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CLINICAL THERAPEUTICS

A Phase 3, Randomized, Double-Blind, Multicenter Study To Evaluate the Safety and Efficacy of Intravenous Iclaprim versus Vancomycin for Treatment of Acute Bacterial Skin and Skin Structure Infections Suspected or Confirmed To Be Due to Gram-Positive Pathogens (REVIVE-2 Study)

Thomas L. Holland,[a] William O'Riordan,[b] Alison McManus,[b] Elliot Shin,[b] Ali Borghei,[c] Thomas M. File, Jr.,[d] Mark H. Wilcox,[e] Antoni Torres,[f,g] Matthew Dryden,[h] Thomas Lodise,[i] Toyoko Oguri,[j] G. Ralph Corey,[a] Patrick McLeroth,[j] Rajesh Shukla,[k] David B. Huang[k]

[a]Duke University Medical Center, Durham, North Carolina, USA
[b]eStudySites, San Diego, California, USA
[c]Long Beach Clinical Trials, Los Angeles, California, USA
[d]Summa Health, Akron, Ohio, USA
[e]Leeds Teaching Hospitals & University of Leeds, Leeds, United Kingdom
[f]Department of Pulmonology, Hospital Clinic of Barcelona, University of Barcelona, Institut d'Investigacions August Pi I Sunyer, Barcelona, Spain
[g]Centro de Investigación Biomedica En Red-Enfermedades Respiratorias, Barcelona, Spain
[h]Department of Microbiology and Infection, Hampshire Hospitals NHS Foundation Trust, Basingstoke, United Kingdom
[i]Albany College of Pharmacy and Health Sciences, Albany, New York
[j]Covance, Princeton, New Jersey, USA
[k]Motif BioSciences, New York, New York, USA, and Rutgers New Jersey Medical School, Newark, New Jersey, USA

ABSTRACT Iclaprim is a novel diaminopyrimidine antibiotic that may be an effective and safe treatment for serious skin infections. The safety and effectiveness of iclaprim were assessed in a global phase 3, double-blind, randomized, active-controlled trial. Six hundred thirteen adults with acute bacterial skin and skin structure infections (ABSSSIs) suspected or confirmed to be due to Gram-positive pathogens were randomized to iclaprim (80 mg) or vancomycin (15 mg/kg of body weight), both of which were administered intravenously every 12 h for 5 to 14 days. The primary endpoint was a ≥20% reduction in lesion size compared with that at the baseline at 48 to 72 h after the start of administration of study drug in the intent-to-treat population. Among patients randomized to iclaprim, 78.3% (231 of 295) met this primary endpoint, whereas 76.7% (234 of 305) of those receiving vancomycin met this primary endpoint (difference, 1.58%; 95% confidence interval, −5.10% to 8.26%). This met the prespecified 10% noninferiority margin. Iclaprim was well tolerated, with most adverse events being categorized as mild. In conclusion, iclaprim was noninferior to vancomycin in this phase 3 clinical trial for the treatment of acute bacterial skin and skin structure infections. On the basis of these results, iclaprim may be an efficacious and safe treatment for skin infections suspected or confirmed to be due to Gram-positive pathogens. (This trial has been registered at ClinicalTrials.gov under identifier NCT02607618.)

KEYWORDS iclaprim, vancomycin, acute bacterial skin and skin structure infections, skin

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Address correspondence to Thomas L. Holland, thomas.holland@duke.edu, or David B. Huang, david.huang@motifbio.com.

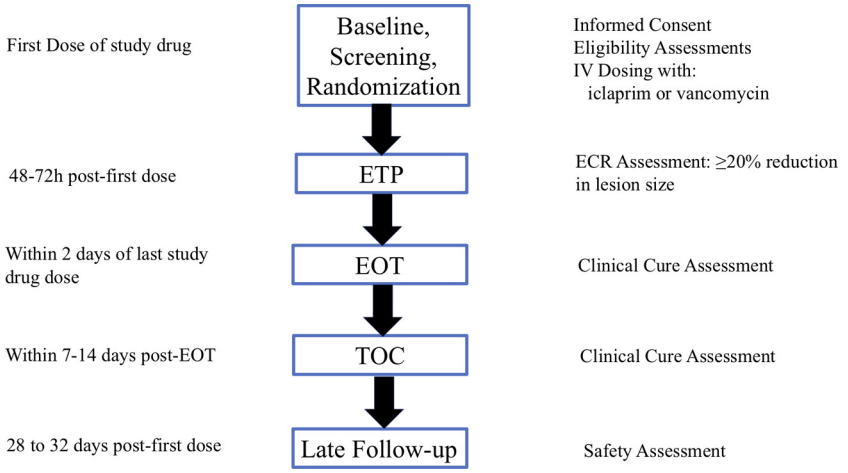

FIG 1 Schedule of visits. Abbreviations: IV, intravenous; ECR, early clinical response; ETP, early time point; EOT, end of therapy; TOC, test of cure.

