

The Fixed-dose combination of Artesunate and Mefloquine: a new, effective tool in the fight against malaria



**ASMQ
FDC** **Artesunate
+Mefloquine**
Fixed-Dose Combination

Executive Summary

Malaria is a major public health problem that continues to affect millions across the world, mainly children under the age of five. The development of multi-drug resistant *Plasmodium falciparum* parasites and resulting failure of treatment with chloroquine and sulfadoxine-pyrimethamine led the World Health Organisation (WHO) to recommend the use of artemisinin-based combination therapies (ACTs) for the treatment of uncomplicated *P. falciparum* malaria in 2001. Recently, delayed parasite clearance indicative of resistance to artemisinin has been reported in some areas of South East Asia, sparking a global response to contain resistant parasites before they spread around the world. Despite these concerns, ACTs remain the best available anti-malarial medicines and are still highly effective in the majority of malaria endemic areas. Fixed-dose combinations of ACTs are preferred and recommended, as they promote adherence to treatment and reduce the potential of selective use of the medicines as monotherapy.

In 2002, the Fixed-Dose Artesunate-Based Combination Therapies (FACT) Consortium, created by the Drugs for Neglected Diseases *initiative* (DNDi) and the WHO Special Program for Research and Training in Tropical Diseases (TDR) developed artesunate (AS)-mefloquine (MQ), ASMQ, as a fixed dose combination (FDC) treatment.

Scientific evidence supporting the efficacy of ASMQ FDC derives from the well-established use of the combined administration of AS and MQ, demonstrated by a large number of studies : since 1992, over 36,000 patients have been treated with AS+MQ in clinical studies performed in twenty countries in South East Asia, the Western Pacific, Africa and Latin America. ASMQ FDC itself has demonstrated efficacy in clinical studies in more than 24,000 patients treated in Thailand, India and Myanmar and in a large intervention study in Brazil.

This document reviews the development of ASMQ FDC, a new, effective tool in the fight against malaria. This story illustrates the power of effective public-private partnerships and how pooling the expertise and resources of research institutes, national malaria control programmes, malaria experts, drug developers, pharmaceutical companies and NGOs across the globe is a critical component to effectively control and ultimately eliminate malaria.

INTRODUCTION

Malaria threatens approximately 3.3 billion people – half of the world's population – in 106 endemic countries. The WHO 2011 World Malaria Report estimates that in 2010, there were 216 million cases of malaria worldwide, 91% of which were due to *Plasmodium falciparum*. Despite being both preventable and treatable, malaria caused **the death of approximately 655,000 people in 2010, 86% of which were children under the age of five.** Most malaria cases and deaths occur in sub-Saharan Africa, but Asia, Latin America, and to a lesser extent, the Middle East and parts of Europe are also affected. Malaria control requires an integrated approach, based on two main components, vector control and case management. The latter relies on early diagnosis and the provision of effective treatment. Currently, the best available treatment for *P. falciparum* malaria is artemisinin-based combination (ACT) therapy. The WHO recommends five artemisinin-based combination therapies (ACTs) for the treatment of uncomplicated *P. falciparum* malaria. **Fixed-dose combinations (FDC) are strongly preferred** and recommended over blistered co-packaged or loose tablets combinations to promote adherence to treatment and to reduce the potential selective use of the medicines as monotherapy.¹

The Artesunate-Mefloquine (MQ) fixed dose combination, ASMQ FDC, was developed as part of the Fixed-dose Artesunate-based Combination Therapies (FACT) project **to offer an easy to use, effective therapy to patients in areas where the combination of AS and MQ is recommended.** With the fixed dose combinations of artesunate and amodiaquine (ASAQ), artemether and lumefantrine (AL), artesunate and pyronaridine and dihydroartemisinin and piperaquine (DHA-PQ), ASMQ FDC strengthens the global ACT portfolio of fixed-dose combinations now available for the treatment of uncomplicated *P. falciparum* malaria. Together with diagnosis and vector control tools, these represent a **key element of the anti-malaria arsenal.**

ASMQ: MOVING FORWARD IN THE FIGHT AGAINST MALARIA

Relevance of ASMQ FDC in Asia

Artemisinin-based combination therapy with mefloquine was adopted in 1994 in Thailand, where the treatment of uncomplicated malaria had been modified several times during the previous 30 years to fight the rapid emergence and spread of drug resistance.² Artesunate-mefloquine ACT was introduced as a 2-day regime to replace mefloquine monotherapy after the spread of resistance to mefloquine; its deployment led to a reduction in the incidence of *P. falciparum* malaria and halted the development of resistance to mefloquine.³ In Cambodia, on the other side of the border, however, mefloquine monotherapy remained the recommended first-line treatment through 2000.

