

Ceftobiprole Compared With Vancomycin Plus Aztreonam in the Treatment of Acute Bacterial Skin and Skin Structure Infections: Results of a Phase 3, Randomized, Double-blind Trial (TARGET)

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Background. The development of novel broad-spectrum antibiotics, with efficacy against both gram-positive and gram-negative bacteria, has the potential to enhance treatment options for acute bacterial skin and skin structure infections (ABSSSIs). Ceftobiprole is an advanced-generation intravenous cephalosporin with broad in vitro activity against gram-positive (including methicillin-resistant *Staphylococcus aureus*) and gram-negative pathogens.

Methods. TARGET was a randomized, double-blind, active-controlled, parallel-group, multicenter, phase 3 noninferiority study that compared ceftobiprole with vancomycin plus aztreonam. The Food and Drug Administration-defined primary efficacy endpoint was early clinical response 48–72 hours after treatment initiation in the intent-to-treat (ITT) population and the European Medicines Agency-defined primary endpoint was investigator-assessed clinical success at the test-of-cure (TOC) visit. Noninferiority was defined as the lower limit of the 95% CI for the difference in success rates (ceftobiprole minus vancomycin/aztreonam) >–10%. Safety was assessed through adverse event and laboratory data collection.

Results. In total, 679 patients were randomized to ceftobiprole (n = 335) or vancomycin/aztreonam (n = 344). Early clinical success rates were 91.3% and 88.1% in the ceftobiprole and vancomycin/aztreonam groups, respectively, and noninferiority was demonstrated (adjusted difference: 3.3%; 95% CI: –1.2, 7.8). Investigator-assessed clinical success at the TOC visit was similar between the 2 groups, and noninferiority was demonstrated for both the ITT (90.1% vs 89.0%) and clinically evaluable (97.9% vs 95.2%) populations. Both treatment groups displayed similar microbiological success and safety profiles.

Conclusions. TARGET demonstrated that ceftobiprole is noninferior to vancomycin/aztreonam in the treatment of ABSSSIs, in terms of early clinical response and investigator-assessed clinical success at the TOC visit.

Clinical Trials Registration. NCT03137173.

Keywords. ceftobiprole; bacterial skin infections; ABSSSI.

Acute bacterial skin and skin structure infections (ABSSSIs) include wound infections, cellulitis/erysipelas, and major cutaneous abscesses [1]. Epidemiological studies suggest increasing incidence in recent decades [2, 3], and in 2011, ABSSSIs were estimated to be responsible for over 750 000 hospitalizations in the United States [2]. ABSSSIs exert considerable burden on both patients and healthcare systems, with an average cost per

hospital admission of \$6400 in the United States in 2014, and an average length of stay of 4 days [4].

Although the causative pathogen in ABSSSIs is not always identified, gram-positive bacteria, particularly *Staphylococcus aureus*, account for the majority of cases, and a rise in the prevalence of methicillin-resistant *S. aureus* (MRSA) infections has been reported in recent decades [3, 5, 6]. Gram-negative infections occur less frequently, but can be challenging to treat, particularly given that empiric treatment typically targets gram-positive bacteria [3, 5].

The development of novel, broad-spectrum antibiotics with efficacy against both gram-positive and gram-negative bacteria has the potential to enhance treatment options for ABSSSIs [5]. Ceftobiprole, the active moiety of the pro-drug ceftobiprole medocartil, is an advanced-generation intravenous (IV) cephalosporin with broad activity in vitro against gram-positive (including MRSA) and gram-negative pathogens [7], and is

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approved in many European and several non-European countries for the treatment of hospital-acquired (excluding ventilator-associated) and community-acquired pneumonia in adults [8].

To evaluate the potential utility of ceftobiprole in patients with ABSSSIs, the present study assessed the efficacy and safety of ceftobiprole compared with a regimen of vancomycin plus aztreonam in hospitalized patients. This is 1 of 2 pivotal studies conducted to support a New Drug Application for ceftobiprole in the United States; the second study is in *S. aureus* bacteremia (ClinicalTrials.gov trial identifier NCT03138773).

METHODS

Study Design

This was a randomized, double-blind, active-controlled, parallel-group, multicenter, phase 3 noninferiority study of ceftobiprole compared with vancomycin plus aztreonam in the treatment of ABSSSIs (ClinicalTrials.gov trial identifier NCT03137173; EudraCT number 2017-001605-32). The study was performed in accordance with US Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidelines for the development of novel antibacterial agents [1, 9].

The trial was conducted in compliance with applicable laws and regulations, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice guidelines and the Declaration of Helsinki, and the protocol was approved by the relevant independent ethics committees/institutional review boards. An independent data safety monitoring board performed safety assessments. Written informed consent was required prior to the conduct of any study procedures.

Participants

The study was conducted at 32 sites in the United States, Bulgaria, Hungary, and Ukraine (see [Supplementary Appendix 1](#) for a list of the investigators), and enrolled hospitalized patients aged 18 years or older, with a diagnosis of ABSSSI, who required IV antibacterial treatment, and had at least 1 of the following: wound infection, cellulitis or erysipelas, or major cutaneous abscess (restricted to 30% or less of the study population). Patients were also required to have at least 1 regional or systemic sign of infection, including lymphadenopathy, fever, leukocytosis or leukopenia, or greater than 10% immature neutrophils.

Exclusion criteria included prior systemic antibacterial treatment within 14 days (or topical antibacterial administration on the primary lesion within 96 hours) prior to the first dose of study drug, primary uncomplicated skin and skin structure infections, diabetic foot infection, gangrene, perianal abscess, concomitant infection at another site (except secondary ABSSSI), infected burns, decubitus or chronic skin ulcer, ischemic ulcer due to peripheral vascular disease, any evolving necrotizing process, infection at vascular catheter sites or thrombophlebitis, and severe sepsis or septic shock.

During the conduct of the study, in order to limit the proportion of injection drug users enrolled, the eligibility criteria were amended to exclude patients with illicit drug use within 12 months of screening, including heroin, other opioids (unless prescribed for medical reasons unrelated to heroin substitution), cocaine/crack cocaine, and amphetamine/methamphetamine, but excluding cannabis use. Full inclusion and exclusion criteria are detailed in [Supplementary Appendix 2](#).

Populations for endpoint analysis included the following: (1) intent-to-treat (ITT), comprising all randomized patients; (2) microbiological ITT (mITT), comprising the subset of the ITT who have confirmed causative pathogens; (3) clinically evaluable (CE), comprising the subset of the ITT who have no major protocol deviations and a completed response outcome assessment; (4) microbiologically evaluable (ME), comprising the subset of the mITT who are also in the CE population; and (5) the safety population, comprising all randomized patients receiving 1 or more doses of study drug.

