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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-1

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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.

Abstract

Background: The objective of this study was to demonstrate the safety and efficacy of iclaprim compared with vancomycin for the treatment of patients with acute bacterial skin and skin structure infections (ABSSSI).

Methods: REVIVE-1 was a Phase 3, 600 patient double-blinded, randomized (1:1), active-controlled trial among patients with ABSSSI, which compared the safety and efficacy of iclaprim 80 mg fixed dose with vancomycin 15mg/kg, both administered intravenously every 12 hours for 5 - 14 days. The primary endpoint of this study was a ⩾20% reduction in lesion size (early clinical response [ECR]) compared with baseline among patients randomized to iclaprim or vancomycin at the early time point (ETP), 48 to 72 hours after the start of administration of study drug in the intent-to-treat (ITT) population.

Results: ECR among patients who received iclaprim and vancomycin at the ETP were 80.9% (241 of 298) of patients receiving iclaprim compared with 81.0% (243 of 300) of those receiving vancomycin (treatment difference: -0.13%, 95% CI: -6.42% to 6.17%). Iclaprim was well tolerated in the study, with most adverse events categorized as mild.

Conclusions: Iclaprim achieved non-inferiority (10% margin) at ETP compared with vancomycin and was well tolerated in this Phase 3 clinical trial for the treatment of ABSSSI. Based on these results, iclaprim appears to be an efficacious and safe treatment for ABSSSI suspected or confirmed to be due to Gram-positive pathogens.

Study Registration Number: NCT02600611

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

Introduction

Acute bacterial skin and skin structure infections (ABSSSI) are potentially serious infections that may require hospitalization, intravenous antibiotics, and/or surgical intervention [1,2]. New therapeutic options with improved efficacy, safety, and/or pharmacodynamics are needed for ABSSSI [3-5]. 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 a Phase 2 clinical trial among patients treated for complicated skin and skin structure infections (cSSSI), clinical cure rates in the intent to treat (ITT) population were 92.9%, 90.3%, and 92.9% at the test of cure visit in the iclaprim 0.8 mg/kg IV q12h, iclaprim 1.6 mg/kg IV q12h, and vancomycin 1 g IV q12h groups, respectively [11]. Because of these characteristics, we conducted a Phase 3 study 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

This Phase 3 study was multi-center, double-blind, randomized 1:1 with two treatment arms: iclaprim 80 mg IV q12h (iclaprim) or vancomycin 15mg/kg IV q12h (vancomycin) (NCT02600611). This study design followed both FDA and EMA guidance. Patients were enrolled between April 2016 and January 2017. The institutional review board at each site approved the protocol, and all patients or their authorized representative provided written

76 informed consent.

77

78 *Patients*

79 The study randomized 598 patients who fulfilled criteria for the ITT population from 51
80 study sites in 7 countries. The ITT population, the prespecified efficacy population for FDA,
81 included all randomized patients. The safety population was defined as all randomized patients
82 who received at least one dose of study medication. Male and female patients ≥18 years of age
83 with suspected or confirmed ABSSSI due to Gram-positive pathogens were eligible for study
84 participation. Key inclusion and exclusion criteria are listed in Table 1.

85

86 *Definitions*

87 ABSSSI was defined as a bacterial infection of the skin with a lesion size ≥ 75cm^2.
88 ABSSSIs were stratified as major cutaneous abscess, cellulitis/erysipelas, and/or wound
89 infections (caused by external trauma [e.g., needle sticks or insect bites]), and had the following
90 characteristics: the presence of purulent or seropurulent drainage before or after surgical
91 intervention of a wound or at least 3 of the following signs and symptoms: discharge, erythema
92 (extending at least 2 cm beyond a wound edge in one direction), swelling and/or induration, heat
93 and/or localized warmth, and/or pain and/or tenderness to palpation.

94 Early clinical response (ECR) was defined as a ≥20% reduction in lesion size compared
95 with baseline. Early time point (ETP) was defined as 48 - 72 hours after the first infusion of
96 study drug. End of treatment (EOT) was defined as the day the infusion of study drug was
97 complete.

