DNDi
Drugs for Neglected Diseases *initiative*

sanofi aventis
Because health matters

□ ASAQ in a few words

- A drug combination that meets the latest WHO guidelines for malaria treatment in Africa
- An innovative fixed-dose formulation

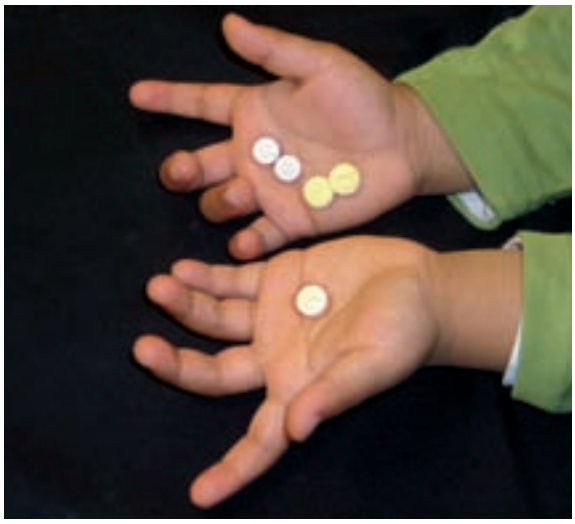
A simple dosing regimen:

- □ 1 tablet per day for 3 days for infants, children and adolescents
- □ 2 tablets once a day for 3 days for adults

Presentations specifically adapted to children

- □ State-of-the-art galenical formulation
- □ Optimized dose ratio to avoid over- and under-dosage

- A combination of well-known drugs with well-documented track records of efficacy and safety
- A commitment to make it available to all patients, right from the start
  - □ <US$1 for adults and <US$0.50 for children in public markets
  - □ Not patented
- Highest standards of quality enforced through the entire manufacturing process
- The concrete result of an innovative partnership between DNDi and sanofi-aventis



In the child's lower hand, the single ASAQ tablet per day is shown in comparison with the upper hand containing 4 tablets needed per day with current treatments.

□ **ASAQ product profile**

■ Introduction

With antimalarial drug resistance a global challenge, patients in malaria-endemic countries need inexpensive, efficacious, field-adapted drugs. Preserving the life span of antimalarial drugs through highly effective combination treatments is a key part of the strategy to roll back malaria.

Safe and rapidly acting, the combination of artesunate (AS) and amodiaquine (AQ) is one of the antimalarial drug combinations **recommended by the World Health Organization (WHO) for Africa**.[1] Fixed-dose formulations, which are easier to use and ensure drugs are taken together and in correct proportions, are needed but are often not available for children.[2] For the approximately 3,000 African children dying every day due to malaria,[3] such an innovation could make a major difference.

This fixed-dose combination of AS and AQ was developed by the FACT partners managed by the non-profit product development organization, DNDi, and with the involvement since 2004 of the world's fourth–largest pharmaceutical company, sanofi-aventis. ASAQ will simplify treatment: **1 tablet a day for children, the population most at risk, over 3 days** to treat uncomplicated malaria.

Available under the name **Artesunate-Amodiaquine Winthrop® (ASAQ)** for public market and the brand name **Coarsucam®** for private market, **ASAQ** has four key features:

- **Adapted…**
  - □ To WHO recommendations
  - □ To needs of patient of all ages
  - □ From two well-known drugs with proven efficacy and safety
- **Accessible…**
  - □ Available
  - □ Affordable
  - □ Non-patented
- **Simple…**
  - □ Regimen that is easy to use
  - □ Prescription
  - □ Management and storage
- **Quality…**
  - □ Formulation
  - □ Development
  - □ Manufacturing
  - □ Implementation

1. Guidelines for the treatment of malaria. World Health Organization. 2006, p. 21 & 23.
2. WHO Director General Margaret Chan opening speech to the 120th session of Executive Board. Speech made in Geneva on 22 January 2007. Available at http://www.who.int/dg/speeches/2007/eb120_opening.
3. Global Forum for Health Research. Monitoring Financial Flows for Health Research. Geneva: 2006, p. 91.

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□ **ASAQ product profile**

■ ASAQ… Adapted

• Adapted to WHO recommendations

ACTs are the way forward. Due to increasing resistance to antimalarials, particularly chloroquine, the World Health Organisation (WHO) recommends Artemisinin-based Combination Therapy (ACT) – the concomitant use of two antimalarials, including an artemisinin derivative.[4] Ideally, these combinations should be formulated as fixed-dose combinations, i.e. both drugs are contained in a single tablet to guarantee treatment compliance.

Artesunate (AS) plus amodiaquine (AQ) is one of the four WHO-recommended ACTs to treat uncomplicated *falciparum* malaria in Africa. Of the 41 countries in sub-Saharan Africa which recommend the use of ACTs, 20 have chosen the artesunate + amodiaquine combination as first-line treatment.[5]

• Adapted to patient needs of all ages

African demographic data of over 88,000 African children and adults[6] were used to select 4 different presentations based on age and weight: infants (4.5-8 kg or 2-11 months), young children (9-17 kg or 1-5 years), children (18-35 kg or 6-13 years), and adults (≥ 36 kg or ≥ 14 years). These AS and AQ doses provide the smallest risks of over- and under-dosage.

