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1 A Pooled Analysis of Patients with Wound Infections in the Phase 3 REVIVE Trials:  
2 Randomized, Double-blind Studies to EVALuate the Safety and Efficacy of Iclaprim Versus  
3 Vancomycin for trEatment of Acute Bacterial Skin and Skin Structure Infections

4

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30

31 **Abstract**

32 **Introduction:** Iclaprim is a diaminopyrimidine antibiotic for the treatment of acute bacterial skin  
33 and skin structure infections (ABSSSI) due to Gram-positive pathogens.

34  
35 **Aim:** This analysis evaluates patients with wound infections from two Phase 3 trials of ABSSSI.

36 **Methodology:** Six-hundred-two patients with wound infections from two phase 3, double-  
37 blinded, randomized, multicenter, active controlled trials (REVIVE-1/-2) were evaluated in a  
38 post-hoc analysis of iclaprim 80 mg compared with vancomycin 15 mg/kg administered  
39 intravenously every 12 hours for 5-14 days. The primary endpoint was to determine whether  
40 iclaprim was non-inferior (10% margin) to vancomycin in achieving a  $\geq 20\%$  reduction from  
41 baseline in lesion size 48-72 hours after starting study drug (early clinical response [ECR]).  
42 Safety was assessed.

43 **Results:** In REVIVE-1, ECR was 83.5% with iclaprim versus 79.7% with vancomycin  
44 (treatment difference 3.77%, 95% CI -4.50%, 12.04%). In REVIVE-2, ECR was 82.7% with  
45 iclaprim versus 76.3% with vancomycin (treatment difference 6.38%, 95% CI -3.35%, 16.12%).  
46 In the pooled dataset, iclaprim had similar ECR rates compared with vancomycin among wound  
47 infection patients (83.2% vs 78.2%) with a treatment difference of 5.01% (95% CI -1.29%,  
48 11.32%). The safety profile was similar in iclaprim- and vancomycin-treated patients, except for  
49 a higher incidence of diarrhea with vancomycin (n=17) compared with iclaprim (n=6) and  
50 fatigue with iclaprim (n=17) compared with vancomycin (n=8).

51  
52 **Conclusion:** Based on early clinical response, iclaprim achieved non-inferiority to vancomycin

53 with a similar safety profile in patients with wound infections suspected or confirmed as caused  
54 by Gram-positive pathogens. Iclaprim may be a valuable treatment option for wound infections.

55

56 Keywords: iclaprim, wound infection, Gram-positive

57

58

59 **Introduction**

60 Wound infections may occur through a break in the skin when bacteria enter and attach to  
61 the tissues so that the normal wound healing process is interrupted [1]. Wound infections can be  
62 post-traumatic occurring due to lacerations, burns, bites and punctures (including intravenous  
63 drug use) or post-surgical. Data on the incidence of wound infections (both post-traumatic and  
64 post-surgical) underestimate the true incidence because most wound infections occur in the  
65 community without hospital reporting. In the United States, *Staphylococcus aureus* has been the  
66 predominant causative pathogen of wound infections with approximately 50% methicillin-  
67 resistance (MRSA) [2].

68 Iclaprim is a diaminopyrimidine antibiotic, which selectively inhibits bacterial  
69 dihydrofolate reductase and is active against Gram-positive pathogens including MRSA [3,4].  
70 Iclaprim is in the same class as trimethoprim, the only FDA approved dihydrofolate reductase  
71 inhibitor, and was designed to be more active than trimethoprim and to overcome trimethoprim  
72 resistance among Gram-positive pathogens [5]. In addition, unlike trimethoprim, iclaprim does  
73 not need to be combined with a sulfonamide, which is commonly associated with adverse events,  
74 including renal toxicity, hepatotoxicity, blood dyscrasias, anaphylaxis, and hypersensitivity  
75 reactions [6].

76 Two identical Phase 3 randomized, double-blind, active-controlled studies (REVIVE-1  
77 and REVIVE-2) were conducted to evaluate iclaprim 80 mg fixed dose compared with  
78 vancomycin 15 mg/kg, both infused over 2 hours, administered every 12 hours to patients with  
79 ABSSSI [7,8]. Iclaprim achieved noninferiority (10% margin) compared to vancomycin for early  
80 clinical response at the early time point in both of these Phase 3 studies. A post-hoc analysis was

81 conducted to evaluate the efficacy and safety data from the pooled REVIVE-1 and -2 studies for  
82 the subset of patients treated for wound infections.

