New Partnerships
The Development of ASMQ - FDC

Jean-René Kiechel

Senior Product Manager

DND*i*

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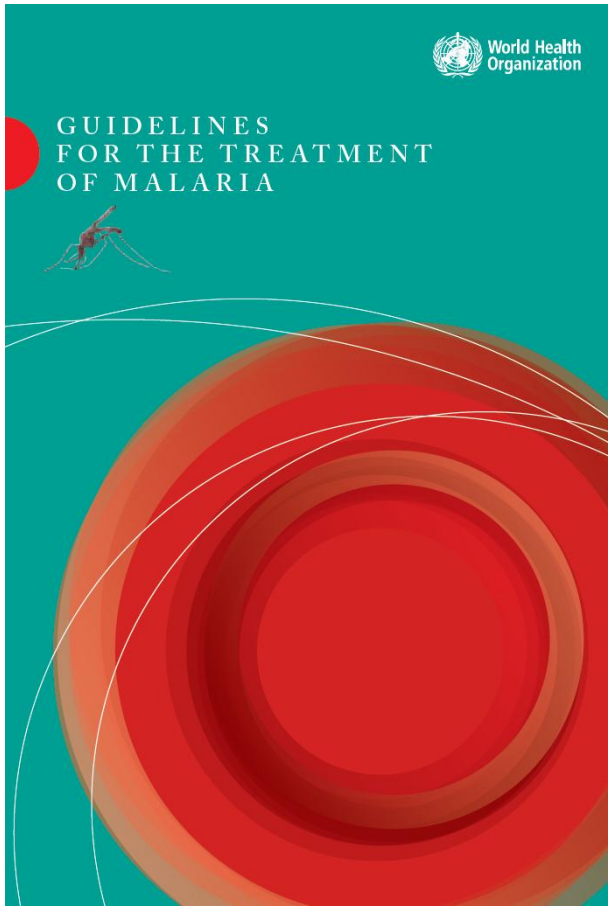
ACTs: World Health Organization Treatment Guidelines (2006)



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

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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

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The International Partnership

Artesunate-Mefloquine Fixed Dose Combination

Industrial Partners:
Farmanguinhos
Cipla

+

DND*i*/TDR:
scientific coordination
& project management

+

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

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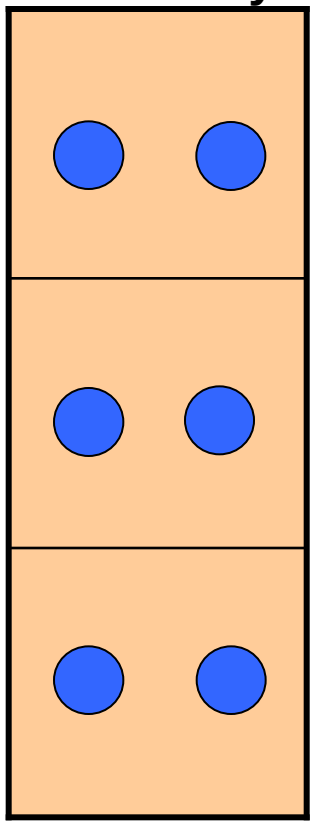
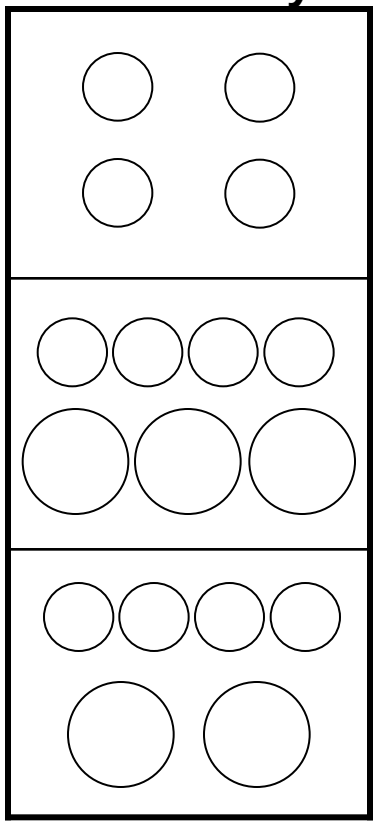
The Blueprint of the Blue ASMQ Tablet

