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

ASTMH 2010 DNDi symposium
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

Infant
(4.5-8 kg)
(2 to 11 months)

Toddler
(9-17 kg)
(1 to 5 years old)

Child
(18-35 kg)
(6 to 13 years old)

Adult
(≥36 kg)
14 years old and above

25mg/67.5mg
50mg/135mg
100mg/270mg
200mg/540mg
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
≥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
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

ASAQ & Coarsucam registered
Marketing authorisation granted
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
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 Commitee Meeting, Bethesda, MD
European Medicines Agency (EMA)  
“Risk Management Plans” Key sections

1. Identified risks

2. Potential risks

3. Missing information
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)
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
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:

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

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparative clinical trials</td>
<td>&gt; 2800 ASAQ patients</td>
</tr>
<tr>
<td>Comparative cohort studies</td>
<td>400 ASAQ patients x n malaria attacks</td>
</tr>
<tr>
<td>Field monitoring programme</td>
<td>~ 15,000 ASAQ-treated malaria attacks</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>~ 20,000 case reports</td>
</tr>
</tbody>
</table>
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