Acute bacterial skin and skin structure infections (ABSSSIs) are common and potentially serious infections that may require hospitalization, intravenous antibiotics, and/or surgical intervention (1, 2). Most are caused by Gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-susceptible *S. aureus* (MSSA), and beta-hemolytic streptococci (2). Currently available treatment options have limitations. New therapeutic options with improved efficacy, safety, and/or pharmacodynamics are needed for ABSSSIs (3, 4). Iclaprim is a diaminopyrimidine which inhibits bacterial dihydrofolate reductase and is active against drug-resistant pathogens (5–8). Iclaprim demonstrates rapid *in vitro* bactericidal activity in time-kill studies in human plasma (9). In the previous phase 3 clinical trial among patients treated for an ABSSSI (the REVIVE-1 study), the rates of early clinical responses (ECR) in the intent-to-treat (ITT) population were 80.9% for iclaprim and 81.0% for vancomycin at the early time point (ETP) (10). We report the results of the second phase 3 study (the REVIVE-2 study) comparing the outcomes of patients treated with either iclaprim or vancomycin for an ABSSSI suspected or confirmed to be due to Gram-positive pathogens.

RESULTS

Demographics. The study randomized 613 patients, and 600 fulfilled the criteria for the ITT population, the prespecified efficacy population for the Food and Drug Administration (FDA), from 40 study sites in 10 countries (Fig. 1). Figure 2 shows the dispositions of the patients. The patients lost to follow-up in each treatment group were similar to the other patients randomized in the severity of their ABSSSIs (5 for iclaprim and 6 for vancomycin). There were 13 patients randomized in error; these were identified prior to unblinding and were not included in the ITT analysis. Of these, 6 had lesions that did not meet the study entry criteria (lesion size < 75 cm^2), and 7 were unable or unwilling to follow study procedures. The baseline and demographic characteristics of the patients treated with either iclaprim or vancomycin were comparable (Tables 1 and 2). The proportions of patients with fever at the baseline in the iclaprim and vancomycin cohorts were 27.1% and 26.2%, respectively. The baseline mean lesion sizes of the patients in the iclaprim and vancomycin cohorts were 372.3 cm^2 (standard deviation [SD], 305.8 cm^2) and 357.0 cm^2 (SD, 271.1 cm^2), respectively. The treatment groups were similar for baseline ABSSSI categories and the findings for laboratory parameters, vital signs, physical examinations, X rays, and electrocardiogram (ECG) evaluations. In addition, no notable differences between treatment groups with respect to prior and concomitant medications or study drug compliance were observed. Both the iclaprim and vancomycin treatment groups had a median of 7 treatment days (range, 5 to 14 days).

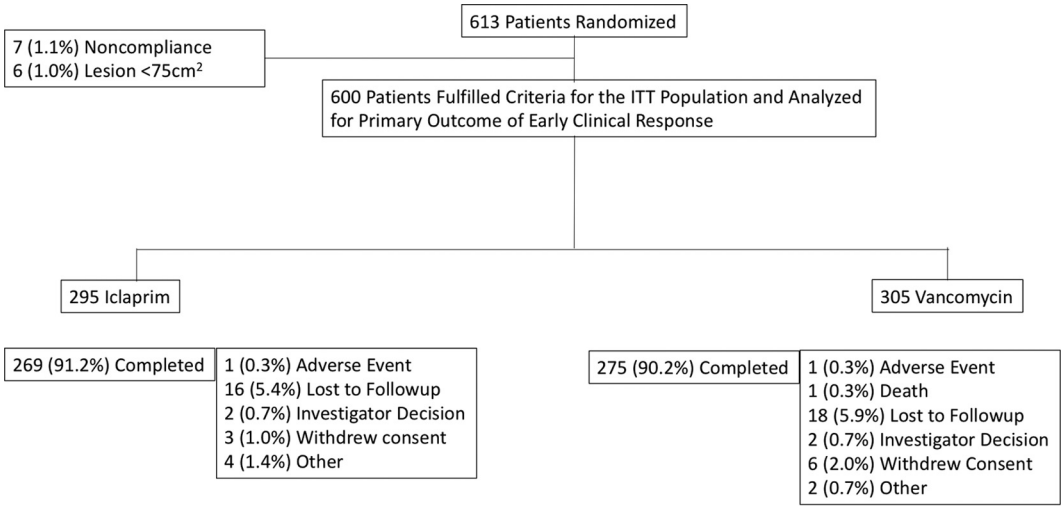

FIG 2 Disposition of patients.

