ASMQ TO TREAT MALARIA
PRESS PACK | April 2008

www.actwithasmq.org

A New Product Delivered by an Innovative Partnership
ASMQ to Treat Malaria

ASMQ IN BRIEF

Artemisinin-based combination treatments (ACTs) are considered to be the best treatments for uncomplicated *P. falciparum* malaria and are a key element of the global malaria control strategy.

Reliable and rapid therapeutic response to ACTs, together with their effect of reducing gametocyte carriage, translates to a potential reduction of malaria transmission and new malaria cases in areas where ACTs are made available.

One of the better documented treatments for malaria, the combination of artesunate (AS)[1] and mefloquine (MQ)[2] has been widely used in Southeast Asia for the past 16 years, and has proven its effectiveness and safety in the treatment of non-complicated *P. falciparum* malaria.[3]

Safe, rapid, and reliably effective, the combination of AS and MQ is one of four World Health Organization (WHO)-recommended ACTs as first-line antimalarial treatment. In its 2006 guidelines,[4] the WHO also recommended that fixed-dose combinations be used whenever possible because, in addition to being easier to use, they ensure that drugs are taken together and in correct proportions.[5]

Credit: Shoklo Malaria Research Unit

ASMQ provides a simple regimen for both chidren and adults.

In line with organizational goals to address the treatment needs of people most threatened by neglected diseases like malaria, Farmanguinhos/Fiocruz and DND*i* developed the artesunate-mefloquine (ASMQ) fixed-dose combination within the multi-partner Fixed-Dose, Artesunate-Based Combination Therapies (FACT) Consortium created by DND*i* and the UNICEF-UNDP-World Bank-WHO Special Programme for Research and Training in Tropical Diseases (TDR) for the project. This new product, which simplifies treatment with a single daily dose of 1 or 2 tablets for 3 days, represents an innovation that can have considerable impact in the areas of recommended use.

ASMQ is targeted as first-line treatment for children and adults suffering from uncomplicated *P. falciparum* malaria cases in Latin America and Asia. Every year, there are approximately 1 million cases of malaria in Latin America (25% of which are *P. falciparum* cases, and the majority of which are in Brazil),[6] and approximately 3 million cases in Asia, where 30% of the global malaria-related mortality is found.[7]

1 Artesunate is a derivative of artemisinin, which is isolated from a Chinese wormwood plant and is widely accepted as the best treatment for malaria.
2 Mefloquine (common trade name: Lariam®) is an antimalarial belonging to the quinine class of antimalarials.
3 Looareesuwan et al. Lancet. 1992;339:821.
4 World Health Organization, *Guidelines for the Treatment of Malaria*, Geneva, Switzerland: World Health Organization; 2006.
5 Chan, M (World Health Organization Director General). Opening Speech to the 120th Session of Executive Board. January 22, 2007; Geneva, Switzerland.
6 Pan-American Health Organization/DPC. Washington DC; 2006. http://www.paho.int. Accessed April 4, 2008.
7 World Health Organization. *World Malaria Report*. Geneva, Switzerland: World Health Organization; 2005, http://www.searo.int. Accessed April 4, 2008.

ASMQ, A NEW PRODUCT...

A New, Fixed-Dose ACT

□ Fixed-Dose Combination Developed in Response to Patient Need

Patients in malaria-endemic countries need inexpensive, efficacious, field-adapted drugs. Fixed-dose ASMQ responds to patient need by offering an easy-to-use, safe, efficacious, and affordable treatment that can serve as an important tool along with other ACTs and malaria control efforts such as insectide-treated bednets. A 2-in-1 tablet for combination therapy has the potential to improve compliance, providing patients with a better chance of cure and less risk of emerging parasitic resistance to treatment.

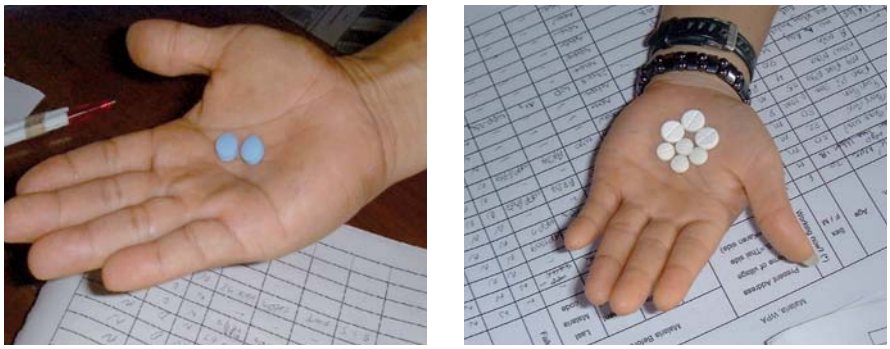
□ Treatment Based on WHO Guidelines

ACTs are the way forward. The combination of AS and MQ is one of the four ACTs recommended by the WHO since 2001.[1] In 2006, the WHO strengthened its earlier recommendations to state that ACTs should be first-line treatment for *P. falciparum* malaria everywhere and in fixed-dose combination when possible.[2]

In accordance with the principles of WHO's 2006 guidelines, fixed-dose ASMQ can be used as an effective first-line treatment for uncomplicated *P. falciparum* malaria, especially in Latin America and Southeast Asia, where a number of countries have adopted the combination as first-line treatment.[3]

□ A Most Convenient Treatment

Fixed-dose ASMQ offers improved convenience versus the non-fixed combination in that (1) there are fewer tablets to take during a full treatment course and (2) the drugs have a 3-year shelf life in tropical conditions. Fixed-dose ASMQ offers greater convenience for both patient and practitioner because **the 2-in-1 combination of ASMQ ensures that both drugs are taken together and in correct proportions**.



Credit: SMRU

Fixed-dose ASMQ is a most convenient treatment: as seen on the left, an adult daily dose is only 2 of the same tablets, whereas, for the non-fixed, a daily dose can be as many as 7 tablets of 2 different drugs.

1 World Health Organization. Antimalarial drug combination therapy: Report of a WHO technical consultation http://mosquito.who.int/cmc_upload/0/000/015/082/use_of_antimalarials2.pdf. Published April 2001. Accessed April 4, 2008.
2 World Health Organization, *Guidelines for the Treatment of Malaria*, Geneva, Switzerland: World Health Organization; 2006.
3 Roll Back Malaria Partnership. *Malaria Landscape Report 2007*. Geneva, Switzerland. Published April 2001. Accessed April 4, 2008.

ASMQ, A NEW PRODUCT...

A Simple Regimen for Children and Adults

□ Easy to Use as 1-2-3

The new ASMQ combination offers a simple prescription which is easy to use, with **once daily administration of 1 or 2 tablets over 3 days for patient of all ages** (from children aged 6 months through adults). The treatment was developed so as to ensure that the adult treatment would be limited to 2 tablets daily for 3 days.

□ Dosage According to Age

The dosing regimen developed for ASMQ is based on age, rather than weight, and was prepared through modeling of a weight-for-age reference database constructed using nutritional data obtained from a national nutritional survey conducted among 180,000 individual Brazilians.[1] [2] Most drugs (including antimalarials) are developed to dose based on weight; however, most antimalarial dosing is based on age due to a lack of scales in rural, remote areas. **With age-based dosing, patients are more likely to receive the dose they need**.

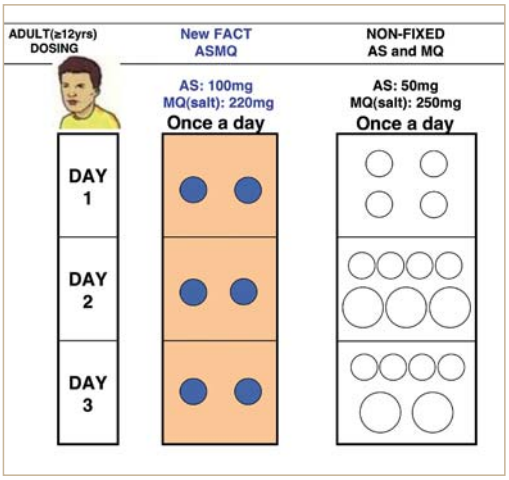
□ Adapted to the Needs of Patient of All Ages, Including Children

Based on the analyses mentioned above,[1] **a 4-category dosing regimen was selected to minimize the risk of over- or under-dosing a patient**. ASMQ can now be found in four different presentations based on age: 6 to 11 months, 1 to 5 years, 6 to 11 years, and 12 years or older.

