

A Phase 3 Randomized Double-Blind Comparison of Ceftobiprole Medocaril Versus Ceftazidime Plus Linezolid for the Treatment of Hospital-Acquired Pneumonia

Samir S. Awad,¹ Alejandro H. Rodriguez,² Yin-Ching Chuang,³ Zsuzsanna Marjanek,⁴ Alex J. Pareigis,⁵ Gilmar Reis,⁶ Thomas W. L. Scheeren,^{7,8} Alejandro S. Sánchez,⁹ Xin Zhou,¹⁰ Mikael Saulay,¹¹ and Marc Engelhardt¹²

¹Section of Surgical Critical Care, Baylor College of Medicine, Houston, Texas; ²Joan XXIII University Hospital, Tarragona, Spain; ³Chi-Mei Medical Center, Tainan City - Yung Kang District, Taiwan; ⁴Javorsky Ödön City Hospital, Argenti Döme, Hungary; ⁵Medical Arts Associates Ltd, Moline, Illinois; ⁶Santa Casa de Belo Horizonte, Brazil; ⁷Department of Anesthesiology, University of Groningen, University Medical Center Groningen, The Netherlands; ⁸Department of Anesthesia and Intensive Care, University Hospital Rostock, Germany; ⁹Policlínico Modelo de Cipolletti, Rio Negro, Argentina; ¹⁰First People's Hospital, Shanghai, China; ¹¹Aptiv Solutions, Allschwil, and ¹²Basilea Pharmaceutica International Ltd, Basel, Switzerland

Background. Ceftobiprole, the active moiety of ceftobiprole medocaril, is a novel broad-spectrum cephalosporin, with bactericidal activity against a wide range of gram-positive bacteria, including *Staphylococcus aureus* (including methicillin-resistant strains) and penicillin- and ceftriaxone-resistant pneumococci, and gram-negative bacteria, including Enterobacteriaceae and *Pseudomonas aeruginosa*.

Methods. This was a double-blind, randomized, multicenter study of 781 patients with hospital-acquired pneumonia (HAP), including 210 with ventilator-associated pneumonia (VAP). Treatment was intravenous ceftobiprole 500 mg every 8 hours, or ceftazidime 2 g every 8 hours plus linezolid 600 mg every 12 hours; primary outcome was clinical cure at the test-of-cure visit.

Results. Overall cure rates for ceftobiprole vs ceftazidime/linezolid were 49.9% vs 52.8% (intent-to-treat [ITT], 95% confidence interval [CI] for the difference, −10.0 to 4.1) and 69.3% vs 71.3% (clinically evaluable [CE], 95% CI, −10.0 to 6.1). Cure rates in HAP (excluding VAP) patients were 59.6% vs 58.8% (ITT, 95% CI, −7.3 to 8.8), and 77.8% vs 76.2% (CE, 95% CI, −6.9 to 10.0). Cure rates in VAP patients were 23.1% vs 36.8% (ITT, 95% CI, −26.0 to −1.5) and 37.7% vs 55.9% (CE, 95% CI, −36.4 to 0). Microbiological eradication rates in HAP (excluding VAP) patients were, respectively, 62.9% vs 67.5% (microbiologically evaluable [ME], 95% CI, −16.7 to 7.6), and in VAP patients 30.4% vs 50.0% (ME, 95% CI, −38.8 to −0.4). Treatment-related adverse events were comparable for ceftobiprole (24.9%) and ceftazidime/linezolid (25.4%).

Conclusions. Ceftobiprole is a safe and effective bactericidal antibiotic for the empiric treatment of HAP (excluding VAP). Further investigations are needed before recommending the use of ceftobiprole in VAP patients.

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Keywords. ceftazidime; ceftobiprole; linezolid; hospital-acquired pneumonia; ventilator-associated pneumonia.

Hospital-acquired pneumonia (HAP) is the second most frequent hospital-acquired infection in adults,

and a leading cause of death in hospitalized patients [1, 2]. Common pathogens in HAP are *Staphylococcus aureus* (including methicillin-resistant *S. aureus* [MRSA]), *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Klebsiella* species, *Escherichia coli*, and *Enterobacter* species; *Streptococcus pneumoniae* may also play a role in HAP [3].

There is a significant unmet need for new antibiotics effective against bacterial pathogens responsible for HAP. Treatment guidelines for HAP recommend

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Correspondence: Marc Engelhardt, MD, Basilea Pharmaceutica International Ltd, Basel Switzerland (marc.engelhardt@basilea.com).

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rapid empiric therapy with combinations of antibiotics based on local resistance patterns and patient risk factors [1].

Ceftobiprole, the active moiety of its prodrug ceftobiprole medocartil, is a novel cephalosporin that binds tightly to the penicillin-binding proteins (PBPs), including those responsible for β -lactam resistance in staphylococci (PBP2a) and pneumococci (PBP2x), with a low propensity for resistance development [4–6]. It demonstrates potent activity against gram-positive pathogens, including MRSA and penicillin-resistant *S. pneumoniae*, together with activity against gram-negative pathogens commonly associated with pneumonia [7–14]. Ceftobiprole demonstrates in vitro activity against *S. aureus* resistant to linezolid, vancomycin, and daptomycin [15], and ceftriaxone-resistant *S. pneumoniae* [16, 17]. It also demonstrates superior bactericidal activity to daptomycin, linezolid, and vancomycin in several animal models of endocarditis [18, 19], osteomyelitis [20, 21], meningitis [22], mediastinitis [23], and peritonitis [24], and good efficacy in animal models of pneumonia and skin infections [25, 26]. Ceftobiprole is therefore a promising agent with potential utility for difficult-to-treat infections.