Efficacy results. (i) Primary endpoint. In the ITT population, an ECR was reported at the ETP for 78.3% (231/295) of the patients in the iclaprim group and for 76.7% (234/305) of the patients in the vancomycin group (difference, 1.58%; 95% confidence interval [CI], −5.10% to 8.26%) (Table 2). A sensitivity analysis adding the 13 excluded patients showed similar results (ECR at ETP for 76.5% of the patients in the iclaprim group and 76.2% of the patients in the vancomycin group; difference, 0.25%; 95% CI, −6.48% to 6.98%).

(ii) Secondary analyses. In the ITT population, the clinical cure rates at the test of cure (TOC) were 77.6% (229/295) and 77.7% (237 of 305) for patients treated with iclaprim and vancomycin, respectively (difference, −0.08%; 95% CI, −6.74% to 6.59%) (Table 3). Using a modified clinical cure TOC analysis, defined by a ≥90% reduction in lesion size compared with that at the baseline, no increase in lesion size since ETP, and no requirement for additional antibiotics, clinical cure was observed in 71.5% and 70.5% of patients receiving iclaprim and vancomycin, respectively (treatment difference, 1.03%; 95% CI, −6.23% to 8.29%). The ECR at ETP was comparable for the iclaprim and vancomycin groups among the ITT predefined populations by lesion type, pathogen, diabetes status, and mild, moderate, and severe renal impairment (Table 3).

For the microbiological outcome at the end of therapy (EOT) and TOC, 384 (64.0%) patients presented with a culture-confirmed Gram-positive pathogen at the baseline. *S. aureus* was the most commonly isolated pathogen ($n = 258$), and of those 258 *S. aureus* isolates, 138 (53.4%) were MRSA (Table 1). The MIC_{50}/MIC_{90} values for iclaprim and vancomycin for *S. aureus* isolates were 0.12/0.5 μg/ml and 1/1 μg/ml, respectively.

Safety results. The adverse events (AEs), severe adverse events (SAEs), deaths, and AEs of special interest among patients in the iclaprim and vancomycin treatment groups are shown in Table 4. AEs leading to study drug discontinuation occurred in 5.4% and 5.6% of the patients in the iclaprim and vancomycin groups, respectively. In the iclaprim and vancomycin groups, similar incidences of nausea (5.7% and 5.6%, respectively), infusion site extravasation (4.3% and 4.0%, respectively), diarrhea (2.7% and 3.6%, respectively), and headache (2.3% and 4.3%, respectively) were reported. Although not an *a priori* hypothesis, there were no drug-related AEs related to nephrotoxicity reported for patients treated with iclaprim, whereas there were 2 (0.7%) drug-related AEs related to nephrotoxicity reported for patients treated with vancomycin. Nephrotoxicity was predefined in the study protocol as an increase in the serum creatinine concentration of 0.5 mg/dl or 50% above that at the baseline for at least two consecutive days. The change in the serum creatinine concentration from the baseline to TOC was 0.7 and 7.7 μmol/liter (0.008 and 0.09 mg/dl) in the patients in the iclaprim

TABLE 1 Baseline and demographic characteristics among the ITT population by treatment

Characteristic	Value(s) for patients treated with:	
	Iclaprim (n = 295)	Vancomycin (n = 305)
Mean (SD) age (yr)	50.0 (15.65)	50.8 (15.03)
No. (%) of patients by gender		
Female	103 (34.9)	108 (35.4)
Male	192 (65.1)	197 (64.6)
No. (%) of patients by race		
White	267 (90.5)	276 (90.5)
Black	12 (4.1)	11 (3.6)
American Indian or Alaska native	2 (0.7)	3 (1.0)
Native Hawaiian or other Pacific Islander	1 (0.3)	3 (1.0)
Multiracial	0	2 (0.7)
Other	13 (4.4)	10 (3.3)
Mean (SD) wt (kg)	84.2 (20.78)	85.5 (22.17)
No. (%) of patients by geographic region		
United States	200 (67.8)	205 (67.2)
Europe	84 (28.5)	94 (30.8)
Latin America	11 (3.7)	6 (2.0)
No. (%) of patients with severe infections[a]	185 (62.7)	198 (64.9)
No. (%) of patients with the following lesion type:		
Major cutaneous abscess	53 (18.0)	45 (14.8)
Cellulitis/erysipelas	115 (39.0)	125 (41.0)
Wound infection	127 (43.1)	135 (44.3)
Mean (SD) lesion size (cm^2)	372.3 (305.752)	357.0 (271.077)
No. (%) of patients with the following comorbidities:		
Diabetes	36 (12.2)	36 (11.8)
Renal impairment with the indicated CL_{CR} (ml/min)		
60–89	35 (12.0)	53 (17.9)
30–59	17 (5.8)	13 (4.4)
≤29	2 (0.7)	2 (0.7)
No. (%) of patients with illicit drug use	144 (48.8)	160 (52.5)
No. (%) of patients with fever (oral temp, >38°C [100.4°F])	80 (27.1)	80 (26.2)
No. of white blood cells/mm^3		
Mean (SD)	9.5 (3.4)	9.4 (3.8)
Median (minimum, maximum)	9.2 (1.7, 22.2)	8.4 (2.9, 23.1)
No. (%) of patients with the following baseline microbiology:		
Exclusively Gram-positive pathogens	171 (89.6)	168 (86.1)
Mixed Gram-positive and Gram-negative pathogens	20 (10.5)	27 (13.8)
No. (%) of patients with concomitant:		
Aztreonam use	13 (4.4)	20 (6.6)
Metronidazole use	9 (3.1)	11 (3.6)