83

## 84 **Materials and Methods**

85 Overall, 1198 patients were included in the intent-to-treat populations in the REVIVE-1  
86 (n=598) and REVIVE-2 (n=600) ABSSSI Phase 3 clinical trials. These Phase 3 studies have  
87 been described previously [7,8]. In brief, both REVIVE-1 and REVIVE-2 studies were 600-  
88 patient, phase 3, double-blinded, randomized (1:1), multi-center, active-controlled trials, non-  
89 inferiority studies that utilized identical study protocols (NCT02600611 and NCT02607618,  
90 respectively) among patients with ABSSSI that compared iclaprim 80 mg fixed dose with  
91 vancomycin 15 mg/kg (adjusted for renal function), both administered intravenously every 12  
92 hours for 5-14 days, according to the investigator assessment of clinical response. The US Food  
93 and Drug Administration (FDA) and the European Medicines Agency (EMA) guidance on trials  
94 for ABSSSI were incorporated into the study design. Patients were enrolled between March  
95 2016 and January 2017 for REVIVE-1 [7] and between January 2016 and August 2017 for  
96 REVIVE-2 [8]. The median duration of treatment was 7 days (range: 1-15 days) for both the  
97 iclaprim and vancomycin groups. The primary objective of each of these Phase 3 studies was to  
98 demonstrate whether iclaprim was non-inferior to vancomycin in achieving  $\geq 20\%$  reduction in  
99 lesion size at 48 to 72 hours after initiation of study drug (early time point) in the intent-to-treat  
100 population. The non-inferiority margin was prespecified as 10%. Study protocols and informed  
101 consent forms were reviewed and approved by an institutional review board at each study site,  
102 and all patients or their authorized representative provided written informed consent prior to any  
103 study-specific procedures.

104 Cases of wound infections were pooled from the REVIVE studies based on the clinicians  
105 assessment and assignment of the ABSSSI as a wound infection prior to treatment  
106 randomization. Per protocol, wound infections were defined as having been caused by external  
107 trauma (e.g., needle sticks or insect bites) and had either the presence of purulent or seropurulent  
108 drainage before or after surgical intervention of the wound or at least 3 of the following signs  
109 and symptoms: discharge, erythema (extending at least 2 cm beyond the wound edge in any  
110 direction), swelling and/or induration, heat and/or localized warmth, and/or pain and/or  
111 tenderness to palpation. Disposition of patients in the pooled REVIVE-1 and REVIVE-2 studies  
112 are shown in **Figure 1**. The data were analyzed separately in the REVIVE-1 and -2 studies and  
113 then pooled to determine the efficacy and safety of the iclaprim and vancomycin arms in this  
114 subset of patients. Safety was assessed based on treatment-emergent adverse events (AEs),  
115 clinical laboratory tests (clinical chemistry, coagulation, hematology, liver function tests),  
116 urinalysis, vital signs, physical examinations and electrocardiograms (ECGs). The pooled  
117 analysis adds larger numbers (i.e., power) and confidence to the interpretation of secondary  
118 endpoints and the safety, especially where numbers were relatively small for specific secondary  
119 endpoints and potentially serious adverse events in the individual trials, among patients treated  
120 with iclaprim compared to vancomycin.

121         At the baseline visit, wound infections were sampled for microbiological culture.  
122 Cultures were performed locally, and isolates were submitted to the central microbiology  
123 laboratory. Antibacterial susceptibility testing was conducted by IHMA Europe Sàrl Laboratories  
124 (Monthey, Switzerland). Susceptibility testing was performed by broth microdilution in  
125 accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines M07-A10 [9]

126 and the standard operating procedures at IHMA laboratories. Quality controls and interpretation  
127 of results were performed in accordance with CLSI M100 [10].

128

### 129 *Ethical Approval*

130 The institutional review board at each site approved the protocol (for a list of the sites, see  
131 ClinicalTrials.gov NCT02600611 and NCT02607618), and all patients or their authorized  
132 representative provided written informed consent.