Ceftobiprole has been shown to be a safe and efficacious option in the treatment of patients with severe community-acquired pneumonia [27]. The aim of this study was to demonstrate that in patients with HAP, ceftobiprole is noninferior to combined treatment with ceftazidime and linezolid for the primary endpoint of clinical cure at the test-of-cure (TOC) visit.

METHODS

Study Design

This was a multicenter, double-blind, randomized controlled trial conducted between 6 April 2005 and 22 May 2007 at 157 sites in Europe, North and South America, and the Asia-Pacific region, following approval by independent ethics committees/institutional review boards for each site. Signed written informed consent was obtained for all participants prior to enrollment.

Participants

Men and women aged 18 years or older were eligible for enrollment if they had a clinical diagnosis of pneumonia after at least 72 hours of hospitalization or stay in a chronic care facility, clinical signs or symptoms of pneumonia (at least 2 of purulent respiratory secretion, tachypnea, or hypoxemia), fever or leukocytosis/leukopenia, new or persistent radiographic infiltrates, and an Acute Physiology and Chronic Health Evaluation II (APACHE II) score ≥ 8 and ≤ 25 . Ventilator-associated pneumonia (VAP) was defined as pneumonia developing >48 hours after onset of mechanical ventilation. Of the 781 HAP patients enrolled, 210 had VAP.

The main exclusion criteria included severe renal impairment (calculated creatinine clearance rate <30 mL/minute or oliguria

<20 mL/hour unresponsive to fluid challenge) or hepatic dysfunction (at least 3 times the upper limit of normal for total bilirubin, alanine aminotransferase or aspartate aminotransferase), evidence of infection with ceftazidime- or ceftobiprole-resistant pathogens, and clinical conditions that would interfere with efficacy assessment, such as sustained shock, active tuberculosis, lung abscess, or post-obstructive pneumonia. With predefined exceptions, participants must not have had systemic antibiotic treatment for >24 hours in the 48 hours before enrollment.

Interventions

Eligible patients were randomized 1:1 to ceftobiprole 500 mg every 8 hours as a 120-minute intravenous infusion, plus placebo every 12 hours as a 60-minute intravenous infusion, or ceftazidime 2 g every 8 hours as a 120-minute intravenous infusion plus linezolid 600 mg every 12 hours as a 60-minute intravenous infusion. For blinding reasons, the 120-minute infusion time was longer than the recommended infusion time in the ceftazidime label. Planned treatment duration was 7 days, to a maximum of 14 days. Additional open-label treatment with a fluoroquinolone or an aminoglycoside was allowed for patients at risk of pseudomonal infection.

Assessments

Clinical assessments were performed at baseline, at days 4, 8, and 14, and at the end of treatment (EOT, within 24 hours after last study drug infusion). The TOC visit was 7–14 days, and the late follow-up visit 28–35 days, after EOT. Mandatory laboratory safety tests were performed at baseline and EOT, and mandatory chest radiographs were performed at baseline and TOC. Samples for bacterial culture and Gram stain were obtained predose, and on days 4, 8, and 14 if sputum or other respiratory tract specimens were available. Blood samples for bacterial culture were obtained at baseline, and on days 4, 8, and 14 if clinically indicated. Pathogen identification and susceptibility testing was confirmed by a central laboratory according to Clinical and Laboratory Standards Institute methodology.

Safety and tolerability were assessed from treatment-emergent adverse events (AEs), changes in pre- to posttreatment physical examination results, vital signs, 12-lead electrocardiogram results, and clinical laboratory results. An independent data monitoring committee assessed blinded safety-related data during the study to ensure the safety of study participants.

Sample Size and Noninferiority Margin

Assuming a clinical cure rate of 50% and a clinically evaluable rate of 60%, a sample size of 770 patients (ITT) was calculated to provide 90% power at a 2-sided significance level (type 1 error) of 5% to demonstrate the noninferiority of ceftobiprole to ceftazidime/linezolid within a margin of 15% for the primary endpoint of clinical cure rate at TOC in the overall study population.

Randomization and Blinding

Participants were randomly assigned to treatment via a central interactive voice response system based on a computer-generated randomization schedule. Randomization was stratified by disease entity (patients with and without VAP) using randomly permuted blocks for each of the 2 strata, and by APACHE II score (8–19; 20–25). Patients with VAP were further stratified by time to randomization after onset of mechanical ventilation (<5 days or ≥5 days of ventilation). The study was conducted in a double-blind fashion.

Statistical Analysis

The primary endpoint was clinical cure (resolution of signs and symptoms of infection, or improvement to such an extent that no further antimicrobial therapy was necessary) at TOC, in the co-primary ITT (all patients randomly assigned to treatment) and clinically evaluable (CE) (patients who received at least 1 dose of study medication and were clinically evaluable at the TOC visit) analysis sets. Patients who received systemic nonstudy antibiotics between baseline and the TOC visit for the treatment of pneumonia were considered to have clinical failure; patients who received systemic nonstudy antibiotics for indications other than pneumonia were excluded from the CE analysis set.

The main secondary endpoint was microbiological eradication at TOC in the microbiologically evaluable analysis set (all patients

in the CE analysis set who had a valid pathogen at baseline and were microbiologically evaluable at the TOC visit) and microbiological ITT analysis set (all patients in the ITT analysis set who had a valid pathogen at baseline). Endpoints were analyzed with a 2-sided 95% confidence interval (CI) for treatment difference. Noninferiority of ceftobiprole to ceftazidime/linezolid was to be concluded if the lower limit of this interval was $\geq -15\%$.

