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A Phase 3, **R**andomized, double-blind, multicenter study to **EV**aluate the safety and efficacy of intravenous **I**claprim versus **V**ancomycin for the tr**E**atment of acute bacterial skin and skin structure infections suspected or confirmed to be due to Gram-positive pathogens: REVIVE-2

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Running Head: Iclaprim for acute skin infections

Summary: Iclaprim achieved non-inferiority compared with vancomycin at its primary endpoint of early clinical response (defined as a ≥20% reduction in lesion size at 48-72 hours compared to baseline) in a Phase 3 study for the treatment of acute bacterial skin and skin structure infections.

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Abstract

Iclaprim is a novel diaminopyrimidine antibiotic that may be an effective and safe treatment for serious skin infections. The safety and efficacy 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 (ABSSSI) suspected or confirmed to be due to Gram-positive pathogens were randomized to iclaprim (80 mg) or vancomycin (15mg/kg), both administered intravenously every 12 hours for 5 - 14 days. The primary endpoint was a ≥20% reduction in lesion size, compared with baseline, at 48 to 72 hours 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, compared with 76.7% (234 of 305) for those receiving vancomycin (treatment difference: 1.58%, 95% CI: -5.10% to 8.26%). This met the pre-specified 10% non-inferiority margin. Iclaprim was well tolerated, with most adverse events categorized as mild. In conclusion, iclaprim was non-inferior to vancomycin and was well tolerated in this Phase 3 clinical trial for the treatment of acute bacterial skin and skin structure infections. Based on 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 ben registered at ClinicalTrials.gov under identifier NCT02607618.)

Keywords: iclaprim, vancomycin, acute bacterial skin and skin structure infections

Introduction

Acute bacterial skin and skin structure infections (ABSSSI) 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 ABSSSI [3-4]. Iclaprim is a diaminopyrimidine, which inhibits bacterial dihydrofolate reductase, and is active against drug-resistant pathogens [6-9]. Iclaprim demonstrates rapid in vitro bactericidal activity in time-kill studies in human plasma [10]. In the previous Phase 3 clinical trial among patients treated for ABSSSI (REVIVE-1), early clinical responses in the intent-to-treat (ITT) population were 80.9% for iclaprim and 81.0% for vancomycin at the early time point [11]. We report the second Phase 3 study (REVIVE-2) comparing the outcomes of patients treated with either iclaprim or vancomycin for ABSSSI suspected or confirmed to be due to Gram-positive pathogens.

Methods

Study design and participants. REVIVE-2 was a double-blind, multicenter phase 3 non-inferiority trial. Patients were randomized 1:1 to treatment with either iclaprim 80 mg IV q12h (iclaprim) or vancomycin 15mg/kg IV q12h (vancomycin) (NCT02600611). 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 suspected or confirmed ABSSSI due to Gram-positive pathogens were eligible for study participation. ABSSSI was defined as a bacterial infection of the skin with a lesion size ≥ 75cm^2. ABSSSIs were classified as major cutaneous abscess, pure cellulitis/erysipelas, and/or wound infections (caused by external trauma [e.g., needle sticks or insect bites]), and had the following characteristics: 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 localized warmth, and/or pain and/or tenderness to palpation. Key inclusion and exclusion criteria are listed in Table 1.

Iclaprim was administered at 80mg (no hepatic impairment or Child-Pugh A) or 40 mg IV q12h (Child-Pugh B). Child-Pugh C patients were excluded. Vancomycin was administered at 15 mg/kg IV and adjusted according to a nomogram with dosing every 12 hours (creatinine clearance [CrCl] ≥50 mL/min), every 24 hours (CrCl ≥35-49 mL/min**),** every 48 hours (CrCl ≥25-34 mL/min), or according to vancomycin trough levels (CrCl <25 mL/min) or creatinine clearance. The unblinded pharmacist prepared infusions for patients who were assigned to the vancomycin arm, maintaining the same infusion volume as used for iclaprim. For each patient, the unblinded pharmacist used the creatinine clearance or vancomycin trough levels (to which the investigator was blinded) to adjust the vancomycin dosage to maintain a trough of 10 - 15 mg/L for patients with an organism with MIC ≤1 mg/L, or 15 - 20 mg/L for those with MIC >1 mg/L. Both iclaprim and vancomycin were infused over 120 minutes in 500mL normal saline.

