The ASMQ - FDC

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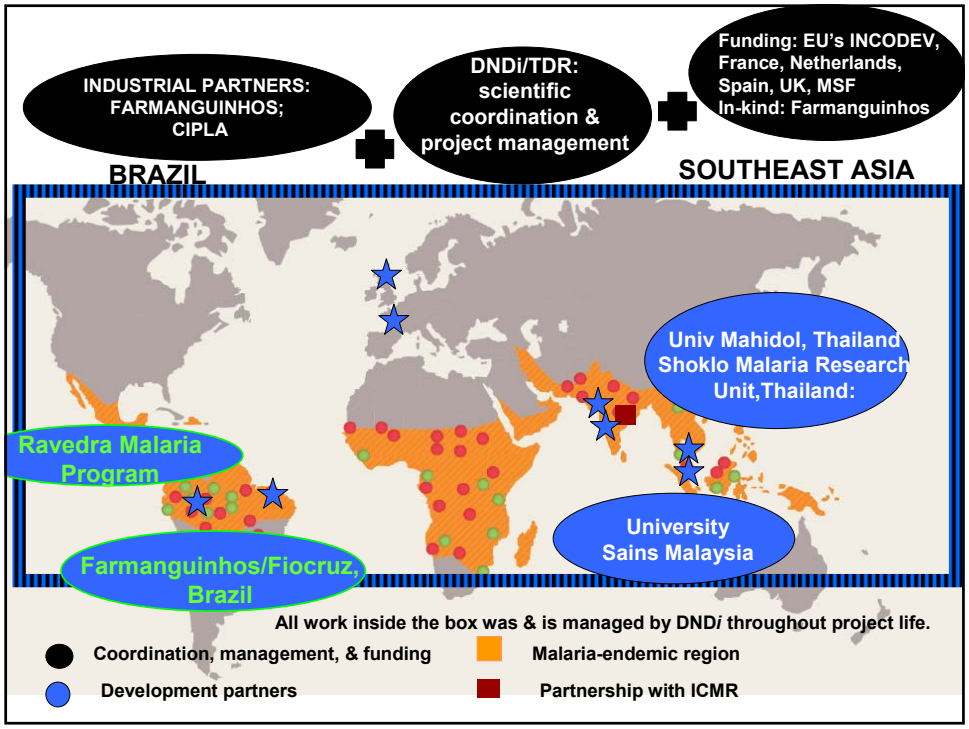
DNDi
Drugs for Neglected Diseases *initiative*



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

3

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

4

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

ADULT(≥12yrs) DOSING	New FACT ASMQ	NON-FIXED AS and MQ
	AS: 100mg MQ(salt): 220mg	AS: 50mg MQ(salt): 250mg
	Once a day	Once a day
DAY 1		
DAY 2		
DAY 3		

Small Tablets – Paediatric Strengths

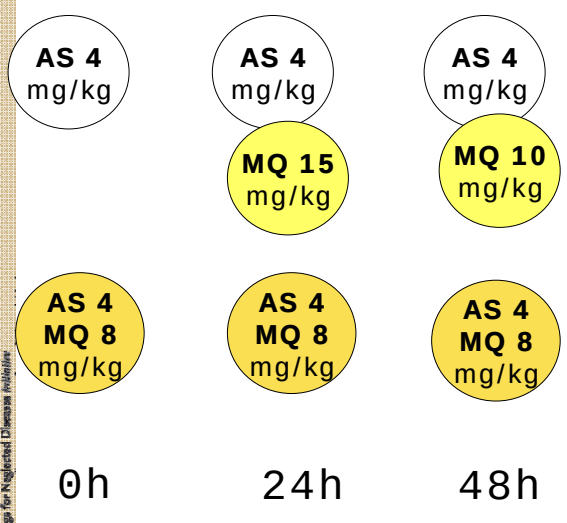
INFANT DOSE < 1 YEAR	New FACT ASMQ	NON-FIXED AS and MQ
	AS: 100mg MQ(salt): 220mg	AS: 50mg MQ(salt): 250mg
	Once a day	Once a day
Day 1		
Day 2		
Day 3		

