

The story of ASAQ: the first antimalarial product development partnership success

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Introduction

ASAQ, the new fixed-dose combination of artesunate (AS) and amodiaquine (AQ), is now available to treat malaria throughout sub-Saharan Africa. The first drug developed by the FACT (fixed-dose, artemisinin-based combination therapy) partners, ASAQ is being made available by the non-profit product development partnership, Drugs for Neglected Diseases initiative (DNDi), in partnership with pharmaceutical company, sanofi-aventis.

ASAQ is an innovative product to treat malaria that is: adapted to the needs of patients of all ages and is a fixed combination of two well-known drugs. Following World Health Organization (WHO) recommendations it uses a simple once-a-day regimen; is easy to manage for the clinician and the patient; is accessible at an affordable price (as a non-patented drug); and is of high quality, in terms of production, packaging and stability.

The development of ASAQ can serve as a model for future drug development to treat neglected diseases. It is important therefore to understand the rationale and the process behind the development; the partners involved in the development, production and promoting availability; and the steps taken in the registration and post-registration phases to ensure that ASAQ reaches the populations who can most benefit from it.

Public health need for improved antimalarial treatments

Globally, approximately 3.6 billion people are at risk of malaria,¹ with 60% of an estimated 350 to 500 million clinical disease episodes occurring annually in sub-Saharan Africa.² In Africa, malaria remains the single largest cause of death for children under the age of five years, where it kills one child every 30 seconds; or approximately 3000 children every day.³ Efficacy studies have shown evidence of rising resistance of *Plasmodium falciparum* to the antimalarial drugs chloroquine and sulphadoxine/pyrimethamine (SP); both widely used for the treatment of uncomplicated malaria.^{4,5}

In response to increasing inefficacy of chloroquine and with the aim of slowing the spread of drug resistance in malaria-endemic regions,⁶ WHO in 2001 recommended the worldwide abandonment of chloroquine and the use of artemisinin-based combination therapies (ACTs) as first-line treatment for uncomplicated falciparum malaria. The combination of artesunate (AS) plus amodiaquine (AQ) was

recommended specifically for Africa, based on clinical evidence that had been compiled by the United Nations Development Programme (UNDP)/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) starting in 1998. Figure 1 shows the countries where ASAQ could be of potential benefit.

In 2006, WHO developed guidelines for the use of ACTs as first-line treatment for falciparum malaria everywhere, and in fixed-dose combinations (FDCs) when possible.⁷ FDCs, which are user-friendly drug regimens,⁸⁻¹¹ have the potential advantages of improving patient compliance and dosing accuracy;¹² eliminating the risks associated with monotherapy;^{13, 14} improving drug safety, effectiveness and acceptability¹²; thereby slowing down the development of resistance to ACTs;¹⁵ and being less expensive than the sum of the individual products as separate tablets or blister packs.¹⁶