Declining efficacy of the AS+MQ combination was first observed in the Trat Province in south-eastern Thailand on the Cambodian border, where the adequate clinical response decreased from 93% in 1997 to 92.5% in 1998 and to 84.6% in 2002.⁴ Because of the history of mefloquine resistance in the region, it was initially considered that the observed treatment failures were due to decreased efficacy of the partner drug, mefloquine. However, it appeared that parasite clearance times were longer than those previously reported for artesunate-mefloquine⁵ and between 2001 and 2003, delayed parasite clear-

ance rates were also observed in patients treated with artemether-lumefantrine in the Battambang Province of northwestern Cambodia.⁶ The increases in the proportions of patients parasitaemic at day 3 observed on the Cambodia-Thailand border indicate that it is the efficacy of artesunate that is diminishing: analysis of a large prospective series of patients recently showed clear evidence that parasite clearance responses after artesunate treatment are slowing on the northwestern border of Thailand with Myanmar.⁷ Delayed parasite clearance following treatment with ACTs has been observed in some areas of Cambodia, Myanmar, Thailand and Vietnam, indicating the presence of artemisinin resistant malaria in the Greater Mekong Sub-Region (GMS).⁸

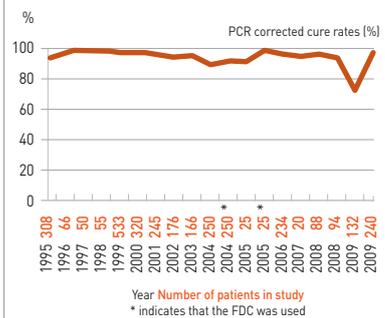
While this information deepens concern about resistance to artemisinins, WHO maintains there is no cause for alarm about the efficacy of ACTs in Myanmar or other countries in the Greater Mekong sub-region. Even though ACTs may take longer to cure patients in settings with artemisinin resistance, they remain the most effective treatment for uncomplicated malaria, provided that the partner medicine in the combination is effective. The large majority of patients with delayed response to artemisinins are cured with the help of the

partner drug.⁹ To address these issues and protect ACTs as an effective treatment, the WHO launched its Global Plan for Artemisinin Resistance Containment (GPARC) in January 2011, mobilizing global and local stakeholders to work towards containing and ultimately eliminating artemisinin resistance where it has emerged, as well as preventing its emergence in or spread to new locations.¹⁰ The GPARC recommends, among other, the manufacture and use of fixed-dose combinations of ACTs to improve compliance with treatment.

Thailand

The efficacy of artesunate and mefloquine has been evaluated in Thailand since 1992; data from 30 studies and over 7,500 children and adults treated with several commercial brands of either loose or fixed dose combination of AS+MQ are available. Sixteen¹¹⁻²⁶ out of twenty four studies carried out before 2009 (including 3,277 patients treated with AS+MQ) used PCR to differentiate recrudescence from reinfection and 14 of those reported cure rates higher than 90%, as shown in Figure 1 below:

Figure 1:
A12+MQ25 PCR-corrected cure rates, Thailand 1995-2009



AS+MQ ACT remains an efficacious antimalarial treatment in this area despite many years of widespread intense deployment. A study conducted in seven provinces of Thailand along the Thai-Cambodian border between January 2009 and December 2011 and recently published showed cure rates with AS+MQ of over 90%.²⁷



Cambodia

According to a recent WHO update, the efficacy of AS+MQ in eastern Cambodia remains high (>95%).²⁸ The summary of available data on AS+MQ efficacy from studies performed in nine Cambodian provinces includes 1,419 children and adults with malaria over the period spanning from 2001 to 2008.^{6,23,29-31} Despite the delayed parasitological clearance times and elevated artesunate IC50, reported cure rates using AS+MQ ranged between 90-100% in most of the sites, with the exception of Pailin in 2003-2004 and Kampot in 2006-2008, where the PCR corrected cures rates with AS+MQ ranged from 79.3% and 86.9% in the 231 patients assessed. It should be noted that the performance of AS+MQ in 2007-2008 in Pailin ranges between 95% and 100%, which has been

attributed to the use of RDTs and the switch to DHA-PQ.

Myanmar

In Myanmar, AS+MQ has been the national protocol for the treatment of *P. falciparum* malaria since 2002, and Médecins Sans Frontières (MSF) have used this combination to treat more than 1.5 million patients since 1996 in the Rakhine state. AS+MQ efficacy data is available from places where MSF provides treatment for malaria. More than 1,200 children and adults from Rakhine, Kachin and Shan states have been assessed following treatment with several brands of AS+MQ, either as loose or fixed-dose combinations.³²⁻³⁵ Despite being used intensely, AS+MQ remains effective for treatment of uncomplicated *P. falciparum* malaria in Myanmar.²⁸ In-

deed, the most recent study performed in Myanmar compared the effectiveness of five artemisinin fixed-dose combination regimens with or without primaquine in uncomplicated *P. falciparum* malaria. ASMQ FDC displayed the highest cure rates, the lowest rates of gametocyte carriage, and the most effective suppression of *P. vivax* malaria up to 63 days after mixed or *P. falciparum* infections, with greater post-treatment prophylaxis than the other drugs.³⁴

