ORIGINAL ARTICLE

Ceftobiprole for Treatment of Complicated *Staphylococcus aureus* Bacteremia

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ABSTRACT

BACKGROUND

Ceftobiprole is a cephalosporin that may be effective for treating complicated *Staphylococcus aureus* bacteremia, including methicillin-resistant *S. aureus*.

METHODS

In this phase 3, double-blind, double-dummy, noninferiority trial, adults with complicated *S. aureus* bacteremia were randomly assigned in a 1:1 ratio to receive ceftobiprole at a dose of 500 mg intravenously every 6 hours for 8 days and every 8 hours thereafter, or daptomycin at a dose of 6 to 10 mg per kilogram of body weight intravenously every 24 hours plus optional aztreonam (at the discretion of the trial-site investigators). The primary outcome, overall treatment success 70 days after randomization (defined as survival, bacteremia clearance, symptom improvement, no new *S. aureus* bacteremia–related complications, and no receipt of other potentially effective antibiotics), with a noninferiority margin of 15%, was adjudicated by a data review committee whose members were unaware of the trial-group assignments. Safety was also assessed.

RESULTS

Of 390 patients who underwent randomization, 387 (189 in the ceftobiprole group and 198 in the daptomycin group) had confirmed *S. aureus* bacteremia and received ceftobiprole or daptomycin (modified intention-to-treat population). A total of 132 of 189 patients (69.8%) in the ceftobiprole group and 136 of 198 patients (68.7%) in the daptomycin group had overall treatment success (adjusted difference, 2.0 percentage points; 95% confidence interval [CI], –7.1 to 11.1). Findings appeared to be consistent between the ceftobiprole and daptomycin groups in key subgroups and with respect to secondary outcomes, including mortality (9.0% and 9.1%, respectively; 95% CI, –6.2 to 5.2) and the percentage of patients with microbiologic eradication (82.0% and 77.3%; 95% CI, –2.9 to 13.0). Adverse events were reported in 121 of 191 patients (63.4%) who received ceftobiprole and 117 of 198 patients (59.1%) who received daptomycin; serious adverse events were reported in 36 patients (18.8%) and 45 patients (22.7%), respectively. Gastrointestinal adverse events (primarily mild nausea) were more frequent with ceftobiprole.

CONCLUSIONS

Ceftobiprole was noninferior to daptomycin with respect to overall treatment success in patients with complicated *S. aureus* bacteremia. (Funded by Basilea Pharmaceutica International and the U.S. Department of Health and Human Services; ERADICATE ClinicalTrials.gov number, NCT03138733.)

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*A list of the members of the ERADICATE Study Group is provided in the Supplementary Appendix, available at NEJM.org.

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Staphylococcus aureus bacteremia is common and frequently lethal.[1,2] Antibiotic treatment options are limited, particularly for patients with methicillin-resistant *S. aureus* (MRSA) infection.[3] The few randomized, controlled studies to inform treatment of *S. aureus* bacteremia[4] include one trial[5] that has provided support for regulatory approval (of daptomycin) for this indication.

Ceftobiprole, the active moiety of the prodrug ceftobiprole medocaril, is a cephalosporin with bactericidal activity against both MRSA and methicillin-susceptible *S. aureus* (MSSA).[6] Ceftobiprole has been shown to have efficacy in trials involving patients with pneumonia[6,7] and acute bacterial skin and skin-structure infections.[8] Here, we report the results of ERADICATE, a phase 3 trial comparing ceftobiprole with daptomycin in patients who had complicated *S. aureus* bacteremia, including those who had endocarditis on the right side of the heart.

Methods

Trial Design and Oversight

This double-blind, double-dummy, randomized, noninferiority trial was conducted at 60 sites in 17 countries from August 2018 through March 2022.[9] An institutional review board at each site approved the protocol, which is available with the full text of this article at NEJM.org. All the patients provided written informed consent. A data and safety monitoring board oversaw the trial.

Basilea Pharmaceutica International (one of the sponsors) designed and conducted the trial and prepared the statistical analysis plan with assistance from the first, penultimate, and last authors and with review by the Food and Drug Administration (FDA) under a special protocol assessment. Employees of Basilea Pharmaceutica International were directly involved in all aspects of the trial, including the trial design; data collection, analysis, and interpretation; and writing of the clinical trial report. All analyses of biologic material were performed in a blinded manner at independent laboratories. Several representatives of Basilea Pharmaceutica International participated in writing the manuscript, and medical writers who were paid by that sponsor assisted with preparation of a first draft of the manuscript. All the authors vouch for the integrity, completeness, and accuracy of the data and assume responsibility for the fidelity of the trial to the protocol and statistical analysis plan.

Patients

Eligible patients were at least 18 years of age and were hospitalized with *S. aureus* bacteremia confirmed by at least one positive blood culture obtained within 72 hours before randomization, with clinical evidence of complicated bacteremia. Complicated *S. aureus* bacteremia was defined as persistent *S. aureus* bacteremia (positive blood cultures despite receipt of appropriate antibiotics for ≥3 days before randomization); *S. aureus* bacteremia associated with long-term hemodialysis; or *S. aureus* bacteremia arising from soft-tissue infection, abdominal abscess, osteoarticular infection, septic thrombophlebitis, septic pulmonary embolus, epidural or cerebral abscess, or native-valve infective endocarditis on the right side of the heart (according to modified Duke criteria[10]). Transesophageal echocardiography (required) and other diagnostic evaluations performed within 7 days after randomization were used to establish the baseline diagnosis of complicated *S. aureus* bacteremia.

Exclusion criteria included unremovable endovascular prosthetic material, pneumonia, and receipt of potentially effective antibiotics for more than 48 hours within 7 days before randomization in the absence of persistent *S. aureus* bacteremia. Full inclusion and exclusion criteria are listed in the protocol and the Supplementary Appendix, available at NEJM.org.

