ASMQ Artesunate +Mefloquine
Fixed-Dose Combination

DNDi
Drugs for Neglected Diseases *initiative*

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The transition from artesunate and mefloquine combinations to fixed-dose combination and patient uptake

Executive Summary

In response to the increasing failure of malaria treatment with chloroquine and sulfadoxine-pyrimethamine in order to contain and control the spread of drug resistance in malaria-endemic regions, artemisinin-based combination therapies (ACTs) are being used as first-line treatment for uncomplicated *P. falciparum* malaria.

ACTs are highly efficacious and fast acting, provide good patient tolerance and reduce the likelihood of developing resistance.

However, despite their efficacy, the non-fixed-dose artesunate combinations may pose issues of patient compliance and ease of use in field conditions. In 2002, to address the treatment needs of the people most threatened by malaria, the Fixed-Dose Artesunate-Based Combination Therapies (FACT) Consortium, created by the Drugs for Neglected Diseases *initiative* (DND*i*) and the Special Program for Research and Training in Tropical Diseases (TDR) developed artesunate–mefloquine (ASMQ) as a fixed-dose combination (FDC) therapy.

FDCs are user friendly, co-formulated drug regimens that improve patient compliance and dosing accuracy, and eliminate the possibility of patients taking only one component of the combination. By avoiding the risks associated with monotherapy and improving drug acceptability, FDCs provide better efficacy and control of the development of resistance to ACTs.

Scientific evidence supporting the efficacy of ASMQ FDC derives from the well-established use of their combined administration, demonstrated by studies in which these drugs have been administrated as different regimens, in non-fixed combination, as single components or as co-blister formulations. As shown in this review, more than 11,000 patients have been documented in clinical studies performed in twenty countries since 1992 from Southeast Asia, Western Pacific countries, Africa and Latin America.

As described, the ASMQ FDC has demonstrated efficacy in clinical studies in Thailand, India, Myanmar and Brazil. In a large intervention study in Brazil, more than 30,000 patients were treated with ASMQ FDC.

This review illustrates the power of effective public-private partnerships in the deployment of FDC therapies in the fight against malaria. DND*i*'s collaborative model with a variety of partners from around the world is an example of how to facilitate the drugs' implementation in endemic countries. Pooling the expertise and resources of research institutes, malaria experts, drug developers and producers, national malaria control programmes and NGOs across the globe is a critical component of the strategy against malaria.

Advantages of ACTs

Malaria is a global disease affecting about 3.3 billion people – half of the world's population – in 108 countries living in endemic areas. Although malaria is both preventable and treatable, it remains one of the world's deadliest diseases, killing more than one million people each year, of which almost 85% are children under the age of five years.

Global estimates of malaria in 2007[1] indicated that 451 million cases of *Plasmodium falciparum* malaria occurred almost entirely in areas of stable transmission. 271 million cases (60%) were estimated in Africa, 177 million (39%) in Central and Southeast Asia and 3 million (1%) in the Americas. More than half of all estimated *P. falciparum* clinical cases occurred in India, Nigeria, the Democratic Republic of the Congo and Myanmar (Burma), where an estimated 1.4 billion people are at risk.

Malaria control requires an integrated approach, including diagnosis, vector control and prompt treatment with effective antimalarials.

In response to the increasing failure of treatment with chloroquine, and to contain and control the spread of drug resistance in malaria-endemic regions, in 2001 the World Health Organization (WHO) recommended the worldwide abandonment of chloroquine and the use of ACTs as first-line treatment for uncomplicated *P. falciparum* malaria.

Artemisinin derivatives include *dihydroartemisinin*, *artesunate* and *artemether*. Fast-acting artemisinin-based compounds are combined with a drug from a different class. These companion drugs include *amodiaquine*, *lumefantrine*, *mefloquine*, *piperaquine* and *sulfadoxine/pyrimethamine*.[2]

The advantages of ACTs are their **high efficacy, fast onset of action, very good patient tolerance and the reduced likelihood of development of resistance.** They can be taken for a shorter duration than artemisinin alone and can be used by pregnant women to prevent malaria-related low birth weights.

In view of the immediate need to secure changes in antimalarial treatment policy, the FACT project from DND*i* started in 2002 to develop two fixed-dose artesunate (AS)-based combination therapies (out of the four initially recommended by WHO) – ASMQ fixed-dose combination (artesunate and mefloquine) and ASAQ fixed-dose combination (artesunate and amodiaquine) – for the treatment of uncomplicated *P. falciparum* malaria to improve compliance and be available in all countries depending on their resistance profile.

The development of the two FDCs, ASMQ and ASAQ, strengthened the available ACT portfolio of fixed-dose combinations – artemether-lumefantrine and dihydroartemisinin-piperaquine – which will be expanded soon by the addition of artesunate-pyronaridine FDC, which has been developed with the support of the Medicines for Malaria Venture (MMV).

