

**Challenges and Successes of the FACT Project through
Innovative Partnerships for the Development of Artesunate
Combination Therapies for Malaria
ASTMH Atlanta, November 5, 2010**

**Public-private partnerships for ASAQ development and
field implementation**

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Sanofi Aventis, Access to Medicines

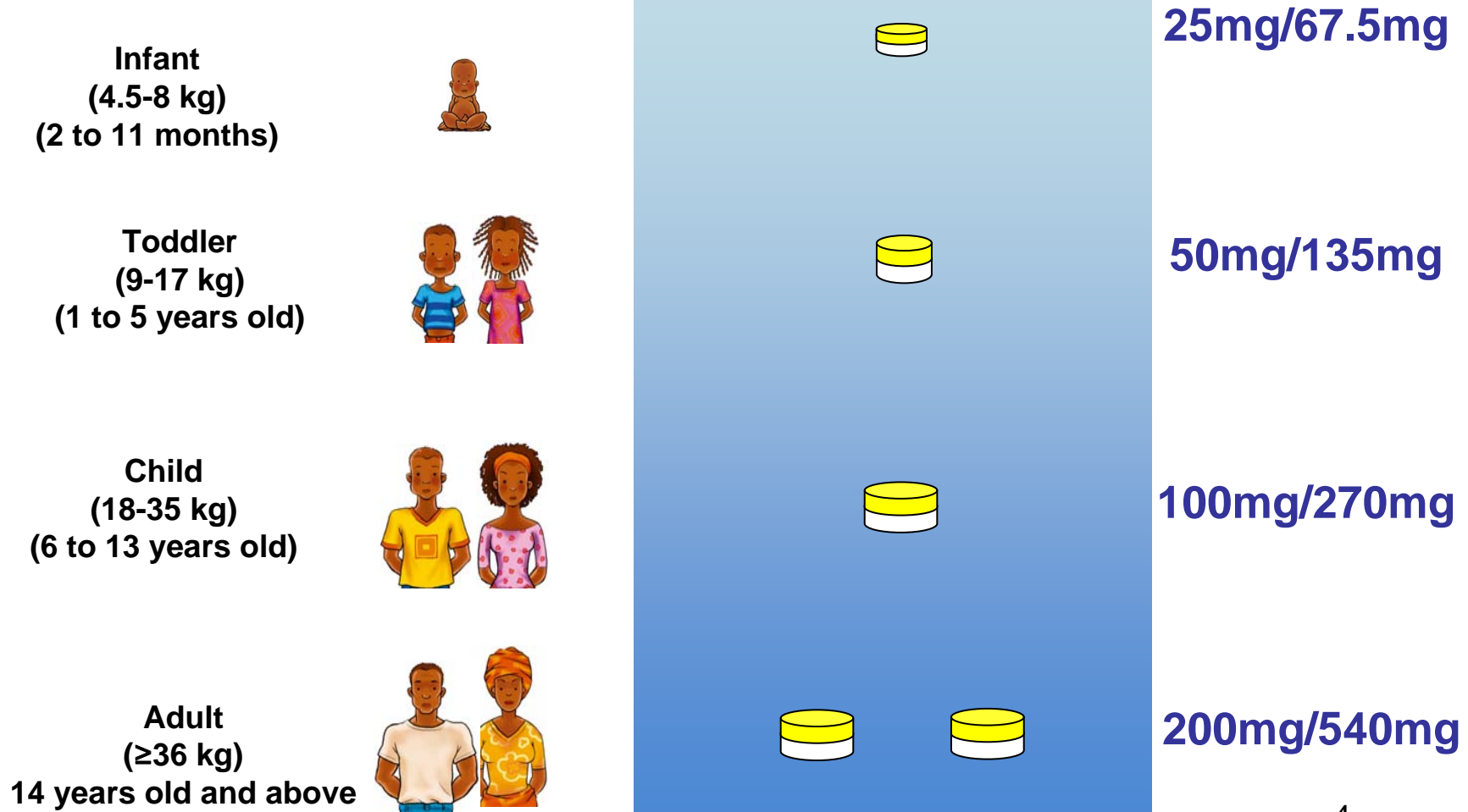
DNDi and Sanofi Aventis partnership for ASAQ