Other countries

The combination of AS+MQ was used in **additional countries in Asia** between 2002 and 2008. Data from 721 children and adults in **Laos** (N=368), **Bangladesh** (N=121), **Vietnam** (N=170) and **India** (N=62) presents PCR cure rates that ranges between 97% and 100%.^{22,24,36-41}

Use of ASMQ in Latin America

In Latin America, AS+MQ efficacy data for various dose regimes is mainly available from Peru, but also from Colombia and Bolivia. The available literature shows cure rates for AS+MQ between 2003 and 2012 of approximately 100%.⁴²⁻⁴⁹ Mefloquine resistance has remained low in Latin America, but few therapeutic efficacy studies have been performed.⁵⁰ ASMQ FDC was assessed in the Juruá valley, an area with one of the highest incidences of *P. falciparum* malaria in Brazil, in a large implementation study, during which a total of 23,845 children and adult patients with uncomplicated *P.*

falciparum malaria received ASMQ FDC between 2006 and 2008.⁵¹ The study showed that early detection of malaria by health care workers and treatment with ASMQ FDC was feasible and efficacious, and significantly reduced the incidence and morbidity of *P. falciparum* malaria. There was also a significant change in the seasonal pattern of malaria before and after intervention, with the elimination of the malaria seasonal peak in the rainy months of the years following the introduction of ASMQ. No serious adverse events relating to the use of FDC of ASMQ were reported.



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Use of ASMQ in Africa: challenges and opportunities

In contrast with the situation in Asia, there is limited experience with the use of AS+MQ in Africa, whether in loose or fixed combination.

Data is available in the literature from seven clinical trials treating uncomplicated malaria in 1,152 children and adults in Africa, using different regimes of artesunate and mefloquine.⁵²⁻⁶⁰ Since 2003, an increasing body of information has been accumulated through clinical research conducted in various African countries that presents AS+MQ PCR corrected efficacy data ranging between 94.7% and 100%. The ACT Cochrane review published in

2009, which compared 50 studies using either AS+MQ; AL; DHA-PQ; AS+AQ; AS+ Sulfadoxine-Pyrimethamine (SP) or AQ+SP concluded that in the absence of mefloquine resistance, AS+MQ is likely to be highly effective in African countries,⁶¹ but concerns regarding poor tolerability in young infants have restricted its use in this setting: according to the WHO, the main reason for restricting the use of AS+MQ in African children so far has been excessive vomiting associated with mefloquine at the recommended dose of 25 mg/kg. However, a recent study found that in children weighing 10-20 kg (mean age of the study pop-

ulation was 4.5 ± 1.7 years) the tolerability of AS+MQ is as good as that of artemether-lumefantrine.⁵⁶ Thus, it has been recommended to reconsider AS+MQ in Africa, with specific concerns regarding toxicity/vomiting in children. DNDi is sponsoring a multi-centre, open-label, prospective, randomised, controlled, phase IV study in Africa to assess efficacy, safety and pharmacokinetics of ASMQ FDC in ~1,000 children with uncomplicated *P. falciparum* malaria from Tanzania, Burkina Faso and Kenya, compared to AL.

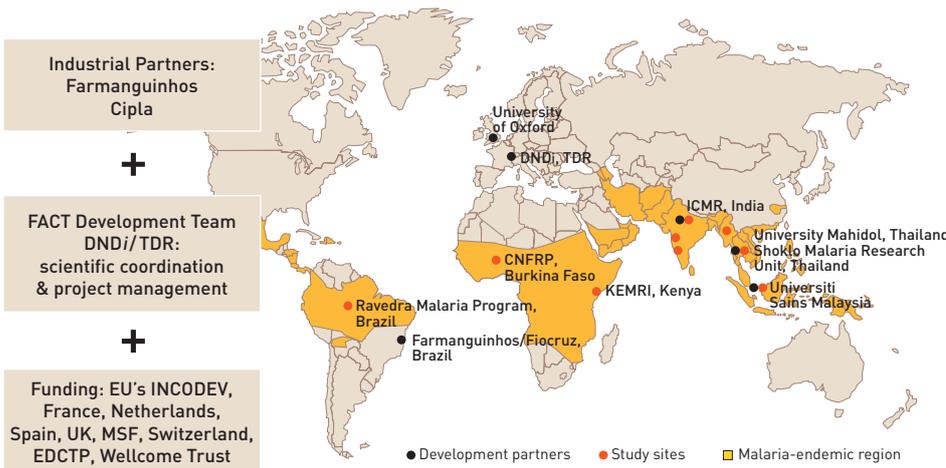
DEVELOPMENT OF ASMQ FDC: THE FACT PROJECT