To address a potential risk of seizure with prolonged ceftobiprole therapy, the FDA requested enrollment of an initial cohort (cohort 1) of 80 patients with a treatment duration of 21 to 28 days. After a prespecified interim safety analysis, enrollment was opened for new patients in a second cohort (cohort 2) with a treatment duration of 21 to 42 days. The treatment duration within these prespecified ranges was determined by the site investigators.

Trial Groups and Randomization

Eligible patients were randomly assigned in a 1:1 ratio to receive ceftobiprole at a dose of 500 mg intravenously every 6 hours during the first 8 days and every 8 hours thereafter, or daptomycin at a

dose of 6 mg per kilogram of body weight every 24 hours with the option to use doses up to 10 mg per kilogram, if consistent with institutional practice (Fig. 1). Patients in the ceftobiprole group received dummy infusions with placebo matching daptomycin, and vice versa. Aztreonam (for daptomycin-treated patients, with the dose determined at the discretion of the trial-site investigators) or matching placebo (for ceftobiprole-treated patients, to maintain blinding) could be added for coverage of gram-negative infections. Dose regimens in both trial groups were adjusted according to renal function. The sponsors, investigators, and trial personnel who were responsible for treatment administration and data collection were unaware of the trial-group assignments; an on-site pharmacist who was aware of the trial-group assignments prepared the trial treatments.

Two sets of peripheral-blood cultures were obtained at baseline, daily for the first 3 days after randomization, and every 48 to 72 hours thereafter until they were negative for *S. aureus* at two time points that were at least 24 hours apart. At least one post-treatment blood culture was obtained in the period between 7 days after the end-of-treatment visit and the post-treatment evaluation visit 70 days after randomization. The identification and antibiotic-susceptibility profile of pathogens isolated from the blood cultures were confirmed at a central laboratory (International Health Management Associates), and additional molecular-strain characterization of clonal types was performed at JMI Laboratories (see the Supplementary Appendix).

PRIMARY AND SECONDARY OUTCOMES

The primary efficacy outcome was overall treatment success at 70 days after randomization. Treatment success was defined as survival, symptom improvement, *S. aureus* bloodstream clearance, absence of new *S. aureus* bacteremia–related complications, and no use of other potentially effective antibiotics (Supplementary Appendix). Secondary efficacy outcomes included death from any cause, microbiologic eradication (clearance of *S. aureus* from blood cultures), overall treatment success at day 70 in the per-protocol population (see the Supplementary Appendix), development of new *S. aureus* bacteremia–related complications, and time to *S. aureus* bloodstream clearance. Safety was assessed on the basis of adverse events categorized according to incidence, type, severity, and relationship to ceftobiprole or daptomycin and on the basis of changes in results of laboratory tests.

STATISTICAL ANALYSIS

The intention-to-treat population included all the patients who had undergone randomization. For the primary analysis, the modified intention-to-treat population included all the patients who had undergone randomization and had received at least one dose of ceftobiprole or daptomycin and who had a confirmed baseline blood culture growing *S. aureus*. An independent data review committee of infectious diseases experts who were unaware of the trial-group assignments reviewed the data from each patient to determine the primary and key secondary outcomes (see the Supplementary Appendix). The safety population included all the patients who had undergone randomization and who had received at least one dose of ceftobiprole or daptomycin.

Assuming treatment success in 40% of the patients in both trial groups, a noninferiority margin of 15%, at least 80% power, and a one-sided alpha level of 0.025, we calculated that 350 patients would be required in the modified intention-to-treat population. We estimated that approximately 90% of the patients in the intention-to-treat population would have confirmed *S. aureus* bacteremia and would be included in the modified intention-to-treat population; therefore, the enrollment target was 390 patients.

The difference in treatment success (ceftobiprole group minus daptomycin group) was determined and a two-sided 95% confidence interval for the difference was computed with the use of the Cochran–Mantel–Haenszel weighting method, with adjustment for dialysis status and antibiotic use before randomization. If noninferiority was declared, then the difference was to be tested for superiority. Patients with missing outcome data were classified as having had treatment failure. No formal hypothesis testing was conducted for secondary or other outcomes, subgroups, or other analysis populations. The data and safety monitoring board reviewed unblinded data, including deaths, for safety. No adjustment of type I error was implemented for these safety reviews.