- In Dec 2004, agreement between DNDi and Sanofi Aventis on ASAQ
 - «No profit, no loss» public price: target US\$ 1 per treatment/adult
 - No patents taken
- Continued collaboration in implementation and post-registration

ASAQ Winthrop key features

- **“ASAQ Winthrop”**: informal name for **Coarsucam[®]** and **Artesunate Amodiaquine Winthrop[®]**
- **Adapted to patients needs**
 - **Optimized AS/AQ ratio, to avoid over and under-dosage**
 - **4 dosages by age or weight range**
 - **Simple dosing regimen**
 - **Soluble tablets**
 - **36 months shelf-life**
- **WHO prequalified 2008**

ASAQ Winthrop



4 dosages, by age and weight range



INFANTS
≥4.5kg to <9 kg
2 - 11 months



TODDLERS
≥9kg to <18kg
1 to 5 years



CHILDREN
≥18kg to <36kg
6 to 13 years



**ADOLESCENTS
ADULTS**
≥36kg
14 years and above



Tiered-pricing policy to ensure sustainable accessibility to the poorest patients

Artesunate-Amodiaquine Winthrop®

Public markets: preferential price, including “no profit-no loss” prices
< \$1 for adults, <0.50 for children



Coarsucam®

Private markets
\$2-3 wholesalers price



ASAQ Winthrop

Status update

Available comparative clinical trial data (1)

Versus loose AS+AQ:

- Burkina Faso: 750 children < 5 years and > 5kg 375 ASAQ

Versus AQ:

- India: 300 adults and children 202 ASAQ

Versus AL:

- Senegal, Mali, Cameroon, Madagascar:
941 adults + children >10 kg 628 ASAQ
- Benin: 225 children <10 years 90 ASAQ
- Liberia: 300 children < 5 years 150 ASAQ
- Liberia: 1000 patients > 5 years 498 ASAQ
- Senegal cohort study: 400 adults and children 200 ASAQ
- Colombia: 210 adults 105 ASAQ

