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A Phase 2 randomized, double-blind, multicenter study to evaluate efficacy and safety of intravenous iclaprim versus vancomycin for the treatment of nosocomial pneumonia suspected or confirmed to be due to Gram-positive pathogens

Running Head: Iclaprim for the treatment of nosocomial pneumonia

*The data in this manuscript were presented at ID Week 2015 in San Diego, California on October 9-11, 2015.

Abstract

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Purpose: The primary objective of this Phase 2 study was to compare the clinical cure rates of two iclaprim dosages with vancomycin in the treatment of patients with nosocomial pneumonia suspected or confirmed to be caused by Gram- positive pathogens.

Methods: This was a double-blind, randomized, multicenter study. A total of 70 patients was randomized 1:1:1 to iclaprim 0.8 mg/kg IV q12h (iclaprim q12h; n = 23), iclaprim 1.2 mg/kg IV q8h (iclaprim q8h; n =24), or vancomycin 1 g IV q12h (vancomycin; n =23) for 7-14 days. The primary endpoint was clinical cure in the intent-to-treat (ITT) population at test of cure (TOC; 7 ± 1 days post treatment) visit.

Findings: Cure rates in the ITT population were 73.9% (17 of 23), 62.5% (15 of 24), and 52.2% (12 of 23) at the TOC visit in the iclaprim q12h, iclaprim q8h, and vancomycin groups, respectively (iclaprim q12h versus vancomycin p = 0.13; and iclaprim q8h versus vancomycin p = 0.47). The death rates within 28 days of the start of treatment were 8.7% (2 of 23), 12.5% (3 of 24), and 21.7% (5 of 23) for the iclaprim q12h, iclaprim q8h, and vancomycin groups, respectively (no statistically significant differences). The adverse event profile of both iclaprim dosaging regimens were similar to that of vancomycin.

Implications: Iclaprim showed both comparable clinical cure rates and safety profile with vancomycin among patients with nosocomial pneumonia. Iclaprim could be an important new therapeutic option for treatment of nosocomial pneumonia, and a pivotal clinical trial is warranted to evaluate its safety and efficacy in this indication.

Study Registration Number: NCT00543608

Keywords: iclaprim, vancomycin, nosocomial pneumonia

47 Nosocomial pneumonia, which includes hospital acquired pneumonia (HAP) and
48 ventilator associated pneumonia (VAP), is a serious and life threatening infection. Nosocomial
49 pneumonia is the most common hospital acquired infection (HAI) accounting for 22% of all
50 HAIs.¹ Based on data reported to the National Healthcare Safety Network at the Centers for
51 Disease Control and Prevention, 2011-2014, *Staphylococcus aureus* accounts for 25% of VAP,
52 the most common cause of VAP.² Despite existing antibiotic therapies, the all-cause mortality
53 rate associated with nosocomial pneumonia is 20-50%; and a meta-analysis of randomized VAP
54 prevention studies estimated the attributable mortality could reach beyond 13%.³ VAP,
55 furthermore, prolongs mechanical ventilation by 8 to 12 days, hospitalization by 12 to 13 days
56 and is associated with an excess cost of approximately \$40,000 per patient.^{4,5} New therapeutic
57 options, with improved efficacy, pharmacodynamics, and/or safety are thus needed for
58 nosocomial pneumonia especially with the increasing prevalence of multidrug Gram-negative
59 and Gram-positive resistant bacteria and the associated poor outcomes and high costs.⁶

60 Iclaprim represents a new generation diaminopyrimidine, which inhibits bacterial
61 dihydrofolate reductase, and is active against emerging drug-resistant pathogens.^{7,8} Iclaprim
62 exhibits potent in vitro activity against Gram-positive pathogens associated with acute bacterial
63 skin and skin structure infections and nosocomial pneumonia including methicillin-resistant *S.*
64 *aureus*, vancomycin-intermediate *S. aureus*, vancomycin-resistant *Enterococcus spp.*, and
65 *Streptococcus spp.*⁷ Iclaprim demonstrates rapid in vitro bactericidal activity in time kill studies

