An Updated Review of Iclaprim: A Potent and Rapidly Bactericidal Antibiotic for the Treatment of Skin and Skin Structure Infections and Nosocomial Pneumonia Caused by Gram-Positive Including Multidrug-Resistant Bacteria

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Antimicrobial resistance is a growing public health threat worldwide [1]. The US Centers for Disease Control and Prevention estimates that each year in the United States, 2 million people become infected with antibiotic-resistant bacteria and at least 23,000 people die each year as a direct result of these infections [2]. The economic impact of antibiotic-resistant infections has been extensively documented; the estimated cost to the health care system in the United States has been placed at more than $8 billion [3]. Patients with resistant infections require longer hospital stays, more doctors’ visits, and lengthier recuperations and experience a higher incidence of long-term disability [4]. Considering these costs, the total economic burden has been estimated at $20 billion, plus $35 billion a year in lost productivity [3, 5].

New antibiotics are needed because of the increased morbidity and mortality associated with multidrug-resistant bacteria. Iclaprim, a bacterial dihydrofolate reductase inhibitor, not currently approved, is being studied for the treatment of skin infections and nosocomial pneumonia caused by Gram-positive bacteria, including multidrug-resistant bacteria. Iclaprim showed noninferiority at –10% to linezolid in 1 of 2 phase 3 studies for the treatment of complicated skin and skin structure infections with a weight-based dose (0.8 mg/kg) but did not show noninferiority at –10% to linezolid in a second phase 3 study. More recently, iclaprim has shown noninferiority at –10% to vancomycin in 2 phase 3 studies for the treatment of acute bacterial skin and skin structure infections with an optimized fixed dose (80 mg). A phase 3 study for the treatment of hospital-acquired bacterial and ventilator-associated bacterial pneumonia is upcoming. If, as anticipated, iclaprim becomes available for the treatment of skin and skin structure infections, it will serve as an alternative to current antibiotics for treatment of severe infections. This article will provide an update to the chemistry, preclinical, pharmacology, microbiology, clinical and regulatory status of iclaprim.

Keywords. bactericidal; iclaprim; multidrug-resistant bacteria; pneumonia; skin infections.

Over decades, methicillin-resistant Staphylococcus aureus (MRSA) has become increasingly common [6]. MRSA causes significantly higher rates of morbidity and mortality compared with nonresistant S. aureus [7]. Furthermore, vancomycin-intermediate S. aureus (VISA) and heterogeneous VISA (hVISA) are reported in cases of vancomycin treatment failures [8]. With the increased use of vancomycin to treat MRSA, the emergence of vancomycin resistance became inevitable [9], although still a relatively uncommon phenomenon. Resistance is also reported among S. aureus isolates to linezolid and daptomycin [10].

Iclaprim is an antibiotic, not currently approved, that is effective against Gram-positive multidrug-resistant bacteria such as MRSA. Iclaprim also has activity against some Gram-negative bacteria (ie, Haemophilus influenzae and Moraxella catarrhalis). There exists only 1 other antibiotic in its class as a dihydrofolate reductase inhibitor, trimethoprim [11]. Iclaprim was designed to overcome trimethoprim resistance with increased potency without the need for co-administration of sulphonamides, thereby avoiding the sulphonamide-associated safety issues such as rashes, hypersensitivity reactions (eg, Stevens Johnson Syndrome), blood dyscrasias, drug-drug interactions leading to hypoglycemia or gastrointestinal hemorrhage, and life-threatening hyperkalemia [12]. This article is intended to provide an update to the chemistry, pharmacology, microbiology, and preclinical, clinical, and regulatory status of iclaprim for health care providers.
DISCOVERY AND MOLECULAR CHARACTERIZATION OF ICLAPRIM

Iclaprim is a selective and potent inhibitor of the bacterial enzyme dihydrofolate reductase (DHFR), a key enzyme required for the synthesis of thymidine. The discovery of iclaprim relied on crystallography to optimize its interactions with DHFR, and the compound was specifically designed to bind to trimethoprim-resistant DHFR by making additional hydrophobic contacts in the substrate-binding pocket of the enzyme [13]. Therefore, iclaprim retains activity against trimethoprim-resistant DHFRs, including the F98Y mutant enzyme most commonly associated with trimethoprim resistance in *S. aureus* and the I100L mutation associated with trimethoprim resistance in *S. pneumoniae* [13]. This improved enzymological profile translates to improved bacterial minimal inhibitory concentrations (MICs) against both wild-type and trimethoprim-resistant bacteria in microbiology studies (see the “Microbiology” section below).