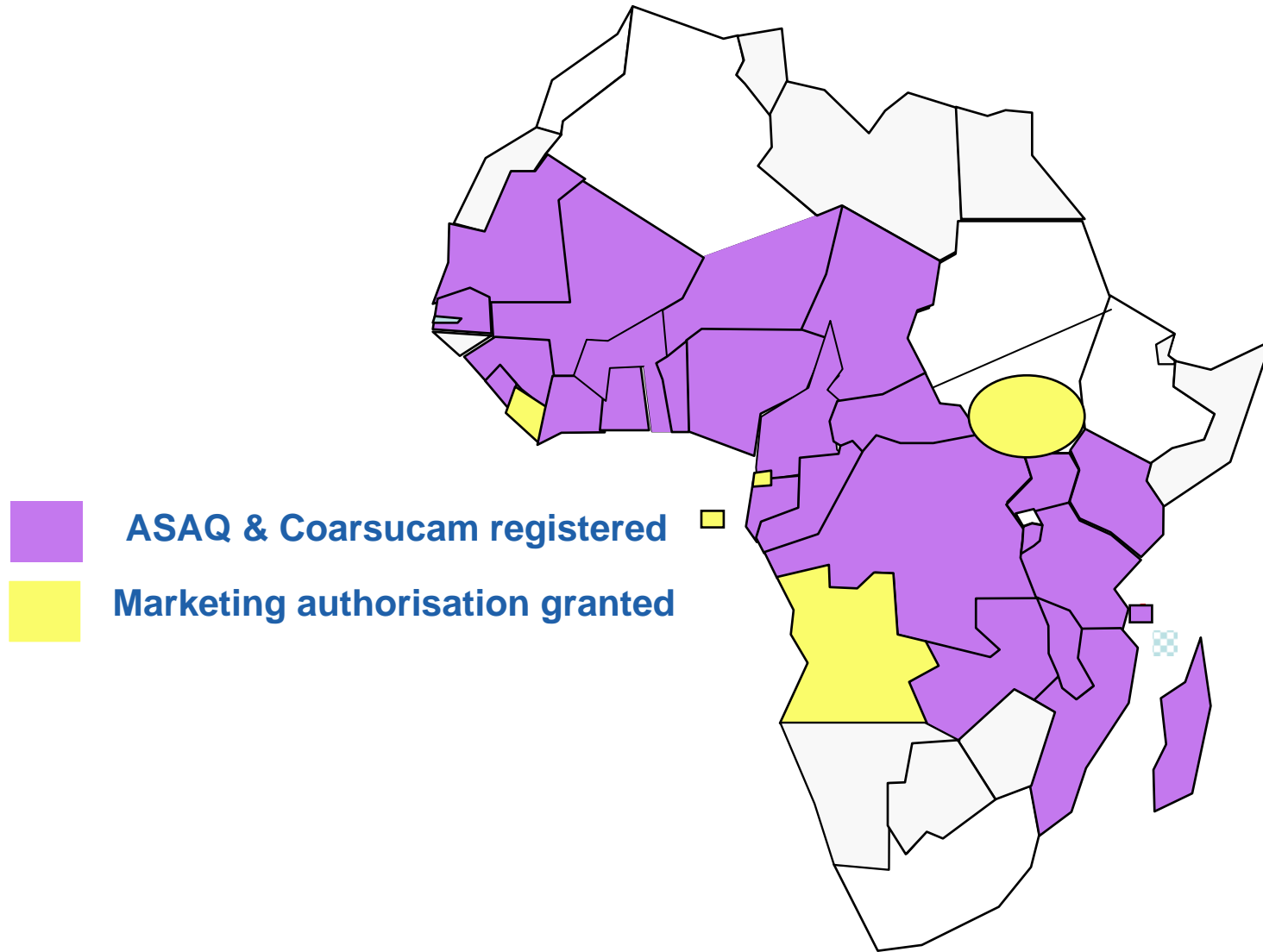
8 studies, 3526 patients, 2248 treated with ASAQ Winthrop

Available comparative clinical trial data (2)

- **Day 28 efficacy rates > 95 %, including in children < 5 years of age**
- **Safety profile similar to AL**
 - **Transient increases in liver transaminases**
 - **Asymptomatic, reversible neutropenia**
 - **Occasional transient rashes**
 - **Nausea, vomiting, exceptionally leading to treatment discontinuation**

Registration status (October 2010)

30 sub-Saharan African countries



Delivery status (July 2010)