66 in human plasma.⁹ Iclaprim concentrates in epithelial lining fluid and alveolar macrophages at
67 concentrations of 20 to 40 fold that of its plasma levels resulting in pulmonary concentrations
68 exceeding the MIC₉₀ for Gram-positive respiratory pathogens.¹⁰ Because of these characteristics
69 of iclaprim, iclaprim is potentially well suited for treating patients with nosocomial pneumonia
70 caused by or suspected Gram-positive bacteria. We present a Phase 2 study comparing the
71 outcomes of patients treated with iclaprim to vancomycin for nosocomial pneumonia suspected
72 or confirmed to be due to Gram-positive pathogens.

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75

Methods

Study Design

77 This Phase 2 study was a multi-center, double-blind, randomized 1:1:1, parallel group
78 study with three treatment arms: iclaprim 0.8 mg/kg IV q12h (iclaprim q12h); iclaprim 1.2
79 mg/kg IV q8h (iclaprim q8h); or vancomycin 1g IV q12h (vancomycin) (NCT00543608).
80 Patients were enrolled between November 17, 2007 and January 14, 2009. The institutional
81 review board at each site approved the protocol, and all patients or their authorized
82 representative provided written informed consent. Patients who met eligibility requirements,
83 which are listed in the patients section below, were randomly assigned, using the method of
84 block randomization with stratification, with equal allocation to one of the three treatment arms
85 using the mechanism of an interactive voice response system as a part of a central randomization
86 process with prospective stratification for APACHE II score¹¹ (8 to 19 versus 20 to < 25) and
87 pneumonia type (HAP or VAP) given potential different outcomes associated with these

88 variables. ClinPhone, the randomization center who generated the random allocation sequence,
89 was provided with the patient's demographic information, weight, pneumonia type, and
90 APACHE II score. Each patient, who was enrolled by Parexel International, was assigned a
91 unique patient number by the central randomization system upon meeting all eligibility
92 requirements. Numbered randomization envelopes, containing treatment assignment and
93 treatment preparation and infusion directions, were provided to the sites' pharmacists/designees.

94

95 *Primary and Secondary Objectives*

96 The primary objective of the study was to compare the clinical cure rates at test of cure
97 (TOC; 7 ± 1 days post treatment) in the ITT population treated with iclaprim q12h or iclaprim
98 q8h regimens with vancomycin among patients with nosocomial pneumonia suspected or
99 confirmed to be due to Gram-positive pathogens. The secondary objectives of the study were: (1)
100 mortality within 28 days after the start of treatment; (2) microbiological outcomes at end of
101 therapy (EOT) and TOC; and (3) safety and tolerability of the two dosages of iclaprim compared
102 with vancomycin.

103

104 *Definitions*

105 HAP was defined as a pneumonia occurring ≥ 48 hours after admission, which was not
106 incubating at the time of admission.¹² VAP was defined as a pneumonia occurring ≥ 48 hours
107 after endotracheal intubation.¹² The investigators, caregivers, and patients remained blinded to
108 the study drug treatment allocation. Only the pharmacist/designee at each site who prepared the
109 study product for infusion was aware of patients' treatment assignments. Patients submitted
110 respiratory samples and two blood culture specimens at baseline for Gram stain and culture.

111 Patients received their first dose of randomly allocated study medication within 24 hours after
112 randomization. Study medications were administered for at least 7 days with continuation of
113 treatment up to 7 additional days at the discretion of the investigator. This administration is in
114 accordance with the American Thoracic Society and Infectious Disease Society of America
115 (ATS/IDSA) guidelines at the time the study was conducted.¹² Patients were evaluated at a
116 baseline assessment and daily during their treatment course, EOT, TOC, and at a late follow-up
117 visit (LFU - 7–14 days after the TOC visit) (Figure 1).