The WHO regards both artesunate and mefloquine as “essential medicines” for the treatment of *P. falciparum* malaria for adults⁶² and children.⁶³ Since 2001, the combination of artesunate and mefloquine has been one of the WHO-recommended ACTs for areas of low to moderate transmission.⁶⁴ Despite its efficacy, the non-fixed dose artesunate-mefloquine combination posed problems regarding patient compliance and the full potential of preventing the development of parasitic resistance. In 2002, in order to address the treatment needs of people most threatened by malaria and underscoring the need for public leadership, the FACT Consortium was created by Médecins Sans Frontières

and then DNDi, together with TDR. The FACT project aimed to develop a FDC of AS and MQ adapted to regions where the loose combination of the drugs had demonstrated excellent efficacy, therefore improving compliance and reducing the likelihood of resistance development, ultimately prolonging the life-span of the ACT. The FACT project received original funding from INCODEV. The FACT core group also included the Brazilian government-owned pharmaceutical company, Farmanguinhos/Fiocruz, Universiti Sains Malaysia, Mahidol University and the Shoklo Malaria Research Unit in Thailand and the University of Oxford, combining epidemiological and drug development expertise. ASMQ FDC

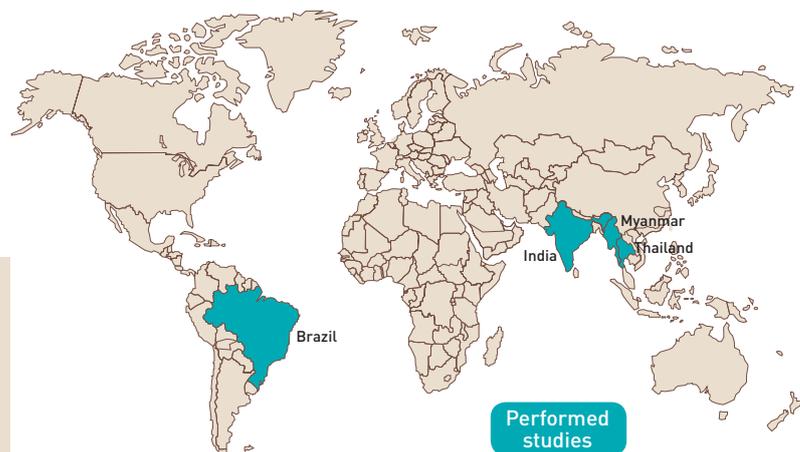
production was scaled up by Farmanguinhos/Fiocruz and ASMQ FDC tablets (25/55 mg and 100/220 mg) were registered in Brazil in 2008. A large intervention study involving over 23,000 patients was performed by the National Malaria Control Programme in Brazil and showed the efficacy of the product in real-life conditions. Through a South-South technology transfer, ASMQ FDC production was transferred to the Indian pharmaceutical company Cipla to ensure availability in India and Asia at affordable, pre-agreed prices and the product was registered in India in 2011. In March 2012, ASMQ FDC was granted approval by the Malaysian National Pharmaceutical Control Bureau (NPCB). Because Malaysia is a PIC/S (Pharmaceutical Inspection Convention Scheme) member, this approval is a major step towards further registration of ASMQ FDC in the region, within the ASEAN Pharmaceutical Harmonization Scheme. In September 2012, Cipla’s ASMQ FDC received WHO prequalification^(a), a recognition of the product’s quality, and an important step in accelerating access to the drug for patients in Asia. DNDi will continue to work towards registration of the product in countries where artesunate-mefloquine combination is part of national treatment policy, as well as promote its use in areas where it could benefit patients suffering from uncomplicated malaria.

Artesunate-Mefloquine Fixed Dose Combination



KEY ELEMENTS AND STUDIES IN THE DEVELOPMENT OF ASMQ FDC

Built on the well-established use of the non-fixed combination of artesunate and mefloquine and following recommendations of WHO and malaria experts, clinical studies were carried out in Thailand, India, Myanmar and Brazil to demonstrate the efficacy of ASMQ FDC, as shown in the following illustration.



<p>Brazil, Intervention study Ph. 3b/4 • N=23,845</p> <p>Myanmar Ph. 4 • N=808 Comparative effectiveness</p> <p>India Ph. 3 • N=77 PK, efficacy & safety</p>	<p>Thailand N=24 • Ph. 1-HNV and N=44 uncomplicated malaria PK & Tolerability N=50 • Ph. 2 PK, efficacy & safety N=50 • Ph. 2b PK, efficacy & safety N=500 • Ph. 3 Efficacy & safety</p>
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(a) <http://apps.who.int/prequal/>

