Pioneering ways of working
through innovative partnerships

2002-2015

THE SUCCESSFUL DEVELOPMENT OF A FIXED DOSE COMBINATION OF ARTESUNATE PLUS AMODIAQUINE ANTIMALARIAL

OCTOBER 2015

DNDi

Drugs for Neglected Diseases *initiative*

When the Drugs for Neglected Diseases Working Group decided to work on malaria projects in 2002, there was an urgent need for a project with rapid impact - particularly for children, as those under five years old have always accounted for the vast majority of deaths from the disease[1]. The first ever fixed dose combination of ASAQ was to be a safe and effective treatment, designed to be a simple regimen of 1 or 2 tablets once a day for 3 days, easy to swallow, so as to ensure good compliance and correct dosing. It also needed to be stable to tropical environments - as it was to be used principally in Africa - affordable, and available as a public good in all malaria-endemic countries through an unrestricted license.

BACKGROUND

At the beginning of the current millennium the malaria epidemic was growing inexorably, claiming around 1.6 million lives yearly[2]. Overreliance on single-agent antimalarial treatments had led to the emergence of parasite resistance against older drugs, and a 'malaria disaster' loomed[3]. In 2001 the World Health Organization (WHO) recommended that artemisinin derivatives, the most recent and potent antimalarial drugs, are to be used in combination therapies (artemisinin combination therapy, ACT) as first-line treatment of uncomplicated *Plasmodium falciparum* malaria[4].

Origins and Objectives of the Fixed-Dose Artesunate Combination Therapy (FACT) Consortium

The Drugs for Neglected Diseases (DND) Working Group was constituted in 1999 by the Médecins Sans Frontières (MSF) Access Campaign, which assembled the team of international experts to review the R&D health needs of patients in developing countries, resulting in the publication of a key document - the Fatal Imbalance Report[5] - describing the lack of R&D into drugs for diseases that affect neglected populations.

In response to increasing drug resistance to antimalarials and the WHO call for ACTs, MSF, along with WHO's TDR[6] and other partners, established the Fixed-Dose Artesunate Combination Therapy project (called "FACT" afterwards) in 2002, with the objective of developing two ACTs: the initiative to develop ACT FDCs was taken prior to the WHO's issuance in 2006 of further guidelines calling for an immediate halt to artemisinin monotherapy[7]. In 2003, upon the recommendation of MSF's DND Working Group, the Drugs for Neglected Diseases *initiative* (DND*i*) was created and took on management of the malaria projects.

Choosing drugs to develop as fixed dose combinations

With the aim of getting affordable, adapted treatments to patients as quickly as possible, combinations of existing treatments were considered because of previously documented evidence of use and their advantageous price. A series of clinical trials sponsored primarily by WHO-TDR, the Wellcome Trust and Epicentre refined the choice to artesunate (AS) in combination with either amodiaquine (AQ), mefloquine (MQ) or sulfadoxine/pyrimethamine (SP). A choice of the best development candidates had to be made and, because malaria experts considered AS+SP to be an interim solution only due to rising SP resistance, the decision was taken to develop two combinations of AS, with AQ and MQ. Based on their use in non-fixed combinations, ASAQ FDC was targeted principally for use in Africa, and ASMQ principally for Asia and Latin America.

(1) 'World Malaria Report' By World Health Organization. www.who.int/malaria/publications/world_malaria_report/en/, 2014.
(2) 'Global malaria mortality between 1980 and 2010: a systematic analysis' By C.J. Murray *et al. Lancet*, Volume 379, Issue 9814, 2012, pp. 413-431, DOI: 10.1016/S0140-6736(12)60034-8.
(3) 'Averting a malaria disaster' By N.J. White *et al. Ibid.* Volume 353, Issue 9168, 1999, pp. 1965-1967.
(4) 'Antimalarial Drug Combination Therapy. Report of a WHO Technical Consultation' By World Health Organization. 2001.
(5) 'Fatal Imbalance: The Crisis in Research and Development for Drugs for Neglected Diseases' By DND Working Group. tinyurl.com/oo5g8h3, 2001.
(6) 'WHO-TDR is the Special Programme for Research and Training in Tropical Diseases, hosted by the WHO and now sponsored by the United Nations Children's Fund (UNICEF), the United Nations Development Programme (UNDP), the World Bank in addition to the WHO.
(7) 'WHO briefing on Malaria Treatment Guidelines and artemisinin monotherapies' By World Health Organization. 2006.

Artesunate and amodiaquine

Artesunate (AS) and amodiaquine (AQ) have distinct mechanisms of action and their pharmacokinetic/pharmacodynamic (PK/PD) characteristics are complementary: AS rapidly and substantially reduces the parasite burden and has a very short half-life (20-45 minutes[8]), whereas AQ (or rather its principal, active metabolite desethylamodiaquine) has a much longer half-life (about 6-18 days[9]) ensuring that it acts long enough to kill any remaining parasites, preventing recrudescence. The artemisinin component in ACTs reduces transmissibility to mosquitoes because of their profound effect on gametocytes, the form of the parasite taken up by mosquitoes and required to complete *Plasmodium's* life cycle. Moreover, an extensive body of human pharmacological data existed for both AS and AQ.

Amodiaquine has been in use since the 1970s for the treatment and prophylaxis of malaria, notably in travellers. The drug was included in the WHO Essential Drug List (EDL) in 1977, removed in 1979 and replaced by CQ, reinstated in 1982 and removed again in 1988 in view of safety concerns in prophylactic use. When used at high doses and prophylactically, AQ had been associated with severe hepatitis and severe neutropenia, including some deaths. By contrast, field experience suggested these toxicities were not evident when malaria patients were treated with AQ.

Given its chequered history when used at different doses and uses, and the need to broaden treatments against CQ-resistant *falciparum* malaria, a systematic review of AQ was conducted[10]. This review confirmed AQ's good tolerability at total doses of up to 35 mg/kg over 3 days and its efficacy, suggesting a role for AQ in the treatment of malaria. Indeed, guided by additional data on AQ the WHO reinstated AQ onto the EDL in 2003. In spite of this re-assessment the 'ghosts from the past' concerning AQ's toxicity were the focus of the FACT Team's vigilance, and a specific Risk Management Plan was subsequently implemented for the Project.

THE DEVELOPMENT OF A SIMPLE, PATIENT-ADAPTED TREATMENT

FDCs are user-friendly drug regimens that have the advantage of reducing the number of tablets to be taken, improving patient compliance and dosing accuracy while ensuring that both components of the ACT are taken by the patient at the intended dose, and are less expensive than the sum of the individual products as separate tablets or blister packs. Moreover, their use prevents the development of resistance to the ACT component drugs[11].

Defining the product profile: the road to innovation for the benefit of patients

With patients' needs in mind, a target product profile (TPP) for ASAQ was developed for a simple to use treatment with a fixed-dose, fast-release, oral formulation for adults and children, including those from six months of age. The FDC had to be properly adapted for field use: formulated for extended stability in tropical conditions and irregular supply lines, with a simplified set of regimes for adult/paediatric use and packaged with the goal of minimizing confusion for optimal use in patients. Dose ranges and tablet strengths were to be adapted for use in infants, children and adults, to be a simple regimen of 1 or 2 tablets once a day for 3 days. Minimizing excipient quantities and compacting the API (active pharmaceutical ingredient) would keep the tablets small, and facilitate administration. The tablets also needed to be able to rapidly disintegrate in aqueous liquids to ease dose administration to infants in a small volume of water. A single daily dose was considered essential to maximise adherence, especially for children dependent on a caregiver to administer the drugs. Finally, the treatment had to be affordable (< 1 USD per adult patient), to ensure widespread access.