118 Clinical cure was defined as complete resolution of all signs and symptoms of pneumonia,
119 for both HAP and VAP, (tachypnea, cough, rigors or shaking chills, rales, pulmonary
120 consolidation, hypoxia, pleuritic chest pain, purulent sputum production and respiratory
121 secretions), improvement or lack of progression of all abnormalities on chest radiograph, and no
122 further antibiotic treatment at the TOC visit. Safety was assessed by Common Terminology
123 Criteria for reported treatment emergent adverse events (TEAEs), serious adverse events (SAEs),
124 hematology, clinical chemistry, urinalysis, vital signs, physical examinations, and
125 electrocardiograms (ECGs).

126

127 *Patients*

128 The study was intended to randomize 135 patients who fulfilled criteria for the ITT
129 population from 51 study sites in 7 countries. Formal statistical sample size considerations were
130 not applied to this study. A sample size of approximately 25 patients per group that fulfilled
131 medical criteria for the modified intent-to-treat (MITT) population was determined to be a
132 clinically reasonable number of patients for this study. It was anticipated that approximately 60%
133 of enrolled patients would be evaluable for efficacy assessments. Based on this calculation, a

134 planned sample size of 135 patients included in the ITT population was expected to result in
135 approximately 25 evaluable patients per treatment arm and provide a reasonable number of
136 patients to assess the safety of iclaprim. However, recruitment was stopped prematurely due to
137 financial reasons only. Figure 2 shows the disposition of patients. The resulting ITT and safety
138 populations contained 70 patients (iclaprim q8h (n = 24), iclaprim q12h (n =23), and vancomycin
139 (n = 23)). The ITT population was defined as all randomized patients who received at least one
140 dose of study medication. All patients with a culture-confirmed Gram-positive pathogen at
141 baseline were included in a MITT population. The clinically evaluable (CE) population included
142 all patients in the ITT population who received at least 5 full days of study medication, or at least
143 2 full days of study treatment for patients whose clinical outcome was considered a failure, and
144 had no major protocol violations.

145 Male and female patients ≥ 18 years of age were included in the study if they or an
146 authorized representative (for VAP patients) had given informed consent, had suspected or
147 confirmed acute HAP or VAP due to Gram-positive pathogens, and had venous access available
148 for intravenous dosing. Suspected or confirmed acute HAP or VAP required all randomized
149 patients to have at least two of the following signs and symptoms: cough, new onset of purulent
150 sputum production or a change (worsening) in character of the sputum, auscultatory findings on
151 pulmonary examination of rales and/or pulmonary consolidation, dyspnea, tachypnea or
152 hypoxemia with a partial pressure oxygen (PO₂) < 60 mmHg **and** at least two of the signs and
153 symptoms fever (oral temperature $> 38^{\circ}\text{C}/100.4^{\circ}\text{F}$) or hypothermia ($< 35^{\circ}\text{C}/95.2^{\circ}\text{F}$), respiratory
154 rate > 30 breaths/min, pulse rate ≥ 120 beats/min, altered mental status, leukocytosis with white
155 blood cell (WBC) count $> 10,000/\text{mm}^6$ or leukopenia with WBC count $< 4,500/\text{mm}^6$; and/or $> 15\%$
156 immature neutrophils (bands). In addition, all patients had a new pulmonary infiltration

157 documented by chest X-ray, a suitable respiratory specimen for culture, and Gram stain, with
158 indication of Gram-positive pathogen, and clinical pulmonary infection scores (CPIS) > 6. The
159 clinical pulmonary score consists of a composite score of temperature, blood leukocytes, tracheal
160 secretions, oxygenation, pulmonary radiography, progression of pulmonary infiltrate, and culture
161 of tracheal aspirate. A CPIS score > 6 at baseline is considered suggestive of pneumonia.¹³