Performed studies

Studies in Thailand

- Ashley E, Stepniewska K, Lindegårdh N, McGready R, Hutagalung R, Hae R, Singhasivanon P, White NJ and Nosten F. Population Pharmacokinetic Assessment of a New Regimen of Mefloquine Used in Combination Treatment of Uncomplicated Falciparum Malaria. Thai-Burmese border. Antimicrob Agents Chemother. 2006 Jul;50(7):2281-5.
- Ashley EA, Lwin KM, McGready R, Simon WH, Phaiphun L, et al. (2006) A randomised comparative study of a new fixed combination of mefloquine artesunate compared to the separate drugs for the treatment of uncomplicated multidrug resistant falciparum malaria in Thailand. Trop Med Int Health 11: 1653-1660.
- Olliaro P; Ramanathan S; Vaillant M; Reuter SE; Evans AM; Krudsood S; Looareesuwan S; Kiechel JR; Taylor WRJ and Navaratnam V. Pharmacokinetics and comparative bio-availability of artesunate and mefloquine administered separately or as a fixed combination product to healthy volunteers and patients with uncomplicated *Plasmodium falciparum* malaria. Journal of Bio-

equivalence & Bioavailability. Vol.2.3 059-066 (2010).

- Krudsood S Looareesuwan S, Tangpukdee N, Wilairatama P, Phumratanaparin W, Leowattana W, Chalermrut K, Ramanathan S, Navaratnam V, Olliaro P, Vaillant M, Kiechel JR, Taylor WRJ. New fixed dose artesunate/mefloquine for treating multidrug resistant *Plasmodium falciparum* in adults – a comparative phase IIb safety and pharmacokinetic study with standard dose non-fixed artesunate plus mefloquine. Thailand. Antimicrob Agents Chemother. Sept. 2010, p. 3730-3737.
- Krudsood S, Looareesuwan S, Wilairatama P, Leowattana W, Tangpukdee N, Chalermrut K, Ramanathan S, Navaratnam V, Olliaro P, Vaillant M, Kiechel JR, Taylor WRJ. Effect of artesunate and mefloquine in combination on the Fridericia corrected QT intervals in *Plasmodium falciparum* infected adults from Thailand. Trop Med Int Health. 2011. Apr;16(4):458-65.

Study in India

- A Phase III, open-label, single-arm study conducted in two sites in India (Goa and

Mangalore) assessed pharmacokinetics, safety and efficacy of ASMQ FDC tablets in adult patients aged 18 to 55 years with uncomplicated *P. falciparum* malaria. Report available, publication in preparation.

Study in Myanmar

- Smithuis F, Moe Kyaw Kyaw, Ohn Phe, Thein Win, Pyay Phyo Aung, Aung Pyay Phyo Oo, Arkar Linn Naing, Mya Yee Nyo, Naing Zaw Htun Myint, Mallika Imwong, Ashley E, Lee SJ, White N. Effectiveness of five artemisinin combination regimens with or without primaquine in uncomplicated falciparum malaria: an open-label randomised trial. Myanmar. Lancet Infect Dis. 2010 Oct;10(10):673-81.

Study in Brazil

- Santelli A. C, Ribeiro I, Daher A, Boulos M, Marchesini P, La Corte R, Barbosa M, de Lucena F, Magalhaes I, de Leon AP, Junger W, Kiechel JR and de Brito Ladislau JL. Effect of artesunate-mefloquine fixed-dose combination in malaria transmission in Amazon basin communities. Malaria Journal 2012, 11:286 doi:10.1186/1475-2875-11-286.

Additional On-going Clinical Studies

These studies will provide relevant information on the use of ASMQ FDC and will compare anti-malarial drugs in more than 6,000 pregnant and paediatric patients in Africa.

Brazil, Rondonia

Ph. 3 • N=264
Efficacy & Safety for *P. vivax* ASMQ+PQ vs. CQ+PQ vs. AL+PAQ

Amazon Basin

Ph. 4 • N=100

Efficacy ASMQ

Thailand

Ph. 3 • N=1000 pregnant women

Cambodia

Ph. 4 • N=50
ASMQ vs. DHA-PQ vs. AL

Nigeria

Ph. 4 • N=270 (60 ASMQ) Sickle cell

Burkina Faso

Ph. 2/3 • N=48 pregnant women PK

Tanzania, Burkina Faso & Kenya

Ph. 4 • N=940 children
Efficacy, safety & PK

Burkina Faso, Ghana, Malawi & Zambia

Ph. 3 • N=3500 pregnant women
ASMQ vs. DHA-PQ vs. ASAQ vs. ALL



Ongoing studies in Africa

- A multicentre, open-label, prospective, randomised, controlled, Phase IV study in Africa, will assess efficacy, safety and pharmacokinetics of ASMQ FDC in 940 children with uncomplicated *P. falciparum* malaria from Tanzania, Burkina Faso and Kenya versus Artemether-Lumefantrine. [DNDi study]
- A randomised, open-label, phase III trial will assess efficacy, safety and pharmacokinetics of ASMQ FDC and dihydroartemisinin-piperazine in about 3,500 pregnant women (2nd and 3rd trimester) with uncomplicated malaria from Burkina Faso, Ghana, Malawi and Zambia compared with ASAQ FDC and artemether-lumefantrine. [PI led study-EDCTP & Umberto D'Alessandro]
- An open-label phase II and III trial to estimate the pharmacokinetic profile of ASMQ FDC for treatment of *P. falciparum* or mixed infection in 48 pregnant women (2nd and 3rd trimester) in Burkina Faso compared to non-pregnant women. [PI led study]