Normal saline placebo infusions were used to maintain the blind when vancomycin was dosed at an interval greater than every 12 hours.

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 hours after randomization. Study medications were administered for at least 5 days with continuation of treatment up to 14 days at the discretion of the investigator based on the assessment of resolution of signs and symptoms of the ABSSSI. This duration of treatment was in accordance with the Infectious Disease Society of America (IDSA) guidelines [12].

Clinical specimens for microbiologic evaluation, including pus from a wound or abscess, and aspirate or skin biopsy 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 isolates were subcultured and sent to a central microbiology laboratory for confirmation of pathogen identity and MICs. S. aureus genotyping was not performed for this study. In order to increase identification of patients with ABSSSI caused by Streptococcus pyogenes (e.g., cellulitis), leading edge punch biopsies were encouraged for patients with pure cellulitis and serological tests (ASO titers) for all patients were obtained at baseline and at test of cure (2-3 weeks after baseline). A beta-hemolytic streptococci was considered present if the patient had a ABSSSI and an elevated titer of ASO at baseline and/or at test of cure or a four fold

rise of antibody at test of cure from baseline. Two sets of blood samples for aerobic/anaerobic cultures 10 minutes apart from different sites peripherally were obtained within 24 hours 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 baseline at the early time point (ETP) 48-72 hours after the start of administration of the study drug in the intent-to-treat (ITT) population. The secondary endpoints of the study included: (1) clinical cure rate at test of cure (TOC) 7 - 14 days after the last dose of study drug, as measured by both the traditional and a modified composite TOC assessments in the ITT population (see below); and (2) safety and tolerability of iclaprim compared with vancomycin.

Clinical cure at the TOC visit, conducted 7 - 14 days post-EOT, was evaluated using two prespecified definitions. First, clinical cure at the TOC visit was defined as complete resolution of all signs and symptoms of ABSSSI such that no further antibiotic treatment or surgical procedure were needed. This definition of clinical cure is used for pivotal Phase 3 studies of ABSSSI [5]. Secondly, a modified clinical cure at TOC was also evaluated as a ≥90% reduction in lesion size compared with baseline, no increase in lesion size since ETP, and no requirement for additional antibiotics (except aztreonam or metronidazole for polymicrobial infections) or unplanned significant surgical procedures after ETP. This modified clinical cure was intended to allow for an additional measure (i.e., 90% reduction in lesion size) similar to the early clinical response (ECR, i.e., 20% reduction in lesion size).

Patients were evaluated at a baseline assessment, then evaluated daily through ETP, and then every 48 - 72 hours through EOT. Treatment duration was 5 - 14 days based on investigator

assessment. Patients were then evaluated at the TOC assessment conducted 7 - 14 days post-EOT, followed by a late follow-up phone call conducted 28 to 32 days after the first dose (Figure 1).

Safety was assessed by Common Terminology Criteria for reported treatment emergent adverse events (TEAEs), 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 vancomycin. Statistical tests for efficacy analyses were two-sided, and at the level of significance alpha = 0.05. Confidence intervals (CIs) were calculated as a two-wided 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 percentage. 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 diabetes, mild, moderate and severe renal impairment. By-patient and by-pathogen bacteriological outcomes at EOT and TOC were presented as frequency distributions of outcomes by treatment group for patients with a confirmed Gram-positive pathogen at baseline. The safety population was defined as all randomized patients who received at least one dose of study medication. The incidence of TEAEs was summarized at the overall patient level, 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 study medication and for SAEs.

Laboratory data, vital signs and ECGs were evaluated by presentation of summary statistics of raw data and changes from baseline.

