-sided exact 1-α confidence interval by taking the intersection of two 1-α/2 one-sided confidence intervals constructed based on the methodology of Wang.[3] Qualitatively similar results are obtained if using other confidence interval techniques.

4.2 Other special/subgroup populations

Because previous analyses in this review pooled CABP Studies P903-24 and P903-31, for reference the tables in this section also document results Clinical Outcome at the TOC visit separately for the two CABP trials. Recall that Study P903-24 enriched for complicated pneumonia patients at higher risk for MRSA pneumonia and used vancomycin in the comparator group. This trial enrolled very few subjects, with only 9 patients in the comparator group of the MITT Population. Therefore, this reviewer did not identify any exploratory findings from this subgroup analysis.

[3] Wang W. On construction of the smallest one-sided confidence interval for the difference of two proportions. *Annals of Statistics* 2010;38(2):1227-1243.

Table 13: Clinical Outcome at TOC visit by age cohort in ABSSSI Study P903-23, MITT Population

Age cohort	Ceftaroline	Comparator	Difference (95% CI)
Age 12 years to <18 years			
Clinical Cure	22/23 (96%)	10/13 (77%)	19% (-6% to 48%)
Clinical Failure	0/23 (0%)	0/13 (0%)	
Indeterminate	1/23 (4%)	3/13 (23%)	
Age 6 years to <12 years			
Clinical Cure	35/36 (97%)	14/15 (93%)	4% (-9% to 27%)
Clinical Failure	0/36 (0%)	1/15 (7%)	
Indeterminate	1/36 (3%)	0/15 (0%)	
Age 24 months to <6 years			
Clinical Cure	22/23 (96%)	11/12 (92%)	4% (-14% to 32%)
Clinical Failure	0/23 (0%)	0/12 (0%)	
Indeterminate	1/23 (4%)	1/12 (8%)	
Age 2 months to <24 months			
Clinical Cure	22/25 (88%)	10/12 (83%)	5% (-20% to 35%)
Clinical Failure	0/25 (0%)	0/12 (0%)	
Indeterminate	3/25 (12%)	2/12 (17%)	

Source: Study P903-23 Clinical Study Report, Table 14.4.4.1B.

Table 14: Clinical Outcome at TOC visit by age cohort in pooled CABP Studies P903-24 and P903-31, MITT Population

Age cohort	Ceftaroline	Comparator	Difference (95% CI)
12 years to <18 years			
Clinical Cure	10/11 (91%)	4/4 (100%)	
Clinical Failure	1/11 (9%)	0/4 (0%)	
Indeterminate	0/11 (0%)	0/4 (0%)	
6 years to <12 years			
Clinical Cure	21/26 (81%)	7/8 (88%)	
Clinical Failure	3/26 (12%)	1/8 (13%)	
Indeterminate	2/26 (8%)	0/8 (0%)	
24 months to <6 years			
Clinical Cure	60/70 (86%)	22/25 (88%)	-2% (-17% to 17%)
Clinical Failure	7/70 (10%)	3/25 (12%)	
Indeterminate	3/70 (4%)	0/25 (0%)	
2 months to <24 months			
Clinical Cure	29/29 (100%)	8/8 (100%)	
Clinical Failure	0/29 (0%)	0/8 (0%)	
Indeterminate	0/29 (0%)	0/8 (0%)	

Source: ADSL and ADCOUT analysis datasets.

Table 15: Clinical Outcome at TOC visit by demographic subgroups in ABSSSI Study P903-23, MITT Population

	Ceftaroline	Comparator	Difference (95% CI)
Male			
Clinical Cure	54/57 (95%)	27/31 (87%)	8% (-5% to 24%)
Clinical Failure	0/57 (0%)	1/31 (3%)	
Indeterminate	3/57 (5%)	3/31 (10%)	
Female			
Clinical Cure	47/50 (94%)	18/21 (86%)	8% (-7% to 29%)
Clinical Failure	0/50 (0%)	0/21 (0%)	
Indeterminate	3/50 (6%)	3/21 (14%)	
White			
Clinical Cure	89/91 (98%)	42/48 (88%)	10% (1% to 23%)
Clinical Failure	0/91 (0%)	1/48 (2%)	
Indeterminate	2/91 (2%)	5/48 (10%)	
Nonwhite			
Clinical Cure	12/16 (75%)	3/4 (75%)	0% (-40% to 55%)
Clinical Failure	0/16 (0%)	0/4 (0%)	
Indeterminate	4/16 (25%)	1/4 (25%)	
Enrolled in US			
Clinical Cure	18/22 (82%)	5/8 (63%)	20% (-16% to 57%)
Clinical Failure	0/22 (0%)	0/8 (0%)	
Indeterminate	4/22 (18%)	3/8 (38%)	
Enrolled outside US			
Clinical Cure	83/85 (98%)	40/44 (91%)	7% (-2% to 19%)
Clinical Failure	0/85 (0%)	1/44 (2%)	
Indeterminate	2/85 (2%)	3/44 (7%)	

Source: ADSL and ADCOUT analysis datasets.