98 Clinical cure at the TOC visit 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 at the TOC visit. This definition of clinical cure is used for pivotal Phase 3 studies of ABSSSI and cSSSI. Second, 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 definition of clinical cure was intended to allow for an objective measure (i.e., 90% reduction in lesion size) similar to the early clinical response (ECR, i.e., 20% reduction in lesion size).

Assessments

Patients were evaluated at a baseline assessment, then evaluated daily through the early time point (ETP) conducted at 48 - 72 hours after the first infusion of study drug and then every 48 - 72 hours through the end of treatment (EOT). Treatment duration was 5 - 14 days based on investigator assessment. Patients were then evaluated at the test-of-cure (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).

Before randomization, adequate clinical specimens were obtained from patients at baseline, EOT and TOC for microbiologic evaluation. 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 minimum inhibitory concentrations (MICs). In order to enrich for ABSSSI caused by *Streptococci pyogenes* (e.g., cellulitis), leading edge punch biopsies were encouraged for patients with cellulitis and serological tests (ASO titers) for all patients were obtained. 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.

Primary Endpoint and Secondary Analyses

The primary endpoint of the study was to compare the ECR (defined as a ≥20% reduction in lesion size at the ETP compared with baseline) at ETP (48-72 hours after the start of administration of the study drug) in the ITT population treated with iclaprim or vancomycin among patients with ABSSSI suspected or confirmed to be due to Gram-positive pathogens. The secondary analyses of the study were: (1) clinical cure rate at TOC (7 - 14 days after the last dose of study drug compared with baseline); and (2) safety and tolerability of iclaprim compared with vancomycin.

Study Treatments

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 from this study. The fixed dose was chosen based on a pharmacokinetic and pharmacodynamics analysis of 470 plasma samples obtained from efficacy and safety evaluations in previous Phase 3 clinical studies [15]. Vancomycin was administered at 15 mg/kg IV and adjusted according to a nomogram with

dosing every q12h (creatinine clearance [CrCl] e ≥50) , q24h (CrCl ≥35-49), q48h (CrCl ≥25-34), or according to daily vancomycin trough levels (CrCl <25) or creatinine clearance. Trough levels were drawn at dose 5 for patients with normal renal function. The unblinded pharmacist prepared infusions for patients who were assigned to the vancomycin arm, notably keeping 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 the site pharmacist who adjusted the vancomycin dosage to maintain a trough of 10 - 15 mg/L for patients with an organism with a MIC was ≤1 mg/L, or 15 - 20 mg/L for those with a 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 where vancomycin was dosed at an interval greater than q12h.

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.

Duration of Treatment

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].

Statistical Methods

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.

The statistical analyses evaluated the efficacy and safety of iclaprim compared with vancomycin. Statistical tests were two-sided, and at the level of significance alpha = 0.05. The non-inferiority assessment was made with a one-sided test at significance level of 0.025. Confidence intervals (CIs) were calculated at a 95% confidence level. 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 had 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 incidence of TEAEs was summarized at the overall patient level, Medical Dictionary for Regulatory Activities (MedDRA) version 18.1 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.

Results

Demographics

Figure 2 shows the disposition of patients. The baseline and demographic characteristics of patients treated with either iclaprim or vancomycin were comparable (Tables 2 and 3). The baseline mean lesion sizes of iclaprim and vancomycin were 333cm^2 and 337 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 among treatment groups with respect to prior medications and treatments or study drug compliance were observed. Both the iclaprim and vancomycin treatment groups had the same median number of treatment days at 7 days (range: 5 – 14 days).

Efficacy Results

Primary Endpoint

In the ITT population, an ECR was reported at ETP for 80.9% (241/298) of patients in the iclaprim and for 81.0% (243/300) of patients in the vancomycin group (% difference: -0.13; 95% Confidence Interval (CI): -6.42, 6.17)) (Table 3).