162 Patients were excluded if they had an Acute Physiology and Chronic Health Evaluation
163 (APACHE) II⁹ score <8 or ≥25 (Patients with APACHE II scores of ≥25 were excluded because
164 outcomes may not be reflective of study drug); pneumonia due to Gram-positive organisms
165 resistant to either study medication; had an underlying medical condition that precluded
166 treatment with iclaprim or vancomycin (i.e., previous allergic reactions to trimethoprim,
167 trimethoprim-sulfamethoxazole, or vancomycin); received previous systemic antimicrobial
168 therapy, effective against Gram-positive pathogens, for ≥24 hours within 48 hours before
169 enrollment; if they required empiric treatment for suspected or confirmed concurrent Gram-
170 negative bacterial infection with antibiotics other than aztreonam; documented or suspected
171 meningitis, endocarditis, or osteomyelitis; known or suspected hypersensitivity to trimethoprim,
172 iclaprim or vancomycin; severe hepatic disease or bilirubin >1.5X upper limit of normal and/or
173 alanine transaminase >3X ULN, baseline QTc interval >470 msec; severe renal impairment
174 defined as creatinine clearance <30 mL/minute; absolute neutrophil count <500 cells/mm⁶; or
175 pulmonary disease that precluded evaluation of therapeutic response (e.g. lung cancer, active
176 tuberculosis, cystic fibrosis, or granulomatous disease).

177

178 *Study Treatments*

179 Iclaprim was administered at 0.8 mg/kg IV q12h or 1.2 mg/kg IV q8h. These two dosages were

180 chosen because of previous efficacy and safety evaluation in Phase 2/3 clinical studies.^{14, 15} The
181 0.8 mg/kg IV q12h dose was expected to be as effective as vancomycin based on data from a
182 Phase 2 study in patients with cSSSI. Given the different indication of pneumonia and the longer
183 infusion rate (60 minutes), the study included a higher dosing regimen (1.2 mg/kg IV q8h) which
184 was also expected to be safe. Based on the tolerability demonstrated in several clinical studies
185 for doses up to 1.6 mg/kg q12h (infused over 30 minutes), it appeared clinically justified to
186 increase the total iclaprim daily dose, thereby enabling an investigation of a possible dosing
187 effect of iclaprim in the treatment of pneumonia. At the time of the study, country specific
188 prescribing recommendations consistently indicated vancomycin should be administered at 1 g
189 IV q12h, however, investigators could prescribe a different dose according to institutional
190 guidelines or based on a specific patient's condition. In addition, local prescribing
191 recommendations were followed for dose adjustments of vancomycin in patients with renal
192 impairment. The maintenance dose of vancomycin was selected according to local standard of
193 care taking into consideration the patient's body weight, creatinine clearance, and plasma levels
194 of vancomycin, based on institutional guidelines. If the institution used a standard vancomycin
195 dosage that did not match the recommended dosing, the unblinded pharmacist used the former to
196 prepare infusions for patients who were assigned to the vancomycin arm, notably keeping the
197 same infusion volume. For each patient the investigator provided the creatinine clearance or data
198 for calculation to the site pharmacist; based on the creatinine clearance level, the site pharmacists
199 adjusted the vancomycin dosage for further infusions on an as needed basis according to either
200 the package insert or local requirements. Both iclaprim and vancomycin were infused over 60
201 minutes in 2 bags 120mL each. To maintain the study blinding and to accommodate the
202 different dosages, all patients received four infusions per day at nominal hours 0, 8, 12, and 16.

203 The protocol permitted concomitant antibiotic treatment with aztreonam for patients
204 whose pneumonia was caused by mixed (Gram-positive and Gram-negative) pathogens.

205

206 *Duration of Treatment*

207 Study treatment was initiated within 24 hours after patient randomization. Planned treatment
208 duration was 7 to 14 days. Study medication was administered beyond 7 days only for patients
209 with persistent signs and symptoms consistent with active infection in accordance with
210 guidelines.¹²

211

212 *Statistical Methods*

213 The statistical analyses evaluated the two dosages of iclaprim compared with vancomycin. An
214 overall quantitative evaluation of efficacy and safety was performed comparing the 3 treatment
215 groups. Demographics and baseline characteristics were summarized using descriptive statistics.