□ Adapted to Children, Including Infants

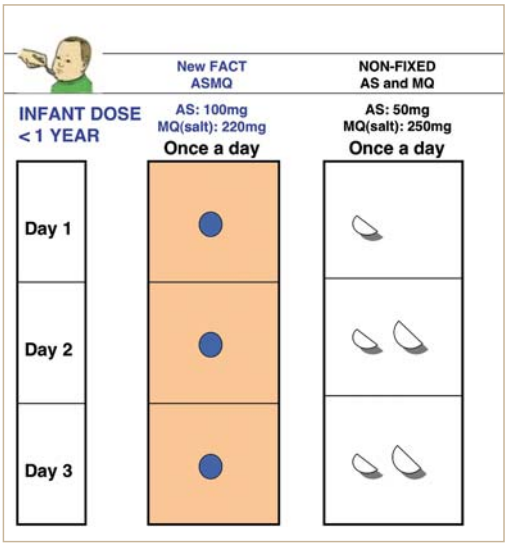
The needs of children, the primary victims of malaria world-wide, are addressed with ASMQ: three presentations of ASMQ are available for children of ages between 6 months and 11 years. Tablets are small (6.0 mm diameter for children <6 years, and 9.6 mm for ≥6 years) and can be crushed, facilitating administration of the drug to younger children.

ASMQ simplifies treat for all ages, with adults taking only 2 tablets daily for 3 days.



*250-mg tablets of mefloquine hydrochloride are equivalent to 228 mg of the free base."

ASMQ simplifies treatment for infants with 1 small tablet given per day for 3 days.



*250-mg tablets of mefloquine hydrochloride are equivalent to 228 mg of the free base."

1 Terlouw et al. Development of age based dose regimens for a new fixed-dose artesunate-mefloquine combination for uncomplicated falciparum malaria. Presented at: the Centenary Meeting of the Royal Society for Tropical Medicine. 13-15 September 13-15, 2007; London, UK. This proof-of-concept work initially done for Brazil is now being replicated for other countries using anthropometric data from other world regions.

2 Instituto Brasileiro de Geografia e Estatística (IBGE), 2006. Pesquisa de Orçamento Familiar , Antropometria e análise do estado nutricional de crianças e adolescentes no Brasil, 2002-2003. Rio de Janeiro: Instituto Brasileiro de Geografia e Estatística (IBGE).

ASMQ, A NEW PRODUCT...

Packaging Adapted for Ease-of-Use by Patients with 3-Year Shelf-Life

□ Simplified Presentation According to Age and Dose

A full treatment (either 1 or 2 blister packs of 3 tablets) is provided per packaging envelope and will allow health care centres and hospitals maximal flexibility in reorganizing supplies according to need (minimizing the risk of running of supplies at point of care) and in using the appropriate dose of medicine for each age of patient without having extra medicine lying around or without having to cut tablets into pieces.

The packaging has been color-coded to easily identify the different dosage for each age range (infants, toddlers, children, and adults), with four different presentations that have been selected to minimize the risk of over- or under-dosing a patient.

□ Simple Prescription

Clear information is provided on the outside of the packaging to facilitate use by both patients and prescribers.

□ Simple Management and Storage

Based on public sector and non-governmental organizations' experience in the field, packaging has been color-coded yellow for easy identification. The sizes of blister packs and envelopes were also minimized to save as much as space as possible and to therefore reduce costs related to storage and shipping.

Farmanguinhos/Fiocruz Packaging for ASMQ provides clear information and is color-coded to facilitate proper use.

□ 3-Year Stability Assured by Packaging

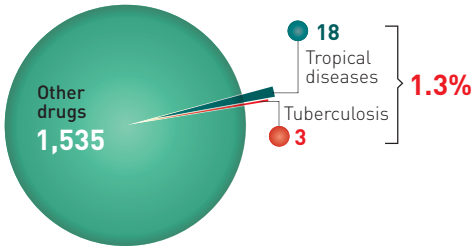
The packaging assures the quality of the product, as demonstrated by its 3-year shelf life in tropical conditions, and guarantees the quality of the active components. ASMQ is the first fixed-dose ACT to have a 3-year shelf-life recommendation – such a long shelf life should facilitate deployment and availability in rural health centres.

ASMQ, A NEW PRODUCT...

First New Product for Neglected Diseases Developed and now Registered in Brazil

ASMQ, the first new product for neglected diseases to be developed and registered in Brazil, represents an important milestone for needs-driven research and development for health tools. Despite Brazil's strength in basic scientific and medical research, diseases such as tuberculosis and leprosy are still highly prevalent, and about 46,000 people die each year from infectious diseases in Brazil.[1]

New Drugs Developed from 1975-2004: 1,556



Only 21 new drugs, out of 1,556, were developed for neglected diseases in the past 30 years.

While tuberculosis and tropical diseases such as malaria make up 12% of the global burden of disease, just 1.3% (only 21 new drugs) of the 1556 new drugs registered between 1975 and 2004 were developed to treat these diseases.[2]

In the case of malaria, only 7 new treatments have been developed over the past 30 years, despite the increasing resistance that has been seen to the most widely recommended and prescribed drugs over the past 50 years. It is mainly because of the lack of new effective treatments that *P. falciparum* malaria is a mass killer[3] whose lethality resurged out of control in the last 30 years, to a point where malaria kills one child every 30 seconds (approximately 3,000 children every day).[4]

□ Development of ASMQ Driven by Public Partners of the FACT Project

The public partner-driven development of ASMQ has involved close collaboration with the Brazilian government, not only in the development and production of this innovative product but also in facilitating the implementation of the new product via the large-scale intervention study, and demonstrates an alternative model to the traditional market-based pharmaceutical model.

Greater government leadership can help to increase the potential impact of new tools like ASMQ and other effective antimalarials: policy has now changed to ACTs in most countries, donor support has increased, and there are now better medicines and improved mechanisms through which to deliver them. However, an enormous gap still remains between newly available funds and drugs, and the patients in need.[3]

A pioneer working relationship was developed with the Brazilian regulatory authorities, Agencia Nacional de Vigilancia Sanitaria (ANVISA). Consultation meetings with ANVISA were organized at different phases of the development, allowing contribution from regulators early on and all the way through to the submission of the regulatory dossier. Technical briefings took place at intervals with open exchange of information and with continuous interaction through the review process. In late 2006, a new piece of Brazilian legislation incorporated expedited review for neglected diseases.

As in the case with ASMQ and the DND*i* FACT Consortium's engagement of the Brazilian government, close collaboration with governments in R&D is essential; governments must provide leadership in order to fully realize the potential impact of new tools for health and in order to guarantee that these tools reach patients.[5]

1 Morel et al. Nature. 2007;449:180.
2 Chirac et al. Lancet. 2006;367:1560.
3 Nosten et al. Am J Trop Med Hyg. 2007;77:181.
4 World Health Organization Expert Committee on Malaria. Twentieth Report. In: *WHO Technical Report Series*. Geneva, Switzerland; 2000. Accessed March 3, 2007.
5 Torreele et al. PLoS Med. 2006;3:e282.

AN INNOVATIVE PARTNERSHIP TO DELIVER A PUBLIC GOOD

Public Good Available At Cost

□ 'At Cost' Price for Governments and NGOs

ASMQ will be available at cost to the public sector of endemic countries at a target price of US$2.50 for the full adult treatment. ASMQ will be available to Brazilian patients free of charge.[1]

□ Available Now

As of April 2008, ASMQ is available in Brazil (and is being used in an intervention study conducted by national authorities – see "Clinical Evidence on Use of ASMQ") and will start becoming available in other countries in Latin America and Southeast Asia over the course of 2008 and 2009.