[a]Severe infections were defined as an infection at the baseline with one or more of the following criteria: the patient fulfilled the published definition for systemic inflammatory response syndrome (SIRS) by having ≥2 of the symptoms consisting of a body temperature of >38°C or <36°C, a heart rate of >90 beats per minute, a respiration rate of >20 breaths per minute, and a leukocyte count of >12,000/mm^3 or <4,000/mm^3 or >10% bands; the patient was evaluated as having severe tenderness or severe erythema at the infection site; and/or the patient had positive blood cultures at the baseline.

and vancomycin groups, respectively. There were no significant differences between treatment groups in the mean values or mean changes in other routine serum laboratory parameters, urinalysis results, vital signs, or physical examinations during treatment or at the EOT, TOC, and follow-up. Eleven (3.7%) patients in the iclaprim

TABLE 2 Microbiological characteristics at study entry for the ITT population by treatment

Characteristic	Iclaprim (n = 295)	Vancomycin (n = 305)
Positive ABSSSI culture	199 (72.9)	214 (73.5)
Staphylococcus aureus		
MRSA	69 (23.4)	69 (22.6)
MSSA	60 (20.3)	60 (19.7)
Beta-hemolytic streptococci	76 (26.1)	93 (28.6)
Positive blood culture at baseline[a]	7/274 (2.6)	13/283 (4.6)
Infection site pathogen		
Multiple	45 (23.2)	59 (28.5)
Single	149 (76.9)	148 (71.5)

[a]In the iclaprim group, there were 2 *S. aureus* isolates, 2 *S. epidermidis* isolates, and 1 isolate each of *S. agalactiae*, *S. dysgalactiae*, and *Micrococcus luteus*. In the vancomycin group, there were 3 *S. aureus* isolates and 1 isolate each of *S. epidermidis*, *S. hominis*, *S. massiliensis*, *S. anginosus*, *S. salivarius*, *Bacillus* spp. (non-*B. anthracis*), *and Atopobium parvulum*, as well as 1 patient with both *S. aureus* and *S. salivarius* and 1 patient with both *S. epidermidis* and *M. luteus*.

group and nine (3.0%) patients in the vancomycin group had increases in alanine aminotransferase or aspartate aminotransferase levels to >3 times the upper limit of normal (ULN) during treatment. Three patients (one in the iclaprim group and two in the vancomycin group) had a diagnosis of acute hepatitis A confirmed by IgM serology. Two of those patients (one in the iclaprim group and one in the vancomycin group) had bilirubin level increases of >2 times the ULN. These increases resolved to baseline values upon discontinuation of the drug in all patients. No subject in this study met Hy's law criteria.

One (0.4%) patient in the iclaprim group and 0 patients in the vancomycin group had QTcF intervals of >500 ms (i.e., 503 ms) or intervals that were increased by >60 ms compared with those at the baseline. The QTc prolongation was not reported as an adverse event and resolved to baseline values upon discontinuation of drug.