A post hoc multivariate logistic regression analysis (MVLRA) was performed on the VAP subgroup to explore individual factors (eg, baseline pathogens, sex, age, comorbidities, vasopressor use) or a combination of factors that might explain differences in clinical and microbiological outcomes between the 2 treatment groups in VAP patients. A total of 37 factors were included in multivariate analyses (using stepwise, forward, and backward factor selection with and without consideration of treatment by factor interactions) to assess their impact on clinical cure, microbiological eradication, and 30-day all-cause-mortality.

RESULTS

Recruitment

Of 795 patients screened (Figure 1), 781 were randomized, with 391 assigned to ceftobiprole and 390 to ceftazidime/linezolid (ITT analysis set). The CE analysis set comprised 251 ceftobiprole and 244 ceftazidime/linezolid patients.

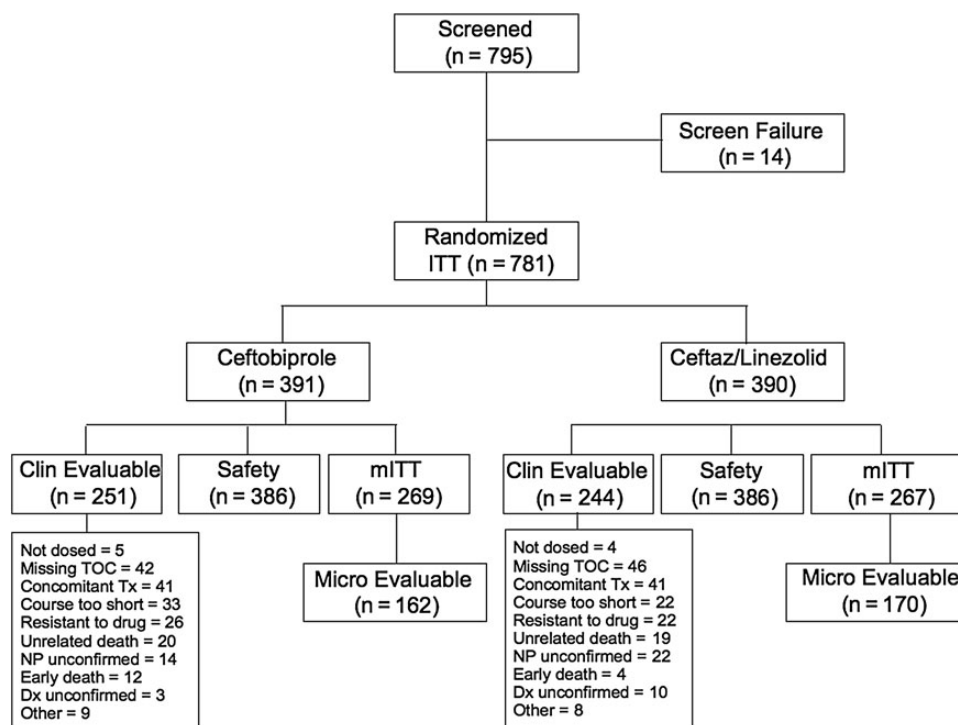


Figure 1. Patient disposition. Abbreviations: Ceftaz, ceftazidime; Dx, diagnosis; mITT, microbiological intent-to-treat; NP, nosocomial pneumonia; TOC, test-of-cure; Tx, treatment.

Table 1. Baseline Demographic and Clinical Characteristics (Intent-to-Treat Analysis Set)

Variable	All Patients, No. (%)		HAP (Excluding VAP), No. (%)		VAP, No. (%)	
	Ceftobiprole (n = 391)	Ceftazidime/Linezolid (n = 390)	Ceftobiprole (n = 287)	Ceftazidime/Linezolid (n = 284)	Ceftobiprole (n = 104)	Ceftazidime/Linezolid (n = 106)
Male sex	278 (71)	243 (62)	202 (70)	170 (60)	76 (73)	73 (69)
Age >65 y	177 (45)	185 (47)	148 (52)	147 (52)	29 (28)	38 (36)
Age < 45 y	81 (21)	65 (17)	42 (15)	34 (12)	39 (38)	31 (29)
European Union	220 (56)	219 (56)	165 (57)	165 (58)	55 (53)	54 (51)
United States	48 (12)	47 (12)	34 (12)	34 (12)	14 (13)	13 (12)
Other region	123 (31)	124 (32)	88 (31)	85 (30)	35 (34)	39 (37)
Smoking	113 (29)	116 (30)	83 (29)	85 (30)	30 (29)	31 (29)
Diabetes mellitus	79 (20)	77 (20)	59 (21)	60 (21)	20 (19)	17 (16)
Chronic care	45 (12)	44 (11)	41 (14)	42 (15)	4 (4)	2 (2)
Emphysema	34 (9)	43 (11)	33 (11)	33 (12)	1 (1)	10 (9)
Asthma	21 (5)	28 (7)	15 (5)	23 (8)	6 (6)	5 (5)
SIRS	283 (72)	286 (73)	217 (76)	226 (80)	66 (63)	60 (57)
CRP >100 mg/L	240 (61)	218 (56)	169 (59)	153 (54)	71 (68)	65 (61)
Prior AB within 24 h	225 (58)	243 (62)	169 (59)	176 (62)	56 (54)	67 (63)
APACHE II ≥ 15	162 (41)	160 (41)	101 (35)	104 (37)	61 (59)	56 (53)
APACHE II ≥ 20	47 (12)	51 (13)	25 (9)	26 (9)	22 (21)	25 (24)
Baseline ventilation	145 (37)	150 (38)	41 (14)	44 (15)	104 (100)	106 (100)
Ventilated ≥ 5 d	76 (19)	86 (22)	0 (0)	0 (0)	76 (73)	86 (81)
Valid baseline pathogen	269 (69)	267 (68)	179 (62)	181 (64)	90 (87)	86 (81)
Valid gram-positive pathogen	136 (35)	149 (38)	85 (30)	102 (36)	51 (49)	47 (44)
Valid gram-negative pathogen	196 (50)	177 (45)	122 (43)	116 (41)	74 (71)	61 (58)
Polymicrobial	95 (24)	92 (24)	50 (17)	56 (20)	45 (43)	36 (34)
<i>Pseudomonas</i>	49 (13)	52 (13)	29 (10)	30 (11)	20 (19)	22 (21)
MRSA	41 (10)	48 (12)	28 (10)	32 (11)	13 (13)	16 (15)
MSSA	55 (14)	72 (18)	27 (9)	44 (15)	28 (27)	28 (26)
Bacteremia	41 (10)	45 (12)	24 (8)	27 (10)	17 (16)	18 (17)
CrCl <50 mL/min	63 (16)	65 (17)	56 (20)	55 (19)	7 (7)	10 (9)
CrCl ≥ 150 mL/min	67 (17)	66 (17)	37 (13)	38 (13)	30 (29)	28 (26)

