WHO recommends artemisinin containing therapies (ACTs) as first-line treatment of acute uncomplicated *Plasmodium falciparum* malaria. However, in 2015, artemisinin resistance had already been confirmed in five countries of the Greater Mekong sub-region: Cambodia, Laos, Vietnam, Thailand and Myanmar. In the absence of alternative treatments and pending the development of non-artemisinin-based containing therapies, reliance is being placed on prolonged courses of ACTs of up to 10 days duration to effect radical cures.

OUR ENGAGEMENT

Jomaa Pharma GmbH is committed to the development of fosmidomycin + piperaquine as a front runner of Non-Artemisinin-based Combination Therapies (NACT) for malaria. It is being developed as a highly effective, safe and well tolerated treatment having the attributes of rapid schizonticidal activity and prolonged post-treatment prophylaxis to meet the challenge of artemisinin resistance. Jomaa Pharma GmbH is supported by Medicines for Malaria Venture (MMV) – a not for profit organisation funded by the Bill And Melinda Gates Foundation – , European and Developing Countries Clinical Trials Programme (EDCTP) and World Health Organisation (WHO).

FOSMIDOMYCIN + PIPERAQUINE

Fosmidomycin was isolated in the late 1970s by Fujisawa Pharmaceuticals (Osaka, Japan) as a naturally occurring antibiotic produced by *Streptomyces lavendulae*. Without knowledge of its molecular target, fosmidomycin was investigated in Phase II studies as a potential treatment for urinary tract infections and while proving effective for acute uncomplicated infections caused by certain bacterial species, it was less effective for the treatment of complicated infections by other species. Due to this restriction and the lack of knowledge about its mode of action (MoA) at that time further development was halted.

Today it is known that fosmidomycin exhibits a unique MoA by blocking the isoprenoid biosynthesis. In all organisms, isoprenoids are synthesised from isopentenyl pyrophosphate (IPP) as a common precursor molecule. In animal and human cells, IPP is produced via the well-known mevalonate pathway. In contrast, many eubacteria and all plant cells synthesise IPP by the DOXP pathway – also designated non-mevalonate or MEP pathway in which 1-Deoxy-D-xylulose-5-phosphate (DOXP) is converted to 2-Methyl-D-erythritol-4-phosphat (MEP). Fosmidomycin acts as a strong inhibitor of DOXP reductoisomerase, the second enzyme in the reaction cascade of the DOXP pathway.

The discovery, that plasmodia, the malaria parasites, rely solely on the non-mevalonate pathway to synthesise IPP, formed the basis of developing fosmidomycin as a highly selective antimalarial agent. Humans – in contrast to the parasites – are reliant on the mevalonate pathway of isoprenoid biosynthesis and have no homologue of the fosmidomycin target, the DOXP reductoisomerase. Inhibitors of this enzyme are highly selective and therefore safe antimalarial agents as has been shown to be the case. An assumed enhancement of fosmidomycin efficacy through combination with other current anti-malaria drugs and antibiotics was investigated in a series of *in vitro* experiments. As a result, an optimal additive and synergistic action was observed with piperaquine as a combination partner.

FOSMIDOMYCIN

- unique mode of antiplasmodial action
- blocking a biochemical target not present in humans
- no apparent human metabolism
- excellent safety and tolerance in humans
- no dose limiting toxicity established in animals even at highest possible exposure
- easy to synthesise
- easy to formulate
- chemically very stable

Piperaquine inhibits the detoxification of heme within the malaria parasite, its accumulation leading to increased membrane permeability of infected red blood cells favouring the influx of fosmidomycin and enhancing the additive effect seen *in vitro*.

The efficacy, safety and tolerance of the combination has been established in proof of concept studies in Gabon in which fosmidomycin, in twice daily doses of 30 mg/kg, and piperaquine, in a once daily dose of 16 mg/kg, were administered orally for

three days to a total of 100 subjects, consisting of 10 adults, 40 children aged 5 to 14 years and 50 children aged one to five years. For the 69 subjects evaluable on day 28, as the primary efficacy endpoint, the cure rate was far above 96 % without a single case of recrudescence even on day 63 post treatment. Fever clearence time is typically less than 40 hours while parasite clearance time never exceeds 50 hours. There were no drug related safety issues and tolerance was excellent despite the high dose of fosmidomycin.

Dose optimisation studies with the aim of halving and possibly quartering the daily dose of fosmidomycin within the constraint of a three-day therapeutic regimen of once daily dosing are planned and currently being prepared for later 2016.

"Antimalarial drug development continues to receive massive public interest and attention – an invaluable image factor for the developer."

THE COMPANY

Jomaa Pharma GmbH was established in 2003 following the acquisition of the predecessor Jomaa Pharmaka GmbH by BioAgency AG and has attracted around 5 million EUR for the preclinical and clinical development of drug combinations containing fosmidomycin. Jomaa Pharmaka GmbH had been founded five years previously by Hassan Jomaa and Ewald Beck as an extension of their academic posts at the University of Giessen for the purpose of attracting venture capital to support innovative drug discovery primarily in the field of infectious disease.

Following its dissociation from BioAgency AG in 2013, Jomaa Pharma GmbH became a privately owned company, financed by corporate and individual investors and operating under the direction of the Managing Director, Dr David Hutchinson. He brings a wealth of experience gained from the successful development of atovaquone and proguanil (Malarone) as one of the classical prophylactic antimalarials on the market. Jomaa Pharma has its office premises in Hamburg and Westerham, respectively. The Company owns the exclusive intellectual property rights to fosmidomycin and combinations thereof for the treatment of malaria infections.

SOME MALARIA KEY FACTS

Malaria is a life-threatening disease caused by parasites of the genus *Plasmodium* of which there are five species infective to humans: *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale* and *P. knowlesi*. It is transmitted through the bites of infected female *Anopheles* mosquitoes.

In 2015, there was transmission in 95 countries putting 3.2 billion people, approximately half of the world's population, at risk. However, between 2000 and 2015, the incidence of malaria fell by 37 %. In the same period malaria death rates among populations at risk fell by 60 % globally across all age groups and by 65 % in children under the age of five years. Sub-saharan Africa carries a disproportionately high share of global malaria accounting for 88 % of the cases and 90 % of the deaths.

Children under the age of five years, pregnant women and people with HIV/AIDS living in endemic areas are most at risk. Other groups include non-immune migrants, mobile populations and travellers. For acute uncomplicated infections caused by *Plasmodium falciparum*, treatment is aimed at the rapid and complete elimination of the parasite from the blood stream to prevent progression to severe and potentially fatal disease. By 2014, the artemisinin containing therapies, although facing growing resistance, had been adopted in 81 countries with 337 million treatment courses being delivered to both the public and private sectors.

WHAT IS OUR AIM?

At Jomaa Pharma we have now reached the advanced development stage of the fosmidomycin + piperaquine malaria therapy at which a strategic alliance with a pharmaceutical partner has become a sensible option for moving further into final trials, approval and market entry. Therefore, we now aim at entering into an alliance with a potent partner to jointly pursue our post-artemisinin next-generation therapy development.

As malaria and antimalarial drug development continue to receive massive public interest and attention, our fosmidomycin + piperaquine combination is a highly ethical drug candidate with an invaluable image and publicity impact factor for the developing alliance. We are seeking to enter into a partnership either with a company having a product on the market that is vulnerable to the major threat to antimalarials – parasite resistance, or a company considering to embark on the antimalaria market with a new ethical drug, thereby exploiting the immense image potential.

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