216 The primary efficacy analysis was performed in the ITT, MITT and the CE populations. The
217 Fisher's Exact Test was used to compare the clinical cure rates for the two iclaprim dosages
218 versus vancomycin using a 2-sided test at the 2.5% level of significance, corresponding to a 2-
219 sided 95% confidence intervals (CI), based on the normal approximation to the binomial
220 distribution. The 2-sided CIs were calculated for the difference in proportions of clinical cure
221 between iclaprim groups, and for the proportion of patients with clinical cure in each treatment
222 group. A similar analysis was conducted for the proportion of patients who had died by Day 28.

223 A Cox Proportional Hazard analysis was conducted to determine treatment effect on the time of
224 death in the ITT population within 28 days from start of treatment. By-patient and by-pathogen
225 bacteriological outcomes at EOT and TOC were presented as frequency distributions of

226 outcomes by treatment group for patients with a confirmed Gram- positive pathogen at baseline.
227 The incidence of TEAEs was summarized at the overall patient level, Medical Dictionary for
228 Regulatory Activities (MedDRA) system organ class level, and preferred term level. Separate
229 tabulations were provided by severity and relationship to study medication and for SAEs.
230 Laboratory data, vital signs and ECGs were evaluated by presentation of summary statistics of
231 raw data and changes from baseline.

232

233

234

Results

Demographics

236 The trial enrolled 70 patients (iclaprim q12h (n = 23), iclaprim q8h (n= 24), and vancomycin (n =
237 23)). Tables 1 and 2 show that the baseline and demographic characteristics of patients treated
238 with either iclaprim or vancomycin were comparable. Treatment groups were similar for baseline
239 CPIS, laboratory parameters, vital signs, physical examinations, X-rays, and ECG evaluations. In
240 addition, no notable differences among treatment groups with respect to prior medications and
241 treatments or study drug compliance were observed. All patients with suspected or confirmed
242 mixed (Gram-positive and aztreonam susceptible Gram-negative) pathogens were treated with
243 aztreonam. If the patient had a confirmed Gram-negative pathogen resistant to aztreonam, the
244 protocol allowed for piperacillin-tazobactam. All patients randomized had APACHE II scores of
245 8-19, except for two patients who were in the 20-25 range (one patient in the iclaprim q12h and
246 one patient in the iclaprim q8h treatment group). The mean and median number of treatment
247 days was 7 (standard deviation [SD] 2.6) in the iclaprim q8h group, 9 (3.4) in the iclaprim q12h
248 group, and 7 (3.5) in the vancomycin group.

249

250 *Efficacy Results*

251 *Primary Endpoint*

252 In the ITT population, a clinical cure was reported at TOC for 17 patients (73.9%) in the iclaprim
253 q12h group, 15 patients (62.5%) in the iclaprim q8h group, and 12 patients (52.2%) in the
254 vancomycin group (Table 3; iclaprim q12h versus vancomycin $p = 0.13$, and iclaprim q8h versus
255 vancomycin $p = 0.47$). These differences were not statistically significant (neither between the
256 two dosages of iclaprim nor between either dosages of iclaprim and vancomycin). These
257 response rates with iclaprim and vancomycin were similar at TOC in the MITT and CE
258 populations (Table 3).

259

260 *Secondary Endpoints*

261 In the ITT population, the clinical cure rates at EOT were 83% (19 of 23), 75% (18 of 24),
262 and 57% (13 of 23) for iclaprim q12h, iclaprim q8h, and vancomycin, respectively (iclaprim
263 q12h versus vancomycin $p = 0.06$, and iclaprim q8h versus vancomycin $p = 0.18$). In the ITT
264 population, the death rates within 28 days from the start of treatment were 12.5% (3 of 24) and
265 8.7% (2 of 23) for the iclaprim q8h and iclaprim q12h regimens, respectively, and were 21.7% (5
266 of 23) for the vancomycin group (not statistically significant) (Table 3). No significant treatment
267 effect on the time to death in the ITT population was found within 28 days from the start of
268 treatment with the Cox Proportional Hazard analysis (vancomycin vs. iclaprim q12h comparison,
269 $p = 0.25$, hazard ratio = 2.6, and 95% CI = 0.5, 1.6 or iclaprim q8h comparison, $p = 0.42$, hazard
270 ratio = 1.3, CI = 0.7, 2.7).