ASMQ: Moving forward in the fight against malaria

► Artesunate (AS) and Mefloquine (MQ) are well-established drugs for the treatment of *P. falciparum* malaria

The early 1980s witnessed a rise of resistance to chloroquine in many parts of Southeast Asia and South America, along with emerging resistance on the east coast of Africa.

Mefloquine became available at a critical time when other drugs were encountering parasite resistance and artemisinin was not yet widely available. The compound was originally discovered by the US-based Walter Reed Army Institute of Research (WRAIR). Mefloquine was not covered by a patent, it was expensive to produce and there was little initial interest in its development. TDR worked with the pharmaceutical firm Hoffman-La Roche to develop a less expensive way to synthesize the drug molecule and sponsored more than 12 clinical research studies in Latin America, Zambia and Thailand, which led to product registration.[3]

When mefloquine was tested in 1980 in Bangkok it was effective against multi-resistant strains of *P. falciparum*.[4] In 1986, the combination of mefloquine and sulphadoxine/pyrimethamine (MSP) was 98% effective in treating *P. falciparum* in more than 5,000 Karen ethnic minority living on the Thai-Burmese border.[5] By 1989, *P. falciparum* had developed resistance to mefloquine and the MSP combination was abandoned.[6]

Artemisinin (qinghaosu), the active principle isolated by Chinese scientists in 1972 from the plant *Artemisia annua*, did not perform well in tablet form in the early 1970s due to the drug's poor solubility and absorption. Chinese scientists improved the solubility and activity of artemisinin by developing new formulations and by modifying the parent compound to create several semi-synthetic derivatives.[7]

In 1990, Wallace Peters[8] and colleagues[9,10] pioneered the idea that antimalarial drug resistance could be prevented by combining unrelated antimalarial agents. This brought researchers to investigate different regimens of mefloquine with artesunate, which proved their efficacy and safety in Bangkok and in Karen refugee camps in Tak province.[11,12]

In camps for displaced persons located along the Thai-Myanmar border, mefloquine and artesunate therapy has been evaluated since 1991[13] and the combination of 25 mg/kg of mefloquine and 12 mg/kg of artesunate given over 3 days (MAS3)[14] was deployed as a first-line treatment. The strategy of artemisinin-based combination therapy with mefloquine was developed and adopted in Thailand in 1994 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.[13] The deployment of the combination led to a reduction in the incidence of *P. falciparum* malaria and has been associated with a halt to the development of resistance to mefloquine.[15]

Based on very large studies that have confirmed its safety and efficacy[16], and through continuous parasitological efficacy monitoring[17], mefloquine and artesunate given over 3 days (MAS3) has remained the treatment of choice since then in this area[18], and over the subsequent 13 years of continuous MAS3 deployment, the cure rates assessed at day 42 remained well above 90%.[13]

Additional extensive clinical evidence on the successful use of artesunate and mefloquine in more than 11,000 patients has also been documented in published clinical trials from Southeast Asia, Western Pacific countries, Africa and Latin America as illustrated in the review of the examples in Table 2.

► The development of ASMQ FDC Therapy by the FACT Consortium

The WHO regards both artesunate (AS) and mefloquine (MQ) as "essential medicines" for the treatment of *P. falciparum* malaria[19] and since 2001[20], the combination of artesunate and mefloquine has been one of the WHO-recommended ACTs for first-line antimalarial treatment[2] to provide adequate cure rates and delay the development of resistance.

Despite its efficacy, the non-fixed-dose artesunate 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 created by DND*i* and TDR developed artesunate–mefloquine (ASMQ) as a fixed-dose combination (FDC). Within the FACT Consortium, Farmanguinhos is the first manufacturing partner of ASMQ FDC.

ASMQ FDC tablets (25/55 mg and 100/220 mg) were granted Brazilian registration approval on March 3, 2008[21] and aim to be registered in countries where artesunate and mefloquine combination is part of the National Malaria Policy, as well as in areas where this FDC could be of benefit to patients affected by uncomplicated malaria. In February 2008, the principles of a technology transfer agreement between Farmanguinhos/Fiocruz and Cipla, India's generic pharmaceutical company, were approved with the support and facilitation of DND*i*. Cipla, in charge of ASMQ FDC manufacturing, will make the product available in Southeast Asia and in other parts of the world at affordable, pre-agreed prices.[22]

Following an expression of interest in National Malaria Control Programmes from Bolivia and Cambodia, ASMQ FDC treatments have been donated by Farmanguinhos and DND*i* according to the Programmes requests.

► ASMQ FDC 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*. 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.