Randomization and Treatment

Eligible patients were randomized 1:1 to ceftobiprole or vancomycin/aztreonam using a computer-generated randomization schedule obtained via an Interactive Web Response System. Randomization was stratified using block randomization by study site and type of ABSSSI.

Ceftobiprole was administered every 8 hours as a 2-hour 500 mg IV infusion. Vancomycin was administered as a 2-hour 1000 mg (or 15 mg/kg) IV infusion every 12 hours (q12h; decision regarding fixed or weight-based dose was made by the investigator on the basis of the site's standard of care), and aztreonam was administered as a 0.5-hour 1000 mg IV infusion q12h. Dose adjustments were performed for patients with renal impairment. Administration and dose adjustment of study drugs were performed in a double-blind manner; patients received active drug or placebo infusions that were matched in frequency, volume, and duration across both groups. Patients were treated for 5–10 days, unless extension to 14 days or fewer was requested by the investigator and approved by a medical monitor. The requirement for aztreonam was reassessed by the investigator at the 72-hour study visit and could be halted if gram-negative coverage was no longer deemed necessary.

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 15–22 days after randomization and 5 or more days after EOT, a survival status visit on day 28 (plus or minus 2 days), and a last follow-up (LFU) visit 28–35 days after last treatment.

Microbiological Assessments

The ABSSSI site specimens were obtained from each patient 24 hours or less prior to study drug administration. Further specimens were collected at day 3, day 5, EOT, TOC, and LFU visits, and at any other time if clinically indicated. Local laboratories

were required to culture and identify pathogens, and perform Gram staining and susceptibility testing, in accordance with standard procedures. All isolated pathogens considered clinically relevant were sent to a central laboratory for identification using matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry and susceptibility testing according to current Clinical and Laboratory Standards Institute methodology [10, 11]; these results were used in the study outcome analysis. Availability of microbiological results was not a prerequisite for enrollment in the study.

Blood samples for culturing were obtained within 6 hours prior to randomization and, if positive, repeated at each visit until 2 consecutive negative results were obtained on separate days. Isolated pathogens from blood cultures were sent to the central laboratory for assessment.

Outcomes

Two region-specific primary endpoints were evaluated in the study. The FDA-defined primary endpoint was early clinical response 48–72 hours after the start of treatment, assessed in the ITT population, with early clinical success defined as meeting all of the following: 20% or greater reduction from baseline in the area of the primary lesion, survival for 72 hours or more from the initiation of the study drug, no use of concomitant systemic or topical antibacterials on the primary lesion, and no unplanned surgical procedures for the ABSSSI after the start of treatment. The EMA-defined primary endpoint was investigator-assessed clinical success at the TOC visit, both in the ITT and CE populations. Clinical success was defined as complete, or near complete, resolution of baseline signs and symptoms of the primary infection, with no further need for antibacterial treatment.

Secondary endpoints included early clinical response and investigator-assessed clinical success in populations other than those for the primary endpoints; clinical response, defined as a 80% or greater reduction in lesion area at the EOT visit and 90% or greater reduction at the TOC visit, with improvement in local signs of infection, no use of any concomitant systemic or topical antibacterials on the primary lesion, and no unplanned surgical procedures; sustained reduction in lesion size, defined as a decrease in the lesion area as per the FDA-defined primary endpoint that is sustained at the EOT and TOC visits; all-cause mortality at day 28; microbiological response; and safety, assessed as the incidence, type, severity, and relationship to study drug of adverse events (AEs), and worsening in laboratory test results.

Statistical Analyses

For both the FDA- and EMA-defined primary endpoints, the observed difference in responders was determined and the 95% confidence interval (CI) calculated using the Cochran-Mantel-Haenszel weights method adjusted for geographic region and

type of ABSSSI. For both endpoints, patients with relevant missing data or who were lost to follow-up were considered as nonresponders. Noninferiority of ceftobiprole to vancomycin/aztreonam was assessed with a 1-sided test at the 2.5% level of significance. If the lower limit of the 95% CI for the difference in response rates (ceftobiprole minus vancomycin/aztreonam) was greater than -10% in the ITT population (FDA-defined endpoint) or ITT and CE population (EMA-defined endpoint), noninferiority would be concluded. The 10% noninferiority margin was selected in line with FDA and EMA guidance documents [1, 9]. Based on estimated early clinical success rates and clinical cure rates derived from prior phase 3 studies in ABSSSIs, a 1-sided α level of 0.025, and a noninferiority margin of 10%, a total of 674 randomized patients were required to achieve 90% or greater power for the demonstration of noninferiority for the FDA- and EMA-defined primary endpoints.

Prespecified analyses of the primary endpoints were performed in subgroups defined by geographical region, baseline ABSSSI type, underlying medical conditions (eg, diabetes mellitus, injection drug use), baseline clinical characteristics, and pathogen.

RESULTS

Patient Disposition and Baseline Characteristics

In total, 679 patients were randomized to ceftobiprole or vancomycin/aztreonam ($n = 335$ and 344 , respectively) between February 19, 2018 and February 22, 2019, of whom 676 received at least 1 dose of study drug (Figure 1). Baseline demographics and clinical characteristics were similar between the 2 treatment groups (Table 1). The proportion of patients in the United States was 62%. Cellulitis/erysipelas and major cutaneous abscess were present in 33% and 28% of enrolled patients, respectively, with wound infections present in the remaining 39% of patients. Current IV drug users accounted for 33% of patients. Overall, 17 (2.5%) patients had concomitant bacteremia.

The majority of patients received treatment for 5–10 days (91.9% and 88.9% in the ceftobiprole and vancomycin/aztreonam groups, respectively). Median duration of treatment was 6.0 and 7.0 days in the ceftobiprole and vancomycin/aztreonam groups, respectively. Median duration of treatment with aztreonam in the comparator group was 3.0 days, with 162 (47.4%), 79 (23.1%), and 43 (12.6%) patients receiving aztreonam for more than 3, 5, and 7 days, respectively.