(8) 'Review of the clinical pharmacokinetics of artesunate and its active metabolite dihydroartemisinin following intravenous, intramuscular, oral or rectal administration' By C.A. Morris *et al. Malar J*, Volume 10, 2011, p 263, DOI: 10.1186/1475-2875-10-263.

(9) 'Pharmacokinetics and tolerability of artesunate and amodiaquine alone and in combination in healthy volunteers' By C. Orrell *et al. Eur J Clin Pharmacol*, Volume 64, Issue 7, 2008, pp. 683-690, DOI: 10.1007/s00228-007-0452-8.

(10) 'Systematic review of amodiaquine treatment in uncomplicated malaria' By P. Olliaro *et al. Lancet*, Volume 348, Issue 9036, 1996, pp. 1196-1201, DOI: 10.1016/S0140-6736(96)06217-4.

(11) 'A major transition in malaria treatment: the adoption and deployment of artemisinin-based combination therapies' By A. Bosman *et al. Am J Trop Med Hyg*, Volume 77, Issue 6 Suppl, 2007, pp. 193-197.

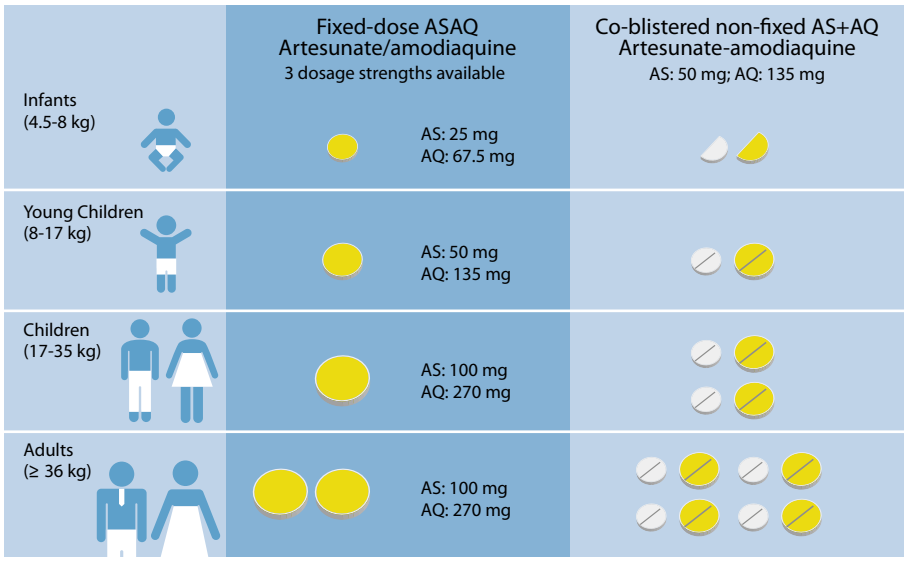
Dose optimisation using age and weight dosing categories: the case of infants and small children

The FACT team involved in specifying ASAQ FDC tablet strengths sought to achieve simple, easy-to-use, safe, and effective drug exposure levels across all age groups using age and weight dosing bands[12]. This consideration was crucial because weighing scales are not available widely and patients or their carers often buy drugs from the informal private sector. Two key elements of the age/weight dosing scheme were, firstly, the need to minimize the number of tablets (to be achieved using one or two low- and high-dose tablets), and, secondly, to maximize the proportion of patients who would receive doses inside of the designated therapeutic dose range (achieved by modelling). The simplified age/weight dose regimen kept the ratio of the APIs the same, facilitating manufacturing. In order to prevent confusion three tablets were manufactured with different diameters - for infants, children, and adults - rather than with varying thickness. Furthermore, the formulation allows fast dissolution of the paediatric product in water, making it easier to administer to infants and small children, and obviating the need for a distinct paediatric formulation. Tablets disperse in taste-masked (sugary) water to overcome AQ bitterness, an approach that is preferred over the distribution of medicines as syrups and suspensions, which are difficult to dose correctly and incur high costs and complications for stability, storage, and transport.

THE DEVELOPMENT OF AN INNOVATIVE ASAQ FDC FORMULATION

The innovative PDP model in the context of which the project was executed was driven by the FACT team and involved a number of partners (see table page 5)

DOSING REGIMENS FOR ASAQ



FACT: AN INNOVATIVE PUBLIC AND PRIVATE PARTNERSHIP

The FACT project pioneered the Product Development Partnership (PDP), a form of public-private partnership (PPP), by bringing together a number of malaria and pharmaceutical development experts - from pharmaceutical companies (large and start-up), non-governmental organisations (NGOs), academia, private and public sponsors who operate in the disease-endemic countries or globally - to collaborate in a flexible, 'virtual' model. The FACT team led and ensured continuity throughout the project, which involved almost the full range of activities associated with drug development, from formulation work through to post registration pharmacovigilance. Initial funding was provided by the EU INCO-DEV Program with other funding bodies involved as the project evolved. Specific subgroups met to oversee the various activities, and input was sought from the WHO, country malaria control programmes, and the Pan-African Conference Against Malaria (APALP). Experts were brought in on an *ad hoc* basis as needs arose. The direct, open dialogue between partners who normally do not work together promoted creativity and 'out of the box thinking' required to overcome the many challenges that arose. FACT team meetings were always kept small and agile involving the relevant key participants, to achieve effective decision-making in a transparent environment. Information was shared not only in these meetings but also through bi-annual progress reports distributed to the extended FACT team.

THE INDUSTRIAL PARTNER: SANOFI

A key element to the success in developing ASAQ was the partnership, from December 2004 onwards, with the industrial partner, Sanofi-Aventis (nowadays known as Sanofi). Once a stable formulation had been identified, the FACT team needed an industrial partner to shoulder the required R&D efforts and to register, manufacture, and distribute the product. Initial discussions had been held with Pfizer, who had generously donated some AQ at the beginning of the development. Sanofi had already initiated a programme to develop a FDC of AS and AQ in 2002, but were still looking for developable formulations with sufficient stability. Also, the company had already been providing AS (branded as Arsumax®), AQ (Flavoquine®) and an AS+AQ co-blister (Arsucam®) to African countries.

(12) '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' By W. Taylor *et al. Bull World Health Organ*, Volume 84, Issue 12, 2006, pp. 956-964.