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

Results

Demographics

The study randomized 613 patients, and 600 fulfilled criteria for the ITT population, the prespecified efficacy population for FDA, from 40 study sites in 10 countries. Figure 2 shows the disposition of patients. The patients lost to followup in each treatment group were similar to 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 study entry criteria (lesion size <75 cm^2) and 7 were unable or unwilling to follow study procedures. The baseline and demographic characteristics of patients treated with either iclaprim or vancomycin were comparable (Tables 2 and 3). The proportion of patients with fever at baseline in the iclaprim and vancomycin cohorts were 27.1% and 26.2%, respectively. The baseline mean (S.D.) lesion sizes of patients in the iclaprim and vancomycin cohorts were 372.3 (305.8) cm^2 and 357.0 (271.1) cm^2, respectively. Treatment groups were similar for baseline ABSSSI categories, laboratory parameters, vital signs, physical examinations, X-rays, and ECG evaluations. In addition, no notable differences were observed between treatment groups with

respect to prior medications and treatments or study drug compliance were observed. Both the iclaprim and vancomycin treatment groups had a median of 7 treatment days (range: 5 – 14 days).

Efficacy Results

Primary Endpoint

In the ITT population, an ECR was reported at ETP for 78.3% (231/295) of patients in the iclaprim group and for 76.7% (234/305) of patients in the vancomycin group (% difference: 1.58; 95% Confidence Interval (CI): -5.10, 8.26)) (Table 3). A sensitivity analysis adding the 13 excluded patients showed similar results (iclaprim 76.5%, vancomycin 76.2%, % difference 0.25, 95% CI: -6.48, 6.98).

Secondary Analyses

In the ITT population, the clinical cure rates at TOC were 77.6% (229/295) and 77.7% (237 of 305) for patients treated with iclaprim and vancomycin group, respectively (% difference: -0.08; 95% CI: -6.74, 6.59) (Table 4). Using a modified clinical cure TOC analysis defined by a ≥90% reduction in lesion size compared with 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, mild, moderate and severe renal impairment (Table 4).

For the microbiological outcome at EOT and TOC, 384 (64.0%) patients presented with a

culture-confirmed Gram-positive pathogen at baseline. S. aureus was the most commonly isolated pathogen (N=258) of which 138 (53.4%) were MRSA (Table 2). The MIC_{50}/MIC_{90} values for iclaprim and vancomycin for S. aureus isolates were 0.12 / 0.5 mcg/mL and 1 / 1 mcg/mL, respectively.

Safety Results

Study drug-related TEAEs, treatment emergent SAEs, and deaths among patients in the iclaprim and vancomycin treatment groups are shown in Table 5. The treatment emergent adverse events leading to discontinuation were 5.4% and 5.6% in the iclaprim and vancomycin group, respectively. Similar incidence of nausea (5.7% and 5.6%), infusion site extravasation (4.3% and 4.0%), diarrhea (2.7% and 3.6%), and headache (2.3% and 4.3%), were reported in patients in the iclaprim group compared to vancomycin group, respectively. Although not an a priori hypothesis, there were no study-drug related TEAE related to nephrotoxicity reported for patients treated with iclaprim compared to 2 (0.7%) for vancomycin. Per the protocol, nephrotoxicity was predefined as an increase in serum creatinine of 0.5 mg/dL or 50% above baseline for at least two consecutive days. The serum creatinine change from baseline to TOC was 0.7 and 7.7 µmol/L (0.008 and 0.09 mg/dL) in patients in the iclaprim group compared to vancomycin group, respectively. There were no significant differences between treatment groups in mean values or mean changes in other routine serum laboratory parameters, urinalysis results, vital signs or physical examinations during treatment, or at EOT, TOC and follow-up between treatment groups. Eleven (3.7%) patients in the iclaprim group, and nine (3.0%) patients in the vancomycin group had increases in ALT or AST values to >3X upper limit of normal (ULN) during treatment. Three patients (one in the iclaprim 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 and one in the vancomycin group) had bilirubin increases >2X ULN. These increases resolved to baseline values upon discontinuation of drug in all patients. No subject met Hy's law criteria in this study.