• Adapted from two well-known drugs with proven efficacy and safety

AS and AQ are well-known drugs. Numerous studies have compared the sanofi-aventis AS + AQ combination with single drugs and/or other ACTs. Multiple studies have cumulatively included approximately 10,000 patients taking the AS + AQ combination (read more in the Clinical Data sheet).

An efficacious and well-tolerated treatment. Evidence of the efficacy and tolerability of the AS + AQ combination is shown by a number of studies as detailed in the Clinical Data sheet. In the one clinical study of the fixed-dose combination to date, efficacy rates for ASAQ were greater than 95%.[7] This study also showed good tolerability of ASAQ, equivalent to the loose AS + AQ association.

4. Guidelines for the treatment of malaria. World Health Organization. 2006, p. 21 & 42.
5. Sources: NMPM-RBM-Afro, 2006.
6. Use of weight-for-age data to optimize tablet strength and dosing regimens for a new fixed-dose artesunate-amodiaquine combination for treating falciparum malaria. Taylor WRJ et al. Bulletin of the World Health Organization. December 2006; 84(12) : 956-64, p. 961.
7. A comparative clinical assessment of fixed-dose artesunate/amodiaquine (AS/AQ) versus loose formulation of artesunate + amodiaquine (AS + AQ). Sirima SB. Data on File – sanofi-aventis.

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□ ASAQ product profile

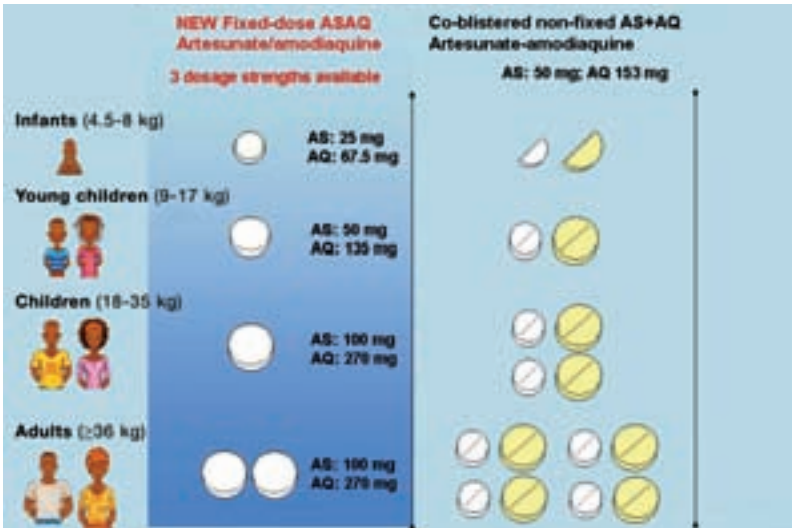
■ ASAQ… Simple

• Simple regimen

A 1-tablet-a-day dosing regimen for the most at-risk population, children, means that ASAQ is **easy-to-use** and will help to improve treatment compliance, thereby reducing the risk of emerging resistance. As a co-formulation, ASAQ avoids the risk that patients would take only one active ingredient and ensures that both drugs are **taken together** and in **correct proportions**. All age groups will have treatment regimens of once-a-day dosing for 3 days: 1 tablet/day for children up to 13 years of age (≤35 kg) or 2 tablets/day for adolescents aged 14 years and above and adults (≥36 kg).

IN THE ADULT'S LOWER HAND, THE 2 ASAQ TABLETS PER DAY DOSING IS SHOWN IN COMPARISON WITH THE UPPER HAND HOLDING 8 TABLETS NEEDED PER DAY WITH CURRENT TREATMENTS.

Simplified 3-Day Dose Regimen of ASAQ



• Simple prescription, adapted to children

The needs of children, the primary victims of malaria, are specifically addressed by ASAQ. To optimize dosing for each age range, and to avoid over- and under-dosing, three different presentations are available for children between 2 months and 13 years of age. Colour coding helps to identify the different dosages.
Tablets are small: 8 mm diameter for infants, 10 mm for young children, and 13 mm for children. They are also easily crushable and can be administered with liquids or semi-liquid food.

□ ASAQ product profile

• Simple prescription, adapted to children (continued)

Four different presentations based on bodyweight
For infants, toddlers, children and adults

• Simple management & storage

Based on public sector and NGO experience, blister and box sizes were minimized to save as much space as possible so as to reduce shipping, storage, and delivery costs.
□ **Public market** and pharmacies involved in the sanofi-aventis "Access Card Programme (CAP)": 1 box with 25 blisters of 3 or 6 tablets per blister.
□ **Private market**: 1 blister of 3 or 6 tablets per box. Each blister contains a complete 3-day treatment.

Early stability studies support a 2-year shelf-life recommendation for tropical conditions. Additional ongoing studies may support an extended shelf-life.