Secondary Analyses

In the ITT population, the clinical cure rates at EOT were 86.9% (259 of 298) and 86.3% (259 of 300) for iclaprim and vancomycin, respectively (% difference: 0.58; 95% CI: -4.88, 6.04). Clinical cure was reported at TOC for 83% (248/298) of patients in the iclaprim and for 87% (262 of 300) of patients in the vancomycin group (% difference: -4.11; 95% CI: -9.78, 1.56)

(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 68.5% and 73.0% of patients receiving iclaprim and vancomycin, respectively (treatment difference: -4.54%, 95% CI: -11.83% to 2.74%). The ECR at ETP was comparable for iclaprim and vancomycin 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, 452 (75.6%) patients presented with a culture-confirmed Gram-positive pathogen at baseline (MITT population). *S. aureus* was the most commonly isolated pathogen (N=335) of which 134 (40%) were MRSA (Table 2). The MIC_{50}/MIC_{90} values for iclaprim and vancomycin for *S. aureus* isolates were 0.12 / 0.25 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 2.7% and 4.4% in patients in the iclaprim and vancomycin group, respectively. An increased incidence of headache (10.2% and 2.4%), nausea (9.9% and 5.7%), secondary ABSSSI infections (6.8% and 3.3%), and fatigue (6.1% and 3.0%), were reported in patients in the iclaprim compared to vancomycin group, respectively. There were no study-drug related TEAE related to nephrotoxicity reported for iclaprim compared to 3 (1.0%; acute kidney injury) for vancomycin. The creatinine change from baseline to TOC was 2.9 and 7.2 µmol/L in patients in the iclaprim 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. Fifteen (5.5%) patients in the iclaprim group, and 10 (3.8%) patients in the vancomycin group had increases in ALT or AST values to >3X upper limit of normal (ULN) during treatment. No patient 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., 527 msec) or increased by >60 msec compared with baseline. The one patient with a QTc prolongation was not reported as an AE and resolved to baseline values upon discontinuation of drug.

Discussion

This Phase 3 study clinical trial mets its primary endpoint, demonstrating that iclaprim is non-inferior to vancomycin in the treatment of ABSSSI caused by Gram-positive organisms with respect to ECR at the early time point of 48-72 hours after the first dose of study drug. No notable differences in the incidence of TEAEs between the treatment groups were observed.

The iclaprim dosage used in this study was fixed (i.e., 80 mg) over a 120 minute infusion, rather than the weight-based dosing of 0.8mg/kg used in previous studies. The weight based-dosing resulted in one Phase 3 study of cSSSI within and one outside the non-inferiority margin of greater than 10%. As a result, iclaprim was not approved by the FDA for the indication of cSSSI. Data supporting the fixed doise was based on modeling of population pharmacokinetics and pharmacodynamics from 470 patients receiving a weight based 0.8 mg/kg dose of iclaprim

in previous Phase 3 cSSSI studies [13]. A population pharmacokinetic analyses of the data from the 470 patients demonstrated no relationship between the clearance of iclaprim and body weight, suggesting that a fixed rather than weight based dose should be used. The estimates of the individual patient PK parameters were used to simulate the plasma iclaprim concentration-time profiles for each patient and from those profiles, the corresponding values for $C_{max/ss}$, $AUC(0\text{-}24)_{SS}$, AUC/MIC, and T > MIC. In these analyses, the MIC value used was based on the MIC_{90} of *S. aureus* of 0.12 mg/mL identified in worldwide surveillance studies [8]. Various fixed dose regimens were examined with respect to maximizing AUC/MIC and T > MIC while minimizing the probability of a steady-state C_{max} ($C_{max/ss}$) ≥ 800 ng/mL. This fixed dose was projected to result in a 30% increase in AUC/MIC and Time > MIC, parameters associated with efficacy in animal infection models, while allowing for an approximately 10% decrease in Cmax, a parameter associated with QTc prolongation in Phase 1 studies, compared with the weight based dose of iclaprim [14].

The IDSA guidelines for the management of adults with ABSSSI include use of either vancomycin, linezolid or daptomycin, all generic, against susceptible MRSA, for the empiric treatment of suspected ABSSSI in patients with risk factors for MRSA [12]. Safety issues or resistance to vancomycin, linezolid, and daptomycin are reported among patients treated for MRSA infections [15-20]. The results of this study suggest that iclaprim may be a useful treatment option for ABSSSI due to Gram-positive pathogens especially since it has an appropriate spectrum of activity, is effective, is not nephrotoxic and does not require therapeutic drug monitoring nor renal dosing adjustments.

