Fosmidomycin as Combination Therapy

The selection of piperaquine as the preferred partner drug on the grounds of its prolonged post-treatment prophylactic effect has addressed the problem of recrudescence.

By complementing the rapid blood schizonticidal activity of fosmidomycin, it has also paved the way for the development of a highly efficacious, well tolerated and safe combination therapy as evidenced by the 100 % cure rate that was achieved in a proof of concept study.

Conducted in Gabon in 2015/16, the study* provided for the enrolment of 100 adults and children from the age of one year with acute uncomplicated *Plasmodium falciparum* malaria.

They were treated with fosmidomycin and piperaquine in doses of 30 mg/kg body weight twice daily and 16-18 mg/kg once daily respectively for three days and followed up for 63 days.

The 100 % cure rate on Day 28 in all evaluable subjects was maintained in all evaluable subjects on Day 63 in the absence of any safety concerns.

Such an outcome is unsurpassed and warrants the further evaluation of this combination with the aim of substantiating a fully compliant, highly efficacious, well tolerated and safe therapy based on an optimised dosing regimen administered over three days.

Impact

The conclusion of the proposed studies with their high prospect of success will provide fosmidomycin with a number of therapeutic options.

- In combination with piperaquine, it will serve as Non-Artemisinin-based Combination Therapy (NACT) in circumstances where the current first line therapies based on the Artemisinin-based Combination Therapies (ACTs) are becoming less effective as the result of the unremitting spread of artemisinin resistance in South-East Asia and the prospect of it extending to sub-Saharan Africa.
- In combination with piperaquine, it will be available as 'stand-by treatment' in conjunction with a Point of Care or Rapid Diagnostic Test (RDT) for travellers.
- Also, in combination with piperaquine, it will provide Seasonal Malaria Chemoprevention (SMC) and Intermittent Preventive Therapy in pregnancy (IPTp), thereby addressing the therapeutic needs of the two most vulnerable populations - young children and pregnant women.
- In combination with clindamycin and artesunate, it will cover the spectrum of antimicrobial activity for the treatment of severe malaria complicated by co-existing bacterial infections.

deutschemalaria

DMG Deutsche Malaria GmbH
Neuer Wall 72 • 20354 Hamburg, Germany
T +49-40-81 80 28 • M +49-40-172 916 13 66

UK Office:
T +44-1959-56 34 87 • F +44-1959-56 29 31
info@deutschemalaria.com

deutschemalaria

DMG Deutsche Malaria GmbH

Based in Hamburg, DMG Deutsche Malaria GmbH is a privately owned company funded by institutional and private shareholiders. Its lean management structure, under the direction of its CEO, Dr David Hutchinson, ensures highly flexible and cost-efficient development within the company's resources.

The company is actively pursuing partnership deals to maximise its performance.

Aims

The company is dedicated to the development of fosmidomycin as a novel antimalarial agent foreseeing its utility as a component of

- 'Stand-by treatment' for travellers to endemic areas in conjunction with a Rapid Diagnostic Test
- Non-Artemisinin-based Combination Therapy (NACTs)
- Seasonal Malaria Chemoprevention and Intermittent Preventive Therapy in pregnancy (IPTp)
- Acute therapy for severe malaria complicated by bacterial co-infections

Malaria as a Global Health Problem

Malaria is a life-threatening infection caused by protozoal parasites of the genus *Plasmodium* dominated by two species

- *P. falciparum* as the most prevalent parasite on the African continent being responsible for the majority of malaria-related deaths
- *P. vivax* as the dominant malaria parasite outside Africa, It is characterised by its tendency to relapse from persisting liver stages

The Burden of Disease

According to the latest World Malaria Report released in November 2017, there were 216 million cases of malaria in 2016 in 91 countries, an increase of 5 million cases over the previous two years.

The estimated number of malaria deaths stood at 445,000 in 2016, a similar number to the previous year. Sub-Saharan Africa carries a disproportionately high share of the global malaria burden with 90 % of cases and 91 % of deaths in the region.

In areas of high transmission, children under five years of age are particularly susceptible to the disease with more than two-thirds of deaths occurring in this age group.

The Challenge of Drug Resistance

The ability of the parasite to develop resistance to antimalarial drugs has undermined their effectiveness particularly when they have been used as monotherapy.

Attempts to curb this through ensuring that the drugs are co-administered in fixed dose combinations is now widely advocated.

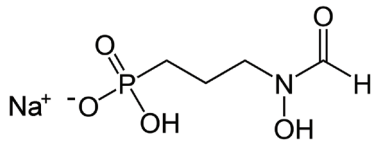
Concerns that the effectiveness of the artemisinin-based combination therapies (ACTs), as the current first line therapies, may become compromised by resistance have surfaced following the detection of artemisinin resistant strains of the parasite in the Greater Mekong Sub-region of South East Asia.

As stated in the August 2018 Status Report of the World Health Organisation[1], resistance has now spread to sub-Saharan Aftica, which will have a devastating effect on the gains that have been made in malaria control in recent years.

Although strenuous efforts are being made to control the spread of artemisinin resistance through the implementation of the Global Plan for the Artemisinin Resistance Containment (GPARC) which relies on early case detection and treatment, it also has as a priority the development of new therapies with novel modes of action within the concept of combination therapy to delay resistance.

Fosmidomycin as a Candidate Antimalarial

Fosmidomycin is an aminopropylphosphonic acid isolated in the 1970s from *Streptomyces lavendulae* by the Fujisawa Pharmaceutical Company in Osaka, Japan. It is currently synthesised as the sodium salt:



Without knowledge of its molecular target, it was formerly investigated as an antibacterial agent.

The discovery of antimalarial activity in 1998 led to a renewal of interest in the compound. It acts by selectively inhibiting two key enzymes, DOXP and IspE, in the non-mevelonate or MEP pathway of isoprenoid biosynthesis on which malaria parasites are essentially dependent for their replication.

In contrast, humans rely solely on the mevalonate or MVA pathway for cellular function and, in the absence of a fosmidomycin target, are unaffected by the drug as demonstrated by the excellent record of safety in clinical use, even when administered at high doses.

As monotherapy, fosmidomycin proved to be highly effective in the initial clearance of parasitaemia when administered orally in doses of 1200mg three times for a minimum of four days. However its overall efficacy was compromised by susceptibility to recrudescent infections.

Such an outcome may be expected when antimalarials are given singly and has resulted in the concept of combination therapy providing for the co-administration of two or more agents with differing modes of action and differing biochemical targets.

References

[1] WHO: Global Malaria Programme. Artemisinin resistance and artemisinin-based combination therapy efficacy. Status Report August 2018

[2] Mombo-Ngoma G, Remppis J, Sievers M, Zoleko Manego R, Endamne L, Lumeka Kabwende, Kremsner PG et al. Efficacy and safety of fosmidomycin-piperaquine as non-artemisinin-based combination therapy for uncomplicated falciparum malaria - A single-arm, age-deescaltion proof of concept study in Gabon. *Clin Infect Dis.* 2018 Jun 1;66(12):1823-1830