Countries in Latin America & Asia Where ASMQ Could Be of Benefit [2]

Continent	Countries	Usage
ASIA	**Cambodia, Malaysia, Myanmar, Thailand**	**AS + MQ recommended as 1st line treatment**
	Bangladesh,[3] India,[4] Laos,[5,6] Vietnam[7]	ASMQ could be of benefit
LATIN AMERICA	**Bolivia, Colombia, Peru, Venezuela, Brazil**	**AS + MQ recommended as a 1st line treatment**
	Ecuador[8]	AS + MQ could be of benefit

□ A Non-Profit Initiative Driven by Public Funds

ASMQ, as part of the FACT Project (which made ASAQ, the fixed-dose combination of artesunate [AS] and amodiaquine [AQ], available in Africa in 2007),[9] has been and is primarily being developed with financial support from non-profit organizations, public institutions, and governments. The European Union (EU INCO DEV), France, the Netherlands, Spain, and the United Kingdom have all provided funding for the DND*i*-coordinated FACT Project along with contributions from Brazil, Médecins Sans Frontières (MSF), and TDR.[10]

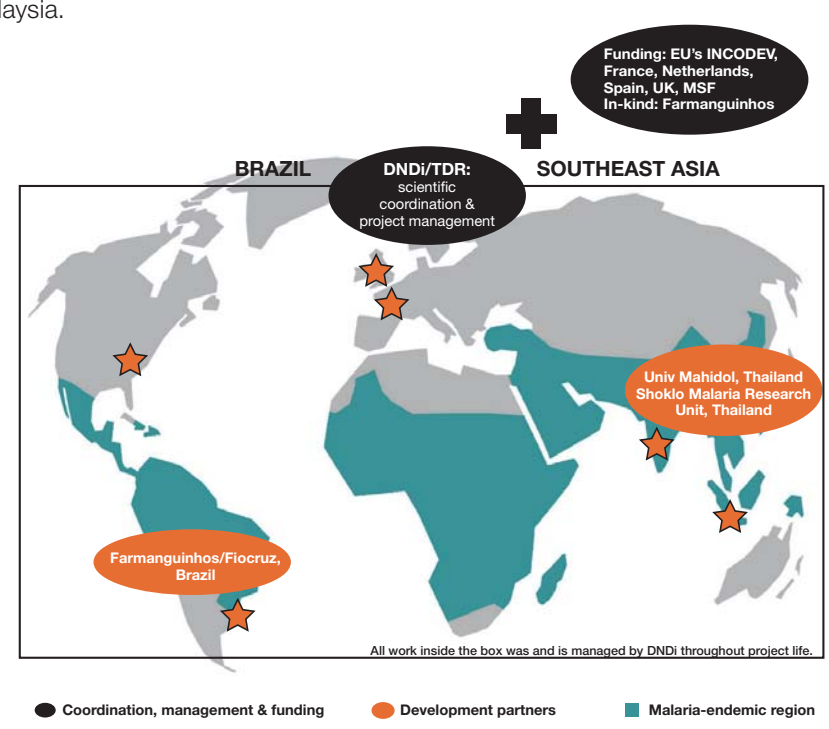
1 In Brazil, there are really NO private sector sales for antimalarials: antimalarials cannot be sold outside the public programme distribution system.
2 The criteria for selection of countries listed under "could be of benefit" was based on the existence of published clinical studies (found via Pubmed search) showing the combination of AS and MQ to be efficacious and safe in these countries. Sample references are included as a footnote
3 van den Broek et al. Trans R Soc Trop Med Hyg. 2005;99:727.
4 Campbell Pet al. Trans R Soc Trop Med Hyg. 2006;100:108.
5 Mayxay et al. Trop Med Int Health. 2006;11:1157.
6 Stohrer et al. Trop Med Int Health. 2004;9:1175.
7 Hung et al. Am J Trop Med Hyg. 2004;71:160.
8 Gomez et al. Acta Trop. 2003;89:47.
9 For more information, see www.actwithasaq.org
10 For more detailed information on ASMQ funding, please refer to "A Product Developed, Delivered, and Supported by Public Partners".

AN INNOVATIVE PARTNERSHIP TO DELIVER A PUBLIC GOOD

Innovative Collaboration Between Brazil and Southeast Asia within DND*i*'s FACT Project Consortium

DND*i*'s FACT Project, modeled with core and support partners, is considered an innovative partnership because ASMQ has been produced as a "non-exclusive, not-for-profit public good" and because developing and developed countries have contributed technology, expertise, relevant assets, and finances (in some cases) to produce ASMQ.

The collaboration between key partners in Brazil and Southeast Asia and the sharing of assets and capabilities between the various partners of the FACT Project is a truly innovative venture. Pivotal clinical research was conducted by Mahidol University, the Shoklo Malaria Research Unit, and the Mae Sot Clinic in Thailand; with key pharmaceutical support, development, and registration carried out by Farmanguinhos/Fiocruz in Brazil; and with valuable support and critical input provided by the University Sains Malaysia.



FACT Network for ASMQ: An Innovative Collaboration Between Brazil and Southeast Asia Coordinated by DNDi

□ FACT Project: A Worldwide Collaboration to Address the Needs of Malaria Sufferers

In 1998, TDR, with support from the US Agency for International Development and the Wellcome Trust, embarked on the search to identify suitable combinations of existing antimalarial drugs to control malaria resistance. From the resulting data analyses, it emerged that the combination of AS and MQ could be a good clinical option in Latin America and Southeast Asia.

The FACT Project began in 2002, under the umbrella of MSF (and then DND*i*) in coordination with TDR, as there was a clear public health need for a fixed-dose combination of AS and MQ, and yet there were no other entities interested in developing a response to the need.

AN INNOVATIVE PARTNERSHIP TO DELIVER A PUBLIC GOOD

A Product Developed, Delivered, & Supported by Public Partners

□ The development cost for DND*i* is EUR 7.8 million with important in-kind contributions from Farmanguinhos/Fiocruz and other partners.

To address the need for new effective antimalarial medications, the FACT Project was established in 2002 with funding from MSF and TDR, and with specific funding allocated by the European Union/INCO-DEV programme.

Throughout the lifespan of the project, public financing has been critical in allowing the project to meet its primary objective of developing two effective antimalarial medicines, ASAQ and ASMQ.

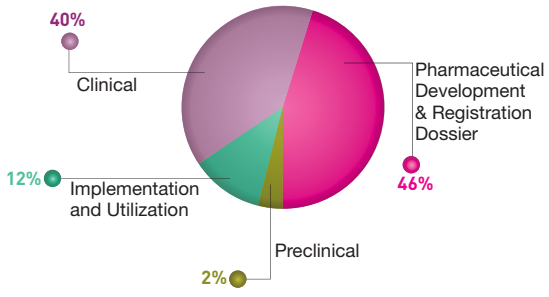
The project budget for ASMQ has been supplied by public funds, including project-specific funding provided by the European Union (Framework Partnership 5; FP5), the French Development Agency (Agence Française de Développement; AFD), and the Dutch Ministry of Foreign Affairs (DGIS).

In addition, core organizational funding from MSF International, the Spanish Agency for International Cooperation (Spanish Agencia Española de Cooperación Internacional; AECI), and the UK Department for International Development (DFID) has been used by DND*i* in order to make the FACT products available.

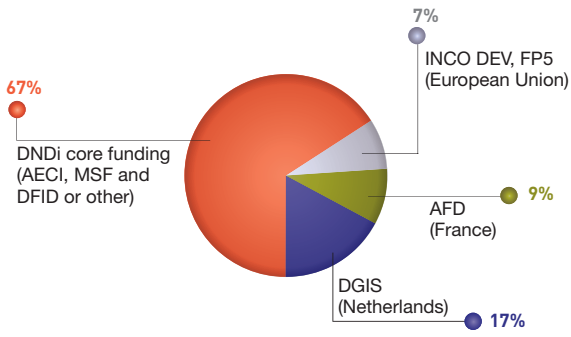
Valuable in-kind contributions have supplemented the total budgetary costs shown; in particular, **the in-kind contributions of Farmanguinhos/Fiocruz and TDR were significant throughout the entire process of ASMQ development** as were the in-kind contributions of individual experts.[1]

□ FACT Project: ASMQ Resources 2002-2010

FROM THE PERIOD OF 2002-2010, EUR 7.8 MILLION HAVE BEEN ALLOCATED BY DNDi FOR ASMQ DEVELOPMENT



Projected Expenditure Breakdown by Development Stage



Funding Resources by Donor

1 Individual experts who have contributed through the entire life of the FACT Project include: the Project Manager affiliated with DND*i*; expert consultants, some independent and others affiliated with Mahidol University, University of Oxford, Shoklo Malaria Research Unit, TDR, University Sains Malaysia, and Wellcome Trust.