There are limitations to this Phase 3 study. First, 70% (419 out 598) of enrollment in this study was from the United States, 28% (170 of 598) from Europe, and 1.5% (9 of 298) from

Latin America. No countries from Asia Pacific were included in this study. Second, it is often challenging to collect appropriate microbiological samples in cellulitis and only 8.3% (50 of 598) of cultures or ASO titers were positive for beta-hemolytic streptococci. Despite attempts to enrich for *Streptococci pyogenes* by leading edge punch biopsies and serological tests, the percentage of patients with an infection documented to be due to these bacteria were low. Third, data on vancomycin trough concentrations were not collected at the central laboratory in this study. Vancomyin dosing based on vancomycin trough concentrations at the local laboratories were not available. However, based on the vancomycin nomogram, >95% of patients had the correct dosing interval for this antibiotic. Fourth, there was an imbalance in the number of patients lost to follow-up between the iclaprim (5.7% (N=17)) and vancomycin (2.0% (N=6)) treatment groups. Among the patients lost to follow-up, 94% (16 of 17) and 100% (6 of 6) patients in the iclaprim and vancomycin treatment groups, respectively, lost to follow-up were intravenous drug users of heroin or amphetamine. As indicated in a prespecified statistical analyses plan, all patients lost to follow-up were considered non-cures. Fifth, an underpowered modified clinical cure 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 at TOC was used. This secondary analyses used an arbitrary reduction (≥90%) in lesion size compared with baseline at TOC. Post-inflammatory changes (e.g., erythema, swelling and/or induration) may linger on for weeks despite resolution of the infection and explain why a lower, modified clinical cure was observed at TOC. Sixth, greater than 50% of ABSSSI randomized were wound infections. For both wound infections and abscesses, surgical therapy is vital to treatment.

In conclusion, in this Phase 3 study, iclaprim was non-inferior to vancomycin with

306 respect to the early clinical response at an early time point in the treatment of ABSSSI caused or
307 suspected by Gram-positive organisms. These results suggest iclaprim may serve as an
308 alternative option for treatment of ABSSSI caused by Gram-positive pathogens, including drug-
309 resistant bacteria.

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Conflict of Interest

DBH is an employee of Motif BioSciences. TMF has served as a consultant for Motif BioSciences, Allergan, Medicines Company, Merck, Nabriva, Paratek, and Cempra. AT has served as a consultant for Motif BioSciences. AFS has served as a consultant to, received research support from, or been a speaker for: Abbott, Actavis, Alios, Astellas, AstraZeneca, Bayer, BMS, Cardeas, Medicines Company, Merck, Pfizer, Roche, Tetraphase, Theravance, and Wockhardt Pharma. MHW has received consulting fees from Abbott Laboratories, Actelion, Astellas, Astra-Zeneca, Bayer, Biomèrieux, Cerexa, Cubist, Durata, The European Tissue Symposium, The Medicines Company, MedImmune, Merck, Motif Biosciences, Nabriva, Optimer, Paratek, Pfizer, Qiagen, Roche, Sanofi-Pasteur, Seres, Summit, and Synthetic Biologics; lecture fees from Abbott, Alere, Astellas, Astra-Zeneca, Merck, Pfizer & Roche; grant support from Abbott, Actelion, Astellas, Biomèrieux, Cubist, Da Volterra, MicroPharm, Morphochem AG, Sanofi-Pasteur, Seres, Summit and The European Tissue Symposium, Merck.
PH is a former employee of Arpida. MD has received speaker's and/or consultancy fees from AstraZeneca, Bayer, Janssen-Cilag, Motif BioSciences, Novartis, Pfizer, and Merck, Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. T.H. has received consultancy fees from Basliea Pharmaceutica, Genentech, Medicines Company, and Motif Biosciences. R.C. has received

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451 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, 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
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	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.