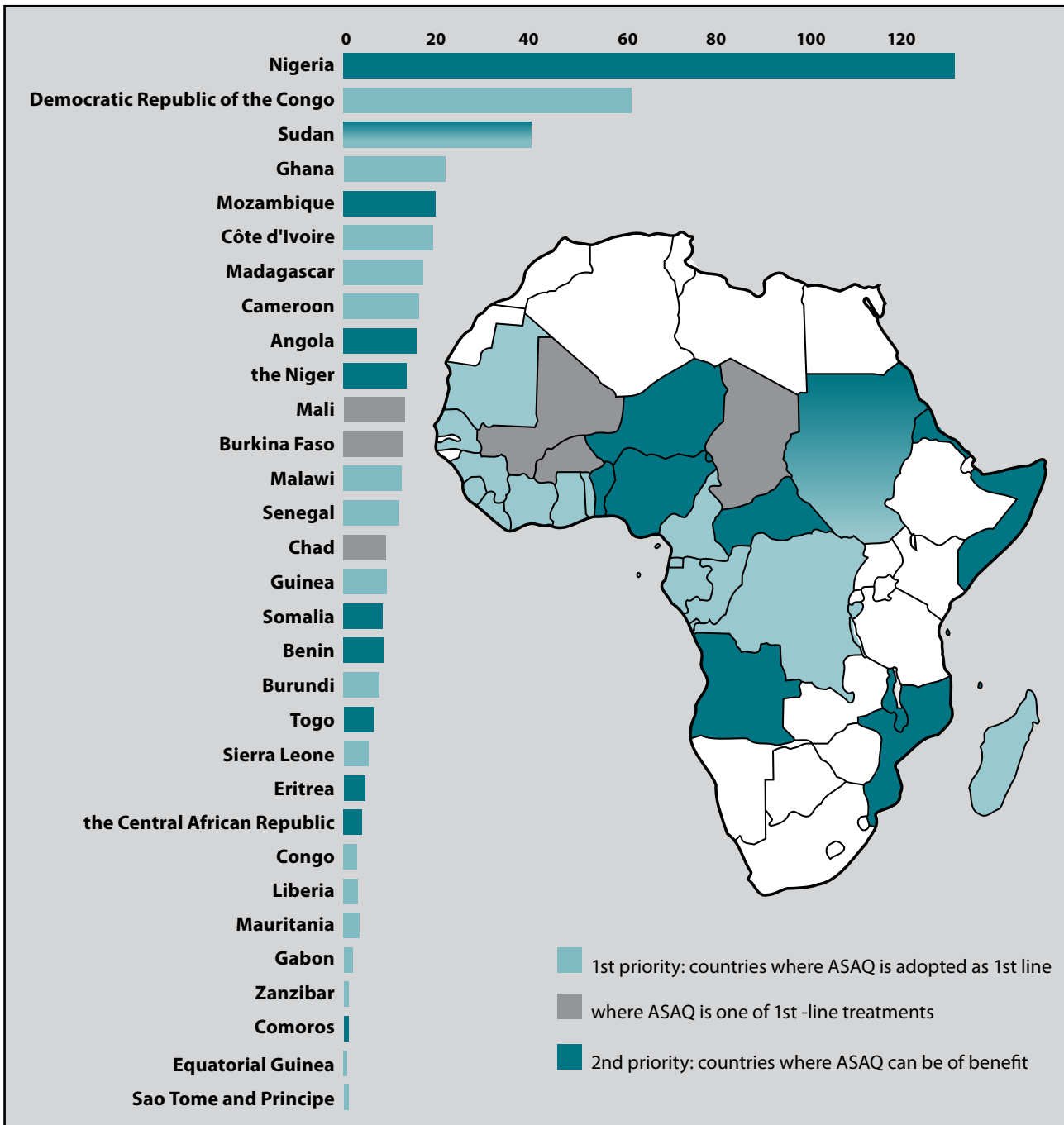
In view of the immediate need to secure changes in antimalarial treatment policy,¹⁷ the FACT project commenced in 2002 to develop two fixed-dose ACTs, including a fixed-dose combination of AS+AQ for international registration that would improve compliance and would be available to all countries where resistance to amodiaquine was low (mainly African countries, but also some Asian countries such as India and Indonesia). Efforts were coordinated by TDR and the Drugs for Neglected Diseases Working Group (DND-WG), which evolved into DNDi in 2003. The development of a fixed-dose combination of AS and AQ was completed by the FACT partners in collaboration with the world's fourth-largest pharmaceutical company, sanofi-aventis, following an agreement signed in December 2004.

Scientific evidence in support of ASAQ

AS and AQ are well-known drugs. Scientific evidence supporting the use of the combination of AS and AQ can be divided into two groups: studies supporting the use of non-fixed-dose combinations of AS plus AQ; and studies supporting the use of fixed-dose combinations (FDC) of ASAQ. Multiple studies have cumulatively included approximately 10 000 patients taking the combination of AS and AQ.

In two separate field studies, which have cumulatively studied ~1500 patients in five sub-Saharan African countries, the documented efficacy of fixed-dose ASAQ has been >95% comparable with both the non-fixed dose combination¹⁸ as well as with Coartem, the only other available fixed-dose ACT. Table 1 outlines the major studies supporting the use of ASAQ.

Figure 1.
Potential public health impact of artesunate + amodiaquine in Africa











The partnership to produce ASAQ

The FACT-ASAQ project, modeled with core and support partners, is considered an innovative partnership because ASAQ has been produced as a “non-exclusive, not-patented, not-for-profit public good” and because developing and developed countries have shared assets and capabilities to produce ASAQ.