Abbreviations: AB, antibiotics; APACHE, Acute Physiology and Chronic Health Evaluation; CrCl, creatinine clearance; CRP, C-reactive protein; HAP, hospital-acquired pneumonia; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; SIRS, systemic inflammatory response syndrome; VAP, ventilator-associated pneumonia.

Three hundred eighty-six patients in each treatment group were available for safety assessment.

Of the 247 patients who discontinued the study, 126 patients (32%) were from the ceftobiprole group, and 121 (31%) were from the ceftazidime/linezolid group. The most common reasons for discontinuation were death (77 ceftobiprole [20%] and 74 ceftazidime/linezolid [19%]), and AEs (14 ceftobiprole [4%], and 6 ceftazidime/linezolid [2%]).

Baseline Data

Baseline demographic and clinical characteristics are provided in Table 1. The study recruited patients in 32 countries; 56%

in Europe, 12% in the United States, 32% in other regions. 71% vs 62% of the patients in the ceftobiprole and the comparator groups, respectively, were men, and 45% vs 47% were aged >65 years. A substantial proportion of the patient population was severely ill: 41% of the patients in each treatment group had an APACHE II score ≥ 15 , and 12% of ceftobiprole patients and 13% of ceftazidime/linezolid patients had an APACHE II score ≥ 20 . Seventy-two percent and 73% of the patients, respectively, presented with systemic inflammatory response syndrome, 10% and 12%, respectively, had bacteremia, and 58% and 62% had received prior antibiotics within 24 hours of enrollment. A pathogen considered to cause pneumonia was

Table 2. Primary Endpoint: Clinical Cure at Test of Cure (Intent-to-Treat and Clinically Evaluable Analysis Sets)

Analysis Set Group	Ceftobiprole		Ceftazidime/Linezolid		Difference (%) ^b	(95% CI) ^c
	No.	No. ^a (%)	No.	No. ^a (%)		
Intent-to-treat						
All patients	391	195 (49.9)	390	206 (52.8)	−2.9	(−10.0 to 4.1)
HAP (excluding VAP)	287	171 (59.6)	284	167 (58.8)	0.8	(−7.3 to 8.8)
VAP	104	24 (23.1)	106	39 (36.8)	−13.7	(−26.0 to −1.5)
HAP, mechanically ventilated	69	21 (30.4)	70	19 (27.1)	3.3	(−11.8 to 18.3)
Clinically evaluable						
All patients	251	174 (69.3)	244	174 (71.3)	−2.0	(−10.0 to 6.1)
HAP (excluding VAP)	198	154 (77.8)	185	141 (76.2)	1.6	(−6.9 to 10.0)
VAP	53	20 (37.7)	59	33 (55.9)	−18.2	(−36.4 to −0)
HAP (excluding VAP), mechanically ventilated	38	21 (55.3)	37	15 (40.5)	14.7	(−7.6 to 37.1)

Abbreviations: CI, confidence interval; HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia.

^a No. of patients with clinical cure at test of cure.

^b Difference ceftobiprole minus ceftazidime/linezolid.

^c Two-sided 95% CI is based on the normal approximation to the difference of the 2 proportions.

found at baseline in 69% of the patients in the ceftobiprole group and in 68% of the patients in the ceftazidime/linezolid group. Ten percent and 12% of the patients, respectively, were infected with MRSA. In patients with VAP, 73% in the ceftobiprole and 81% in the ceftazidime/linezolid group had been ventilated for ≥ 5 days prior to enrollment.

Outcomes

Results for the primary endpoint are provided in Table 2. The study achieved its primary objective demonstrating noninferiority of ceftobiprole to ceftazidime/linezolid for clinical cure rate at the TOC visit within the protocol-defined margin of 15% in the coprimary ITT and CE analysis sets. The cure rates in the ITT analysis set were 49.9% and 52.8% for ceftobiprole and ceftazidime/linezolid, respectively (difference, −2.9% [95% CI, −10.0 to 4.1]), and 69.3% and 71.3%, respectively (−2.0% [95% CI, −10.0 to 6.1]), in the CE analysis set.

Consistent with regulatory guidance distinguishing HAP (excluding VAP) and VAP [28, 29], further efficacy analyses were conducted of the HAP (excluding VAP) and VAP patient populations. The results for HAP (excluding VAP) patients and VAP patients are therefore discussed separately below.