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

Characteristics	Iclaprim (n=298)	Vancomycin (n=300)
Age (years), mean (SD) median	46.4 (13.3) 47	48.2 (14.8) 49
Gender, n (%)		
Female	109 (36.6)	129 (43.0)
Male	189 (63.4)	171 (57.0)
Race, n (%)		
White	266 (89.3)	269 (89.7)
Black	4 (1.3)	7 (2.3)
American Indian or Alaska Native	6 (2.0)	3 (1.0)
Native Hawaiian or other Pacific Islander	2 (0.7)	2 (0.7)
Multi-racial	3 (1.0)	0
Other	17 (5.7)	19 (6.3)
Weight (kg), mean (SD) Median, min, max	81 (20.0) 76 (48.0, 161.6)	80 (18.2) 77 (44.6, 144.0)
Geographic region, n (%)		
US	219 (73.5)	200 (66.7)
Europe	75 (25.2)	95 (31.7)
Latin America	4 (1.3)	5 (1.7)
Severe Infections*	211 (70.8)	198 (66.0)
Lesion Type		
Major Cutaneous Abscess, n (%)	40 (13.4)	55 (18.3)

Cellulitis / Erysipelas, n (%)	76 (25.5)	87 (29.0)
Wound Infection, n (%)	182 (61.1)	158 (52.7)
Mean Lesion Size, cm^2 (SD)	333 (317.1)	337 (317.5)
Comorbidities, n (%)		
Diabetes	20 (6.7)	35 (11.7)
Renal failure	36 (12.1)	56 (18.7)
Intravenous drug use	190 (66.4)	149 (49.7)
Fever (oral temperature >38ºC/100.4ºF), n (%)	90 (30.2)	84 (28.0)
Leukocytes (per mm^3), mean (SD) median (min, max)	9.7 (3.8) 9.2 (3.2, 24.9)	9.3 (3.4) 8.7 (2.9, 25.4)
Baseline Microbiology, n (%)		
Exclusively Gram-positive pathogens	212 (90.6)	199 (90.0)
Mixed Gram-positive and Gram-negative	22 (9.4)	22 (10.0)
Concomitant aztreonam use, n (%)	7 (2.3)	9 (3.0)
Concomitant metronidazole use, n (%)	3 (1.0)	3 (1.0)

*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=298)	Vancomycin (n=300)
Positive ABSSSI Culture	232 (77.8)	220 (73.3)
Staphylococcus aureus		
MRSA	73 (24.5)	61 (20.3)
MSSA	97 (32.6)	104 (34.7)
Streptococcus beta-hemolytic	25	25
Positive Blood Culture at Baseline, n (%)	15 (5.4)	14 (5.0)
Infection Site Pathogen, (%)		
Multiple	68 (28.1)	57 (25.1)
Single	174 (71.9)	170 (74.9)

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

476 by treatment

Clinical Responses	Iclaprim (n=298)	Vancomycin (n=300)	Treatment Difference (%; 95% Confidence Interval)
Primary Endpoint			
Early Clinical Response (ECR) at ETP in ITT	241 (80.9%)	243 (81.0%)	-0.13 (-6.42, 6.17)
Secondary Analyses			
ECR at ETP among major cutaneous abscess	35/40 (87.5)	49/55 (89.1)	-1.59 (-14.74, 11.56)
ECR at ETP among cellulitis / erysipelas	54/76 (71.1)	68/87 (78.2)	-7.11 (-20.50, 6.28)
ECR at ETP among wound infections	152/182 (83.5)	126/158 (79.7)	3.77 (-4.50, 12.04)
ECR at ETP among MRSA infected	59/73 (80.8%)	50/61 (82.0%)	-1.15 (-17.94, 15.80)
ECR at ETP among MSSA infected	81/97 (84.4%)	88/104 (85.4%)	-1.06 (-14.94, 12.85)
ECR at ETP among *S. pyogenes* infected	20/25 (80.0%)	18/25 (72.0%)	8.00 (-32.98, 33.86)
ECR at ETP among Diabetics	16/20 (80.0%)	26/35 (74%)	5.71 (-21.94, 32.74)
ECR at ETP among Mild Renal Impairment (creatinine clearance of 60-89 ml/min)	24/30 (80%)	35/44 (80%)	0.45 (-22.43, 23.52)
ECR at ETP among Moderate and Severe Renal Impairment	5/6 (83%)	9/12 (75%)	8.00 (-46.02, 52.44)

(creatinine clearance of <60 ml/min)			
ECR at ETP in per-protocol	228 (84.8%)	232 (86.2%)	-1.49 (-7.44, 4.46)
Clinical Cure at TOC	248 (83.2%)	262 (87.3%)	-4.11 (-9.78, 1.56)
Modified Clinical Cure* at TOC	204 (68.5%)	219 (73.0%)	-4.54% (-11.8 to 2.7)

* 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.