Efficacy Analysis

Early Clinical Response

The proportion of patients with early clinical success in the ITT population at 48–72 hours after the start of treatment was 91.3% and 88.1% in the ceftobiprole and vancomycin/aztreonam groups, respectively, with an adjusted difference (ceftobiprole minus vancomycin/aztreonam) of 3.3% (95% CI:

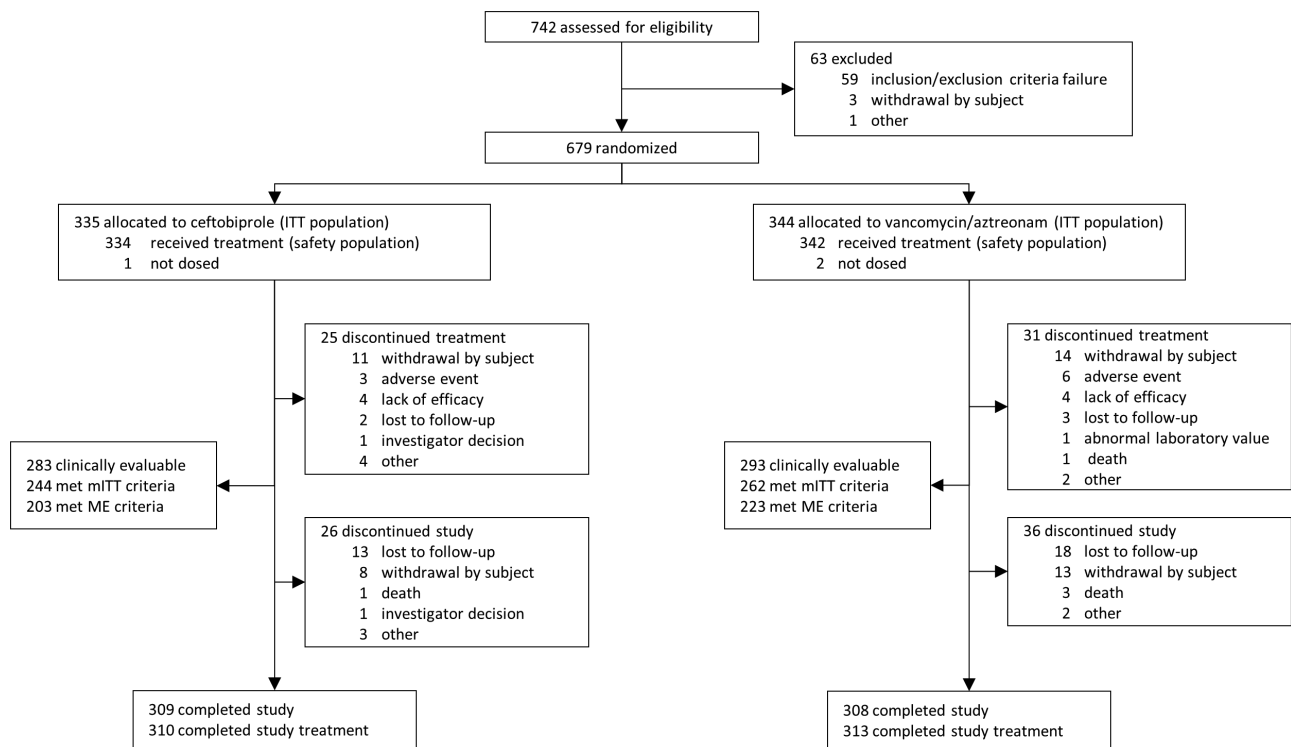


Figure 1. Patient disposition. One patient in the vancomycin/aztreonam group died post-randomization but prior to receiving a first dose of drug. Abbreviations: ITT, intent-to treat; ME, microbiologically evaluable; mITT, microbiological intent-to-treat population.

Table 1. Baseline Demographics, Clinical Characteristics, and ABSSSI Characteristics (ITT Population)

Characteristic	Ceftibiprole (n = 335)	Vancomycin/Aztreonam (n = 344)
Age, median (min–max), y	51.0 (18.0–89.0)	50.0 (20.0–87.0)
Gender, male, n (%)	198 (59.1)	201 (58.4)
Race, white, n (%)	318 (94.9)	330 (95.9)
Geographic region, n (%)		
North America	203 (60.6)	215 (62.5)
Europe	132 (39.4)	129 (37.5)
Type of ABSSSI, n (%)		
Wound infection	127 (37.9)	140 (40.7)
Cellulitis/erysipelas	112 (33.4)	111 (32.3)
Major cutaneous abscess	96 (28.7)	93 (27.0)
Lesion size, median (min–max), cm ²	249.3 (75.5–2604.0)	273.5 (67.5–5166.0)
Diabetes mellitus, n (%)	36 (10.7)	42 (12.2)
Current illicit drug use, n (%)	118 (35.2)	127 (36.9)
Current injection drug use	108 (32.2)	117 (34.0)
Creatinine clearance <50 mL/minute, n (%)	10 (3.0)	12 (3.5)
Fever, ^a n (%)	120 (35.8)	120 (34.9)
White blood cell count >10.0 or <4.0 × 10 ⁹ /L, n (%)	113 (33.7)	126 (36.6)
>10% immature neutrophils, n (%)	27 (8.1)	36 (10.5)
Prior systemic antibacterial treatment, n (%)	0	1 (0.3)
Incision and drainage, ^b n (%)	46 (13.7)	51 (14.8)
Debridement, ^b n (%)	24 (7.2)	24 (7.0)

Abbreviations: ABSSSI, acute bacterial skin and skin structure infection; ITT, intent-to-treat; min–max, minimum–maximum.

^a>38°C/100.4°F measured orally, >38.5°C/101.3°F measured tympanically, or >37.5°C/99.5°F measured axillary.

^bProcedure with a stop date before the first study drug date. Additional procedures required during the study in ceftibiprole vs vancomycin/aztreonam-treated patients included: incision and drainage in 129 (38.5%) vs 130 (37.8%) patients and debridement in 20 (6.0%) vs 19 (5.5%) patients, respectively.