AN INNOVATIVE PARTNERSHIP TO DELIVER A PUBLIC GOOD

South-South Technology Transfer Between Brazil and India

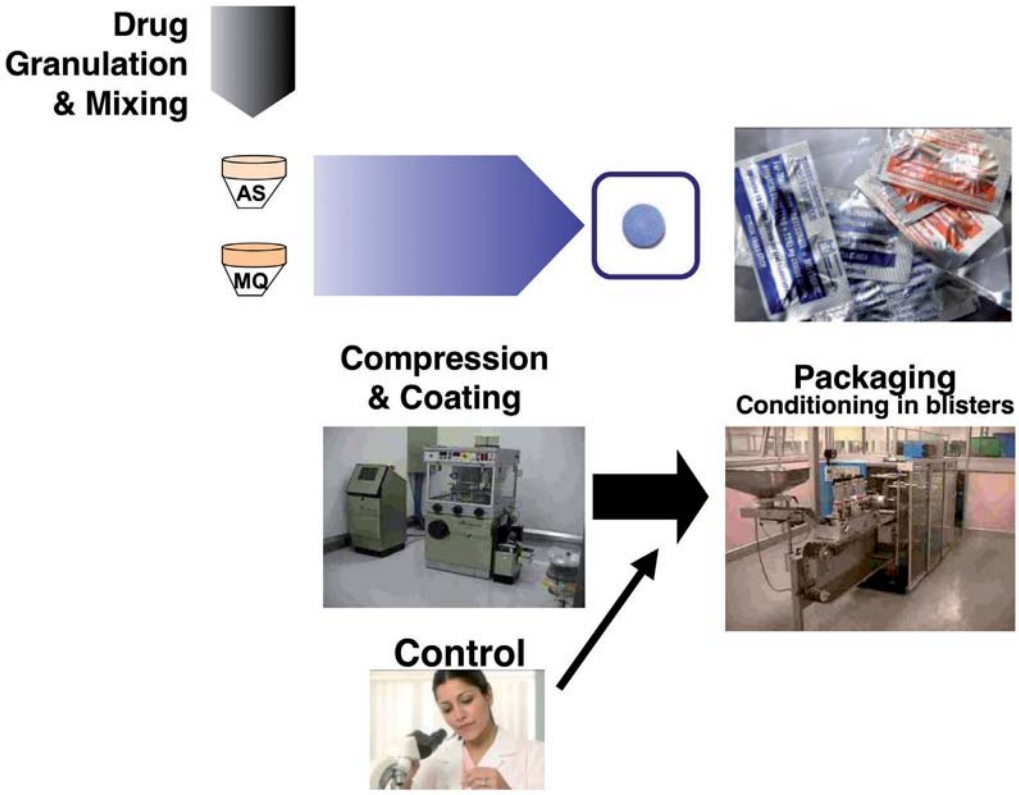
In February 2008, the principles of a technology transfer agreement, with the support and facilitation of DND*i*, were agreed upon by the Brazilian government-owned pharmaceutical company, Farmanguinhos/Fiocruz, and India's generic pharmaceutical company, Cipla.

This South-South technology transfer agreement, the first between Brazil and India in malaria, is also the first technology transfer project involving a public pharmaceutical company and a private pharmaceutical company and allows for reciprocal exchange between organizations.

With facilitation provided by DND*i*, Farmanguinhos/Fiocruz will transfer information on development and production to Cipla, which will scale the production so as to address patient needs for ASMQ in Asia, the continent where ACTs (including AS and MQ) were first shown to be effective.

The partners will share results of ongoing work and new studies. Farmanguinhos/Fiocruz will be responsible for registration of ASMQ throughout Latin America. Cipla will be in charge of all registration efforts through Southeast Asia. The strategy for Africa will be developed according to needs.

The 2-in-1 Tablet: Pharmaceutical Innovation in Making ASMQ a Fixed-Dose ACT



THE EVIDENCE FOR ASMQ IN THE TREATMENT OF MALARIA

Well-Established Use of the Non-Fixed Combination of AS and MQ

□ The Combination of AS and MQ is Well-Documented in Latin America and Southeast Asia

Over the past 16 years, the combination of AS and MQ has been documented as a highly successful treatment for malaria and has been shown to be of great benefit in areas where multi-drug resistance exists. Deployment of the combination of AS and MQ has been shown to reduce the number of new cases of *P.falciparum* malaria and has also been associated with a drop in mefloquine resistance.[1,2] To date, the combination has been primarily studied and used in Southeast Asia and in Latin America.[3]

□ Extensive Clinical Evidence, Particularly in Southeast Asia

Asia is the home of the ACT, both in terms of its physical origins (artemisinin was originally found in China) and also in its functional origins (the concept of artemisinin-based combination therapy was first considered in Asia as a strategy to mitigate the resurgence of malaria and the intensifying spread of antimalarial drug resistance). In areas where multi-drug resistance occurs, the combination of AS and MQ has shown well-documented safety and efficacy in >30 studies involving >7,000 patients receiving the combination in Bangladesh, Cambodia, Laos, Myanmar, and Thailand.[4,5,6,7,8].

□ First Introduced by Peru in 2000 to Latin America

In 2000, the first Latin American study on the efficacy and safety of the combination of AS and MQ was conducted in the Peruvian Amazon Basin, where over 50% of patients with *P. falciparum* malaria type failed to respond to treatment with either chloroquine or sulfadoxine-pyrimethamine.[9] The objective of the study was to compare the use of the MQ alone or the combination of AS and MQ. In a total of 98 patients who received either MQ alone or in combination of AS and MQ, a 100% efficacy rate was seen at 28-day follow-up, and the combination was well tolerated. Evidence from this study was used by national authorities in Peru to revise its malaria treatment policy and to adopt the combination of AS and MQ. Further evidence on the efficacy and safety of the AS and MQ combination has been documented in Bolivia, Colombia, Venezuela, and Brazil, supporting each country's treatment policy to use the combination of AS and MQ as a first-line treatment for uncomplicated *P. falciparum* malaria.[10]

1 Nosten et al. J Infect Dis. 1994;170:971.
2 Luxemburger et al. Trans R Soc Trop Med Hyg. 1994;88:213.
3 Nosten et al. Am J Trop Med Hyg. 2007; p187
4 Zwang. *Mefloquine-artesunate: an individual patient meta-analysis of 5,277 patients*. Mae Sot, Thailand: Shoklo Malaria Research Unit; 2006.
5 van den Broek et al. Trans R Soc Trop Med Hyg. 2005;99:727.
6 Mayxay et al. Clin Infect Dis. 2004;39:1139.
7 Denis et al. Trop Med Int Health. 2006;11:1360.
8 Nosten et al. Lancet. 2002: 297.
9 Marquino W, et al. Am J Trop Med Hyg. 2003: 608.
10 A list of all published studies on AS + MQ can be provided upon request.

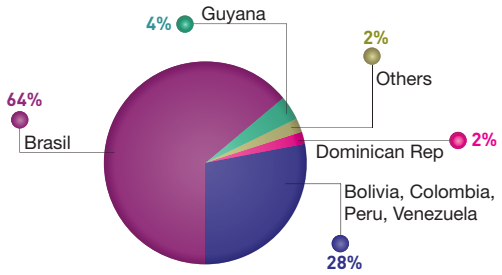
THE EVIDENCE FOR ASMQ IN THE TREATMENT OF MALARIA

Combination of AS and MQ Recommended by WHO Since 2001

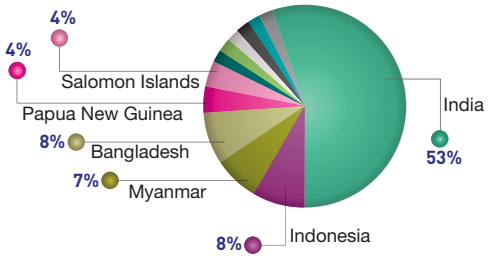
□ To Treat Multi-Drug Resistant Malaria

The WHO recommends this ACT for treatment of uncomplicated *P. falciparum* malaria in areas where there is multi-drug resistance. There is abundant evidence in support of the efficacy and safety of the combination of AS and MQ for the treatment of uncomplicated *P. falciparum* malaria. Considerable efficacy has been shown in areas where multi-antimalarial resistance has been seen, such as along the border between northwestern Thailand and Myanmar. Deployment of the combination of AS and MQ has been shown to reduce the number of new cases of *P. falciparum* malaria and has also been associated with a decrease in mefloquine resistance over time.[1]

***P. FALCIPARUM* MALARIA IN LATIN AMERICA**
TOTAL NUMBER OF CASES: ~ 228,000
(proportion by country shown)



***P. FALCIPARUM* MALARIA IN ASIA**
TOTAL NUMBER OF CASES: > 1.5 MILLION
(proportion by country shown)



□ In Latin America and Southeast Asia

The WHO recommends both the combination of AS and MQ as well as fixed-dose artemether-lumefantrine (Coartem®) for first-line use in Latin America and Southeast Asia.