Table 1: Recommended Dosage for ASMQ FDC Tablets

Weight (Kg)	Age	Recommended Dose
5 - 8	2 - 11 months	One ASMQ FDC Tablet 25/55 mg[1] daily for 3 days
9 - 17	1 – 6 years	Two ASMQ FDC Tablets 25/55 mg[1] daily for 3 days
18 - 29	7 – 12 years	One ASMQ FDC Tablet 100/220 mg[2] daily for 3 days
≥ 30	≥ 13 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 in 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. ASMQ has a bitter taste similar to mefloquine.

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) and 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. DND*i* and partners have recently submitted a full product development dossier for WHO Pre-qualification, including stability studies of three years of shelf-life for ASMQ FDC tablets.

Risks with repeated administration: According to the WHO Malaria Guidelines 2010, the reuse of mefloquine within 60 days of first treatment is associated with an increased risk of neuropsychiatric reactions. Therefore, in cases where the initial treatment was AS+MQ, a medication without mefloquine should be given instead, in the event of a new *P. falciparum* malaria infection in this period.

Adverse Events: In pivotal clinical studies of ASMQ FDC tablets compared with the "loose 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 the events are identical to the manifestations of malaria.
According to an individual patient meta-analysis of mefloquine-artesunate tolerability from 5,487 patients treated for *P. falciparum* malaria along the Thai-Myanmar border, the frequency of patients having 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.
Within medical literature, adverse events that have been 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 were reported rarely.

Pricing and Accessibility: US$ 2.50 is currently the price per adult treatment of ASMQ FDC (at cost price) and compares favorably with the loose AS+MQ combination. DND*i* and partners are working on options to reduce the price in the coming years.

In Brazil, where ASMQ is produced by Farmanguinhos, the government provides treatment free to patients. Other initiatives designed to expand access to ACTs, the most effective treatment for malaria, include:

i - The Affordable Medicines Facility – an innovative financing mechanism designed to expand access to ACTs.[23]

ii - The Strategic Fund – an initiative for Pan American Health Organization (PAHO) Member States designated to provide support to overcome obstacles that countries tend to face in the acquisition of essential public health supplies.[24]

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 by diversifying sources of high-quality artemisinin; stabilising supplies and preventing cyclical fluctuations in artemisinin availability; lowering the cost of artemisinin production and creating improved varieties of *Artemisia* with higher artemisinin yields.[25]
Partners such as Artepal.org are working on the transfer of technology to reinforce local production capacity of *Artemisia annua*, mostly in Africa and Asia.[26]
With regard to mefloquine, the number of active ingredient manufacturers is currently limited - which might pose a risk for future availability.

ASMQ Evidence-based Efficacy

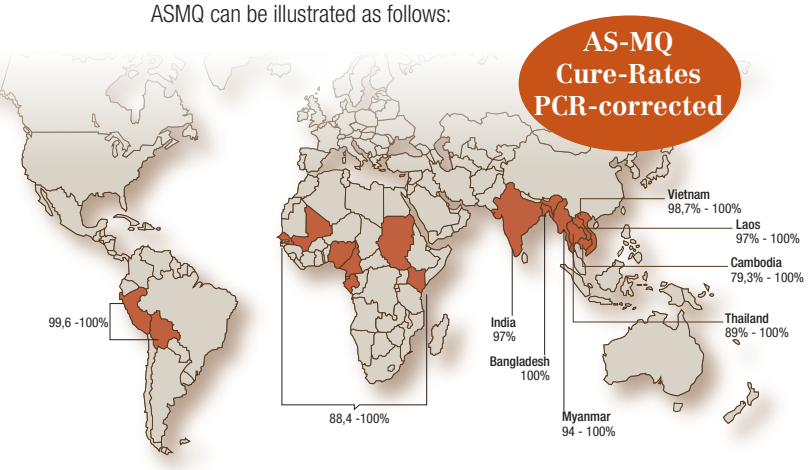
Scientific evidence supporting the development of ASMQ FDC derives from the well-established use of their combined administration, as demonstrated by studies in which these drugs have been administrated as different regimens, in non-fixed combination, as single components or as co-blister formulations.
As shown in Table 2, clinical data from published studies are reported from more than 11,000 patients treated with AS+MQ in 74 open and randomised trials, some of them multinational studies, conducted in 20 countries from three continents since 1992:

Table 2: Clinical data from published studies on AS+MQ*

Countries	Number of studies	Number of patients	Total patients per continent	Years of studies	Year of publications
South East Asia					
Thailand	24	5964	7333	1992-2009	1995-2010
Myanmar	3	1139		1998-2004	2004-2006
India	2	109		2001-2007	2006-2010
Bangladesh	1	121		2003	2005
Western Pacific					
Cambodia	18	1401	2221	2001-2008	2006-2009
Laos	4	368		2002-2007	2004-2010
Vietnam	2	452		1997-2001	2004
Latin America					
Peru	3	372	592	2000-2005	2003-2007
Bolivia	1	70		2001	2004
Ecuador	1	100			2003
Colombia	1	50		2006-2007	2010
Africa					
Senegal	2	299	1817	2003-2008	2007-2010
Mali	1	232		2004-2005	2008
Gabon	2	92		2005-2006	2007-2010
Nigeria	3	619		1994-2008	1998-200
Sudan	2	68		2000-2003	2003-2005
Cameroon	2	274		2006-2009	2010
Kenya	1	129		2004	2006
Cameroon, Benin and Ivory Coast	1	104		2001	2002

** References available on request*

Strictly considering PCR-corrected efficacy data, the global situation on ASMQ can be illustrated as follows:



Results from the western border of Thailand presented in 1997 conclude that, since 1992, there has been no decline in the efficacy of a three-day AS+MQ regimen within the community studied.