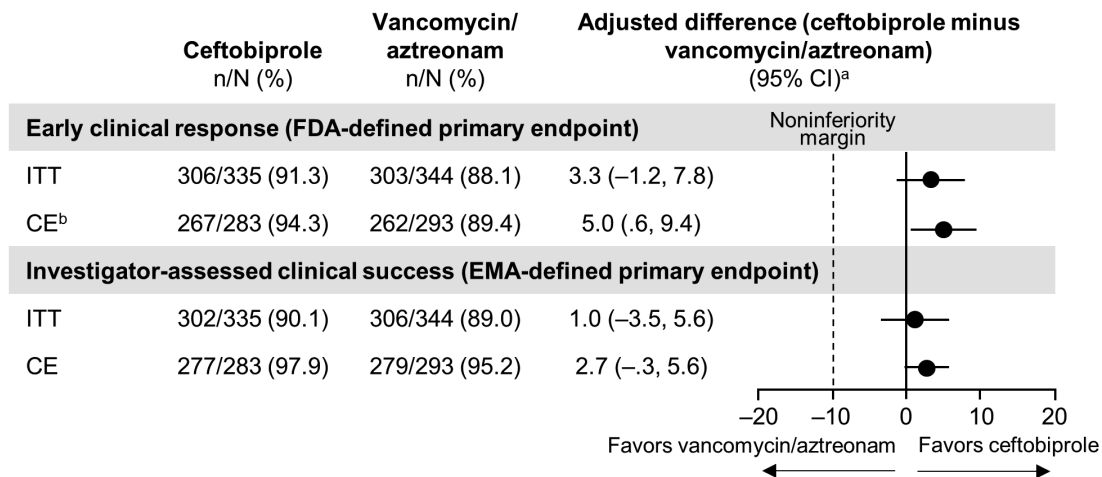


Figure 2. Primary endpoint analyses. ^aProportion differences (95% CI) (ceftobiprole minus vancomycin/aztreonam) were computed using the Cochran-Mantel-Haenszel weights method adjusted for geographical region and actual type of ABSSSI. ^bSecondary endpoint. The objective for the FDA-defined primary endpoint was based on a noninferiority assessment of the ITT population only. The EMA-defined primary endpoint was based on a noninferiority assessment in both the ITT and CE populations. Abbreviations: ABSSSI, acute bacterial skin and skin structure infection; CE, clinically evaluable; CI, confidence interval; EMA, European Medicines Agency; FDA, Food and Drug Administration; ITT, intent-to-treat.

−1.2, 7.8) (Figure 2). Noninferiority was concluded given that the lower bound of the 95% CI was well above the prespecified −10% noninferiority margin. In the CE population, ceftobiprole was superior to vancomycin/aztreonam (5.0%; 95% CI: .6, 9.4; $P = .0262$) (Figure 2). Consistent results were reported in prespecified subgroup analyses (Figure 3).

Investigator-assessed Clinical Success

At the TOC visit, the proportion of patients achieving investigator-assessed clinical success was similar in the ceftobiprole and vancomycin/aztreonam groups: 90.1% and 89.0% in the ITT population and 97.9% and 95.2% in the CE population, respectively. Noninferiority was achieved for both the ITT (adjusted difference: 1.0%; 95% CI: −3.5, 5.6) and CE (adjusted difference: 2.7%; 95% CI: −.3, 5.6) populations (Figure 2). In the ceftobiprole and vancomycin/aztreonam groups, respectively, investigator-assessed clinical success was sustained at the LFU visit in 87.5% and 83.7% of patients in the ITT population and in 95.1% and 90.1% of patients in the CE population (Table 2). Consistent results were reported in prespecified subgroup analyses (Figure 3).

Additional Secondary Endpoints

Secondary endpoint results are presented in Table 2. In the ITT population, 80.3% and 76.2% of patients in the ceftobiprole and vancomycin/aztreonam groups, respectively, achieved clinical responses that were sustained at both the EOT and TOC time points. Sustained reductions in lesion sizes were found in 84.8% and 80.8% of patients, respectively. No patients died prior to day 28 in the ceftobiprole group, whereas 2 patients died in the vancomycin/aztreonam group (on days 2 and 28); survival rates at day 28 were not significantly different between the 2 groups.

Microbiological Efficacy

Microbiological response rates (defined as eradication or presumed eradication) increased over time and were similar between patients treated with ceftobiprole and vancomycin/aztreonam (Figure 4). Kaplan–Meier analyses revealed that time to microbiological eradication was significantly shorter with ceftobiprole compared with vancomycin/aztreonam ($P = .0245$, log-rank test). In subgroups defined by causative pathogen, microbiological response rates were generally similar between treatment groups, except in patients infected with methicillin-susceptible *S. aureus* (MSSA) in the ME population, for which response rates were higher with ceftobiprole (97.8%) compared with vancomycin/aztreonam (87.7%) (difference in proportion: 10.0%; 95% CI: 3.1, 17.0; $P = .0084$) (Table 3). Of note, response rates for ceftobiprole were similar for MRSA and MSSA infections (Table 3). Susceptibility testing results are presented in Table 4. No *S. aureus* isolates with a ceftobiprole minimum inhibitory concentration of 2 mg/L or greater were identified, which is consistent with recent surveillance data [12].

Safety

Treatment-emergent AEs were reported in an overall higher proportion of patients in the ceftobiprole group (44.3%) compared with the vancomycin/aztreonam group (38.6%) (Table 5). The majority of AEs were mild or moderate, with a smaller proportion of patients experiencing severe AEs in the ceftobiprole group compared with the vancomycin/aztreonam group (2.7% vs 7.0%). The proportion of treatment-related AEs was similar in the 2 groups (19.8% and 18.1% in the ceftobiprole and vancomycin/aztreonam groups, respectively). There were no cases of *Clostridium difficile* colitis reported in either treatment group (data not shown).