133

### 134 **Results**

135 Of the 602 patients treated in the pooled REVIVE-1 and -2 studies with wound  
136 infections, 51% (309/602) were treated with iclaprim and 49% (293/602) with vancomycin.  
137 Similar demographics and baseline characteristics were observed in the iclaprim and vancomycin  
138 groups in the intent to treat population; 69% of patients were male, mean age was approximately  
139 46 years old, and 91% were white (**Table 1**). A high proportion of patients with wound  
140 infections were intravenous drug users (86% in the iclaprim arm and 82% in the vancomycin  
141 arm).

142 The mean lesion size of the wound infections was approximately 307 cm<sup>2</sup> and in the  
143 subpopulation with available isolates, the most common pathogen was *S. aureus* (72%; 363/505)  
144 (**Table 2**). In both treatment arms, MRSA accounted for 49% (177/363) of *S. aureus* isolates in  
145 wound infections. *Streptococcus anginosus* group pathogens constituted 21% (106/505) of  
146 isolates, and *Streptococcus pyogenes* 6% (32/505) of isolates. Seven (2%) patients treated with  
147 iclaprim and 18 (6%) patients treated with vancomycin had positive blood cultures.

148           The iclaprim group had a clinical response rate of 83.2% (95% CI 78.5, 87.2) at the early  
149 time point compared with 78.2% (95% CI 73.0, 82.8) in the vancomycin group among the subset  
150 of patients with wound infections in the intent-to-treat analysis of the pooled trials (**Figure 2**).  
151 The treatment difference was +5.01% with 95% confidence interval of -1.29% to 11.32%,  
152 thereby iclaprim established noninferiority to vancomycin in this subgroup of patients. End of  
153 treatment (EOT) response rates were 92.6% and 89.1% in the iclaprim and vancomycin groups,  
154 respectively, and clinical cure rates at the test-of-cure (TOC, 7-14 days after the end of  
155 treatment) were similar between the two groups (84.8% in the iclaprim group compared with  
156 84.3% in the vancomycin group).

157           In patients with available isolates, the EOT and TOC response rates were 93.9% and  
158 86.3%, respectively, in the pooled iclaprim arms compared with 91.7% and 88.4%, respectively,  
159 in the vancomycin arms. The MIC<sub>50</sub>/MIC<sub>90</sub> for iclaprim were 0.06/0.12 µg/mL and for  
160 vancomycin were 1/1 µg/mL against *S. aureus* isolates; MIC<sub>50</sub>/MIC<sub>90</sub> values against MRSA were  
161 0.03/0.12 µg/mL for iclaprim and 1/1 µg/mL for vancomycin. Among patients with treatment  
162 failures, nearly 80% of pathogens from the culture of the wound infections had an iclaprim MIC  
163 of 0.03 or 0.06 µg/ml. The treatment success rate was not different between those that had single  
164 (iclaprim 83.6% and vancomycin 78.4%) compared to multiple pathogens identified from wound  
165 infections (iclaprim 83.1% and vancomycin 78.1%).

166           Iclaprim and vancomycin had similar adverse event profiles in patients with wound  
167 infections (**Table 3**). Adverse events leading to discontinuation of study therapy occurred in 2%  
168 of the iclaprim-treated patients and in 5% of those treated with vancomycin. Approximately 50-  
169 54% of patients experienced an adverse event during the study; of these, the most common in  
170 both treatment groups were nausea and headache. Study drug-related adverse events were

171 reported in 21% and 19% of patients in the iclaprim and vancomycin groups, respectively.  
172 Notable differences in adverse events during the study included diarrhea in 2% (N=6) of patients  
173 given iclaprim compared with 6% (N=17) of patients treated with vancomycin, and fatigue in 6%  
174 (N=17) versus 3% (N=8) of patients receiving iclaprim or vancomycin, respectively. One patient  
175 treated with iclaprim experienced asymptomatic QTcF prolongation to 503 msec (Day1  
176 preinfusion QTcF 429 msec).

177

## 178 **Discussion**

179 In this post-hoc analysis of the two Phase 3 REVIVE studies, iclaprim achieved non-  
180 inferiority to vancomycin in patients with wound infections, based on clinical response at the  
181 early time point. In the Phase 3 REVIVE studies, patients with wound infections were a majority  
182 of those enrolled and treated for ABSSSIs.