PARTNERS INVOLVED IN THE FACT PROJECT AND THEIR ROLES

Development Step	Institutions involved
Pharmaceutical and Preclinical Development	
Vital expert advice to the efforts of the FACT Project throughout the entire period of development	University of Oxford/Mahidol University, Thailand TDR
Financial and technical support of initial pharmaceutical development	TDR University of Bordeaux, France
Pre-formulation, coordination and local support with partners in Bordeaux region	Faculty of Pharmacy, Université Victor Segalen Bordeaux 2 (TropiVal), France
Formulation of the combination product adapted with appropriate stability, biopharmaceutical characteristics, and with a viable manufacturing process	Ellipse Pharma, France
Development and validation of analytical methods for pharmaceutical development	Universiti Sains Malaysia (USM), Malaysia Ellipse Pharma, France
Biobatches and first scale-up, coordinated with Rottendorf Pharma, Germany	Ellipse Pharma, France
Set of GLP toxicology studies on single drugs and combinations	Unitox and Genotox, Brazil
Extended PK and toxicological evaluation of the combination in animals	Sanofi
Development and utilization of toxico-kinetic protocols, bio analytical methods, assay development, and first pharmacokinetic studies[13,14]	Universiti Sains Malaysia
First industrial scale-up and GMP production of the FDC for clinical and stability studies	Rottendorf Pharma, Germany Créapharm, France Ellipse Pharma, France
Innovative partnership signed with industrial partner	Sanofi: Contract signed, December 2004
Bio-analytical determinations in clinical studies in Africa	Parexel/Synexel Laboratories SAS, Poitiers, France
Clinical Development	
Preliminary dosing design study	TDR with University of Liverpool (for dose determination)
Phase I for PK data, biopharmaceutical quality and bioavailability	Universiti Sains Malaysia
Field-based Phase III to examine efficacy and tolerability of ASAQ *vs* non-fixed AS+AQ in children < 5 years of age	Centre National de Recherche et de Formation sur le Paludisme (CNRFP) (Burkina Faso); Cardinal Health (France)
Financial and technical support of intervention research (field studies) in Senegal[15,16], and clinical evaluation in pregnancy[17]	TDR IRD
Support for 10-year survey of efficacy, tolerability, and pharmacovigilance in Senegal[18]	Institut de Recherche pour le Développement (IRD), Senegal; Ministère Français des Affaires Étrangères (FAC 2000 programme); Ministère Français de la Recherche (PAL+), France; 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
Comparative efficacy and safety (ATAQ EASY multicenter study in 941 patients in Cameroun, Mali, Madagascar, Senegal) with ASAQ and AL[19]	Sanofi with Principal Investigators of the countries
Access	
Industrial scale-up	Sanofi
Registration and Prequalification	Sanofi
Field studies and pharmacovigilance observations in Senegal	IRD, Senegal
Risk Management Plan 2007	Sanofi, MMV
Zenufa (technology transfer)	Zenufa, supported by DND*i*, AEDES, Bertin Pharma, Sanofi, Agence Française de Développement (AFD), MSF, DFID UK, and the Swiss agency for Development and Cooperation (SDC)

(13) 'Tolerability and pharmacokinetics of non-fixed and fixed combinations of artesunate and amodiaquine in Malaysian healthy normal volunteers' By V. Navaratnam *et al. Eur J Clin Pharmacol*, Volume 65, Issue 8, 2009, pp. 809-821, DOI: 10.1007/s00228-009-0656-1.

(14) 'Validation of high performance liquid chromatography-electrochemical detection methods with simultaneous extraction procedure for the determination of artesunate, dihydroartemisinin, amodiaquine and desethylamodiaquine in human plasma for application in clinical pharmacological studies of artesunate-amodiaquine drug combination' By C.S. Lai *et al. J Chromatogr B Analyt Technol Biomed Life Sci*, Volume 877, Issue 5-6, 2009, pp. 558-562, DOI: 10.1016/j.jchromb.2008.12.037.

(15) 'Efficacy and safety of artesunate plus amodiaquine in routine use for the treatment of uncomplicated malaria in Casamance, southern Senegal' By P. Brasseur *et al. Malar J*, Volume 6, 2007, p 150, DOI: 10.1186/1475-2875-6-150.

(16) 'Dosing accuracy of artesunate and amodiaquine as treatment for *falciparum* malaria in Casamance, Senegal' By P. Brasseur *et al. Trop Med Int Health*, Volume 14, Issue 1, 2009, pp. 79-87, DOI: 10.1111/j.1365-3156.2008.02190.x.,

(17) 'Probabilistic record linkage for monitoring the safety of artemisinin-based combination therapy in the first trimester of pregnancy in Senegal' By S. Dellicour *et al. Drug Saf*, Volume 36, Issue 7, 2013, pp. 505-513, DOI: 10.1007/s40264-013-0059-1.

(18) 'Anti-malarial drug safety information obtained through routine monitoring in a rural district of South-Western Senegal' By P. Brasseur *et al. Malar J*, Volume 11, 2012, p 402, DOI: 10.1186/1475-2875-11-402.

(19) 'Randomized, multicentre assessment of the efficacy and safety of ASAQ--a fixed-dose artesunate-amodiaquine combination therapy in the treatment of uncomplicated *Plasmodium falciparum* malaria' By J.L. Ndiaye *et al. Ibid. Volume 8*, 2009, p 125, DOI: 10.1186/1475-2875-8-125.

Overcoming challenges in combining AS and AQ in a single tablet: the stability challenge

Significant challenges emerged during formulation development when attempts were made to combine the two 'incompatible' APIs AS and AQ in a quality solid form as the starting point for a viable, scalable manufacturing process[20]. The water molecules that bind the AQ hydrochloride salt, high humidity, and high temperatures conspire to degrade AS. Ellipse Pharmaceuticals, with the project team, tenaciously pursued various approaches, and eventually optimized the stability with a bi-layer formulation and the addition of an excipient for pH stabilization. All other quality characteristics (size, disintegration, solubility) were maintained. Another crucial advance for ensuring long-term stability of the product in tropical conditions was the decision to blistering the tablets in double aluminium foil, as proposed by DND*i*. The many iterative stability tests that were required in overcoming these formulation challenges were time-consuming, required stress testing and added up to significant delays. However, by 2008 these improvements permitted ASAQ Winthrop® to achieve WHO prequalification programme approval, the first to include a three-year shelf-life. This has important consequences for patient access and availability, overcoming losses due to problems in supply lines, stock management and drug distribution systems in the key tropical African markets.

Simplified and robust packaging

Aluminium-aluminium blisters were selected to ensure stability and improve ASAQ's shelf-life. Considerable efforts were also made to optimize the initial package design along the lines proposed by Sanofi following recommendation by MSF to make the instructions easily understandable by patients and caregivers who may lack reading skills. The new packaging used pictograms, logos, and colours. Furthermore, packages were reduced in size to minimize shipping, storage, and delivery costs.

PATIENT-ADAPTED ASAQ PACKAGING: TABLET BLISTERS

Evolution of packaging to include pictograms, logos, and colours, following recommendations by MSF, to ease understanding by patients and caregivers who may lack reading skills

1st blister pack (2006)

Coarsucam™

2nd blister pack (2007)

ASAQ Winthrop®

(a) 14 years and older (≥36kg);
(b) 6-13 years (18-35kg);
(c) 1-5 years (9-17kg);
(d) 2-11 months (4.5 – 8kg)

(a)

(b)

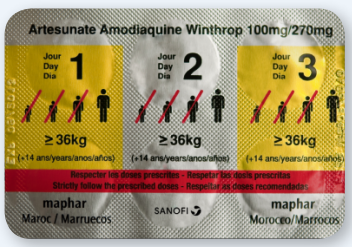
(c)

(d)

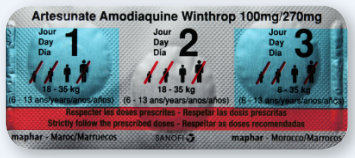
3rd blister pack (2010)

ASAQ Winthrop®

(a) 14 years and older (≥36kg);
(b) 6-13 years (18-35kg);
(c) 1-5 years (9-17kg);
(d) 2-11 months (4.5 – 8kg)

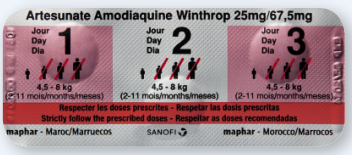


(a)



(b)

(c)



(d)

(20) 'The initial pharmaceutical development of an artesunate/amodiaquine oral formulation for the treatment of malaria: a public-private partnership' By C. Lacaze *et al. Ibid.* Volume 10, 2011, p 142, DOI: 10.1186/1475-2875-10-142.