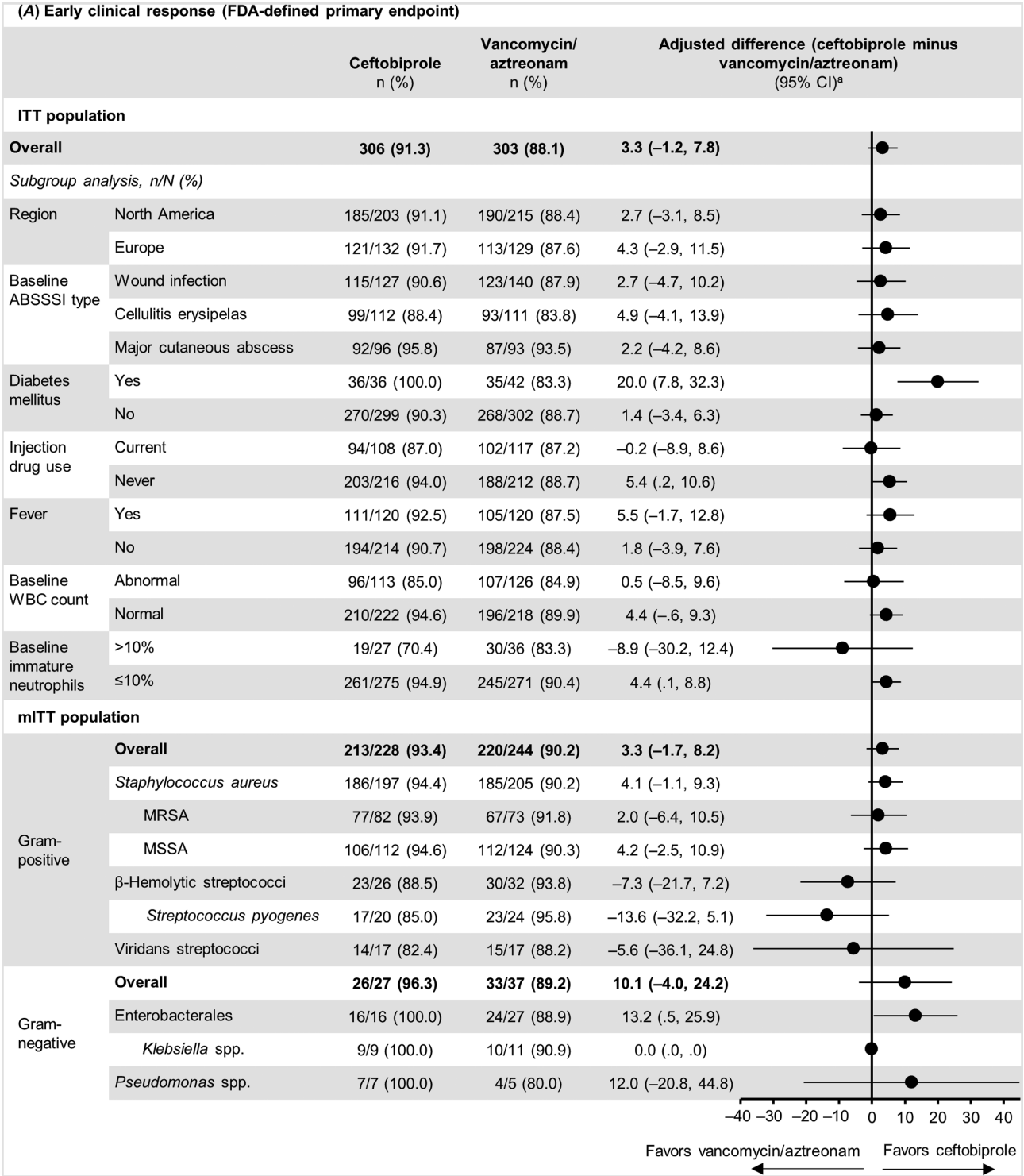


Figure 3. Early clinical response (A) and investigator-assessed clinical success at the TOC visit (B) in select subgroups defined by region (ITT), infection type (ITT), comorbidities (ITT), and causative pathogen (mITT). ^aProportion differences (95% CI) (ceftobiprole minus vancomycin/aztreonam) were computed using the Cochran-Mantel-Haenszel weights method adjusted for geographical region and actual type of ABSSSI. Abbreviations: ABSSSI, acute bacterial skin and skin structure infection; CI, confidence interval; EMA, European Medicines Agency; FDA, Food and Drug Administration; ITT, intent-to-treat; mITT, microbiological intent-to-treat; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; NE, not evaluable; n/N, number of patients achieving the endpoint/total number of patients evaluated; TOC, test-of-cure; WBC, white blood cell.

(B) Investigator-assessed clinical success at the TOC visit (EMA-defined primary endpoint)

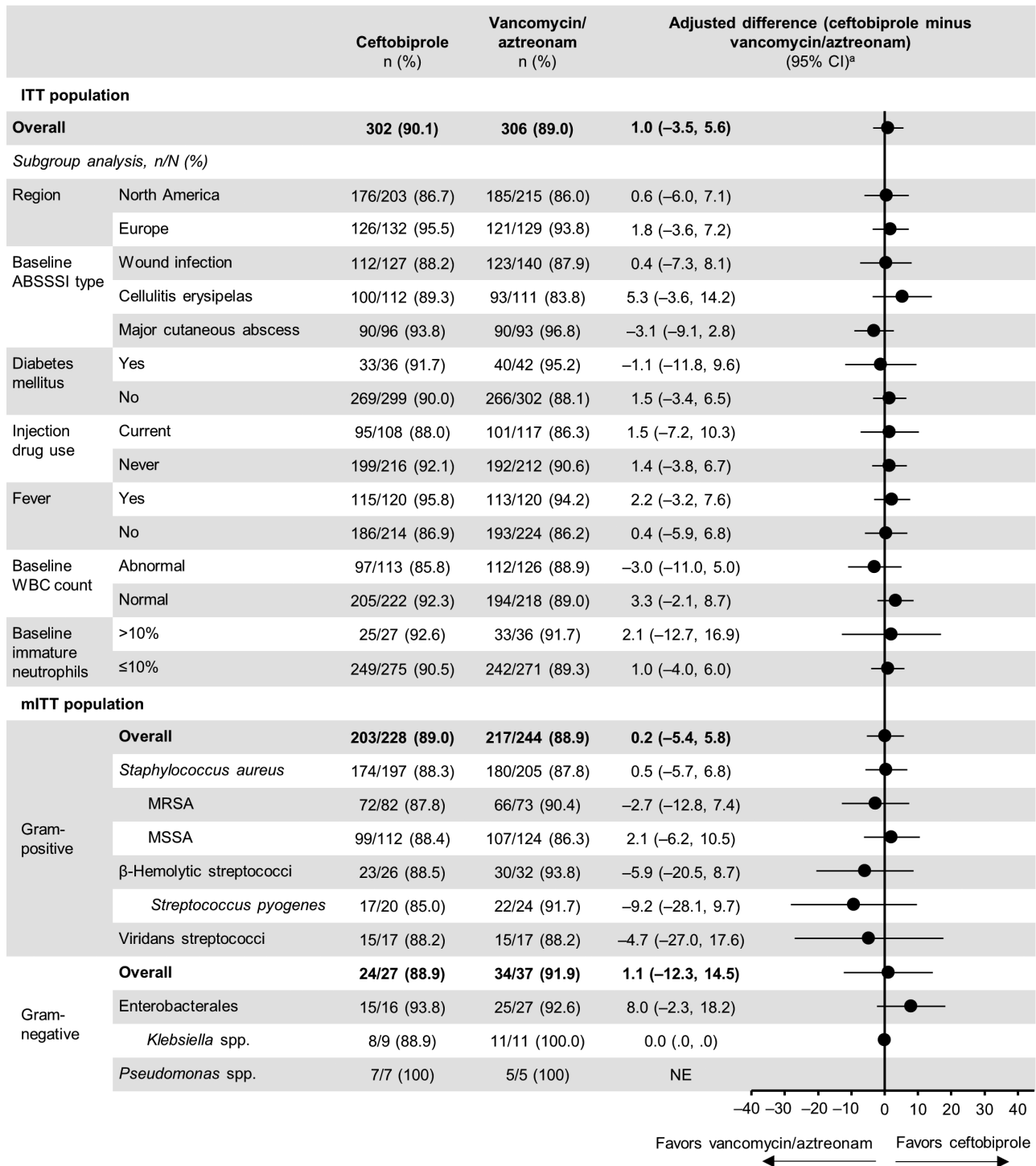


Figure 3. Continued.

