

New Partnerships

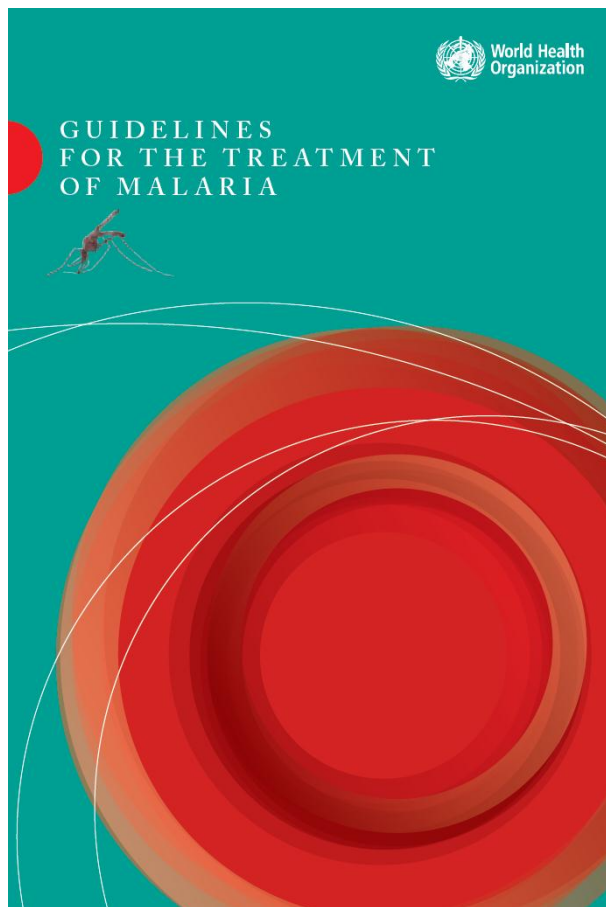
The Development of ASMQ - FDC



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ACTs: World Health Organization Treatment Guidelines (2006)



In order to fight resistance:

1. ACTs should be first-line treatment for *falciparum* malaria everywhere
2. These ideally should be formulated in fixed dose combinations when possible

WHO Guidelines (2010)

Recommendations Strengthened: FDC

- Combination of AS and MQ is one of the 5 ACTs recommended by WHO as effective first-line treatments for uncomplicated *P. falciparum* malaria
- Fixed-dose combinations (FDC) are **highly preferable** to the loose individual medicines co-blistered or co-dispensed
 - Promote adherence to the treatment
 - Contribute to delaying artemisinin resistance (avoid monotherapy)

Why Develop Easy-to-Use Fixed-Dose Combinations (FDCs)?

- Facilitate compliance
- Decrease risks of resistance development
- Improve use in the field
- Improve deployment of ACTs