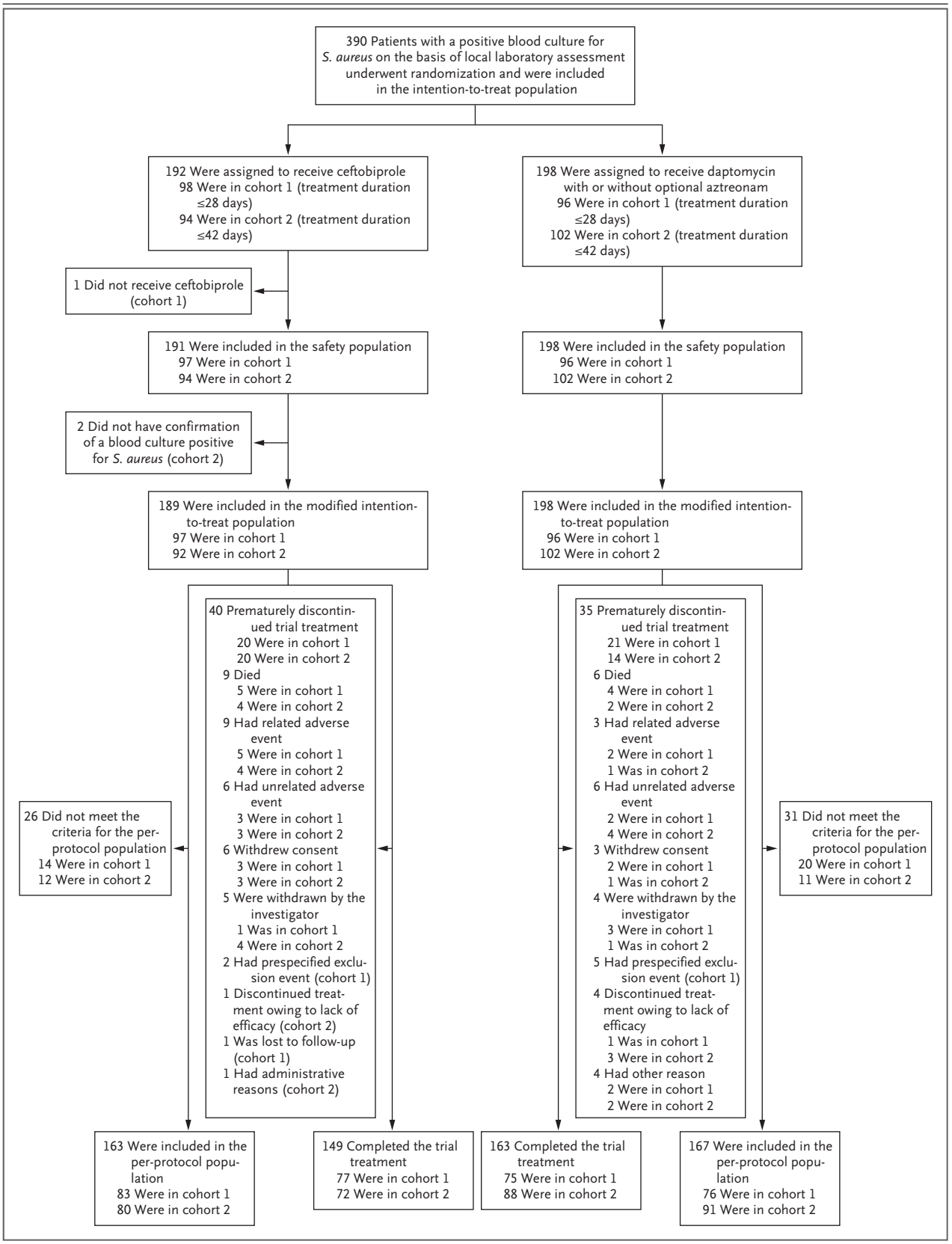
390 Patients with a positive blood culture for S. aureus on the basis of local laboratory assessment underwent randomization and were included in the intention-to-treat population
192 Were assigned to receive ceftobiprole
98 Were in cohort 1 (treatment duration ≤28 days)
94 Were in cohort 2 (treatment duration ≤42 days)
198 Were assigned to receive daptomycin with or without optional aztreonam
96 Were in cohort 1 (treatment duration ≤28 days)
102 Were in cohort 2 (treatment duration ≤42 days)
1 Did not receive ceftobiprole (cohort 1)
191 Were included in the safety population
97 Were in cohort 1
94 Were in cohort 2
198 Were included in the safety population
96 Were in cohort 1
102 Were in cohort 2
2 Did not have confirmation of a blood culture positive for S. aureus (cohort 2)
189 Were included in the modified intention-to-treat population
97 Were in cohort 1
92 Were in cohort 2
198 Were included in the modified intention-to-treat population
96 Were in cohort 1
102 Were in cohort 2
40 Prematurely discontinued trial treatment
20 Were in cohort 1
20 Were in cohort 2
9 Died
5 Were in cohort 1
4 Were in cohort 2
9 Had related adverse event
5 Were in cohort 1
4 Were in cohort 2
6 Had unrelated adverse event
3 Were in cohort 1
3 Were in cohort 2
6 Withdrew consent
3 Were in cohort 1
3 Were in cohort 2
5 Were withdrawn by the investigator
1 Was in cohort 1
4 Were in cohort 2
2 Had prespecified exclusion event (cohort 1)
1 Discontinued treatment owing to lack of efficacy (cohort 2)
1 Was lost to follow-up (cohort 1)
1 Had administrative reasons (cohort 2)
35 Prematurely discontinued trial treatment
21 Were in cohort 1
14 Were in cohort 2
6 Died
4 Were in cohort 1
2 Were in cohort 2
3 Had related adverse event
2 Were in cohort 1
1 Was in cohort 2
6 Had unrelated adverse event
2 Were in cohort 1
4 Were in cohort 2
3 Withdrew consent
2 Were in cohort 1
1 Was in cohort 2
4 Were withdrawn by the investigator
3 Were in cohort 1
1 Was in cohort 2
5 Had prespecified exclusion event (cohort 1)
4 Discontinued treatment owing to lack of efficacy
1 Was in cohort 1
3 Were in cohort 2
4 Had other reason
2 Were in cohort 1
2 Were in cohort 2
26 Did not meet the criteria for the per-protocol population
14 Were in cohort 1
12 Were in cohort 2
31 Did not meet the criteria for the per-protocol population
20 Were in cohort 1
11 Were in cohort 2
163 Were included in the per-protocol population
83 Were in cohort 1
80 Were in cohort 2
149 Completed the trial treatment
77 Were in cohort 1
72 Were in cohort 2
163 Completed the trial treatment
75 Were in cohort 1
88 Were in cohort 2
167 Were included in the per-protocol population
76 Were in cohort 1
91 Were in cohort 2

Figure 1 (facing page). Randomization and Treatment.
Among the patients assigned to receive ceftobiprole who were categorized as not having confirmation of a blood culture positive for *Staphylococcus aureus*, two patients had a positive blood culture for *S. aureus* according to local microbiologic assessment, but the central microbiologic assessment showed coagulase-negative staphylococcus or *Brevibacterium casei*.