Rates of serious AEs and AEs leading to treatment discontinuation were lower in the ceftobiprole group compared with the vancomycin/aztreonam group (Table 5). AEs leading to death occurred in 1 patient in the ceftobiprole group (accidental illicit drug overdose, day 31) and 2 in the vancomycin/aztreonam

group (1 case of respiratory failure, day 2; and 1 case of cardiac arrest, multiorgan failure, and septic shock, day 28), all of which were considered to be not related to the study drug.

Elevations in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) more than 8 times the

Table 2. Secondary Efficacy Endpoint Results

Characteristic	Ceftobiprole, n (%)	Vancomycin/Aztreonam, n (%)	Difference in Proportion, % (95% CI)
Clinical response^a			
ITT population, n	335	344	
At EOT	283 (84.5)	277 (80.5)	
At TOC	290 (86.6)	293 (85.2)	
At EOT and TOC	269 (80.3)	262 (76.2)	4.2 (–2.0, 10.3)
CE population, n	283	293	
At EOT	251 (88.7)	246 (84.0)	
At TOC	267 (94.3)	267 (91.1)	
At EOT and TOC	248 (87.6)	240 (81.9)	6.0 (2, 11.8)
Sustained reduction in lesions size^b			
ITT population, n	335	344	
At EOT and TOC	284 (84.8)	278 (80.8)	4.0 (–1.6, 9.6)
CE population, n	283	293	
At EOT and TOC	262 (92.6)	254 (86.7)	6.0 (1.2, 10.9)
Investigator-assessed clinical success^c			
ITT population, n	335	344	
48–72 hours after start of treatment	311 (92.8)	307 (89.2)	3.6 (–.7, 7.8)
At TOC	302 (90.1)	306 (89.0)	1.0 (–3.5, 5.6)
Sustained at LFU	293 (87.5)	288 (83.7)	3.5 (–1.7, 8.7)
CE population, n	283	293	
48–72 hours after start of treatment	264 (93.3)	264 (90.1)	3.1 (–1.3, 7.5)
At TOC	277 (97.9)	279 (95.2)	2.7 (–.3, 5.6)
Sustained at LFU	269 (95.1)	264 (90.1)	4.8 (6, 9.1)
All-cause mortality at day 28			
ITT population, n	335	344	
KM survival rate estimate (95% CI) ^d	100.0 (100.0, 100.0)	99.1 (97.2, 99.7)	...

Proportion differences (95% CI) (ceftobiprole minus vancomycin/aztreonam) were computed using the Cochran-Mantel-Haenszel weights method adjusted for geographical region and actual type of ABSSSI.

Abbreviations: ABSSSI, acute bacterial skin and skin structure infection; CE, clinically evaluable; CI, confidence interval; EOT, end of treatment; FDA, Food and Drug Administration; ITT, intent-to-treat; KM, Kaplan-Meier; LFU, last follow-up; TOC, test-of-cure.

^aDefined as $\geq 80\%$ reduction in lesion area at the EOT visit and $\geq 90\%$ reduction at the TOC visit, with improvement in local signs of infection, no use of any concomitant systemic antibacterial (or topical at the primary lesion), and no unplanned surgical procedures.

^bDefined as $\geq 20\%$ reduction in lesion area 48–72 hours after the start of treatment (FDA-defined primary endpoint) that was sustained at the EOT and TOC visits.

^cClinical success at TOC was defined as complete, or near complete, resolution of baseline signs and symptoms of the primary infection, with no further need for antibacterial treatment; sustained clinical success at LFU also required no new signs or symptoms of the ABSSSI between the TOC and LFU visits.

^dSurvival rate is the estimated probability that a patient will remain event-free up to the specified time point; survival rate was obtained from the KM survival estimate; the Greenwood formula was used for CIs of KM estimates.

upper-limit-of-normal (ULN) occurred in 2 patients (0.6%) in the ceftobiprole group and in 6 patients (1.8%) in the vancomycin/aztreonam group. Elevations in bilirubin more than 2 times the ULN occurred in 2 different patients, 1 patient (0.3%) in each treatment group. No Hy's law cases were noted. Significant changes in hepatic transaminases and renal function, defined as Common Terminology Criteria for Adverse Events values that shifted from grade 0–2 to grade 3–4, were uncommon and less frequent in the ceftobiprole group compared with the vancomycin/aztreonam group, in terms of the serum levels of ALT (1.2% vs 2.0%), AST (0.9% vs 2.0%), and creatinine (6.9% vs 11.1%). No shifts to grade 3–4 event values were reported for serum bilirubin levels.

DISCUSSION

The TARGET study demonstrated the noninferiority of ceftobiprole to vancomycin/aztreonam in the treatment of

ABSSSIs for both the FDA-defined primary endpoint of early clinical response (48–72 hours after the start of treatment) and the EMA-defined primary endpoint of investigator-assessed clinical success at the TOC visit. In the CE population, ceftobiprole was significantly better than vancomycin/aztreonam for early clinical success, albeit this was a secondary endpoint in this study. These results are consistent with previous phase 3 studies with ceftobiprole in complicated skin and soft tissue infections (cSSTIs), which indicated noninferiority of ceftobiprole to vancomycin in gram-positive infections, and to vancomycin/ceftazidime in both gram-positive and gram-negative infections [13, 14]. Of note, we observed higher microbiological response rates with ceftobiprole compared with vancomycin/aztreonam in the ME population infected with MSSA. This is consistent with previous retrospective cohort studies, which demonstrated that vancomycin may be inferior to β -lactams for the treatment of MSSA bloodstream infections [15, 16].