DISCUSSION

In this study, iclaprim was noninferior to vancomycin in the treatment of ABSSSIs suspected or confirmed to be caused by Gram-positive organisms, based on the

TABLE 3 Clinical responses for primary endpoint and secondary analyses in the ITT population by treatment

Clinical response	Value(s) for patients receiving: Iclaprim (n = 295)	Vancomycin (n = 305)	Treatment difference (% [95% CI])
Primary endpoint of ECR at ETP in ITT population			
Total no. (%) of patients	231 (78.3)	234 (76.7)	1.58 (−5.10, 8.26)
No. of patients in the United States/total no. (%)	173/200 (86.5)	164/205 (80.0)	6.50 (−3.35, 16.14)
No. of patients in the European Union and Latin America/ total no. (%)	58/95 (61.1)	70/100 (70.0)	−8.9 (−24.02, 5.11)
Secondary analyses			
No. (%) of patients with ECR at ETP among patients with:			
Major cutaneous abscesses	45 (84.9)	40 (88.9)	−3.98 (−17.29, 9.33)
Cellulitis/erysipelas	81 (70.4)	91 (72.8)	−2.37 (−13.79, 9.05)
Wound infections	105 (82.7)	103 (76.3)	6.38 (−3.35, 16.12)
No. (%) of patients with ECR at ETP/total no. (%) among:			
MRSA-infected patients	61/69 (88.4)	53/69 (76.8)	11.59 (−5.80, 28.48)
MSSA-infected patients	50/60 (83.3)	51/60 (85.0)	−1.67 (−20.15, 16.90)
S. pyogenes-infected patients	64/76 (84.2)	74/93 (79.6)	4.6 (−4.29, 11.07)
Diabetic patients	26/36 (72.2)	29/36 (80.6)	−8.33 (−31.95, 15.99)
Patients with mild renal impairment (CL_{CR} = 60–89 ml/min)	27/35 (77.1)	39/53 (73.6)	3.56 (−17.38, 24.72)
Patients with moderate and severe renal impairment (CL_{CR} < 60 ml/min)	13/19 (68.4)	11/15 (73.3)	−12.2 (−45.42, 24.19)
No. (%) of patients with:			
Clinical cure at TOC	229 (77.6)	237 (77.7)	−0.08 (−6.74, 6.59)
Modified clinical cure[a] at TOC	211 (71.5)	215 (70.5)	1.03% (−6.23 to 8.29)

[a]A modified clinical cure was defined as a ≥90% reduction in lesion size compared to that at the baseline, no increase in lesion size since ETP, and no requirement for additional antibiotics (except aztreonam or metronidazole) or unplanned significant surgical procedures after ETP.

TABLE 4 Safety parameters by treatment

AE category[a]	No. (%) of patients treated with: Iclaprim (n = 299)	Vancomycin (n = 302)
No. (%) of patients with any AE	140 (46.8)	133 (44.0)
No. (%) of patients with drug-related AEs	42 (14.0)	39 (12.9)
No. (%) of patients with AEs leading to discontinuation of study drug	16 (5.4)	17 (5.6)
No. (%) of patients with any SAE	16 (5.4)	14 (4.6)
No. (%) of patients with drug-related SAEs	1 (0.3)	2 (0.7)
No. (%) of patients with SAEs leading to discontinuation study drug	5 (1.7)	5 (1.7)
No. (%) of deaths	0	1 (0.3)
No. (%) of patients with the following AEs by system organ class[b]:		
Nausea	17 (5.7)	17 (5.6)
Infusion site extravasation	13 (4.3)	12 (4.0)
Hypokalemia	6 (2.0)	11 (3.6)
Diarrhea	8 (2.7)	11 (3.6)
Vomiting	7 (2.3)	7 (2.3)
Pyrexia	7 (2.3)	5 (1.7)
Hypertension	7 (2.3)	5 (1.7)
Headache	7 (2.3)	13 (4.3)
Anemia	6 (2.0)	6 (2.0)
Increased AST concn[c]	6 (2.0)	5 (1.7)
Increased ALT concn[c]	5 (1.7)	7 (2.3)
Pruritus	2 (0.7)	7 (2.3)
No. (%) of patients with AEs of special interest (nephrotoxicity)	0	2 (0.7)
Mean (SD) QTcF prolongation (ms)	9.9 (14.6)	3.8 (16.3)
Serum creatinine changes		
Mean (SD) serum creatinine change (μmol/liter) from baseline to TOC	0.7 (18.0)	7.7 (39.8)
Mean (SD) serum creatinine change (mg/dl) from baseline to TOC	0.008 (0.20)	0.09 (0.45)

[a]Abbreviations: AE, adverse event; SAE, severe adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[b]The order of the AEs by system organ class is from the most frequent (top) to the least frequent (bottom) for iclaprim.
[c]Investigator reported.

primary endpoint of an early clinical response. This phase 3 clinical trial also met its secondary endpoints, demonstrating that the clinical cure rates at both the traditional and the modified composite TOC were similar for patients treated with iclaprim and vancomycin. Similar treatment outcomes were also noted across *a priori* identified subgroups. No notable differences in the incidence of adverse events between the treatment groups were observed.

The results of the REVIVE-2 study were broadly similar to those of the REVIVE-1 study, an identically designed trial in which iclaprim also achieved noninferiority to vancomycin. Taken together, these results suggest that iclaprim is efficacious and safe for the treatment of serious skin infections suspected to be due to Gram-positive pathogens.