The FACT-ASAQ project was facilitated by the extensive research networks built primarily by the two coordinators (MSF, later DNDI; and TDR) with a number of critical partners: Centre National de Recherche

et de Formation sur le Paludisme (CNRFP), Mahidol University, Université Victor Segalen Bordeaux II (TROPICAL), University of Oxford, and University Sains Malaysia (Table 2). All partners contributed their technology, experience, relevant assets, and in some cases finances, to various aspects of the project. When necessary, protocols, scientific methods and other information were discussed and disseminated as part of the training and technology transfer among the partners. In addition to these partners, other organizations, including contract research organizations (CROs) and some smaller pharmaceutical companies, also contributed to the project.

Figure 2. Simplified dosing regimen with fixed-dose ASAQ. The bi-layer formulation of ASAQ allows for AS and AQ to be taken together, in correct proportions, and with less tablets as compared with non-fixed dose options

	Fixed-dose ASAQ artesunate/amodiaquine 3 dosage strengths available	Co-blistered, non-fixed AS+AQ artesunate/amodiaquine AS: 50mg; AQ: 13mg
Infants (<8 kg)	 AS: 25 mg AQ: 67.5 mg	
Young children (8–17 kg)	 AS: 50 mg AQ: 135 mg	
Children (17–35 kg)	 AS: 100 mg AQ: 270 mg	
Adults (>35 kg)	 AS: 100 mg AQ: 270 mg	

Since the end of 2004, DNDi and the FACT partners have collaborated with sanofi-aventis. Existing data – including the stable ASAQ formulation developed by the FACT partnership – was exchanged with sanofi-aventis, who then carried out additional pre-clinical and clinical studies, which were used to compile the marketing authorization application and/or registration file.

As with most product development partnerships (PDPs), funding for the development and production of ASAQ came from both public (original public donors, EU INCO DEV FP5,²² and TDR have been joined by the following governments: Dutch DGIS,²³ French AFD,²⁴ Swiss SDC,²⁵ and UK DFID²⁶) and private sources (MSF and sanofi-aventis). In the unprecedented agreement signed between DNDi and sanofi-aventis, no patent protection was sought, and a non-exclusivity agreement was signed between the two parties. Non-exclusivity implies that a marketing authorization will enable third parties to submit simplified applications for a generic version of the drug. ASAQ is being provided for the benefit of underprivileged patients, and both DNDi and sanofi-aventis intend wide distribution across malaria-endemic regions.

Getting ASAQ to the patients who need it

Without compromising drug quality, efficacy, or safety, sanofi-aventis, with the support of DNDi, chose to register ASAQ in Morocco and in malaria-endemic countries as well as to apply for WHO prequalification, in order to allow internationally recognized experts to assess the quality, safety and efficacy of ASAQ. sanofi-aventis manufactures ASAQ and has followed the customary approach to first register a drug in the country of manufacture and to register the

brand (in this case, Coarsucam®). The registration process started in December 2005, with marketing authorization granted on 1 February 2007. As of July 2007, ASAQ has also been registered in 17 African countries (Benin, Burkina Faso, Cameroon, Central African Republic, Chad, Congo, Democratic Republic of Congo, Gabon, Ghana, Guinea, Ivory Coast, Kenya, Madagascar, Mali, Mauritania, Tanzania (Zanzibar) and Togo). The WHO prequalification process has been chosen based on WHO's regulatory documentation on artesunate and on amodiaquine: Arsumax® (sanofi-aventis artesunate) is already WHO prequalified. The prequalification dossier was submitted to WHO on 23 February 2007.

ASAQ is packaged as Artesunate-Amodiaquine Winthrop® (ASAQ) in boxes of 25 individual blisters at cost price (<US\$ 0.50 for children less than 5 years of age and <US\$ 1 for older children and adults – constituting a 'no profit, no loss' price) to the public market (national health services and nongovernmental organizations) in malaria-endemic countries. The drug is also available as Coarsucam™ in individual boxes to the private market at prices adapted to local markets, and Coarsucam™ Impact Malaria (boxes of 25 blisters) for the sanofi-aventis Access Card Program (CAP)²⁷ pharmacies. This tiered form of pricing is aimed at protecting the different antimalarial markets, while offering uniform quality of the same drug. It can be described as a 'one drug, two prices, three packaging' arrangement.