RESULTS

TRIAL PATIENTS

Between August 29, 2018, and March 11, 2022, a total of 390 patients at 60 sites in 17 countries were enrolled, with the majority of patients enrolled in Eastern Europe (Fig. 1, and Table S1 in the Supplementary Appendix); 194 were enrolled into cohort 1 and 196 were enrolled into cohort 2 (maximum treatment durations of 28 and 42 days, respectively). The modified intention-to-treat population included 387 patients. All the patients had confirmed complicated *S. aureus* bacteremia and received ceftobiprole (189 patients) or daptomycin (198 patients).

PATIENT CHARACTERISTICS

Baseline characteristics and prespecified risk factors for *S. aureus* bacteremia or infective endocarditis were balanced between the two trial groups (Table 1). The overall trial population was generally representative of patients with *S. aureus* bacteremia (Table S2).

The median duration of treatment was 21 days in each group (interquartile range, 21 to 25 in the ceftobiprole group and 21 to 23 in the daptomycin group); the duration according to the category of complicated *S. aureus* bacteremia is shown in Table S3. Aztreonam was used in 41.4% of daptomycin-treated patients (in 31.3% at baseline) for a median of 8.0 days; a similar percentage of patients in the ceftobiprole group received matching placebo. The median daptomycin dose was 6.1 mg per kilogram per day; overall, 22 of 198 patients (11.1%) received a daptomycin dose higher than 7.0 mg per kilogram per day.

Among the 387 patients in the modified intention-to-treat population, complicated *S. aureus* bacteremia was related to soft-tissue infection in 237 (61.2%), osteoarticular infection in 67 (17.3%), hemodialysis in 49 (12.7%), and endocarditis on the right side of the heart in 25 (6.5%). Seven patients (5 in the daptomycin group and 2 in the ceftobiprole group) in cohort 1 received a diagnosis of endocarditis on the left side of the heart after randomization and were withdrawn from the trial in accordance with the protocol. Three patients in cohort 2 received a diagnosis of endocarditis on the left side of the heart in the first week after randomization; all were retained in the trial at the discretion of the site investigators (Table S4). A total of 94 patients in the modified intention-to-treat population (24.3%) had complicated MRSA bacteremia (45 in the ceftobiprole group and 49 in the daptomycin group) (Table 1). The minimum inhibitory concentration (MIC) of ceftobiprole was higher for MRSA (0.5 to 2 mg per liter) than for MSSA (0.12 to 1 mg per liter); however, all tested baseline MRSA isolates were susceptible to both ceftobiprole and daptomycin (Fig. S1).

EFFICACY OUTCOMES

A total of 132 of 189 patients (69.8%) in the ceftobiprole group and 136 of 198 patients (68.7%) in the daptomycin group had overall treatment success (adjusted difference, 2.0 percentage points; 95% confidence interval [CI], –7.1 to 11.1) (Table 2). The lower boundary of the 95% confidence interval was –7.1%, which was greater than the prespecified margin of –15%, findings that showed the noninferiority of ceftobiprole to daptomycin. The superiority of ceftobiprole over daptomycin was not achieved. Differences in treatment success were similar across prespecified secondary analyses (Table 2).

The reasons for treatment failure, as determined by the data review committee, were similar in the two trial groups (Table S6). There were 17 deaths in the ceftobiprole group and 18 deaths in the daptomycin group (mortality, 9.0% and 9.1%; adjusted difference, –0.5 percentage points; 95% CI, –6.2 to 5.2). Of these deaths, 7 in the ceftobiprole group and 6 in the daptomycin group were attributed by the data review committee to *S. aureus* bacteremia.

In total, 155 of 189 patients (82.0%) had microbiologic eradication in the ceftobiprole group, as compared with 153 of 198 patients (77.3%) in the daptomycin group (adjusted difference, 5.1 percentage points; 95% CI, –2.9 to 13.0). The time to *S. aureus* bloodstream clearance was the same in both groups (median, 4 days; 95% CI, 3 to 5). New metastatic foci or other complications of *S. aureus* bacteremia were diagnosed in

Table 1. Characteristics of the Patients at Baseline (Modified Intention-to-Treat Population).*