Subgroup Analyses of the Primary Endpoint

In the ITT analysis set, 73% of all patients enrolled were HAP (excluding VAP) patients (287 in the ceftobiprole group and 284 in the ceftazidime/linezolid group). Baseline characteristics of HAP (excluding VAP) patients were comparable to those of the overall study population (Table 1). Noninferiority of ceftobiprole to ceftazidime/linezolid for clinical cure at TOC was

demonstrated in patients with HAP (excluding VAP) within the predefined noninferiority margin of −15%. The cure rates at TOC for HAP (excluding VAP) patients in the ITT analysis set were 59.6% for ceftobiprole and 58.8% for ceftazidime/linezolid (difference, 0.8 [95% CI, −7.3 to 8.8]), and 77.8% and 76.2%, respectively, in the CE analysis set (difference, 1.6 [95% CI, −6.9 to 10.0]) (Table 2). Results for the primary endpoint in HAP (excluding VAP) patients were also comparable for ceftobiprole and ceftazidime/linezolid when analyzed by baseline demographic and clinical characteristics. Clinical cure rates for HAP (excluding VAP) patients were comparable in subgroup analyses by sex, geographical region, age, and disease severity (APACHE II score) (Table 3).

In the CE analysis set, a higher proportion of HAP (excluding VAP) patients in the ceftobiprole group than in the ceftazidime/linezolid group (CE, 86.9% vs 78.4%; difference 8.5 [95% CI, −9–16.1]) showed early improvement (4 days after onset of therapy) as assessed by the investigator based on the resolution of clinical signs and symptoms. The largest difference was for patients with a baseline culture positive for MRSA, with 94.7% in the ceftobiprole group having early improvement vs 52.6% in the ceftazidime/linezolid group (difference, 42.1 [95% CI, 17.5–66.7]) (Table 4).

Of the 198 ceftobiprole and 185 ceftazidime/linezolid HAP (excluding VAP) patients in the CE analysis set, 38 (19%) and 37 (20%), respectively, required mechanical ventilation during treatment, or developed pneumonia within 48 hours after the start of ventilation (ie, did not fall within the definition of VAP). For these ventilated HAP (excluding VAP) patients, higher cure rates were observed in the ceftobiprole group than in the

Table 3. Clinical Cure Rates at Test of Cure by Demographic and Clinical Characteristics (Clinically Evaluable Analysis Set) in Patients With Hospital-Acquired Pneumonia (Excluding Ventilator-Associated Pneumonia)

	Ceftobiprole			Ceftazidime/Linezolid			Difference (%) ^a	(95% CI) ^b
	No.	n	%	No.	n	%		
HAP (excluding VAP)	198	154	77.8	185	141	76.2	1.6	(−6.9 to 10.0)
Age								
18–44 y	27	24	88.9	22	18	81.8	7.1	(−12.9 to 27.1)
45–64 y	60	48	80.0	66	52	78.8	1.2	(−12.9 to 15.3)
≥65 y	111	82	73.9	97	71	73.2	0.7	(−11.3 to 12.7)
Sex								
Male	139	107	77.0	112	86	76.8	0.2	(−10.3 to 10.7)
Female	59	47	79.7	73	55	75.3	4.3	(−9.9 to 18.6)
Geographical region								
United States	27	20	74.1	24	14	58.3	15.7	(−10.0 to 41.5)
Europe ^c	112	93	83.0	104	90	86.5	−3.5	(−13.1 to 6.1)
Other ^d	59	41	69.5	57	37	64.9	4.6	(−12.5 to 21.7)
APACHE II score								
8–19	185	146	78.9	171	134	78.4	0.6	(−8.0 to 9.1)
20–25	13	8	61.5	14	7	50.0	11.5	(−25.7 to 48.8)
Care facility								
ICU	73	51	69.9	59	39	66.1	3.8	(−12.3 to 19.8)
Non-ICU	125	103	82.4	126	102	81.0	1.4	(−8.1 to 11.0)
Prestudy antibiotics ^e								
No antibiotics	53	44	83.0	59	49	83.1	−0.0	(−14.0 to 13.9)
Using ≤24 h	65	52	80.0	59	45	76.3	3.7	(−10.8 to 18.3)
Using >24 h	80	58	72.5	67	47	70.1	2.4	(−12.3 to 17.0)
Antipseudomonal antibiotics ^f								
Yes	27	15	55.6	19	10	52.6	2.9	(−26.3 to 32.2)
No	171	139	81.3	166	131	78.9	2.4	(−6.2 to 10.9)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; HAP, hospital-acquired pneumonia; n, number of patients with a clinical outcome of cure; ICU, intensive care unit; VAP, ventilator-associated pneumonia.

^a Ceftobiprole minus ceftazidime/linezolid.

^b Two-sided 95% CI is based on normal approximation to the difference of the 2 proportions.

^c Europe includes Belgium, Bulgaria, Czech Republic, France, Germany, Great Britain, Hungary, Latvia, Lithuania, Poland, Romania, Russia, Serbia, Montenegro, Spain, Switzerland, and Ukraine.

^d Other region includes Argentina, Australia, Brazil, Canada, Chile, Democratic People's Republic of Korea, Honduras, India, Israel, Mexico, People's Republic of China, Peru, South Africa, Taiwan, and Thailand.

^e The window for prestudy antibiotics was limited to 72 hours prior to baseline.

^f Empirical treatment with antibiotic therapy was added to the study drug regimen for 48 hours in patients with a suspected infection due to *Pseudomonas aeruginosa* or for 5–7 days for patients with proven infection due to *P. aeruginosa*.

ceftazidime/linezolid group: 55.3% vs 40.5%, respectively (CE; difference, 14.7 [95% CI, −7.6 to 37.1]) (Table 2).

