ASAQ Winthrop®
Risk Management Plan Rationale

Fixed-dose combination of artesunate-amodiaquine
DNDi – Sanofi partnership
Made in Morocco
Launched 2007, WHO prequalified 2008

2007: “ASAQ Field Monitoring Plan”, to proactively gather data on
   Safety
   Efficacy in various settings

2008: “ASAQ Field Monitoring Plan” Formalized as a Risk Management Plan
   Presented to the WHO, February 2009
1. **Important identified risks**: to be minimized with specific information
   - Intake during first trimester of pregnancy
   - Allergy

2. **Important potential risks**: to be quantified
   - Hepatotoxicity, neutropenia, agranulocytosis,
   - Somnolence, audiometric dysfunction, extra-pyramidal symptoms
   - Decreased efficacy (parasite resistance)

3. **Important missing information**: to be documented
   - Safety of repeated administrations
   - Specific populations (HIV/AIDS patients…)
   - Second and third trimester of pregnancy
   - Safety in non parasitemic patients
   - Drug interactions & Interactions with traditional drugs and remedies
   - Efficacy in species other than *P. falciparum*
ASAQ Winthrop® Risk Management Plan

Methods

Total: 19 studies (Sanofi, DNDi, Investigator-Sponsored studies)

- **Randomized clinical trials versus comparator**
  - Efficacy in various malaria transmission settings
  - Clinical safety
  - Biological safety, ECG data
  - Data in specific populations (HIV+, pregnancy)
  - Data in other species (**P. vivax**)

- **Randomized cohort studies**
  - Efficacy / effectiveness and safety in Iterative administrations
  - ECG and audiometric data

- **Large scale implementation study**
  - Effectiveness
  - Clinical safety in patients without parasites
  - Pharmacovigilance

- **+ Pharmacovigilance data**
ASAQ: CLINICAL STUDIES SITES

+ Brazil
Colombia
India
Myanmar
Vietnam
Repeated treatment with ASAQ vs AL in children < 5 years, Tororo, Uganda

2-year study period

42 days follow-up

413 children:
  208 ASAQ
  205 AL

6027 malaria episodes treated
Number of patients per malaria episode

Number of patients

Number of episodes
Primary endpoint: PCR corrected treatment response at D28 for the 1st episode

**ITT population ASAQ Winthrop®**  
\[ n = 198 \]

<table>
<thead>
<tr>
<th></th>
<th>ASAQ Winthrop® n=198</th>
<th>AL n=201</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCF</td>
<td>0</td>
<td>3(1.5%)</td>
</tr>
<tr>
<td>LPF</td>
<td>5 (2.5%)</td>
<td>3 (1.5%)</td>
</tr>
<tr>
<td>ACPR</td>
<td>192 (97.0%)</td>
<td>194 (96.5%)</td>
</tr>
<tr>
<td>NA</td>
<td>1 (0.5%)</td>
<td>1 (0.5%)</td>
</tr>
</tbody>
</table>

Non inferiority demonstrated with an inferior limit of the 95% CI [-0.030; 0;039] of the difference of PCRs ACPR rates between groups > 5%

**PP population ASAQ Winthrop®**  
\[ n = 197 \]

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Non inferiority demonstrated with an inferior limit of the 95% CI [-0.028; 0;037] of the difference of PCRs ACPR rates between groups > 5%
### Treatment Emergent Adverse Events
All malaria attacks – Safety population

<table>
<thead>
<tr>
<th>n (%)</th>
<th>ASAQ Winthrop® (n = 208)</th>
<th>AL (n = 205)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with any TEAE</td>
<td>120 (57.7%)</td>
<td>127 (62.0%)</td>
</tr>
<tr>
<td>Patients with any Serious TEAE</td>
<td>16 (7.7%)</td>
<td>9 (4.4%)</td>
</tr>
<tr>
<td>Patients with any TEAE leading to death</td>
<td>1 (0.5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Patients with any TEAE leading to permanent treatment discontinuation</td>
<td>2 (1.0%) *</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

* Non related to treatment
One death (E16, ASAQ group) : severe malaria + severe anaemia + severe congestive heart failure
Reported Treatment Emergent Adverse Events, by malaria episode

Reported AEs (%) according to malaria attack and treatment group

Coarsucam®/ASAQ Winthrop®
(n = 234 AEs)

ASAQ ASA
n=234 AEs

Coartem®
(n = 251 AEs)