ENSURING ACCESSIBILITY TO AN AFFORDABLE, NON- PATENTED PRODUCT

One of the key components of the agreement between DND*i* and Sanofi, signed in December 2004, was that the treatment would be made available at cost for the public sector, at prices lower than those available at the time, i.e. less than US$ 1 for an adult treatment (the cost of Arsucam®, artesunate-amodiaquine) and less than US$ 0.50 for a paediatric treatment in the non-profit public sector. Sanofi did not seek any patent protection in the FACT Project, in a decision made to be consistent with DND*i*'s intellectual property policy to develop drugs as public goods whenever possible, and with both partners' determination to make the new medicine as widely available as possible to patients in greatest need. Sanofi agreed to pay DND*i* 3% of the net private sector turnover over a period of seven years. DND*i* later used these royalty payments to support the ASAQ FDC Risk Management Plan (RMP; see Funding, page 13). At the time when it joined FACT, Sanofi was already firmly engaged in antimalarials, with a strong presence in Africa. It is highly unusual for a Pharma company to engage in full drug development for products that are not protected by critical patents. This decision was to a great extent driven by the company's CEO's personal commitment to engage in drug development for malaria and other tropical diseases in Africa.

Effect on price

Following DND*i*'s announcement in April 2005 that the ASAQ FDC would be available in mid-2006 at a price targeted at less than $1 per adult treatment, Novartis responded with its first significant price reduction (in 2006) by reducing the price of AL (Coartem®) from, on average, $1.57 per treatment to $1 (depending on the strength). Prior to this, the price had remained stable since 2001. The median price of the ASAQ FDC has declined since first becoming prequalified in October 2008 from $1.0 (range 0.7-1.1) to $ 0.9 in 2012, significantly lower than that of AL in 2012 ($1.6).

The Global Fund's Affordable Medicines Facility malaria (AMFm, 2010-2012), was a financing mechanism designed to increase the affordability and availability of quality ACTs through negotiated manufacturer price reductions, subsidies, and communications campaigns. A series of pilot programmes was carried out in 8 countries, with DND*i* involved in analysing the effects of the pilot phase of the AMFm in Ghana, where it was found to be particularly successful. Despite the programmes' limited duration, large improvements in availability, price, and market share of quality-assured ACTs were seen in the majority of countries, particularly in the private for-profit sector[21].

ASAQ: QUALITY DEVELOPMENT AND IMPLEMENTATION

The development of ASAQ FDC has been carried out with a view to delivering an adapted product to patients in endemic countries in a short-time frame, and is characterised by the quality of its innovative formulation, manufacture, development, and implementation.

The starting point, and basis for the ASAQ clinical strategy, was the extensive information on the safety and efficacy of non-fixed dose ('loose') AS/AQ that was already available from 37 studies; this body of data was derived from about 10,000 patients who had received AS and AQ in various doses and ratios (a number of these AS/AQ studies are listed in the table page 8). Evidence of the safety of the Sanofi AS+AQ combination was also available from a number of studies. In the largest of these, performed in Senegal in over 3,000 patients, no adverse events requiring in-patient hospitalisation were reported[22].

(21) 'Effect of the Affordable Medicines Facility--malaria (AMFm) on the availability, price, and market share of quality-assured artemisinin-based combination therapies in seven countries: a before-and-after analysis of outlet survey data' By S. Tougher *et al. Lancet*, Volume 380, Issue 9857, 2012, pp. 1916-1926, DOI: 10.1016/S0140-6736(12)61732-2.

(22) 'Dosing accuracy of artesunate and amodiaquine as treatment for *falciparum* malaria in Casamance, Senegal' By P. Brasseur *et al. Trop Med Int Health*, Volume 14, Issue 1, 2009, pp. 79-87, DOI: 10.1111/j.1365-3156.2008.02190.x.

CLINICAL AS/AQ STUDIES PRIOR TO THE DEVELOPMENT OF ASAQ AND SINCE

Year	Location	Number of enrolled patients	Patients treated with AS/AQ
1999	**Gabon**	220	110
1999	**Kenya**	400	200
1999	**Senegal**	321	160
2000-5	**Senegal** Djembeye	137	137
2000-5	**Senegal** Mlomp	723	723
2000-5	**Senegal** Oussouye	208	208
2002	**Rwanda** Mashesha	122	61
2002	**Rwanda** Rukara	95	49
2002	**Rwanda** Kicukiro	91	48
2002	**Zanzibar** Kivunge	297	148
2002	**Zanzibar** Micheweni	105	54
2003	**Angola** Kuito	187	97
2003	**RDC** Boende	279	136
2003	**South Sudan** Nuba	161	80
2003	**Sudan** Malakal	269	134
2003	**Uganda** Amudat	212	106
2003	**Uganda** Jinja	543	189
2004	**Angola** Caala	137	69
2004	**Congo** Kindamba	298	101
2004	**Guinee** Dabola	220	110
2004	**Mali** Bancouna	753	252
2004	**Rwanda** Mashesha	269	89
2004	**Rwanda** Rukara	270	89
2004	**Rwanda** Kicukiro	223	74
2004	**Sierra Leone** Kailahun	126	126
2004	**Uganda** Tororo	541	194
2004	**Uganda** Apac	542	174
2004	**Uganda** Arua	534	174
2005	**Burkina Faso** Puytenga	890	890
2005	**Uganda** Tororo	408	204
2006	**Cameroon**	166	110
2006	**Madagascar**	179	119
2006	**Mali** Bougoula	203	135
2006	**Senegal**	392	264
2006	**Uganda** Kampala	730	242
2008	**Burkina Faso** Nanoro	810	295
2008	**Gabon**	226	80
2008	**Mozambique** Manhica	420	210
2008	**Nigeria** Afokang	261	92
2008	**Nigeria** Pamol	233	82
2008	**Uganda** Mbarara	319	160
2008	**Zambia** Ndola	245	85
2009	**Kenya**	54	54
2009	**Liberia**	1,300	648

Modified from '*Plasmodium falciparum* clearance in clinical studies of artesunate-amodiaquine and comparator treatments in sub-Saharan Africa, 1999-2009' By J. Zwang *et al. Malar J*, Volume 13, 2014, p 114, DOI: 10.1186/1475-2875-13-114.

Despite the large body of evidence on the use of AS and AQ it was necessary to provide a formal registration file for use in endemic countries for the ASAQ FDC. A Phase I cross-over study in Malaysia of FDC ASAQ (2004-2005), compared to non-fixed ASAQ, was conducted in healthy volunteers to confirm comparable exposure of the two formulations[23]. Sanofi sponsored an additional Phase I study (in 2006) to compare fasting and fed subjects, which resulted in a recommendation not to use the drug with a high-fat meal because concentrations of AS and dihydroartemisinin were reduced whilst those for AQ and desethyl-AQ were increased[24].

The FACT development project carried out a large pivotal Phase III trial with the support of the CRO Cardinal Health Inc. for data management and final report generation. It was conducted over two malaria seasons from October 2004 to February 2006 in Burkina Faso, and recruited 750 children aged between 6 and 60 months (but weighing >5 kg). FDC ASAQ achieved a cure rate of 92.1%, a result that was non-inferior to the loose combination[25]. The FACT team was confident that the clinical data from the phase I and III studies, which demonstrated that both formulations were essentially equivalent, was sufficient for filing for registration. The Medicines and Healthcare products Regulatory Agency (MHRA) in the UK, however, advised in addition a direct comparison with artemether lumefantrine (AL), considered the reference FDC ACT at that time. Therefore, a second, multicentre, Phase III study (ATAQ EASY), sponsored by Sanofi, was conducted from March to December 2006 in adults and children >10 kg in Senegal, Cameroon, Mali, and Madagascar. A total of 941 patients were recruited and non-inferiority was demonstrated between FDC ASAQ and the reference AL[26].