- 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

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 Once a day	AS: 50mg MQ(salt): 250mg Once a day
DAY 1		
DAY 2		
DAY 3		

Small Tablets – Paediatric Strengths

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

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

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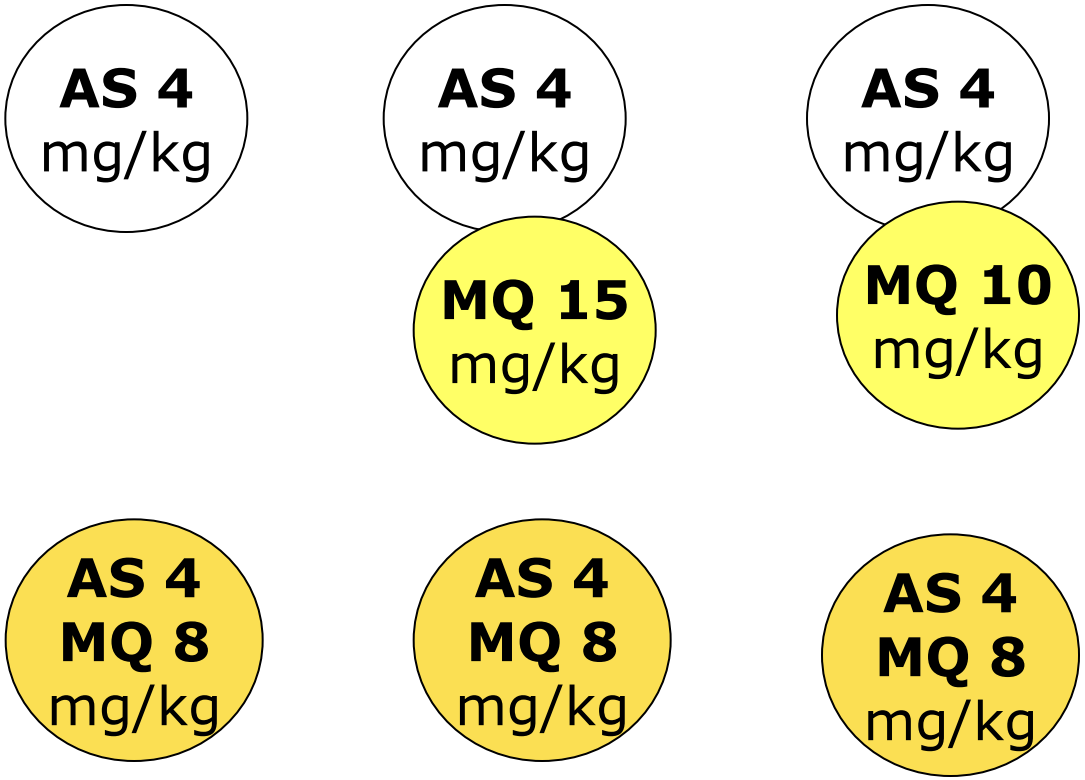
PK Profiling of FDC ASMQ in HNVs and Patients: AS+MQ Regimens