The bulk of data on the use of AS+MQ is reported from 21 comparative studies conducted in seven Asian countries (N=4146) as detailed in Table 3. 60% of these patients randomly allocated to artesunate for three days and mefloquine 24-25 mg/kg were from Thailand, specifically from the western border with Myanmar and from Bangkok (N=2521). Reported PCR-corrected efficacy data from the Thai-Burmese border ranges between 90 and 100% during the 12-year period from 1995 to 2007.

The AS+MQ efficacy results published in 2006 from eight Cambodian provinces present evidence of emerging resistance to artemisinins in western Cambodia, which is of significant relevance for the fight against malaria worldwide.

► Nine key elements and studies in the development of ASMQ FDC

The following evidence-based data reflect critical elements in the development of ASMQ FDC treatment:

1) A single-dose, randomised, crossover design study in healthy volunteers and a multiple-dose, randomised, parallel-group study in patients with uncomplicated *P. falciparum* malaria[28] to assess the pharmacokinetics of artesunate, dihydroartemisinin, the artesunate metabolite and predominant species, and mefloquine.

The two formulations were bioequivalent in terms of mefloquine pharmacokinetics in healthy volunteers and uncomplicated *P. falciparum* malaria patients; the 90% confidence intervals for dose-normalised area under the curve (AUC_{last} and AUC_{inf}) and maximum observed concentration (Cmax) were within the 80–125% bioequivalence limits. For artesunate/dihydroartemisinin, the lower bound of the 90% confidence intervals for the comparison between co-formulated and separate products extended below the 80% limit; and AUC and Cmax values were 15–25% and 25–40% lower than those observed after administration of the separate products.

Table 3: Clinical data from published studies on AS+MQ

Year/Country	Author	Year of Study	Drugs: AS 3 days + MQ 24-25 mg/Kg	Number and age of patients treated with AS+MQ	AS+MQ Cure rate PCR corrected
1998 Thailand	van Vugt M	1995 to 1996	AS+MQ and artemether-benflumetol	N=308 / 5 – 65 yr	94%
2000 Thailand	van Vugt M	1997 to 1998	AS+MQ and AL	N=50 / 3 – 61 yr	100%
2001 Thailand	Lefevre G	1998 to 1999	AS+MQ and AL	N=55 / >15 yr	100%
2002 Thailand	van Vugt M	1998 to 2000	AS+MQ, atovaquone-proguanil and atovaquone-proguanil-AS	N=486 / 2 – 68 yr	96%
2003 Thailand	Suputtamongkol Y	1999 to 2001	AS+MQ and MQ-PQ	N=238 Children and adults	97,5%
2004 Thailand	Ashley EA	2002 to 2003	AS+MQ, DHA-PQ and DHA-PQ+AS	N=176 / 1 – 65 yr	94,9%
2005 Thailand	Hutagalung R	2001 to 2002	AS+MQ and AL	N=242 / 2 – 72 yr	96,3%
2005 Thailand	Ashley EA	2003 to 2004	AS+MQ and DHA-PQ	N=166 / 1 – 65 yr	95,7%
2006 Thailand	Ashley EA	2004 to 2005	AS+MQ and ASMQ	N=500 / 10 m – 65 yr	89,2% and 91,9%
2010 Thailand	Valecha N	2005 to 2007	AS+MQ and DHA-PQ	N=234 / 3 m – 65 yr	97%
2000 Thailand[27]	McGready R	1995 to 1997	AS+MQ and quinine	N=66 / 15 – 37 yr 2nd and 3rd trimesters	98,2%
2004 Myanmar	Smithuis F	2000 to 2001	AS+MQ supervised and unsupervised	N=177 & 180 / >1 yr and adults	100 % and 96%
2006 Myanmar	Smithuis F	2003 to 2004	AS+MQ and DHA-PQ	N=325 / >1 yr and adults	99,7 % and 100%
2004 Laos	Mayxay M	2002 to 2003	AS+MQ, CQ+SP and AL	N=110 / >1 yr and adults	100%
2004 Laos	Stohrer JM	2003	AS+MQ and AL	N=53 / 2 – 66 yr	100%
2006 Laos	Mayxay M	2004	AS+MQ and DHA-PQ	N=107 / >1 yr and adults	99%
2010 Laos	Valecha N	2005 to 2007	AS+MQ and DHA-PQ	N=98 / 3m – 65 yr	97%
2006 Cambodia-Battambang	Denis MB	2003 to 2004	AS+MQ and AL	N=55 / 5 – 50 yr	92,4%
2007 Cambodia-Oddar Meanchey and Siem Reap	Janssens B	2002 to 2003	AS+MQ and DHA-PQ	N=195 / 1 – 57 yr	97,5%
2009 Cambodia-Pailin and Thailand-Tak	Dondorp AM	2007 to 2008	AS+MQ and AS	N=40 / Pailin >5 yr & adults Tak >16 yr & adults	95%
2004 Vietnam	Hien TT	2001	AS+MQ, DHA-TP and DHA-PQ	N=38 & 77 / 8 – 56 yr	100% and 98,7%
2005 Bangladesh	van den Broek IV	2003	AS+MQ, CQ+SP and AL	N=121 / 1.2 m – 80 yr	100%
2010 India	Valecha N	2005 to 2007	AS+MQ and DHA-PQ	N=49 / 3m – 65 yr	97%