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□ ASAQ product profile

■ ASAQ… Accessible

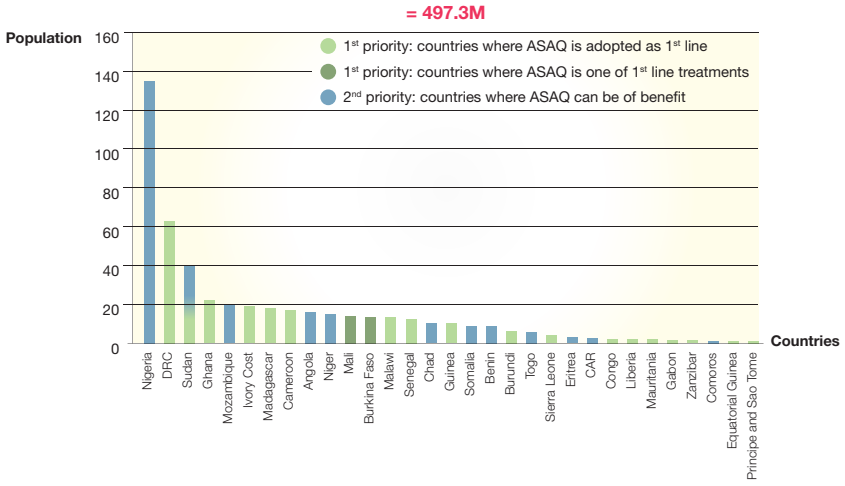
• Available in malaria-endemic countries

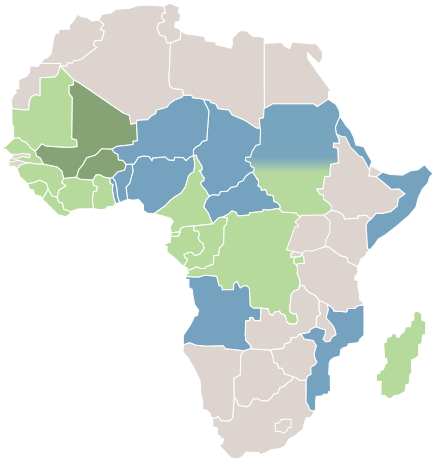
ASAQ will start being available in 2007, as local marketing authorisations are being granted. Over 25 applications have been filed, in many sub-Saharan countries.

First priority are the 20 countries that have already adopted ASAQ as first-line treatment. Second priority will be countries where ASAQ can be of benefit, based on national and international efficacy data.

Outside of Africa, ASAQ could be beneficial in some other countries in Asia or Latin America, depending on resistance patterns.

Population in millions in 31 countries where ASAQ could be considered as 1st line treatment for uncomplicated malaria in Africa





Source: RBM-WHOAfro, 2006

• Affordable right from the start

For a full treatment cost of <US$0.50 for children less than 5 years old and <US$1 for older children and adults, ASAQ will be available at a "no profit-no loss" price to public organisations of endemic countries, international institutions, NGOs, and programs promoting access to drugs in pharmacies. Further price reduction may be possible, depending on the costs of active ingredients and on amounts ordered by international organisations and the countries concerned.

Different price levels will apply to different drug distribution channels that cater to the needs of different population segments.

□ **Public market:** Artesunate Amodiaquine Winthrop® (AS/AQ Winthrop) sold at "no profit-no loss" price.

□ **Private market:** Coarsucam® for private markets (normal price adapted to local markets) and Coarsucam® Impact Malaria ("no profit-no loss" price) for "Access Card Programme (CAP)" pharmacies.

• Non-patented

No patent protection has been sought because this product is provided for the benefit of underprivileged patients, and both DNDi and sanofi-aventis intend wide distribution to those patients in greatest need.

□ **ASAQ product profile**

■ ASAQ… Quality

• Quality formulation

The novel ASAQ "bilayer" tablet provides a separation of the two compounds as studies showed that, when mixed together, AS and AQ are not sufficiently stable. One of DNDi's FACT partners, Ellipse Pharma, initially developed this innovation as well as a process of manufacturing which allowed them to reduce the size and number of tablets to be administered and to obtain stable products with a 2-year shelf-life in tropical climates when packaged appropriately. **Licensed from DNDi** in December 2004, these innovations are now utilized by sanofi-aventis in large-scale production.

• Quality Manufacturing

Made in the South for use in the South, ASAQ is produced in Morocco, in line with sanofi-aventis' commitment to maintain its industrial assets in "Southern" countries, with the same quality standards worldwide. **Product quality assurance**, guaranteeing the high quality and purity of the active ingredients, is ensured throughout the supply and production chain. The ASAQ manufacturing site in Morocco complies with international manufacturing standards and with the worldwide sanofi-aventis quality standards.

• Quality Development

The regulatory approval process aims at ensuring that ASAQ is made available to patients as soon as possible, while, at the same time, demonstrating adherence to international quality standards. In order to expedite access of this quality product to the patients who need it most and in **compliance with international regulatory standards**, sanofi-aventis has submitted a full registration dossier in Morocco, where the non-fixed combination is already registered. **Marketing approval was granted by Moroccan authorities on February 1, 2007**. As further evidence that ASAQ meets international quality standards, sanofi-aventis submitted a dossier to the WHO pre-qualification process in February 2007.

• Quality Implementation

Providing drugs is not enough. To ensure equitable access to and proper use throughout all levels of the health care system, DNDi and sanofi-aventis will engage a number of partners, including individual experts, countries and regions, WHO and international organisations, funding agencies, and NGOs.

Information and education initiatives, aimed at healthcare personnel and malaria patients, will accompany implementation, if requested by countries, to encourage proper malaria management (including the appropriate use of ACTs), and to increase awareness of malaria prevention.