One (0.4%) patient in the iclaprim group and 0 patients in the vancomycin group had QTcF intervals >500 msec (i.e., 503 msec) or increased by >60 msec compared with 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 non-inferior to vancomycin in the treatment of ABSSSI suspected or confirmed to be caused by Gram-positive organisms, based on the primary endpoint of early clinical response. This Phase 3 study clinical trial also met its secondary endpoints, demonstrating that the clinical cure rates at TOC, 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 TEAEs between the treatment groups were observed.

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

In contrast to previous cSSSI studies, 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 [4], the fixed dose maximizes by 30% the AUC/MIC and time above MIC, the parameters most closely associated with efficacy in animal infection models, while reducing by 10% the steady-state C_{max} ($C_{max/ss}$), a parameter associated with QTc prolongation in Phase 1 studies. In this study, there was only 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 treatment of moderate to severe Gram-positive skin infections include vancomycin, linezolid or daptomycin [12]. Safety issues or resistance to these agents are reported among patients treated for MRSA infections [15-20]. The results of this study, in combination with those of REVIVE-1, suggest that iclaprim may be a useful addition to the treatment armamentarium. Advantages of iclaprim are that it does not appear nephrotoxic, does not require dose adjustments for renal impairment, and does not require therapeutic drug monitoring.

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

There are limitations to this Phase 3 study. First, 67.5% (405 out 600) of enrolled patients in this study were from the United States, 29.7% (178 of 600) from Europe, and 2.8% (17 of 600) from Latin America. A high proportion 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 not analyzed at the

central laboratory and local laboratory trough values are not available. However, based on 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 <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 MSSA when obtained from ABSSSI. Compared to vancomycin, beta-lactam drugs are likely a superior agent for MSSA. Fourth, leading edge biopsies and ASO titers were measured to determine GAS etiology of ABSSSI. These diagnostic methodologies are not specific for GAS and may overestimate the true frequency of GAS for ABSSSI.

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

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407 Table 1: Key inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
Provision of informed consent	ABSSSI 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 hours of randomization considered to be pathogen-related:	Skin and/or skin structure infection that could be treated by surgery alone
Fever (>38°C/100.4°F orally, rectally, or tympanically)	Infections associated with a prosthetic device, and suspected or confirmed osteomyelitis or septic arthritis or endocarditis
Enlarged and/or tender proximal lymphadenopathy and/or lymphangitis	Known or suspected concurrent infection or conditions requiring systemic anti-microbial treatment, prophylaxis, or suppression therapy
Elevated total peripheral white blood cells (WBCs) >10,000/mm^3	Known or suspected human immunodeficiency virus (HIV)-infected patients with a cluster of differentiation (CD4) count <200 cells/mm^3 recorded in the last 30 - 60 days; absolute neutrophil count (ANC) <500 cells/mm^3; organ transplant within the preceding 6 months; requirement for corticosteroids >20 mg/day prednisolone or equivalent, or received corticosteroids >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: patients known to have congenital or sporadic syndromes of QTcF prolongation; type I A or III anti-arrhythmic drugs; nonsustained ventricular tachycardia (NSVT) defined as >10 consecutive ventricular beats at a rate of >120 beats per minute (bpm) with a duration of <30 seconds, bradycardia (<40 bpm), and QT/QTcF interval outside the normal range defined as: QTcF >500 msec

Elevated C-reactive protein	Received more than one dose of a short-acting (i.e., q12h dosing 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.