In conclusion, these differences in the exposure to artesunate/dihydroartemisinin were considered unlikely to be of clinical relevance as plasma concentrations exceed the minimum parasiticidal concentrations of *P. falciparum*. Both plasma concentration comparisons and the investigation of parasite clearance data in patients support the statement above regarding absence of clinical relevance.

2) A multiple-dose, randomised, controlled, parallel-group, open-label phase II study[29] **in adults** with mono-infection with *P. falciparum* malaria.

This study was designed to develop a population pharmacokinetic model describing this new dosage regimen of mefloquine given as loose tablets together with artesunate in equivalent doses over 3 days. In two randomised trials in Thailand which evaluated the efficacy, safety and tolerability of this new regimen, the members of a subgroup of 50 patients were randomised to have capillary blood sampling before treatment and at five randomly assigned time points during the 63-day follow-up.

Mefloquine levels in capillary whole blood were assayed by liquid chromatography with UV detection. A one-compartment model with first-order absorption and elimination was selected to describe the kinetics of mefloquine. For capillary whole-blood mefloquine, the area under the concentration curve (AUC) was 40% higher than previous estimates for patients given the equivalent conventional-dose regimen (mefloquine given as 15 mg/kg and then 10 mg/kg on the second and third day of treatment). Splitting the 25 mg/kg dose of mefloquine into three doses of 8 mg/kg each resulted in improved oral bioavailability compared to the conventional split-dose regimen.

This new way of administering AS and MQ is well tolerated and results in an equivalent therapeutic response.

3) A comparative phase IIb safety and pharmacokinetic study with standard dose non-fixed artesunate plus mefloquine in Thailand.[30]

The new ASMQ FDC was assessed in adults, hospitalised for 28 days with uncomplicated, drug-resistant *P. falciparum* malaria. Patients (n=25/arm) were treated with: (i) two fixed-dose tablets (AS/MQ arm: AS 100 mg and MQ 200 mg per tablet) daily for 3 days or (ii) non-fixed AS (AS+MQ arm: 4 mg/kg/d for 3 days) + MQ (15 mg/kg on day 1, and 10 mg/kg on day 2), dosed by weight.

Clinical, laboratory, ECG recordings adverse events (AEs), efficacy and pharmacokinetic parameters were assessed over 28 days. Both regimens were well tolerated. No AEs were drug related. Two serious AEs, malaria-induced hypotension occurring in the AS/MQ arm, necessitated rescue treatment. There were no significant changes in haematology, biochemistry, PR and QRS intervals.

For all patients, QT intervals were significantly prolonged on day 3 (407 ms) and day 7 (399 ms) vs. day 0 (389 ms) in parallel with significant falls in heart rates [67 (day 3) and 73 (day 7) vs. 83 (day 0) beats/min] due to the resolution of the fever related to malaria. Fixed/non-fixed formulations were bioequivalent for MQ but not for AS and DHA. One AS/MQ patient developed a new infection on day 28; his day-28 plasma MQ concentration was 503.8 ng/mL.

ASMQ FDC was well tolerated and had broadly similar pharmacokinetic profiles to non-fixed AS/MQ, and is thus a suitable replacement considering the data from this phase II study. Useful ECG data for ASMQ FDC could be generated for this ACT.

4) A multiple-dose, randomised, controlled, parallel-group, open-label and pivotal phase III study[31] **in adults and children** with mono-infection with *P. falciparum* or mixed infection with *P. vivax*.

The new ASMQ FDC was compared with the conventional regimen of separate tablets for the treatment of uncomplicated multidrug-resistant *P. falciparum* malaria.

