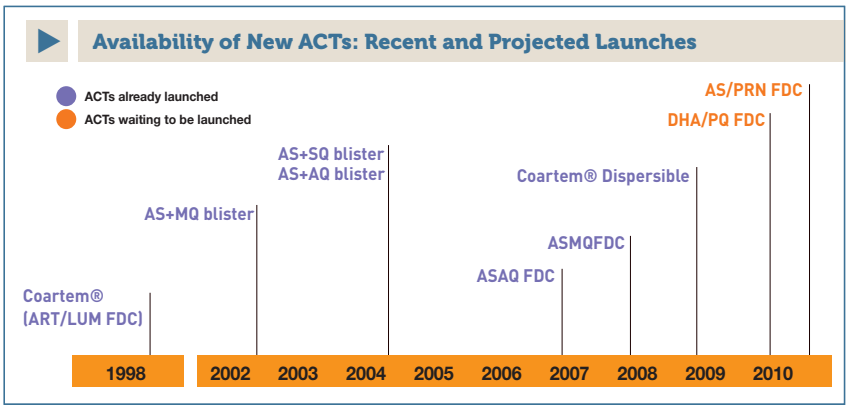
R&D Portfolio
BY DISEASE

Malaria

Further progress made in fighting an old disease as FACT products gain ground in Africa and Latin America



The past year has seen efforts by DND*i* and our industrial partners take further hold in the field of malaria treatment, particularly with the WHO prequalification of ASAQ, its growing use in the public market, and the proactive monitoring plan of ASAQ in "real-life" conditions, which includes the most ambitious proactive pharmacovigilance programme ever launched in Africa, for any drug. Important progress has also been seen with ASMQ as the first purchase was made by Brazilian authorities in April 2009, and plans for technology transfer to Asia and study of its possible use in Africa are afoot.

As we in the world malaria community move forward in meeting the needs of those suffering from malaria, one of the main strategies for malaria prevention and control is prompt and effective treatment. It has been well established that drug combinations are a strategic and viable option in improving efficacy, and in delaying development and selection of resistant parasites (after lessons learned with widespread resistance to chloroquine and SP).

Artemisinin-based combination therapy is nowadays the best therapeutic option for treating drug-resistant malaria and retarding the development or spread of parasite resistance. Since 2001, the WHO has recommended combination therapies containing an artemisinin derivative and, in 2006, strengthened its recommendations to say that fixed-dose combinations (FDCs) should be used wherever possible.

The advantages of using FDCs have been well documented in several disease areas, including malaria, tuberculosis and HIV/AIDS. FDCs offer several potential advantages: increasing patient adherence to treatment, delaying the development of parasite resistance, decreasing total treatment cost (including production, storage, and transport), reducing the risk of me-


In 2009, ASAQ is reaching more and more patients, including at this MSF treatment programme in Guinea.

dication errors by prescribers or patients themselves, and preventing the risk of medication given in combination to be taken only as monotherapy.
Following the recommendations of WHO and independent malaria experts, DND*i* developed fixed-dose combination of ACTs (FDC-ACTs or 'FACT's) as part of its overall R&D efforts begun in 2003.
In building partnerships with industrial partners – sanofi-aventis for ASAQ and Farmanguinhos/Fiocruz for ASMQ - from an initial network of public partners, DND*i* has ensured that these products be developed as non-exclusive public goods and at cost so that the largest potential global health benefit could be attained
As a result of these efforts, new effective, easy-to-use and affordable FDC-ACTs are now available or under development. Through DND*i* and its partners, artesunate-amodiaquine (ASAQ), and artesunate-mefloquine (ASMQ) are now available. In addition, efforts by Medicines for Malaria Venture (MMV), have led to the availability of a paediatric version of artemether-lumefantrine (AL), and the development of dihydroartemisinin-piperaquine (DHA/PQ), which is expected to become available in the second quarter of 2010.