(23) 'Tolerability and pharmacokinetics of non-fixed and fixed combinations of artesunate and amodiaquine in Malaysian healthy normal volunteers' By V. Navaratnam *et al. Eur J Clin Pharmacol*, Volume 65, Issue 8, 2009, pp. 809-821, DOI: 10.1007/s00228-009-0656-1.

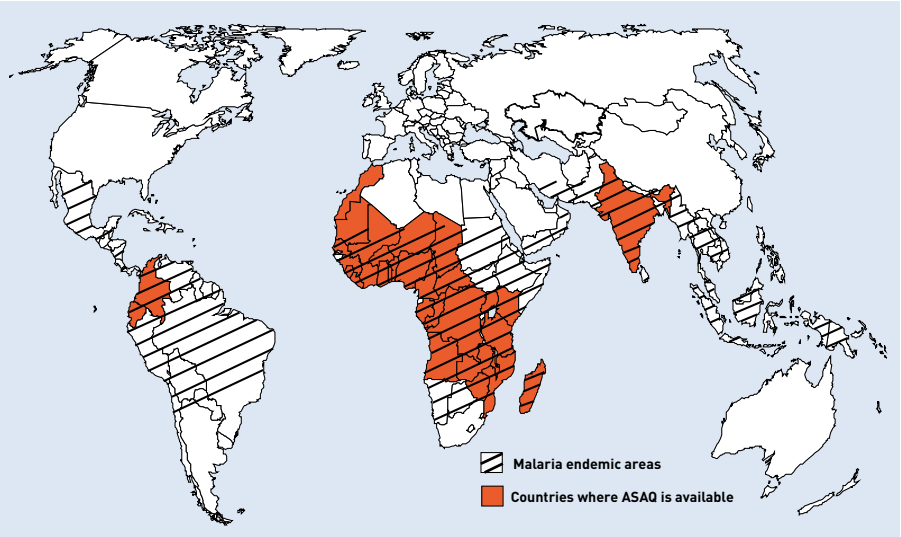
(24) 'Bioavailability of a co-formulated combination of amodiaquine and artesunate under fed and fasted conditions. A randomised, open-label crossover study' By S. Fitoussi *et al. Arzneimittelforschung*, Volume 59, Issue 7, 2009, pp. 370-376, DOI: 10.1055/s-0031-1296410.

(25) 'The efficacy and safety of a new fixed-dose combination of amodiaquine and artesunate in young African children with acute uncomplicated *Plasmodium falciparum*' By S.B. Sirima *et al. Malar J*, Volume 8, 2009, p 48, DOI: 10.1186/1475-2875-8-48.

(26) 'Randomized, multicentre assessment of the efficacy and safety of ASAQ--a fixed-dose artesunate-amodiaquine combination therapy in the treatment of uncomplicated *Plasmodium falciparum* malaria' By J.L. Ndiaye *et al. Malar J*, Volume 8, 2009, p 125, DOI: 10.1186/1475-2875-8-125.

Registration

The role and experience of Sanofi in the regulatory process was instrumental in achieving registration. It also helped by its prior presence in many African markets. The initial plan had been to register ASAQ simultaneously in Europe and in malaria-endemic countries. However, European registration was problematic because artesunate was not yet registered in the EU and was therefore considered a New Chemical Entity (NCE), despite its widespread use. A priority consideration of the FACT team was the urgency of bringing an ASAQ FDC to patients. ASAQ was therefore initially submitted for registration in Morocco in 2005, where it was manufactured in a GMP-compliant, Sanofi-owned plant. ASAQ was registered in 2007 in Morocco, firstly as Coarsucam™ and then as ASAQ Winthrop®, and by the time WHO prequalification was granted in 2008 it was already registered in 15 malaria-endemic African countries.



WHO prequalification was chosen as it enabled access to Global Fund tenders, allowing ASAQ to be purchased by international funding bodies thereby enabling additional, immediate access to ASAQ by NGOs, National Malaria control programmes, and others. The demands of WHO prequalification are essentially equivalent to those of national drug regulatory authorities i.e. this is a stringent process. It is interesting to note that the WHO Department of Medicines Policy and Standards expressed a particular interest in the registration process of ASAQ as a public health good, by setting up a pilot project bringing together all regulatory authorities in Africa in a regulatory harmonisation process. The non-restrictive agreement with Sanofi has allowed the development of ASAQ FDC products by other generic companies, several of whom have also now been granted WHO prequalification status (see Figure page 10).

To date ASAQ FDC has been registered in 35 countries by Sanofi, of which 33 are in Africa.

TIMING OF ASAQ REGISTRATION IN MALARIA-ENDEMIC COUNTRIES

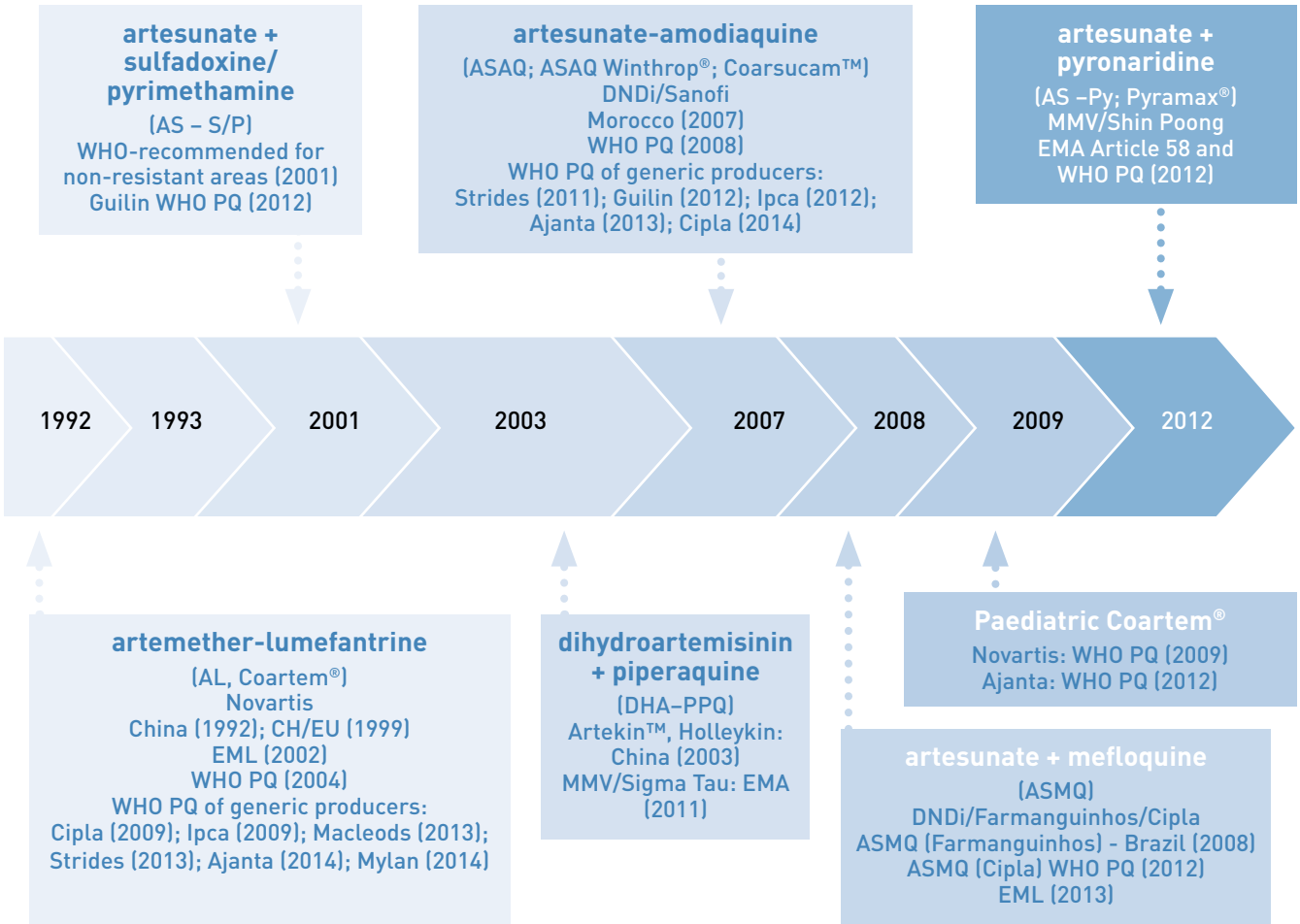
Country	First Approval
Angola	Import Licence
Benin	27.11.2006
Burkina Faso	22.12.2006
Burundi	Import Licence
Cameroon	25.06.2007
CAR	31.05.2007
Chad	08.05.2007
Congo	24.01.2007
Cote d'Ivoire	12.03.2007
DRC	25.01.2007
Ecuador	In process
Gabon	30.11.2006
Ghana	27.04.2007