On the north-western border of Thailand, 500 adults and children with uncomplicated *P. falciparum* malaria were randomised to receive either the new fixed combination or separate tablets. The day-63 PCR-adjusted cure rates were 91.9% (95% CI 88.2–95.6) in the fixed combination group and 89.2% (85.0–93.4) in the loose tablets group (P = 0.3). There was a lower incidence of early vomiting in the group receiving the fixed-dose combination.

ASMQ FDC was efficacious, well tolerated and convenient to administer.

5) Individual patient meta-analysis of mefloquine–artesunate tolerability from 5,487 patients treated for *P. falciparum* malaria along the Thai–Myanmar border.[32]

An individual-patient meta-analysis of 16 published studies from a single centre pooled a total of 5,487 patients randomly assigned to receive one of 10 different dosing and timing schedules of artesunate 4 mg/kg/d once daily for three days combined with mefloquine 15 mg/kg (M15) or mefloquine 25 mg/kg (M25) over one to three days.

In the M25 groups, patients who were younger, febrile or vomiting on admission before treatment were at higher risk for drug vomiting while the risk of early vomiting was decreased when treated with M888/FDC or administering artesunate before mefloquine. Splitting the dose of mefloquine to the 8/8/8 mg/kg schedule over three days significantly reduced the incidence of gastrointestinal AEs (abdominal pain, anorexia, nausea and late vomiting), as well as experiencing any AE. The M888/FDC groups were at lower risks for anorexia, muscle pain, palpitation and fatigue compared to the M25 SD groups. The incidence of serious neurological reaction of all MAS combinations was 2 per 1,000.

MAS is comparatively well tolerated for primary infections. M888/FDC offered the best safety profile compared to other modes of administering AS and MQ in a combination treatment.

6) 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[33] in adult patients aged 18 to 55 years with uncomplicated *P. falciparum* malaria.

The day-63 PCR-adjusted cure rates from the 66 subjects that completed the day-63 follow-up were 100%. 98.6% of patients had parasite counts of 0 at 48 hours after the first dose, thus documenting the rapid parasite clearance. The median fever clearance time was 8 hours.

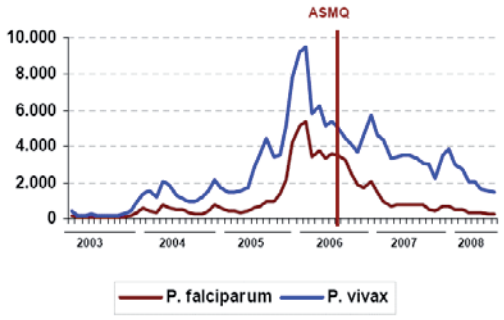
During the entire study there were no early treatment failures, late clinical failures, mixed infections or severe malarial infections. In patients who tested positive for gametocytes at day 0, the median time to a gametocyte count of 0 was seven days, while all patients who tested positive for gametocytes after day 0 were cleared by day 3.

7) An open label, intervention and implementation study in Brazil[34] conducted from July 2006 to December 2008 by the Malaria Programme in Brazil to evaluate the impact of the programmatic use of ASMQ FDC in the reduction of *P. falciparum* malaria incidence in comparison with the standard antimalarial regimen.

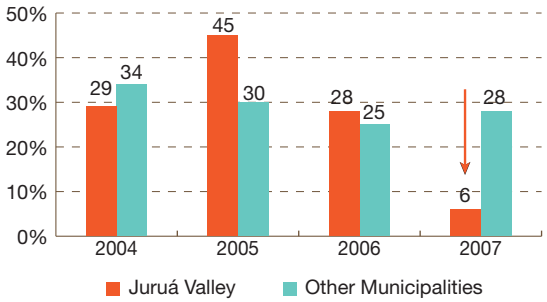
This effectiveness study was conducted in seven municipalities in the Acre State. Patients were administered one or two tablets of ASMQ FDC (25/55 mg or 100/220 mg) daily for three days, or the standard regimen of quinine plus doxycycline and primaquine. Patients were followed up on day 7 and day 40, and a thick blood smear analysis was performed. The total population treated with ASMQ FDC tablets was 31,453 patients older than six months, with confirmed diagnosis of *P. falciparum* mono-infection.

A reduction in the total number of monthly malaria cases was observed following the introduction of ASMQ FDC tablets in July 2006 as well as in the ratio of *P. falciparum* to *P. vivax* infections as shown in the following charts.