Enabling pharmacovigilance of the deployed ACT and ensuring drug efficacy and quality are also vital. In addition to efforts by national programs and international programs like the WHO, DNDi will bring support to sanofi-aventis and other partners such as Epicentre/MSF to conduct follow-up studies of efficacy and safety in the field so that high-quality clinical data on ASAQ is collected through sentinel sites in Africa.

□ **Additional information**

■ Clinical Data Supporting the Use of Non-Fixed AS + AQ Association and the Fixed-Dose ASAQ Combination

• Non-fixed association of AS+AQ: Supporting data from 37 studies

Information on the efficacy and safety of the non-fixed AS+AQ association is available from a total of 37 studies, involving approximately 10,000 patients who received AS + AQ in various drugs' ratios.

Evidence of the safety of the sanofi-aventis AS + AQ combination is available from a number of studies. In the largest study, performed in Senegal in over 3,000 patients, no adverse events requiring in-patient hospitalisation were reported.[8] The most commonly reported adverse events possibly related to treatment were vomiting (5.6%), pruritus (3.8%) and dizziness (3.1%). It is important to mention that some patients had been complaining of vomiting and/or dizziness prior to the treatment, as often seen in malaria attacks.

The most comprehensive review of efficacy of the non-fixed AS+AQ association was recently conducted by Olliaro and al.[9] who performed a meta-analysis of 30 studies, published and unpublished, conducted with AS+AQ in various drug ratios during 1999-2006. Out of these 30 studies, 27 were comparative versus other ACT or single products, and 3 were non comparative. The efficacy studies enrolled 11,751 patients, including 5,272 patients who received AS+AQ. Overall, AS+AQ was found to be more effective than single agent treatment or non artemisinin based combinations. AS+AQ Day 28 cure rates after PCR correction were similar to other ACTs. Safety data were not reported uniformly across all studies. AS+AQ was found to be "well tolerated", and the incidence of vomiting, the most commonly reported event, was similar between AS+AQ and other treatments.

• Fixed-dose ASAQ: An efficacious and well-tolerated new treatment

The fixed-dose combination was tested in one study to date, carried out in Burkina Faso, comparing the fixed-dose ASAQ combination to the loose AS+AQ association. This study included 750 children between 6 and 59 months old, with uncomplicated *falciparum* malaria. No significant difference was seen between the efficacy of both presentations, based on the PCR-corrected parasite clearance at Day 28, irrespective of the analysis method used (intent–to-treat or per protocol). **The analysis of the most clinically relevant population shows cure rates of 95.7% for the fixed-dose ASAQ combination** and 96% for the loose-dose combination. The incidence of general adverse events was consistent with what can be expected for young patients presenting with malaria. It is difficult to assign reports of fatigue, nausea, vomiting to the study drugs, the malaria infection itself or to concomitant conditions. Based on what is known of AS and AQ safety profile, no unexpected adverse events occurred during this study.

8-Artesunate (AS) plus amodiaquine (AQ) for treating falciparum malaria – assessing its efficacy and tolerability during six years of field deployment in Southern Senegal. Brasseur Ph et al. ASTMH Atlanta Nov 2006; abstract 306.

9-P. Olliaro, M. Vaillant, R. Phalkey, J. Guthmann, G. Dorsey, P. Brasseur, et al. Artesunate + Amodiaquine (AS+AQ) for the treatment of uncomplicated falciparum malaria: an inventory of clinical studies and systematic review of safety and efficacy data. Abstracts of the American Society of Tropical Medicine and Hygiene 55th Annual Meeting, Atlanta November 12-16, 2006. Abstract.n°307: Am J Trop Med Hyg 2006; 75 (Supplement 5).

□ **Innovative Partnership**

■ DNDi and sanofi-aventis

Since December 2004, DNDi and sanofi-aventis have been collaborating closely on industrial, preclinical and clinical product development to optimise the quality of the drug and to expedite its availability.

• Product development

Following the agreement signed in 2004, DNDi exchanged product data with sanofi-aventis who in turn shared their development programme. From the formulation developed by DNDi, sanofi-aventis carried out the industrial development programme, which takes into account available findings and comprises ongoing work as well as new studies.

DNDi has pursued the pharmaceutical and clinical investigations of the FACT programme, and sanofi-aventis has carried out numerous studies as well as the industrial scale-up and development (for further information, please see the individual ASAQ contributions of each partner).

• Drug registration

The development studies have been used to compile the marketing authorisation application. Sanofi-aventis has registered the drug with the regulatory authorities in Morocco where the product is manufactured and then in the other countries concerned. Sanofi-aventis submitted a full dossier for WHO prequalification in February 2007.

• Price

The drug will be available at cost in the public sector, i.e. national health services of the countries concerned, NGOs, and international organisations.

DNDi and sanofi-aventis commit to a reduced cost price in the public sector. In return for the use of information and findings provided by DNDi, sanofi-aventis agreed to pay DNDi 3% of the net private sector turnover over a period of seven years. DNDi has decided to use this payment to lower the drug's public sector sale price.

• Non-exclusivity of the product

DNDi and sanofi-aventis have agreed not to take any patent covering this artesunate + amodiaquine fixed-dose combination.