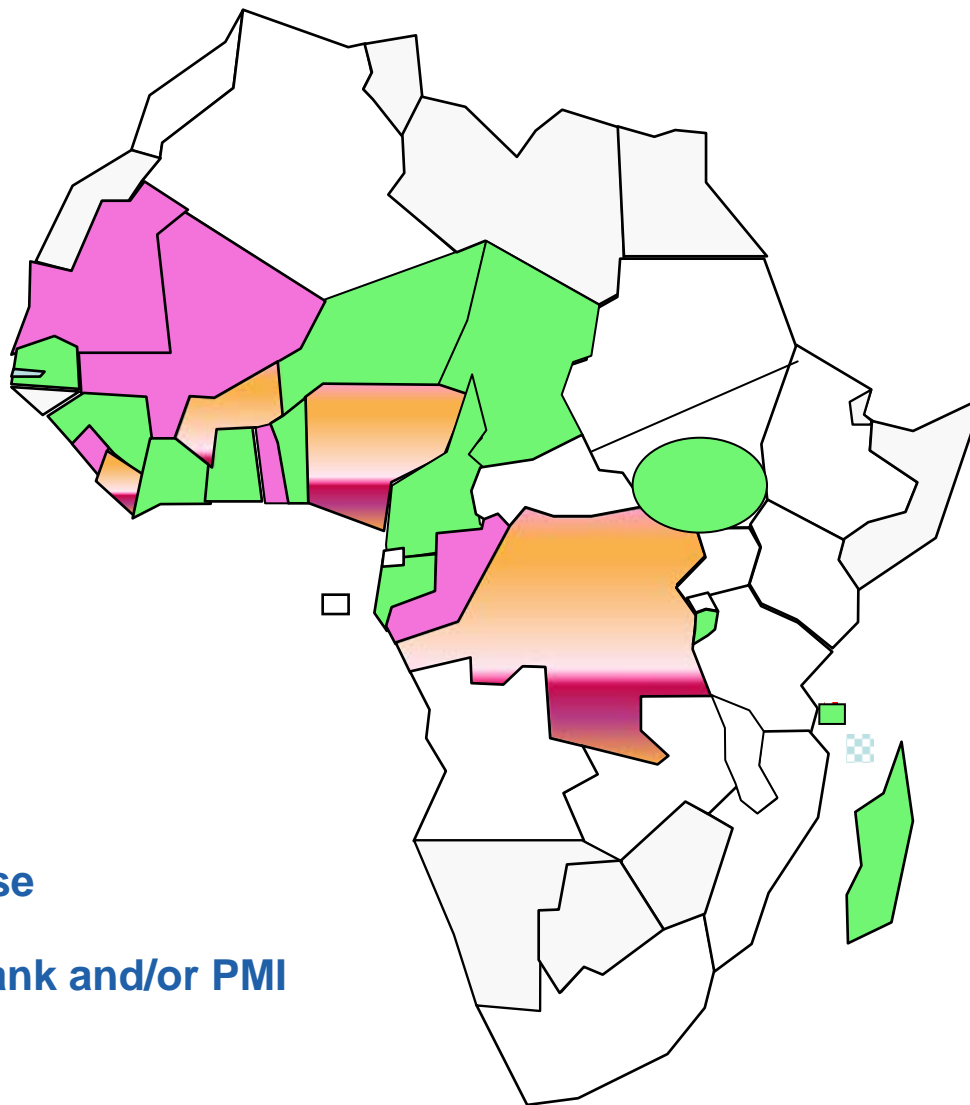
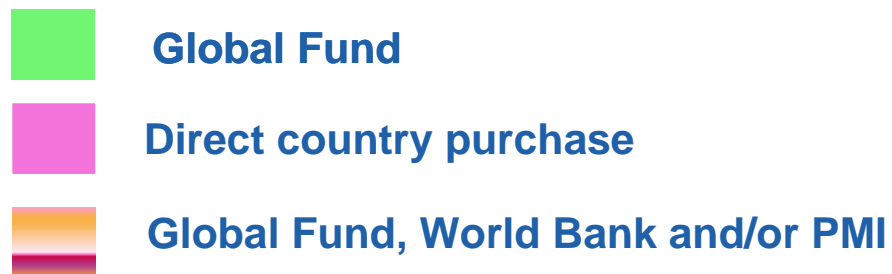
21 countries

2008: 6 million treatments

2009: 25 million treatments

July 2010 27 million delivered

50 million expected by end 2010



ASAQ Winthrop

Pending issues :

Risk Management Plan

ASAQ Winthrop Risk Management Plan Rationale

Counterfeits and substandard versions will soon follow ASAQ launch : safety issues, rumours, controversies

Available data from clinical studies have limitations:

