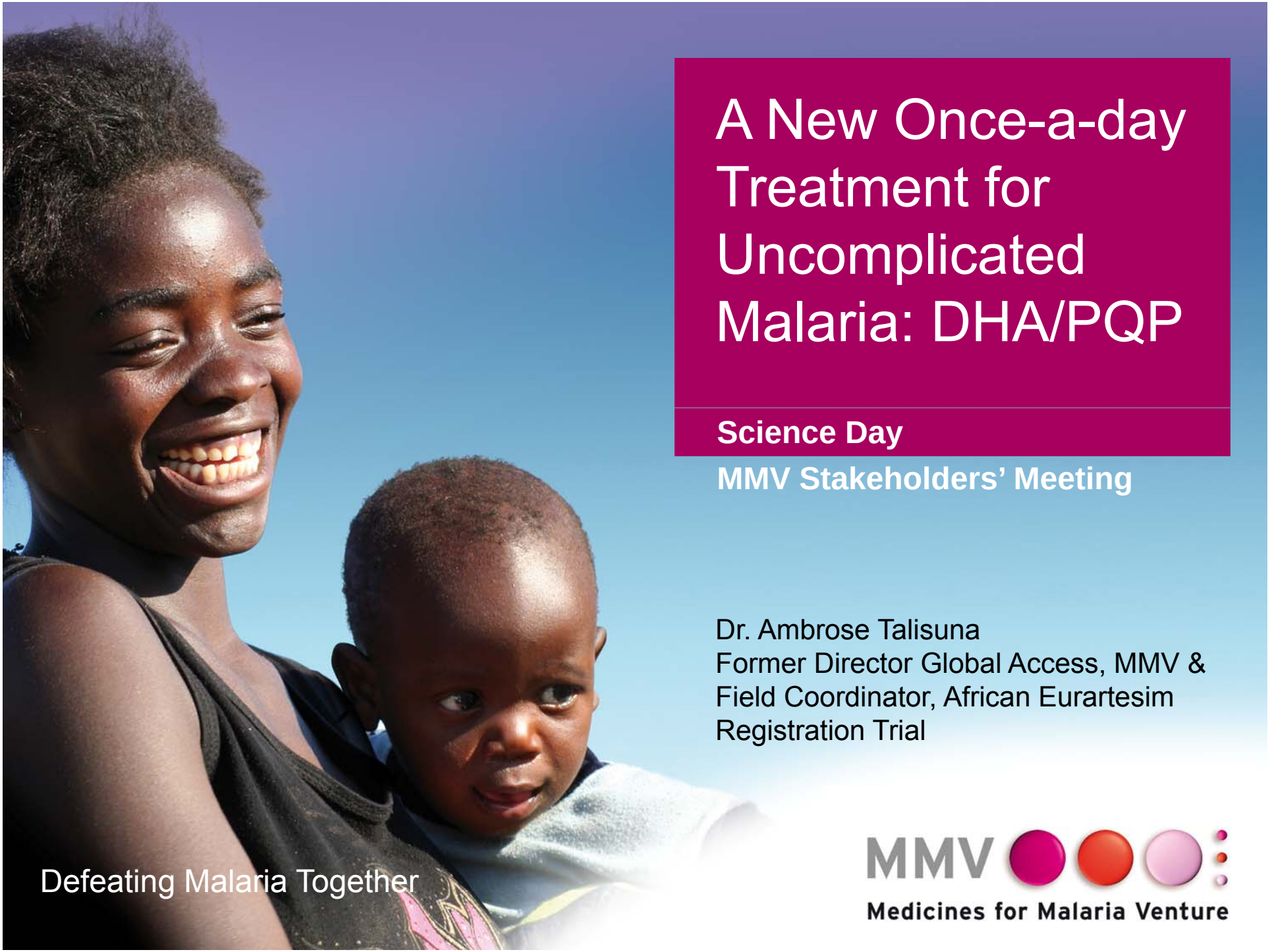

A New Once-a-day Treatment for Uncomplicated Malaria: DHA/PQP

Science Day

MMV Stakeholders' Meeting

Dr. Ambrose Talisuna
Former Director Global Access, MMV &
Field Coordinator, African Eurartesim
Registration Trial

Defeating Malaria Together

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Where are we with DHA-PQP today?