AL
n=251 AEs

<table>
<thead>
<tr>
<th>Malaria attack no.</th>
<th>Coarsucam®/ASAQ Winthrop®</th>
<th>Coartem®</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33.9%</td>
<td>20%</td>
</tr>
<tr>
<td>2</td>
<td>12.4%</td>
<td>10%</td>
</tr>
<tr>
<td>3</td>
<td>10.0%</td>
<td>5.0%</td>
</tr>
<tr>
<td>4</td>
<td>12.0%</td>
<td>6.0%</td>
</tr>
<tr>
<td>5</td>
<td>9.8%</td>
<td>4.4%</td>
</tr>
<tr>
<td>6</td>
<td>6.4%</td>
<td>3.6%</td>
</tr>
<tr>
<td>7</td>
<td>7.2%</td>
<td>5.2%</td>
</tr>
<tr>
<td>8</td>
<td>5.1%</td>
<td>2.8%</td>
</tr>
<tr>
<td>9</td>
<td>2.8%</td>
<td>3.0%</td>
</tr>
<tr>
<td>10</td>
<td>2.6%</td>
<td>1.7%</td>
</tr>
<tr>
<td>11</td>
<td>1.7%</td>
<td>1.3%</td>
</tr>
<tr>
<td>12</td>
<td>1.0%</td>
<td>0.4%</td>
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<tr>
<td>13</td>
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<td>0.4%</td>
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<tr>
<td>14</td>
<td>0.8%</td>
<td>0.4%</td>
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<tr>
<td>15</td>
<td>0.8%</td>
<td>0.9%</td>
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<tr>
<td>16</td>
<td>0.8%</td>
<td>0.4%</td>
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<tr>
<td>17</td>
<td>0.4%</td>
<td>0.4%</td>
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<tr>
<td>18</td>
<td>0.4%</td>
<td>0.4%</td>
</tr>
<tr>
<td>19</td>
<td>0.4%</td>
<td>0.4%</td>
</tr>
<tr>
<td>20</td>
<td>0.9%</td>
<td>0.9%</td>
</tr>
<tr>
<td>21</td>
<td>0.4%</td>
<td>0.9%</td>
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<tr>
<td>22</td>
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<td>0.9%</td>
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<tr>
<td>23</td>
<td>0.4%</td>
<td>0.9%</td>
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<tr>
<td>24</td>
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<td>0.9%</td>
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<tr>
<td>25</td>
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</tr>
<tr>
<td>26</td>
<td>0.9%</td>
<td>0.9%</td>
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Adverse Events of Special Interest

increased ALAT in ASAQ treatment group
Adverse Events of Special Interest
increased ALAT in AL treatment group

Patient no. 139 - attack no.7

Patient no. 317 - attack no.5

Patient no. 301 - attack no.8

Patient no. 056 - attack no.9

Episodes 4 & 5: Coartem® administered from D0 to D3

Episodes 7, 8 & 9: Coartem® administered from D0 to D3

Episodes 8, 9 & 10: Coartem® administered from D0 to D3

ALAT (IU/L) UNL = 45 IU/L

study product administration (D0-D3)
Malaria attacks over time

Insecticide-Treated Nets distribution

In spite of supervised distribution of bednets during summer 2009, no decrease in malaria incidence was observed.
Repeated treatment with ASAQ vs AL in children < 5 years, Tororo, Uganda

Paper to be submitted
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4 Department of Medicine, Makerere University College of Health Sciences
5 East Africa WWARN, Kenyatta Hospital Estate, Nairobi, Kenya

Scientific Committee: MV Kombila, Ph Brasseur, M Danis, Ogobara Doumbo, Laurence Adonis, P Ambroise-Thomas

Other collaborations: Marielle Boyou (Libreville), Hervé Bogreau (Marseille)
ASAQ Winthrop® Risk Management Plan

Summary

Completed trials: 8,058 patients treated with ASAQ Winthrop

EFFICACY: Day 28 efficacy rates consistently > 95%

SAFETY
  ▫ Similar to comparators
    - No unexpected clinical adverse events
    - Asymptomatic, transient increases in liver transaminases and neutropenia
  ▫ No impact of repeated administrations on safety in children
  ▫ Extrapyramidal syndromes added to Summary of Product Characteristics

Ongoing trials: > 17,000 patients treated with ASAQ Winthrop
ASAQ Winthrop® availability 2013

Registered in 32 countries (30 in Africa, Colombia, India)

> 200 million treatments distributed

Internal source: Commercial Operations ATM
Partnerships

- DNDi
- National Malaria Control Programs
- Academic teams
- Medicines for Malaria Venture
- Morocco and Ghana WHO collaborative Centres for Pharmacovigilance
- WWARN : efficacy data
- ACT Consortium : safety data
- Sanofi teams in Africa