New Partnerships
The Development of ASMQ - FDC

Jean-René Kiechel
Senior Product Manager
DNDi

January 2011
In order to fight resistance:

1. ACTs should be first-line treatment for *falciparum* malaria everywhere

2. These ideally should be formulated in fixed dose combinations when possible
WHO Guidelines (2010)
Recommendations Strengthened: FDC

- Combination of AS and MQ is one of the 5 ACTs recommended by WHO as effective first-line treatments for uncomplicated *P. falciparum* malaria
- Fixed-dose combinations (FDC) are highly preferable to the loose individual medicines co-blistered or co-dispensed
  - Promote adherence to the treatment
  - Contribute to delaying artemisinin resistance (avoid monotherapy)
Why Develop Easy-to-Use Fixed-Dose Combinations (FDCs)?

- Facilitate compliance
- Decrease risks of resistance development
- Improve use in the field
- Improve deployment of ACTs

A better treatment for *falciparum* malaria
The International Partnership
Artesunate-Mefloquine Fixed Dose Combination

Industrial Partners: Farmanguinhos, Cipla

DNDi/TDR: scientific coordination & project management

Funding: EU’s INCODEV, France, Netherlands, Spain, UK, MSF
The Blueprint of the Blue ASMQ Tablet

- Quality components (AS, MQ, Excipients)
- Smallest possible size (Minimum excipients)
- Good aspect (Coating)
- Paediatric strengths; rapid disintegration in water
- Simple (1 or 2 tablets for 3 days)
- Stable (Process and Tropical conditions)
- Adequate biopharmaceutical properties
Simplified Dosing Regimen: Easy as 1-2-3 for Adults (≥12 yr)

<table>
<thead>
<tr>
<th>ADULT(≥12yrs) DOSING</th>
<th>New FACT ASMQ</th>
<th>NON-FIXED AS and MQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAY 1</td>
<td>AS: 100mg</td>
<td>AS: 50mg</td>
</tr>
<tr>
<td></td>
<td>MQ(salt): 220mg</td>
<td>MQ(salt): 250mg</td>
</tr>
<tr>
<td></td>
<td>Once a day</td>
<td>Once a day</td>
</tr>
<tr>
<td>DAY 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAY 3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Small Tablets – Paediatric Strengths

INFANT DOSE
< 1 YEAR

Once a day

Day 1

Day 2

Day 3

New FACT ASMQ
AS: 100mg
MQ(salt): 220mg

NON-FIXED ASP and MQ
AS: 50mg
MQ(salt): 250mg
A Specific Dosage for Each Patient

<table>
<thead>
<tr>
<th>Weight (Kg)</th>
<th>Age</th>
<th>Recommended Dose</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 – 8</td>
<td>2 – 11 months</td>
<td>One Tablet 25/55 mg¹ daily for 3 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 – 17</td>
<td>1 – 6 years</td>
<td>Two Tablets 25/55 mg¹ daily for 3 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 – 29</td>
<td>7 – 12 years</td>
<td>One Tablet 100/220 mg² daily for 3 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 30</td>
<td>≥ 13 years</td>
<td>Two Tablets 100/220 mg² daily for 3 days</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Mefloquine HCl 55 mg are equivalent to 50 mg of mefloquine
2. Mefloquine HCl 220 mg are equivalent to 200 mg of mefloquine
PK Profiling of FDC ASMQ in HNVs and Patients: AS+MQ Regimens

- **AS 4 mg/kg**
- **MQ 15 mg/kg**
- **AS 4 mg/kg**
- **MQ 10 mg/kg**
- **AS 4 mg/kg**
- **MQ 8 mg/kg**

- **0h**
- **24h**
- **48h**

- Well researched
- Highly effective
- Scarcely practical

- popPK of the split dose
- PKs of the FDC?
Predicted and Measured Profiles for MQ in Adult Patients (Thailand)

- **FDC**: 8mg/kg/d x3d
- **non-MQ**: 15+10MKD at 24,48H as loose combination with AS

**28 days**
Fixed Combination vs Loose Drugs

- November 2004 – June 2005
- 500 patients
- Age: 6 months- 65 years
- 9 weeks follow up

Efficacy

PCR-adjusted cure rate at D63
[95% CI]

AS-MQ FIXED
92%
[87-95]

AS-MQ LOOSE
89%
[84-93]

P=0.4

Early vomiting

- < 1 h after dose.