- **In 2004, MMV and sigma-tau Pharmaceutiche joined hands to develop DHA/PQP to international standards**
- **Today, DHA/PQP is being reviewed by the European Medicines Agency (EMA)**

Current difficulties regarding treatment of malaria

- **Problems related to antimalarial drugs**
  - Widespread resistance to most available antimalarial drugs
  - Limited availability of new drugs (specially GMP-produced)
    - Limited availability of pediatric-friendly formulations
    - Limited shelf-life of the artemisinin derivatives

- **Access issues**
    - Price
    - Distribution challenges
    - “Counterfeit” drugs
    - Fragile health systems
    - Cultural issues

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What does WHO recommend for the treatment of uncomplicated *P.falciparum* malaria?

- Use of combination therapy, preferably using artemisinin derivatives as one of the partner drugs

- ***Artemisinin derivatives (oral formulations) and partner medicines of ACTs should not be used as monotherapy***

- The following ACTs are recommended by WHO:
  - artemether / lumefantrine
  - artesunate / amodiaquine
  - artesunate + mefloquine
  - artesunate + sulfadoxine-pyrimethamine
  - **dihydroartemisinin / piperaquine***

*Update in 2010 Guidelines

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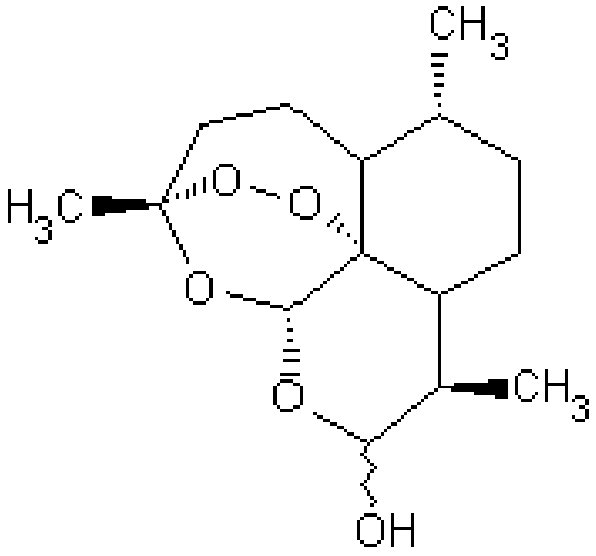
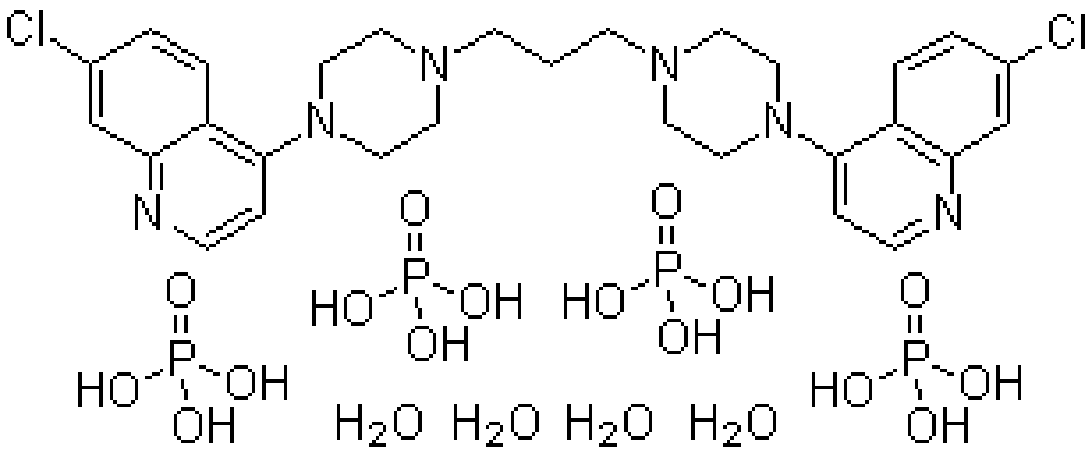
What is DHA/PQP?