Noninferiority was not demonstrated in VAP patients. The cure rates at TOC for VAP patients in the ITT analysis set were 23.1% for ceftobiprole and 36.8% for ceftazidime/linezolid (difference, −13.7 [95% CI, −26.0 to −1.5]) (Table 2). An MVLRA did not reveal any specific patient factors in VAP patients that could explain the differential clinical and microbiological outcome between the treatment arms in this subgroup. The subgroup of VAP patients was relatively small, and was

characterized by a substantial heterogeneity in baseline characteristics (Table 1).

Subgroup Analyses of Secondary Endpoints

Microbiological Eradication

For the main secondary endpoint, the microbiological eradication rates at TOC for HAP (excluding VAP) patients in the microbiologically evaluable analysis set were 62.9% for ceftobiprole and 67.5% for ceftazidime/linezolid (difference, −4.6% [95% CI, −16.7 to 7.6]) (Table 5). For patients with VAP, the

Table 4. Clinical Improvement at Day 4 (Intent-to-Treat and Clinically Evaluable Analysis Sets) in Patients With Hospital-Acquired Pneumonia (Excluding Ventilator-Associated Pneumonia)

Analysis Set Group	Ceftobiprole		Ceftazidime/Linezolid		Difference (%) ^a	(95% CI) ^b
	No.	n (%)	No.	n (%)		
ITT						
HAP (excluding VAP)	287	221 (77.0)	284	214 (75.4)	1.7	(−5.3 to 8.6)
Any valid gram-positive	85	69 (81.2)	102	75 (73.5)	7.6	(−4.3 to 19.6)
Any <i>Staphylococcus aureus</i>	55	45 (81.8)	76	55 (72.4)	9.4	(−4.9 to 23.8)
Any MRSA	28	22 (78.6)	32	19 (59.4)	19.2	(−3.6 to 42.0)
Clinically evaluable						
HAP (excluding VAP)	198	172 (86.9)	185	145 (78.4)	8.5	(.9–16.1)
Any valid gram-positive	61	53 (86.9)	69	51 (73.9)	13.0	(−.4 to 26.4)
Any <i>S. aureus</i>	39	36 (92.3)	49	35 (71.4)	20.9	(5.7–36.0)
Any MRSA	19	18 (94.7)	19	10 (52.6)	42.1	(17.5–66.7)

Clinical improvement was assessed by the investigator. All categories include monomicrobial and polymicrobial infections.

Abbreviations: CI, confidence interval; HAP, hospital-acquired pneumonia; ITT, intent-to-treat; MRSA, methicillin-resistant *Staphylococcus aureus*; n, number of patients with clinical improvement at Day 4; VAP, ventilator-associated pneumonia.

^a Difference for ceftobiprole minus ceftazidime/linezolid.

^b Two-sided 95% CI is based on the normal approximation to the difference of the 2 proportions.

rates were 30.4% for ceftobiprole and 50.0% for ceftazidime/linezolid (difference, −19.6% [95% CI, −38.8 to −0.4]) (Table 5).

Clinical Cure and Microbiological Eradication by Pathogen

Clinical cure and microbiological eradication rates by pathogen in patients with HAP (excluding VAP) were similar for gram-positive and most gram-negative pathogens (Table 6). For the most prevalent Enterobacteriaceae and for *P. aeruginosa*, clinical cure and microbiological eradication rates were similar between treatment groups. For the relatively small number of patients with *Haemophilus* and *Acinetobacter* species as

baseline pathogens, numerically lower clinical cure and microbiological eradication rates were observed in the ceftobiprole group.

Mortality

Thirty-day all-cause mortality (ACM) and 30-day pneumonia-specific mortality were similar between the ceftobiprole and ceftazidime/linezolid treatment groups. For HAP (excluding VAP) patients in the ITT analysis set, 30-day ACM was 16.7% for ceftobiprole and 18.0% for ceftazidime/linezolid (difference, −1.2 [95% CI, −7.4 to 5.0]), and pneumonia-specific mortality was 5.9% and 5.6%, respectively (difference, 0.3 [95% CI, −3.5 to

Table 5. Microbiological Eradication at Test of Cure (Microbiological Intent-to-Treat and Microbiologically Evaluable Analysis Sets)

Analysis Set Group	Ceftobiprole		Ceftazidime/Linezolid		Difference (%) ^a	(95% CI) ^b
	No.	n (%)	No.	n (%)		
Microbiological ITT						
All patients	269	105 (39.0)	267	127 (47.6)	−8.5	(−16.9 to −.2)
HAP (excluding VAP)	179	87 (48.6)	181	97 (53.6)	−5.0	(−15.3 to 5.3)
VAP	90	18 (20.0)	86	30 (34.9)	−14.9	(−27.9 to −1.9)
Microbiologically evaluable						
All patients	162	87 (53.7)	170	106 (62.4)	−8.6	(−19.2 to 1.9)
HAP (excluding VAP)	116	73 (62.9)	120	81 (67.5)	−4.6	(−16.7 to 7.6)
VAP	46	14 (30.4)	50	25 (50.0)	−19.6	(−38.8 to −0.4)

Abbreviations: CI, confidence interval; HAP, hospital-acquired pneumonia; ITT, intent-to-treat; n, number of patients with microbiological eradication at test of cure; VAP, ventilator-associated pneumonia.

^a Difference for ceftobiprole minus ceftazidime/linezolid.

^b Two-sided 95% CI is based on the normal approximation to the difference of the 2 proportions.

