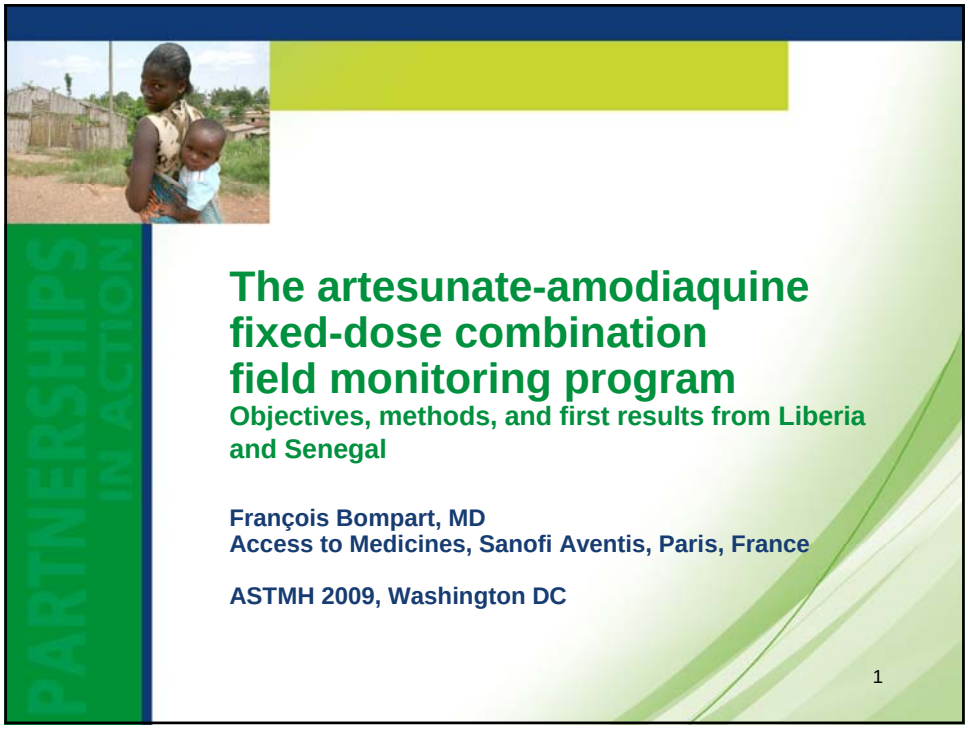

Artesunate-amodiaquine fixed-dose combination « ASAQ »

- **Developed by Sanofi-Aventis and DNDi**
  - **Once-a-day dosing, 1 or 2 tablets**
  - **Soluble tablets**
- **Registered since 2007 in 24 African countries**
- **Pre-qualified by the WHO in 2008**
- **Over 20 million treatments distributed in 2009**

2

The ASAQ field monitoring program

Objective: proactively gather good quality safety and efficacy data on ASAQ, to quantify potential risks and to document missing information, in a variety of malaria transmission settings

3

The ASAQ field monitoring program Rationale

Counterfeits and substandard generics will soon follow ASAQ launch : safety issues, rumors, controversies

Clinical studies data have limitations

- **Limited patient numbers**
- **Controlled conditions**
- **Single malaria episodes**

Limited pharmacovigilance systems in sub-Saharan Africa

- **No pharmacovigilance data from industrialized countries for malaria drugs**
- **Coartem Oct 1998 – Aug 2008**
  - **> 200 million treatments**
  - **137 spontaneous reports, 60% from Africa***

* Dec 3, 2008 FDA Advisory Commitee Meeting, Bethesda, MD

4

Artemisinin derivatives safety issues

- Biological
  Transient reticulocytes decreases and transaminases increases
- Neurotoxicity
  Seen with oil-soluble artemisinin derivatives in animals
  A report of irreversible hearing loss after treatment of adult patients with artemether-lumefantrine
- Pregnancy
  Fetal resorption in rodents: not recommended during first trimester of pregnancy