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□ **Innovative Partnership**

■ ASAQ: Contribution of DNDi and FACT Partners

• Rationale for AS+AQ in Africa

In 1998, the UNICEF-UNDP-World Bank-WHO's Special Programme for Research and Training in Tropical Diseases (TDR) was charged by the US Agency for International Development and the Wellcome Trust with the task of identifying suitable combinations of existing antimalarial drugs to control malaria resistance. From their data analyses, it emerged that AS+AQ could be a good clinical option in many parts of Africa.

In 2001 the World Health Organization recommended, in particular, the use of four artemisinin-based combination therapies (ACTs), including the combination of AS+AQ. However, in the case of AS+AQ, there was neither a co-formulation nor any development partners.

• FACT Project: ASAQ, 2002-2009

FACT 2002-2006: ASAQ Development through Registration

The FACT (Fixed-Dose Artesunate Combination Therapy) project began in 2002, under the umbrella of MSF (and then DNDi) in coordination with TDR.

□ Objective: to develop a fixed-dose combination of AS+AQ for international registration that would improve compliance and would be available to all countries where resistance to amodiaquine was low (mainly African countries, but also some Asian countries like India and Indonesia)

□ Key partners (*who signed onto the original EU INCO-DEV grant*): Centre National de Recherche et de Formation sur le Paludisme (CNRFP), Instituto de Tecnologia em Farmacos of Farmanguinhos, Mahidol University, Université Victor Segalen Bordeaux 2 (TROPIVAL), University of Oxford, University Sains Malaysia.

DEVELOPMENT STEP	INSTITUTIONS INVOLVED
Pharmaceutical and Preclinical Development	
Vital to the efforts of the FACT Project throughout the entire period of development has been the contribution and expert advice of academics	University of Oxford / Mahidol University (Thailand).
Preformulation, coordination and local support with partners in Bordeaux region	Tropival of Univ Bordeaux II (France)
Formulation of combination product adapted with appropriate stability and biopharmaceutical characteristics and with a viable manufacturing process	Ellipse Pharma (France)
Development and validation of analytical methods	
First scale up coordinated with Rottendorf Pharma	
Set of GLP toxicology studies on single drugs and combinations	Unitox and Genotox (Brazil)
Development and utilization of toxico-kinetic protocols, bioanalytical methods	University Sains Malaysia (USM) (Malaysia)
First industrial scale up and GMP production of the FDC for clinical and stability studies	Rottendorf Pharma (Germany) - Créapharm (France)
Innovative partnership signed with industrial partner	sanofi-aventis: Contract signed, Dec 2004
Clinical Development	
Phase I for PK data, biopharmaceutical quality, and bioavailability	USM (Malaysia)
Field-based Phase III to examine efficacy and tolerability of ASAQ vs non-fixed AS+AQ in children <5 years of age	CNRFP (Burkina Faso) Cardinal Health (France)
Support of 10-year survey of efficacy, tolerability, and pharmacovigilance in Senegal	Institut de Recherche pour le Développement (IRD) (Senegal) Ministère français des Affaires Étrangères (FAC 2000 programme) Ministère français de la Recherche (PAL+), TDR. As of 2007: Ongoing in year 7
Support of meta-analysis of 31 clinical studies examining AS+AQ vs other antimalarials	TDR with FACT partners, MSF/Epicentre

□ Innovative Partnership

FACT 2007-2009: Post-Registration Activities

Through 2009, DNDi intends to play an active role in facilitating FACT implementation by engaging partners that include pharmaceutical companies, national malaria programs, research institutes, contract research organisations, WHO, TDR, and NGOs.

DNDi has convened an independent panel of experts, the FACT Implementation Advisory Group, to provide independent advice and critical guidance about issues related to AS/AQ implementation and to advise on issues related to the rational use and towards ensuring equitable access.

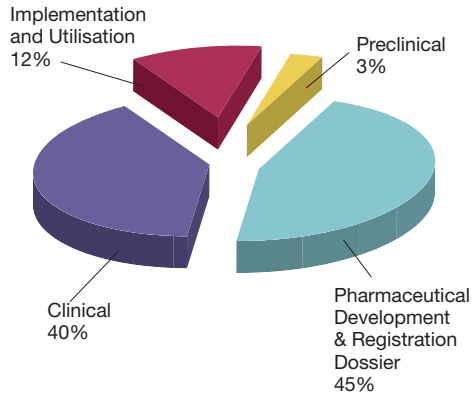
ILLUSTRATIONS OF THE NEXT STEPS	INSTITUTIONS INVOLVED
Clinical study that will serve to facilitate the adoption of a new antimalarial policy	ICMR (India); sanofi-aventis (drug supply)
Workshop meeting to engage national malaria control program managers and international & regional organizations	KEMRI (Kenya) 30 (including NMCPMs, WHO, MMV, etc) attended meeting in Nairobi, Sept 2006.
Tolerability study	Epicentre / MSF, sanofi-aventis

• FACT Project: Resources 2002-2009

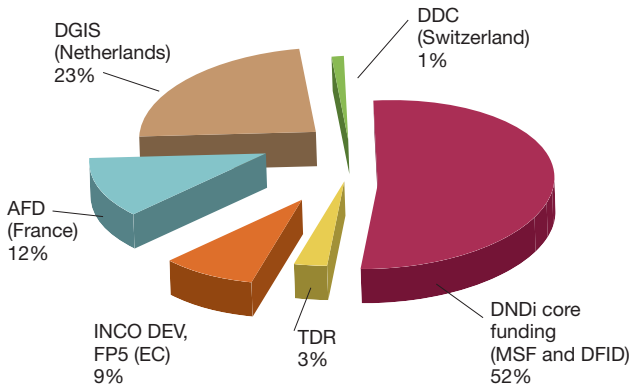
For the DNDi FACT Project, valuable in-kind contributions have supplemented the total budgetary costs of ASAQ covered by partners shown below.