271 For the microbiological outcome at EOT and TOC, although all 70 patients presented

272 with a Gram-positive stain (ITT population), a culture-confirmed Gram-positive pathogen could
273 be identified at baseline (MITT population) for only 21 patients (30%). The most common
274 isolated pathogen was *S. aureus* (15 MITT patients, 71%) and 6 of these (40%) were MRSA.
275 The other Gram-positive organisms isolated are shown in Table 2. Among the mixed infections,
276 all, but one, Gram-negative bacteria were susceptible to aztreonam. One patient randomized to
277 vancomycin treatment had an *Acinetobacter baumannii*, which was resistant to aztreonam but
278 susceptible to and treated with piperacillin-tazobactam (MIC 8/2 mcg/mL). The iclaprim and
279 vancomycin MIC range for the 15 *S. aureus* isolates was 0.03-2 mcg/mL and ≤ 0.5 -1 mcg/mL,
280 respectively. Due to the low numbers in the treatment groups and the associated imbalances,
281 statistical evaluation of bacteriological outcomes or overall therapeutic responses at EOT and
282 TOC (by-patient or by-pathogen) were not considered meaningful. Among patients infected
283 with *S. aureus*, clinical cure was 5 of 7 in the iclaprim q12h group, 3 of 5 in the iclaprim q8h
284 group and 0 of 3 in the vancomycin group. No vancomycin trough concentrations were collected
285 during the study. There was only one clinical failure among the 15 patients (6.7%) in the MITT
286 population treated with iclaprim. This patient was infected with MRSA, and there was no
287 association with a high MIC. Two of six patients (33%) in the MITT population treated with
288 vancomycin were clinical failures.

289

290 *Safety Results*

291 The two dosages of iclaprim and vancomycin were generally well tolerated (Table 4). No
292 new or unexpected safety concerns emerged. The high incidence of TEAEs and the number of
293 deaths reported during the study were not surprising considering the clinical indication under
294 study, concomitant illnesses, and medical history of these patients. Overall drug-related TEAEs

295 occurred in 12.5%, 17.4%, and 30.4% of patients in the iclaprim q8h, iclaprim q12h and
296 vancomycin treatment groups, respectively. Only one specific type of TEAE, cardiac failure in
297 three patients treated with iclaprim q8h, was reported for more than 10% of patients in any
298 treatment group; cardiac failure was not considered related to study drug in any of the three
299 patients. SAEs were reported for 19 patients: 16.7%, 21.7% and 43.5% for iclaprim q8h,
300 iclaprim q12h and vancomycin, respectively. There were 10 deaths within 28 days after initiation
301 of treatment: two, three and five deaths occurred in iclaprim q12h, iclaprim q8h, and vancomycin
302 groups, respectively; none was considered related to study treatment. Table 5 lists the causes
303 and timing of deaths relative to study drug administration.

304 Most of the abnormalities and changes in laboratory values were not clinically significant.
305 One patient treated with vancomycin had a notable increase in creatinine and blood urea nitrogen
306 and was withdrawn from the study but included in the ITT study outcome. There were no
307 significant differences in mean values or mean changes in urinalysis results, vital signs or
308 physical examinations during treatment, or at EOT, TOC and follow-up between treatment
309 groups. Four patients had shifts in ALT/AST values to >3X upper limits of normal (ULN) during
310 treatment: two patients in the iclaprim q8h group and two in the vancomycin group. There were
311 no ALT/AST increases to >5X ULN. No patients had bilirubin increases >2X ULN.