Although the existing armamentarium of FDCs for the treatment of uncomplicated malaria is relatively limited nowadays, there are an increasing number of FDC-ACT manufacturers. With the April 2009 launch of the AMFm, DND*i* joined MSF in its call for the exclusive use of FDC to further incentivise drug makers to enlarge the FDC-ACT pipeline.

ASMQ, FIXED-DOSE ARTESUNATE/MEFLOQUINE COMBINATION THERAPY

A public good developed and supported by public partners crosses continents

- **Stage:** Phase IV post-registration monitoring and access
- **Partners:** Farmanguinhos, Brazil; Epicentre, France; MSF International; Shoklo Malaria Research Unit, Thailand; University Sains Malaysia; Oxford University, UK; TDR; Cipla, India; Catalent, USA; ICMR, India; GVK BIO, India; Tanzania; Quintiles, USA
- **DND*i* project managers and coordinator:** Jean-René Kiechel, Patrice Piola, Gwenaëlle Carn
- **Project start:** January 2002

Among the most studied ACTs is the three-day treatment with artesunate (AS) and mefloquine (MQ), which has shown to be a highly effective therapy against uncomplicated falciparum malaria. Used in the field for 16 years, the combination of AS and MQ has been one of four ACTs recommended by WHO since 2001 as first-line treatment for uncomplicated falciparum malaria.

ASMQ, the new co-formulation of AS and MQ, offers a simple regimen for children and adults that is as easy as 1-2-3: a single daily dose of one or two tablets over three days. This co-formulation was one of two malaria projects undertaken in 2002 by a number of public and private partners coordinated by TDR and MSF (who turned over the project to DND*i* upon its foundation) as part of the FACT (Fixed-Dose, Artesunate-Containing Therapy) Project.

April 2009 marked an important milestone for ASMQ as the first public order was completed by Brazil. DNDi's public industrial partner Farmanguinhos/Fiocruz successfully registered ASMQ in April 2008, and the co-formulation has been used by Brazilian national authorities as part of an intervention study, where preliminary results after one year show a greater than 70% drop in *P. falciparum* malaria cases and an approximate 65% reduction in malaria-related hospital admissions.
The study has now treated over 23,000 patients with ASMQ. Work is ongoing to clean the data set and finalise the results.

In 2009, registration processes for ASMQ in 2 or 3 other countries in Latin America are being navigated; it will be submitted for PAHO prequalification; and Farmanguinhos/Fiocruz will continue its technology transfer to the Indian generics manufacturer, Cipla, in order to facilitate its future availability in Southeast Asia. Further clinical research with partners is in preparation to examine the potential therapeutic value of ASMQ in pregnancy and in Africa. A clinical study in India has recently been completed, with analysis ongoing, and a dossier for registration in India will be submitted by the end of 2009.

ASMQ is the only fixed-dose ACT available with a 3-year shelf life and is optimised for rural and remote settings by an innovative weight- & age-based dosing regimen of >180,000 individuals. This work, as well as preliminary results from the Brazilian intervention study, was presented during the 57th American Society of Tropical Medicine & Hygiene in December 2008 and is available at www.dndi.org

The color-coded and age-based packaging of ASMQ provides clear information that is meant to facilitate proper use in the most remote of settings.

ASAQ, FIXED-DOSE ARTESUNATE/AMODIAQUINE COMBINATION THERAPY

More than 20 million of ASAQ treatments to be delivered for African malaria patients during 2009

- **Stage:** Phase IV post-registration monitoring and access
- **Target disease:** malaria
- **Partners:** sanofi-aventis, France; Medicines for Malaria Venture, Switzerland; National Centre for Research and Development on Malaria, Burkina Faso; University Sains Malaysia; Oxford University, UK; Institute of Research for Development (IRD), Senegal; Mahidol University, Thailand; Ellipse Pharmaceuticals, France; MSF; Epicentre, France; TDR; Catalent, USA; KEMRI, Kenya ; ICMR, India; GVK BIO, India; Quintiles, USA; Cardinal Systems, France; Epicentre, France; MS; Komfo Anokye Teaching Hospital, Ghana
- **DND*i* project managers and coordinator:** Jean-René Kiechel, Gwenaëlle Carn
- **Project start:** January 2002.