183 While some wound infections may be treated with either topical (if minor) or oral  
184 antibacterial agents, the mean lesion size of the ABSSSI in the REVIVE trials was  
185 approximately 300 cm<sup>2</sup>, which is substantial and commensurate with a need for intravenous  
186 therapy. Additionally, some patients do not have good oral antibacterial options because of  
187 variable bioavailability, resistant bacteria or toxicity. In the REVIVE studies, between 2-6% of  
188 patients had bacteremia, for which intravenous antibiotics are appropriate.

189 The most commonly identified pathogen at baseline from the wound infections was *S.*  
190 *aureus* (72% in both treatment groups). Of the *S. aureus*, approximately 50% were MRSA in  
191 both treatment groups. The next most commonly identified pathogen at baseline from the wound  
192 infections were *S. anginosus* group (approximately 20% in both treatment groups). This may be

193 explained by the high rate of illicit drug users, who may lick their needles before injecting  
194 themselves, contaminating them with oral flora such as *S. anginosus*.

195         The ECR of 83% among patients with wound infections treated with iclaprim in the  
196 pooled REVIVE studies is similar to that observed with vancomycin in these studies (78%) and  
197 is consistent with similar studies in patients with wound infections treated with other currently  
198 used antibiotics. In the ESTABLISH-1 Phase 3 study, tedizolid was compared with linezolid in  
199 patients with ABSSSI [11]. Among patients with wound infections, the early clinical response  
200 rates were 86% in the tedizolid arm and 84% in the linezolid arm. Similar rates were observed in  
201 the identical study, ESTABLISH-2 [12]. In the OASIS-1 and OASIS-2 Phase 3 studies,  
202 omadacycline was compared with linezolid in patients with ABSSSI. Among patients with  
203 wound infection, the early clinical response rates were 84% in the omadacycline arm and 80% in  
204 the linezolid arm [13]. In the Phase 3 studies of delafloxacin compared with vancomycin plus  
205 aztreonam in patients with ABSSSI, among patients with wound infection, the early clinical  
206 response rates in the two studies were 78% and 84% in the delafloxacin arms and 81% in both of  
207 the vancomycin/aztreonam arms, respectively [14].

208         In the pooled REVIVE studies, there were several differences in the characteristics of the  
209 wound infections as well as the underlying patient comorbidities compared with cellulitis and/or  
210 abscesses [15]. The mean lesion size for wound infections was smaller than those for  
211 cellulitis/abscesses (307 cm<sup>2</sup> vs 390 cm<sup>2</sup>). In addition, patients with wound infections were  
212 slightly younger with a mean age of 46 years in both arms compared with 52 years in the  
213 remaining population studied. Less of the population with wound infections also had diabetes  
214 and renal impairment compared with those with cellulitis/abscesses (diabetes: 7% vs 14%;

215 CrCl<90mL/min: 12% vs 24%), although a higher percentage of patients with wound infections  
216 were intravenous drug users (84% vs 20%).

217 The limitations of this analysis include that this is a post hoc analysis, although the  
218 sample size in this subpopulation was quite robust and represented approximately half of the  
219 patient populations in each treatment arm in both studies. Another limitation is the lack of  
220 reporting of types of wound infection, such as surgical site infections, and whether different  
221 types of wound infection influence surgical and antimicrobial outcomes by treatment with  
222 iclaprim or vancomycin. Nevertheless, these analyses provide important data on the outcomes of  
223 patients collectively with wound infections.

224 In conclusion, iclaprim was non-inferior to vancomycin in the treatment of patients with  
225 Gram-positive wound infections with a favorable safety profile. Iclaprim may be a valuable  
226 treatment option for patients with wound infections suspected or confirmed to be due to Gram-  
227 positive pathogens.

228

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231 DBH is an employee of Motif BioSciences. TLH has received consultancy fees from  
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244 Trius Therapeutics, ContraFect, Theravance, and Astellas Pharma and served on an advisory  
245 board for Pfizer, Polymedix, Trius Therapeutics, Rib-x Pharmaceuticals, Seachaid  
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## References

- 253 1. Pulido-Cejudo A, Guzman-Gutierrez M, Jalife-Montano A, Ortiz-Covarrubias A,  
254 Martinez-Ordaz JL, Noyola-Villalobos HF, Hurtado-Lopez LM. 2017. Management of  
255 acute bacterial skin and skin structure infections with a focus on patients at high risk of  
256 treatment failure. *Ther Adv Infectious Dis* 4:143-161.
- 257 2. Ray GT, Suaya JA, Baxter R. 2013. Microbiology of skin and soft tissue infections in the  
258 age of community-acquired methicillin-resistant *Staphylococcus aureus*. *DMID* 76:24-30.
- 259 3. Sader HS, Fritsche TR, Jones RN. 2009. Potency and bactericidal activity of iclaprim  
260 against recent clinical gram-positive isolates. *Antimicrob Agents Chemother* 53:2171-