Characteristic	Ceftobiprole (N=189)	Daptomycin (N=198)	Overall (N=387)
Age — yr			
Median	57.0	58.0	58.0
Range	20–89	19–91	19–91
Male sex — no. (%)	128 (67.7)	140 (70.7)	268 (69.3)
Race or ethnic group — no. (%)†			
White	179 (94.7)	192 (97.0)	371 (95.9)
Black	4 (2.1)	5 (2.5)	9 (2.3)
Other race	6 (3.2)	1 (0.5)	7 (1.8)
Hispanic or Latino	14 (7.4)	15 (7.6)	29 (7.5)
Body-mass index‡	27.2±5.5	28.1±6.2	27.6±5.9
Geographic region — no. (%)			
Europe	175 (92.6)	185 (93.4)	360 (93.0)
Latin America or South Africa	9 (4.8)	8 (4.0)	17 (4.4)
North America	5 (2.6)	5 (2.5)	10 (2.6)
Median duration of administration of ceftobiprole or daptomycin (IQR) — days	21 (21–25)	21 (21–23)	21 (21–24)
Receipt of daptomycin at a daily dose >7 mg/kg — no. (%)	NA	22 (11.1)	
Receipt of aztreonam or matching placebo§	69 (36.5)	62 (31.3)	131 (33.9)
Use of systemic antibiotics ≤7 days before randomization — no. (%)¶	139 (73.5)	134 (67.7)	273 (70.5)
Echocardiography performed on or before day 7 — no. (%)	188 (99.5)	197 (99.5)	385 (99.5)
Transthoracic echocardiography	173 (91.5)	184 (92.9)	357 (92.2)
Transesophageal echocardiography	146 (77.2)	149 (75.3)	295 (76.2)
Risk factors for *S. aureus* bacteremia or infective endocarditis — no. (%)			
Surgery in preceding 30 days	73 (38.6)	83 (41.9)	156 (40.3)
Diabetes mellitus	69 (36.5)	66 (33.3)	135 (34.9)
Trauma in preceding 30 days	24 (12.7)	13 (6.6)	37 (9.6)
History of injection-drug use	13 (6.9)	10 (5.1)	23 (5.9)
Chronic liver disease	7 (3.7)	5 (2.5)	12 (3.1)
History of *S. aureus* infection within past 12 mo	5 (2.6)	7 (3.5)	12 (3.1)
Immunosuppressed condition	7 (3.7)	3 (1.5)	10 (2.6)
History of preexisting or acquired valvular heart disease	4 (2.1)	2 (1.0)	6 (1.6)
Categories of complicated *S. aureus* bacteremia — no. (%)‖			
Any complicated *S. aureus* bacteremia	189 (100.0)	198 (100.0)	387 (100.0)
Soft-tissue infections**	116 (61.4)	121 (61.1)	237 (61.2)
Osteoarticular infections††	32 (16.9)	35 (17.7)	67 (17.3)
Abdominal abscesses‡‡	26 (13.8)	29 (14.6)	55 (14.2)
Hemodialysis-associated *S. aureus* bacteremia§§	24 (12.7)	25 (12.6)	49 (12.7)
Persistent *S. aureus* bacteremia¶¶	16 (8.5)	16 (8.1)	32 (8.3)
Infective endocarditis on right side of heart	15 (7.9)	10 (5.1)	25 (6.5)
Estimated creatinine clearance <50 ml/min, excluding dialysis patients — no. (%)	17 (9.0)	14 (7.1)	31 (8.0)
Methicillin-resistant *S. aureus* bacteremia	45 (23.8)	49 (24.7)	94 (24.3)

Table 1. (Continued.)

* Plus–minus values are means ±SD. The modified intention-to-treat population included all the patients with a blood culture positive for *Staphylococcus aureus* at baseline who received any amount of ceftobiprole or daptomycin. IQR denotes interquartile range.
† Race and ethnic group were reported by the patients. In the "other race" category, race was missing for 1 patient in the ceftobiprole group. Ethnic group was not reported for 1 patient in each trial group.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters. Body-mass index was missing for 2 patients in the ceftobiprole group.
§ A total of 82 patients (43.4%) in the ceftobiprole group received matching placebo and 82 patients (41.4%) in the daptomycin group received aztreonam at any time.
¶ This category includes the use of systemic antibiotics other than aztreonam. The most frequent previously used antibiotics were third-generation cephalosporins (mainly ceftriaxone and ceftazidime, in 109 patients overall [28.2%]), glycopeptides (mainly vancomycin, in 65 patients [16.8%]) and combinations of β-lactam antibiotics with β-lactamase inhibitors (in 48 patients [12.4%]). Eight patients in the ceftobiprole group (4.2%) and 10 patients in the daptomycin group (5.1%) received potentially effective systemic antibacterial treatment for more than 48 hours within the 7 days before randomization.
‖ Categories of complicated *S. aureus* bacteremia were determined by the trial investigators, except for persistent *S. aureus* bacteremia, which was determined by the independent data review committee and was defined as failure of bloodstream clearance, based on at least one positive blood culture for *S. aureus* within the 72 hours before randomization, after previous appropriate antistaphylococcal treatment for at least 3 complete days. All enrolled patients had confirmed complicated *S. aureus* bacteremia.
** This category includes 70 patients with phlegmon, 56 with wound or ulcer, 39 with abscess, 28 with cellulitis or erysipelas, 13 with anorectal infections, 11 with deep neck-space infections, 8 with gangrene in the leg, and 10 with other soft-tissue infections. Necrotizing fasciitis was reported in 7 patients (5 with wound infections or phlegmons and 2 with no other soft-tissue infection).
†† This category includes 41 patients with septic arthritis and 30 patients with osteomyelitis.
‡‡ This category includes psoas abscess (in 18 patients), hepatic abscess (in 12 patients), pancreatic or omental abscess (in 11 patients), and other abdominal abscesses such as pelvic abscess or renal abscess (in 15 patients); 1 patient had two abscess locations (hepatic and other).
§§ Patients receiving peritoneal dialysis were also eligible to participate in the trial; however, none were enrolled.
¶¶ Persistent *S. aureus* bacteremia was defined as failure of bloodstream clearance, with a positive blood culture for *S. aureus* within the 72 hours before randomization, after previous appropriate antistaphylococcal treatment (except treatment failure with daptomycin therapy) for at least 3 complete days, as assessed by the data review committee.

11 of 189 patients (5.8%) in the ceftobiprole group and 11 of 198 patients (5.6%) in the daptomycin group (adjusted difference, 0.1 percentage points; 95% CI, −4.6 to 4.8). The data review committee adjudicated relapse of *S. aureus* bacteremia in 2 patients in the ceftobiprole group and 4 patients in the daptomycin group before the availability of bacterial genotypic data. Subsequent genotyping of paired bacterial isolates showed reinfection (with a different *S. aureus* strain) in both ceftobiprole-treated patients and relapse (with the same *S. aureus* strain) in all 3 daptomycin-treated patients for whom paired isolates were available. Resistance that developed during treatment with increases of at least a factor of 4 in the MIC was observed in 3 patients who received daptomycin (2 of whom had MSSA infection and 1 of whom had MRSA infection); 1 of these patients also had relapse. No resistance that developed during treatment was observed in the ceftobiprole group.