□ Potential for Geographical Extension of ASMQ

In Latin America, where approximately 228,000 cases of *P. falciparum* malaria were reported in 2006,[2] fixed-dose ASMQ will be made available for use in 5 of the countries with the highest burden (Bolivia, Brazil, Colombia, Peru, and Venezuela).

In Southeast Asia, approximately 1.5 million cases of *P. falciparum* malaria were reported in 2005, and more than half the cases of malaria in Myanmar and in Thailand were *P. falciparum* malaria.[3] Fixed-dose ASMQ is planned for first deployment in countries like Cambodia, Malaysia, Myanmar, and Thailand where clinical evidence strongly supports availability. In other countries, such as Bangladesh and India, further research is being carried out to determine its added value to the treatment situation in each country.

In Africa, there have been anecdotal concerns about the tolerability of mefloquine use as monotherapy. Recent data from small studies documented the potential of AS and MQ for use in this region.[4,5] A DND*i*-supported study is planned in Tanzania so as to assess the potential utility of fixed-dose ASMQ in African children, the population most burdened by malaria. If ASMQ is shown to be both safe and efficacious in Africa, efforts will be made to facilitate deployment on the continent, where there are >300 million cases of *falciparum* malaria every year.

1 Nosten et al. J Infect Dis. 1994;170:971.
2 Pan-American Health Organization/DPC. http://www.paho.int. Published 2006. Accessed March 28, 2008.
3 World Health Organization. World Malaria Report. Available at http://www.searo.int and http://www.wpro.who.int. Published 2005. Accessed on April 4, 2008.
4 Bhatt et al. East Afr Med J. 2006;83:236.
5 Ramharter et al. J Antimicrob Chemother. 2007;60:1091.

THE EVIDENCE FOR ASMQ IN THE TREATMENT OF MALARIA

International Quality Registration Dossier Supported by Published Data

The ASMQ dossier was officially granted registration approval on March 3, 2008.

Prepared in collaboration with DND*i*'s FACT Project partners, an international registration file was prepared with quality (chemistry, manufacturing, and control [CMC]), non-clinical safety, and clinical components. All parts of the file were in Common Technical Document (CTD) format and in accordance with International Conference on Harmonization (ICH) standards.

The quality (or CMC) file, in CTD format and in line with ICH recommendations and standards, has been developed for the registration of fixed-dose ASMQ. Stability testing has shown ASMQ, with packaging developed for the tropical climate, to have a long shelf life of 3 years.

The safety (or preclinical) file includes information on the well-established use of the combination and a limited non-clinical safety programme, including a full genotoxicity evaluation. Preclinical studies were performed in Brazil and received critical input from independent experts and the University of Bordeaux.

The clinical file included data from a Phase I study in 24 healthy normal volunteers, a Phase II analysis in 50 adult patients, and the pivotal Phase III field study in 500 Thai paediatric and adult patients.[1] All studies adhered to international Good Clinical Practices.

Supportive safety information included a large safety meta-analysis with data on the adverse events with the combination of AS and MQ from 18 clinical trials conducted along the Thai-Burmese border in the period between January 1992 and June 2005.

The registration file also included information on age-weight evaluation, allowing more convenient and appropriate dosing, as well as a review of the extensive published efficacy and safety data.

The team at Farmanguinhos/ Fiocruz, in Brazil, packaging ASMQ.

1 For more information on the clinical component of the dossier, see "Clinical Evidence on Use of ASMQ".

THE EVIDENCE FOR ASMQ IN THE TREATMENT OF MALARIA

Clinical Evidence on Use of ASMQ

AS and MQ are both well-known drugs and have been used together successfully for more than fifteen years. Documented research on over 15,000 patients in both Latin America and Southeast Asia have demonstrated the safety and efficacy of the combination of AS and MQ.

Scientific evidence supporting the tolerability and efficacy of the combination of AS and MQ can be grouped into two types: studies supporting the use of non-fixed-dose combinations of AS plus MQ; and studies supporting the use of fixed-dose combinations (FDC) of ASMQ.

What the Clinical Evidence Says About ASMQ…			
✔	Efficacious	×	Not recommended in 1st trimester pregnancy or severe malaria
✔	Safe	×	Cumulative toxicity with repeated dosing
✔	Well tolerated		
✔	Favourable PK profile		
✔	Simple regimen		
✔	Competitively priced		
✔	Convenient as fixed-dose combination		
The evidence supports deployment of the fixed-dose ASMQ anywhere the combination of AS and MQ is used.			

A number of studies have been conducted with the support of DND*i*. The table below summarizes the key clinical evidence that has been accumulated by FACT Project partners in the course of the development of the ASMQ FDC.

□ Studies Investigating Combination of AS and MQ

Type of Study	Location and Study Duration	Patient Population	Primary Objective	Major Findings
Studies Using Non-Fixed Association of AS and MQ				
Population Pharmacokinetic Assessment of New Dose Regimen (MQ 8mg/kg/d for 3 days)[1]	Shoklo Malaria Research Unit, Mae Sot Clinic; Tak province, Thailand 2002-2004	N=1029 (adult and child) n=343 treated with AS+MQ (8mg/kg/d)	Population PK assessment of absorption and elimination of MQ given 8 mg/kg/d for 3 days vs traditional 2-day regimen on 15 mg/kg on D2 and 10 mg/kg on D3 of 3-day treatment	Similar D63, PCR-adjusted parasitological cure rates (>95%) seen with both regimens. Increased bioavailability seen with new MQ 8 mg/kg/d regimen. Absorption was 40% higher than with traditional dosing. New regimen also well tolerated.

1 Ashley et al. Antimicrob Agents Chemother. 2006;50:2281-5.

THE EVIDENCE FOR ASMQ IN THE TREATMENT OF MALARIA

Type of Study	Location and Study Duration	Patient Population	Primary Objective	Major Findings
Individual Patient Meta-Analysis of Combination of AS and MQ – 18 Clinical Studies[1]	Shoklo Malaria Research Unit, Mae Sot Clinic; Thailand 1992-2005	N=5,277 patients 0-4 yrs of age: n=564 (10.7%) 5-14 yrs of age: n=2,227 (42.7%)	Systematic review to examine safety and tolerability of combination of AS and MQ by examining incidence and type of adverse events (25 different types included) seen in field studies over 13-year period.	In 18 studies examined, 11 different regimens of MQ were used. Most common adverse events (>20% incidence): anorexia, dizziness, headache, nausea, sleep disturbance. Lowest incidence density of adverse events (AEs) seen with dosing regimen of fixed-dose ASMQ.
Studies Investigating Fixed-Dose ASMQ				
Phase I Study Comparing Fixed-Dose ASMQ vs Non-Fixed Combination[2]	Mahidol University, Thailand; 2005-2006	N=24 Healthy adult volunteers	PK and safety of fixed-dose ASMQ with new dosing regimen (8 mg/kg/d) vs non-fixed combination and traditional regimen	Comparative bioavailability (for both MQ and artesunate/ dihydroartemisin (DHA)) seen between fixed-dose ASMQ and non-fixed combination.
Phase II Study Comparing Fixed-Dose ASMQ vs Non-Fixed Combination[3]	Mahidol University, Thailand; 2004-2005	N=50 Adult patients	Efficacy: PCR-adjusted parasitological cure rate at day 28 Tolerability: AEs Intensive sampling for PK; ECG Analysis	ASMQ is efficacious and well-tolerated, as is the non-fixed combination. Higher drug exposure seen in patients vs volunteers. No clinically significant effect on QTc interval found for fixed-dose ASMQ or non-fixed combination.
Phase III Field Study Comparing Fixed-Dose ASMQ vs Non-Fixed Combination[4]	Shoklo Malaria Research Unit, Mae Sot Clinic Tak province, Thailand 2004-2005	N=500 patients aged 6 months to 65 years	Efficacy: PCR-adjusted parasitological cure rate at day 63; fever and parasite clearance Tolerability: AEs	Efficacy at 63-day follow-up was 91.9% for fixed-dose ASMQ (compared with 89.2% for non-fixed combination [p=0.3]). Fixed-dose ASMQ also showed good tolerability profile (with lower incidence of early vomiting vs non-fixed). Fixed-dose ASMQ was found to be convenient to use.