In contrast to previous studies of complicated skin and skin structure infections (19), a fixed iclaprim dose was used in this study. This fixed dose of iclaprim was selected because, compared to the weight-based dosing regimen used in the previous phase 3 studies (20), the fixed dose maximizes by 30% the area under the concentration-time curve/MIC and the time above the MIC, the parameters most closely associated with efficacy in animal infection models, while it reduces by 10% the steady-state maximum concentration in plasma ($C_{max,ss}$), a parameter associated with QTc prolongation in

phase 1 studies. In this study, there was one patient who received iclaprim (0.3%) with subsequent QTc prolongation. Consequently, the fixed dose of iclaprim may be important, especially in patients with borderline QTc prolongation, diabetes, obesity, and decreased renal function. No dosage adjustments of iclaprim are needed in these populations.

Currently recommended agents for the treatment of moderate to severe skin infections caused by Gram-positive pathogens include vancomycin, linezolid, or daptomycin (11). Safety issues or resistance to these agents has been reported among patients treated for MRSA infections (12–17). The results of this study, in combination with those of the REVIVE-1 study, suggest that iclaprim may be a useful addition to the treatment armamentarium. The advantages of iclaprim are that it does not appear to be nephrotoxic, does not require dose adjustments for renal impairment, and does not require therapeutic drug monitoring.

A strength of this phase 3 study is the fact that greater than 40% of the randomized patients had wound infections. This group of infections is typically more difficult to cure than abscesses and cellulitis, and the inclusion of these patients enhances the generalizability of the study findings to this important population.

There are limitations to this phase 3 study. First, 67.5% (405 out 600) of the patients enrolled in this study were from the United States, 29.7% (178 of 600) were from Europe, and 2.8% (17 of 600) were from Latin America. High proportions of injection drug users (~50%) were included in both treatment groups. Therefore, the results may not be generalizable to other practice settings. Second, data on vancomycin trough concentrations were not analyzed at the central laboratory, and local laboratory trough values were not available. However, on the basis of adherence to the prespecified vancomycin dosing nomogram, greater than 95% of patients had the correct dosing interval for this antibiotic, including those patients with renal impairment (creatinine clearance [CL_{CR}] $<$ 75 ml/min), for whom the initial dosing interval was based on renal clearance. Third, vancomycin was used instead of a beta-lactam drug for the treatment of MSSA infections when MSSA was obtained from patients with an ABSSSI. Beta-lactam drugs are likely superior to vancomycin for the treatment of MSSA infections. Fourth, leading-edge biopsy specimens and anti-streptolysin O (ASO) titers were measured to determine the etiology of group A streptococci (GAS) causing ABSSSIs. These diagnostic methodologies are not specific for GAS and may overestimate the true frequency of GAS as a cause of ABSSSIs.

In conclusion, in this phase 3 study, iclaprim was noninferior to vancomycin with respect to the early clinical response at an early time point in the treatment of ABSSSIs caused or suspected to be caused by Gram-positive organisms. These results suggest that iclaprim may serve as an alternative option for the treatment of ABSSSIs caused by Gram-positive pathogens, including certain drug-resistant bacteria. In hospitalized ABSSSI patients with comorbidities, such as renal impairment and/or diabetes, iclaprim may provide advantages over vancomycin due to the fixed dose regimen and absence of nephrotoxicity.

MATERIALS AND METHODS

Study design and participants. The REVIVE-2 study was a double-blind, multicenter phase 3 noninferiority trial (ClinicalTrials.gov identifier NCT02600611). Patients were randomized 1:1 to treatment with either iclaprim at 80 mg intravenously (i.v.) every 12 h (q12h) (iclaprim) or vancomycin at 15 mg/kg i.v. q12h (vancomycin). This study design followed both Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidance. Patients were enrolled between April 2016 and August 2017. The institutional review board at each site approved the protocol, and all patients or their authorized representative provided written informed consent.