408 Table 2: Baseline and demographic characteristics among the ITT population by treatment

Characteristics	Iclaprim (n=295)	Vancomycin (n=305)
Age (yr), mean (SD) median	50.0 (15.65)	50.8 (15.03)
Gender, no. (%)		
Female	103 (34.9)	108 (35.4)
Male	192 (65.1)	197 (64.6)
Race, no. (%)		
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)
Multi-racial	0	2 (0.7)
Other	13 (4.4)	10 (3.3)
Weight (kg), mean (SD)	84.2 (20.78)	85.5 (22.17)
Geographic region, no. (%)		
United States	200 (67.8)	205 (67.2)
Europe	84 (28.5)	94 (30.8)
Latin America	11 (3.7)	6 (2.0)
Severe Infections[a]	185 (62.7)	198 (64.9)
Lesion Type		
Major Cutaneous Abscess, no. (%)	53 (18.0)	45 (14.8)

Cellulitis / Erysipelas, no. (%)	115 (39.0)	125 (41.0)
Wound Infection, no. (%)	127 (43.1)	135 (44.3)
Mean lesion Size, cm^2 (SD)	372.3 (305.752)	357.00 (271.077)
Comorbidities, no. (%)		
Diabetes	36 (12.2)	36 (11.8)
Renal Impairment, CrCL (ml/min) 60-89 30-59 <=29	 35 (12.0) 17(5.8) 2 (0.7)	 53 (17.9) 13 (4.4) 2(0.7)
Illicit drug use	144 (48.8)	160 (52.5)
Fever (oral temperature >38ºC/100.4ºF), no. (%)	80 (27.1)	80 (26.2)
Leukocytes (per mm^3), mean (SD) median (min, max)	9.5 (3.4) 9.2 (1.7, 22.2)	9.4 (3.8) 8.4 (2.9, 23.1)
Baseline microbiology, no. (%)		
Exclusively Gram-positive pathogens	170 (89.5)	167 (86.1)
Mixed Gram-positive and Gram-negative	20 (10.5)	27 (13.9)
Concomitant aztreonam use, no. (%)	13 (4.4)	20 (6.6)
Concomitant metronidazole use, no. (%)	9 (3.1)	11 (3.6)

[a]Severe infections defined as an infection at baseline with one or more of the following criteria: fulfilled the published definition for systemic inflammatory response syndrome (SIRS) by having ≥2 of the following findings: body temperature >38°C or <36°C, heart rate >90 bpm, respiration rate >20 breaths/minute, and WBC >12000/mm^3 or <4000/mm^3 or >10% bands;

evaluated as having severe tenderness or severe erythema at the infection site; and/or Positive blood cultures at baseline.

Table 3: Microbiological characteristics at study entry for the ITT population by treatment

Pathogen	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, no. (%)[a]	7/274 (2.6)	13/283 (4.6)
Infection Site Pathogen, no. (%)		
Multiple	21 (11.0)	26 (13.4)
Single	149 (78.4)	141 (72.7)

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

447 Table 4: Clinical responses for primary endpoint and secondary analyses in the ITT population

448 by treatment

Clinical Responses	Iclaprim (n=295)	Vancomycin (n=305)	Treatment Difference (%; 95% Confidence Interval)
Primary Endpoint			
Early Clinical Response (ECR) at Early Time Point (ETP) in ITT, no. (%) - Total	231 (78.3)	234 (76.7%)	1.58 (-5.10, 8.26)
Early Clinical Response (ECR) at Early Time Point (ETP) in ITT, no. (%) - US	173/200 (86.5)	164/205 (80.0)	6.50 (-3.35, 16.14)
Early Clinical Response (ECR) at Early Time Point (ETP) in ITT, no. (%) – EU and LA	58/95 (61.1)	70/100 (70.0)	-8.9 (-24.02, 5.11)
Secondary Analyses			
ECR at ETP among major cutaneous abscess, no. (%)	45 (84.9)	40 (88.9)	-3.98 (-17.29, 9.33)
ECR at ETP among cellulitis / erysipelas, no. (%)	81 (70.4)	91 (72.8)	-2.37 (-13.79, 9.05)
ECR at ETP among wound infections, no. (%)	105 (82.7)	103 (76.3)	6.38 (-3.35, 16.12)
ECR at ETP among MRSA infected, no./total no. (%)	61/69 (88.4)	53/69 (76.8)	11.59 (-5.80, 28.48)