- **Patients numbers**
- **Controlled conditions**
- **Single malaria episodes**

Limited pharmacovigilance systems in sub-Saharan Africa

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

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

European Medicines Agency (EMA) “Risk Management Plans” Key sections

- 1. Identified risks**
- 2. Potential risks**
- 3. Missing information**

WHO Department of Medicines Policy and Standards “ASAQ Winthrop Risk Management Plan” Table of Contents (1)

1. Identified risks: to be minimized with specific information

Intake during first trimester of pregnancy
Allergy

2. Potential risks: to be quantified in large-scale studies

Hepatotoxicity
Neutropenia / agranulocytosis
Somnolence
Audiometric dysfunction
Extra-pyramidal symptoms
Decreased efficacy (parasite resistance)

WHO Department of Medicines Policy and Standards

“ASAQ Winthrop Risk Management Plan” Table of Contents (2)

3. Missing information: to be documented in new studies

Safety of repeated administrations

Specific populations (HIV/AIDS patients...)

Second and third trimester of pregnancy

Safety profile in non parasitaemic patients

Drug interactions & Interactions with traditional drugs and remedies

Efficacy in species other than *P. falciparum*

ASAQ Winthrop Risk Management Plan

Key Features

- Variety of study designs to address multiple safety issues and information gaps
- Variety of study settings to address different malaria transmission patterns
- 1st Risk Management Plan submitted to the WHO
- 1st Risk Management Plan entirely set up in Africa
- Complements and reinforces “normal” pharmacovigilance activities

ASAQ Winthrop Risk Management Plan

Methods

- | | |
|--|---------------|
| 1. Randomized comparative clinical trials | > 5 |
| 2. Randomized comparative cohorts | 2 |
| 3. Large-scale safety study | 1 |
| 4. Field monitoring programme | 1 |

ASAQ Winthrop Risk Management Plan

Recent achievements

Two completed clinical cohort studies: ASAQ vs AL repeated administrations over 2 years

Senegal: 366 children and adults, 496 malaria episodes.

Uganda: 413 children, 6033 malaria episodes:

E1	E2	E3	E4	E5	E6	E7	E8	E9	E10	E11	E12	E13
413	397	396	394	391	382	378	366	355	344	336	315	291
E14	E15	E16	E17	E18	E19	E20	E21	E22	E23	E24	E25	E26
260	231	195	160	130	97	73	52	37	20	13	6	1