490 Table 5: Safety Parameters by Treatment

Category	Iclaprim (N=293)	Vancomycin (N=297)
Any drug-related TEAE*	151 (51.5%)	128 (43.1%)
Study drug related TEAE	57 (19.5%)	53 (17.8%)
TEAE leading to discontinuation of study drug	8 (2.7%)	12 (4.4%)
TEAE related SAEs*	8 (2.7%)	12 (4.0%)
QTc prolongation	1 (0.4)	0 (0)
Mean serum creatinine (umol/L) change from baseline to TOC	2.9 (13.1)	7.2 (25.3)
Deaths	0	1 (0.3%)
TEAE by system organ class		
Headache	30 (10.2%)	7 (2.4%)
Nausea	29 (9.9%)	17 (5.7%)
Secondary ABSSSI (skin bacterial infection or wound infection)	20 (6.8%)	10 (3.3%)
Fatigue	18 (6.1%)	9 (3.0%)
Vomiting	14 (4.8%)	15 (5.1%)
Pyrexia	12 (4.1%)	12 (4.0%)
Peripheral edema	8 (2.7%)	9 (3.0%)
Increased ALT*	6 (2.0%)	5 (1.7%)
Increased AST*	6 (2.0%)	1 (4.3%)
Chills	6 (2.0%)	6 (2.0%)

Pain in extremity	6 (2.0%)	5 (1.7%)
Peripheral swelling	4 (1.4%)	8 (2.7%)

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.

*Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; TEAE, treatment emergent adverse events; SAE, severe adverse event; ALT, Alanine aminotransferase; AST, aspartate aminotransferase

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

Note: Two patients were randomized in error by a site because the patients reported they were unable or unwilling to adhere to study-designated procedures and restrictions. No baseline screening or study drug were administered to these two patients.

Figure 1: Schedule of visits

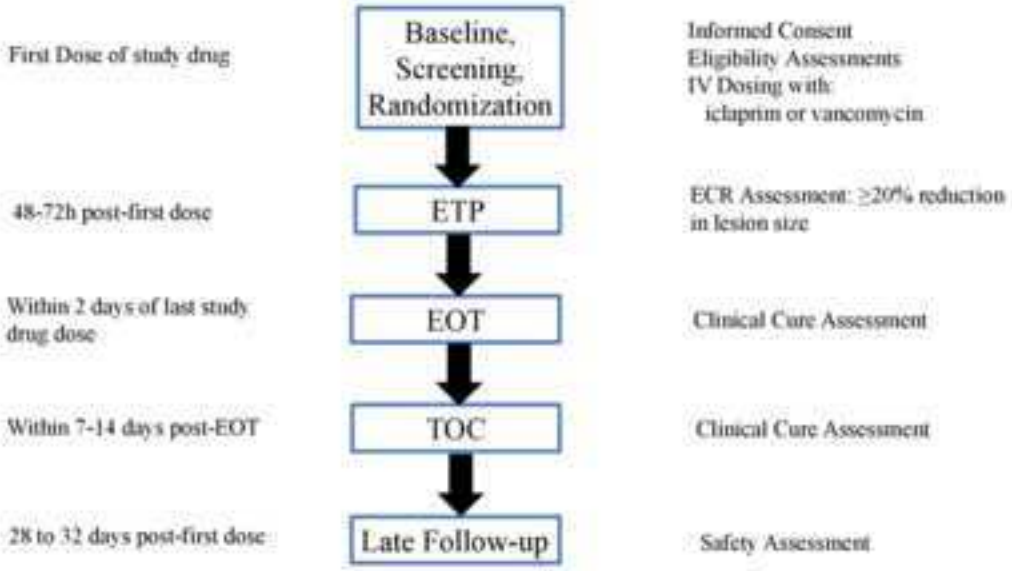

Figure (.tif and .eps files only)

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