Motif BioSciences, Inc.
www.motifbio.com

Potent late-stage antibiotic for serious and life-threatening bacterial infections

Motif Bio's iclaprim shows rapid bactericidal activity and low propensity for induction of resistance and is in late-stage clinical testing for acute bacterial skin and skin structure infections.

The need for new antibiotics to combat multidrug-resistant infections is increasingly urgent in the hospital setting, where patients often succumb to serious and life-threatening infections that require immediate treatment with the best available antibiotic.

Motif Bio is a clinical-stage biopharmaceutical company developing new antibiotics against serious and life-threatening infections caused by multidrug-resistant bacteria. Its lead product candidate, iclaprim, is being developed for the treatment of the most common and serious bacterial infections, such as acute bacterial skin and skin structure infections (ABSSSIs) and hospital-acquired bacterial pneumonia (HABP), including infections caused by resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA).

Rapid bactericidal activity

Iclaprim belongs to the underutilized class of selective dihydrofolate reductase (DHFR) inhibitors. Its mechanism of action targets the folate synthesis pathway, which has a key role in bacterial DNA replication[1]. Designed to overcome resistance to trimethoprim, iclaprim shows a much higher affinity for the DHFR binding site of bacteria than trimethoprim does. *In vitro* data show that iclaprim alone is at least as potent as trimethoprim plus sulfamethoxazole against Gram-positive pathogens.

An independent report from JMI Laboratories in 2015 has also shown that iclaprim is 16 times more potent than trimethoprim alone *in vitro* against a range of Gram-positive bacteria collected from patients with ABSSSI and HABP worldwide (2012–2014), including *S. aureus*. The minimum inhibitory concentration of iclaprim required to kill 90% of tested strains of *S. aureus* (MIC_{90}) was 0.12 µg/ml, compared with 1.0 µg/ml of vancomycin, 1.0 µg/ml of linezolid or 2.0 µg/ml of trimethoprim.

Iclaprim is rapidly bactericidal (**Fig. 1a**), and has a low propensity for induction of resistance *in vitro* (**Fig. 1b**).

Late-stage clinical program

Originally discovered by F. Hoffman-La Roche, iclaprim was licensed to and developed by Arpida. Two phase 3 studies (ASSIST-1 and -2) were conducted in patients with complicated skin and skin structure infections, which showed similar safety and efficacy between iclaprim and linezolid for clinical cure rates at test of cure (pooled clinical cure rate: iclaprim, 82% and linezolid, 85%). The US Food and Drug Administration (FDA) declined to approve iclaprim on the basis of the data submitted in 2008. Since then, the regulatory environment has evolved in response to the urgent need for new antibiotics.

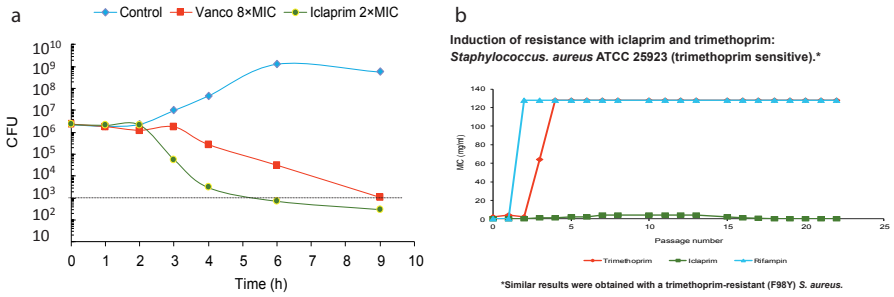

Figure 1: Iclaprim bactericidal activity and low resistance profile. (**a**) Iclaprim is rapidly bactericidal *in vitro*. Time-kill curve for a representative clinical strain of methicillin-resistant *Staphylococcus aureus* (MRSA). Iclaprim killed 99.9% of MRSA within 4–6 hours of drug exposure, versus 8–10 hours for vancomycin. CFU, colony-forming units. (**b**) Iclaprim has a low propensity for induction of resistance *in vitro*. Serial passage study for a representative clinical strain of *S. aureus*. Iclaprim induced only a small change in minimum inhibitory concentration (MIC) after 22 repeat passages, whereas trimethoprim and rifampin induced large changes in MIC after 2–3 passages. Additionally, iclaprim caused no mutations in dihydrofolate reductase genes.

Motif Bio acquired exclusive worldwide rights to iclaprim in December 2014 and, building on previous experience, it has improved the original development program and returned iclaprim to late-stage clinical testing. The new pivotal phase 3 clinical trials aim to obtain marketing approval for an intravenous formulation of iclaprim for the treatment of ABSSSI, with input from the FDA and European Medicines Evaluation Board.

The REVIVE (Randomized Evaluation of Intravenous Iclaprim Vancomycin Treatment) clinical trials aim to show noninferiority of iclaprim to vancomycin while eliciting a much faster bactericidal profile, thereby potentially reducing the length of hospital stay and resulting in pharmacoeconomic savings. REVIVE-1 and -2 will each enroll 600 adult patients who are hospitalized with ABSSSIs and have a lesion-size area of at least 75 cm^2. The primary endpoint will be at least a 20% reduction in lesion size at 48–72 hours after the first dose of treatment. The key secondary endpoint will be clinical cure at 1–2 weeks after the end of treatment.

Iclaprim will be administered at a fixed dose (80 mg of intravenous infusion in 500 ml of saline every 12 hours), which optimizes the pharmacodynamic parameters associated with antibacterial efficacy while minimizing safety events. Dosing of the first patient was announced in March 2016, and both trials are anticipated to be completed in the second half of 2017. A pivotal phase 3 trial in patients with HABP is planned for late 2016.

New frontline treatment option

Iclaprim may be an appropriate initial antibiotic for selected patients, because of its low renal toxicity profile and low propensity for the development of resistance. "We believe the iclaprim patient will be a hospitalized patient who has a serious and life-threatening MRSA infection with specific comorbidities, such as diabetes, obesity and renal impairment that may make treatment more complex," said David Huang, chief medical officer at Motif Bio. "In these patients, you cannot afford to get the initial antibiotic wrong—it has to be the right choice from the initial onset of infection."

The FDA has granted iclaprim a fast-track designation and a qualified infectious diseases product (QIDP) designation for ABSSSI and HABP, making it eligible for 10 years of market exclusivity from the date of new drug approval. Ten years of data exclusivity is also expected in Europe. If approved, iclaprim could be ready for commercialization in 2018.

Motif Bio is planning to commercialize iclaprim in the United States and is actively seeking partners outside the country. "With trials expected to complete in the second half of 2017, we are keen to begin engaging with strategic partners now," said Graham Lumsden, CEO of Motif Bio.

1. Morgan, A. *et al. Future Microbiol.* **4**, 131–143 (2009).

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