1 Zwang. *Mefloquine-artesunate: an individual patient meta-analysis of 5,277 patients*. Mae Sot, Thailand: Shoklo Malaria Research Unit; 2006.
2 Navaratnam et al. Presented at: ASMQ Regional Technical Briefing; January 2007, Bangkok, Thailand.
3 Krudsood et al. Presented at: Annual Meeting of American Society of Tropical Medicine & Hygiene; November 2006, Atlanta.
4 Ashley et al. Trop Med Int Health. 2006;11:1653.

THE EVIDENCE FOR ASMQ IN THE TREATMENT OF MALARIA

Type of Study	Location and Study Duration	Patient Population	Primary Objective	Major Findings
Development of Age-Based Dosing Regimens for Fixed-Dose ASMQ [1,2]	Model utilizing Brazilian demographic database	Database created using anthropometric data from Brazilian survey of >180,000 individuals	To determine age-based dosing regimen for real-life, programmatic use in Latin America and Asia. Goals are to determine an easy-to-use regimen that maximizes efficacy and minimizes toxicity.	A 4-category regimen was found to be the best to minimize over- and under-dosing. This regimen was adopted for fixed-dose ASMQ.
Intervention Study to Investigate Impact of Programmatic Use of Fixed-Dose ACTs (ASMQ)[3]	3 municipalities in Acre, Brazil (Amazonian basin) 2006-present (ongoing)	N=17,082 patients with *falciparum* malaria	To study the public health impact of programmatic use of ASMQ by examining change in reported incidence, the proportion of *vivax:falciparum* infection, gametocydal carriage and number of malaria-related hospital admissions.	Preliminary results seen after 1 year: • 69.8% reduction in reported number of cases with falciparum malaria • 62.1% reduction in malaria-related hospital admissions Training of health agents proved easy, most likely due to the convenient packaging and dose regimen.

1 Terlouw et al. Presented at: the Centenary Meeting of the Royal Society for Tropical Medicine. September 13-15, 2007; London, UK.This proof-of-concept work initially done for Brazil is now being replicated for other countries using anthropometric data from other world regions.
2 Instituto Brasileiro de Geografia e Estatística (IBGE), 2006. Pesquisa de Orçamento Familiar , Antropometria e análise do estado nutricional de crianças e adolescentes no Brasil, 2002-2003. Rio de Janeiro: Instituto Brasileiro de Geografia e Estatística (IBGE).
3 Health Surveillance Secretary, Brazilian Ministry of Health. *Implementation of the new treatment for P falciparum*. Brasilia, Brazil: Brazilian Ministry of Health; 2008.

THE EVIDENCE FOR ASMQ IN TREATMENT OF MALARIA

Large Intervention Study in the Amazon Basin

□ Juruá Valley of Acre state – Brazil – An Evaluation of ASMQ in Programmatic Use

In 3 municipalities in the Amazon Basin (Cruzeiro do Sul, Mâncio Lima, and Rodrigues Alves), there is a high incidence of malaria: in 2005, approximately 40,000 people in these regions suffered from malaria with circa 12,000 *falciparum* cases. Because of this high burden of disease and concerns about increasing antimalarial resistance, a decision was taken to study the impact of ASMQ in programmatic use within the region.

99% of malaria cases in Brazil are found in the Amazonian basin.

First-line treatment regimen in use at time of start of intervention:

- *Quinine-Doxycycline + Primaquine ;*
- *Limitations: 7-day treatment course, not well tolerated, high tablet burden, and increasing parasitic resistance.*

An intervention study, with funding from the Ministry of Health and PAHO-RAVEDRA/AMI (the Pan-American Health Organization[PAHO] – Amazon Network for the Surveillance of Antimalarial Drug Resistance [RAVEDRA] / Amazon Malaria Initiative [AMI]), was begun in 2006 by the National Programme of Control of Malaria and health authorities in the states of Acre. In the first year of the study, approximately 17,000 patients were treated. A significant impact was seen on the incidence of malaria in the region.

□ Positive Impact of ASMQ Used Programmatically in Real-Life Conditions

Preliminary results after 1 year

- ***70% drop*** *in* P. Falciparum *malaria cases*
- ***> 60% reduction*** *in malaria-related hospital admissions*

Preliminary results of the 1-year intervention[1] **shows the significant impact of ASMQ used in conditions of controlled deployment in programmatic use**. Following the introduction of fixed-dose combination in 3 of the 22 state municipalities, *P. Falciparum* malaria cases were reduced in the state from 32,829 in 2006 to 9,921 cases in 2007, accounting for a 69.8% drop. In addition, malaria-related hospitalizations showed a reduction of 62.1%, from 2,590 to 981 hospitalizations in the same period.

Scenes from Acre state, where a high burden of malaria led health officials to launch the intervention study

1 Health Surveillance Secretary, Brazilian Ministry of Health. *Implementation of the new treatment for P falciparum*. Brasilia, Brazil: Brazilian Ministry of Health; 2008.

MORE ABOUT...

The FACT Project Consortium: A Worldwide Collaboration To Develop and To Deliver ASMQ

In 1998, TDR, with support from the US Agency for International Development and the Wellcome Trust, embarked on the search to identify suitable combinations of existing antimalarial drugs to control malaria resistance. From their data analyses, it emerged that the combination of AS and MQ could be a good clinical option in Latin America and Southeast Asia. When, in 2001, the WHO recommended AS and MQ as one of four artemisinin-based combination therapies (ACTs), there was neither a co-formulation nor any development partners.

The FACT Project began in 2002, under the umbrella of MSF (and then DND*i*) in coordination with TDR.

- **Objective:** To develop a fixed-dose combination of AS and MQ for international registration that would improve compliance and would be available to all countries where the toxicity of mefloquine was low (mainly in Latin America and Southeast Asia), but also potentially in all endemic regions, including multi-drug resistant areas and Africa.
- **Key partners (*who signed on to the original EU INCO-DEV grant*)**: Centre National de Recherche et de Formation sur le Paludisme (CNRFP) in Burkina Faso, Instituto de Tecnologia em Fármacos of Farmanguinhos/Fiocruz, Mahidol University, Université Victor Segalen Bordeaux 2 (TROPIVAL), University of Oxford, University Sains Malaysia, TDR, and MSF, followed by DND*i*. These partners were represented in a FACT development project team by international experts contributing to the development plan and supporting the management and assessment of project progress.

□ FACT 2002-2007: ASMQ Development through Registration

DEVELOPMENT STEP	INSTITUTIONS INVOLVED
Pharmaceutical and Preclinical Development	
Pharmaceutical development (with Catalent, formerly Cardinal Health); clinical batch production; report and quality dossier generation; monitoring of toxicology studies performed in contract laboratory. Formulation of the fixed-dose combination product with appropriate stability and biopharmaceutical characteristics, and with a viable manufacturing process. Development and validation of analytical methods	Farmanguinhos/Fiocruz (Brazil)
Support in pharmaceutical development and registration file preparation	Catalent (formerly Cardinal Health) (France)
Contribution on Good Laboratory Practices (GLP) genotoxicity and toxicology studies on single drugs and combinations	Independent expert; University of Bordeaux (France)
Set of GLP toxicology and genotoxicity studies and reports on single drugs and combinations	Unitox and Genotox (Brazil)
Development of bioanalytical methods and blood level determinations in toxicokinetic and pharmacokinetic studies. Pharmacokinetic evaluation. Analytical support for method development	University Sains Malaysia (USM; Malaysia)

MORE ABOUT... the FACT Project Consortium

Clinical Development	
Population pharmacokinetics, clinical study support	University of Oxford (UK)
Phase I in healthy normal volunteers for pharmacokinetic data, biopharmaceutical quality, tolerability, and bioavailability (PK/PD analysis)	Mahidol University (Thailand); USM (Malaysia); Quintiles (USA)
Phase II in patients for pharmacokinetics, efficacy, and tolerability of fixed-dose ASMQ versus non-fixed AS+MQ	Mahidol University (Thailand); USM (Malaysia); Quintiles (USA)
Phase III field study examining efficacy and tolerability of fixed-dose ASMQ versus non-fixed AS+MQ	Shoklo Malaria Research Unit, Mae Sot Clinic, Mahidol University (Thailand); Quintiles (USA)
Individual patient meta-analysis examining the use of AS and MQ in 5,277 patients	Shoklo Malaria Research Unit (Thailand)

□ FACT 2008-2010: ASMQ Development through Implementation

Through 2010, DND*i* intends to play an active role in facilitating FACT implementation by engaging partners: Pharmaceutical companies, national malaria programmes, research institutes, contract research organizations, and NGOs, as well as the WHO and TDR.