Table 16: Clinical Outcome at TOC visit by demographic subgroups in pooled CABP Studies P903-24 and P903-31, MITT Population

	Ceftaroline	Comparator	Difference (95% CI)
Study P903-24			
Clinical Cure	26/29 (90%)	9/9 (100%)	-10% (-27% to 19%)
Clinical Failure	3/29 (10%)	0/9 (0%)	
Indeterminate	0/29 (0%)	0/9 (0%)	
Study P903-31			
Clinical Cure	94/107 (88%)	32/36 (89%)	-1% (-13% to 14%)
Clinical Failure	8/107 (8%)	4/36 (11%)	
Indeterminate	5/107 (5%)	0/36 (0%)	
Male			
Clinical Cure	71/77 (92%)	21/24 (88%)	5% (-9% to 23%)
Clinical Failure	3/77 (4%)	3/24 (13%)	
Indeterminate	3/77 (4%)	0/24 (0%)	
Female			
Clinical Cure	49/59 (83%)	20/21 (95%)	-12% (-25% to 6%)
Clinical Failure	8/59 (14%)	1/21 (5%)	
Indeterminate	2/59 (3%)	0/21 (0%)	
White			
Clinical Cure	116/132 (88%)	39/43 (91%)	-3% (-12% to 10%)
Clinical Failure	11/132 (8%)	4/43 (9%)	
Indeterminate	5/132 (4%)	0/43 (0%)	
Nonwhite			
Clinical Cure	4/4 (100%)	2/2 (100%)	0% (-61% to 84%)
Clinical Failure	0/4 (0%)	0/2 (0%)	
Indeterminate	0/4 (0%)	0/2 (0%)	
Enrolled in US			
Clinical Cure	16/20 (80%)	6/7 (86%)	-6% (-34% to 36%)
Clinical Failure	2/20 (10%)	1/7 (14%)	
Indeterminate	2/20 (10%)	0/7 (0%)	
Enrolled outside US			
Clinical Cure	104/116 (90%)	35/38 (92%)	-3% (-12% to 11%)
Clinical Failure	9/116 (8%)	3/38 (8%)	
Indeterminate	3/116 (3%)	0/38 (0%)	

Source: ADSL and ADCOUT analysis datasets.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical issues, collective evidence, conclusions and recommendations

The main statistical issues in this review revolved around the fact that efficacy of ceftaroline for ABSSSI and CABP was being extrapolated from adults to pediatrics, and therefore that the reviewed pediatric trials were not designed or sized to provide direct evidence. Consequently, there was no pre-specified primary efficacy analysis and formal inferential statistics were not used.

The efficacy results did not, however, raise any concerns for ceftaroline. Baseline characteristics were generally well balanced between the randomized ceftaroline and comparator groups, and lack of compliance or protocol adherence did not appear to compromise the interpretability of the results. In ABSSSI Study P903-23 the nominal confidence limits for (ceftaroline – comparator) treatment effects ruled out large losses in efficacy for ceftaroline using a clinical cure endpoint at the TOC visit or several different definitions for Day 3 response. In pooled CABP Studies P903-24 and P903-31 the confidence intervals for treatment effects did not guarantee tight preservation of efficacy, but point estimates for success rates showed no difference between the ceftaroline group and comparator group with respect to clinical response at Day 4, clinical stability at Day 4, or clinical cure at the TOC visit.

The primary objective of each reviewed trial was to evaluate safety and tolerability. There were not noticeable statistical differences between randomized ceftaroline and comparator groups in terms of treatment emergent adverse events, drug-related adverse events, serious adverse events, or events within specific organ classes. No deaths were observed in either arm of any of the three reviewed trials. The most common adverse events for pediatric subjects treated with ceftaroline included diarrhea, vomiting, and rash. As serious events that may impact the benefit-to-risk profile of ceftaroline were very rare, deference is made to the Medical Officer regarding review of narratives and assessments of causality for SAEs.

Overall, in light of the clinical judgment that safety and efficacy in ABSSSI and CABP can generally be extrapolated from adults to pediatrics, the statistical evidence in the reviewed trials support the safety and efficacy of ceftaroline for pediatric patients.

5.2 Labeling recommendations

The Applicant proposes to indicate ceftaroline for ABSSSI and CABP in both adult and pediatric subjects, to make corresponding updates to the Dosage and Administration label section to include pediatric dosing information, and to include results of pediatric trials in the Clinical Studies section of the label.

The Applicant proposes that Section 8.4 of the label on Pediatric Use includes the following statements. *"The clinical cure rates in the Teflaro[4] group (Modified Intent To*

[4] Teflaro is the brand name of ceftaroline fosamil.