- 261 2175.
- 262 4. Schneider P, Hawser S, Islam K. 2003. Iclaprim, a novel diaminopyrimidine with potent  
263 activity on trimethoprim sensitive and resistant bacteria. *Bioorg Med Chem Lett* 13:4217-  
264 4221.
- 265 5. Oefner C, Bandera M, Haldimann A, Laue H, Schulz H, Mukhija S, Parisi S, Weiss L,  
266 Lociuro S, Dale GE. 2009. Increased hydrophobic interactions of iclaprim with  
267 *Staphylococcus aureus* dihydrofolate reductase are responsible for the increase in affinity  
268 and antibacterial activity. *J Antimicrob Chemother* 63:687-698.
- 269 6. Ho JM, Juurlink DN. 2011. Considerations when prescribing trimethoprim-  
270 sulfamethoxazole. *CMAJ* 183:1851-1858.
- 271 7. Huang DB, O’Riordan W, Overcash JS, Heller B. 2018. A Phase 3, Randomized, double-  
272 blind, multicenter study to Evaluate the safety and efficacy of intravenous Iclaprim  
273 versus Vancomycin for the treatment of acute bacterial skin and skin structure infections  
274 suspected or confirmed to be due to Gram-positive pathogens: REVIVE-1. *Clinical*  
275 *Infectious Diseases* 66:1222-1229.
- 276 8. Holland TL, O’Riordan W, McManus A, Shin E, Borghei A, File TM Jr, Wilcox MH,  
277 Torres A, Dryden M, Lodise T, Oguri T, Corey GR, McLeroth P, Shukla R, Huang DB.  
278 2018. A phase 3, randomized, double-blind, multicenter study to evaluate the safety and  
279 efficacy of intravenous iclaprim versus vancomycin for treatment of acute bacterial skin  
280 and skin structure infections suspected or confirmed to be due to Gram-positive  
281 pathogens (REVIVE-2 Study). *Antimicrob Agents Chemother* 62:e02580-17.
- 282 9. CLSI. M07-A10. 2015. Methods for dilution antimicrobial susceptibility tests for bacteria  
283 that grow aerobically; approved standard: tenth edition. Wayne, PA, Clinical and

- 284 Laboratory Standards Institute.
- 285 10. CLSI. M100. 2017. Performance standards for antimicrobial susceptibility testing: 27th  
286 informational supplement. Wayne, PA, Clinical and Laboratory Standards Institute.
- 287 11. Morrissey I, Maher K, Hawser S. 2009. Activity of iclaprim against clinical isolates of  
288 *Streptococcus pyogenes* and *Streptococcus agalactiae*. *J Antimicrob Chemother* 63:413-  
289 414.
- 290 12. Moran GJ, Fang E, Corey GR, et al. 2014. Tedizolid for 6 days versus linezolid for 10  
291 days for acute bacterial skin and skin-structure infections (ESTABLISH-2): a  
292 randomised, double-blind, phase 3, non-inferiority trial. *Lancet Infect Dis* 14:696, 2014.
- 293 13. Armstrong ES, Chitra S, Sirbu A, Garrity-Ryan L, Manley A, Tzanis E, McGovern PC,  
294 Steenbergen JN. Efficacy of Omadacycline and Linezolid against characterized drug  
295 resistant *S. aureus* from combined Phase 3 ABSSSI studies. ASM Microbe; 2018 June 7-  
296 11; Atlanta, USA.
- 297 14. BAXDELA (delafloxacin) [package insert]. 2017. Lincolnshire, Illinois: Melinta  
298 Therapeutics, Inc.
- 299 15. Huang DB, Corey GR, Holland TL, Lodise T, O'Riordan W, Wilcox MH, File TM Jr,  
300 Dryden M, Balsler B, Desplats E, Torres A. 2018. Pooled analysis of the phase 3 REVIVE  
301 trials: randomised, double-blind studies to evaluate the safety and efficacy of iclaprim  
302 versus vancomycin for treatment of acute bacterial skin and skin-structure infections. *Int*  
303 *J Antimicrob Agents*. 52:233-240.