In order to receive external advice and critical guidance about issues related to ASMQ implementation and recommendations on issues related to rational use and the ensuring of equitable access, DND*i* has convened an independent panel of experts, the FACT Implementation Advisory Group, who meet on an annual basis.

Examples of Ongoing & Next Steps Sponsored by DND*i*	Institutions Involved
Efficacy, safety, and population pharmacokinetics study in India	Indian Council for Medical Research (ICMR; India); Farmanguinhos/Fiocruz
Regional scientific symposium with participation of national malaria control programme managers and international and regional organizations	Farmanguinhos/Fiocruz and DND*i*, Rio, April 2008
Meeting of FACT Implementation Advisory group	DND*i*, Geneva, April 2008
Regional workshop briefing to engage national malaria control program managers and international & regional organizations	India & Southeast Asia; 4th quarter 2008
Continuing work on age-based dosing optimization per region to be provided for upcoming meeting on WHO Malaria Treatment Guidelines	University of Liverpool (UK)
Efficacy and safety study of ASMQ in Tanzania	National Institute for Medical Research (NIMR; Tanzania)

DND*i* will also contribute to a number of other studies by offering drug supplies, technical input, or bioanalytical work. Examples of such activities include continuing support in the large-scale intervention study of ACTs in programmatic use in Amazon Basin, in Brazil (see “Large Intervention Study in the Amazon Basin” section), a Malaria-in-Pregnancy Consortium-led pharmacokinetic study in pregnant women in Brazil and Burkina Faso, and a MSF-conducted effectiveness field study comparing 5 ACT regimens, including fixed-dose ASMQ, in Myanmar.

MORE ABOUT... Farmanguinhos/Fiocruz

About 46,000 people die each year from infectious diseases in Brazil.[1] Fiocruz, part of the Brazilian Ministry of Health, is working hard to remedy the situation by taking such steps as facilitating health tool R&D via the establishment of dedicated centers (such as Farmanguinhos/Fiocruz) for vaccine and drug development. ASMQ represents a key early step as the first medicine for neglected diseases to be registered in Brazil.

A part of the Oswaldo Cruz Foundation (Fiocruz) of the Government of the Federative Republic of Brazil, Farmanguinhos/Fiocruz is one of the largest pharmaceutical laboratories in Brazil and has a long history of drug production in the field of neglected diseases, particularly for the treatment of AIDS. Located in the state of Rio de Janeiro, Farmanguinhos/Fiocruz produces more than two billion pharmaceutical components per year, not just for AIDS but also for the treatment of endemic diseases such as malaria (ASMQ; primaquine and chloroquine), leprosy, tuberculosis, and filariasis.

Also within the Oswald Cruz Foundation is a public laboratory, Biomanguinhos, the world's largest producer of vaccine against yellow fever, and the only WHO-certified vaccine laboratory in Latin America.

□ History

Aimed to combat rural endemic diseases, the Ministry of Health (MS) created a facility for the research and production of medicines in 1956. Twenty years later, the laboratory expanded and was integrated into the Oswaldo Cruz Foundation (Fiocruz): this was the beginning of the drug research institute, Farmanguinhos/Fiocruz. Today, Farmanguinhos/Fiocruz is one of the most important national laboratories, ensuring the Brazilian population's access to essential medicines.

Farmanguinhos/Fiocruz aims to be a centre of reference in research, technology, and production of medicines. To achieve this goal, Farmanguinhos/Fiocruz has a strategy to promote partnerships with the public and private sectors to produce drugs either from plants or chemical synthesis and to develop pharmaceutical formulations.

- Farmaguinhos/Fiocruz is working to produce a cheaper alternative to the antiretroviral (ART), efavirenz.
- Farmanguinhos/Fiocruz has successfully engaged in technology transfer of ART production technology to Ukraine in exchange for production technology of recombinant human insulin.
- ASMQ is the first new drug developed from the laboratory through production by Farmanguinhos/Fiocruz, which has contributed to the FACT Project Consortium in five key areas: pharmaceutical development, preclinical toxicology studies, production, registration, and distribution of ASMQ.

1 Morel et al. Nature. 2007;449:180.

MORE ABOUT... DND*i*

□ Mission

Founded in 2003, DND*i* (Drugs for Neglected Diseases *initiative*) is a needs-driven, not-for-profit product development partnership (PDP) working to research and develop new treatments for neglected diseases such as sleeping sickness (human African trypanosomiasis; HAT), visceral leishmaniasis (VL), Chagas disease, and malaria.

□ Founding Members

DND*i* drew Founding Partners primarily from the public sector in neglected disease-endemic countries: the Oswaldo Cruz Foundation/Farmanguinhos in Brazil, the Indian Council for Medical Research (ICMR), the Kenya Medical Research Institute (KEMRI), and the Ministry of Health in Malaysia, along with Médecins Sans Frontières, the Institut Pasteur, and the UNICEF/UNDP/World Bank/WHO's Special Programme for Research and Training in Tropical Diseases (TDR) as permanent observer. Today, DND*i* is a small team of permanent staff in Geneva along with 5 regional support offices in Kenya, India, Brazil, Malaysia, and the USA, and two regional project support offices in Democratic Republic of Congo and Japan.

□ Collaborative Mode of Operation

DND*i* follows the virtual research model adopted by other PDPs, whereby most research is outsourced and actively managed by DND*i* personnel. As an integral part of its mission, DND*i* utilizes South-South and North-South collaborations in working with R&D partners. While using and supporting existing capacity in countries where the diseases are endemic, DND*i* helps to build additional capacity in a sustainable manner through technology transfer in the field of drug R&D for neglected diseases. This includes early-stage access to molecules, pharmaceutical and clinical development, and working closely with regional experts & researchers through, for example, the Leishmaniasis East Africa Platform (LEAP) and Human African Trypanosomiasis (HAT) platforms.

□ Regional Networks

DND*i* has built regional networks of scientists and clinicians actively involved in the research of new drugs for neglected diseases in Asia, Africa, and Latin America, as well as in the conduct of clinical trials in endemic countries.

□ Current Portfolio

DND*i* has 18 projects in its portfolio as of January 2008: 9 discovery, 3 preclinical, 4 clinical, and 2 post-clinical projects. Discovery projects range from library screening on validated targets and reformulation studies to therapeutic switching. Three preclinical projects will be ready to enter clinical studies by 2009, and clinical projects are ongoing for VL (combination therapies, regional extension of existing drugs) and for HAT (nifurtimox-eflornithine combination therapy [NECT]).

□ Delivered Products

Two fixed-dose antimalarial ACTs (FACT's 'ASAQ' and 'ASMQ') have been developed and registered by DND*i* and its FACT Project partners; these public goods are treatments which are easy to use (1-2 tablets a day over a 3-day treatment course) for both children and adults. Over 1 million treatments of ASAQ, the fixed-dose combination (FDC) of artesunate and amodiaquine, have now been distributed by industrial partner, sanofi-aventis, and the treatment is now registered in 21 African countries.

□ Funding

In order to achieve its objectives of building a robust pipeline and delivering 6-8 new treatments by 2014, DND*i* requires a total of EUR 274 million. To date, a number of public institutional and private donors have contributed EUR 74 million to DND*i*.
To learn more about DND*i*'s activities, please visit www.dndi.org or contact info@dndi.org.

