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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

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

Introduction

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

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

in human plasma.[9] Iclaprim concentrates in epithelial lining fluid and alveolar macrophages at concentrations of 20 to 40 fold that of its plasma levels resulting in pulmonary concentrations exceeding the MIC_{90} for Gram-positive respiratory pathogens.[10] Because of these characteristics of iclaprim, iclaprim is potentially well suited for treating patients with nosocomial pneumonia caused by or suspected Gram-positive bacteria. We present a Phase 2 study comparing the outcomes of patients treated with iclaprim to vancomycin for nosocomial pneumonia suspected or confirmed to be due to Gram-positive pathogens.

Methods

Study Design

This Phase 2 study was a multi-center, double-blind, randomized 1:1:1, parallel group study with three treatment arms: iclaprim 0.8 mg/kg IV q12h (iclaprim q12h); iclaprim 1.2 mg/kg IV q8h (iclaprim q8h); or vancomycin 1g IV q12h (vancomycin) (NCT00543608). Patients were enrolled between November 17, 2007 and January 14, 2009. The institutional review board at each site approved the protocol, and all patients or their authorized representative provided written informed consent. Patients who met eligibility requirements, which are listed in the patients section below, were randomly assigned, using the method of block randomization with stratification, with equal allocation to one of the three treatment arms using the mechanism of an interactive voice response system as a part of a central randomization process with prospective stratification for APACHE II score[11] (8 to 19 versus 20 to < 25) and pneumonia type (HAP or VAP) given potential different outcomes associated with these

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

Primary and Secondary Objectives

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

Definitions

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

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

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

Patients

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

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

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

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

Patients were excluded if they had an Acute Physiology and Chronic Health Evaluation (APACHE) II[9] score <8 or ≥25 (Patients with APACHE II scores of ≥25 were excluded because outcomes may not be reflective of study drug); pneumonia due to Gram-positive organisms resistant to either study medication; had an underlying medical condition that precluded treatment with iclaprim or vancomycin (i.e., previous allergic reactions to trimethoprim, trimethoprim-sulfamethoxazole, or vancomycin); received previous systemic antimicrobial therapy, effective against Gram-positive pathogens, for ≥24 hours within 48 hours before enrollment; if they required empiric treatment for suspected or confirmed concurrent Gram-negative bacterial infection with antibiotics other than aztreonam; documented or suspected meningitis, endocarditis, or osteomyelitis; known or suspected hypersensitivity to trimethoprim, iclaprim or vancomycin; severe hepatic disease or bilirubin >1.5X upper limit of normal and/or alanine transaminase >3X ULN, baseline QTc interval >470 msec; severe renal impairment defined as creatinine clearance <30 mL/minute; absolute neutrophil count <500 cells/mm[6]; or pulmonary disease that precluded evaluation of therapeutic response (e.g. lung cancer, active tuberculosis, cystic fibrosis, or granulomatous disease).

Study Treatments

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

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

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

Duration of Treatment

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

Statistical Methods

The statistical analyses evaluated the two dosages of iclaprim compared with vancomycin. An overall quantitative evaluation of efficacy and safety was performed comparing the 3 treatment groups. Demographics and baseline characteristics were summarized using descriptive statistics. The primary efficacy analysis was performed in the ITT, MITT and the CE populations. The Fisher's Exact Test was used to compare the clinical cure rates for the two iclaprim dosages versus vancomycin using a 2-sided test at the 2.5% level of significance, corresponding to a 2-sided 95% confidence intervals (CI), based on the normal approximation to the binomial distribution. The 2-sided CIs were calculated for the difference in proportions of clinical cure between iclaprim groups, and for the proportion of patients with clinical cure in each treatment group. A similar analysis was conducted for the proportion of patients who had died by Day 28. A Cox Proportional Hazard analysis was conducted to determine treatment effect on the time of death in the ITT population within 28 days from start of treatment. 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) 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

The trial enrolled 70 patients (iclaprim q12h (n = 23), iclaprim q8h (n= 24), and vancomycin (n = 23)). Tables 1 and 2 show that the baseline and demographic characteristics of patients treated with either iclaprim or vancomycin were comparable. Treatment groups were similar for baseline CPIS, 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. All patients with suspected or confirmed mixed (Gram-positive and aztreonam susceptible Gram-negative) pathogens were treated with aztreonam. If the patient had a confirmed Gram-negative pathogen resistant to aztreonam, the protocol allowed for piperacillin-tazobactam. All patients randomized had APACHE II scores of 8-19, except for two patients who were in the 20-25 range (one patient in the iclaprim q12h and one patient in the iclaprim q8h treatment group). The mean and median number of treatment days was 7 (standard deviation [SD] 2.6) in the iclaprim q8h group, 9 (3.4) in the iclaprim q12h group, and 7 (3.5) in the vancomycin group.

Efficacy Results

Primary Endpoint

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

Secondary Endpoints

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

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

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

Safety Results

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

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

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

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

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

Discussion

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

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

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

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

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

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

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

concentrates in ELF and AM at 0.25- and 2.5- fold, respectively.[21] In addition, iclaprim concentrations in plasma, ELF and AM after a single IV dose of 1.6 mg/kg exceeded iclaprim MICs for penicillin- susceptible S. pneumoniae (MIC_{90} 0.06 mg/L) and methicillin-resistant S. aureus (MIC_{90} 0.12 mg/L) for up to 7 hours; mean iclaprim concentrations in ELF exceeded the iclaprim MICs observed for S. pneumoniae with intermediate penicillin resistance (MIC_{90} 2 mg/L) and full resistance (MIC_{90} 4 mg/L) for up to 7 and 4 hours, respectively.

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

Acknowledgements

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Captions

Figure 1: Schedule of visits

Figure 2: Disposition of Patients

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

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

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

Table 4: Safety Parameters by Treatment

Table 5: Cause of death by treatment

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. R.C. has received consultancy fees from Cempra Pharmaceuticals, PRA International, Furiex Pharmaceuticals, Inimex Pharmaceuticals, Dr. Reddy's Laboratories, Cubist Pharmaceuticals, Cerexa/Forest Laboratories, AstraZeneca, GlaxoSmithKline, Pfizer, Merck, Trius Therapeutics, ContraFect, Theravance, and Astellas Pharma and served on an advisory board for Pfizer, Polymedix, Trius Therapeutics, Rib-x Pharmaceuticals, Seachaid Phar- maceuticals, BioCryst Pharmaceuticals, Durata Therapeutics,

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