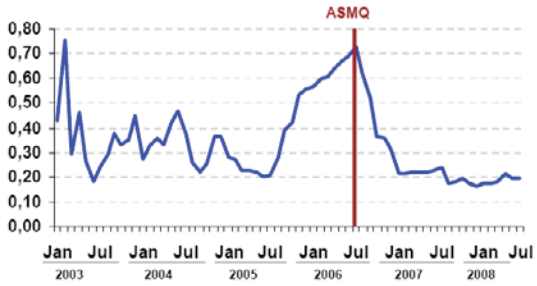
Monthly malaria cases: 2003-2008



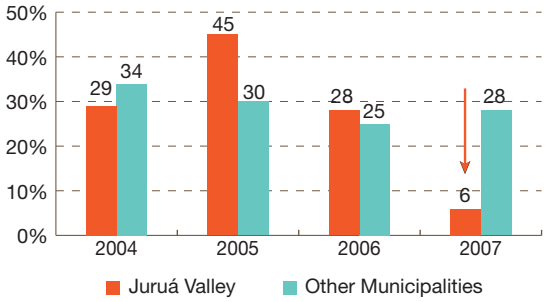
Proportion of patients with recurrrent *P. falciparum* infections in Vale do Juruá compared to other municipalities



Monthly *P. falciparum/vivax* ratio: 2003-2008



Proportion of slides with gametocytes in Vale do Juruá compared to other municipalities



In line with the decrease in the proportion of *P. falciparum* malaria following the introduction of ASMQ FDC tablets, additional benefits were reported from the Juruá Valley in the Acre State, one of the sites of the intervention study. A decrease in the proportion of patients with recurrent *P. falciparum* infections, and the proportion of slides with gametocytes compared to other municipalities was also observed, as shown in the charts on the right.

8) An open randomised comparison of the effectiveness of four fixed-dose ACTs and loose artesunate–mefloquine in Burmese adults and children.[35]

The effectiveness of all four WHO-recommended fixed-dose ACTs (artesunate–mefloquine, artesunate–amodiaquine, dihydroartemisinin–piperaquine, artemether–lumefantrine) and loose artesunate–mefloquine were compared in clinics in Rakhine state, Kachin state and Shan state in Myanmar (Burma) between December 2008 and March 2009 in Burmese adults and children older than six months with acute uncomplicated *P. falciparum* malaria or mixed infection. All patients were also randomly assigned to receive either a single dose of primaquine 0.75 mg base/kg or not.

Patients were followed up for 63 days. 155 patients received artesunate–amodiaquine, 162 artemether–lumefantrine, 169 artesunate–mefloquine, 161 loose artesunate–mefloquine, and 161 dihydroartemisinin–piperaquine. By day 63 of follow-up, 14 patients on artesunate–amodiaquine had recrudescent *P. falciparum* infections, a rate significantly higher than that for artemether–lumefantrine (2 patients), fixed-dose artesunate–mefloquine (0 patients), loose artesunate–mefloquine (2 patients) and dihydroartemisinin–piperaquine (2 patients). Mixed *P. falciparum* and *P. vivax* infections were common: 129 (16%) had a mixed infection at presentation and 330 (41%) patients had one or more episodes of *P. vivax* infection during follow-up. The addition of a single dose of primaquine (0.75 mg/kg) reduced *P. falciparum* gametocyte carriage substantially: rate ratio 11.9. All regimens were well tolerated. Adverse events were reported by 599 patients, most commonly vomiting and dizziness. Other side-effects were less common and were not related to a specific treatment.

In conclusion, artesunate–mefloquine provided the greatest post-treatment suppression of malaria with an advantage of the FDC compared to the other mode of administration. Adding a single dose of primaquine would substantially reduce transmission potential. *P. vivax* malaria, observed around day 40 after administration of ASMQ FDC, not recurrent *P. falciparum* malaria, is the main complication after treatment of *P. falciparum* infections in this region.

9) A series of additional clinical studies using ASMQ FDC is ongoing:

- 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.
- A single, prospective, non-randomised, effectiveness trial of ASMQ FDC in Juruá 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.
- A randomised, open-label, phase III trial will assess efficacy, safety and pharmacokinetics of ASMQ FDC and dihydroartemisinin–piperaquine 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.
- A randomised, open-label, phase III trial will assess efficacy, safety and pharmacokinetics of ASMQ FDC and dihydroartemisinin–piperaquine in about 1,000 pregnant women (2nd and 3rd trimester) with uncomplicated malaria from Thailand compared with artemether–lumefantrine.
- An open-label phase II and III trial to assess the pharmacokinetic of ASMQ FDC for treatment of *P. falciparum* or mixed infection in 56 pregnant women (2nd and 3rd trimester) in Brazil compared to non-pregnant women.

- A multi-center, open-label, randomised, phase IV trial of ASMQ FDC and artemether–lumefantrine for the treatment of uncomplicated *P. falciparum* malaria parasitemia in 274 pregnant women (2nd and 3rd trimester) in Brazil to assess the safety and efficacy of current recommended therapies for uncomplicated malaria in Brazil.
- A multi-center, open-label, randomised, phase IV trial of ASMQ FDC, artemether–lumefantrine and chloroquine for the treatment of uncomplicated *P. vivax* malaria in 720 pregnant women (2nd and 3rd trimester) in Brazil to assess the safety and efficacy of the 3 different regimens for the treatment of uncomplicated *P. vivax* malaria parasitemia in pregnant women. The data from this study will be used to determine future national malaria treatment policies.
- 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.