Iclaprim is 20-fold more potent in inhibiting DHFR than trimethoprim [13]. From a structural perspective, iclaprim shares many similarities and some key differences when compared with trimethoprim. Iclaprim is a tricyclic, and trimethoprim is a dicyclic diaminopyrimidine. Both trimethoprim and iclaprim interrupt the folate synthesis pathway at the same point, blocking the progression from dihydropteroic acid to tetrahydrofolic acid (Figure 1).

Iclaprim is a racemate, and both enantiomers have been shown to be equipotent against various bacterial DHFR enzymes and to exhibit similar antimicrobial activity against a broad range of bacteria (Table 2) [14].

ADMINISTRATION

Iclaprim is produced as a sterile concentrate already in solution that is dosed at 80 mg intravenously by dilution into 250-mL or 500-mL common solutions such as normal saline, 5% dextrose, or lactated ringers; these are infused over 120 minutes every 12 hours for 5 to 14 days for the treatment of acute bacterial skin and skin structure infections and nosocomial pneumonia caused by or suspected to be Gram-positive bacteria. In addition, an oral dosage formulation of iclaprim is being developed.

PRECLINICAL SAFETY

Iclaprim has been extensively evaluated for potential adverse effects in in vitro studies and conventional toxicology studies in animals following oral and intravenous (IV) drug administration (unpublished data). Iclaprim is rapidly distributed to tissues after IV administration and achieves plasma levels in humans that provide adequate exposure multiples to the desired therapeutic exposures (unpublished data). The drug is extensively metabolized by both phase I and phase II enzymes; none of the metabolites show antimicrobial activity. Urinary excretion is the primary route of elimination of the drug in humans.

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**Figure 1.** Dihydrofolate reductase inhibited by iclaprim in the folate synthesis pathway.
The drug is a substrate of CYP3A4 (eg, warfarin) and CYP2C19 (eg, omeprazole); no inhibition or induction of these enzymes has been observed in vitro or in human studies that would suggest the potential for important drug interaction issues (unpublished data). The potential effect of the drug on major transporters was also evaluated. Similar to trimethoprim, significant inhibition of several primarily renal transporters was observed (OCT1, OCT2 [eg, metformin], and MATE2-K) (unpublished data). Importantly, no consequent effect (ie, hypoglycemia) of OCT inhibition was seen clinically in patients receiving metformin and iclaprim, and this effect is thought to be clinically unimportant [15].

Overall, the comprehensive preclinical safety studies with iclaprim demonstrate strong support for demonstration of safety of the drug in clinical studies.

PHARMACOLOGY

Preclinical Pharmacology

Iclaprim is rapidly bactericidal against Gram-positive bacteria in vitro, with > 99% reduction of bacterial colony-forming units (CFUs) occurring within 8–24 hrs of exposure to concentrations as low as 2-fold above the MIC [16]. In addition, iclaprim exhibits a significant postantibiotic effect for up to 10 hours at sub-MIC concentrations, consistent with its effect on thymidine biosynthetic pathways [16]. This combination of rapid bactericidal activity followed by a prolonged postantibiotic effect has been exploited during development to maintain the efficacy of iclaprim between dosing periods in the clinic, thereby supporting twice-daily dosing regimens in clinical studies.

Iclaprim has been studied in serial passage studies. After 17 serial passages of *S. aureus* strains in the presence of subtherapeutic levels of iclaprim, there was only a modest increase in MIC from 0.12 to 1 µg/mL, which returned to baseline after removal of iclaprim. In contrast, trimethoprim showed the development of high-level resistance (MIC > 128 µg/mL) within 12 passages in a similar experiment using subtherapeutic concentrations of trimethoprim (unpublished data).