ECR at ETP among MSSA infected, no./total no. (%)	50/60 (83.3)	51/60 (85.0)	-1.67 (-20.15, 16.90)
ECR at ETP among S. pyogenes infected, no./total no. (%)	64/76 (84.2)	74/93 (79.6)	4.6 (-4.29, 11.07)
ECR at ETP among diabetics, no./total no. (%)	26/36 (72.2)	29/36 (80.6)	-8.33 (-31.95, 15.99)
ECR at ETP among mild renal impairment (creatinine clearance 60-89 ml/min), no./total no. (%)	27/35 (77.1)	39/53 (73.6)	3.56 (-17.38, 24.72)
ECR at ETP among moderate and severe renal impairment (creatinine clearance <60 ml/min) , no./total no. (%)	13/19 (68.4)	11/15 (73.3)	-12.2 (-45.42, 24.19)
Clinical cure at TOC, no. (%)	229 (77.6%)	237 (77.7%)	-0.08 (-6.74, 6.59)
Modified clinical cure[a] at TOC, no. (%)	211 (71.5%)	215 (70.5%)	1.03% (-6.23 to 8.29)

[a]Modified clinical cure defined as a ≥90% reduction in lesion size compared to 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.

455 Table 5: Safety Parameters by Treatment

Category	Iclaprim (N=299)	Vancomycin (N=302)
Any drug-related TEAE[a], no. (%)	140 (46.8%)	133 (44.0%)
Study drug related TEAE, no. (%)	42 (14.0%)	39 (12.9%)
TEAE leading to discontinuation of study drug, no. (%)	16 (5.4%)	17 (5.6%)
TEAE related SAEs[a], no. (%)	14 (4.7%)	12 (4.0%)
Mean QTcF prolongation, msec (SD)	9.9 (14.6)	3.8 (16.3)
Mean serum creatinine change from baseline to TOC, umol/L (SD)	0.7 (18.0)	7.7 (39.8)
Mean serum creatinine change from baseline to TOC, mg/dL (SD)	0.008 (0.20)	0.09 (0.45)
Nephrotoxicity	0	2 (0.7)
Deaths, no. (%)	0	1 (0.3)
TEAE by system organ class, no. (%)		
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[b]	6 (2.0)	5 (1.7)
Increased ALT[b]	5 (1.7)	7 (2.3)
Pruritis	2 (0.7)	7 (2.3)

Note: The order of the TEAE by system organ class was listed in the order of most frequent (top) to least frequent (bottom) for iclaprim.

[a]Abbreviations: TEAE, treatment emergent adverse events; SAE, severe adverse event; ALT, Alanine aminotransferase; AST, aspartate aminotransferase

