

A Phase 3, Randomized, Investigator-blinded Trial Comparing Ceftobiprole With a Standard-of-care Cephalosporin, With or Without Vancomycin, for the Treatment of Pneumonia in Pediatric Patients

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Background: The advanced-generation, broad-spectrum, intravenous (IV) cephalosporin, ceftobiprole, is an effective and well-tolerated treatment for adults with hospital-acquired pneumonia (HAP) or community-acquired pneumonia (CAP), but its effects in pediatric patients have not been established.

Methods: In this multicenter, investigator-blinded, active-controlled, phase 3 study, patients 3 months to <18 years old with HAP or CAP requiring hospitalization were randomized (2:1) to ceftobiprole versus standard-of-care (SoC) IV cephalosporin treatments (ceftazidime or ceftriaxone), with or without vancomycin. After at least 3 days' IV treatment, patients demonstrating clinical improvement could be switched to an oral antibiotic, to complete a minimum of 7 days' treatment.

Results: Overall, 138 patients were randomized to ceftobiprole (n = 94) or a SoC cephalosporin (n = 44). Median time to oral switch was 6.0 days in the ceftobiprole group and 8.0 days in the SoC cephalosporin group. While on IV therapy, adverse events and treatment-related adverse events were reported by 20.2% and 8.5% of ceftobiprole-treated patients and 18.2% and 0% of SoC cephalosporin-treated patients. Early clinical response rates at day 4 in the intention-to-treat population were 95.7% and 93.2% (between-group difference, 2.6%; 95% confidence interval, -5.5% to 14.7%) in the ceftobiprole and comparator groups, and clinical cure rates at the test-of-cure visit were 90.4% and 97.7% (between-group difference, -7.3%; 95% confidence interval, -15.7% to 3.6%), respectively.

Conclusions: Ceftobiprole was well tolerated and, in this small phase 3 study, demonstrated similar efficacy to SoC cephalosporins in pediatric patients with HAP or CAP requiring hospitalization.

Key Words: ceftobiprole, cephalosporin, community-acquired pneumonia, hospital-acquired pneumonia, pediatric patients

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Pneumonia is the leading cause of death in children younger than 5 years of age worldwide, accounting for 15% of all deaths in this age group in 2013.¹ Globally, in 2015, an estimated 0.9 million deaths among children <5 years of age were attributed to pneumonia.² Although the majority of deaths, 0.7 million, occurred in the World Health Organization Africa and South-East Asia regions,² pneumonia remains a significant cause of childhood morbidity and mortality in more industrialized countries.³ A systematic review published in 2013 estimated that there are up to 1.5 million hospitalized cases and around 3000 deaths each year due to pneumonia in children younger than 5 years who live in the wealthiest regions of the world (North America, Europe, Australia, New Zealand and Japan).³

The etiology of pediatric pneumonia appears to vary depending on age, clinical setting and disease severity. Viruses are the most common causative pathogens in pediatric patients overall, accounting for 30%–67% of cases of community-acquired pneumonia (CAP) in this population.⁴ They are considered to be the sole cause of CAP in up to 50% of cases in younger children,⁴ but the likelihood of a viral etiology decreases with age.^{5,6} *Streptococcus pneumoniae* and *Haemophilus influenzae* type B are considered to be major bacterial causes of CAP, and *S. pneumoniae* is responsible for around one-third of radiologically confirmed cases in patients <2 years of age.^{4,7} *Staphylococcus aureus* is an increasing cause of CAP in children and methicillin-resistant *S. aureus* (MRSA) has been reported to be the causative pathogen in three-quarters (74%) of children requiring hospitalization for *S. aureus* pneumonia in a single-center surveillance study from the United States.⁸ In nosocomial pneumonia in pediatric populations, Gram-negative bacteria, including *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Enterobacter* species, *Escherichia coli* and *H. influenzae*, are the predominant bacterial pathogens,^{9–14} whereas *S. aureus* (including MRSA) is typically the most common Gram-positive pathogen.^{9,10,12,14}

Ceftobiprole, the active moiety of the prodrug ceftobiprole medocartil, is an advanced-generation intravenous (IV) cephalosporin with broad in vitro activity against Gram-positive (including MRSA) and Gram-negative pathogens.^{15,16} It is licensed in many European and non-European countries for the treatment of hospital-acquired pneumonia (HAP; excluding ventilator-associated pneumonia) and CAP in adults.¹⁷ In 2 large-scale pivotal studies,

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ceftobiprole demonstrated noninferiority to ceftazidime plus linezolid in adults with HAP¹⁸ and to ceftriaxone with or without linezolid in adults with CAP.¹⁹ The recent phase 3 TARGET study also showed that ceftobiprole is noninferior to vancomycin plus aztreonam in the treatment of adults with acute bacterial skin and skin structure infections (ABSSSIs).²⁰

While the efficacy and safety of ceftobiprole have been demonstrated in adults, little is known about its effects in pediatric patients. The objective of this phase 3 study was, therefore, to evaluate the safety and efficacy of ceftobiprole versus standard-of-care (SoC) cephalosporin treatments, with or without vancomycin, in pediatric patients with HAP or CAP requiring hospitalization.