Field monitoring programme initiated in Côte d'Ivoire, supported by MMV

4 study sites, 15,000 malaria episodes expected

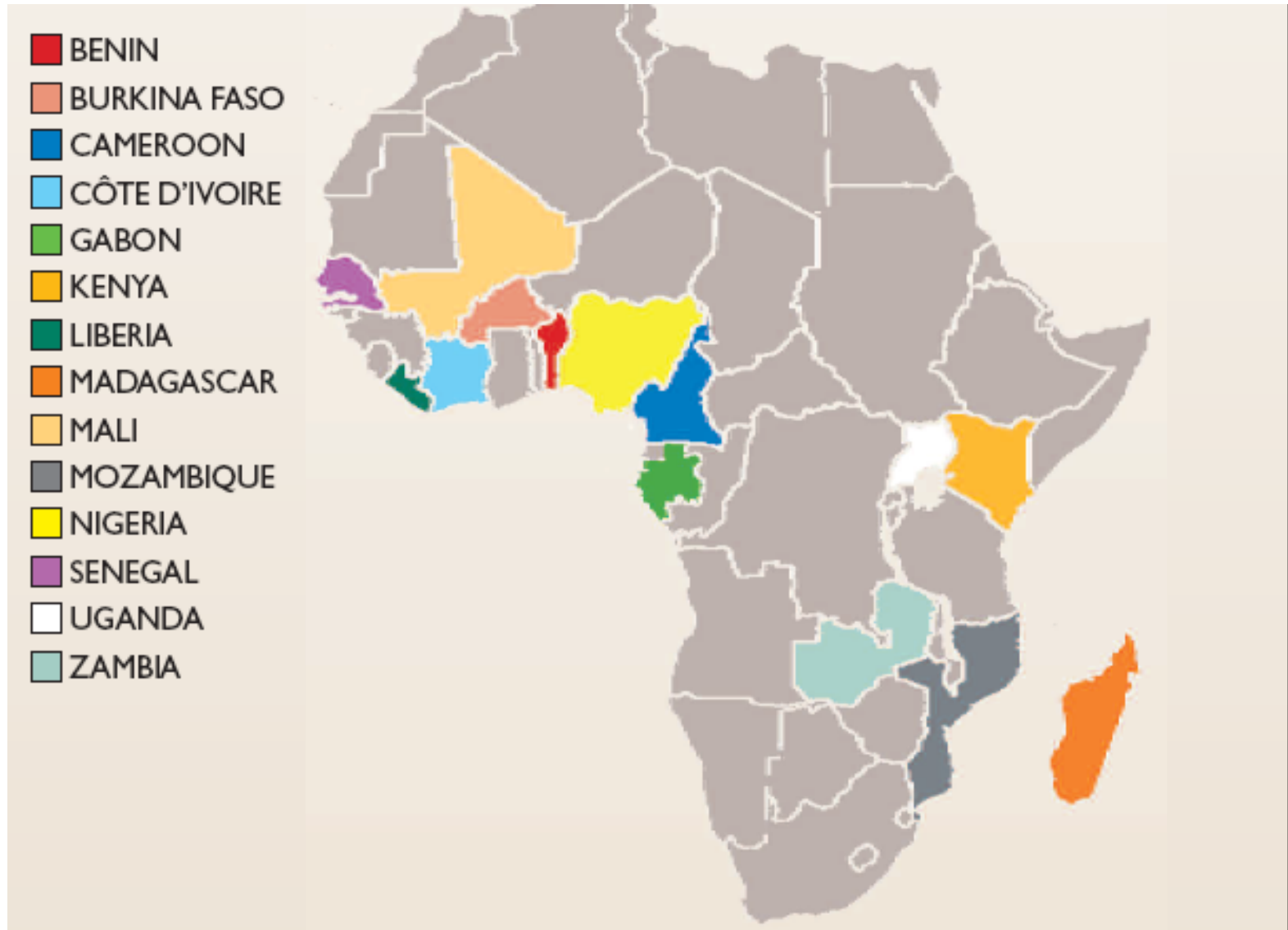
Evaluation of 4 artemisinin-based combinations in uncomplicated malaria in African children completed ("4ABC Study", Dr U. d'Alessandro, MMV, EDCTP)

ASAQ Winthrop Risk Management Plan

Expected database

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

ASAQ Winthrop clinical study sites in Africa



How can partnerships improve access to ACTs?

How can we improve access to ACTs?

Development: ACTs with

- simple dosing regimen
- adapted to children needs
- suitable for community-based management

Affordability: apply sustainable pricing policy that ensures ACT access to poorest patients

Ongoing monitoring of efficacy and safety: critical importance of continued post-launch monitoring of efficacy and safety “in the field”

Information and Education: for appropriate use of ACTs and comprehensive disease management

Expanding partnerships for ASAQ Winthrop

- **DNDi & Sanofi Aventis** : development, registration, distribution
- **MMV** : Risk Management Plan
- **National Malaria Control Programmes** : ACT distribution, information and education on malaria and appropriate use of ACTs
- **Government agencies**: pharmacovigilance, ACT procurement
- **Funding organizations**: ACT procurement
- **Clinical investigators & scientists** : data on ACT efficacy and safety
- **WWARN** : ACT resistance monitoring
- **Research & Development partnerships** to meet future challenges, especially resistance to artemisinin derivatives

Acknowledgements