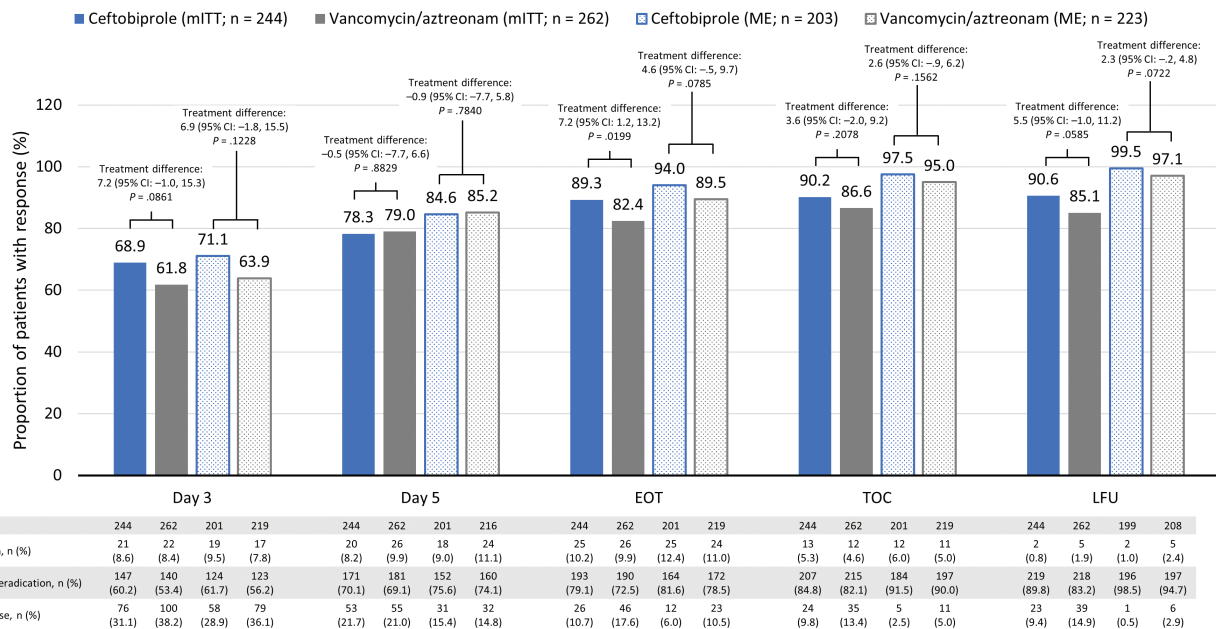


Figure 4. Microbiological response by study visit (mITT and ME populations). Proportion differences (95% CI) (ceftobiprole minus vancomycin/aztreonam) were computed using the Cochran-Mantel-Haenszel weights method adjusted for geographical region and actual type of ABSSSI. P-values were computed using the Cochran-Mantel-Haenszel test for general association between treatment group and response. Microbiological response was defined as eradication or presumed eradication (eradication defined as no growth of the baseline pathogen[s] based on post-treatment cultures obtained from the primary infection site at the respective time points; presumed eradication was defined as no post-treatment culture due to lack of culturable material accompanied by investigator-assessed clinical success). Abbreviations: ABSSSI, acute bacterial skin and skin structure infection; CI, confidence interval; EOT, end-of-treatment; LFU, last follow-up; ME, microbiologically evaluable; mITT, microbiological intent-to-treat; TOC, test-of-cure.

The safety findings of ceftobiprole in this study were consistent with its established safety profile [8], including that reported in previous studies in cSSTIs and pneumonia [13, 14, 17, 18]. The most common AEs were related to gastrointestinal disorders and less than 2% of patients experienced AEs leading to treatment discontinuation, suggesting that ceftobiprole is well tolerated in the majority of patients.

When MRSA is suspected or confirmed, treatment guidelines from the Infectious Diseases Society of America include several antibacterial options, such as vancomycin, linezolid, clindamycin, daptomycin, ceftaroline, doxycycline, sulfamethoxazole-trimethoprim, or telavancin, with specific recommendations varying depending on the severity of infection and type of ABSSSI [19]. Since these guidelines

Table 3. Microbiological Response (Documented or Presumed Eradication) at TOC Visit in Select Subgroups Defined by Causative Pathogen (mITT and ME Populations)

Subgroup	mITT Population		ME Population	
	Ceftobiprole (n = 244)	Vancomycin/Aztreonam (n = 262)	Ceftobiprole (n = 203)	Vancomycin/Aztreonam (n = 223)
Gram-positive, n/N (%)	206/228 (90.4)	210/244 (86.1)	184/189 (97.4)	192/206 (93.2)
<i>Staphylococcus aureus</i>	178/197 (90.4)	174/205 (84.9)	161/164 (98.2)	158/171 (92.4)
MRSA	75/82 (91.5)	67/73 (91.8)	70/71 (98.6)	62/62 (100.0)
MSSA	100/112 (89.3)	100/124 (80.6)	88/90 (97.8)	93/106 (87.7)
β-Hemolytic streptococci	23/26 (88.5)	30/32 (93.8)	20/21 (95.2)	28/30 (93.3)
<i>Streptococcus pyogenes</i>	18/20 (90.0)	22/24 (91.7)	15/15 (100.0)	20/22 (90.9)
Viridans streptococci	15/17 (88.2)	15/17 (88.2)	13/13 (100.0)	14/14 (100.0)
<i>Streptococcus anginosus</i>	5/6 (83.3)	4/6 (66.7)	5/5 (100.0)	4/4 (100.0)
Gram-negative, n/N (%)	22/27 (81.5)	32/37 (86.5)	19/23 (82.6)	31/34 (91.2)
Enterobacterales	13/16 (81.3)	25/27 (92.6)	12/15 (80.0)	24/25 (96.0)
<i>Klebsiella pneumoniae</i>	8/8 (100.0)	5/5 (100.0)	7/7 (100.0)	5/5 (100.0)
<i>Pseudomonas</i> spp.	6/7 (85.7)	5/5 (100.0)	6/7 (85.7)	5/5 (100.0)

Abbreviations: ME, microbiologically evaluable; mITT, microbiological intent-to-treat; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; TOC, test-of-cure.

Table 4. Minimal Inhibitory Concentrations Against Baseline Causative Pathogens (mITT Population, by Treatment Group)

Baseline Pathogen	Ceftobiprole				Vancomycin			
	n ^a	MIC ₅₀ , mg/L	MIC ₉₀ , mg/L	MIC Range, mg/L	n ^a	MIC ₅₀ , mg/L	MIC ₉₀ , mg/L	MIC Range, mg/L
Gram-positive ^b	199	0.5	1	≤0.015–4	209	0.5	1	≤0.25–1
<i>Staphylococcus aureus</i>	185	0.5	1	≤0.015–1	193	1	1	≤0.25–1
MRSA	78	1	1	0.25–1	73	1	1	≤0.25–1
MSSA	109	0.25	0.5	≤0.015–0.5	120	1	1	≤0.25–1
β-Hemolytic streptococci	22	≤0.015	0.03	≤0.015–0.03	29	0.25	0.5	0.25–0.5
<i>Streptococcus pyogenes</i>	19	≤0.015	0.03	≤0.015–0.03	23	0.25	0.25	0.25–0.5
Gram-negative ^c	19	0.03	>64	≤0.015–>64	5	NA	NA	NA
Enterobacterales	13	≤0.015	>64	≤0.015–>64	NA	NA	NA	NA

Abbreviations: MIC, minimum inhibitory concentration; mITT, microbiological intent-to-treat; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; NA, not available.