⇨**Risks to be quantified**

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Amodiaquine safety issues

- Documented issues in **prophylactic use**
  - **1 in 1,700 serious reactions**
  - **1 in 2,200 blood disorders**
  - **1 in 15,650 hepatic disorders**
  - **1 in 15,650 fatal reactions**
- Other issues in malaria treatment
  - **Tiredness, nausea, vomiting (malaria symptoms ?)**
  - **Extra-pyramidal syndromes**

⇨**Risks to be quantified**

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Artesunate + Amodiaquine
Missing information

- **Safety of repeated administrations**
- **Specific populations (HIV/AIDS patients…)**
- **Second and third trimester of pregnancy**
- **Safety profile in non parasitemic patients**
- **Drug interactions**
- **Interactions with traditional drugs and remedies**
- **Efficacy in species other than *P. falciparum***

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The ASAQ field monitoring program

Objective: proactively gather good quality safety and efficacy data on ASAQ, to quantify potential risks and to document missing information in a variety of malaria transmission settings

Methods

1. **Randomized comparative clinical trial**
2. **Randomized comparative cohort**
3. **Large-scale safety study**
4. **"Real life" implementation study**

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1. **Randomized comparative clinical trials**
2. Large-scale safety study
3. Randomized comparative cohorts
4. "Real life" implementation study

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1. Randomized Comparative Clinical Trials

- **Key features**
  - **Comparative design**
  - **Laboratory-confirmed malaria**
  - **Single malaria episodes**
  - **Clinical and biological safety assessments**

- **Settings**

Benin (IRD)
90 ASAQ patients, completed

Liberia (DNDi, Epicentre, MSF-Switzerland)
150 ASAQ patients, ongoing analysis

African multicentric trial (EDCTP)
1190 ASAQ patients, ongoing analysis

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1. Randomized comparative clinical trials
2. **Large-scale safety study**
3. Randomized comparative cohorts
4. "Real life" implementation study

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2. Large-scale safety study

Key features

- **Comparative design: ASAQ vs. AL**
- **1000 patients**
- **Patients > 6 years : able to express subjective symptoms**
- **Confirmed malaria**
- **Clinical and laboratory safety assessments**

Setting : Liberia (DNDi, Epicentre, MSF-Switzerland)

500 ASAQ patients, ongoing analysis

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Study site

MSF Comprehensive Healthcare Center (CHC), Saclepea, Nimba County, Liberia.

- *Plasmodium falciparum* predominant species of malaria
- Remote, rural region – holoendemic malaria
- "Real life" setting

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Objectives

Principal objective

To describe the clinical tolerability of ASAQ in patients ≥ 6 years with uncomplicated *P.falciparum* malaria, compared to AL

Secondary objectives

- Assess efficacy of ASAQ and AL at 28 days
- Assess biological safety
- Day 0 & Day 7 blood levels of desethyl-amodiaquine and lumefantrine.
- Promote awareness of drug safety & pharmacovigilance amongst health-care workers

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Study procedures

Collection of adverse events

Follow up Day	Treatment administration	Symptoms & clinical exam	AST/ALT Biochemistry	Full blood count	Blood smear
0	X	X	X	X	X
1	X	X			
2	X	X			X
7		X		X	
28		X	X	X	X

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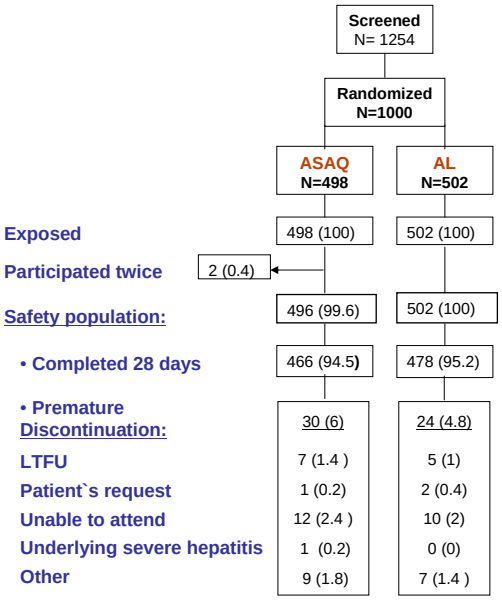
Patient disposition



Study start: 29.09 2008
End of recruitment: 21.04.2009
End of follow up: 19.05.2009