MATERIALS AND METHODS

Patients

Patients 3 months to <18 years of age with a body weight of ≥ 5 kg and a diagnosis of HAP (pneumonia acquired after ≥ 48 hours of hospitalization) or CAP requiring hospitalization and administration of IV antibiotic treatment were enrolled. Exclusion criteria included use of systemic antibacterial treatment for >24 hours in the 48 hours before randomization for the current episode of pneumonia (except patients with CAP who failed to improve after at least 48 hours of prior antibiotic therapy and required a change in treatment), mechanical ventilation for >48 hours, viral pneumonia without bacterial superinfection and known resistance to study antibiotic treatments. Full inclusion and exclusion criteria are detailed in Text (Supplemental Digital Content 1, <http://links.lww.com/INF/E304>).

Study Design

This was a multicenter, randomized, investigator-blinded, active-controlled, phase 3 study of ceftobiprole versus SoC cephalosporin treatments, with or without vancomycin, in pediatric patients with HAP or CAP requiring hospitalization (ClinicalTrials.gov identifier: NCT03439124; EudraCT number: 2013-004615-45). The study was conducted at 12 sites in Bulgaria, Georgia, Hungary and Romania between November 27, 2017 and March 16, 2020.

Patients were stratified by 4 age groups (3 months to <2 years, 2 years to <6 years, 6 years to <12 years and 12 years to <18 years) and by diagnosis of HAP or CAP. Eligible patients were then randomized 2:1 to receive ceftobiprole or comparator cephalosporin antibiotics (ceftazidime \pm vancomycin [for HAP] or ceftriaxone \pm vancomycin [for CAP]). Randomization was carried out using a central Interactive Web-based Response System based on a computer-generated randomization schedule. At each study site, at least 1 investigator was blinded to the treatment assignment and was solely responsible for the conduct of clinical assessments that included efficacy and safety. The blinded investigator was also responsible for determining the duration of IV treatment, the decision to discontinue IV treatment and the timepoint to switch to an oral antibiotic. To maintain blinding, the blinded investigator did not observe the subject at times when the study antibiotics were being administered. All other study site staff, including the principal investigator, pharmacists and nursing staff, were unblinded. The unblinded investigator was responsible for establishing the need for vancomycin treatment, for monitoring vancomycin serum concentrations and for adjustment of the vancomycin dose. The subject and their parent/guardian were also unblinded and were reminded at each interaction with the blinded investigator not to disclose the treatment assignment.

The treatment phase was at least 7 days, with possible extension to 14 days. Ceftobiprole was administered IV every 8 hours, age-adjusted for dose (maximum, 500 mg per dose and 1500 mg

daily) and infusion duration, as follows: 20 mg/kg administered over 4 hours in patients 3 months to <2 years of age, 20 mg/kg over 2 hours in patients 2 years to <6 years of age, 15 mg/kg over 2 hours in patients 6 years to <12 years of age and 10 mg/kg over 2 hours in patients 12 years to <18 years of age. These dosing regimens were selected based on the level of ceftobiprole drug exposure shown to be effective in treating HAP and CAP in adults, pharmacokinetic and safety data from a previous single-dose study in patients 3 months to <18 years of age,²¹ the adverse event (AE) profile of ceftobiprole in adults, results of a toxicity study in juvenile animals and pharmacokinetic modeling data. Regarding the comparator cephalosporins, ceftazidime was administered at 50 mg/kg as an IV infusion every 8 hours, up to a maximum dose of 6 g/d. Ceftriaxone was administered at 50–80 mg/kg as a single 0.5-hour daily IV infusion, up to a maximum dose of 2 g/d. Dose modifications of ceftobiprole and the comparator cephalosporin antibiotics were not permitted.

For patients receiving a comparator antibiotic, vancomycin (10–15 mg/kg as an IV infusion every 6 hours) was also administered when MRSA was confirmed or suspected. Dose adjustments of vancomycin were performed to maintain steady-state trough blood levels at between 15 and 20 mg/L. Vancomycin doses were modified for patients with renal impairment. Concomitant treatment with amikacin, gentamicin or tobramycin for confirmed or suspected infection caused by *P. aeruginosa* could be added at the discretion of the blinded investigator.

After a minimum of 3 days' treatment with IV antibiotics, patients who met the standardized criteria for clinical improvement (see Text, Supplemental Digital Content 2, <http://links.lww.com/INF/E305>) could be switched to an oral antibiotic, at the discretion of the blinded investigator, to complete a minimum of 7 days' treatment. A macrolide was permitted for this oral switch. If required, prolongation of IV or oral antibiotic treatment was allowed for up to a total of 14 days. Patients who required concomitant treatment with a macrolide during the study (other than the switch outlined above) and those with no adequate response to IV study treatment within the first 3 days were withdrawn from the study and treated with an appropriate nonstudy, SoC antibiotic regimen.