DHA (Dihydroartemisinin):

- The active metabolite of the artemisinin compounds artesunate and artemether



PQP (Piperaquine) phosphate:

- A bisquinoline drug with PK properties similar to Chloroquine

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What was known about DHA/PQP?

Transactions of the Royal Society of Tropical Medicine and Hygiene (2007) 101, 858–866

REVIEW

Efficacy and safety of dihydroartemisinin-piperaquine

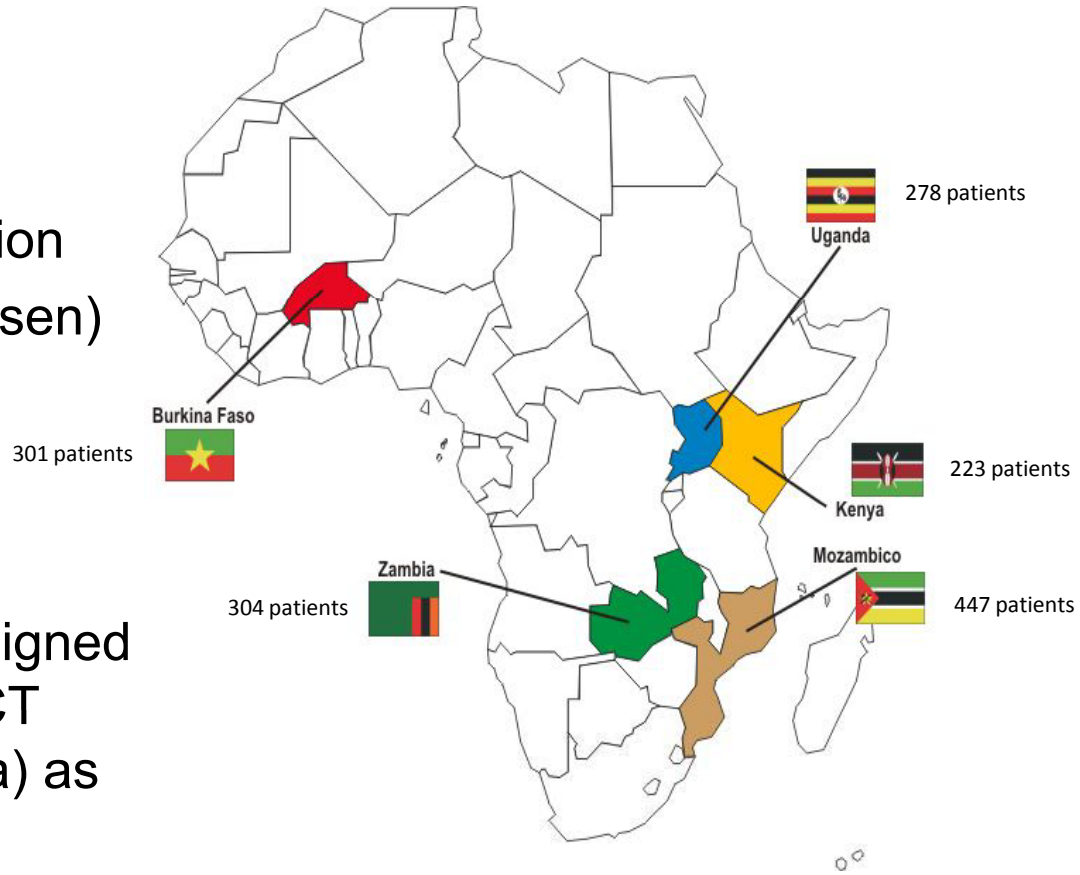
H.Y. Myint[a], E.A. Ashley[b], N.P.J. Day[a,c], F. Nosten[a,c,d], N.J. White[a,c,*]

- Review of 14 studies, with up to 22 study arms
- 2,636 patients treated with DHA-PQP
- Most studies in Southeast Asia, very few in Africa
- All age groups, although mostly adult data
- Efficacy assessed over 28-63 days consistently exceeding 95% in the treatment of multidrug resistant falciparum malaria.
- Tolerability uniformly good, and no serious adverse effects identified.