Pharmacokinetic/pharmacodynamic (PK/PD) analysis of the data from a thigh infection model indicated that area under the curve (AUC)/MIC and time above MIC (T > MIC) were the parameters most closely associated with efficacy of iclaprim in vivo (unpublished data). No specific AUC/MIC or T > MIC target was identified in these experiments because of the high concentrations of thymidine in serum and tissues of mice (100-fold greater than human), which bypasses the DHFR enzyme. As shown in Figure 2 for *S. pneumoniae*, the correlation coefficient $R^2$ is 0.86 for efficacy vs both AUC/MIC and T > MIC, whereas $R^2 = 0.4$ for $C_{max}$/AUC; similar correlations were observed with *S. aureus*. These data suggest that duration of exposure is more important than peak drug concentrations in optimizing the efficacy of iclaprim.

Human Pharmacokinetics

Iclaprim achieves high concentrations in skin and skin structure and lung compartments. Iclaprim also rapidly concentrates in the gastrointestinal tract, adrenal glands, kidneys, and liver, with a high volume of distribution exceeding 4–5 times the total body water volume. Iclaprim has 93% plasma protein binding. Iclaprim and its metabolites are rapidly and extensively excreted in the bile and urinary route. Iclaprim is metabolized by both phase 1 (CYP3A4 and CYP23C19) and phase 2 (CYP2C9 and CYP2D6) enzymes. Most of the phase 1 metabolites are subsequently conjugated to glucuronide metabolites. Less than 2% of unchanged iclaprim was found in urine and feces, confirming extensive metabolism.

Pharmacokinetic parameters of iclaprim from population PK in cSSSI pivotal studies with dosing of 0.8 mg/kg every 12 hours gave similar values to those obtained in phase 1 PK studies (Table 1). The initial phase 1 studies of weight-based doses of iclaprim showed the PK of iclaprim to be linear, with dose-proportional increases in both AUC and $C_{max}$ over a wide range
of doses [14]. Exposure did not change over time for up to 10 sequential days of dosing, nor was exposure altered in subjects with renal impairment. A 2-fold increase in AUC was observed in subjects with moderate hepatic impairment, suggesting that dose adjustments may be indicated in that population. Iclaprim is not a potent inhibitor of CYP450 enzymes, and drug-drug interaction (DDI) studies showed a less-than-2-fold increase in iclaprim levels in the presence of of the CYP3A4 inhibitor ketoconazole. Therefore, no dose adjustments are indicated when iclaprim is co-administered with inhibitors or substrates of CYP450 enzymes. In addition, unlike trimethoprim-sulfamethoxazole, iclaprim has no effect on renal excretion of potassium and serum potassium concentrations.

Clinical phase 1 drug distribution studies showed that IV-administered iclaprim diffuses readily into the lung. The concentrations in alveolar macrophages and pulmonary epithelial fluid were 20–40-fold higher than in plasma, suggesting that the drug accumulates in tissues that are relevant to pulmonary infection [17].

Human Dose Optimization

In order to optimize the dosing regimen for the REVIVE phase 3 clinical trials of ABSSSI [18, 19], the PK data from the phase 3 ASSIST trials of cSSSI were analyzed for information that could improve the efficacy and safety parameters in patients. An important observation from the PK parameters in ASSIST, in which patients were dosed with 0.8 mg/kg of iclaprim using a 30-minute infusion twice daily, was that the clearance of iclaprim does not change with body weight [20]. Therefore, a fixed dose of iclaprim was pursued in REVIVE [15], rather than the weight-based dosing used in ASSIST. Population PK/PD modeling was conducted using the PK data obtained by sparse sampling on patients in the ASSIST trials to examine the effect of dose and infusion rate on the parameters most important for efficacy (eg, maximize AUC/MIC and T > MIC) and for safety (eg, minimize C\text{min}). Through an interactive modeling process, a dose of 80 mg, given as a 2-hour infusion every 12 hours, was determined to provide the optimal regimen for all 3 parameters [20]. This regimen was projected to result in a 28% increase in AUC/MIC and a 32% increase in T > MIC compared with the weight-based regimen used in ASSIST, while keeping the mean C\text{max} below the 800 ng/mL level that was associated with QTc prolongation in phase 1. Combined with the previously noted postantibiotic effect, this modified dosing regimen translated into an improved efficacy and safety profile in the REVIVE studies, as detailed below.