ASAQ, the new fixed-dose combination (FDC) of artesunate (AS) and amodiaquine (AQ), was the first drug to be made available by DND*i*. Over 5.3 million treatments were distributed in 2008. Now available in 24 countries in sub-Saharan Africa, with over 20 million treatments to be delivered in 2009, the continuing focus of this post-registration project is to support sanofi-aventis the implementation of ASAQ for the treatment of uncomplicated falciparum malaria after its registration in endemic countries, mainly in sub-Saharan Africa, India, and Indonesia.

ASAQ provides a true innovation in patient treatment by being a tropical-stable bilayer co-formulation, which allows AS and AQ to be taken together and in the correct proportions in a simplified three-day dosing regimen where the most vulnerable population, children under the age of five, take one tablet per day.

To continue their pioneering efforts as the 1st public-private partnership to deliver a needs-adapted antimalarial medicine, sanofi-aventis and DND*i* continue to work to enlarge the partnership by involving national malaria control programs and pharmacovigilance systems, as well as international organizations and agencies.

DND*i*, sanofi-aventis and additional partners, in particular MMV and national malaria control programmes, are implementing a comprehensive "ASAQ Deployment Monitoring Plan" that aims to collect high-quality data on ASAQ effectiveness and safety profile in "the field". This programme includes a series of proactive clinical studies conducted in several countries of sub-Saharan Africa with different levels of disease transmission. Some of the studies are underway while others are still in the design phase.

Key ongoing studies include two post-registration studies being done in collaboration with MSF, Epicentre, and the national malaria control programme in Liberia: 1300 patients have been enrolled in these studies, which will assess the tolerability and efficacy of ASAQ in comparison with artemether-lumefrantine (Coartem™). In Ivory Coast, two clinical studies are being set up in a collaboration between sanofi-aventis, MMV, and DND*i*: these studies will collect relevant 'real-life' efficacy, effectiveness and pharmacovigilance data in over 15,000 patients at a district level.

Ultimately, more than 20,000 patients will be followed as part of this monitoring plan. These results will provide a comprehensive overview of the efficacy and safety of ASAQ in the long run and will also allow innovative pharmacovigilance methods to be developed, suited to the needs and resources of countries in sub-Saharan Africa.

The deployment monitoring plan as well as additional clinical data supporting the use of ASAQ has been presented over the past 6 months at international meetings such as ASTMH and the 3rd Annual East African Health Sciences in March 2009. Highlights of these data and the plan can be found on www.actwithasaq.org.

- **Just published:** ASAQ is found to be efficacious and well-tolerated in pivotal Phase III field study carried out in Burkina Faso children: the study showed 28-Day PCR-corrected parasitological and clinical cure rates were ≥95% in both arms comparing the fixed-dose ASAQ combination with the non-fixed AS+AQ association in 750 children with uncomplicated *P. falciparum* malaria. Sirima SB, et al. *Malar J.* 2009 8(1):48.

- A recent population pharmacokinetic analysis has shown that there is a pharmacological equivalence of ASAQ with the well-established separate products

- Meta-analyses – individual and aggregate – presented at ASTMH and in the process of publication

- Results published in Eur J Clin Pharmacol in May 2009 show that ASAQ is well-tolerated and with a comparable pharmacokinetic profile as the separate products

- A multi-center, non-inferiority trial comparing ASAQ with Coartem® (fixed-dose artemether-lumefantrine) in Cameroon, Madagascar, Mali, and Senegal, has shown that ASAQ is as efficacious and well-tolerated as Coartem® in a total of 941 patients including in 112 paediatric patients less than 5 years old. Nadiaye et al. *Malaria J*; 8 (125)

DNDi
Drugs for Neglected Diseases *initiative*

Malaria

3.2 billion people at risk

WHAT IS THE ANNUAL IMPACT OF MALARIA?