What was needed?

- A **GMP product** to be studied under GCP in the following populations:
  - African children, the primary target population
  - Adults (SE Asia chosen)

- MMV and sigma-tau designed two large multicentre RCT trials (Africa and SE Asia) as part of the clinical development plan for DHA/PQP



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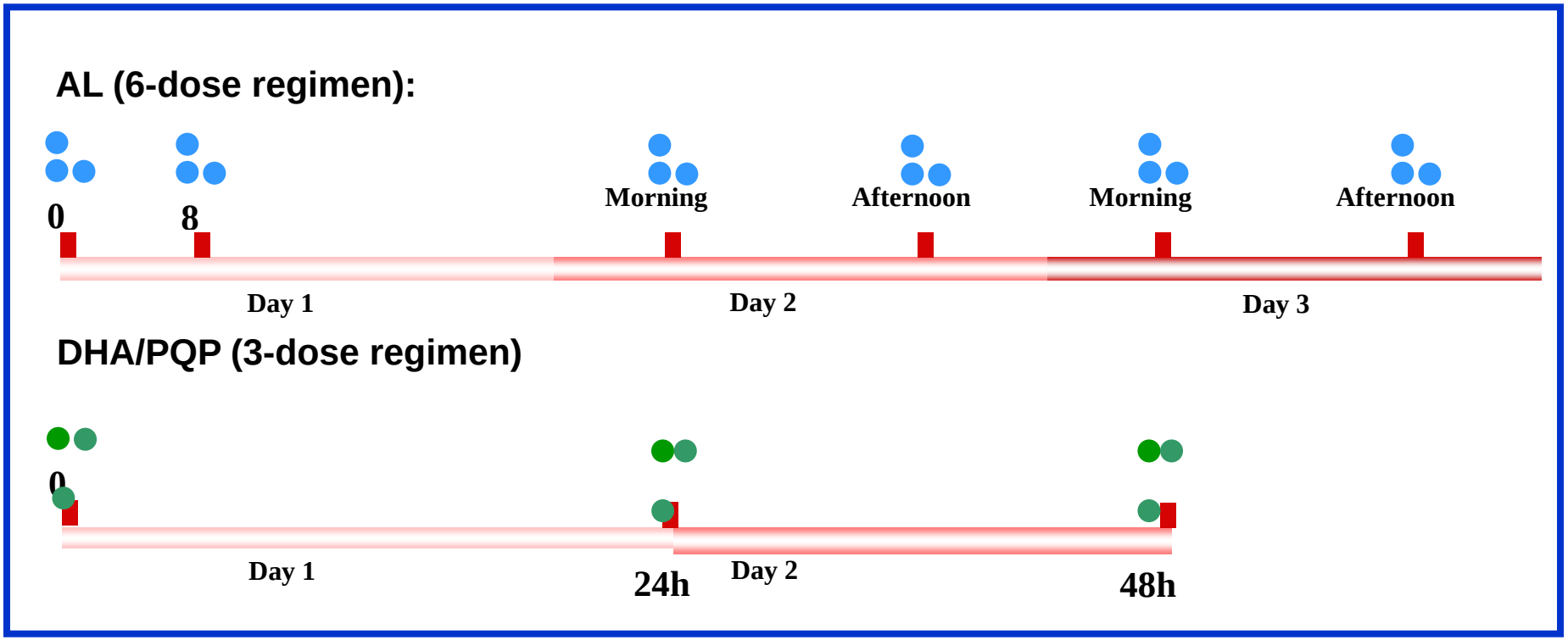
African Study outline

A large open label, randomised clinical trial (~1500 children, < 5 years), performed in 5 different African countries to assess the non-inferiority of DHA/PQP when compared to the standard combination therapy artemether/lumefantrine (AL), for the treatment of uncomplicated