Table 6. Clinical Cure and Microbiological Eradication, by Pathogen (Microbiologically Evaluable Analysis Set)

Pathogen	HAP (excluding VAP), No. (%)		VAP, No. (%)		All Patients, No. (%)	
	Ceftobiprole (n = 116)	Ceftazidime/ Linezolid (n = 120)	Ceftobiprole (n = 46)	Ceftazidime/ Linezolid (n = 50)	Ceftobiprole (n = 162)	Ceftazidime/ Linezolid (n = 170)
<i>Staphylococcus aureus</i>	39	49	25	28	64	77
Clinical cure	28 (72)	36 (73)	9 (36)	16 (57)	37 (58)	52 (68)
Microbiological eradication	23 (59)	31 (63)	10 (40)	18 (64)	33 (52)	49 (64)
MSSA	20	30	17	19	37	49
Clinical cure	15 (75)	24 (80)	5 (29)	10 (53)	20 (54)	34 (69)
Microbiological eradication	15 (75)	21 (70)	5 (29)	12 (63)	20 (54)	33 (67)
MRSA	19	19	8	9	27	28
Clinical cure	13 (68)	12 (63)	4 (50)	6 (67)	17 (63)	18 (64)
Microbiological eradication	8 (42)	10 (53)	5 (63)	6 (67)	13 (48)	16 (57)
<i>Streptococcus pneumoniae</i>	7	14	4	1	11	15
Clinical cure	7 (100)	13 (93)	0 (0)	1 (100)	7 (64)	14 (93)
Microbiological eradication	7 (100)	13 (93)	0 (0)	1 (100)	7 (64)	14 (93)
Enterobacteriaceae	46^a	45^b	18	16	64	61
Clinical cure	33 (72)	32 (71)	5 (28)	6 (38)	38 (59)	38 (62)
Microbiological eradication	29 (63)	32 (71)	6 (33)	7 (44)	35 (55)	39 (64)
<i>Escherichia coli</i>	14	11	6	3	20	14
Clinical cure	8 (57)	7 (64)	2 (33)	1 (33)	10 (50)	8 (57)
Microbiological eradication	8 (57)	7 (64)	2 (33)	1 (33)	10 (50)	8 (57)
<i>Klebsiella pneumoniae</i>	12	19	4	4	16	23
Clinical cure	11 (92)	15 (79)	0 (0)	1 (25)	11 (69)	16 (70)
Microbiological eradication	10 (83)	15 (79)	0 (0)	1 (25)	10 (63)	16 (70)
<i>Enterobacter</i> species	9	7	3	2	12	9
Clinical cure	7 (78)	3 (43)	1 (33)	0 (0)	8 (75)	3 (33)
Microbiological eradication	6 (67)	3 (43)	2 (66)	0 (0)	8 (75)	3 (33)
<i>Proteus</i> species	5	5	2	5	7	10
Clinical cure	4 (80)	2 (40)	0 (0)	1 (20)	4 (57)	3 (30)
Microbiological eradication	3 (60)	2 (40)	0 (0)	2 (40)	3 (43)	4 (40)
<i>Serratia</i> species	5	4	3	3	8	7
Clinical cure	3 (60)	2 (50)	1 (33)	3 (100)	4 (50)	5 (71)
Microbiological eradication	2 (40)	2 (50)	1 (33)	3 (100)	3 (38)	5 (71)
<i>Pseudomonas aeruginosa</i>	16	20	11	14	27	34
Clinical cure	12 (75)	14 (70)	5 (45)	10 (71)	17 (63)	24 (71)
Microbiological eradication	9 (56)	11 (55)	4 (36)	8 (57)	13 (48)	19 (56)
<i>Acinetobacter baumannii</i>	8	12	6	5	14	17
Clinical cure	4 (50)	9 (75)	3 (50)	4 (80)	7 (50)	13 (77)
Microbiological eradication	4 (50)	9 (75)	3 (50)	3 (60)	7 (50)	12 (71)
<i>Haemophilus</i>	5	9	4	0	9	9
Clinical cure	2 (40)	9 (100)	1 (25)	na	3 (33)	9 (100)
Microbiological eradication	2 (40)	9 (100)	1 (25)	na	3 (33)	9 (100)

Numbers in bold refer to the number of patients with a pathogen in the respective group.

Abbreviations: HAP, hospital-acquired pneumonia; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; n, number of patients with an outcome of clinical cure or eradication for the respective pathogen at test of cure; VAP, ventilator-associated pneumonia.

^a Forty-six patients with Enterobacteriaceae isolated at baseline, including *E. coli* (monomicrobial), n = 11; *E. coli* plus *Klebsiella* spp, n = 1; *E. coli* plus *Proteus* spp, n = 1; *E. coli* plus *Providencia* spp, n = 1; *K. pneumoniae* (monomicrobial), n = 9; *Klebsiella oxytoca*, n = 1; *K. pneumoniae* plus *Proteus* spp, n = 1; *K. pneumoniae* plus *Serratia* spp, n = 1; *K. pneumoniae* plus *Enterobacter* spp, n = 1; *Enterobacter* spp, n = 8; *Serratia* spp, n = 5; *Proteus mirabilis*, n = 3; *Citrobacter* spp, n = 2; *Providencia* spp, n = 1.

^b Forty-five patients with Enterobacteriaceae isolated at baseline, including *E. coli* (monomicrobial), n = 8; *E. coli* plus *K. pneumoniae*, n = 1; *E. coli* plus *Proteus* spp, n = 1; *E. coli* plus *K. pneumoniae* plus *Serratia* spp, n = 1; *K. pneumoniae* (monomicrobial), n = 14; *Klebsiella oxytoca*, n = 1; *Klebsiella* spp, n = 2; *K. pneumoniae* plus *Proteus* spp, n = 2; *K. pneumoniae* plus *Proteus* spp plus *Serratia* spp, n = 1; *Enterobacter* spp, n = 7; *Serratia* spp, n = 2; *Proteus mirabilis*, n = 3; *Citrobacter* spp, n = 1; *Hafnia alvei*, n = 1.