Ongoing data analysis

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1. Randomized comparative clinical trials
2. Large-scale safety study
3. **Randomized comparative cohorts**
4. "Real life" implementation study

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3. Randomized Comparative Cohort Studies

- **Key features**
  - **Comparative design: ASAQ vs. AL**
  - **Repeated administrations: same treatment for each attack, over a 2-year period**
  - **Laboratory-confirmed malaria**
  - **Clinical and laboratory safety assessments**
- **Settings**
  - **Senegal**
  - **Uganda**

400 ASAQ patients x n' malaria attacks

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« SMART-ACCESS » study, Senegal

Dept of Parasitology,
UCAD, Dakar University Senegal

Study site: **Keur Socé**
EIR: 9-12/year
Seasonal transmission
Children and adults
Follow-up Day 28
ECG and audiometric data
August 2007 to January 2009

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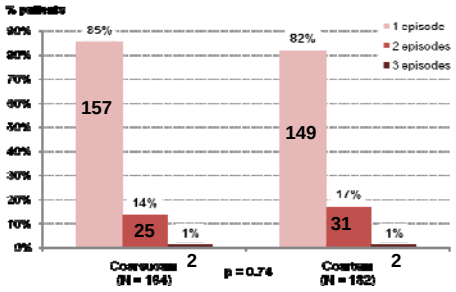
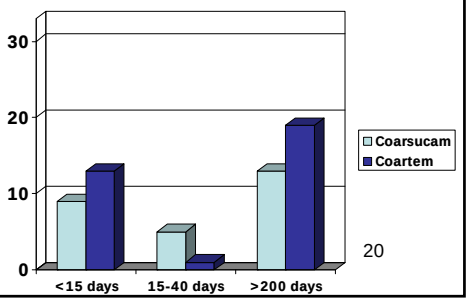
"SMART-ACCESS" study, Senegal
Patients' distribution



Number of malaria episodes by treatment group - ITT

Time for recurrence of 2nd episode by treatment group - ITT



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« SMART-CURE » study, Uganda

A.Yeka, A.Talisuna
Uganda Malaria Surveillance Project
Mulago Hospital, Kampala
Uganda

Study site: Tororo

- **EIR > 500 / year**
- **Children ≤ 5 years at inclusion**
- **Follow-up Day 42**
- **Study start June 2008**

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« SMART-CURE» study, Uganda enrollment status per number of malaria episodes June 2008 - October 2009

Date 2009	Enrolled patient number / episode																			Total
	E 1	E 2	E 3	E 4	E 5	E 6	E 7	E 8	E 9	E10	E11	E 12	E 13	E 14	E 15	E 16	E 17	E 18	E 19	
16/01	413	383	345	279	217	127	73	29	9	1										1876
06Feb	413	386	362	306	258	162	104	59	22	5										2077
03 Ma	413	388	370	325	286	194	129	80	42	15	3									2245
01 Ap	413	389	382	340	319	243	177	116	76	39	15	6								2515
23 Ap	413	390	388	347	339	258	219	145	101	65	28	11	2							2706
27May	413	394	394	358	356	301	259	206	149	104	69	31	18	2						3054
01Jul	413	394	394	371	356	316	285	247	198	141	97	59	29	14	3	1				3318
04Aug	413	394	394	375	363	334	308	262	227	184	133	83	53	31	12	4	1			3571
01Sep	413	394	394	377	368	342	320	282	244	200	163	118	74	41	25	12	4			3771
30 Sep	413	*394*	394	378	372	347	328	295	261	218	182	136	93	59	34	18	7	1		3930

End of follow-up planned June 2010

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1. Randomized comparative clinical trials
2. Large-scale safety study
3. Randomized comparative cohorts
4. **"Real life" implementation study**

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4. Implementation Study

1. Safety assessment program over 2 years

To assess

- ASAQ clinical safety in a health district population
- Impact of ASAQ deployment on malaria epidemiology over time

2. Nested effectiveness study

To assess impact of ASAQ deployment on

- *In vivo* effectiveness
- Clinical and biological safety
- Evolution of parasite resistance

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Implementation Study
Safety Assessment Program