SAFETY OUTCOMES

There were similar frequencies of adverse events in patients receiving ceftobiprole (121 of 191 patients [63.4%]) and those receiving daptomycin (117 of 198 patients [59.1%]) (Table 3, Table S7, and Table S8). Adverse events that were considered by the investigators to be related to ceftobiprole or daptomycin were more common with ceftobiprole (25 of 191 patients [13.1%] than with daptomycin (11 of 198 patients [5.6%]), with a higher incidence of gastrointestinal disorders in the ceftobiprole group (in 18 of 191 patients [9.4%] vs. 3 of 198 patients [1.5%]). More patients in the ceftobiprole group than in the daptomycin group had hypokalemia (17 of 191 patients [8.9%] vs. 5 of 198 patients [2.5%]). Serious adverse events were reported in 36 of 191 patients (18.8%) in the ceftobiprole group and 45 of 198 patients (22.7%) in the daptomycin group. Of these serious adverse events, the investigator attributed few to ceftobiprole (2 of 191 patients [1.0%]) or daptomycin (4 of 198 patients [2.0%]).

Among the patients in the ceftobiprole group who discontinued that agent owing to drug-related adverse events (9 of 191 patients [4.7%]), the most common reasons for discontinuation were allergic events (in 4 patients) and gastroin-

Table 2. Primary and Secondary Efficacy Outcomes (Modified Intention-to-Treat Population).*

Treatment Success or Failure and Secondary Outcomes	Ceftobiprole \(N=189)	Daptomycin (N=198)	Adjusted Treatment Difference (95% CI)†
	no. of patients/total no. (%)		*percentage points*
Primary outcome			
Overall treatment success at the post-treatment evaluation visit	132 (69.8)	136 (68.7)	2.0 (–7.1 to 11.1)
Reason for treatment failure‡			
Any treatment failure	57 (30.2)	62 (31.3)	
Discontinuation owing to lack of efficacy	9 (4.8)	10 (5.1)	
New or worsening *S. aureus* complications§	11 (5.8)	11 (5.6)	
Relapse of *S. aureus* bacteremia	2 (1.1)	4 (2.0)	
Use of nontrial antibiotics for *S. aureus* bacteremia	20 (10.6)	19 (9.6)	
Use of nontrial antibiotics for other indication	11 (5.8)	13 (6.6)	
Death	17 (9.0)	18 (9.1)	
Missing data to determine outcome¶	16 (8.5)	17 (8.6)	
Use of antibiotic treatment beyond trial-specified duration	9 (4.8)	15 (7.6)	
Secondary outcomes‖			
Death through the post-treatment evaluation visit	17 (9.0)	18 (9.1)	–0.5 (–6.2 to 5.2)
Death due to *S. aureus* bacteremia	7 (3.7)	6 (3.0)	
Microbiologic eradication at the post-treatment evaluation visit	155 (82.0)	153 (77.3)	5.1 (–2.9 to 13.0)
Overall treatment success at the post-treatment evaluation visit in the per-protocol population**	127/163 (77.9)	130/167 (77.8)	0.6 (–8.3 to 9.5)
Development of new metastatic foci or other complications of *S. aureus* bacteremia after day 7	11 (5.8)	11 (5.6)	0.1 (–4.6 to 4.8)
Median time to *S. aureus* bloodstream clearance — days (95% CI)††	4 (3 to 5)	4 (3 to 5)	

* Overall treatment success (the primary outcome) was defined as survival, symptom improvement, *S. aureus* bloodstream clearance, no new *S. aureus* bacteremia complications, and no use of other potentially effective antibiotics. Results for overall treatment success in the intention-to-treat population are shown in Table S5.

† Shown are between-group differences for ceftobiprole minus daptomycin (with or without aztreonam). Confidence intervals were calculated with the use of a Cochran–Mantel–Haenszel weighting method adjusted for actual stratum (dialysis status and previous use of antibacterial treatment). Formal hypothesis testing was performed only for the primary outcome in the modified intention-to-treat analysis. Confidence intervals for secondary outcomes should not be used to reject or not reject the null hypothesis of a treatment effect.

‡ Overall treatment success was assessed by the independent data review committee. Patients whose outcomes were not adjudicated as treatment success were assigned the applicable reason or reasons for treatment failure from the eight possibilities listed.

§ This category included the following new or worsening complications in the ceftobiprole group: epidural abscess (in 2 patients), gangrene (in 2 patients), renal or perirenal abscess (in 2 patients); and mediastinitis, osteomyelitis, phlegmon (femur), psoas abscess, or recurrent skin infection (in 1 patient each). This category included the following new or worsening complications in the daptomycin group: osteomyelitis (in 6 patients); infective endocarditis on the left side of the heart (in 2 patients); and bursitis, epidural abscess, or progressive arthritis (in 1 patient each).

¶ "Missing data to determine outcome" was defined as missing information to determine treatment success or failure, including a missing post-treatment evaluation visit or other missing key data to evaluate the primary outcome, loss to follow-up, early withdrawal of consent, or missing blood cultures in the period between 7 days after the end-of-treatment visit and the post-treatment evaluation visit.

‖ All secondary outcomes were evaluated by the independent data review committee, except for time to *S. aureus* bloodstream clearance, which was calculated with the use of a programmed algorithm.

** The per-protocol population consisted of patients in the modified intention-to-treat population who had complied with important aspects of the trial, including no major protocol deviations and no receipt of potentially effective systemic antibacterial treatment for more than 48 hours within 7 days before randomization and no missing outcome data for the primary outcome.

†† Bloodstream clearance was defined as two consecutive blood cultures that were negative for *S. aureus*, obtained at least 1 trial day apart, without any subsequent *S. aureus* relapse or reinfection according to assessment by the data review committee. The first day with a negative blood culture or negative blood cultures was used for calculating the time from randomization to bloodstream clearance. Data on patients without bloodstream clearance were censored at the last trial visit.

