The ASMQ - FDC

Jean-René Kiechel
Senior Product Manager, DNDi

November 2009

DNDi
Drugs for Neglected Diseases initiative

INDUSTRIAL PARTNERS: FARMANGUINHOS; CIPLA

BRAZIL

DNDI/TDR: scientific coordination & project management

SOUTHEAST ASIA

Funding: EU's INCODEV, France, Netherlands, Spain, UK, MSF
In-kind: Farmanguinhos

Univ Mahidol, Thailand
Shoklo Malaria Research Unit, Thailand:

Kavedra Malana Program

Unversity Sains Malaysia

Farmanguinhos/Fiocruz, Brazil

Malaria-endemic region

Coordination, management, & funding

Development partners

Partnership with ICMR

All work inside the box was & is managed by DNDI throughout project life.
Why Develop Easy-to-Use Fixed-Dose Combinations (FDCs)?

- Facilitate compliance
- Improve use in the field
  - At health centres and at home
- Decrease risks of resistance development
- Better deployment and use of ACTs

**Improved therapy for *falciparum* malaria**

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)

**Adult (≥12 yrs) Dosing**

**New FACT ASMQ**
- **DAY 1**: AS: 100mg MQ(salt): 220mg
- **DAY 2**: Once a day
- **DAY 3**: Once a day

**Non-Fixed AS and MQ**
- **DAY 1**: AS: 50mg MQ(salt): 250mg
- **DAY 2**: Once a day
- **DAY 3**: Once a day

**Small Tablets – Paediatric Strengths**

**Infant Dose < 1 YEAR**

**New FACT ASMQ**
- **DAY 1**: AS: 100mg MQ(salt): 220mg
- **DAY 2**: Once a day
- **DAY 3**: Once a day

**Non-Fixed AS and MQ**
- **DAY 1**: AS: 50mg MQ(salt): 250mg
- **DAY 2**: Once a day
- **DAY 3**: Once a day
ASMQ – Clinical Evidence to Date

- AS and MQ used in field for past 16 years. Extensive published clinical data.
- Phase I
  - PK & safety of FDC compared to non-fixed combination in HNVs
- Phase II
  - PK, efficacy, & safety in patients comparing FDC and non-fixed combination
- ECG data for the combinations (Phase I and II)
- Phase III
  - Clinical field study with the FDC and the non-fixed combination in Thailand
- Meta-analysis of safety and tolerability (data from SMRU; 5500 patients)
- Intervention study of >25,000 patients in Brazil

PK Profiling of FDC ASMQ in HNVs and Patients: AS+MQ Regimens

- 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)

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

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

Cost - US$2.50 (full-course adult treatment)
ASMQ Worldwide:
Available in 2008 through Public Partnership with Brazil-Funded Farmanguinhos

- **Brazil**
  - Registered in March 2008
  - Recommended as 1st-line treatment in 3 states

- **Asia**
  - Industrial partner: Cipla
  - Completed studies: India, Myanmar

- **Africa**
  - A role for ASMQ?
    Clinical studies needed.

---

THANK YOU!

www.dndi.org
ASMQ in Africa – Why?

1. Clinical data on AS-MQ (co-blister and fixed dose combination) in Asia, Latin America.
   Some data in Africa (particularly with co-blister) but insufficient safety and tolerability data in children and none with DNDi FDC

2. Further clinical data on the combination of AS with MQ in African children are needed.
   - indicated in the WHO treatment guidelines (2006)
   - recommended by Experts (FACT Advisory group)

3. Maciej. et al, 2008: The clinical benefits of using multiple first-line therapies (MFT) against malaria suggest that MFT policies should play a key role in malaria elimination and control programmes.

4. Artemisinin Resistance in Plasmodium falciparum Malaria. Need of strong partner with AS

5. ASMQ as an alternative treatment and easy to use (FDC, once a day)
   ⇒ DNDi has started a study in Tanzania.

Pop PK of Mefloquine 8 mg/kg/d

AUC was 40% higher than previous estimates in patients treated with mefloquine (15+10 mg/kg)

Results - Early vomiting

• 30% lower risk if mefloquine dose is split (CI95 19-40)

• Risk factors:
  female, higher parasite count, fever, younger age
  – (0-4 years: OR=6.84 P=0.001)

Side-effects

Julien Zwang’s report, 2009