In working to facilitate the implementation and availability of ASAQ, DNDi is engaging a number of partners, including individual experts, countries and regions, WHO and other international organizations, national malaria programmes, research institutes, contract research organizations, funding agencies, and nongovernmental

Table 1.
Studies examining ASAQ

Study name	Study location & duration	Patient population	Primary objective	Major findings
Artesunate and amodiaquine for the treatment of uncomplicated falciparum malaria: a systematic review of safety and efficacy data. ¹⁹	19 countries (18 African). Relevant studies took place from 1999–2006.	Meta-analysis reviewed 27 comparative studies: 4173 patients on AS+AQ and 6477 on a comparator drug.	A systematic review of all documented studies evaluating the efficacy and safety of AS+AQ for uncomplicated falciparum malaria.	For relevant studies (not all had 28-day PCR-corrected data nor robust safety data): AS+AQ more effective than single agent treatment or non-artemisinin-based combinations. AS+AQ day 28 cure rates after PCR correction similar to other ACTs. AS+AQ “well tolerated”.
Use of weight-for-age data to optimize tablet strength and dosing regimens for ASAQ for treating falciparum malaria. ²⁰	Sub-Saharan Africa. March 2006.	Weight-for-age reference database of 88 054 individuals from sub-Saharan Africa. Data taken from demographic health surveys, observational and intervention studies, and standardized for sex, age and malaria risk.	To design a practical age-based dosing regimen that provides the smallest risks of over- and under-dosage by minimizing the number of age categories and maximizing the proportions of patients predicted to receive doses of AQ and AS within newly defined therapeutic ranges.	Optimal paediatric strength (p): 25/67.5 mg AS/AQ. Optimal adult strength (a): 100/270 mg AS/AQ. Overall dosing accuracy of 83.4% and 99.9% for amodiaquine and artesunate, respectively, was seen with regimen of five age categories: 0–1 months: ½ p 2–11 months: 1 p 1–5 years: 2 p 6–13 years: 1 a > 14 years: 2 a
A comparative clinical assessment of fixed-dose artesunate/ amodiaquine (ASAQ), versus loose formulation of artesunate + amodiaquine. ¹⁸	Burkina Faso. October 2004–February 2006.	750 children with acute uncomplicated falciparum malaria. Aged 6 to 59 months, ≥5kg.	To evaluate the efficacy of ASAQ as compared with the non-fixed combination (AS+AQ) in terms of PCR-corrected parasitological cure rate on day 28. Safety also assessed.	Efficacy Fixed-dose ASAQ cure rate: 95.7%. Non-fixed-dose AS+AQ cure rate: 96%. Safety No unexpected adverse events occurred during this study, with the FDC easier to use and well tolerated.
Comparison of fixed-dose combinations, artesunate/ amodiaquine (ASAQ) versus artemether-lumefantrine (AL), in the treatment of uncomplicated falciparum malaria. ²¹	4 countries: Cameroon, Madagascar, Mali, Senegal. March–December 2006.	941 patients including 437 children infected with <i>P. falciparum</i> . Adults or children weighing ≥10kg.	To evaluate the efficacy (clinical and PCR-corrected parasitological cure rate on day 28 of ASAQ compared with AL (Coartem®)).	Preliminary results show >95% PCR-corrected cure rate at day 28 for both fixed-dose ASAQ and ARLUM, with good clinical and biological safety seen.

Table 2.
Key partners responsible for the development of ASAQ

Development step	Institutions involved
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 (United Kingdom) / Mahidol University (Thailand).
Pharmaceutical and preclinical development	Pharmaceutical and preclinical development
Preformulation of fixed-dose combinations of ASAQ by developing fixed-ratio oral forms, coordination and local support with partners in the Bordeaux region.	Tropival of Université Victor Segalen Bordeaux II (France).
Formulation of combination product adapted with appropriate stability and biopharmaceutical characteristics and with a viable manufacturing process. Development and validation of analytical methods. First scale-up coordinated with Rottendorf Pharma.	Ellipse Pharma (France).
Set of good laboratory practice-based 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 good manufacturing practice-based 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	Clinical development
Phase I for pharmacokinetic data, biopharmaceutical quality and bioavailability.	USM (Malaysia).
Field-based Phase III to examine efficacy and tolerability of fixed-dose ASAQ vs. non-fixed AS+AQ in children <5 years of age.	CNRFP (Burkina Faso). Cardinal Systems (France).
Support of 10-year survey of efficacy, tolerability, and pharmacovigilance in Senegal.	Institut de Recherche pour le Développement (IRD) (Sénégal), Ministère Français des Affaires Etrangères (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.