Table 3. Adverse Events Occurring during Treatment (Safety Population).*

Event	Ceftobiprole (N=191)	Daptomycin (N=198)
	number (percent)	
Any adverse event	121 (63.4)	117 (59.1)
Any drug-related adverse event†	25 (13.1)	11 (5.6)
Severe adverse event	29 (15.2)	38 (19.2)
Any drug-related severe adverse event†	1 (0.5)	2 (1.0)
Serious adverse event	36 (18.8)	45 (22.7)
Any drug-related serious adverse event†	2 (1.0)	4 (2.0)
Adverse event leading to discontinuation of ceftobiprole or daptomycin	18 (9.4)	18 (9.1)
Any drug-related adverse event leading to discontinuation of ceftobiprole or daptomycin†	9 (4.7)	3 (1.5)
Ceftobiprole- or daptomycin-related adverse events occurring in >1% of patients in either group, according to preferred term‡		
Diarrhea	8 (4.2)	2 (1.0)
Nausea	10 (5.2)	0
Vomiting	6 (3.1)	1 (0.5)
Upper abdominal pain	2 (1.0)	0
Dysgeusia	2 (1.0)	0
Allergic dermatitis	2 (1.0)	0
Acute eosinophilic pneumonia	0	2 (1.0)
Urticaria	2 (1.0)	0

* All adverse events that occurred in at least one patient are listed according to system organ class and preferred term in Table S8. The safety population included all the patients who had received any amount of ceftobiprole or daptomycin. Adverse events that occurred during treatment include those with an onset date and time on or after the date and time of the first dose of ceftobiprole or daptomycin up to the last follow-up visit. Patients with multiple adverse events were counted once for each adverse-event category and preferred term.

† Relatedness to ceftobiprole or daptomycin was assessed by the investigators, who were unaware of the trial-group assignments.

‡ No *Clostridioides difficile*–associated adverse events were reported in either group. Three patients in the ceftobiprole group had seizures (one that was determined by the investigators to be related to the ceftobiprole), and two patients in the daptomycin group had seizures that were determined by the investigators to be unrelated to daptomycin.

testinal events (in 3 patients). In contrast, daptomycin-related discontinuations, observed in 3 of 198 patients (1.5%), were due to eosinophilic pneumonia (in 2 patients) and myopathy (in 1 patient). Three patients had seizures in the ceftobiprole group (one seizure was considered by the investigators to be related to ceftobiprole), as compared with two seizures in the daptomycin group (both considered to be unrelated to daptomycin) (Table S9).

BACTERIAL GENOTYPE AND OUTCOME

Bacterial clonal types did not differ meaningfully between the trial groups (Table S10). No relationship between ceftobiprole or daptomycin MICs for *S. aureus* and patient outcomes was observed in either trial group.

SUBGROUP ANALYSES

In subgroup analyses of the primary outcome in patients with MRSA or MSSA infection, those with or without previous antibiotic treatment, and those within the same baseline category of complicated *S. aureus* bacteremia, findings appeared to be consistent between the trial groups (Fig. 2). Among patients with MSSA, *S. aureus* bloodstream clearance appeared to be consistent between the trial groups (133 of 141 patients in

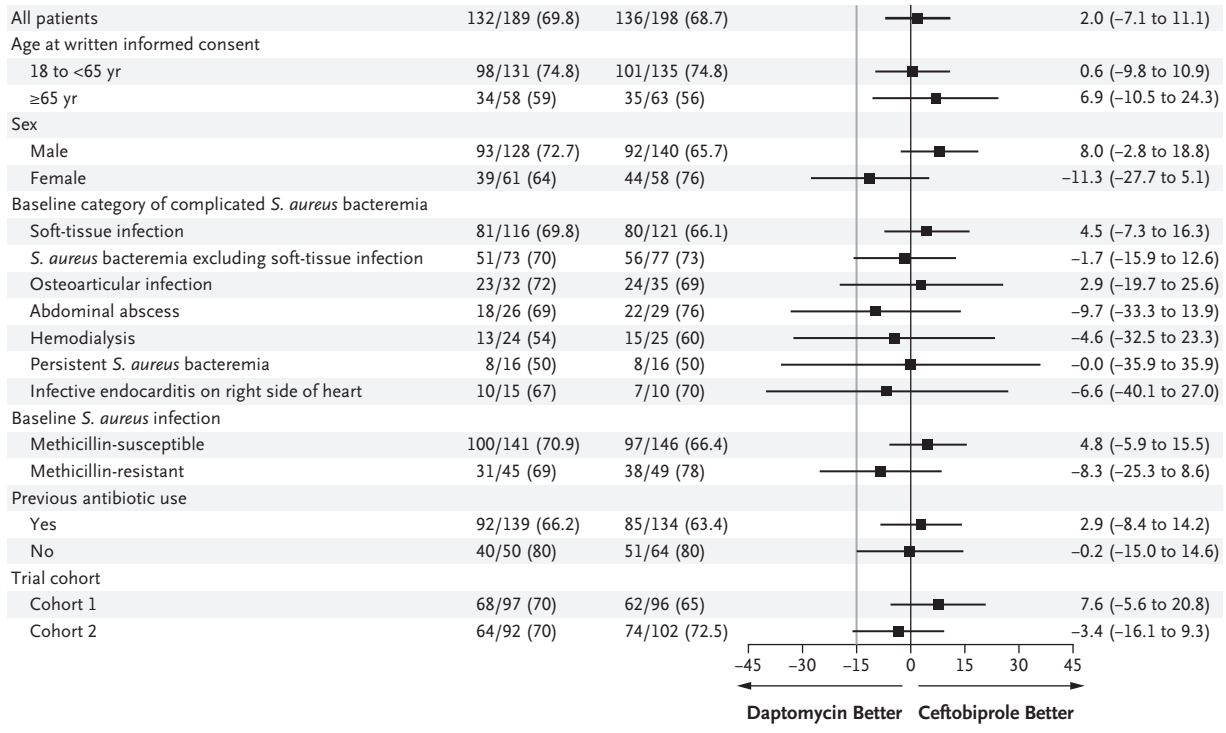

Figure 2. Overall Treatment Success at the Post-Baseline Evaluation Visit, According to Patient Characteristics at Baseline (Modified Intention-to-Treat Analysis Population).