Country	First Approval
Guinea	27.12.2006
India	08.09.2010
Kenya	30.03.2007
Liberia	Import Licence & registration on going
Madagascar	20.12.2006
Malawi	30.06.2010
Mali	17.02.2007
Mauritania	14.02.2007
Morocco	18.06.2007 (*)
Mozambique	06.07.2009
Niger	14.03.2007
Nigeria	27.09.2007

Country	First Approval
RSA	Submission in process
Rwanda	Registration on going
Senegal	14.12.2007
Sierra Leone	To be confirmed
South Sudan	Registration on Essential Medicine List obtained, awaiting procedure
Tanzania	07.01.2009
Togo	23.01.2007
Uganda	09.01.2009
Zambia	01.03.2010
Zanzibar	30.01.2007
Zimbabwe	Submission in process

(*) Approval of product with extended shelf-life, 04.02.2010.

FIRST REGISTRATION OF WHO PREQUALIFIED AND/OR EMA APPROVED ACTS



Pharmacovigilance and the Risk Management Plan

One consideration for post-marketing surveillance was that, despite AS and AQ's past extensive use, this involved a variety of doses, API ratios, and quality standards. Another consideration was that ASAQ would be used in resource-poor countries whose pharmacovigilance systems might under-report ASAQ-related adverse drug reactions (ADRs), and engage in limited investigation of suspected ADRs.

During 2005-2006, adverse events had been collected following the use of various AS+AQ formulations that had been manufactured in Ghana by a local manufacturer. It was therefore felt important to gather quality efficacy and safety data for the ASAQ FDC developed by the FACT team (ASAQ Winthrop®) through a variety of proactive studies, each providing different types of data. A post-registration programme to monitor ASAQ efficacy and safety in the field was developed as a Risk Management Plan, the first of its kind to be submitted to the WHO (in 2009), consisting of a variety of clinical studies performed by Sanofi, DND*i*, and partners. As part of this a large trial, carried out in partnership with MSF/Epicentre and involving 1,000 adults and children patients, led to regulatory approval in Liberia[27,28]. Sanofi and MMV, with support from DND*i*, undertook an extensive Phase IV field programme ('implementation study') to assess the real-life safety and effectiveness of ASAQ Winthrop® in the health district of Agboville, Côte d'Ivoire, involving 15,000 patients over 2-3 years, and results are expected in 2015.

All data from this pharmacovigilance programme are pooled in a common database with the goal of providing extensive information on the medicine's efficacy and safety.

(27) 'Tolerability and safety of artesunate-amodiaquine and artemether-lumefantrine fixed dose combinations for the treatment of uncomplicated *Plasmodium falciparum* malaria: two open-label, randomized trials in Nimba County, Liberia' By B. Schramm *et al. Ibid.* Volume 12, 2013b, p 250, DOI: 10.1186/1475-2875-12-250.

(28) 'Efficacy of artesunate-amodiaquine and artemether-lumefantrine fixed-dose combinations for the treatment of uncomplicated *Plasmodium falciparum* malaria among children aged six to 59 months in Nimba County, Liberia: an open-label randomized non-inferiority trial' By B. Schramm *et al. Ibid.*, p 251, DOI: 10.1186/1475-2875-12-251.

ASAQ efficacy data sets are shared with the Worldwide Antimalarial Resistance Network (WWARN), while the safety data are shared with the Liverpool School of Tropical Medicine.

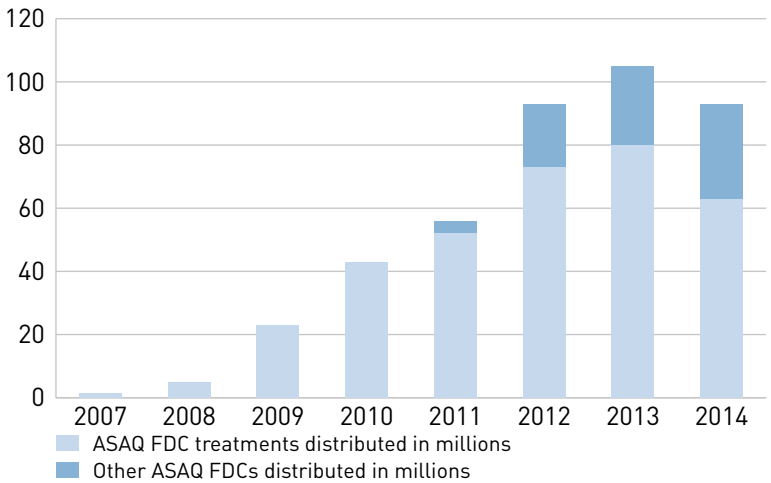
DEPLOYMENT OF ASAQ

Distribution

Distribution and marketing were the sole responsibility of Sanofi and were highly successful: yearly sales of ASAQ, as ASAQ Winthrop® and Coarsucam™, initially at 0.5 million treatments in 2007, prior to prequalification by WHO, increased to 5 million treatments once prequalification was attributed in 2008. Currently over 400 million treatments have now been distributed worldwide, including products developed by generic companies thanks to the non-exclusivity agreement with Sanofi. It is impossible to calculate the precise impact of ASAQ in terms of lives saved (and distinguish their impact from the use of other interventions such as bed-nets and other ACTs), but it is self-evident and explicitly cited as a reason by the WHO that ACTs have made a significant contribution to the spectacular reduction in malaria morbidity and mortality over the past 10 years[29].

Marketing was facilitated by Sanofi's presence in Africa, where it continues to have visibility and community engagement. Part of Sanofi's 'Access to Medicines' efforts included providing a wide variety of quality educational materials to patients and health workers on malaria prevention, diagnosis, treatment, and proper use of medicines. Along with Novartis, Sanofi and generic companies have played an instrumental role in shaping the market for FDC antimalarials.

OVER 400 MILLION TREATMENTS DELIVERED BY 2015.



Yearly distribution (in millions) of ASAQ Winthrop® and ASAQ generics.