^aA patient could have >1 causative baseline pathogen. MIC₅₀, MIC₉₀, and MIC range were only calculated when total count was >10 patients.

^bAdditional gram-positive pathogens at baseline (n) in the ceftobiprole group: *Clostridium irregulare* (1), *Enterococcus faecalis* (3), *Staphylococcus lugdunensis* (1), *Streptococcus agalactiae* (3). Additional gram-positive pathogens at baseline (n) in the vancomycin/aztreonam group: *Streptococcus agalactiae* (6).

^cAdditional gram-negative pathogens at baseline (n) in the ceftobiprole group: *Acinetobacter baumannii* (2), *Prevotella bivia* (1), *Proteus mirabilis* (1), *Pseudomonas aeruginosa* (3), *Pseudomonas oryzihabitans* (1), *Pseudomonas*, nonspecified (1). Additional gram-negative pathogens at baseline (n) in the vancomycin/aztreonam group: *Bacteroides fragilis* (3), *Prevotella denticola* (1), *Prevotella oralis* (1).

were issued in 2014, additional agents have become available, including tedizolid, dalbavancin, oritavancin, and delafloxacin [5]. With the exception of delafloxacin, these agents are all indicated in gram-positive infections only

Table 5. Adverse Events (Safety Analysis Population)

Characteristic	Ceftobiprole (n = 334), n (%)	Vancomycin/Aztreonam (n = 342), n (%)
Number of patients with at least 1 AE	148 (44.3)	132 (38.6)
AEs leading to death ^a	1 (0.3)	2 (0.6)
Serious AEs	6 (1.8)	12 (3.5)
AE leading to treatment discontinuation	6 (1.8)	10 (2.9)
Treatment-related AEs	66 (19.8)	62 (18.1)
Treatment-related serious AEs	1 (0.3)	2 (0.6)
AEs occurring in ≥2% of patients per group		
Nausea	36 (10.8)	20 (5.8)
Headache	19 (5.7)	24 (7.0)
Diarrhea	21 (6.3)	16 (4.7)
Skin bacterial infection	14 (4.2)	17 (5.0)
ALT increased	8 (2.4)	10 (2.9)
AST increased	7 (2.1)	10 (2.9)
Injection-site reaction	7 (2.1)	8 (2.3)
Vomiting	7 (2.1)	7 (2.0)
Constipation	7 (2.1)	6 (1.8)
Rash	5 (1.5)	7 (2.0)
Pyrexia	3 (0.9)	8 (2.3)
Edema peripheral	3 (0.9)	7 (2.0)
Abdominal pain	1 (0.3)	8 (2.3)
Dysgeusia	7 (2.1)	0

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

^aOne patient in the ceftobiprole group died on day 42 (having completed treatment on day 6) as a result of accidental illicit drug overdose. Of the 2 patients who died in the vancomycin/aztreonam group, 1 died on day 2 as a result of sepsis, left buttock abscess, intravenous drug use, and respiratory failure, and the other died on day 28 due to septic shock resulting from bacteremia and intravenous drug use. None of the 3 reported deaths were considered related to the study drug.

[5]. Our study results, together with previous studies with ceftobiprole in this setting [13, 14], suggest that ceftobiprole has the potential to be an effective broad-spectrum treatment option for ABSSSIs, with suitability for use in those with gram-positive (including MRSA), gram-negative, or mixed gram-positive/gram-negative infections. Unlike with vancomycin [19], monitoring of serum trough concentrations is not required with ceftobiprole, which may help reduce the burden on healthcare systems.

Our study has a number of strengths. Few patients were lost to follow-up and more than 90% of randomized patients completed the study treatment. The proportion of patients with each of the 3 main types of ABSSSI was well balanced, aiding the generalizability of the study results. In addition, the proportion of patients with cutaneous abscess did not comprise greater than 30% of the study population, in accordance with FDA guidance [1]. During the conduct of the study, the eligibility criteria were amended to exclude patients with illicit drug use within 12 months of screening. This approach allowed for a study population that is more representative of the general population, while providing a reasonable sample size of current illicit drug users (n = 245; 36.1%), almost all of whom were current injection drug users (n = 225; 33.1%). Our study population also reflected the dominance of gram-positive pathogens in ABSSSIs; within the mITT population, 93% of cases involved gram-positive pathogens. While a lower proportion (13%) involved gram-negative pathogens, this still represented a sample size of over 60 patients. The study is also representative of outcomes in patients with ABSSSIs requiring hospitalization and IV therapy, including US patients, who made up 62% of study participants. In addition, the results for the primary endpoints were similar between patients in North America and Europe, indicating that all the results from

this study are generalizable across clinical settings in both continents.

Limitations of the study include the low number of patients in some of the subgroups analyzed, which should therefore be interpreted with caution. In particular, the study was not powered to evaluate outcomes in subgroups defined by causative pathogen. In addition, like all explanatory randomized controlled trials, generalizability of the results may be limited due to the need for internal validity. This is due to the enrollment of a patient population that may be less heterogeneous than seen in clinical practice and the use of interventions that may not always be pragmatic.

In conclusion, the present study demonstrated the noninferiority of ceftobiprole to vancomycin/aztreonam in the treatment of patients with a representative selection of ABSSSIs, including both gram-positive and gram-negative infections. These results are generalizable to the typical ABSSSI admissions in United States and European hospitals, and support the potential use of ceftobiprole as a single broad-spectrum agent to treat gram-positive, gram-negative, and polymicrobial ABSSSIs across multiple inpatient subgroup populations.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. All authors contributed to data acquisition and to the development, critical review, and final approval of this manuscript. M. E., M. S., J. I. S., M. E. J., and K. A. H. contributed to the study design.

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Potential conflicts of interest. M. E., M. S., J. I. S., M. E. J., and K. A. H. are employees of Basilea Pharmaceutica International Ltd. D. I. is a contractor for Basilea Pharmaceutica International Ltd. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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