304 **Table 1.** Demographics and baseline characteristics of patients with wound infections.

Characteristics	REVIVE-1		REVIVE-2		Pooled REVIVE	
	Iclaprim	Vancomycin	Iclaprim	Vancomycin	Iclaprim	Vancomycin
	(n=182)	(n=158)	(n=127)	(n=135)	(n=309)	(n=293)
Age, years, mean (SD)	45.0 (12.0)	45.2 (12.0)	47.8 (12.8)	46.2 (13.3)	46.1 (12.4)	45.7 (12.6)
Male, n (%)	127 (69.8)	100 (63.3)	86 (67.7)	101 (74.8)	213 (68.9)	201 (68.6)
Race, n (%)						
White	165 (90.7)	148 (93.7)	117 (92.1)	116 (85.9)	282 (91.3)	264 (90.1)
Black	3 (1.6)	3 (1.9)	3 (2.4)	8 (5.9)	6 (1.9)	11 (3.8)
Other	14 (7.7)	7 (4.4)	7 (5.5)	11 (8.1)	21 (6.8)	18 (6.1)
Lesion Size, cm <sup>2</sup> , mean (SD)	302 (256)	315 (278)	314 (222)	299 (203)	307 (242)	308 (247)
Diabetes, n (%)	5 (3)	13 (8)	10 (8)	14 (10)	15 (5)	27 (9)
Creatinine clearance, n (%)						
≥90 ml/min	163 (91.6)	136 (88.3)	108 (85.0)	115 (86.5)	271 (88.9)	251 (87.5)
60 - <90 ml/min	14 (7.9)	15 (9.7)	17 (13.4)	14 (10.5)	31 (10.2)	29 (10.1)
15 - <60 ml/min	1 (0.6)	3 (1.9)	2 (1.6)	4 (3.0)	3 (1.0)	7 (2.4)
Intravenous drug use, n (%)	170 (93)	134 (85)	95 (75)	106 (79)	265 (86)	240 (82)
Geographic region, n (%)						
United States	176 (96.7)	148 (93.7)	113 (89.0)	122 (90.4)	289 (93.5)	270 (92.2)
Europe	6 (3.3)	10 (6.3)	14 (11.)	12 (8.9)	20 (6.5)	22 (7.5)
Latin America	0	0	0	1 (0.7)	0	1 (0.3)
Bacteremia, n (%)	7 (3.8)	9 (5.7)	0	9 (6.7)	7 (2.3)	18 (6.1)
Co-administration of aztreonam, n (%)	6 (3.3)	7 (4.4)	12 (9.4)	13 (9.6)	18 (5.8)	20 (6.8)
Co-administration of metronidazole, n (%)	1 (0.5)	1 (0.6)	5 (3.9)	6 (4.4)	6 (1.9)	7 (2.4)

306 **Table 2.** Microbiological findings at baseline for patients with wound infections in the REVIVE studies.

Baseline Microbiology, n (%)	REVIVE-1		REVIVE-2		Pooled REVIVE	
	Iclaprim	Vancomycin	Iclaprim	Vancomycin	Iclaprim	Vancomycin
	(n=151)	(n=128)	(n=112)	(n=114)	(n=263)	(n=242)
<i>S. aureus</i>	115 (76.2)	98 (76.6)	74 (66.1)	76 (66.7)	189 (71.9)	174 (71.9)
MRSA	56 (37.1)	39 (30.5)	39 (34.8)	43 (37.7)	95 (36.1)	82 (33.9)
MSSA	59 (39.1)	59 (46.1)	36 (32.1)	33 (28.9)	95 (36.1)	92 (38.0)
<i>S. anginosus</i> Group	30 (19.9)	21 (16.4)	27 (24.1)	28 (24.6)	57 (21.7)	49 (20.2)
<i>S. pyogenes</i>	12 (7.9)	11 (8.6)	5 (4.5)	4 (3.5)	17 (6.5)	15 (6.2)
<i>S. mitis</i> Group	5 (3.3)	3 (2.3)	9 (8.0)	3 (2.6)	14 (5.3)	6 (2.5)

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**Table 3.** Treatment-emergent safety profile in patients with wound infections.

