

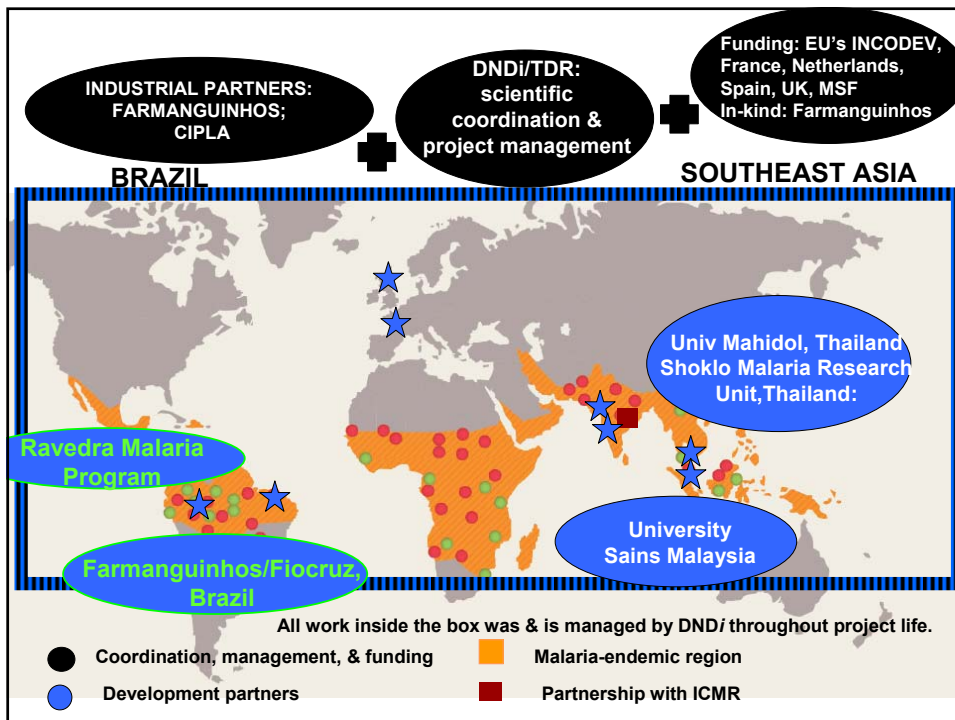
The ASMQ - FDC



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Senior Product Manager, DNDi

November 2009

DNDi
Drugs for Neglected Diseases *initiative*



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

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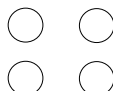
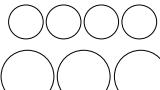
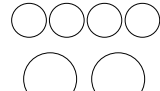
The Blueprint of the Blue ASMQ Tablet

- 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



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Simplified Dosing Regimen: Easy as 1-2-3 for Adults (≥12 yr)

ADULT (≥12yrs) DOSING	New FACT ASMQ	NON-FIXED AS and MQ
 <div style="border: 1px solid black; padding: 5px; width: 50px; margin: 5px auto;">DAY 1</div> <div style="border: 1px solid black; padding: 5px; width: 50px; margin: 5px auto;">DAY 2</div> <div style="border: 1px solid black; padding: 5px; width: 50px; margin: 5px auto;">DAY 3</div>	<p style="color: red;">AS: 100mg MQ(salt): 220mg</p> <p>Once a day</p> <div style="border: 1px solid black; padding: 5px; width: 80px; margin: 5px auto;">  </div> <div style="border: 1px solid black; padding: 5px; width: 80px; margin: 5px auto;">  </div> <div style="border: 1px solid black; padding: 5px; width: 80px; margin: 5px auto;">  </div>	<p style="color: red;">AS: 50mg MQ(salt): 250mg</p> <p>Once a day</p> <div style="border: 1px solid black; padding: 5px; width: 100px; margin: 5px auto;">  </div> <div style="border: 1px solid black; padding: 5px; width: 100px; margin: 5px auto;">  </div> <div style="border: 1px solid black; padding: 5px; width: 100px; margin: 5px auto;">  </div>

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Small Tablets – Paediatric Strengths