[b]Investigator reported

Figure Legend

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

Figure 2: Disposition of patients

Figure 1: Schedule of visits

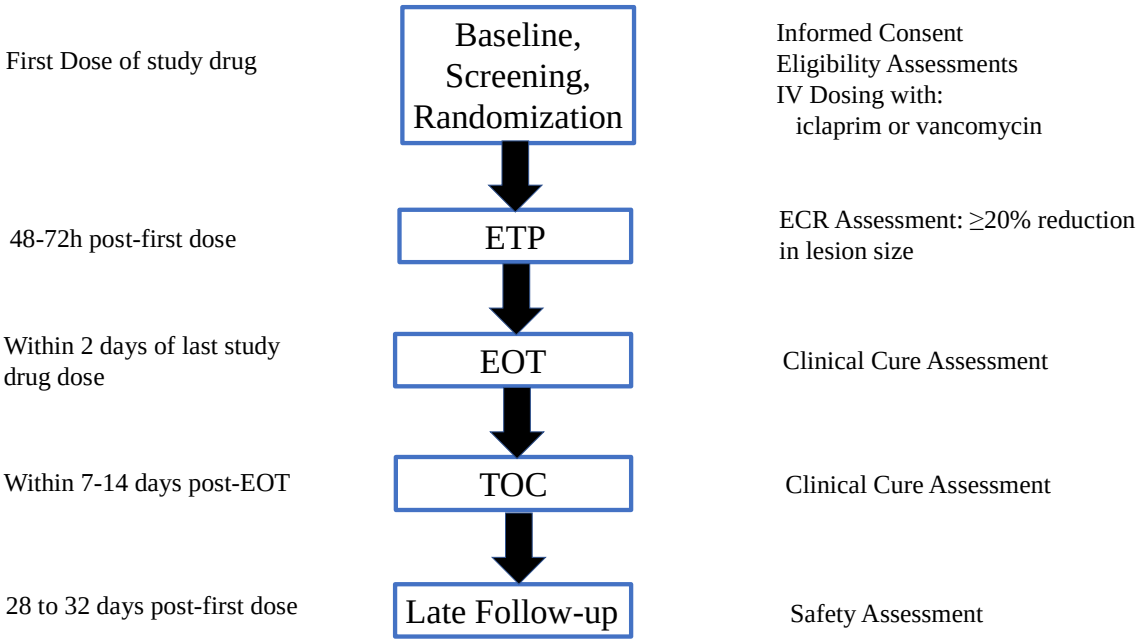
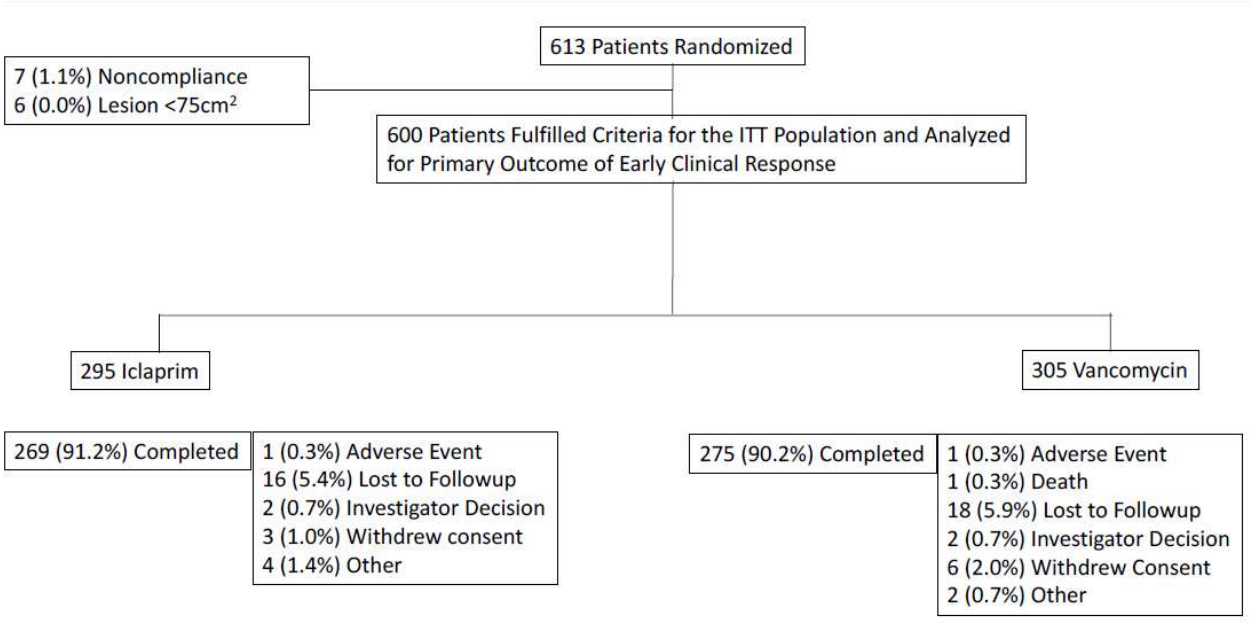


Figure 2: Disposition of Patients



Conflict of Interest

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