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

7

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

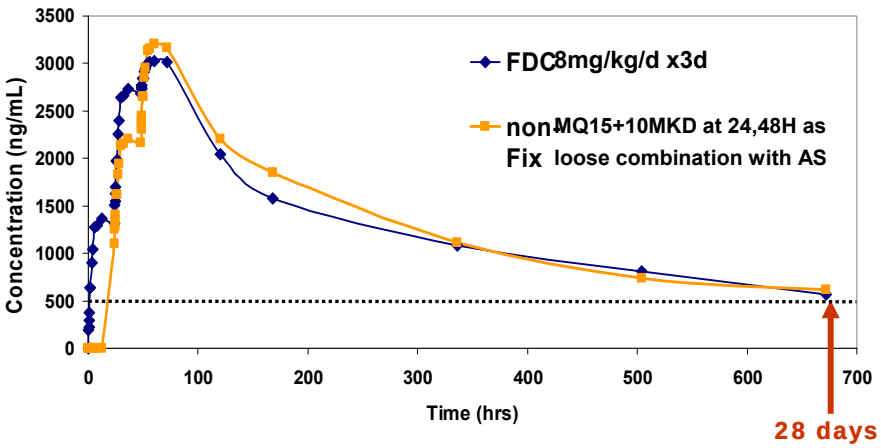


✓Well researched
✓Highly effective
✓Scarcely practical

✓popPK of the split dose
➢PKs of the FDC?

8

Predicted and Measured Profiles for MQ in Adult Patients (Thailand)

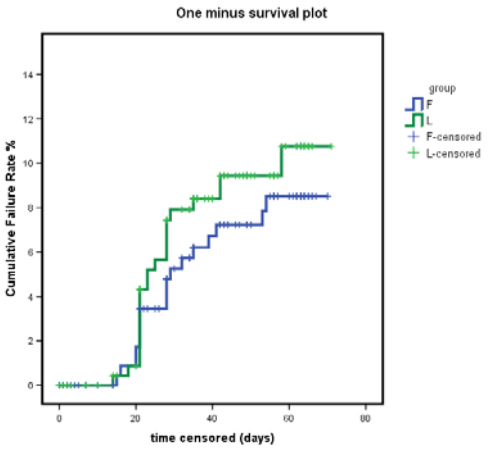


Fixed Combination vs Loose Drugs

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

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

Efficacy



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

AS-MQ FIXED 92%

[87-95]

AS-MQ LOOSE 89%

[84-93]

P=0.4

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

Early vomiting

- < 1 h after dose.

	Fixed N%	Loose	
– Day 0	8 (3%)	2 (0.8%)	
– Day 1	0	8 (3%)	p=0.004 [1]
– Day 2	0	2 (0.8%)	

- 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

13

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)

14

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.

15

THANK YOU !

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16

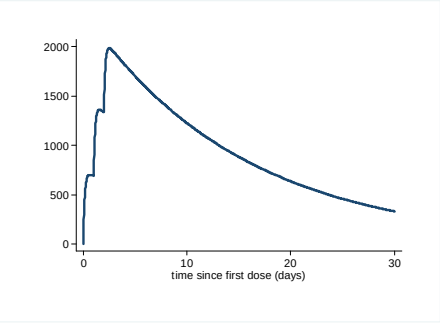
ASMQ in Africa – Why?

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.

17

Pop PK of Mefloquine 8 mg/kg/d



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

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

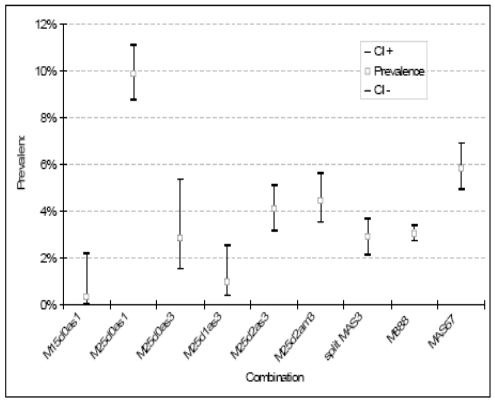
18

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

Results - Early vomiting

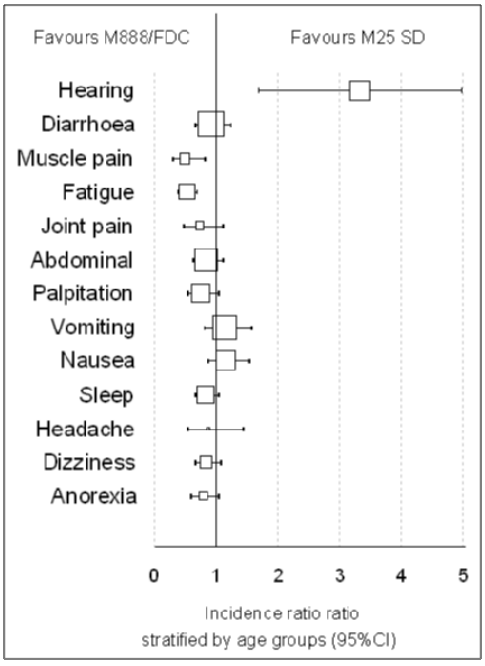
Early vomiting by drug regimen

Figure 4 : Early vomiting by mefloquine-artesunate drug regimen



- 30% lower risk if mefloquine dose is split (CI^{95} 19-40)
- Risk factors: female, higher parasite count, fever, younger age
  - (0-4 years: OR=6.84 P=0.001)

19



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