**MICROBIOLOGY**

Iclaprim is active against common skin (ie, *S. aureus* MIC\textsubscript{90} = 0.12 µg/mL, *Streptococci pyogenes* MIC\textsubscript{90} = 0.25 µg/mL, *Streptococci agalactiae* MIC\textsubscript{90} = 0.25 µg/mL, and other *Streptococci* spp.) (Table 2) and respiratory pathogens (ie, *Streptococcus pneumoniae* MIC\textsubscript{90} = 2 µg/mL, *S. aureus* MIC\textsubscript{90} = 0.12 µg/mL, *Haemophilus influenzae* MIC\textsubscript{90} = 0.12 µg/mL, and *Moraxella catarrhalis* MIC\textsubscript{90} = 0.12 µg/mL), including emerging drug-resistant pathogens (Table 2) [21]. Comparison of MICs shows that iclaprim is at least 8-fold more potent against Gram-positive bacteria than trimethoprim. Iclaprim was active (defined as an MIC ≤1 µg/mL) against MRSA isolates that were nonsusceptible to daptomycin (71%), linezolid (100%), or vancomycin (67%). In time-kill curves analyses, iclaprim demonstrated ≥3 log\textsubscript{10} reduction in CFU/mL at 4–8 hours for tested strains and isolates nonsusceptible to daptomycin, linezolid, or vancomycin (Figure 3) [22].

**CLINICAL**

One phase 2 and 2 phase 3 clinical trials have been completed for iclaprim for the treatment of cSSSIs (called ASSIST-1 and ASSIST-2), 2 phase 3 clinical trials for the treatment of ABSSSI (called REVIVE-1 and REVIVE-2), and 1 phase 2 clinical trial for the treatment of hospital-acquired bacterial pneumonia (HABP) (Table 3).

**Phase 2 for the Treatment of cSSSI**

A randomized, double-blind phase 2 study compared the efficacy and safety of iclaprim with those of vancomycin in patients with cSSSI [23]. Eighty-seven patients were randomized to receive 0.8 mg/kg or 1.6 mg/kg of iclaprim or 1 g of vancomycin, all administered twice a day for 10 days. Patient demographics recorded at baseline were similar in all treatment groups. Nearly all patients had signs and symptoms of discharge, erythema, swelling, induration, heat, localized warmth, pain and tenderness to palpation, and evidence of systemic signs and symptoms of infection such as fever (38°C/100.4°F), enlarged and/or tender proximal lymphadenopathy and/or lymphangitis, elevated WBCs (>10,000/mm\textsuperscript{3}), and/or >10% bands.

Clinical cure rates for the 0.8 mg/kg (26/28, 92.9%) and 1.6 mg/kg (28/31, 90.3%) iclaprim intent-to-treat (ITT) treatment groups were comparable to that of the vancomycin treatment group (26/28, 92.9%). Infection sources and/or types included ulcers, cellulitis, animal bites, burns, and major abscesses. There were no significant differences in the clinical cure rate for the infection types at day 10 or at the test of cure (TOC) visit across study arms. Iclaprim exhibited a microbiological eradication rate for *S. aureus*, the pathogen most
frequently isolated at baseline, of 80% for the 0.8 mg/kg group and 72% for the 1.6 mg/kg group, compared with 59% for the group treated with vancomycin.

Iclaprim exhibited a safety profile similar to that of vancomycin. Among patients reporting adverse events considered related to the study drug, 2 were from the 1.6 mg/kg iclaprim group (pruritis and erythema) and 3 were from the vancomycin group (tremor, pruritis, and dermatitis medicamentosa). No drug-related adverse events were recorded in the 0.8 mg/kg group.