- A Randomised Trial to Compare the Safety, Tolerability and Efficacy of bi-monthly intermittent preventive treatment with either artesunate plus mefloquine or amodiaquine plus sulfadoxine-pyrimethamine with the standard regimen of daily proguanil for the prevention of malaria and related complications in patients with sickle cell anemia in Nigeria. [PI led study- Prof. Brian Greenwood]

Ongoing studies in Asia

- A randomised, open-label, phase III trial will assess efficacy, safety and pharmacokinetics of ASMQ FDC and dihydroartemisinin-piperazine in about 1,000 pregnant women (2nd and 3rd trimester) with uncomplicated malaria from Thailand compared with artemether-lumefantrine. [PI led study-Prof. François Nosten]
- A single arm, prospective evaluation of clinical and parasitological response to directly observed treatment with ASMQ,

artemether-lumefantrine and DHA-PQ for *P. falciparum* and DHA-PQ for *P. vivax* in Cambodia. [NMCP led study]

Ongoing studies in Latin America

- A single, prospective, non-randomised, effectiveness trial of ASMQ FDC in Jurua Valley, State of Acre, Brazil will evaluate clinical and parasitological responses of 100 individuals with uncomplicated malaria by *P. falciparum* treated with ASMQ FDC for three days and monitored clinically and biochemically for 42 days. [PI led study]
- A study conducted in 220 patients will evaluate the safety and efficacy of Artemisinin-based Combination Therapy for the treatment of uncomplicated *Plasmodium vivax* Malaria, comparing ASMQ to AL and chloroquine, all followed by primaquine. [PI led study]



ASMQ PRODUCT PROFILE

Treatment: ASMQ FDC tablets are indicated for the treatment of acute uncomplicated *P. falciparum* malaria, resulting from *P. falciparum* mono-infection and mixed infections with *P. vivax*, in combination with primaquine for radical cure. For severe malaria, oral drugs are not an option.

Dosage: Dosing of ASMQ FDC tablets is based on four age-weight categories. The recommended daily dose for each category is a best approximation of the target dose for each drug: 4 mg/kg for artesunate and 8 mg/kg for mefloquine, corresponding to a total dose of

12 mg/kg and 24 mg/kg, respectively. In patients at the extremes of weight for the corresponding age (such as in cases of malnutrition and obesity), the dose should be adjusted according to the weight of the patient.

Recommended Dosage for ASMQ FDC Tablets – Asia

Asia		Latin America		Recommended Dose
Weight (Kg)	Age	Weight (Kg)	Age	
5 – 8	6 – 11 months	5 – 8	6 – 11 months	One ASMQ FDC Tablet 25/55 mg ¹ daily for 3 days
9 – 17	1 – 6 years	9 – 17	1 – 5 years	Two ASMQ FDC Tablets 25/55 mg ¹ daily for 3 days
18 – 29	7 – 12 years	18 – 29	6 – 11 years	One ASMQ FDC Tablet 100/220 mg ² daily for 3 days
> 30	> 13 years	> 30	> 12 years	Two ASMQ FDC Tablets 100/220 mg ² daily for 3 days

¹ Mefloquine HCl 55 mg are equivalent to 50 mg of mefloquine
² Mefloquine HCl 220 mg are equivalent to 200 mg of mefloquine

Children: For children who are unable to swallow tablets, the tablet(s), which are small (6.0 mm diameter for children <6 years, and 9.6 mm for children >6 years) should be placed on a spoon with water and allowed to disintegrate before oral administration.

Infants: ASMQ FDC tablets 25/55mg are not recommended for treatment of infants weighing less than 5 kg.

Pregnancy: In accordance with WHO Guidelines for the Treatment of Malaria, ASMQ FDC tablets may be used in the second and third trimester of pregnancy but should not be used in the first trimester.

Food and Efficacy: Food does not appear to affect the pharmacokinetic properties of mefloquine when given in combination with artesunate.

Dosing and Vomiting: If vomiting occurs within 30 minutes of drug administration, the full daily dose of ASMQ FDC tablets should be repeated. If vomiting occurs more than 30 minutes after dosing, half the recommended daily dose of ASMQ FDC tablets should be given.

Product Stability and Storage: The shelf-life of ASMQ FDC tablets is three years as approved by ANVISA (National Health Surveillance Agency Brazil - Agência Nacional de Vigilância Sanitária). Based on real time stability data collected by Cipla, a two year shelf life was approved by WHO for the FDC produced in India. ASMQ FDC is blister-packed in Alu-Alu

in order to assure maximum stability and product integrity in tropical climates. Appropriate transportation and storage facilities contribute to maintaining product stability in tropical conditions in malaria-endemic countries.