6.4 Million Euros from Public and Private Resources Allocated for ASAQ, 2002-2009

Allocations by Development Stage



Funding Resources By Donor



□ **Innovative Partnership**

■ ASAQ: Contribution of sanofi-aventis

In the partnership with DNDi on ASAQ development, sanofi-aventis contributed resources and expertise in 5 main fields:

- Industrial pharmaceutical development: development of processes required to reach production on an industrial scale at the Maphar – sanofi-aventis plant in Casablanca, Morocco,
- Scientific: pre-clinical pharmaco-toxicology studies were designed to further document the safety profile of AS+AQ in animals, as per the latest international requirements,
- Regulatory: preparation of registration files for Morocco, sub-Saharan malaria endemic countries and WHO pre-qualification process,
- Marketing: preparation of ASAQ launch and marketing in endemic countries, through private and public distribution channels,
- Medical: preparation and implementation of follow-up clinical studies.

■ sanofi-aventis' Impact Malaria Program

Effective malaria treatments are often not accessible to those who need it, because of their price, inappropriate distribution channels or lack of information. sanofi- aventis has developed a comprehensive program, called Impact Malaria, that aims at mobilizing the expertise and resources of a major pharmaceutical firm against malaria.

• 4 strategic axes of Impact Malaria:

1. Research and development of new antimalarial drugs, to anticipate resistance to existing compounds, is carried out by the sanofi-aventis R&D department. Sanofi-aventis R&D currently has several malaria drugs and vaccines projects. The most advanced one is ferroquine, a compound that is active against chloroquine-resistant falciparum, developed with the Université des Sciences et Technologies of Lille (France) (Pr J. Brocard).

2. Improvement of existing drugs to meet the needs and requirements of patients and health care providers. The ASAQ fixed-dose combination developed by the DNDi and Impact Malaria is an example of how existing drugs can be further developed for the benefit of patients. This new formulation will greatly reduce the number of tablets taken by patients, and will decrease the likelihood of development of resistances.

3. Development of Information Education and Communication tools to ensure that drugs are appropriately used, along with other effective interventions. Tools are developed to help healthcare providers, at all levels of the "healthcare pyramid", to appropriately use antimalarial drugs. Tools are also developed for patients to understand how they can prevent malaria through simple measures such as using insecticide-impregnated bednets. Communication and training tools are developed with local malaria programs and tailored to the target populations, taking into account their local structures, conditions, specificities, literacy rates, etc.

4. Pricing policies that give access to high quality drugs to all population segments. Production costs have been optimized to offer the lowest possible prices without compromising quality. Drugs are made available through both the public and the private distribution channels to reach all population segments. For patients who cannot afford brand name antimalarial drugs, the "CAP Program" gives them access to drugs at a "no profit-no loss" price through local pharmacies. The same "no profit-no loss" approach is used for sales to the public sector, NGOs, etc.

Safe and effective drugs are indispensable in the fight against malaria. However, drugs alone will not suffice to reduce morbidity and mortality. Our involvement goes beyond the provision of affordable, high quality drugs, by supporting projects that will demonstrate what efforts are required for an effective and sustainable control of malaria in a variety of settings.

□ **Innovative Partnership**

■ DNDi: addressing the therapeutic needs of the most neglected

Founded in 2003 to address the needs of patients with the most neglected diseases, DNDi (Drugs for Neglected Diseases initiative) is a collaborative, patients' needs-driven, virtual, not-for-profit drug R&D organization that develops new treatments for some of the most neglected communicable diseases (malaria, sleeping sickness, leishmaniasis, and Chagas disease).

In pursuing these new treatments, DNDi manages R&D networks built on South-South and North-South collaborations and helps to build additional capacity in a sustainable manner through technology transfer in the field of drug R&D for neglected diseases. DNDi also works to raise awareness about the need to develop new drugs for neglected diseases and to advocate for increased public responsibility.

Vital to DNDi's efforts have been its Founding Partners, who include several public sector organisations in neglected disease-endemic countries - the Foundation Oswaldo Cruz /Farmanguinhos in Brazil, the Indian Council for Medical Research (ICMR), Kenya Medical Research Institute (KEMRI), and the Ministry of Health in Malaysia - along with the international humanitarian organisation Médecins Sans Frontières, the Institut Pasteur, and with the UNICEF-UNDP-World Bank-WHO's Special Programme for Research and Training in Tropical Diseases (WHO/TDR) as special observer.