312 Abnormal ECGs were observed in all 3 groups at baseline and during treatment. Most of
313 the ECG changes were not clinically significant. During treatment, 22 patients had QTcB and/or
314 QTcF intervals >500 msec or increased by >30 msec compared with baseline: 11, 7 and 4
315 patients in the iclaprim q12h group, iclaprim q8h group, and vancomycin groups, respectively.
316 The QTc prolongation was reported as an AE in 2 patients in the iclaprim q12h group and one of
317 these patients was withdrawn from treatment. One patient in the iclaprim q12h group, who had a

318 medical history that included hypertrophic cardiomyopathy, paroxysmal atrial fibrillation, arterial
319 hypertension, coronary artery disease, first degree atrioventricular block, experienced ventricular
320 tachycardia after one day of treatment, and died the same day. No increase in the QTc interval
321 was registered for this patient. The patient had a post infusion QTc interval of 410 msec, which
322 was repeated a minute later with a reading of 389 msec. The patient had a 3-year history of
323 cardiac arrhythmias and the event was judged unrelated to study drug treatment. One patient in
324 the vancomycin group was withdrawn for sick sinus syndrome which the investigator judged as
325 probably treatment related. ECG showed flattened T-waves, QTc interval of 454 msec and a
326 heart rate 124-126 bpm without any other abnormalities

327

328

Discussion

329 This abridged Phase 2 study showed that both iclaprim q12h and iclaprim q8h dosages
330 were at least as effective as vancomycin in the treatment of nosocomial pneumonia caused by
331 Gram-positive organisms with respect to clinical cure rates at EOT and TOC and Day 28
332 mortality rates. Both iclaprim dosages and vancomycin were generally well tolerated. No new or
333 unexpected suspected adverse events emerged. Although transient and reversible QTc
334 prolongation was identified more frequently among patients receiving iclaprim, no notable
335 differences in the incidence of TEAEs among the treatment groups were observed.

336 There are limitations to this Phase 2 study. Most notably, the study was stopped for
337 financial reasons after randomization of 70 patients of a planned 135 patients. The statistical
338 power of the study was therefore compromised with an increase in the risk of a Type II error.
339 Second, the vancomycin dosage used in this study was 1 g IV q12h, which is a lower dosage

340 compared to the currently recommended weight based dosaging of 15 mg/kg every 12h with
341 targeted serum vancomycin concentrations (15-20 mg/mL) for nosocomial pneumonia caused by
342 MRSA.¹² Unfortunately, data on vancomycin trough concentrations from the local institution
343 were not collected in this study. The lower vancomycin dosage used could explain the lower
344 clinical cure rates of the control group. Third, the treatment choice of nosocomial pneumonia
345 caused by MSSA are beta-lactams because of their decreased incidence of relapse or increased
346 resolution of signs and symptoms compared to vancomycin. There were not many patients that
347 had mono-microbial infections with Gram-positive pathogens, and the Gram-positive pathogens
348 were not MRSA of which vancomycin has an indication for treating.

349 The iclaprim dosages used in this study were weight based. However, based on modeling
350 of pharmacokinetics and pharmacodynamics, a fixed dosage of 80 mg of iclaprim showed a 30%
351 increase in AUC/MIC and T/MIC, parameters associated with efficacy in animal models, while
352 allowing for an approximately 10% decrease in C_{max}, parameter associated with QTc
353 prolongation.²² This fixed dosage of iclaprim is being studied in two Phase 3 studies for the
354 treatment of acute bacterial skin and skin structure infections.