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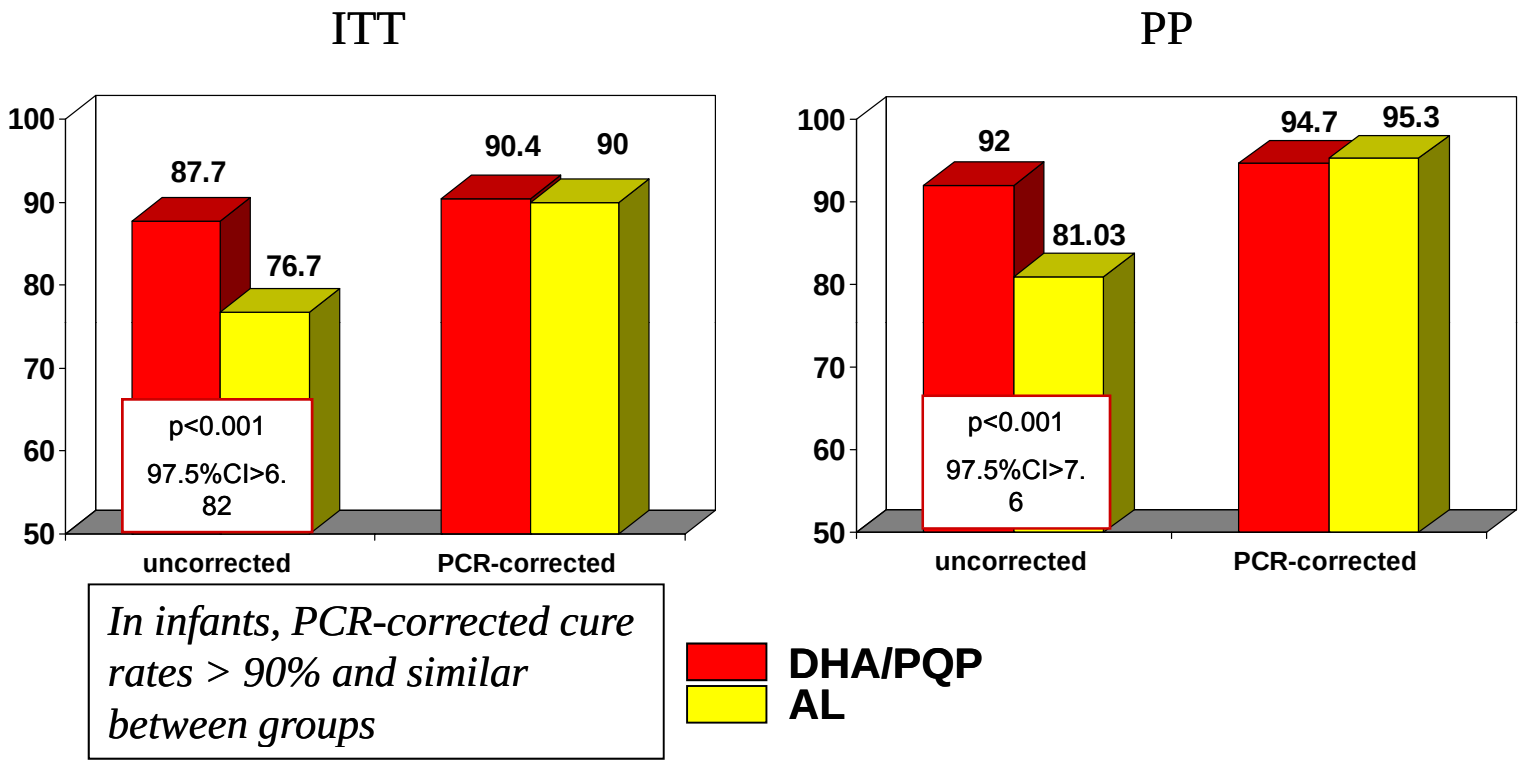
Results: D28 PCR corrected (primary endpoint) and uncorrected ACPR