**Phase 3 for the Treatment of cSSSI**

Two randomized, double-blind phase 3 studies compared the efficacy and safety of iclaprim with those of linezolid in patients with cSSSI. In ASSIST-1, 497 patients were randomized to receive 0.8 mg/kg of iclaprim (n = 249) or 600 mg of linezolid (n = 248), both administered twice a day for 7–14 days [22]. In ASSIST-2, 494 patients were randomized to receive 0.8 mg/kg of iclaprim (n = 251) or 600 mg of linezolid (n = 243), both administered twice a day for 7–14 days [23]. The average treatment duration for both iclaprim and linezolid was 10 days. Patient demographics (age, gender, race, body mass index), lesion types (approximately 25% major abscess, 30% wound infections, and 45% cellulitis/ulcers/burns), laboratory parameters (eg, WBC counts), vital signs (eg, fever), and systemic signs and symptoms of infection recorded at baseline were similar in all treatment groups. The primary end point was clinical cure, as defined as resolution of all signs and symptoms (discharge, erythema, swelling and/or induration, heat and/or localized warmth, and/or pain or tenderness to palpation) present at baseline of cSSSI and not receiving any new systemic or topical antibacterial treatment.

Based on the Sponsor analysis, in ASSIST-1, iclaprim clinical cure rates at TOC were comparable with linezolid at 83.1% (207/249) and 88.7% (220/248), respectively (treatment difference, –5.6%; 95% confidence interval [CI], –11.72% to 0.6%) [22]. In ASSIST-2, iclaprim clinical cure rates at TOC were comparable, with linezolid at 81.3% (204/251) and 81.9% (199/243), respectively (treatment difference, –0.6%; 95% CI, –7.7% to 6.5%) [23]. The pooled clinical cure rates for iclaprim and linezolid were 82.2% (411/500) and 85.3% (419/491), respectively (treatment difference, –3.1%; 95% CI, –7.9% to 1.6%). Iclaprim was well tolerated in both studies, with most adverse events, such as headache, nausea, vomiting, and fatigue, categorized as mild. However, because the 2 studies did not independently meet the noninferiority margin of 10% for clinical cure, the Food and Drug Administration (FDA) did not approve iclaprim for the treatment of cSSSI.

**Phase 3 for the Treatment of ABSSSI**

Two randomized, double-blind phase 3 studies compared the efficacy and safety of iclaprim with those of vancomycin in...
Table 3. Phase 2 and 3 Clinical Trials Studying Iclaprim

| Indication | Phase | Dosages | Year     | Results                                                                 | Reference |
|------------|-------|---------|----------|-------------------------------------------------------------------------|-----------|
| HABP       | 2     | Iclaprim 0.8 mg/kg IV q12h; iclaprim 1.2 mg/kg IV q8h; vancomycin 1 g IV q12h | 2007–2008 | Iclaprim comparable to vancomycin at clinical cure at test of cure (iclaprim q12h 73.9% [17/23], iclaprim q8h 62.9% [15/24], vancomycin 1g 52.2% [12/23]). Iclaprim comparable to vancomycin at day 28 mortality (iclaprim q12h 8.7% [2/23], iclaprim q8h 12.5% [3/24], vancomycin 1 g 21.7% [5/23]). | [24]      |
| cSSSI      | 2     | Iclaprim 0.8 mg/kg IV q12h; iclaprim 1.6 mg/kg IV q12h; vancomycin 1 g IV q12h | 2006–2007 | Iclaprim noninferior to vancomycin at primary FDA end point of clinical cure at test of cure (iclaprim 0.8 mg/kg 92.9% [28/31] compared with vancomycin 92.9% [26/28]). | [23]      |
| cSSSI      | 3     | Iclaprim 0.8 mg/kg IV q12h; linezolid 600 mg IV q12h | 2007–2008 | In ASSIST-1, iclaprim clinical cure (iclaprim 83.1% [207/249] comparable to linezolid (88.7% [220/248]) at test of cure (treatment difference, –5.6%; 95% CI, –11.72% to 0.6%). | [18]      |
| cSSSI      | 3     | Iclaprim 0.8 mg/kg IV q12h; linezolid 600 mg IV q12h | 2007–2008 | In ASSIST-2, iclaprim clinical cure (iclaprim 81.3% [204/251]) noninferior to linezolid (81.9% [199/243]) at test of cure (treatment difference, –0.6%; 95% CI, –7.77% to 6.5%). | [19]      |
| ABSSSI     | 3     | Iclaprim 80 mg IV q12h; vancomycin 15 mg/kg IV q12h | 2016–2017 | In REVIVE-1, iclaprim noninferior to vancomycin at primary FDA end point of early clinical response (iclaprim 80.9% [241/298] compared with vancomycin 81.0% [243/300]). | [15]      |
| ABSSSI     | 3     | Iclaprim 80 mg IV q12h; vancomycin 15 mg/kg IV q12h | 2016–2017 | In REVIVE-2, iclaprim noninferior to vancomycin at primary FDA end point of early clinical response (iclaprim 78.3% [231/295] compared with vancomycin 76.7% [234/305]). | Unpublished |