DNDi today is team of committed people who are dedicated to maintaining the momentum achieved since the launch of the initiative in 2003. With a small team of permanent staff in Geneva along with 5 regional support liaison offices (Brazil, Kenya, India, Malaysia, and the US), 2 regional project support offices (Democratic Republic of Congo and Japan), and several short-term consultants, DNDi has made significant headway in achieving DNDi's mission:

• Portfolio

DNDi is building a portfolio, which already contains strong projects for two of the target diseases (human African trypanosomiasis (HAT) and visceral leishmaniasis) and taps networks of expertise in many different fields. This portfolio is designed to meet the primary R&D objective of making 6-8 new treatments available to patients by 2014, and also to create a robust pipeline for all target diseases into the future.
In addition to the 2 FACT-related projects, DNDi's portfolio (as of February 2007) contains 20 projects – 11 discovery, 4 preclinical, 5 clinical – focused on drug R&D for the kinetoplastid diseases of HAT, VL, and Chagas disease.

• Partnerships Enabling Access to Research Capacity

DNDi has helped to establish two disease-specific platforms (HAT and VL) in Africa, that develop clinical research capacity in endemic regions. DNDi has also attracted quality R&D partners for all stages of drug development: from the many partners of the Pan-Asian Natural Products Screening Platform to a late-stage industrial partner like sanofi-aventis to develop and distribute ASAQ.

• Policy

Government support is essential to sustain needs-driven R&D for new health tools and to implement effective interventions when available. DNDi advocates that governments set needs-driven global health R&D priorities and create novel funding mechanisms to support essential health R&D (visit www.researchappeal.org). Funding for neglected diseases drug R&D by DNDi has been secured from a number of governments including France, the Netherlands, and the UK.

To learn more about DNDi's activities, please visit www.dndi.org.

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□ Innovative Partnership

■ sanofi-aventis

Sanofi-aventis is one of the **world leaders in the pharmaceutical industry, ranking number 1 in Europe**. The Group operates in more than 100 countries. Net sales reached **28.4 billion euros in 2006**, of which 25.8 billion euros in **pharmaceuticals** and 2.5 billion euros in **vaccines**.

Sanofi Pasteur, the vaccines business of the sanofi-aventis Group, sold more than a billion doses of vaccine in 2006, making it possible to protect more than 500 million people across the globe, which is about 1.5 million per day. The company offers the broadest range of vaccines, providing protection against 20 bacterial and viral diseases.

Sanofi-aventis is present in **7 major therapeutic areas**: Metabolic Disorders, Cardiovascular, Thrombosis, Central Nervous System, Oncology, Internal Medicine and Vaccines.

• Top 15 Drugs

Drug	Therapeutic area	2006 net sales (M €)
Lovenox®	Thrombosis	2,435
Plavix®	Thrombosis	2,229
Stilnox®/Ambien®	Central Nervous System	2,026
Taxotere®	Oncology	1,752
Eloxatin®	Oncology	1,693
Lantus®	Metabolism	1,666
Copaxone®	Central Nervous System	1,069
Aprovel®	Cardiovascular	1,015
Tritace®	Cardiovascular	977
Allegra®	Allergy	688
Amaryl®	Metabolism	451
Xatral®	Urology	353
Actonel®	Osteoporosis	351
Depakine®	Central Nervous System	301
Nasacort®	Allergy	283

• Vaccines

Vaccines	2006 net sales (M €)
Polio/Whooping Cough/Hib Vaccines	633
Adult Booster Vaccines	337
Influenza Vaccines	835
Travel Vaccines	239
Meningitis/Pneumonia Vaccines	310
Other vaccines	179
TOTAL	**2,533**

• Research & Development (R&D)

With a budget of **4.4 billion euros in 2006**, the Group's R&D portfolio includes 125 projects in development. forty-six of those projects are in late-stage development phases - phase II b and III. R&D activities are located at 28 places on 3 continents.

• Stock Market

The Group is listed in Paris (EURONEXT: SAN) and in New York (NYSE: SNY), and is **one of the largest market capitalizations in Paris**.

□ Background on malaria

Malaria, one of the three most important diseases in Africa according to WHO,[10] is a major cause of morbidity and mortality worldwide, especially in developing countries where it has serious economic and social costs. The disease is present in over 100 countries and threatens half of the world's population.[11]

Every year, 350 to 500 million cases of malaria occur worldwide, with over 1 million deaths, affecting mostly children in sub-Saharan Africa. The child death rate from malaria doubled between 1990 and 2002.[12] Malaria remains the single largest cause of death for children under five in Africa, where it kills one child every 30 seconds – this translates to the deaths of approximately 3,000 children every day.[13]

Malaria is caused by a parasite, called *Plasmodium*, that is transmitted from man to man by the bite of anopheline mosquitoes. Four species of the parasite are involved: *Plasmodium falciparum, P. malariae, P. vivax and P. ovale.* The most common and most dangerous species is *P. falciparum*.