Outlook

Based on the well-established use of AS+MQ administered as different regimens (non-fixed-dose combination or co-blister) and with key elements and studies linked to the development of the FDC, ASMQ FDC tablets were registered in Brazil in 2008. The product is manufactured by Farmanguinhos and marketed as artesunato+mefloquina 25/55 mg and artesunato+mefloquina 100/220 mg.[36]

Following the large intervention study in Acre, a State of the Basin of Amazon river, sponsored by the National Malaria Control Programme, the ASMQ FDC is now an alternative first-line treatment for uncomplicated *P. falciparum* malaria according to National Malaria Policy in Brazil[37] and to date over 100,000 treatments have been ordered by Brazilian government agencies. Malaria transmission in Brazil occurs mainly in the Amazon region from which 97% of malaria cases are reported.

In addition, the ASMQ FDC registration process is underway in 3 additional malaria endemic countries in Latin America — Peru, Bolivia and Venezuela — which have already adopted the non-fixed AS+MQ combination for treating uncomplicated *P. falciparum* malaria.

The technology transfer between Farmanguinhos in Brazil and Cipla in India will contribute to extending the availability of the ASMQ FDC in all Asia and in other parts of the world.[38]

The ongoing studies referred to previously will provide much needed information on the use of the ASMQ FDC and will compare antimalarials in more than 6,000 pregnant and paediatric patients in Africa, and consider treatment of the blood stage of *P. vivax* malaria.

With several quality-assured ACTs[39] available in the market and very promising ACTs in the pipeline[40], coupled with the pragmatic strategies of the newly launched AMFm[41], which is field testing the US Institute of Medicine Plan to subsidise antimalarials, it is the right time to reflect on and discuss which antimalarial should be used in different situations, who should receive these treatments[42], and how to define the role of ASMQ FDC in the control and elimination of malaria:

• Improving compliance contributes to reducing the development of resistance and increasing efficacy:

The worldwide epidemiology of resistance in *P. falciparum* is well known as is the possibility that the best antimalarial (artemisinin-based drugs) could be rendered useless if existing medicines are not used appropriately and in line with other health strategies for the containment of decreased parasite clearance after treatment with artemisinin derivatives as observed in western Cambodia and eastern Thailand.[43] By combining two active pharmaceutical ingredients in one single tablet, ASMQ FDC contributes to improving treatment against malaria, both in adults and children.

The deployment of ASMQ FDC in areas with the immediate benefit to patients suffering from uncomplicated malaria in countries which have already adopted ACTs in the Asia Pacific region and in the Americas is of great public health relevance. According to the 2008 World Malaria Report[44], the estimated number of malaria cases in countries where AS+MQ is part of the national policy is more than 6.5 million. 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[45], Latin America and for some African patients.[46]

• Multiple first-line therapies could minimise malaria transmission:

The population at risk in the 108 malaria-endemic countries and territories is targeted in the strategy "from control to elimination" of malaria. About one fifth of the world's population (1.2 billion) live in areas with a high risk of malaria. The largest populations at any risk of malaria are found in Southeast Asia and Western Pacific region. Africa has the largest number of people living in areas with a high risk of malaria, followed by Southeast Asia.

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.[47] Deployment of mFTs is proposed as one of the strategies to reduce drug pressure on the parasite pool.[48] If these models are to be followed, the question of where and how ASMQ FDC should be deployed remains open for discussion.

• Simplifying the treatment of children to decrease malaria mortality:

Available data specific to child infection and mortality rates show that more than 80% of the 243 million cases and 863,000 deaths due to malaria (about 90% caused by *P. falciparum*) estimated by WHO for 2008[49] occurred in children younger than 5 years of age in sub-Saharan Africa. With specific presentations for children aged between 6 months and 11 years, ASMQ FDC addresses the needs of children, the primary victims of malaria worldwide.

The ACT Cochrane review published in 2009[46], which compared[50] studies using either AS+MQ, AL, DHA-PQ, AS+AQ, AS+SP or AQ+SP, concludes that in the absence of resistance to mefloquine, AS+MQ is likely to be highly effective in African countries. According to the WHO 2010 Malaria Guidelines, 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. Based on some recent publications[50], WHO recommended[2] reconsidering AS+MQ in Africa, with specific concerns regarding toxicity/vomiting in children.

To provide additional information on the tolerability of ASMQ FDC, DND*i* 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 children with uncomplicated *P. falciparum* malaria from Tanzania, Burkina Faso and Kenya versus artemether–lumefantrine treatment.

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Abbreviations and acronyms

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