Abbreviations: ABSSSI, acute bacterial skin and skin structure infection; cSSSI, complicated skin and skin structure infections; HABP, hospital-acquired pneumonia; IV, intravenous; VABP, ventilator-associated bacterial pneumonia.
patients with ABSSSI. The inclusion criteria for these 2 studies were a bacterial infection of the skin (major cutaneous abscess, cellulitis/erysipelas, and/or wound infections) with a lesion size area of at least 75 cm² and the presence of purulent or seropurulent drainage or at least 3 signs and symptoms of infection (discharge, erythema, swelling, warmth, and/or pain). One study has completed (REVIVE-1) [15], and the second is awaiting completion of final analyses (REVIVE-2). In REVIVE-1, 598 patients were randomized to receive 80 mg of iclaprim or 15 mg/kg of vancomycin, each administered twice a day for 5–14 days. The actual mean duration of treatment in each group was 7 days for both iclaprim and vancomycin. For each patient, the unblinded pharmacist relayed the creatinine clearance or vancomycin trough levels (to which the investigator was blinded) to adjust the vancomycin dosage to maintain a trough of 10–15 mg/L for patients with an organism with an MIC that was ≤1 mg/L, or 15–20 mg/L for those with an MIC >1 mg/L. Patient demographics recorded at baseline were similar in all treatment groups. The primary end point, which was FDA approved on the basis of its clinical relevance, of this study was a ≥20% reduction in lesion size (early clinical response [ECR]) compared with baseline among patients randomized to iclaprim or vancomycin at the early time point (ETP), 48 to 72 hours after the start of administration of the study drug in the ITT population.

In REVIVE-1, iclaprim achieved noninferiority compared with vancomycin; 80.9% (241 of 298) of patients receiving iclaprim demonstrated an ECR at the ETP compared with 81.0% (243 of 300) of patients receiving vancomycin (treatment difference, −0.1%; 95% CI, −6.42% to 6.17%) [15]. In REVIVE-2, the topline results showed that iclaprim achieved noninferiority compared with vancomycin; 78.3% (231 of 295) of patients receiving iclaprim demonstrated an ECR at the ETP compared with 76.7% (234 of 305) of patients receiving vancomycin (treatment difference, 1.58%; 95% CI, −5.10% to 8.26%) (unpublished data). Iclaprim was well tolerated in both studies, with most adverse events, such as headache, nausea, vomiting, and fatigue, categorized as mild. In REVIVE-1, the most common adverse effects (≥5%) for iclaprim- and vancomycin-treated patients were headache (10.2% and 2.4%), nausea (9.9% and 5.7%), secondary ABSSSI (6.8% and 3.3%), fatigue (6.1% and 3.0%), and vomiting (4.8% and 5.1%), respectively. In REVIVE-2, the most common adverse event (≥5%) for iclaprim- and vancomycin-treated patients was nausea (5.7% and 5.6%, respectively).