- **Day 0: All patients attending health centres with suspected uncomplicated malaria attack**
  - Prescription of ASAQ
  - Registry for longitudinal malaria prevalence
  - Informed consent for
    - blood smear (*post-hoc* reading in Abidjan)
    - home visits for safety assessment
- **Day 3 to Day 10: trained community health worker visits patient at home to assess tolerability and compliance**
  - Simple oral interview (AE report form, number of tablets intake)
  - Referral to health centre if necessary

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Implementation study
Nested Effectiveness Study

- **<u>Performed twice</u> : beginning of the program, and after 18 months of implementation**
- **Number of patients : n = 290 per period**
- **Study procedures**
  - **Confirmed malaria diagnosis**
  - **Supervised intake for first ASAQ dose**
  - **PCR-adjusted effectiveness assessment Day 28**
  - **Tolerability assessments**
    - **Clinical**
    - **Biological (haematology and biochemical) D0, D3, D14, D28**
  - **Day 7 desethylamodiaquine assay**
  - ***In vitro* parasites sensitivity tests ("drug pressure" assessment)**
- **Started October 2009**

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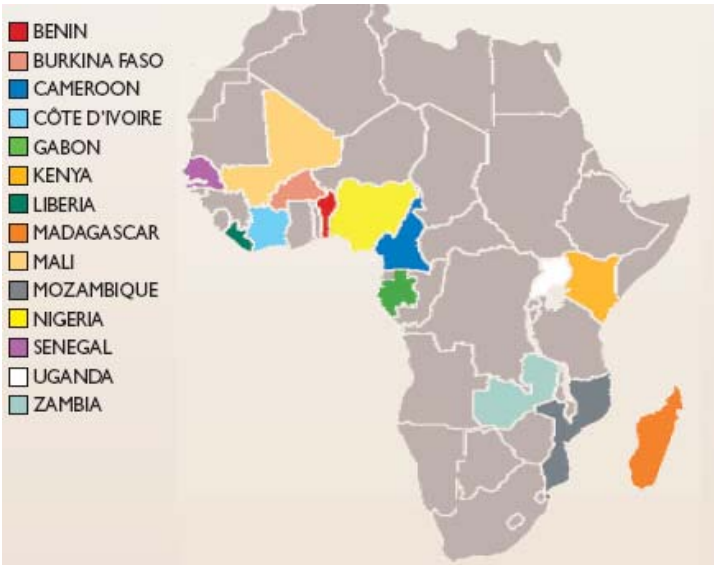
ASAQ clinical study sites



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ASAQ field monitoring program
Total expected database

Comparative clinical trials:	**> 2800 ASAQ patients**
Comparative cohort studies :	**400 ASAQ patients x n malaria attacks**
Implementation study :	**~ 15,000 ASAQ-treated malaria attacks**
TOTAL	**~ 20,000 case reports**

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ASAQ field monitoring program
Key Stakeholders

- National Malaria Control Programs
- National Pharmacovigilance Units
- Independent Safety Monitoring Board
- WHO Department of Medicines Policy and Standards:
  - ASAQ Risk Management Plan submitted March 2009

DNDi Drugs for Neglected Diseases initiative
sanofi aventis Because health matters
Medicines for Malaria Venture

Conclusion

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ASAQ field monitoring program
Key Features

- **Variety of study designs and malaria transmission settings to address multiple issues and information gaps = shed light from different angles on ASAQ efficacy and safety**
- **1st Risk Management Plan submitted to the WHO**
- **1st Risk Management Plan set up entirely in Africa**
- **Dynamic program**

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ASAQ field monitoring program
Conclusion: our objectives

- **Short-term:** design innovative ways of collecting quality data on ASAQ safety and efficacy
- **Medium-term**: contribute to the design of Risk Management Plans for future new antimalarials
- **Longer term**: beyond antimalarials, contribute to strengthening of pharmacovigilance systems in Africa, adapted to the needs and resources of the countries

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Acknowledgments

- National Malaria Control Programs
- National Pharmacovigilance Units
- Clinical experts, pharmacovigilance experts, etc.
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DNDi
Drugs for Neglected Diseases initiative

sanofi aventis
Because health matters

Medicines for Malaria Venture