Treat [MITT] Population) were similar in patients ≥ 18 years of age compared with patients 2 months to < 18 years of age in both the ABSSSI and CABP trials. Results from the clinical studies in (b) (4) *show that* (b) (4) *demonstrated a safety profile that was compatible with treatment of ABSSSI and CABP at the clinical dosages studied. In summary, the safety findings were similar to those seen in the adult studies, and no safety concerns were identified beyond those already known to be cephalosporin class effects."*

For ABSSSI Study P903-23 the Applicant seeks to include the italicized summary below in the Clinical Studies label section.

The ABSSSI pediatric trial was a randomized, parallel-group, active controlled trial in pediatric patients 2 months to < 18 years of age. A total of 163 children from 2 months to < 18 years of age with clinically documented acute bacterial skin and skin structure infection were enrolled in a randomized, multi-center, multinational parallel group, active controlled trial comparing Teflaro to vancomycin or cefazolin (each with optional aztreonam). Treatment duration was 5 to 14 days. A switch to oral therapy with either cephalexin, clindamycin, or linezolid after Study Day 3 was allowed. The Modified Intent-to-Treat (MITT) population included all patients who received any amount of study drug according to their randomized treatment group. To evaluate the treatment effect of Teflaro, an analysis was conducted in 159 patients with ABSSSI in the MITT population. This analysis evaluated responder rates based on achieving both cessation of lesion spread and absence of fever on (b) (4) *Day 3.* (b) (4)

Clinical cure rates at test of cure visit (8 to 15 days after the end of therapy) for the ABSSSI pediatric trial were 94.4% (101/107) for Teflaro and 86.5% (45/52) for the comparator, with a treatment difference of 7.9 (95% CI -1.2, 20.2).

There are several ways in which this text could be misleading. First, as discussed in Section 3.2.1 of this review the ABSSSI trial used three different definitions for Day 3 response, and the Applicant only proposes to report results using the definition giving the most favorable treatment effect for ceftaroline. Note, however, that this definition requiring cessation of lesion spread and absence of fever is consistent with how Day 3 response rates are reported in the ceftaroline label for the adult ABSSSI trials. Second, the results suggests favorable numerical trends with respect to the clinical outcomes at the TOC visit, but do not mention that virtually all subjects who did not achieve clinical cure had indeterminate values rather than a clinical failure classification.

For CABP labeling the Applicant only seeks to include results for Study P903-31 in the Clinical Studies section, and not Study P903-24 that enriched for complicated pneumonia and MRSA infections. The reason is that ceftaroline is not indicated in adults for CABP due to MRSA, so efficacy could not be extrapolated from adults to pediatrics for these types of patients. The Applicant proposes the italicized summary below.

The CABP pediatric trial was a randomized, parallel-group, active controlled trial in pediatric patients 2 months to < 18 years of age. A total of 161 children with a diagnosis of CABP were enrolled in a randomized, multi-center, multinational, active controlled trial comparing Teflaro with ceftriaxone. Patients with new or progressive pulmonary infiltrate(s) on chest radiography and signs and symptoms consistent with CABP including acute onset or worsening symptoms of cough, tachypnea, sputum production, grunting, chest pain, cyanosis, or increased work of breathing with the need for hospitalization and IV therapy were enrolled in the trial. Treatment duration was 5 to 14 days. A switch to oral therapy with amoxicillin clavulanate was allowed on Study Day 4. To evaluate the treatment effect of Teflaro, an analysis was conducted in 143 patients with CABP in the MITT population. This analysis evaluated responder rates at (b) (4) *Day 4 based on achieving improvement in at least 2 out of 7 symptoms (cough, dyspnea, chest pain, sputum production, chills, feeling of warmth / feverish and exercise intolerance or lethargy) and have worsening in none of these symptoms.* (b) (4)

Clinical cure rates at test of cure were 87.9% (94/107) for Teflaro and 88.9% (32/36) for the comparator, with a treatment difference of -1.0 (95% CI -11.5, 14.1).

The above text is an accurate summary of the results for Study P903-31, but does not define the MITT Population.

According to the February 2013 FDA draft guidance[5] on good review practice for pediatric information incorporated into human prescription drug and biological products labeling, data can be sufficient to warrant a pediatric indication or use if there are "*sufficient data from studies in adults with supporting data in a pediatric population that allow extrapolation of effectiveness to a pediatric population*." Further, in the Clinical Studies section of the label "*a more detailed discussion of the pediatric clinical data summarized in the Pediatric Use subsection should be provided*."

Based on this guidance, the statistical evidence of safety and efficacy from the reviewed trials support indicating ceftaroline for pediatric ABSSSI and CABP, and describing results of pediatric trials in the Clinical Studies section of the label. However, the precise description of trial results will depend on labeling discussions with the Applicant.

[5] www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm341394.pdf. Accessed 03-21-2016.

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/s/

DANIEL B RUBIN
04/26/2016

KAREN M HIGGINS
04/27/2016
I concur.