Safety Parameter, n (%)	REVIVE-1		REVIVE-2		Pooled REVIVE	
	Iclaprim (N=180)	Vancomycin (N=157)	Iclaprim (N=127)	Vancomycin (N=133)	Iclaprim (N=307)	Vancomycin (N=290)
Death	0	1 (<1)	0	0	0	1 (<1)
Serious AEs	3 (2)	7 (5)	3 (2)	3 (2)	6 (2)	10 (3)
AEs leading to discontinuation	4 (2)	9 (6)	3 (2)	5 (4)	7 (2)	14 (5)
Any AE	114 (63)	85 (54)	53 (42)	61 (46)	167 (54)	146 (50)
Drug-related AEs	49 (27)	39(25)	16 (13)	17(13)	65 (21)	56 (19)
Most common AEs (>5%)						
Nausea	23 (13)	14 (9)	9 (7)	9 (7)	32 (10)	23 (8)
Headache	29 (16)	19 (12)	4 (3)	7 (5)	33 (11)	26 (9)
Vomiting	12 (7)	11 (7)	3 (2)	5 (4)	15 (5)	16 (6)
Diarrhea	4 (2)	11 (7)	2 (2)	6 (5)	6 (2)	17 (6)
Infusion site extravasation	11 (6)	9 (6)	10 (8)	7 (5)	21 (7)	16 (6)
Fatigue	17 (9)	7 (5)	0	1 (1)	17 (6)	8 (3)
Secondary skin bacterial infection	14 (8)	9 (6)	2 (2)	1 (1)	16 (5)	10 (3)

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312 **Figure 1.**

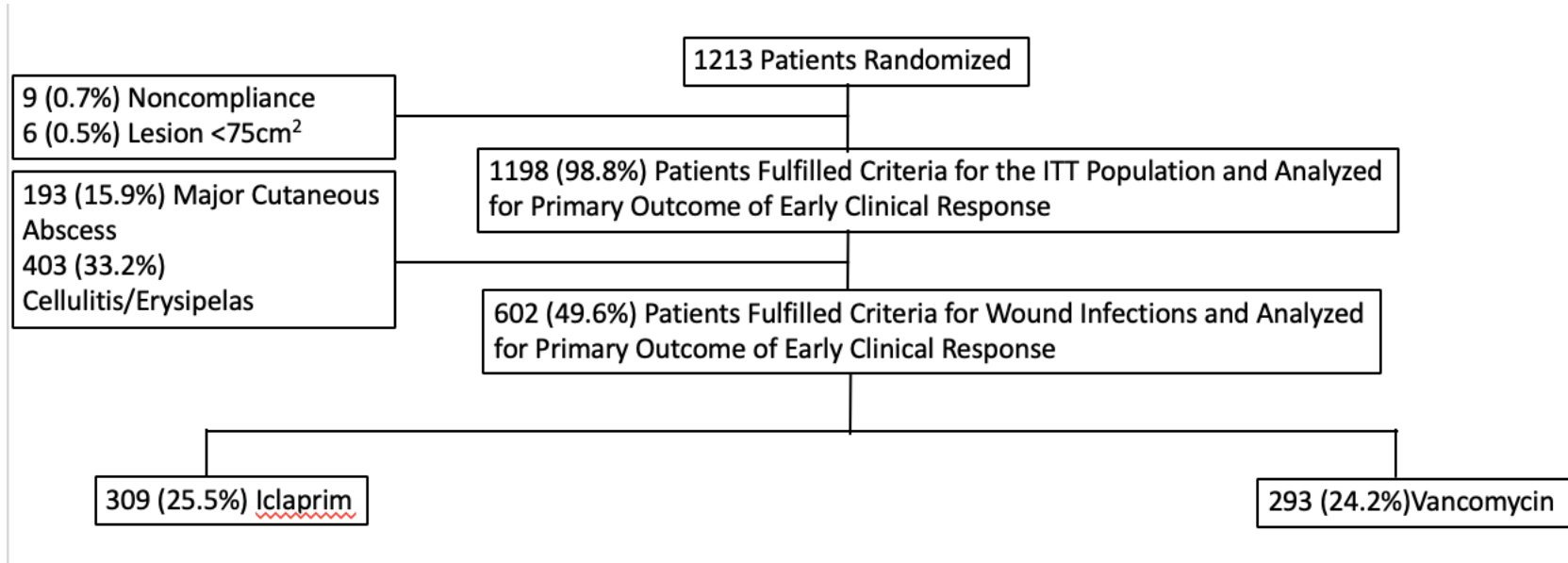
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314 Disposition of patients in the pooled REVIVE-1 and REVIVE-2 studies.