By 2009 DND*i*, supported by the Office Technique d'Etude et de Coopération Internationale (OTECI), investigated how the supply of high-quality, affordable FDC ASAQ could be further expanded. Following evaluation of about a hundred partners with GMP capabilities, Zenufa (Tanzania) was selected, and in 2011 a Technology Transfer contract was signed. The manufacturing site has been audited with success, and the manufacturing of batches required for registration has been performed. Bioequivalence studies for the WHO Prequalification dossier are currently ongoing. The Registration file for two strengths of ASAQ is being finalized, with the aim of filing the dossier (including the bioequivalence study) in late 2015, and of obtaining WHO prequalification and registration in the first African countries in 2016.

Concerns of emerging ACT resistance

Resistance to AS, first reported in 2007[30] and defined genetically in 2014[31], is still confined to the greater Mekong sub-region. However, there are now reports that the genetic mutation associated with AS resistance is more extensive than first thought with dihydroartemisinin-piperaquine failures rising in Cambodia[32]. However ASAQ remains highly effective in most parts of Africa where it has been used or tested. Having a large volume of this quality fixed dose product on the market at an affordable price has proportionally reduced the quantities of poor quality/counterfeit treatments available and contributes to the prevention of emerging AS resistance on the continent. Zwang *et al* reported[33] that ASAQ-mediated parasite clearance in sub-Saharan African patients is particularly rapid as compared to other ACTs. The WWARN recently analysed pooled data from a number of ASAQ formulations[34], providing strong evidence for the added benefit of administering ACTs as FDCs. It found that the loose NFDC (non-fixed dose combination) with 25 or 30 mg/kg AQ was associated with a greater risk of recrudescence as compared to FDCs, concluding that the latter are superior in ensuring optimal dosing and efficacy, results that also confirm earlier findings[35].

(29) 'World Malaria Report' By World Health Organization. www.who.int/malaria/publications/world_malaria_report/en/, 2014.
(30) 'PFMDR1 and *in vivo* resistance to artesunate-mefloquine in *falciparum* malaria on the Cambodian-Thai border' By A.P. Alker *et al. American Journal of Tropical Medicine and Hygiene*, Volume 76, Issue 4, 2007, pp. 641-647.
(31) 'A molecular marker of artemisinin-resistant *Plasmodium falciparum* malaria' By F. Ariey *et al. Nature*, Volume 505, Issue 7481, 2014, pp. 50-55, DOI: 10.1038/nature12876.
(32) 'Artemisinin resistance - modelling the potential human and economic costs' By Y. Lubell *et al. Malar J*, Volume 13, Issue 1, 2014, p 452, DOI: 10.1186/1475-2875-13-452.
(33) '*Plasmodium falciparum* clearance in clinical studies of artesunate-amodiaquine and comparator treatments in sub-Saharan Africa, 1999-2009' By J. Zwang *et al. Malar J*, Volume 13, 2014, p 114, DOI: 10.1186/1475-2875-13-114.
(34) 'The effect of dosing strategies on the therapeutic efficacy of artesunate-amodiaquine for uncomplicated malaria: a meta-analysis of individual patient data' By Worldwide Antimalarial Resistance Network (WWARN) AS-AQ Study Group. *BMC Medicine*, Volume 13, Issue 66, 2015, pp. doi:10.1186/s12916-12015-10301-z.
(35) 'Dosing accuracy of artesunate and amodiaquine as treatment for *falciparum* malaria in Casamance, Senegal' By P. Brasseur *et al. Trop Med Int Health*, Volume 14, Issue 1, 2009, pp. 79-87, DOI: 10.1111/j.1365-3156.2008.02190.x.

KEY DATES IN THE DEVELOPMENT OF ASAQ, SINCE 2001

2001
- WHO recommends Artemisinin-based Combination Therapies to fight malaria

2002
- FACT consortium set up by Drugs for Neglected Diseases Working Group of the MSF Access Campaign in coordination with WHO-TDR

2003
- Drugs for Neglected Diseases *initiative* established
- Pharmaceutical development of ASAQ Fixed Dose Combination (FDC)

2004
- Phase I study initiated in healthy human volunteers in Malaysia
- Pivotal phase III clinical study initiated in Burkina Faso to evaluate efficacy and tolerability of FDC *vs* loose combination in 750 children < 5 years of age
- Partnership agreement between DND*i* and Sanofi to jointly develop ASAQ Winthrop®, a non-patented ASAQ FDC to be sold at cost-plus a small margin

2005
- Sanofi-Aventis submits full registration dossier for ASAQ Winthrop®, to Moroccan drug regulatory authorities

2006
- Phase I study to compare fasting and fed subjects
- Phase III ATAQ-EASY multicentre study of Coarsucam ™ (ASAQ FDC) *vs* Coartem® (AL) in 941 African children and adults
- WHO recommends immediate halt to artemisinin monotherapy

2007
- Marketing authorisation granted for Coarsucam™ in Morocco
- Marketing authorisation granted for ASAQ Winthrop® in Morocco
- Registration applications submitted to 30 other African countries
- Introduction on the market of ASAQ Winthrop®, manufactured and packaged at Sanofi's Morocco plant

2008
- WHO prequalification (PQ) of ASAQ Winthrop®
- Tolerability (Phase IV) and efficacy of ASAQ FDC *vs* AL in children 6-59 months old in Liberia

2009
- DND*i* and Sanofi submit Risk Management Plan (RMP) to WHO – the first document of its kind to be submitted to the WHO
- Phase IV field study on 15,000 patients initiated by MMV and Sanofi – the largest study included in the RMP

2010
- ASAQ FDC obtains WHO authorization for its 3 year shelf life – the first of any prequalified FDC artemisinin-based treatments

2011
- ASAQ FDC added to WHO Essential Medicines List
- Technology transfer agreement signed between DND*i* and Zenufa, aimed at ensuring a second African supplier
- WHO PQ of Strides (India) generic ASAQ FDC

2012
- WHO PQ of Guilin (China) and Ipca (India) generic ASAQ FDCs

2013
- WHO PQ of Ajanta (India) generic ASAQ FDC

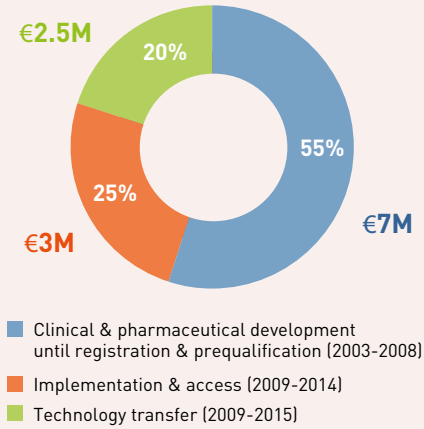
2014
- Sanofi and DND*i* receive the Corporate Social Responsibility Excellence award from the Association of Strategic Alliance Professionals (ASAP)
- WHO PQ of Cipla (India) generic ASAQ FDC

2015
- Prequalification dossier for Zenufa plant in Tanzania to be submitted
- Results from Phase IV PV study in Côte d'Ivoire to become available
- Over 400 million ASAQ FDC treatments distributed by Sanofi and generic sources in 33 African countries