	New FACT ASMQ	NON-FIXED AS and MQ
<p style="color: red;">INFANT DOSE < 1 YEAR</p> 	<p style="color: red;">AS: 100mg MQ(salt): 220mg</p> <p>Once a day</p>	<p style="color: red;">AS: 50mg MQ(salt): 250mg</p> <p>Once a day</p>
Day 1	<div style="border: 1px solid black; padding: 5px; width: 60px; margin: 5px auto;">  </div>	<div style="border: 1px solid black; padding: 5px; width: 60px; margin: 5px auto;">  </div>
Day 2	<div style="border: 1px solid black; padding: 5px; width: 60px; margin: 5px auto;">  </div>	<div style="border: 1px solid black; padding: 5px; width: 60px; margin: 5px auto;">  </div>
Day 3	<div style="border: 1px solid black; padding: 5px; width: 60px; margin: 5px auto;">  </div>	<div style="border: 1px solid black; padding: 5px; width: 60px; margin: 5px auto;">  </div>

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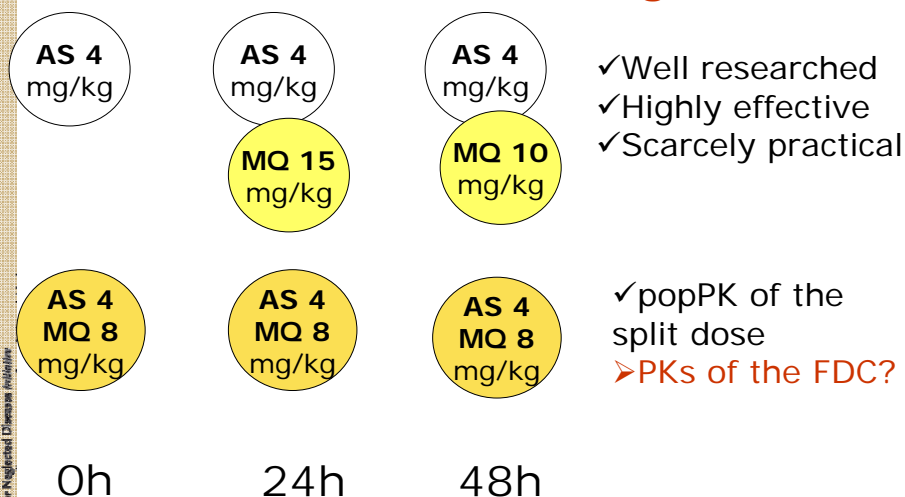
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ASMQ – Clinical Evidence to Date

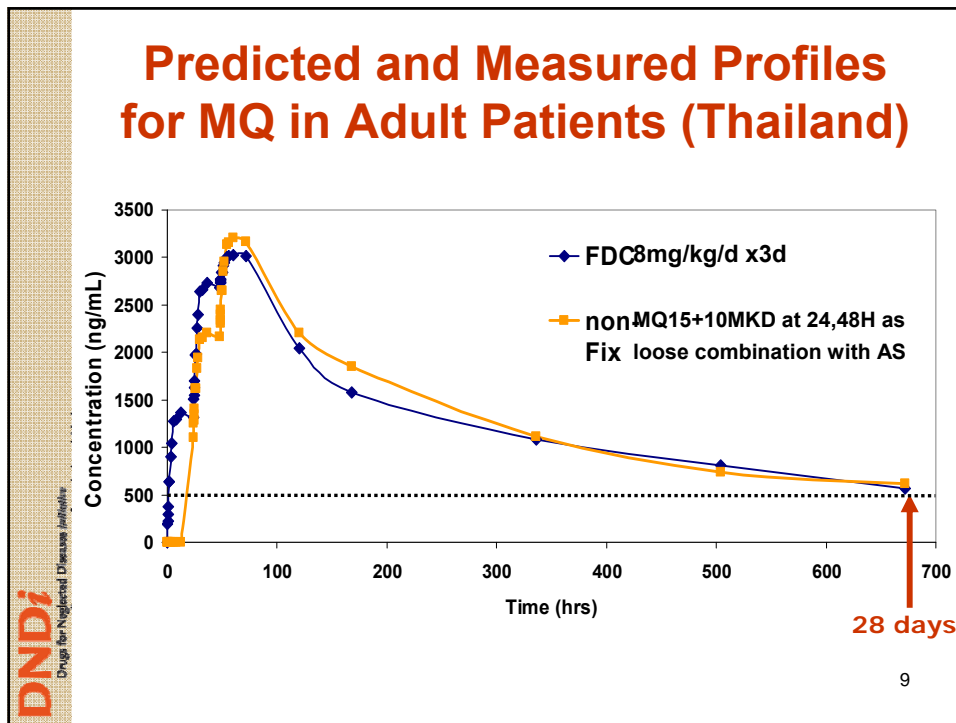
- AS and MQ used in field for past 16 years. Extensive published clinical data.
- Phase I
 - PK & safety of FDC compared to non-fixed combination in HNVs
- Phase II
 - PK, efficacy, & safety in patients comparing FDC and non-fixed combination
- ECG data for the combinations (Phase I and II)
- Phase III
 - 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