A better treatment for *falciparum* malaria

The International Partnership

Artesunate-Mefloquine Fixed Dose Combination

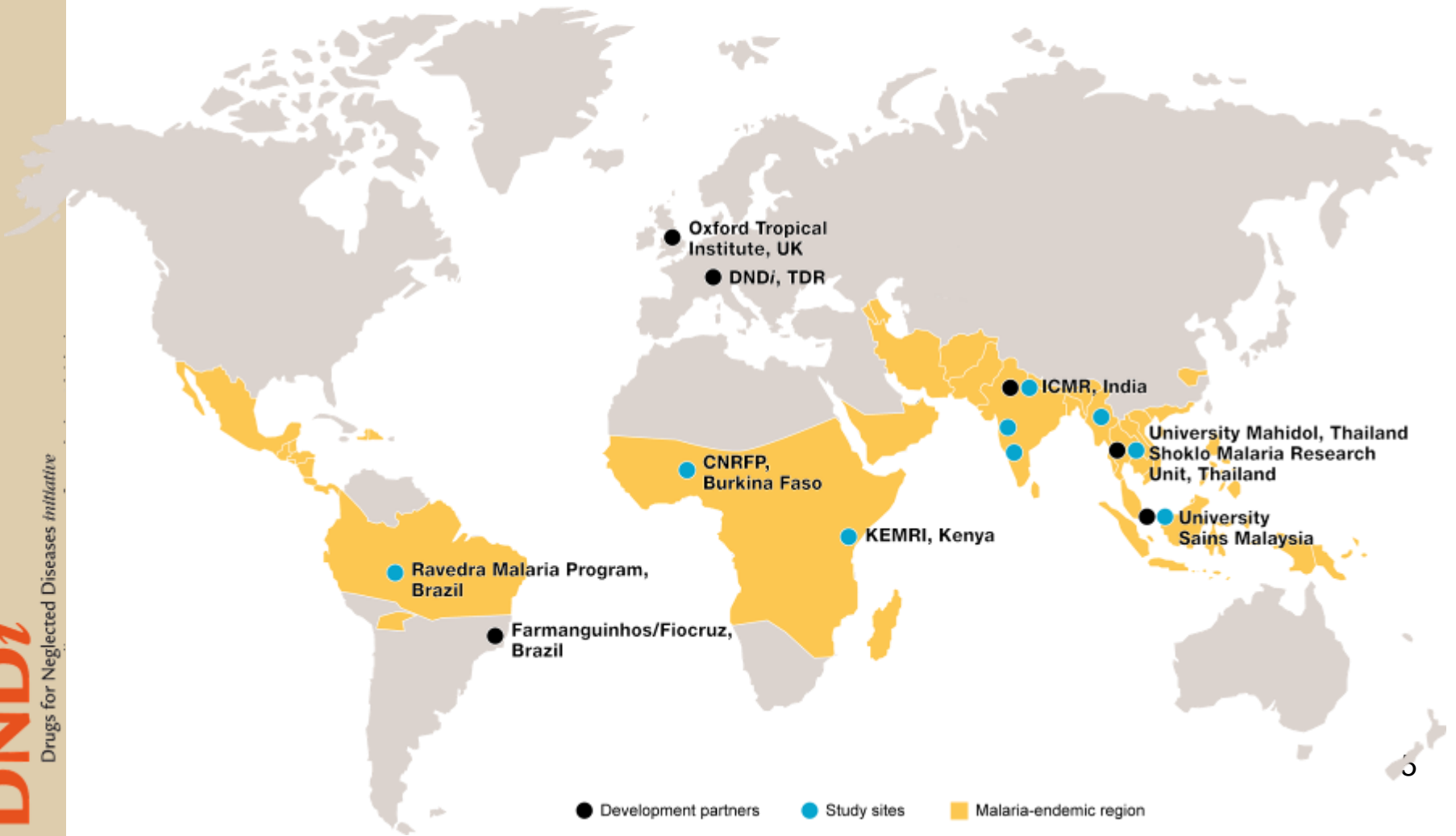
Industrial Partners:
Farmanguinhos
Cipla



DNDi/TDR:
scientific coordination
& project management



Funding: EU's INCODEV,
France, Netherlands,
Spain, UK, MSF



● Development partners ● Study sites ■ Malaria-endemic region

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

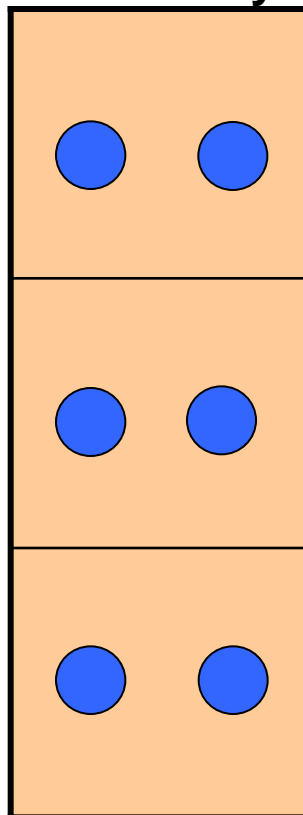
Simplified Dosing Regimen: Easy as 1-2-3 for Adults (≥ 12 yr)