Male and female patients ≥18 years of age with a suspected or confirmed ABSSSI due to Gram-positive pathogens were eligible for study participation. An ABSSSI was defined as a bacterial infection of the skin with a lesion size of ≥75 cm^2. ABSSSIs were classified as major cutaneous abscesses, pure cellulitis/erysipelas, and/or wound infections (caused by external trauma [e.g., needle sticks or insect bites]) and had characteristics of the presence of purulent or seropurulent drainage before or after surgical intervention of a wound or at least 3 of the following signs and symptoms: discharge, erythema (extending at least 2 cm beyond a wound edge in one direction), swelling and/or induration, heat and/or

TABLE 5 Key inclusion and exclusion criteria[a]

Inclusion criteria	Exclusion criteria
Provision of informed consent	ABSSSIs of the following categories: severely impaired arterial blood supply such that amputation of the infected anatomical site was likely, more than one abscess, infected diabetic foot ulcers, infected decubitus ulcers, infected human or animal bites, necrotizing fasciitis or gangrene, uncomplicated skin or skin structure infection, self-limiting infections
Evidence of systemic involvement as defined by having at least 1 of the following conditions within 24 h of randomization considered to be pathogen related:	Skin and/or skin structure infection that could be treated by surgery alone
Fever (temp, >38°C [100.4°F] orally, rectally, or tympanically)	Infections associated with a prosthetic device and suspected or confirmed osteomyelitis, septic arthritis, or endocarditis
Enlarged and/or tender proximal lymphadenopathy and/or lymphangitis	Known or suspected concurrent infection or conditions requiring systemic antimicrobial treatment, prophylaxis, or suppression therapy
Elevated total peripheral WBC count of >10,000/mm^3	Known or suspected HIV infection with a cluster of differentiation (CD4) count of <200 cells/mm^3 recorded in the last 30–60 days; ANC of <500 cells/mm^3; organ transplant within the preceding 6 mo; requirement for corticosteroids at >20 mg/day prednisolone or equivalent; or receipt of corticosteroids at >20 mg per day prednisolone or equivalent in the past 3 days
>10% immature neutrophils (bands) regardless of total peripheral WBC count	Cardiovascular conditions and treatments consisting of congenital or sporadic syndromes of QTcF prolongation; receipt of type IA or III antiarrhythmic drugs; or NSVT, defined as >10 consecutive ventricular beats at a rate of >120 bpm with a duration of <30 s, bradycardia (<40 bpm), and a QT/QTcF interval outside the normal range (defined as a QTcF interval of >500 ms)
Elevated C-reactive protein levels	Receipt of more than one dose of a short-acting (i.e., dosing q12h or less) systemic antibiotic active against Gram-positive pathogens within the last 7 days, unless there was documented evidence of treatment failure or demonstrated resistance of Gram-positive pathogens to the prior antibiotic therapy

[a]Abbreviations: HIV, human immunodeficiency virus; ANC, absolute neutrophil count; WBC, white blood cell; NSVT, nonsustained ventricular tachycardia; bpm, beats per minute.

localized warmth, and/or pain and/or tenderness to palpation. Key inclusion and exclusion criteria are listed in Table 5.

Iclaprim was administered at 80 mg (no hepatic impairment or a Child-Pugh score of A) or 40 mg i.v. q12h (a Child-Pugh score of B). Patients with a Child-Pugh score of C were excluded. Vancomycin was administered at 15 mg/kg i.v., and the dose was adjusted according to a nomogram with dosing every 12 h (creatinine clearance [CL_{CR}] $\geq$ 50 ml/min), every 24 h (CL_{CR} $\geq$ 35 to 49 ml/min), every 48 h (CL_{CR} $\geq$ 25 to 34 ml/min), or according to vancomycin trough levels (CL_{CR} $<$ 25 ml/min) or creatinine clearance. The unblind pharmacist prepared the infusions for patients who were assigned to the vancomycin arm, maintaining the same infusion volume used for iclaprim. For each patient, the unblind pharmacist used the creatinine clearance or vancomycin trough levels (to which the investigator was blind) to adjust the vancomycin dosage to maintain a trough concentration of 10 to 15 mg/liter for patients with an organism with an MIC of $\leq$1 mg/liter or 15 to 20 mg/liter for those with an organism with an MIC of >1 mg/liter. Both iclaprim and vancomycin were infused over 120 min in 500 ml normal saline. Normal saline placebo infusions were used to maintain the blind when vancomycin was dosed at an interval greater than every 12 h.

The protocol permitted concomitant antibiotic treatment with aztreonam or metronidazole for patients in whom Gram staining of culturable material or cultures indicated Gram-negative and anaerobic bacteria, respectively. Systemic antibiotics (other than aztreonam and metronidazole) or topical antibiotics at the site of the ABSSSI under investigation were prohibited.

Patients received their first dose of randomly allocated study medication within 24 h after randomization. Study medications were administered for at least 5 days, with continuation of the treatment for up to 14 days occurring at the discretion of the investigator on the basis of an assessment of the resolution of signs and symptoms of the ABSSSI. This duration of treatment was in accordance with Infectious Diseases Society of America (IDSA) guidelines (11).