Table 7. Treatment-Related Adverse Events Reported in $\geq 1\%$ of Patients in at Least 1 Treatment Group (Safety Analysis Set)

Adverse Event	Ceftobiprole (n = 386), No. (%)	Ceftazidime/ Linezolid (n = 386), No. (%)
Total No. of subjects with at least 1 related adverse event	96 (24.9)	98 (25.4)
Hyponatremia	17 (4.4)	10 (2.6)
Diarrhea	12 (3.1)	25 (6.5)
Nausea	8 (2.1)	8 (2.1)
Phlebitis	8 (2.1)	5 (1.3)
Oral candidiasis	6 (1.6)	4 (1.0)
Hypokalemia	6 (1.6)	3 (0.8)
Vomiting	6 (1.6)	3 (0.8)
Dysgeusia	5 (1.3)	0
Pyrexia	4 (1.0)	2 (0.5)
Rash	3 (0.8)	6 (1.6)
Alanine aminotransferase increased	3 (0.8)	6 (1.6)
Aspartate aminotransferase increased	3 (0.8)	4 (1.0)

4.1]). For VAP patients, 30-day ACM was 26.9% for ceftobiprole and 19.8% for ceftazidime/linezolid (difference, 7.1 [95% CI, -4.3 to 18.5]), and pneumonia-specific mortality was 8.7% and 7.5%, respectively (difference, 1.1 [95% CI, -6.3 to 8.5]).

Safety and Tolerability

Treatment-related AEs were reported for 96 ceftobiprole patients (24.9%) and 98 ceftazidime/linezolid patients (25.4%) (Table 7). Ceftobiprole patients had fewer treatment-related events of diarrhea than patients treated with ceftazidime/linezolid (3.1% and 6.5%, respectively), whereas hyponatremia was observed more frequently with ceftobiprole than with ceftazidime/linezolid (4.4% and 2.6%, respectively). Dysgeusia occurred only in patients treated with ceftobiprole (1.3%), as ceftobiprole medocartil is known to arouse a caramel taste. There were 15 treatment-related serious AEs reported for ceftobiprole (3.9%), and 12 (3.1%) for ceftazidime/linezolid. No clinically relevant differences in other laboratory values, vital signs, physical examinations, or electrocardiograms were observed between treatment groups.

DISCUSSION

The results of this large global study demonstrate that ceftobiprole is noninferior to ceftazidime plus linezolid for clinical cure at the TOC visit in treating patients with HAP. Noninferiority of ceftobiprole to ceftazidime/linezolid was also demonstrated in the large subgroup of HAP (excluding VAP) patients but not in the smaller subgroup of VAP patients. The overall

safety profile of ceftobiprole was consistent with that of other cephalosporins.

The population of this study was representative of nosocomial pneumonia patients in terms of age, underlying conditions, and severity of disease, which is reflected in the mortality rate of approximately 19% in the overall study population (17% in HAP [excluding VAP] and 23% in VAP) [30–33]. Patients in the study had a broad range of gram-positive and gram-negative bacteria typically causing HAP [3].

Differences in clinical cure and eradication rates by pathogen between treatment groups, with a tendency toward higher cure and eradication rates in the ceftazidime/linezolid group, were observed overall (all patients, see Table 6). However, for gram-positive pathogens and most of the gram-negative pathogens, these differences were driven by the inferior outcome of ceftobiprole in the subgroup of VAP patients. For pathogens in the larger group of HAP (excluding VAP) patients, clinical cure and microbiological eradication rates were similar for gram-positive pathogens and also most gram-negative pathogens. Analyses of clinical and microbiological outcome by baseline pathogen show comparable results between treatment groups for gram-positive pathogens, *E. coli*, *Klebsiella pneumoniae*, *Enterobacter* species, *Proteus mirabilis*, and *P. aeruginosa*. Only for *Acinetobacter baumannii* and *Haemophilus* species were numerically lower clinical cure and microbiological eradication rates observed in the ceftobiprole group, but this has to be interpreted with caution due to the small sample size.

Noninferiority of ceftobiprole compared with ceftazidime/linezolid was not demonstrated in VAP patients. The fact that clinical cure and mortality rates in mechanically ventilated HAP (excluding VAP) patients (ie, ventilated patients who did not have VAP) either favored ceftobiprole or were comparable to those for ceftazidime/linezolid suggests that mechanical ventilation itself does not account for the outcome in VAP patients. A multivariate analysis did not reveal any specific patient factors that could explain the differential outcome in VAP patients in both treatment arms. The substantial heterogeneity in baseline characteristics of VAP patients [34–36] is the most likely explanation for the differential outcome in VAP patients. Moreover, a population pharmacokinetic model showed that ceftobiprole plasma concentrations were sufficient for a targeted minimum inhibitory concentration of 4 mg/L in 92% of all patients, suggesting that plasma concentrations of ceftobiprole were also adequate in VAP patients [37].

In summary, ceftobiprole is a novel cephalosporin with broad-spectrum and bactericidal activity against gram-positive and gram-negative pathogens typically found in HAP, including MRSA and *P. aeruginosa*. This large, double-blind, randomized study demonstrates that ceftobiprole is noninferior to the combination of ceftazidime and linezolid, and is therefore a safe and effective monotherapy for the empiric treatment of HAP

(excluding VAP). Whether the early improvement observed in a higher proportion of HAP (excluding VAP) patients in the ceftobiprole group translates into additional benefits from the use of ceftobiprole requires further investigation.

Notes

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