Risks with repeated administration: According to the WHO malaria treatment guidelines, reuse of mefloquine within 60 days of first treatment is associated with an increased risk of neuropsychiatric reactions and, in cases where the initial treatment was AS+MQ, second-line treatment that does not contain mefloquine should be given instead.^(b)

Adverse Events: In pivotal clinical studies of ASMQ FDC tablets compared with the non-fixed combination, about 50% of patients experienced adverse reactions in both groups, which occurred principally within the first 28 days after the start of treatment. The following adverse events –vomiting, dizziness, sleep disorders, nausea, abdominal pain, diarrhea, headache, anorexia, fatigue, palpitations, myalgia, arthralgia, hearing impairment, hyperbilirubinaemia, hallucination, hepatitis, blurred vision or other visual disturbance and pruritus– were reported during clinical studies in patients with acute, uncomplicated *P. falciparum* malaria and were considered at least possibly related to treatment with ASMQ FDC tablets. Some of these events are identical to the manifestations of malaria. According to an individual patient me-

ta-analysis of mefloquine-artesunate tolerability from 5,487 patients treated for *P. falciparum* malaria along the Thai-Myanmar border, the frequency of patients experiencing at least one adverse event was 49%, the overall incidence rate of early vomiting was 3.4% and the incidence of serious neurological reaction was 2 per 1,000 (DNDi, internal communication).

Within medical literature, adverse events reported to occur with artesunate plus mefloquine combinations include weakness, urticaria, other skin rashes, rigors, tremor, confusion and numbness. Serious psychiatric adverse events and acute intravascular haemolysis with haemoglobinuria are rarely reported.

Pricing and Accessibility: ASMQ FDC is made available at cost price.

Sustainability of raw materials: Artemisinin is derived from the Chinese plant sweet wormwood (*Artemisia annua*). There are ongoing initiatives addressing various concerns related to the sustainable availability of artemisinins that aim to (i) diversify sources of high-quality artemisinin (ii) stabilize supplies and prevent cyclical fluctuations in artemisinin availability (iii) lower the cost of artemisinin production and (iv) create improved varieties of *Artemisia* with higher artemisinin yields.

The price of artesunate is continuously increasing, mainly because of shortages of Artemisinin. The imminent availability

(b) <http://www.rollbackmalaria.org/artemisininenterprise/index.html>

of biosynthetic artemisinin under development by Sanofi & partners (expected for end 2012) should contribute to stabilize pricing fluctuations. Partners such as Artepall^(c) are working

on the transfer of technology to reinforce local production capacity of *Artemisia annua*, mostly in Africa and Asia. With regard to mefloquine, the number of active ingredient manufacturers is

currently limited –which might pose a risk for future availability. DNDi is working with partners to look for alternative options to lower the MQ active product ingredient (API) cost.

OUTLOOK

At a time of growing concerns about the spread of resistance to artemisinin, it is essential to make the best use of the most effective antimalarial drugs at our disposal: even though non-artemisinin based combination therapies are currently being investigated, they will not be available to patients for at least another five years.^(d) By combining two active pharmaceutical ingredients into a single tablet, ASMQ FDC contributes to improving compliance to treatment, thus reducing the development of resistance and increasing efficacy. The deployment of ASMQ FDC in countries which have already adopted AS+MQ as their national treatment policy, both in Asia and in the Americas, will be of immediate benefit for patients suffering from uncomplicated malaria. According to WHO, it is estimated that more than 1.2 million of malaria cases occurred in the nine countries (Brazil, Bolivia, Cambodia, Colombia, Malaysia, Myanmar, Peru, Thailand and Venezuela) where AS+MQ is part of the national malaria protocol for the treatment of uncomplicated malaria.^(e) In addition, depending on the resistance profile of the country and the national strategy adopted towards reducing drug pressure, ASMQ FDC may also be useful in other countries in Asia, Latin America and Africa.

ASMQ FDC and ACTs in general are part of an integrated strategy to control and ultimately eliminate malaria. This includes universal coverage of prevention methods (i.e. insecticide-treated nets) and universal access to diagnosis and treatment. The Global Plan for Artemisinin Resistance Containment, GPARC, issues the following recommendations to prevent the loss of ACTs:^(f)

- **Stop the spread** of artemisinin-resistance parasites by deploying an array of tools and strategies specifically adapted to each region where resistance occurs.

- **Increase monitoring and surveillance** to assess ACT therapeutic efficacy, rapidly identify new foci of resistance and provide information for containment and prevention activities.
- **Improve access to diagnosis and rational treatment with ACTs:** consistent, accurate diagnostic testing, better access to ACTs for confirmed cases, as well as compliance with ACT treatment are essential. The GPARC recommends the manufacture and use of fixed-dose combinations of ACTs to increase compliance.