The treatment period was followed by an end-of-treatment (EOT) visit within 24 hours after the last treatment, a test-of-cure (TOC) visit 7–14 days after the EOT assessment and a last follow-up (LFU) visit 28–35 days after the EOT assessment for all patients. Patients who discontinued study treatment for any reason were to remain in the study as part of the safety follow-up.

Ethics

The study was conducted in compliance with relevant local laws/regulations, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice guidelines and the amended Declaration of Helsinki. An Independent Ethics Committee/Institutional Review Board at each site approved the study protocol and an independent Data Safety Monitoring Board monitored the safety data to ensure patient safety. Each child's parent or legal guardian provided written informed consent. If appropriate, the child's assent was also sought before participation in the trial.

Clinical and Microbiologic Assessments

Clinical safety and efficacy assessments were undertaken at baseline (screening), on each day of active treatment and at the EOT, TOC and LFU visits. Safety assessments included treatment-emergent AEs, along with intermittent evaluation of laboratory parameters, vital signs, pulse oximetry and physical examination. Efficacy assessments included pneumonia signs and symptoms

(10 signs and symptoms marked as “absent” or “present” at baseline, and as “absent,” “improved,” “unchanged” or “worsened” on every day of active treatment and at the TOC and LFU visits: fever [$>38.5^{\circ}\text{C}$], hypothermia, tachypnea, dyspnea, retractions [suprasternal, intercostal or subcostal], grunting, nasal flaring, apnea, altered mental status and hypoxemia [pulse oximetry measurement $\leq 92\%$ on room air]) and requirement for hospitalization.

Blood and sputum samples for culture and Gram staining were obtained, if feasible, at screening and at the EOT and TOC visits to test for microbiologic outcome (microbiologic eradication, presumed microbiologic eradication, microbiologic persistence, presumed microbiologic persistence, superinfection or microbiologically nonevaluable). Samples were obtained at the LFU visit only if considered necessary by the blinded investigator to evaluate microbiologic relapse. Pathogen identification and antibiotic susceptibility testing were undertaken locally or regionally using routine methods, with subsequent confirmation at a central microbiology laboratory.

Endpoints

Patient populations for endpoint analysis included: (1) intent-to-treat (ITT), comprising all randomized patients; (2) safety, comprising all randomized patients who received at least 1 dose of study drug; (3) clinically evaluable, comprising patients with no major protocol deviations; (4) microbiologic ITT (mITT), comprising the subset of ITT patients with a valid pathogen identified at baseline; (5) microbiologically evaluable, comprising all patients in the clinically evaluable population with a valid pathogen identified at baseline and a microbiologic assessment at the TOC visit and (6) pharmacokinetics (note, pharmacokinetics data will be reported separately).

The primary endpoint was the cumulative incidence of AEs during the first 3 days of study treatment and at the EOT, TOC and LFU visits (safety population). The cumulative incidence of AEs while on IV therapy was also assessed. Secondary endpoints included a comparison of early clinical response at day 4 and clinical cure rates at the EOT, TOC and LFU visits (ITT and clinically evaluable populations). Early clinical response and clinical cure were defined as signs and symptoms of pneumonia normalized or improved to an extent that further antibiotic therapy was not necessary (the latter criterion was not applied at day 4 as patients were still receiving study antibiotics), with lack of progression of chest radiograph abnormalities post-baseline (if available). Clinical and microbiologic relapse rates at the LFU visit were also compared (all efficacy populations). Other secondary endpoints included microbiologic eradication rates (mITT and microbiologically evaluable populations) at the TOC visit, duration of IV antibiotic treatment, time to oral antibiotic switch and duration of hospitalization.

Statistical Analyses

It was planned that a total of 138 patients would be enrolled, with a minimum of 50 patients in each age cohort (<6 and ≥ 6 years). There was no requirement for a minimum number of patients with HAP or CAP. Treatment of 92 patients (safety population) with ceftobiprole was calculated to yield a $>95\%$ probability of observing at least 1 AE type if the actual probability of the event was $>3.2\%$. In an age-stratified analysis, if at least 33 patients who received ceftobiprole were <6 years and at least 33 were ≥ 6 years of age, this would yield a 95% probability of observing at least 1 AE type in each of the 2 age cohorts if the actual probability of the event was $>8.7\%$.

No formal hypothesis testing was performed. For the primary endpoint, descriptive statistics and frequency tables were used to describe the AE profile of ceftobiprole (during the first 3 days of IV therapy, while on IV therapy and throughout the study).

Early clinical response and clinical cure rates (ITT and clinically evaluable populations) were compared between ceftobiprole and the comparator cephalosporins on day 4 and at the EOT, TOC and LFU visits; between-group differences were determined along with the respective 95% confidence interval (CI). Patients who were assessed as clinically unevaluable or who were withdrawn from the study before the TOC visit, but after ≥ 1 dose of study treatment, were counted as clinical failures. Time to oral antibiotic switch was assessed using Kaplan-Meier methods. All statistical analyses were performed using the software package SAS version 9.3 or higher (SAS Institute Inc., Cary, NC).