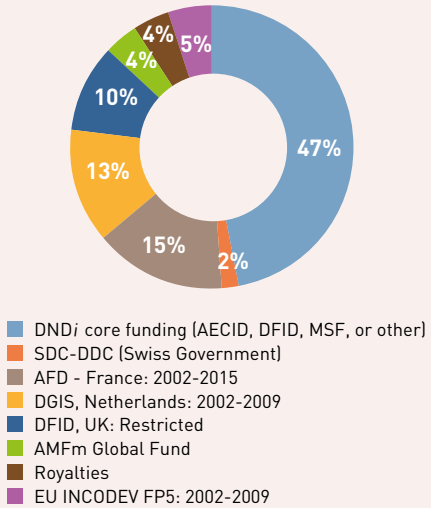
FUNDING, COST, AND TIME ANALYSIS OF THE FACT PROJECT

ASAQ DEVELOPMENT COSTS FOR DND*i*: €12.5M BETWEEN 2002-2015

FACT costs breakdown (does not include manufacturing expenditure or partner contribution)



FACT funding partners and their relative contributions



The overall costs at DND*i* for developing and monitoring the implementation of ASAQ were €12.5M[36], over an overall time span of 12 years. ASAQ did not require early discovery and is based on well-established APIs, decreasing the number of preclinical data to be documented by new studies. Yet, ASAQ still required testing in Phase I and III trials (the costly clinical phases). These expenditures did not include investments made in parallel by Sanofi prior to registration and to support its implementation. However it is fair to say that the development was cost-effective, and this for a product recommended by WHO that has treated (so far) 350 million patients suffering from a potentially deadly disease. In a recent publication, DND*i* [36] estimated that the cost of development for an improved treatment ranges from €6 to €20 million and from €30 to €40 million for a new chemical entity.[37]

Nearly half of the Project's financial support came from DND*i*'s core funding; 15% was contributed by the Agence Française de Développement (AFD, France), and 13% by the Directorate-General for International Cooperation (DGIS, The Netherlands). The remainder was funded by the Department for International Development (DFID, UK, 10%), the EU INCODEV FP5 (5%), the Global Fund's Affordable Medicines Facility-malaria (4%), the Swiss Agency for Development and Cooperation (SDC, Switzerland, 2%), and royalties awarded to DND*i* (4%). The largest portion of the costs went to development and registration.

(36) 'Ten years of experience & lessons learned by DND*i*; An innovative approach to R&D for neglected patients.' By DND*i*. January 2014.
(37) It is important to note that applying the usual attrition rate in the field of infectious diseases, the cost of developing an improved treatment would be €10-40 million and €100-150 for a new chemical entity.

CONCLUSIONS

When the FACT project was launched in 2002 there was a desperate need for an adapted and affordable treatment for patients, particularly for infants and children in Africa. The aim was to develop a treatment which could be made available to patients in a short time-frame, whilst new chemical entities were undergoing a much lengthier development elsewhere. The stable ASAQ FDC bi-layer tablet in its aluminium packaging has resulted in a treatment with extensive stability in tropical climates. The simple regimen of 1 or 2 tablets once a day for 3 days is suitable for all age groups through the use of age and weight dosing bands, in addition to which the tablets disintegrate rapidly in water to ease administration to infants and young children. Today ASAQ FDC has become the second most widely used treatment in Africa, after artemether-lumefantrine, with over 400 million treatments of ASAQ Winthrop® and other generic products distributed, confounding the concerns of some partners and stakeholders expressed during its early development.

The development of ASAQ FDC has been characterized by several innovations:

- the innovative approach to developing this product with public and private partners;
- the innovative formulation development characterized by incremental quality improvements in the product, in order to respond to patients' needs as defined in the target product profile;
- the innovative partnership with a major pharmaceutical company, Sanofi, including agreement to develop ASAQ FDC as a non-patented product at cost-plus a small margin, as a public good;
- the innovative implementation strategy - manufacturing ASAQ FDC at Sanofi's facility in Morocco and registering it 33 endemic countries in Africa;
- the innovative Risk Management Plan with Sanofi and MMV, the first of its kind to be submitted to the WHO and to be entirely undertaken in Africa, which has strengthened its implementation in endemic countries; and
- the choice of a regulatory strategy which involved the WHO and aimed to expedite access in endemic countries, so minimizing delays (and therefore loss of life) in bringing this important drug to malaria patients who need it most.

The agreement to make ASAQ Winthrop® without licence and available at a low price (less than US$ 1 for adults and US$ 0.5 for children for 3 days treatment), led to competition with other generic products. Subsequent WHO prequalification of these products has led to increased purchases by procurement agencies, who in turn distribute it at low cost to patients. This has resulted in increased patient access not only to ASAQ FDC, but also to other ACTs. As public health tools, all ACTs have a vital role to play within national control programmes in fighting this deadly disease.

The FACT experience holds widely applicable lessons that may instruct the development of additional medicines for neglected patients. Developing an ASAQ FDC for malaria involved working with multiple public and privately owned partners - for funding, pharmaceutical and clinical development, manufacturing, access etc. - in a 'virtual' structure that facilitated 'out of the box' thinking towards a shared, agreed goal. The project was kept lean, efficient, flexible, and transparent throughout with global experts playing a pivotal role. The overall project costs and timelines are remarkable by any standard, and delays might even have been shorter were it not for the inherent regulatory obstacles related to the combination itself, and with more streamlined, flexible regulatory procedures in place. A further benefit has been the enhancement of local R&D capacity in endemic countries.

The complementary partnership between Sanofi and DND*i* was the cornerstone to FACT's success. Sanofi's in-house corporate expertise, drug development and registration know-how as well as manufacturing capabilities and critical understanding of how to manage process costs, were central to the success of ASAQ's development. There was excellent synergy between Sanofi's capabilities and DND*i*'s understanding of specific difficulties in bringing antimalarials to patients in malaria-endemic countries, with an emphasis on product stability and ensuring appropriate packaging and pricing.

Sanofi and DND*i* received the Corporate Social Responsibility Excellence award from the Association of Strategic Alliance Professionals (ASAP) in March 2014. The award recognizes the significant and measurable 'positive social impact' of 10 years of public-private partnership in the fight against malaria.

The Medicines for Malaria Venture (MMV) and DND*i* have been long term partners. Since their establishment in 1999, MMV has become a world leader in the field of malaria research and development, succeeding in developing the most robust and diverse portfolio of antimalarial treatments ever seen in the history of the disease[38]. The ASAQ and ASMQ projects were formally transferred from DND*i* to the MMV Access and Product Management team on the occasion of the World Health Assembly in Geneva in May 2015, in order to help maximize future patient access to these treatments.

(38) 'Malaria medicines: a glass half full?' By T.N.C. Wells *et al. Nature Reviews in Drug Discovery*, Volume 14, Issue June 2015, 2015, pp. 424-442.

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Key partners in the FACT Consortium led by DND*i*

- UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR)
- Sanofi, France
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- Instituto de Tecnologia em Fármacos of Farmanguinhos/ Fiocruz, Brazil
- Mahidol University, Thailand
- Mae Sot Clinic/Shoklo Malaria Research Unit, Thailand
- Médecins Sans Frontières (MSF), International
- Université Victor Segalen Bordeaux 2 (TropiVal), France
- Ellipse Pharmaceuticals (now Bertin Pharma), France
- University of Oxford, UK
- Universiti Sains Malaysia, Malaysia

Members from each organization were represented on the FACT project team.

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- Médecins Sans Frontières (MSF), International
- Other private foundations and individuals

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This publication has been drafted and edited by medical writer Rob Hooft van Huijsduijnen.

Finally, it is with sadness and gratitude that we wish to pay homage to the late Jacques Pinel, who was a key member of the Drugs for Neglected Diseases working group – the precursor to DND*i* – and an excellent advisor and mentor to the FACT project.

Graphic design: BRIEF – Photo credits: Tejeda Pedro, Sanofi, Antonio Mendes, Kerri Elizabeth Price, Anna Wang, Claude Mahoudeau-MSF.

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