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

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

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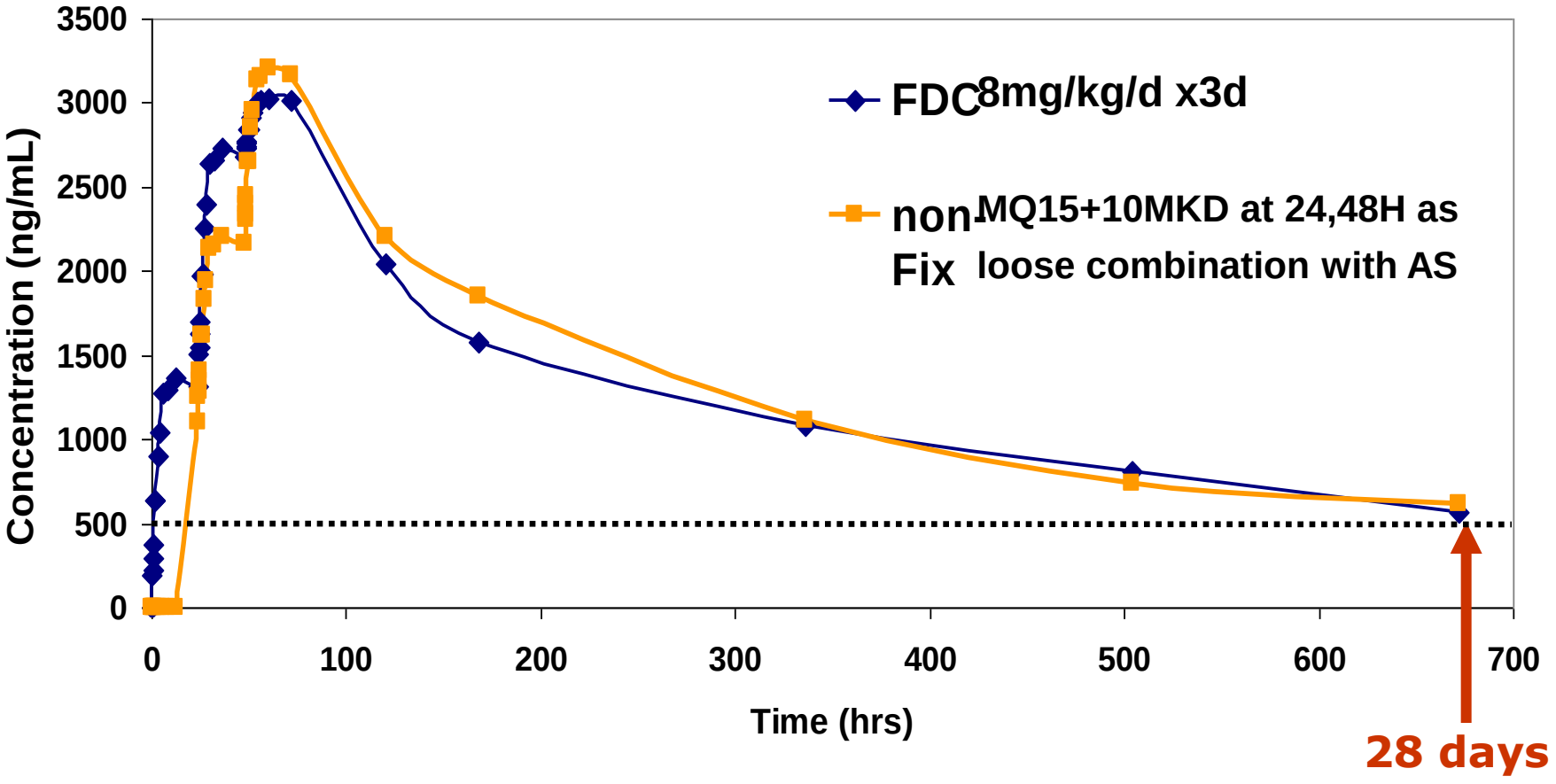
Predicted and Measured Profiles for MQ in Adult Patients (Thailand)