Data Availability

After publication, the data will be made available to others on reasonable request to the corresponding author.

RESULTS

Patient Disposition and Baseline Characteristics

Patient disposition is presented in Figure 1. In total, 138 pediatric patients with HAP or CAP requiring hospitalization were randomized to receive ceftobiprole ($n = 94$) or SoC cephalosporin treatments ($n = 44$; ceftriaxone [$n = 41$] or ceftazidime [$n = 3$]) (ITT population). Five patients in the comparator group received concomitant vancomycin. No patient in either treatment group received concomitant aminoglycoside treatment for confirmed or suspected infection by *P. aeruginosa*. All 138 patients received at least 1 dose of study treatment and were included in the safety population. Major protocol deviations were observed in 6 patients (6.4%) who received ceftobiprole and 3 (6.8%) who were treated with SoC cephalosporins; these patients were excluded from the clinically evaluable population. Five patients in the ceftobiprole group and 1 in the comparator group were included in the mITT population, that is, patients with a valid pathogen identified at baseline. All of these patients except one (a patient in the ceftobiprole group) were included in the microbiologically evaluable population.

Baseline demographics and clinical characteristics were broadly similar between the 2 treatment groups (Table 1). Of the 138 randomized patients, 130 had a diagnosis of CAP (ceftobiprole, $n = 89$; comparator, $n = 41$) and 8 had HAP (ceftobiprole, $n = 5$; comparator, $n = 3$). A total of 70 patients (50.7%) were 3 months to <6 years of age and 68 (49.3%) were 6 years to <18 years of age.

Treatment Exposure

Median (range) doses of ceftobiprole ($n = 94$), ceftriaxone ($n = 41$) and ceftazidime ($n = 3$) received were 19.1 mg/kg (5.9–20.2 mg/kg), 56.0 mg/kg (22.7–105.3 mg/kg) and 50.3 mg/kg (50.0–50.4 mg/kg), respectively. Median (range) dose of vancomycin was 12.5 mg/kg (10.0–15.0 mg/kg). Compliance rates in both treatment groups approached 100%.

Time to switch to oral treatment is shown in Figure 2. Median (95% CI) time to oral switch was 6.0 days (5.0–7.0 days) in patients who received ceftobiprole and 8.0 days (6.0–8.0 days) in patients who received SoC cephalosporin treatments.

Safety

Treatment-emergent AEs observed during the first 3 days of IV therapy, while on IV therapy and throughout the whole study duration are summarized in Table 2 and Table (Supplemental Digital Content 3, <http://links.lww.com/INF/E306>). During the first 3 days of IV therapy, AEs were reported by 11.7% of patients in the ceftobiprole group (treatment-related in 6.4% of patients) and 11.4% of patients in the comparator group (no treatment-related