With several quality-assured ACTs available on the market and promising ACTs in the pipeline,^(g) coupled with the pragmatic strategies of the newly tested AMFm^(f) to subsidize antimalarial treatments, it is the right time to reflect on and discuss which anti-malarial should be used in different situations, who should receive these treatments, and how to define the role of each available ACT FDC, including ASMQ, in the control and elimination of malaria, within the landscape of artemisinin resistance containment challenges.

Opportunities

Expanding the use of ASMQ FDC to Africa to benefit children: in 2011, approximately 86% of global malaria deaths were among children less than five years of age, most of which in sub-Saharan Africa. With specific presentations for children between 6 months and 11 years of age, ASMQ FDC addresses the needs of these vulnerable patients. On-going studies will determine the efficacy and safety of ASMQ FDC in sub-Saharan African children. The collaborative procedure between the World Health Organization Prequalification of Medicines Programme and national medicines regulatory authorities will accelerate registration of the drug in concerned countries now that it is prequalified.

Multiple first-line therapies minimize malaria transmission: ASMQ FDC could play a role within the strategy of multiple first-line therapies (mFTs). The gametocytocidal effects of the artemisinin derivative and the prophylactic effect of a longer-acting partner drug (both active drugs taken together) are predicted to have the greatest impact on transmission across all areas in the short-term time scale of one of the published models.⁽⁶⁶⁾ Deployment of mFTs is proposed as one of the strategies to reduce drug pressure on the parasite pool.⁽⁶⁷⁾ If these models are to be followed, the question of where and how ASMQ FDC should be deployed remains open for discussion.

Treatment of *Plasmodium vivax* malaria: *P. vivax* malaria is the most frequent type of malaria in Asia and Latin America. Current guidelines for the radical cure of *P. vivax* malaria recommend a 14-day treatment regimen of primaquine together with chloroquine or an ACT, depending on chloroquine sensitivity.⁽⁹⁾ *P. vivax* infection recurrence after *P. falciparum* is frequent, either because of relapses due to simultaneously acquired hypnozoites, or to dormant, previously acquired hypnozoites. In either case, it carries significant morbidity, impairs recovery and worsens the socioeconomic burden of malaria. It was recently shown that the risk of *P. vivax* infection recurrence after either *P. falciparum* infection or mixed infection was lower in patients who were treated with a long-lasting ACT (such as ASMQ) than in those who received a rapidly eliminated antimalarial.⁽⁶⁸⁾ Further studies are needed to determine the long-term benefits and potential disadvantages of prolonged post-exposure prophylaxis and determine whether ASMQ FDC could play a role in reducing transmission of *P. vivax* malaria.

(c) <http://www.artepall.org>

(d) <http://www.mmv.org/research-development/tackling-resistance>

(e) <http://www.mmv.org/research-development/science-portfolio>

(f) <http://www.theglobalfund.org/en/amfm/>

(g) http://www.who.int/medicines/areas/quality_safety/quality_assurance/PQProcedure-assessmentandacceleratednationalreg-QAS12-497_01062012.pdf

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Abbreviations and acronyms

- | | | | |
|---|--|---|---|
| ACT - Artemisinin-based combination therapy | AUC - Area under concentration curve | FDC - Fixed-dose combination | MSP - Mefloquine and Sulphadoxine/Pyrimethamine |
| AE - Adverse event | CQ - Chloroquine | MAS - Mefloquine and Artesunate | PAHO - Pan American Health Organization |
| AL - Artemether-lumefantrine | DHA-PQ - Dihydroartemisinin-piperazine | MAS3 - 25 mg/kg Mefloquine and 12 mg/kg Artesunate over three days | PCR - Polymerase chain reaction |
| AMFm - Affordable Medicines Facility - malaria | DHA-TP - Dihydroartemisinin-trimethoprim-piperazine | M15 - 15 mg/kg of Mefloquine over one to three days | SD - Single dose |
| ANVISA - National Health Surveillance Agency Brazil | DNDi - Drugs for Neglected Diseases initiative | M25 - 25 mg/kg of Mefloquine over three to three days | SP - Sulfadoxine-pyrimethamine |
| AS - Artesunate | DND-WG - Drugs for Neglected Diseases Working Group | M888 FDC - 8 mg/kg of Mefloquine per day during three days | TDR - Special programme for Research and Training in Tropical Diseases |
| ASMQ FDC - Artesunate and Mefloquine fixed-dose combination | ECG - Electrocardiograph | mFTs - Multiple first-line therapies | UV - Ultraviolet |
| ASAQ FDC - Artesunate and Amodiaquine fixed-dose combination | FACTs - Fixed-dose Artesunate-based Combination Therapies | MQ - Mefloquine | WRAIR - Walter Reed Army Institute of Research |
| | | | WHO - World Health Organization |