

## The artesunate-amodiaquine fixed-dose combination field monitoring program

Objectives, methods, and first results from Liberia  
and Senegal

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### 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



## 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

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## 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 Committee Meeting, Bethesda, MD

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## 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

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### 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  $\geq 6$  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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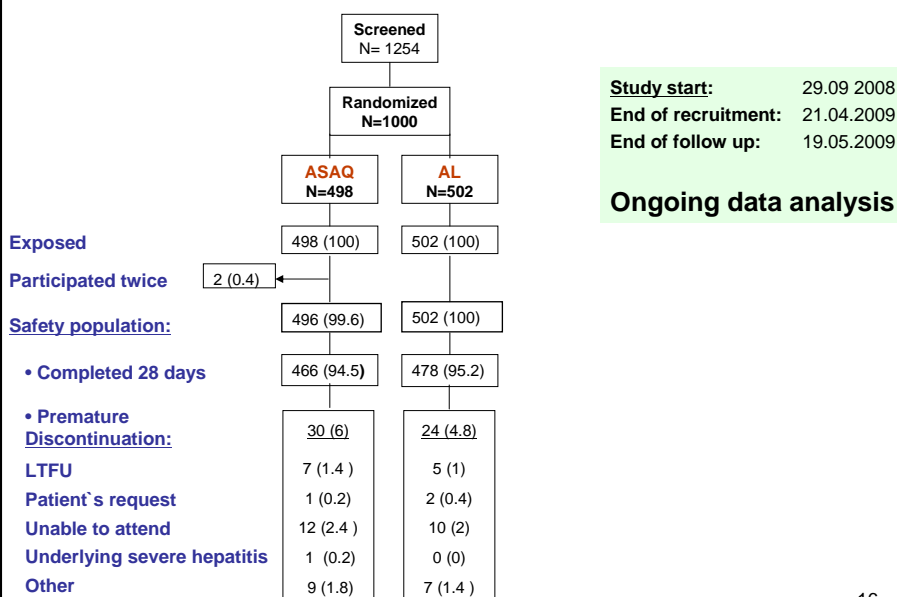
## Study procedures

### 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



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1. Randomized comparative clinical trials
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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

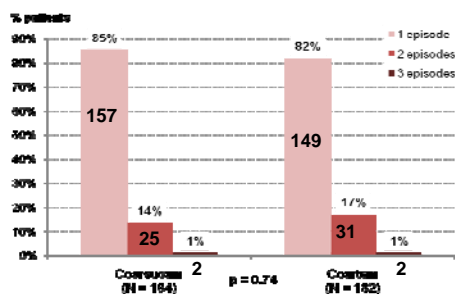


Dept of Parasitology,  
UCAD, Dakar University Senegal

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

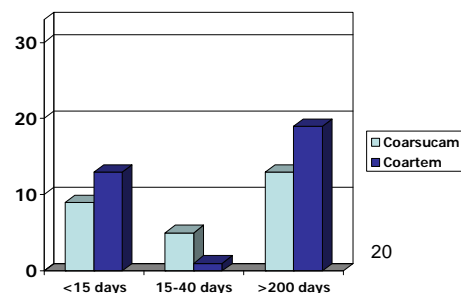
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## “SMART-ACCESS” study, Senegal Patients’ distribution



Number of malaria episodes by treatment group - ITT

Time for recurrence of 2<sup>nd</sup> episode by treatment group - ITT





## « 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	E 10	E 11	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			3774
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

- **Performed twice : 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

## Conclusion



## 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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- National Malaria Control Programs
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