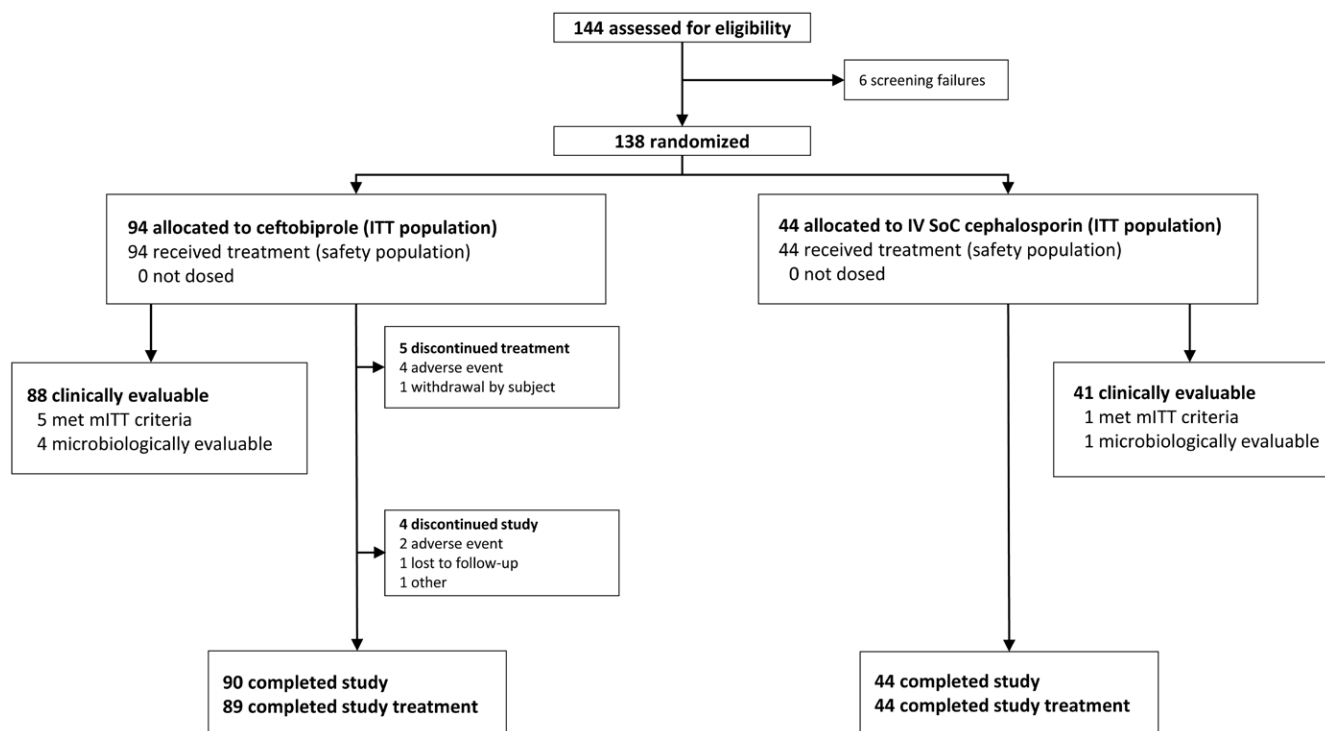


FIGURE 1. Consort flow diagram for trial screening and randomization.

AEs). While on IV therapy, AEs were reported by 20.2% of patients in the ceftobiprole group (treatment-related in 8.5% of patients) and 18.2% of those in the comparator group (no treatment-related AEs). During the period on IV therapy, 1 severe AE and 2 serious AEs were reported in the ceftobiprole group, while no such events were reported in the comparator group. Overall, 4 patients discontinued ceftobiprole due to an AE (including the patients with severe and serious AEs described above). One patient experienced an AE that was both severe and serious but was considered to be unrelated to study treatment. In this case, a worsening of pneumonia (increased tachypnea) was reported after the first dose. The patient was transferred to the intensive care unit and placed on mechanical ventilation. After the second dose of study treatment, mechanical

ventilation was discontinued. The second serious AE in the ceftobiprole group was hypersensitivity reported during the eighth dose of study treatment. The event was considered to be possibly related to ceftobiprole, and, subsequently, the study treatment was stopped. A third patient had an AE of pleurisy and discontinued ceftobiprole on day 4; the pleurisy was considered by the investigator to be moderate and not related to ceftobiprole. The fourth patient discontinued ceftobiprole due to an AE of urticaria on day 2. The AE resolved the same day and the investigator considered it to be mild and probably related to ceftobiprole. No patients discontinued IV SoC cephalosporins because of AEs.

The most common AEs in either treatment group (observed in ≥3% of either group) while on IV therapy were vomiting,

TABLE 1. Baseline Demographics and Clinical Characteristics by Treatment Group in the Intent-to-Treat Population

Characteristic	Ceftobiprole (n = 94)	IV SoC Cephalosporin (n = 44)	Overall (N = 138)
Median age, yr (range)	5.0 (0.6–17.0)	6.0 (1.0–17.0)	5.0 (0.6–17.0)
Age strata, n (%)			
3 mo to <2 yr	12 (12.8)	2 (4.5)	14 (10.1)
2 to <6 yr	37 (39.4)	19 (43.2)	56 (40.6)
6 to <12 yr	27 (28.7)	12 (27.3)	39 (28.3)
12 to <18 yr	18 (19.1)	11 (25.0)	29 (21.0)
Male, n (%)	53 (56.4)	21 (47.7)	74 (53.6)
White race, n (%)	94 (100.0)	43 (97.7)	137 (99.3)
Median weight, kg (range)	20.0 (7.2–85.0)	19.8 (9.5–88.0)	20.0 (7.2–88.0)
Median height, cm (range)	116.0 (71.0–184.0)	119.5 (77.0–175.0)	117.0 (71.0–184.0)
Median BMI, kg/m ² (range)	16.2 (8.8–32.8)	15.8 (12.8–28.7)	16.0 (8.8–32.8)
Type of pneumonia, n (%)			
CAP	89 (94.7)	41 (93.2)	130 (94.2)
HAP	5 (5.3)	3 (6.8)	8 (5.8)

BMI indicates body mass index.