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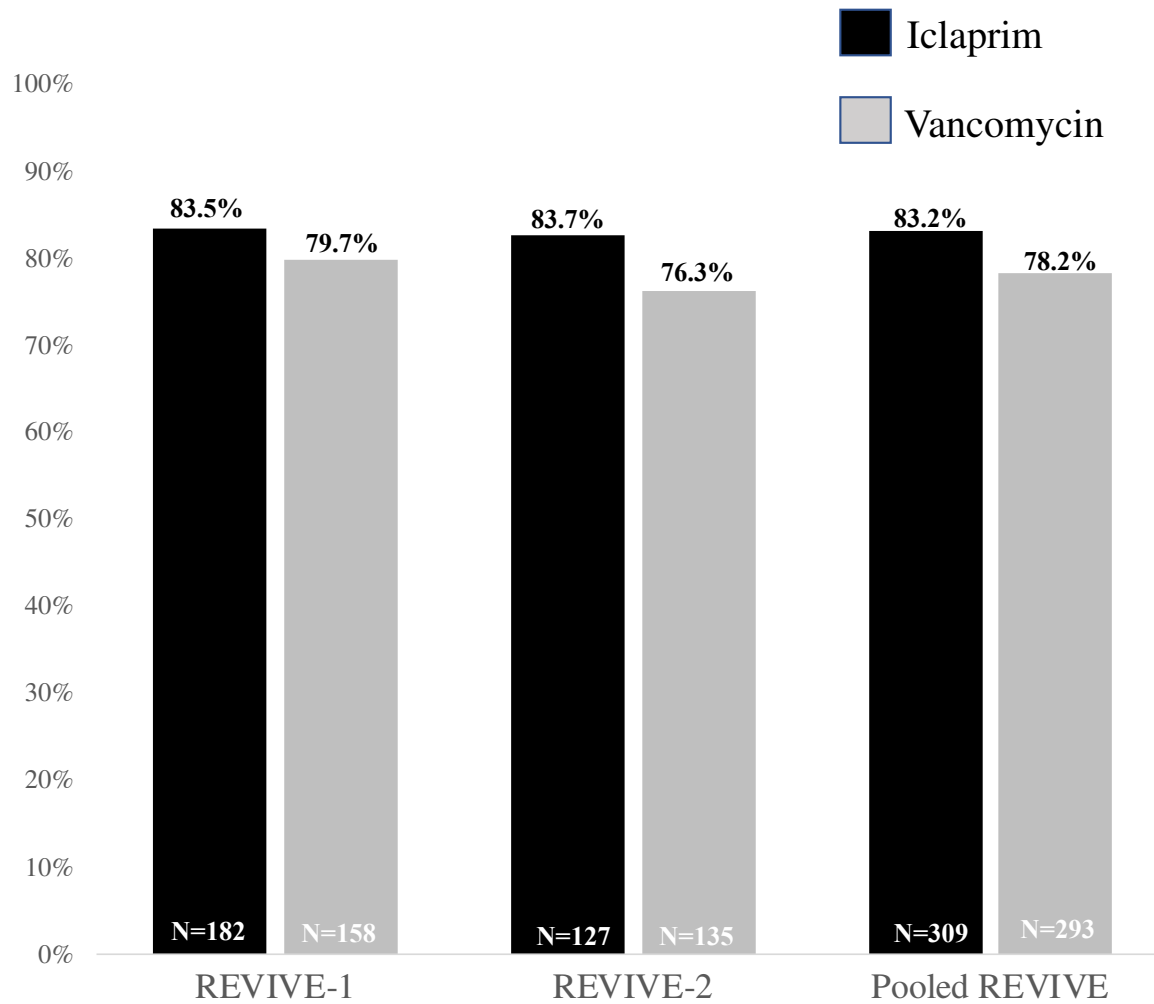
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322 **Figure 2.**

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324 Early clinical response at the early time point for iclaprim and vancomycin arms in patients with wound infections in the REVIVE  
325 studies.



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