- **DHA/PQP highly efficacious at D28 (also D42) and non-inferior to AL**
  Uncorrected: DHA/PQP better than AL

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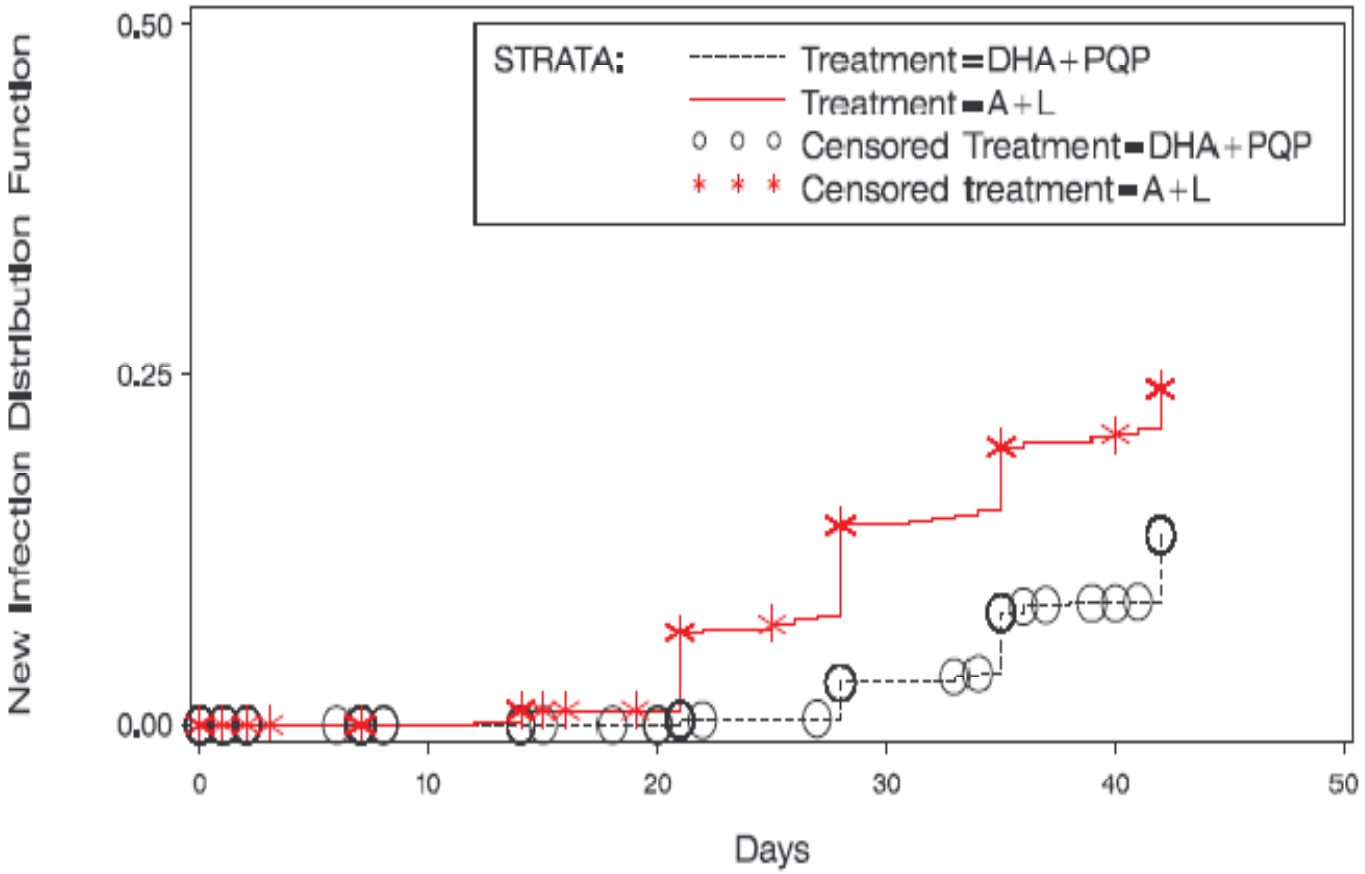
Results: New infections