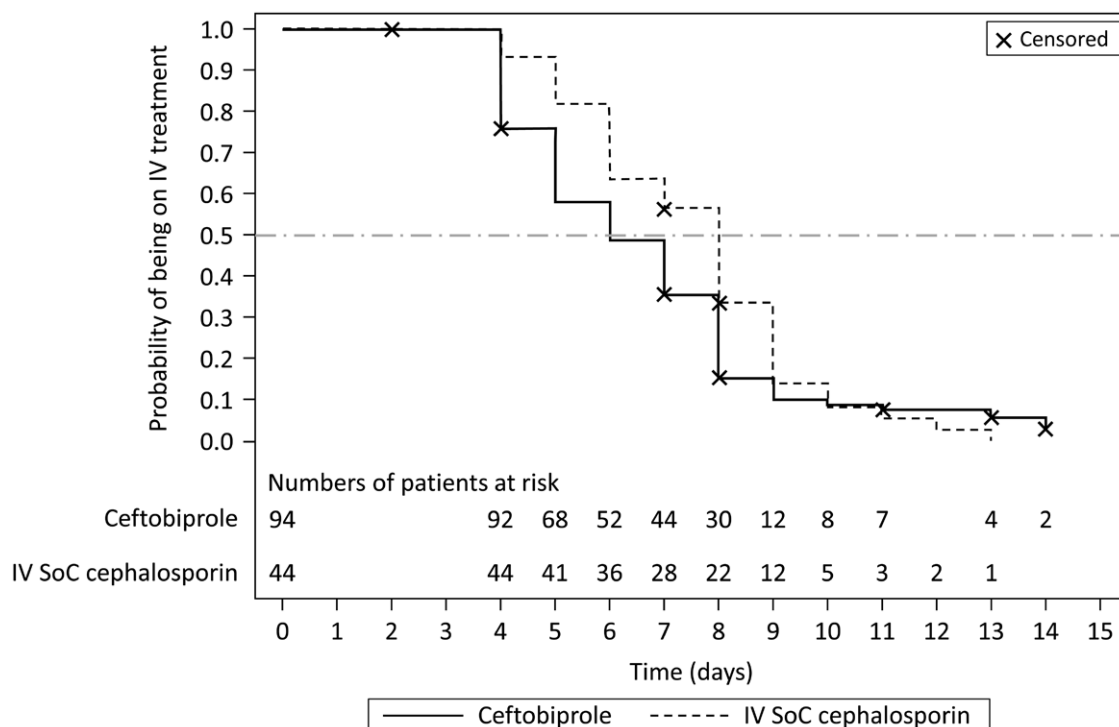


FIGURE 2. Kaplan-Meier curve of the time to switch to oral antibiotic in the intent-to-treat population.

diarrhea and headache. There were no fatal AEs in either group at any time during the study.

Efficacy

Clinical Outcomes

Early clinical response and clinical cure rates in the ITT and clinically evaluable study populations on day 4 and at the EOT, TOC and LFU visits are shown in Figure 3. In the ITT population, the early clinical response rate on day 4 was 95.7% and 93.2%, respectively, in the ceftibiprole and SoC cephalosporin treatment groups. The between-group difference was 2.6% (95% CI, -5.5% to 14.7%). The clinical cure rates at the TOC visit were 90.4% and 97.7% for the ceftibiprole and SoC cephalosporin treatment groups, respectively. The between-group difference was -7.3% (95% CI, -15.7% to 3.6%). At the LFU visit, clinical cure was maintained in 86.2% of patients treated with ceftibiprole and 100% of patients treated with SoC cephalosporin. No clinical relapses were observed in either treatment group at the LFU visit. Four patients in the ceftibiprole group received antibiotics for infections other than pneumonia after the TOC visit but before the LFU visit (eg, 1 patient received amoxicillin/clavulanic acid for otitis media). Owing to the conservative definition of clinical cure in this study, the clinical outcome for these patients was considered to be treatment failure at the LFU visit despite no relapse of pneumonia occurring. Similar results were observed in the clinically evaluable population.

Microbiologic Outcomes

Microbiologic outcomes at TOC among the 5 ceftibiprole-treated patients in the mITT population were presumed eradication in 3 patients, presumed persistence in 1 patient and microbiologically nonevaluable in 1 patient. All 5 patients had a diagnosis of CAP and the infecting pathogens identified at the baseline visit were *S. aureus* (n = 3), *H. influenzae* (n = 1) and *H. parainfluenzae*

(n = 1). Outcomes for these patients at the LFU visit were presumed eradication maintained in 2 patients, presumed persistence maintained in 1 patient and not evaluable in 2 patients. The single mITT patient in the comparator group had a diagnosis of CAP and the infecting pathogen was identified as *H. parainfluenzae*. Microbiologic outcomes at the TOC and LFU visits for this patient were presumed eradication and presumed eradication maintained, respectively.

Hospitalizations

Median (range) duration of hospitalization was 6.0 days (2.0–14.0 days) in patients who received ceftibiprole and 7.0 days (3.0–13.0 days) in patients who received SoC cephalosporin treatments.

DISCUSSION

In this randomized, phase 3 study, the safety and tolerability findings for ceftibiprole in pediatric patients with HAP or CAP were consistent with the established safety profile for ceftibiprole in adults.¹⁷ AEs reported during ceftibiprole treatment tended to be mild or moderate in intensity and were most commonly gastrointestinal in nature; this is consistent with results published in adult populations.¹⁷ The frequency of treatment-related AEs during IV therapy was comparable in this pediatric population (8.5%) with rates reported among a pediatric cohort with CAP treated with ceftriaxone (9.9%) or ceftriaxone (7.7%),²² and lower than those reported among adults with CAP (35.8%), HAP (24.9%) or ABSSSIs (19.8%).^{18–20} Only 4.3% of patients in this study discontinued ceftibiprole due to AEs, suggesting that ceftibiprole is well tolerated by most pediatric patients. This result is consistent with the rates of discontinuations for AEs reported in adult patients with CAP (5.8%), HAP (3.6%) and ABSSSIs (1.8%).^{18–20}