organizations. Such activities include for instance: the coordination of a study by its founding partner, the Indian Council of Medical Research, to facilitate the adoption of a new antimalarial policy in India; a regional workshop convened with another founding partner, the Kenya Medical Research Institute, to engage national malaria control programme managers and international and regional organizations; and the sponsorship of a tolerability study to be coordinated by MSF/Epicentre. DNDi has convened an independent panel of experts, the FACT Implementation Advisory Group, to provide independent advice and critical guidance about issues related to ASAQ implementation and rational use and towards ensuring equitable access. Also, DNDi will use the sanofi-aventis

payment (3% of the net private sector earnings over a period of seven years) to further lower the drug's public sector sale price.

Implications of ASAQ for development of other needs-driven drugs

DNDi was founded in 2003 as an independent, not-for-profit product development partnership (PDP) by five publicly-funded research organizations: Malaysian Ministry of Health, Kenya Medical Research Institute, Indian Council of Medical Research, Oswaldo Cruz Foundation in Brazil, and the Institut Pasteur in France, along with MSF and TDR (as permanent observer). DNDi is the first

initiative of its kind committed to fighting against the most neglected diseases (such as human African trypanosomiasis, leishmaniasis, and Chagas disease) which burden the developing world. As a patient-needs-driven, 'virtual' R&D organization, DNDi does not conduct research but instead capitalizes on existing fragmented R&D capacity, complementing it with additional expertise as needed. DNDi's project portfolio in June 2007 includes 22 projects at different stages of development.

DNDi anticipates the launch of the second product of the FACT partnership: an FDC of AS and mefloquine (MQ) targeted for South-East Asia and Latin America. Having developed ASMQ in collaboration with Farmanguinhos (a state-owned pharmaceutical company in Brazil), DNDi will manufacture, register, and market the

drug in collaboration with Cipla, a major pharmaceutical company in India, for South-East Asia. A major impetus to undertake this project was that the loose combination of AS and MQ has been widely used in Thailand for the past 13 years, and has been proven to be effective and safe for the treatment of uncomplicated falciparum malaria in South-East Asia and Latin America.²⁸⁻³¹

The successful launch of ASAQ is clear evidence of DNDi's progress as a PDP, whose strength lies with its focused management of private and public partners. By virtue of the success of the FACT project, PDPs have been clearly demonstrated as being capable of producing public goods.

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Biographies



Bernard Pécoul, Executive Director of the Drugs for Neglected Diseases initiative (DNDi), has served as a physician with Médecins Sans Frontières (MSF) and has managed public health projects in Honduras, Malaysia and Thailand. Co-founder and Director of Research and Training at Epicentre, he also served as Executive Director of the French section of MSF, overseeing 100 field projects in 40 countries. From 1998 to 2003, he was Executive Director of the MSF Campaign for Access to Essential Medicines, where he advocated for policies to lower drug prices, increase research into neglected diseases, and re-produce unprofitable but medically necessary drugs.

Ann-Marie Sevcsik, Scientific Communications Manager at the Drugs for Neglected Diseases initiative (DNDi), has worked in medical communications for the past three years after doing medical, molecular research on hepatitis and HIV during graduate work at the University of California, San Francisco, and undergraduate studies at Harvard University.

John Amuasi, a frequent consultant with the Drugs for Neglected Diseases initiative (DNDi), trained as a physician in Ghana and recently graduated from the University of Minnesota in the USA with a masters in health policy.

Graciela Diap is Medical Coordinator for the new fixed-dose combination of artesunate and amodiaquine (ASAQ) in the new Fixed-dose Artesunate-based Combination Therapies to treat *falciparum* malaria (FACT) project and facilitated and accelerated the optimal implementation of ASAQ in Africa. Trained in internal medicine, she has spent 15 years working with MSF.

Jean-René Kiechel, Manager of the new Fixed-dose Artesunate-based Combination Therapies to treat *falciparum* malaria (FACT) project, has gained over 30 years experience in pharmaceutical research and development (R&D) since earning a PhD in Chemistry (minor in Pharmacology) from the University of Basel in Switzerland. He has worked in various industry-based scientific management positions in France, Switzerland and the USA with Sandoz, Bristol-Myers Squibb, Rhone-Poulenc Rorer, and sanofi-aventis, and has contributed to the successful registration of half a dozen drugs and several investigational new drug (IND) applications.