355 Acknowledging the limitations of this Phase 2 study, the results suggest that iclaprim
356 could be a useful and effective treatment option for nosocomial pneumonia due to Gram-positive
357 pathogens especially because iclaprim is not nephrotoxic and does not required therapeutic drug
358 monitoring nor renal dosing. Three antibiotics are FDA approved for the treatment of
359 nosocomial pneumonia caused by Gram-positive pathogens: vancomycin, linezolid and
360 telavancin. The recently published ATS/IDSA guidelines for the management of adults with
361 HAP and VAP recommend use of either vancomycin or linezolid against susceptible MRSA, for
362 the empiric treatment of suspected HAP or VAP in patients with risk factors for MRSA, those

363 being treated in units where >10%-20% of VAP/HAP *S. aureus* isolates are methicillin resistant,
364 and when the prevalence of MRSA is not known.¹² Despite the availability of vancomycin and
365 linezolid, the 30-day all-cause mortality of patients with MRSA nosocomial pneumonia is 28%¹⁷
366 to 60%.¹⁸ Resistance to vancomycin and linezolid is occasionally reported among patients treated
367 for nosocomial pneumonia.^{19,20} For example, an outbreak with linezolid and methicillin-
368 resistance *S. aureus* in an intensive care department in Madrid, Spain, was reported.¹⁸ Among *S.*
369 *aureus* isolates, the emergence of plasmid-transferable linezolid resistance mediated by the *cfr*
370 gene was reported in some cases of VAP.¹⁸ Although relatively rare, the occurrence of *cfr* in
371 MRSA isolates and its propensity to spread horizontally make it a significant concern for the
372 treatment of hospital-acquired infections, including HAP, caused by *S. aureus*. Vancomycin is
373 associated with nephrotoxicity, requires monitoring of trough concentrations, and adjusted
374 dosaging in patients with renal impairment. Linezolid is associated with myelosuppression,
375 serotonin syndrome and hypoglycemia among patients receiving insulin or oral hypoglycemic
376 agents. Telavancin has black box safety warnings, the highest level of FDA safety warning,
377 which include potential for QTc prolongation, potential birth defects when used by pregnant
378 women, and decreased efficacy in patients ≥ 65 years and in those with creatinine clearance ≤ 50
379 mL/minute.

380 In the treatment of nosocomial pneumonia, it is critical that adequate concentrations of
381 antibiotic(s) are achieved in the lower respiratory tract. In a clinical study investigating the
382 tissue distribution of a single IV dose of iclaprim in relevant lung compartments, high
383 concentrations were found in epithelial lining fluid (ELF) and alveolar macrophages (AM), notably
384 achieving levels up to 20- and 40-fold higher, respectively, than in plasma.¹⁰ In comparison,
385 linezolid concentrates in ELF and AM at 3.3- and 0.14- fold, respectively; vancomycin

386 concentrates in ELF and AM at 0.25- and 2.5- fold, respectively.²¹ In addition, iclaprim
387 concentrations in plasma, ELF and AM after a single IV dose of 1.6 mg/kg exceeded iclaprim
388 MICs for penicillin- susceptible *S. pneumoniae* (MIC₉₀ 0.06 mg/L) and methicillin-resistant *S.*
389 *aureus* (MIC₉₀ 0.12 mg/L) for up to 7 hours; mean iclaprim concentrations in ELF exceeded the
390 iclaprim MICs observed for *S. pneumoniae* with intermediate penicillin resistance (MIC₉₀ 2
391 mg/L) and full resistance (MIC₉₀ 4 mg/L) for up to 7 and 4 hours, respectively.

392 In conclusion, in this shortened Phase 2 study, iclaprim was similar as vancomycin in the
393 treatment of nosocomial pneumonia caused or suspected by Gram-positive organisms with
394 respect to clinical cure rate and mortality rate at Day 28. These results warrant a pivotal clinical
395 trial to evaluate the safety and efficacy of iclaprim for this indication.

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Captions

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434 Figure 1: Schedule of visits

435 Figure 2: Disposition of Patients

436 Table 1: Baseline and demographic characteristics among the ITT population by treatment

437 Table 2: Microbiological characteristics at study entry for the MITT population by treatment

438 Table 3: Clinical cure rates at test of cure and mortality within Day 28 in all populations by
439 treatment

440 Table 4: Safety Parameters by Treatment

441 Table 5: Cause of death by treatment

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Conflict of Interest

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