The ASMQ - FDC

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DNDi
Drugs for Neglected Diseases initiative

INDUSTRIAL PARTNERS:
FARMANGUINHOS; CIPLA

DNDi/TDR:
scientific coordination & project management

SOUTHEAST ASIA

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

All work inside the box was & is managed by DNDi throughout project life.

Coordination, management, & funding
Malaria-endemic region
Development partners
Partnership with ICMR
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**

- **DAY 1**: New FACT ASMQ
  - AS: 100mg
  - MQ(salt): 220mg
  - Once a day
- **DAY 2**: NON-FIXED AS and MQ
  - AS: 50mg
  - MQ(salt): 250mg
  - Once a day

**INFANT DOSE < 1 YEAR**

- **NEW FACT ASMQ**
  - AS: 100mg
  - MQ(salt): 220mg
  - Once a day
- **NON-FIXED AS and MQ**
  - AS: 50mg
  - MQ(salt): 250mg
  - Once a day

Small Tablets – Paediatric Strengths
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

<table>
<thead>
<tr>
<th>Regimen</th>
<th>0h</th>
<th>24h</th>
<th>48h</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS 4 mg/kg</td>
<td>MQ 15 mg/kg</td>
<td>- Well researched - Highly effective - Scarcely practical</td>
<td></td>
</tr>
<tr>
<td>AS 4 mg/kg</td>
<td>MQ 10 mg/kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AS 4 mg/kg</td>
<td>MQ 8 mg/kg</td>
<td></td>
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</tr>
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</table>

- 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


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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

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**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.

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**Pop PK of Mefloquine 8 mg/kg/d**

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

Predicted population pharmacokinetic profile for mefloquine 8mg/kg/day for 3 days with artemesunate.

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