MORE ABOUT... Malaria

□ How is malaria transmitted?

Malaria is caused by a parasite, called *Plasmodium*, that is transmitted from person to person by the bite of anopheline mosquitoes. Four species of the parasite are involved: *Plasmodium falciparum, P. malariae, P. vivax and P. ovale. P. falciparum* is the main cause of severe clinical malaria and death.

□ What are the symptoms/presentations?

Malaria begins as a flu-like illness 8 to 30 days after infection. Symptoms include fever (with or without other signs or symptoms, such as headache, muscular aches and weakness, vomiting, diarrhea). Typical cycles of fever, shaking chills and drenching sweats may then develop. The periodicity of these cycles depends on the species of parasite, coinciding with parasite multiplication and destruction of red blood cells, which also leads to anemia.

□ How fatal/serious is malaria?

MALARIA'S IMPACT [3]

Total number of cases
Every year, 350 to 500 million (new) cases of malaria occur worldwide

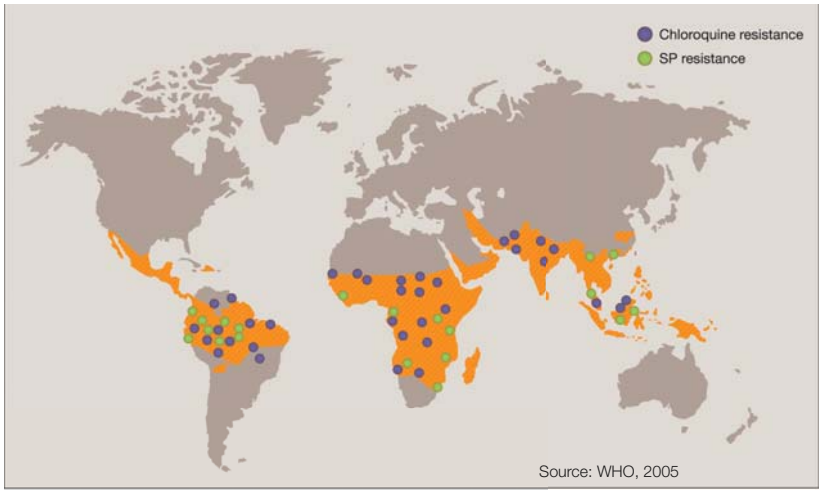
Deaths
Every year, malaria causes over 1 million deaths, affecting mostly children in sub-Saharan Africa

Disability Adjusted Life Years (DALYs)
42,280,000 DALYs (The sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability)

P. falciparum malaria, the most common and most dangerous form, can be fatal if untreated or treated with insufficiently effective drugs. Death may occur when infected red blood cells block blood vessels supplying the brain (cerebral malaria), or when other vital organs have been damaged. In areas where the disease is highly endemic, people are infected so frequently that they develop a degree of acquired immunity and may become asymptomatic carriers of infection.

□ Where does malaria occur?

Malaria is present in over 100 countries and threatens half of the world's population.[1] The disease is mainly confined to poorer tropical areas of Africa, Asia and Latin America. Malaria is present in 21 countries of the Americas and is responsible for about 1 million cases each year. Malaria also remains a major public health problem in Southeast Asia: of the 11 countries in the region, 10 are malaria-endemic.[2]



1 World Health Organization. Introduction. In: *World Malaria Report*. Geneva, Switzerland: World Health Organization; 2005,
2 WHO Disease Information, http://www.who.int/tdr/diseases/malaria/diseaseinfo.htm. Accessed April 6, 2008.
3 Global Forum for Health Research. Monitoring Financial Flows for Health Research. Geneva: 2005, p. 59.

MORE ABOUT... Malaria

□ What is the impact of malaria?

Malaria is a major cause of morbidity and mortality worldwide, especially in developing countries where it has serious economic and social costs. Malaria deepens poverty: patients are often bedridden and incapable of carrying out normal daily activities. The economic cost of malaria is a slowing of economic growth by 1.3% per year in endemic areas.[1]

□ What are the current treatments and their limitations?

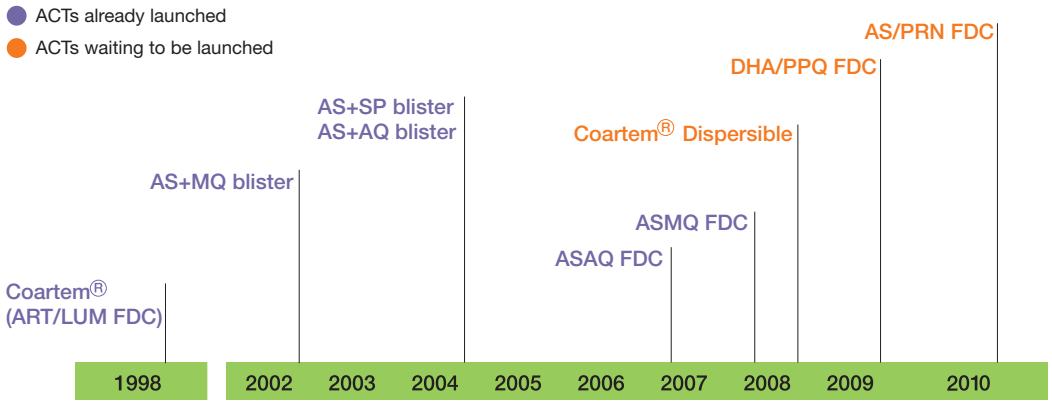
Effective treatments exist, but there are limitations:

- Widespread drug resistance: chloroquine, one of the easiest to use and most available malaria treatments, is no longer effective, with parasite resistance more than 90% in many parts of the world.[2]
- Existing combination therapies, now adopted as first-line treatment in most malaria-endemic countries, can be expensive and have complicated treatment regimens
- No fixed-dose ACTs are available in paediatric strength for Latin America and Southeast Asia (fixed-dose ASAQ has been available in Africa since March 2007)
- The countries suffering the most from malaria lack the necessary capacity and funding to deliver the drugs to the patients who need them

□ What's the current state of R&D for malaria treatments?

After a long sleep in malaria drug R&D (as mentioned in "First New Product for Neglected Diseases Developed and Now Registered in Brazil"), there are now several compounds at various stages of antimalarial drug development around the world. The PDP, Medicines for Malaria Venture (MMV), is a key partner in many of these projects.

Availability of New ACTs: Recent and Projected Launches



The immediate availability of ASMQ represents a key development in the efforts to implement a successful global malaria control strategy by reducing the likelihood of resistance, thereby helping to protect the artemisinin class and contributing to the efforts to make available a number of new ACTs in the future.

1 WHO Disease Information, http://www.who.int/tdr/diseases/malaria/diseaseinfo.htm. Accessed April 6, 2008.
2 WHO Disease Information, http://www.who.int/tdr/diseases/malaria/diseaseinfo.htm. Accessed April 6, 2008.

To learn more…

WHO Global Malaria Program: www.who.int/malaria/

Roll Back Malaria: www.rbm.who.int

TDR: www.who.int/tdr/diseases/malaria/default.htm

Medicines for Malaria Venture: www.mmv.org

Shoklo Malaria Research Unit: www.shoklo-unit.com

Impact Malaria: www.impact-malaria.com

ASAQ: www.actwithasaq.org

Farmanguinhos/Fiocruz: www.far.fiocruz.br/

Drugs for Neglected Diseases initiative: www.dndi.org

- DNDi's regional support offices:
  - Africa: www.dndiafrica.org
  - India: www.dndiindia.org
  - Latin America: www.dndi.org.br
  - Malaysia: www.dndiasia.org
  - North America: www.dndina.org
- DNDi also has project support offices in Democratic Republic of Congo and Japan

DNDi's Founding Partners:

- Médecins Sans Frontières: www.msf.org
- Oswaldo Cruz Foundation/Fiocruz (Brazil): www.fiocruz.br
- Indian Council of Medical Research (India): www.icmr.nic.in
- Institut Pasteur (France): www.pasteur.fr
- Ministry of Health (Malaysia): www.moh.gov.my
- Kenya Medical Research Institute (Kenya): www.kemri.org
- Permanent observer: WHO Special Programme for Research and Training in Tropical Diseases (TDR) - www.who.int/tdr