ADULT (≥ 12 yrs)
DOSING



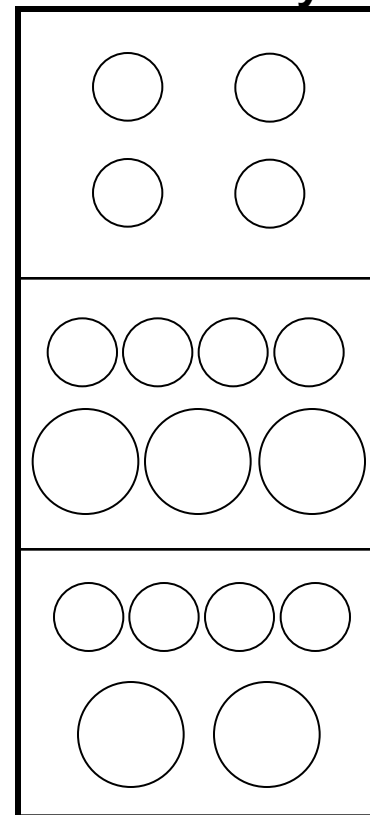
New FACT
ASMQ

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



	New FACT ASMQ	NON-FIXED AS and MQ
INFANT DOSE < 1 YEAR	AS: 100mg MQ(salt): 220mg	AS: 50mg MQ(salt): 250mg
	Once a day	Once a day
Day 1		
Day 2		
Day 3		 8

A Specific Dosage for Each Patient

RECOMMENDED DOSAGE FOR ASMQ FDC TABLETS

Weight (Kg)	Age	Recommended Dose	Day 1	Day 2	Day 3
 5 – 8	2 – 11 months	One Tablet 25/55 mg ¹ daily for 3 days	●	●	●
 9 – 17	1 – 6 years	Two Tablets 25/55 mg ¹ daily for 3 days	● ●	● ●	● ●
 18 – 29	7 – 12 years	One Tablet 100/220 mg ² daily for 3 days	●	●	●
 ≥ 30	≥ 13 years	Two Tablets 100/220 mg ² daily for 3 days	● ●	● ●	● ●

1. Mefloquine HCl 55 mg are equivalent to 50 mg of mefloquine
2. Mefloquine HCl 220 mg are equivalent to 200 mg of mefloquine