<table>
<thead>
<tr>
<th></th>
<th>Fixed N%</th>
<th>Loose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0</td>
<td>8 (3%)</td>
<td>2 (0.8%)</td>
</tr>
<tr>
<td>Day 1</td>
<td>0</td>
<td>8 (3%)</td>
</tr>
<tr>
<td>Day 2</td>
<td>0</td>
<td>2 (0.8%)</td>
</tr>
</tbody>
</table>

- Rescue therapy: 2 patients (Loose group)

\(^1\) Fishers Exact Test
Tolerability

✓ “Splitting the dose of mefloquine significantly reduced the incidence of gastro-intestinal adverse events (abdominal pain, anorexia, nausea, and late vomiting), as well as experiencing any adverse event.”

✓ “The M888/FDC offered the best safety profile.”

Mefloquine-artesunate: an Individual Patient Meta-Analysis on Tolerability in 5,487 Patients treated for *P. falciparum* along the Thai-Myanmar border

Julien Zwang’s report, 2009
Clinical study in India (2008)

Assessment of efficacy, safety and population pharmacokinetics of the fixed-dose combination of Artesunate-Mefloquine (AS/MQ) in the treatment of uncomplicated *P. falciparum* malaria in India
Results

Efficacy:

• Cure rate at Day 63 after PCR genotyping was 100% in PP population (N=66). 1 treatment failure which was a late parasitological failure (new infection).

Safety:

• No serious adverse events (SAE) reported. AS/MQ FDC well tolerated and found to be safe in this study.

Population Pharmacokinetics:

• Development of a model based on sparse sampling (AS/DHA/MQ)

• Simulation of individual PK data
  – DHA eq. peak comparable to «loose» combination of AS and MQ tablets
  – MQ kinetics: D 28 levels comparable to historical comparison/BKK study (400 – 600 ng/ml)
**Objective**: to evaluate the impact of programmatic use of ASMQ in the reduction of *falciparum* malaria incidence in comparison with the standard regimen used in Brazil

- Acre State; Juruá Valley: 3 municipalities with 103,809 inhabitants, total
  - 86% of malaria cases

- Malaria treatment through the public sector only
Results

• More than 30,000 patients included

• Successful study implementation in programmatic context, in collaboration with MoH and PAHO

• Significant impact of ASMQ in malaria reduction and change in Pf/Pv ratio after an epidemic period

• Lower positivity and gametocytes in follow-up smears

• No significant adverse events identified through passive notification system
AS-MQ in Summary

✅ Efficacious
✅ Safe
✅ Well-tolerated
✅ Favourable PK profile
✅ Simple regimen
✅ Durable combination
✅ Convenient coformulation
✅ 3-year shelf life

❌ Not recommended in severe malaria
❌ Use in pregnancy needs further study
❌ Cumulative toxicity with repeated dosing
ASMQ: A Well Studied Combination

- Developed in South East Asia
- 74 clinical studies published
- 18 years experience in Thailand

- 3 continents & 20 countries:
  - > 11,000 patients with « loose » combination
  - > 30,000 patients with the FDC
  - 5,500 patients in tolerability analysis
ASMQ FDC Status 2010

Brazil
- Registration in Brazil (2008)
- Adopted by Malaria Programme

Asia
- Technology transfer to Cipla
- To be filed and implemented in India and in ASEAN countries (2010-2011)
- Donation to Cambodia

Africa
- Clinical study
THANK YOU TO OUR PARTNERS

www.dndi.org