**Phase 2 for the Treatment of HABP**

A randomized, double-blind phase 2 study compared the efficacy and safety of iclaprim with those of vancomycin in patients with nosocomial pneumonia suspected or confirmed to be caused by Gram-positive pathogens [24]. Patients were diagnosed with pneumonia by having at least 2 of the following signs and symptoms: cough; new onset of purulent sputum production or a change (worsening) in character of sputum; dyspnea, tachypnea, or hypoxemia with a partial pressure oxygen <60 mm Hg and at least 2 signs and symptoms of systemic infection such as fever or respiratory rate >30 breaths/min; pulse rate >120 beats/min; altered mental status; WBC count >10 000/mm³ or <4500/mm³; and/or >15% immature neutrophils (bands). In addition, all patients had a new pulmonary infiltration documented by chest radiograph, a suitable respiratory specimen for culture, a Gram stain with a Gram-positive pathogen, and a clinical pulmonary infection score (CPIS) ≥6. Seventy patients were randomized to receive 0.8 mg/kg IV q12h (n = 23) or 1.2 mg/kg q8h (n = 24) of iclaprim or 1 g q12 h of vancomycin (n = 23), all administered twice a day for 7–14 days. Aztreonam was permitted for patients whose pneumonia was caused by mixed (gram-positive and aztreonam-susceptible gram-negative) pathogens. Patient demographics and microbiology recorded at baseline were similar in all treatment groups. The most common isolated pathogen was S. aureus (71%), and 40% of these were MRSA. There were no ventilator-associated pneumonia (VAP) patients in the study. The primary end point was clinical cure, defined as complete resolution of all signs and symptoms of pneumonia (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.

Cure rates in the ITT population were 73.9% (17 of 23), 62.5% (15 of 24), and 52.2% (12 of 23) in the iclaprim q12h, iclaprim q8h, and vancomycin groups, respectively (iclaprim q12h vs vancomycin, P = .13; iclaprim q8h vs vancomycin, P = .47). The mortality 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 dosing regimen was similar to that of vancomycin. The following treatment-emergent adverse events were reported in 2 or more patients: thrombocytopenia (vancomycin 2, iclaprim 1), diarrhea (vancomycin 2, iclaprim 0), and prolonged QTc (vancomycin 0, iclaprim 2).

**REGULATORY**

Iclaprim is being developed to treat ABSSSI, HABP including VABP, and other infections attributed to Gram-positive pathogens including multidrug-resistant pathogens.

Two phase 3 clinical studies in cSSSI (ie, ASSIST-1 and -2), statistically powered to demonstrate noninferiority to linezolid with a prespecified margin of 12.5%, were completed in 2007. In November 2008, an FDA Advisory Committee meeting was held to discuss the efficacy data from these 2 phase 3 studies. The Advisory Committee recommended that iclaprim not be approved...
for the cSSSI indication based on these data because the noninferiority margin of greater than 10% in ASSIST-2 (ie, –11.7%) was considered unacceptable. A complete response letter from the FDA stated, among other items, that “an additional study or studies would be required to demonstrate the effectiveness of iclaprim.” In October 2009, the iclaprim marketing authorization application for Europe was withdrawn.

In 2015, the FDA granted QIDP status and Fast Track status for iclaprim for ABSSSI and HABP. Motif has conducted 2 additional phase 3 studies in patients with ABSSSI (ie, REVIVE-1 and -2) to assess the noninferiority at –10% of iclaprim to vancomycin. Both REVIVE-1 and -2 have met this end point.

SUMMARY

Iclaprim is a diaminoopyrimidine antibiotic that is administered as a fixed intravenous dose and is potent, rapidly bactericidal, has good tissue penetration in skin and skin structures and in lung compartments, and it has completed 2 phase 3 studies for cSSSI. In addition, iclaprim has completed 2 phase 3 studies for ABSSSI; REVIVE-1 and -2 demonstrated noninferiority to vancomycin for the FDA-approved primary end point of early clinical response. Iclaprim has completed 1 phase 2 study for HABP including VABP, which showed comparable efficacy and safety for the primary end points of TOC and day 28 mortality. Based on these data, iclaprim, if approved, has the potential to offer an alternative treatment option for patients with ABSSSI or HABP, including VABP.

Acknowledgments

Financial support. This work was supported by Motif Bio plc, New York, USA.

Potential conflicts of interest. D.B.H. is an employee of Motif BioSciences. M.V., J.M., C.S., and R.P. are consultants for Motif BioSciences. T.H. has received consultancy fees from Basilea Pharmaceutica, Genentech, Medicines Company, and Motif Biosciences. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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