Clinical specimens for microbiologic evaluation, including pus from a wound or abscess and aspirate or a skin biopsy specimen from the leading edge of cellulitis, were obtained from patients prior to randomization. At subsequent visits, additional specimens were obtained for patients with persistent clinical signs or symptoms. Specimens were evaluated by the local microbiology laboratory, and the isolates were subcultured and sent to a central microbiology laboratory for confirmation of the pathogen identity and MICs. *S. aureus* genotyping was not performed for this study. In order to increase the identification of patients with ABSSSIs caused by *Streptococcus pyogenes* (e.g., cellulitis), the collection of leading-edge punch biopsy specimens was encouraged for patients with pure cellulitis, and serological tests (ASO titer determinations) were performed for all patients at the baseline and at the test of cure (2 to 3 weeks after the baseline). A beta-hemolytic streptococcus was considered present if the patient had an ABSSSI and an elevated titer of ASO at the baseline and/or at the test of cure or a 4-fold rise of the

antibody titer at the test of cure from that at the baseline. Two sets of blood samples for aerobic/anaerobic cultures were obtained 10 min apart from different sites peripherally within the 24 h before the first dose of study drug.

Endpoints. The primary efficacy endpoint of the study was the proportion of patients who achieved an early clinical response (ECR), defined as a ≥20% reduction in lesion size compared with that at the baseline at the early time point (ETP) of 48 to 72 h after the start of administration of the study drug in the intent-to-treat (ITT) population. The secondary endpoints of the study included (i) the clinical cure rate at the test of cure (TOC), which was at 7 to 14 days after the last dose of study drug, as measured by both the traditional and modified composite TOC assessments in the ITT population (see below), and (ii) the safety and tolerability of iclaprim compared with those of vancomycin.

Clinical cure at the TOC visit, determined 7 to 14 days after the EOT, was evaluated using two prespecified definitions. First, clinical cure at the TOC visit was defined as the complete resolution of all signs and symptoms of ABSSSIs, such that no further antibiotic treatment or surgical procedure was needed. This definition of clinical cure is used for pivotal phase 3 studies of ABSSSIs (18). Second, a modified clinical cure at the TOC was also evaluated as a ≥90% reduction in the lesion size compared with that at the baseline, no increase in lesion size since the ETP, and no requirement for additional antibiotics (except aztreonam or metronidazole for polymicrobial infections) or unplanned significant surgical procedures after the ETP. This modified clinical cure was intended to allow for an additional measure (i.e., a 90% reduction in lesion size), similar to the early clinical response (ECR; i.e., a 20% reduction in lesion size).

Patients were evaluated at a baseline assessment, then evaluated daily through ETP, and then evaluated every 48 to 72 h through the EOT. The treatment duration was 5 to 14 days and was based on investigator assessment. Patients were then evaluated at the TOC assessment, conducted 7 to 14 days after the EOT, followed by a late follow-up phone call conducted 28 to 32 days after the first dose (Fig. 1).

Safety was assessed by the use of common terminology criteria for reported adverse events (AEs), serious adverse events (SAEs), hematology, clinical chemistry, liver function tests, coagulation, urinalysis, vital signs, physical examinations, and electrocardiograms (ECGs).

Statistical analysis. The statistical analyses evaluated the efficacy and safety of iclaprim compared with those of vancomycin. Statistical tests for efficacy analyses were two-sided and at a level of significance with an alpha value of 0.05. Confidence intervals (CIs) were calculated as a two-sided 95% confidence interval. Continuous data were summarized by treatment group using the number of patients in the analysis population (*n*), mean, standard deviation (SD), median, and range, and categorical data were summarized by treatment group using *n* and the percentage of patients. Demographics and baseline characteristics were summarized using descriptive statistics. The primary efficacy analysis was performed in the ITT population. Secondary analyses were performed in the ITT predefined populations that included patients with diabetes and mild, moderate, and severe renal impairment. By-patient and by-pathogen bacteriological outcomes at the EOT and TOC were presented as frequency distributions of outcomes by treatment group for patients with a confirmed Gram-positive pathogen at the baseline. The safety population was defined as all randomized patients who received at least one dose of study medication. The incidence of AEs was summarized at the overall patient level, the Medical Dictionary for Regulatory Activities (MedDRA; version 20.0) system organ class level, and preferred term level. Separate tabulations were provided by severity and relationship to the study medication and for SAEs. Laboratory data, vital signs, and ECGs were evaluated by presentation of summary statistics of raw data and changes from the baseline.

Six hundred patients (approximately 300 per treatment group) randomized 1:1 were targeted for this study. Using Farrington and Manning's method for noninferiority (NI) testing with a one-sided alpha value of 0.025, assuming a 75% ECR rate in each group, and a 10% noninferiority-bound delta value, a sample size of 295 ITT patients per treatment group was required for 80% power.

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