The percentage-point difference is the between-group difference of ceftobiprole minus daptomycin with or without aztreonam, adjusted for actual stratum (dialysis status and previous use of antibacterial treatment) with the use of the Cochran–Mantel–Haenszel weights method. "Previous antibiotic use" is potentially effective antibiotic treatment for *S. aureus* within 7 days before randomization.

the ceftobiprole group [94.3%] at a median of 3 days from the time of randomization and 139 of 146 patients in the daptomycin group [95.2%] at a median of 4 days). In patients with MRSA infection, clearance occurred at a median of 5 days in 42 of 45 patients (93%) in the ceftobiprole group and 43 of 49 patients (88%) in the daptomycin group (Fig. S2). The percentage of patients with overall treatment success was not higher among patients who received daptomycin doses above 7 mg per kilogram (36% treatment success) than among those who received the standard dose (73% treatment success) (Table S11).

DISCUSSION

In this double-blind trial involving patients with complicated *S. aureus* bacteremia, ceftobiprole was noninferior to daptomycin with respect to overall treatment success. These findings remained consistent among key subgroups, including patients with either MRSA or MSSA infection. In addition, microbiologic eradication, relapse of bacteremia, and new or worsening *S. aureus* bacteremia complications were similar in the two trial groups, findings that further indicate that ceftobiprole was not less effective than daptomycin.

The only previous approval of a new antibiotic (daptomycin) for *S. aureus* bacteremia occurred more than 15 years ago.[5] The current trial differs from the daptomycin registrational trial in several important ways, including the use of a double-blind trial design, a smaller noninferiority margin, and a larger sample size.[5] The percentage of patients with overall treatment success in both trial groups was higher in the current trial than in the daptomycin trial. This

difference may be due to a lower incidence of administrative failures (including those related to the use of potentially effective nontrial antibiotics), a longer median duration of therapy (21 days vs. 14 days), and more aggressive source control in the current trial, as well as potential improvements in clinical practice.[2]

Although our trial was not powered for subgroup evaluations, the results with respect to patients with MRSA infection warrant attention because this is the most likely pathogen for which ceftobiprole will be used. MRSA strains had phenotypically higher ceftobiprole MICs than MSSA strains, a difference that was anticipated from surveillance data.[11] However, the ceftobiprole MICs for all isolates were 2 mg per liter or lower and were covered by the ceftobiprole dose used. The point estimate for the adjusted difference in treatment success was lower for MRSA than for MSSA. Considering the small number of treatment failures in patients with MRSA bacteremia (14 in the ceftobiprole group and 11 in the daptomycin group), this discrepancy could be attributed to random variation. It is notable that patients with MRSA bacteremia in the ceftobiprole and daptomycin groups had similar microbiologic-specific outcomes (time to blood culture clearance, incidence of microbiologic eradication, relapse, and new *S. aureus* bacteremia–related complications). In addition, no major difference in efficacy according to MRSA or MSSA subgroups was observed in other phase 3 trials of ceftobiprole (Table S12).[6-8]

The strengths of this trial include the fact that it was a large trial for *S. aureus* bacteremia and used an active double-blind design to minimize the risk of bias. In addition, there was a standardized diagnostic evaluation including transesophageal echocardiography in 76% of the patients and detailed attention to outcome ascertainment by a data review committee whose members were unaware of the trial-group assignments. Furthermore, the results were consistent across all secondary outcomes and in key subgroups.

Our trial has limitations. Approximately one quarter of the patients had MRSA infection, so definitive conclusions about efficacy in this subgroup were precluded. Because more than 80% of the patients who were enrolled in the trial were in Eastern Europe, most trial patients were White. However, the results are probably generalizable to patients in the United States for four reasons. First, the *S. aureus* clonal types in this trial are similar to those found in the United States. Second, Black and White patients with *S. aureus* bacteremia have similar clinical outcomes despite differences in underlying risk factors.[12] Third, more than 12% of the enrolled population in the current trial were receiving hemodialysis, which is a major risk factor for *S. aureus* bacteremia and an important contributor to racial and ethnic disparities in infection.[13] Finally, outcomes were similar among White and non-White populations in previous phase 3 trials of ceftobiprole.[6-8]

Daptomycin was primarily administered at the FDA-approved dose of 6 mg per kilogram per day, which is lower than the dose sometimes used in clinical practice. However, higher doses of daptomycin were not associated with better patient outcomes. More than half the enrolled patients with *S. aureus* bacteremia had soft-tissue infections, which may be associated with a more favorable prognosis than other forms of complicated *S. aureus* bacteremia. Soft-tissue infections in this trial included severe manifestations such as necrotizing fasciitis. Furthermore, the overall outcomes in patients with *S. aureus* bacteremia due to soft-tissue infections were similar to those in patients with other types of complicated bacteremia.

Ceftobiprole was noninferior to daptomycin for the treatment of *S. aureus* bacteremia. The results of this double-blind trial show that ceftobiprole may be a useful treatment option for patients with complicated *S. aureus* bacteremia, including infective endocarditis on the right side of the heart, caused by either MSSA or MRSA.

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APPENDIX

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