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



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Fixed Combination vs Loose Drugs

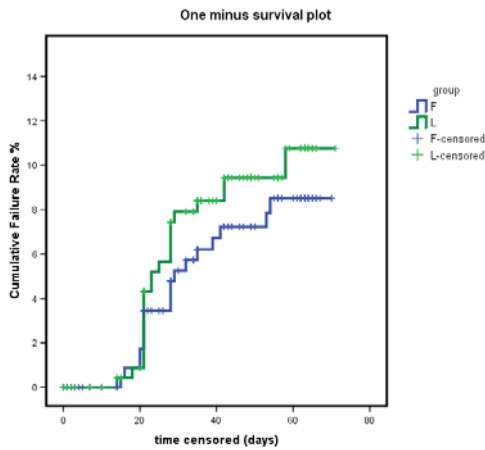
- November 2004 – June 2005
- 500 patients
- Age: 6 months- 65 years
- 9 weeks follow up

Reference: Ashley EA et al. *Trop Med Int Health*. Nov 2006;11(11):1653-1660.

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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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Reference: Ashley EA et al. *Trop Med Int Health*. Nov 2006;11(11):1653-1660.

Early vomiting

- < 1 h after dose.

	Fixed N%	Loose
– Day 0	8 (3%)	2 (0.8%)
– Day 1	0	8 (3%)
– Day 2	0	2 (0.8%)

p=0.004¹

- 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)

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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.

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THANK YOU !



www.dndi.org

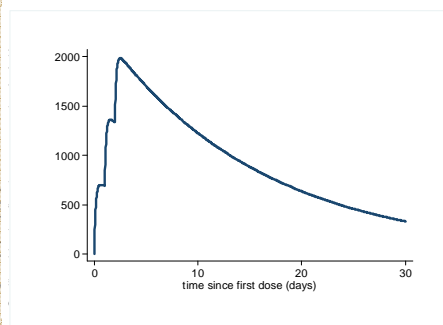
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ASMQ in Africa – Why?

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 artesunate.

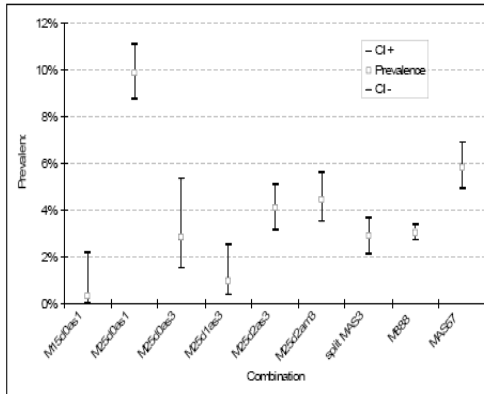
Reference: Ashley EA et al. *Antimicrob Agents Chemother.* Jul 2006;50(7):2281-2285.

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Results - Early vomiting

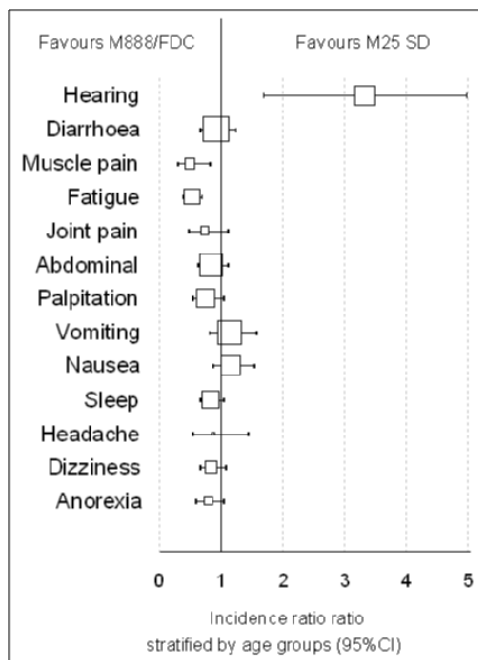
Early vomiting by drug regimen

Figure 4 : Early vomiting by mefloquine-artesunate drug regimen



- 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



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* 20