TABLE 2. Summary of Treatment-emergent Adverse Events Occurring During the First 3 Days of IV Therapy, While on IV Therapy and Throughout the Study Duration in the Safety Population

Patients With ≥ 1 AE, n (%)	First 3 Days of IV Therapy		While on IV Therapy		Overall Study Duration*	
	IV SoC		IV SoC		IV SoC	
	Ceftobiprole (n = 94)	Cephalosporin (n = 44)	Ceftobiprole (n = 94)	Cephalosporin (n = 44)	Ceftobiprole (n = 94)	Cephalosporin (n = 44)
Any AE	11 (11.7)	5 (11.4)	19 (20.2)	8 (18.2)	30 (31.9)	13 (29.5)
Treatment-related AE	6 (6.4)	0	8 (8.5)	0	9 (9.6)	0
Severe AE	1 (1.1)	0	1 (1.1)	0	3 (3.2)	0
Treatment-related severe AE	0	0	0	0	0	0
Serious AE	1 (1.1)	0	2 (2.1)	0	7 (7.4)	2 (4.5)
Treatment-related serious AE	0	0	1 (1.1)	0	1 (1.1)	0
AE leading to treatment discontinuation	2 (2.1)	0	4 (4.3)	0	4 (4.3)	0
AE leading to death	0	0	0	0	0	0
AEs occurring in ≥3% of either treatment group at any time during the study						
Vomiting	3 (3.2)	0	4 (4.3)	1 (2.3)	7 (7.4)	1 (2.3)
Diarrhea	1 (1.1)	2 (4.5)	1 (1.1)	4 (9.1)	2 (2.1)	4 (9.1)
Viral infection	0	1 (2.3)	2 (2.1)	1 (2.3)	4 (4.3)	1 (2.3)
Headache	2 (2.1)	0	3 (3.2)	0	3 (3.2)	0
Pneumonia	1 (1.1)	0	1 (1.1)	0	3 (3.2)	0
Bronchitis	0	0	0	0	0	2 (4.5)

*Up to last follow-up visit.

In the current study, rates of AEs, severe AEs and serious AEs while patients were on IV therapy were similar between the ceftobiprole and SoC cephalosporin treatment groups (20.2% vs. 18.2%, 1.1% vs. 0% and 2.1% vs. 0%, respectively), indicating similar tolerability. The rate of those AEs considered related to study treatment was 8.5% in the ceftobiprole group and 0% in the SoC cephalosporin group. However, due to the small cohort size and 2:1 randomization ratio, the study lacks power to determine whether these differences are significant. The intensity and nature of the AEs reported in the comparator group were consistent with previous reports for IV cephalosporins in pediatric patients with CAP.^{22,23}

At the TOC visit, clinical cure rates in pediatric patients with pneumonia who were treated with ceftobiprole (94.7% of whom had

CAP) were similar to those observed in adult patients with CAP (ITT, 90.4% vs. 76.4%; clinically evaluable, 90.9% vs. 86.6%, respectively).¹⁹ It was not possible to compare efficacy in patients with HAP versus CAP, nor was it possible to indirectly compare the pediatric HAP results with the published data in adults.¹⁸ This is due to the small numbers of patients with HAP (n = 8) enrolled in this study, which is consistent with the very low rates of HAP patient recruitment observed in earlier pediatric pneumonia studies.^{24,25}

In our study, most patients achieved clinical response at both day 4 and EOT, and the results were similar between the 2 treatment groups. Based on historical study data, achieving symptom improvement at day 4 is considered a relevant treatment response in CAP.²⁶ As a result, it is endorsed by the US Food and Drug