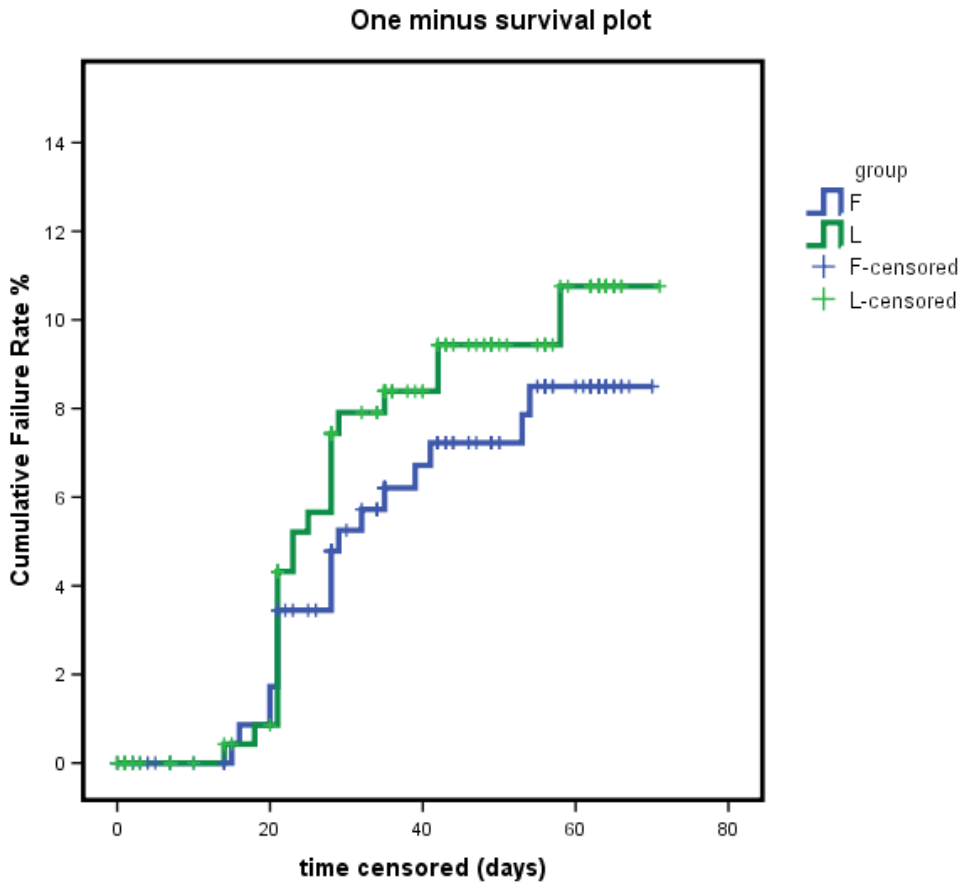


Fixed Combination vs Loose Drugs

- 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.

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

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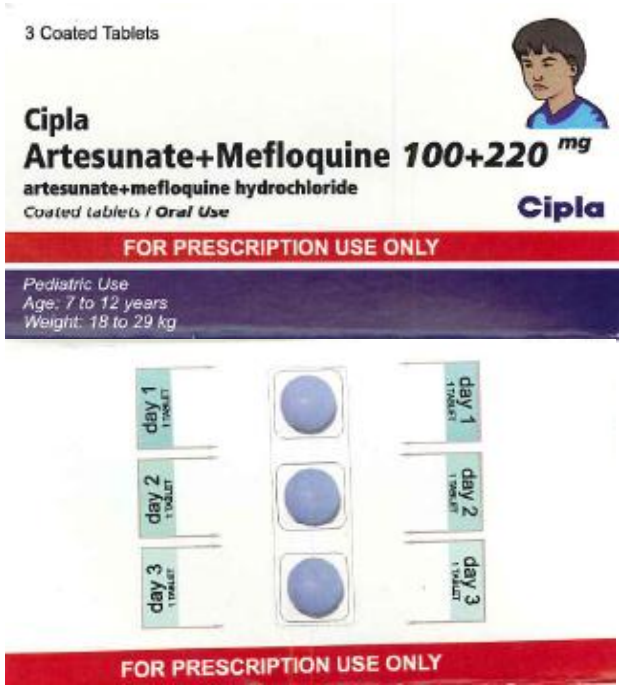
ASMQ: A Well Studied Combination

- 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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