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)

1. **Day 1**: 1 tablet
2. **Day 2**: 1 tablet
3. **Day 3**: 1 tablet

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

Non-FIXED AS and MQ
- AS: 50mg
- MQ(salt): 250mg

Once a day

Small Tablets – Paediatric Strengths

- **Infant Dose (<1 year)**
  - AS: 50mg
  - MQ(salt): 130mg
  - Once a day

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

- **Non-FIXED AS and MQ**
  - AS: 50mg
  - MQ(salt): 250mg
  - Once a day
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

Intervention Trial – Brazil
Artesunate-Mefloquine FDC

Background
- Funding: MOH and PAHO/RVREDa
- Steering Committee: MOH, PAHO, Farmanguinhos and DNDi
- 7 municipalities in 2 states in the Amazon Basin (Acre and Pará)
- High burden of malaria
- MOH priority municipalities

Preliminary Results at 1 Year
Real Impact Seen in Programmatic Use

After 1 year of program including ASMQ:
- ~70% drop in reported falciparum malaria cases
- >60% reduction in malaria-related hospital admissions
- 17,000 patients treated

Myanmar study:
comparative study of ACTs
(2008-2009)
Frank Smithuis, MSF

Comparing the effectiveness of 5 artemisinin combination treatment regimens

- 1. AA Artesunate-amodiaquine
- 2. AL Artemether-lumefantrine
- 3. AM-F Artesunate-mefloquine Fixed dose combination
- 4. AM-L Artesunate-mefloquine Loose tablets
- 5. DP Dihydroartemisinin-piperaquine

Half patients with primaquine 0.75 mg/kg (sd) and half without.
Sample size; 800
Effect on gametocytes

![Gametocyte positivity graph](image)

Proportion of patients positive for gametocytes after treatment (no PQ)

- AA
- AL
- AMF
- AML
- DP

Days follow up: 0, 7, 14, 21, 28, 35, 42, 49

Gametocyte positivity rate:

- 0%
- 10%
- 20%
- 30%
- 40%
- 50%

Effect on P. Vivax

![Patients with at least 1 vivax appearance after treatment](image)

Patients with at least 1 vivax appearance after treatment:

- AA
- AL
- AMF
- AML
- DP

Significant difference between AM-FDC and AL (p<0.001) and AM-LT (p=0.01)

Indian study:

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 (2008-2009)

Patient Disposition

<table>
<thead>
<tr>
<th>Patient Disposition</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT analysis population</td>
<td>77 (100.0)</td>
</tr>
<tr>
<td>Completed treatment period</td>
<td>74 (96.1)</td>
</tr>
<tr>
<td>PP analysis population</td>
<td>66 (85.7)</td>
</tr>
<tr>
<td>Early Terminations/ Withdrawals</td>
<td>11 (14.3)</td>
</tr>
<tr>
<td>Consent withdrawn</td>
<td>4 (5.2)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>6 (7.8)</td>
</tr>
<tr>
<td>Protocol violation</td>
<td>1 (1.3)</td>
</tr>
</tbody>
</table>
### Cure rate before and after PCR correction at end of 63 days

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cure rate at end of 63 Days before PCR correction- PP population (N=66)</th>
<th>Cure rate at end of 63 Days after PCR correction- PP population (N=66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients with ACPR</td>
<td>65 (98.5)</td>
<td>66 (100%)</td>
</tr>
<tr>
<td>Cure rate (%)</td>
<td>98.5</td>
<td>100%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients with new infection</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>No. of patients classified as cured after PCR genotyping</td>
<td>66 (100%)</td>
</tr>
</tbody>
</table>

### ASMQ: 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
  - Ongoing studies: India, Myanmar (MSF)

### 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 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.

www.dndi.org