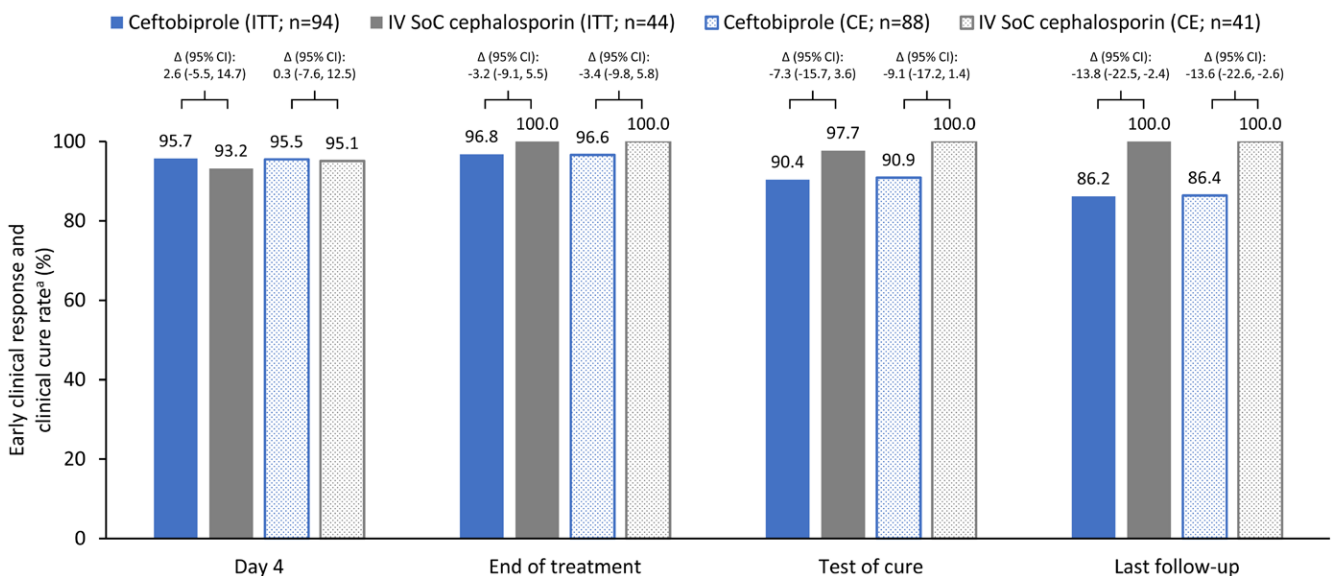


FIGURE 3. Early clinical response and clinical cure rates on day 4 and at the end-of-treatment, test-of-cure and last follow-up visits in the intent-to-treat and clinically evaluable populations. Early clinical response was assessed at day 4 and clinical cure at end-of-treatment, test-of-cure and last follow-up visits. CE indicates clinically evaluable.

Administration as a primary outcome measure in clinical trials investigating new antibiotics for CAP.²⁷ The importance of early treatment response has been further confirmed in a recent analysis of patient-level data from 6 CAP trials submitted to the Food and Drug Administration after 2014. In this study of 4645 patients, concordance between early and late outcomes was found for 85.6% of patients. Moreover, early endpoint response had a positive predictive value of 92.9% for late endpoint success.²⁸ The Foundation for the National Institutes of Health Biomarkers Consortium also noted that an early endpoint of symptom improvement plus survival (up to day 7 of treatment) may be clinically relevant for patients with HAP.²⁹ Clinical improvement at day 4 provides a useful indication of the comparative clinical efficacy of the 2 IV antibiotic approaches before the switch to physician-selected oral therapy has the potential to confound the comparison.²⁷

A high clinical cure rate was observed at the TOC and LFU visits in both treatment groups. A slightly higher cure rate was reported for the SoC cephalosporin group compared with the ceftobiprole group; however, these results must be interpreted with caution as the study was not powered to compare efficacy and the sample size in the comparator group was small. The results were also confounded by the inclusion of 4 patients in the ceftobiprole treatment group who received antibiotic therapy for infections other than pneumonia between the TOC and LFU visits; the clinical outcome in these patients was considered to be treatment failure, despite no relapse of pneumonia occurring. Evaluation of clinical cure at the TOC and LFU visits also reflects the combined efficacy of the IV study drugs and physician-selected oral antibiotics. Two previous studies of IV ceftriaxone in pediatric CAP, with an optional oral switch, have reported high clinical cure rates at the TOC visits (88.9% and 100%, respectively), which are similar to those reported here in both treatment groups.^{22,23} Consistent with the clinical cure endpoint, results of the Kaplan-Meier analyses of time to switch to oral therapy and time to hospital discharge were similar between the 2 treatment groups.

The study design was robust with clearly defined outcome measures and inclusive eligibility criteria, and was reflective of similar recent studies conducted in pediatric pneumonia.^{22,23} Limitations of the study include the small number of patients with HAP, which is indicative of the general difficulty in recruiting pediatric patients with nonventilator-associated HAP into clinical trials.^{24,25,30–32} An additional challenge is that of obtaining sputum samples from pediatric patients, leading to limited microbiologic data. The problem in obtaining microbiologically evaluable samples also meant that a bacterial etiology could not be confirmed at baseline. Although randomization should control statistically for an imbalance in causative pathogens between the 2 treatment groups, this possibility cannot be entirely ruled out. Lack of microbiologic data is a common limitation of studies in pediatric pneumonia.^{22,23} Another limitation is the exclusion of some patients who may be encountered in clinical practice, such as patients with ventilator-associated pneumonia (which is a major risk factor for HAP)^{33–35} or those who are immunocompromised; the findings from this study cannot be applied to these patient groups. Racial homogeneity of the study population may also limit applicability of the results, although this is mitigated by the fact that the pathophysiology of pneumonia does not differ between racial groups and the pharmacokinetic profile of ceftobiprole is not altered by ethnicity.^{21,36}

In conclusion, ceftobiprole was well tolerated and demonstrated similar efficacy to SoC cephalosporin antibiotics in pediatric patients with HAP or CAP requiring hospitalization. These findings suggest that ceftobiprole may be considered as an additional option for the treatment of pneumonia (excluding ventilator-associated pneumonia) in hospitalized pediatric patients.

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