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

AS 4
mg/kg

AS 4
mg/kg

AS 4
mg/kg

MQ 15
mg/kg

MQ 10
mg/kg

- ✓ Well researched
- ✓ Highly effective
- ✓ Scarcely practical

AS 4
MQ 8
mg/kg

AS 4
MQ 8
mg/kg

AS 4
MQ 8
mg/kg

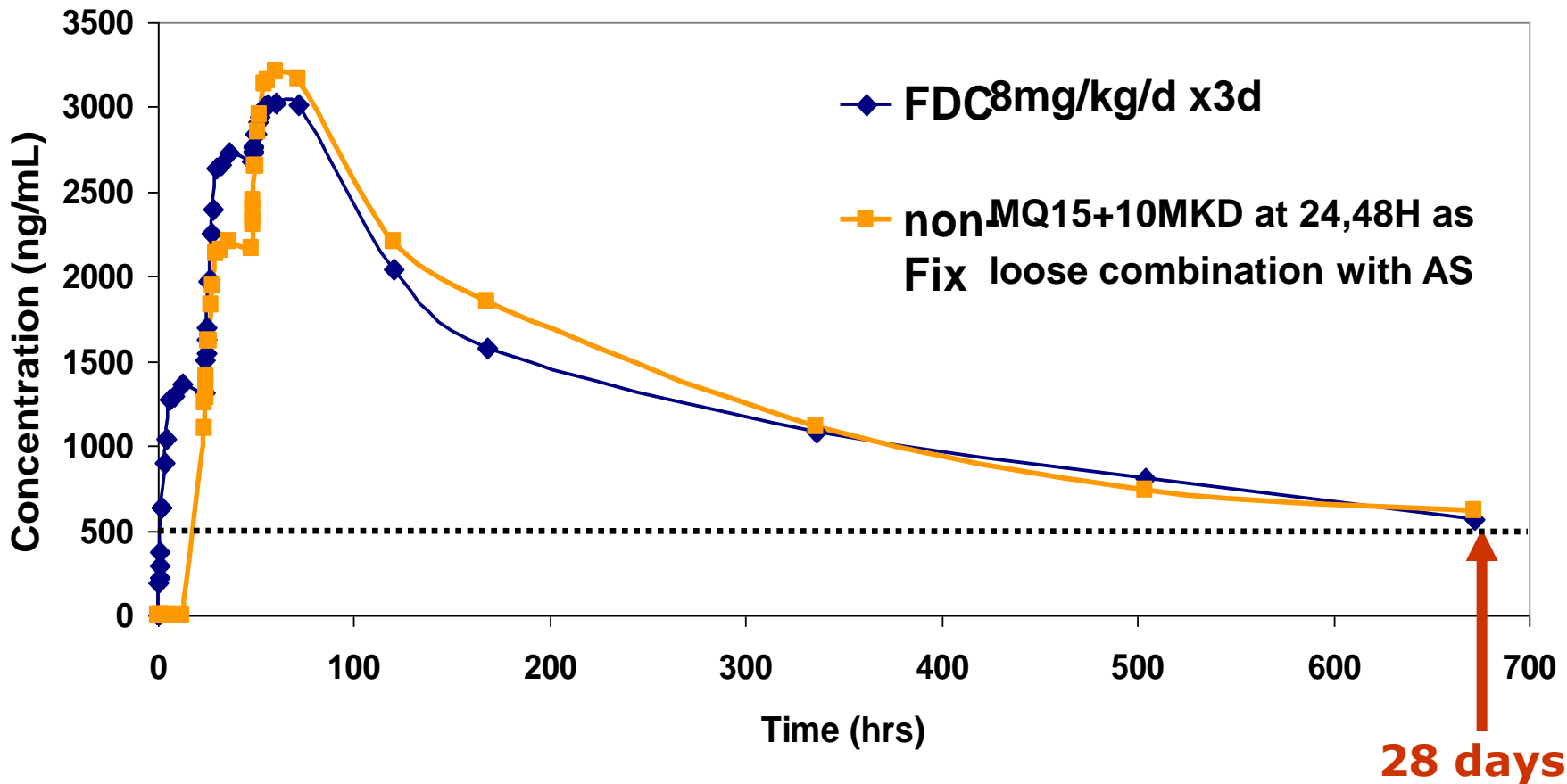
- ✓ popPK of the split dose
- PKs of the FDC?