• Malaria and poverty

Malaria and poverty are interrelated in a vicious circle:

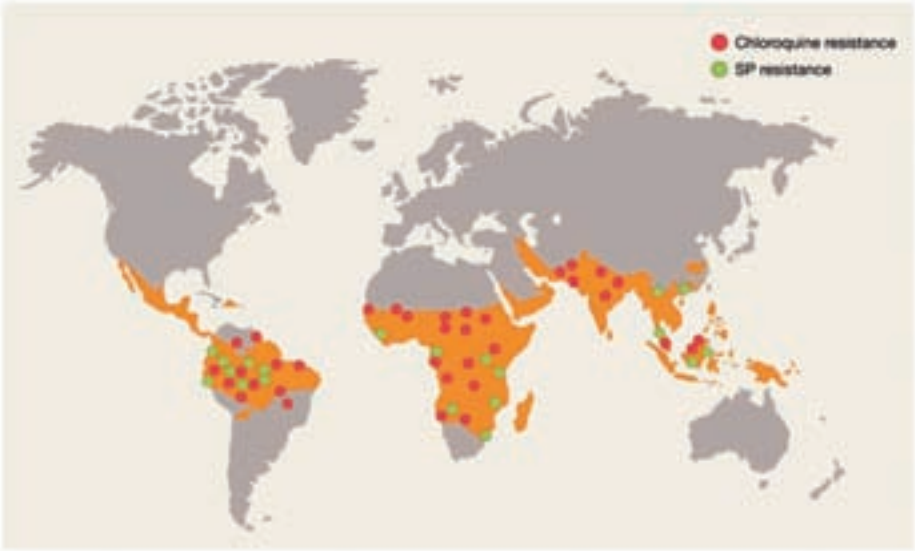
□ Malaria thrives where uncontrolled water spots and warm temperatures enable Anopheles mosquitoes to breed, and where infected patients act as parasite reservoirs. These conditions - which once existed in the United States, Australia and Southern Europe - are common in many parts of the developing world.

□ Malaria deepens poverty: patients are often bedridden and incapable of carrying out normal daily activities. Malaria is thought to slow annual economic growth by 1,3% in African countries with high prevalence of malaria.[14] The economic cost of malaria in Africa is estimated at $12 billion every year.[15]

• Treatments for malaria

Treatments exist but, in recent decades, drugs such as chloroquine or sulphadoxine-pyrimethamine have become increasingly ineffective due to drug resistance.

Resistance to chloroquine now reaches over 90% in many parts of Africa. The spread of resistance is a serious threat to global public health (see map below).



Source: WHO, 2005

10. Data on the Roll Back Malaria website – WHO: http://www.rbm.who.int/ consulted in September 2006.
11. World Health Organization. World Malaria Report. Geneva: WHO ; 2005, Introduction.
12. Global Forum for Health Research. Monitoring Financial Flows for Health Research. Geneva: 2005, p. 59.
13. Global Forum for Health Research. Monitoring Financial Flows for Health Research. Geneva: 2006, p. 91.
14. Gallup J and Sachs JD. The economic burden of malaria. Am J Trop Med Hyg 2001 ; 64: 85-96, p. 19.
15. Sachs J and Malaney P. The economic and social burden of malaria. Nature 2002 ; 415: 680-5.

As a response to increasing levels of resistance to antimalarial medicines the World Health Organization (WHO) since 2001 has actively encouraged malaria-endemic countries to use combination therapies, preferably those containing artemisinin derivatives (ACTs – artemisinin-based combination therapies), and to fixed-dose combinations when possible.

Why the need for fixed-dose combinations?

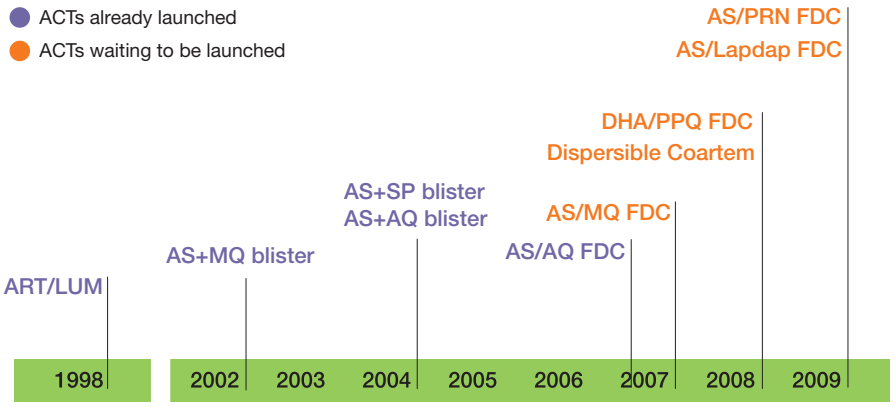
Compliance to treatment is essential to ensure treatment effectiveness and to prevent future resistance to ACT. But when combinations are provided as two separate drugs, patients might take only of one the two drugs or fail to complete the whole course. Taking one drug without the other increases the risk of resistance. Fixed-dose combinations (FDC's) combine two drugs into one tablet, instead of separate tablets, to ensure that the patients take both drugs in the right dose.

What is the current state of drug R&D for malaria?

Between 1975 and 2004, only 7 of 1393 new chemical entities (NCE's) approved were targeted at malaria.[16]

Worldwide, several compounds are at various stages of antimalarial drug development around the world, with the Medicines for Malaria Venture (MMV) being a key partner in many of these projects. Sanofi-aventis currently has several active projects. The most advanced one is ferroquine, a compound that is active against chloroquine-resistant falciparum and currently in phase II clinical development.

A number of new ACTs will be launched between 2007 and 2009



Source : WHO, 2005

The immediate availability of ASAQ represents a key development in the efforts to roll back malaria by reducing the likelihood of resistance, thereby contributing to the efforts to make available a number of ACTs for the management of malaria in the future.

16. Chirac P, Torreele E. Global framework on essential health R&D. Lancet. 2006 ; 367 : p. 1560.