350 to 500 million new cases [1]
Over 1 million deaths [1]
42,280,000 DALYs [2]

Malaria is the leading parasitic cause of morbidity and mortality worldwide, especially in developing countries where it has serious economic and social costs.

Malaria is thought to slow annual economic growth by 1.3% in endemic areas with high prevalence. The economic cost of malaria in Africa alone is estimated at US$12 billion every year [3].

HOW IS MALARIA TRANSMITTED?

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

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

• **Widespread drug resistance**: chloroquine, one of the easiest to use and most available malaria treatments, is no longer effective, with parasite resistance at more than 90% in some parts of the world (4)

• **Existing combination therapies**, now adopted as first-line treatment in most malaria-endemic countries, can be expensive and have complicated treatment regimens

• **Limited access o**f neglected patients **to the few paediatric strength, fixed-dose ACTs which are available**

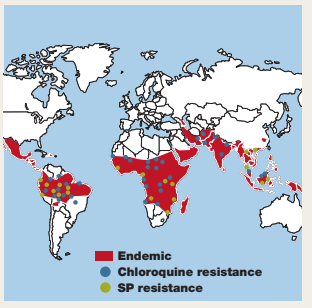
• The countries suffering the most from malaria lack the necessary capacity and funding to deliver the drugs to the patients who need them.

WHAT ARE THE CURRENT PATIENT TREATMENT NEEDS?

Patients in malaria-endemic countries need inexpensive, efficacious, and field-adapted drugs.

WHERE DOES MALARIA OCCUR?

Malaria is present in over 100 countries and threatens half of the world's population. **In sub-Saharan Africa, where it is the single largest cause of death for children under five, malaria kills one child every 30 seconds** – approximately 3,000 children every day.



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. Death may be due to brain damage (cerebral malaria), or damage to vital organs.

WHAT IS DND*i* DOING TO ADDRESS UNMET TREATMENT NEEDS?

DND*i*'s malaria-specific portfolio aims to facilitate the widespread availability of the two products delivered by its diverse partners in the Fixed-Dose Artesunate Combination Therapy (FACT) Project.

Because of numerous antimalarial R&D activities (eg. Medecines for Malaria Venture), DND*i* is phasing out its malaria activities to focus on the kinetoplastid diseases.

The FACT Project has produced 2 fixed-dose ACTs which are:

– Easy to use as given in a single daily dose of 1 or 2 tablets for 3 days

– A 2-in-1 fixed-dose combination (FDC) of drugs that ensures both drugs are taken together and in correct proportions

– Age-based dosing to facilitate proper dosing in rural, remote areas

• ASAQ – FDC of artesunate and amodiaquine for treatment of malaria in sub-Saharan Africa; now registered in 24 countries

• ASMQ – FDC of artesunate and mefloquine registered in Brazil in March 2008 and in use by Brazilian national authorities as part of ongoing intervention study

Through 2014, DND*i* will support the proper use to work to facilitate access to of these FACTs along with the other effective ACTs so as to maintain the effectiveness of artemisinin as a first-line treatment.

(1) World Health Organization. Introduction. In: World Malaria Report. Geneva, Switzerland: World Health Organization; 2005. **(2)** DALYs are a measure of societal impact, being the sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability. **(3)** Global Forum for Health Research. Monitoring Financial Flows for Health Research. Geneva: 2005, p. 59. **(4)** Mayxay M, Nair S, Sudimack D, Imwong M, Tanomsing N, Pongvongsa T, et al. Am J Trop Med Hyg. 77; 2007: 36-43