0h

24h

48h

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

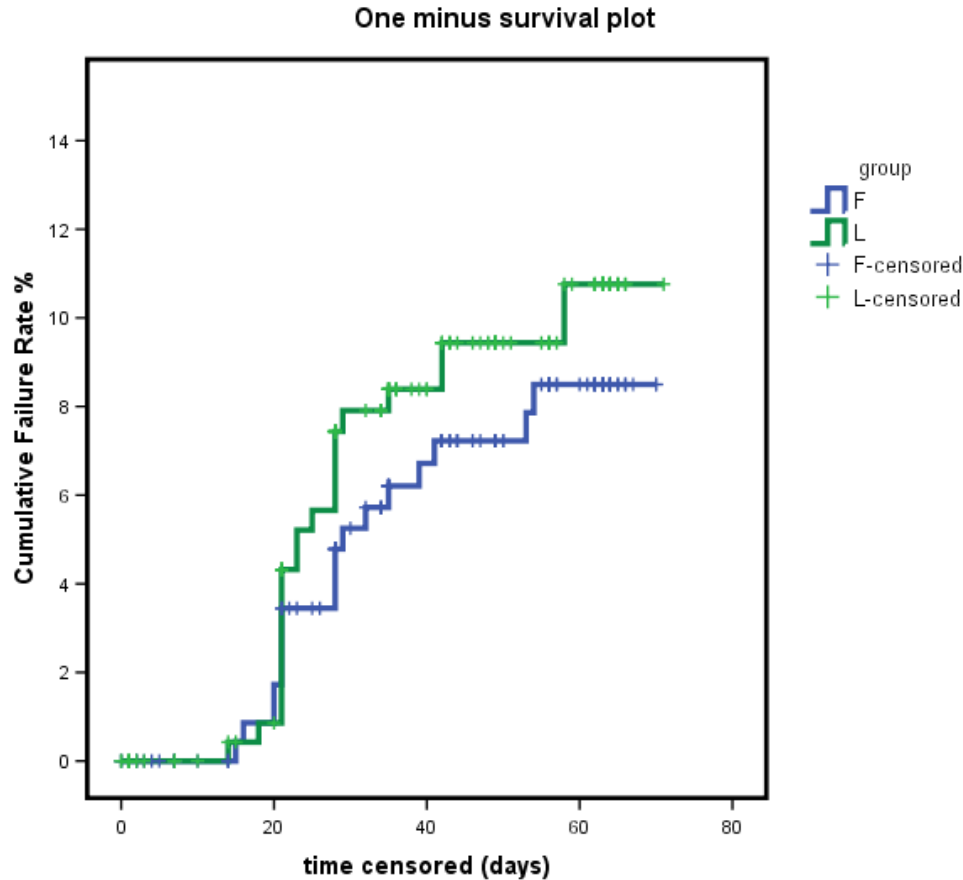


Fixed Combination vs Loose Drugs



- 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.

	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

Clinical study in India (2008)

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



Results

Efficacy:

- Cure rate at Day 63 **after PCR genotyping was 100%** in PP population (N=66). 1 treatment failure which was a late parasitological failure (new infection).

Safety:

- No serious adverse events (SAE) reported. AS/MQ FDC well tolerated and found to be safe in this study.

Population Pharmacokinetics:

- Development of a model based on sparse sampling (AS/DHA/MQ)
- Simulation of individual PK data
 - DHA eq. peak comparable to «loose» combination of AS and MQ tablets
 - MQ kinetics: D 28 levels comparable to historical comparison/BKK study (400 – 600 ng/ml)

Intervention Trial – Brazil

Artesunate-Mefloquine FDC

- **Objective:** to evaluate the impact of programmatic use of ASMQ in the reduction of *falciparum* malaria incidence in comparison with the standard regimen used in Brazil
- Acre State; Juruá Valley: 3 municipalities with 103,809 inhabitants, total
 - 86% of malaria cases
- Malaria treatment through the public sector only



Results

- More than 30,000 patients included
- Successful study implementation in programmatic context, in collaboration with MoH and PAHO
- Significant impact of ASMQ in malaria reduction and change in Pf/Pv ratio after an epidemic period
- Lower positivity and gametocytes in follow-up smears
- No significant adverse events identified through passive notification system

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

ASMQ: A Well Studied Combination

- Developed in South East Asia
- 74 clinical studies published
- 18 years experience in Thailand
- 3 continents & 20 countries:
 - > 11,000 patients with « loose » combination
 - > **30,000** patients with the FDC
 - 5,500 patients in tolerability analysis



ASMQ FDC Status 2010



Brazil

- Registration in Brazil (2008)
- Adopted by Malaria Programme

Asia

- Technology transfer to Cipla
- To be filed and implemented in India and in ASEAN countries (2010-2011)
- Donation to Cambodia

Africa

- Clinical study

THANK YOU TO OUR PARTNERS



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