- **More new infections in the AL group**
- **Better post treatment prophylactic effect for DHA/PQP (longer half life of partner drug?)**

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Conclusions: African study

- **The study demonstrated that DHA/PQP is non-inferior to AL on the PCR-corrected cure rate at Day 28 (primary end-point).**
- **Since performance of AL is consistent with expectations, this also demonstrates that DHA/PQP is efficacious.**
- **Efficacy among the youngest children (<1year of age) is maintained**
- **The study showed superiority of DHA/PQP vs AL on the uncorrected cure rate at Day 28. DHA/PQP reduced the rate of new infections in a statistically and clinically significant way as compared to AL.**
- **The two treatment groups showed a very similar efficacy and safety profile as for the other considered end-points.**

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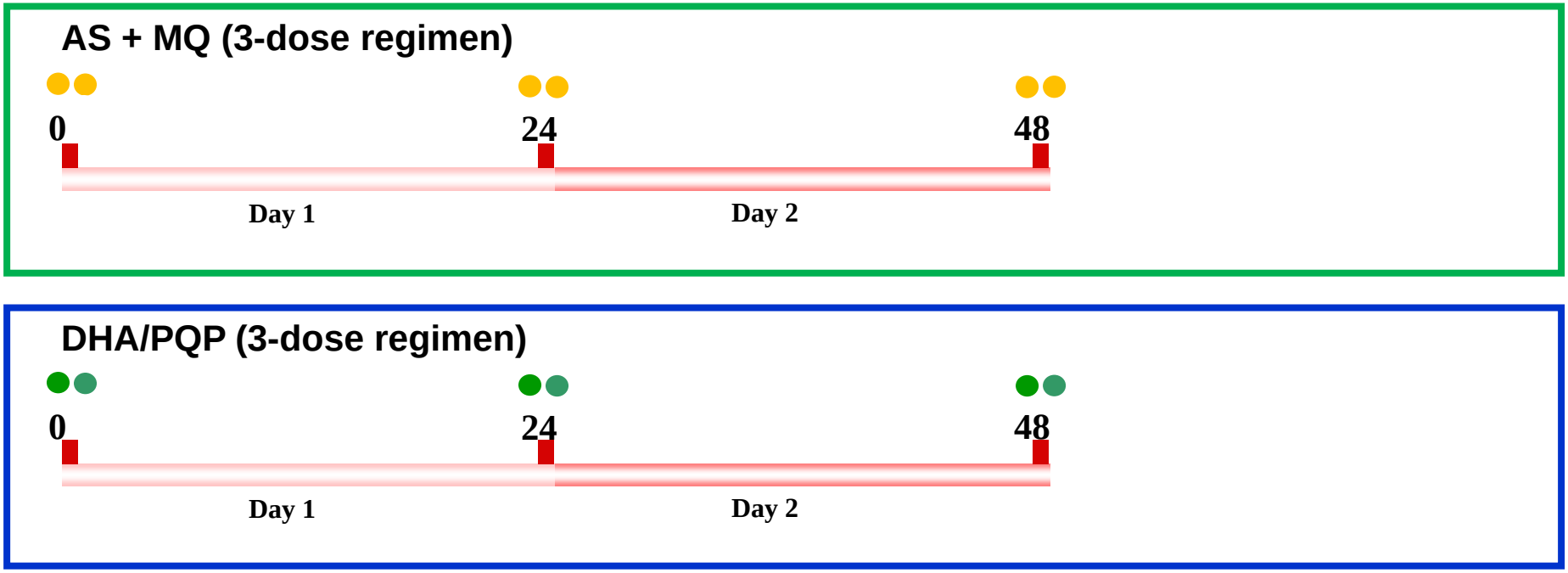
SE Asian Study outline

A large open label, randomised clinical trial (~1,150 patients, including children), conducted in Laos, Thailand and India to assess the non-inferiority of DHA/PQP when compared to artesunate + mefloquine (AS + MQ), for the treatment of uncomplicated malaria



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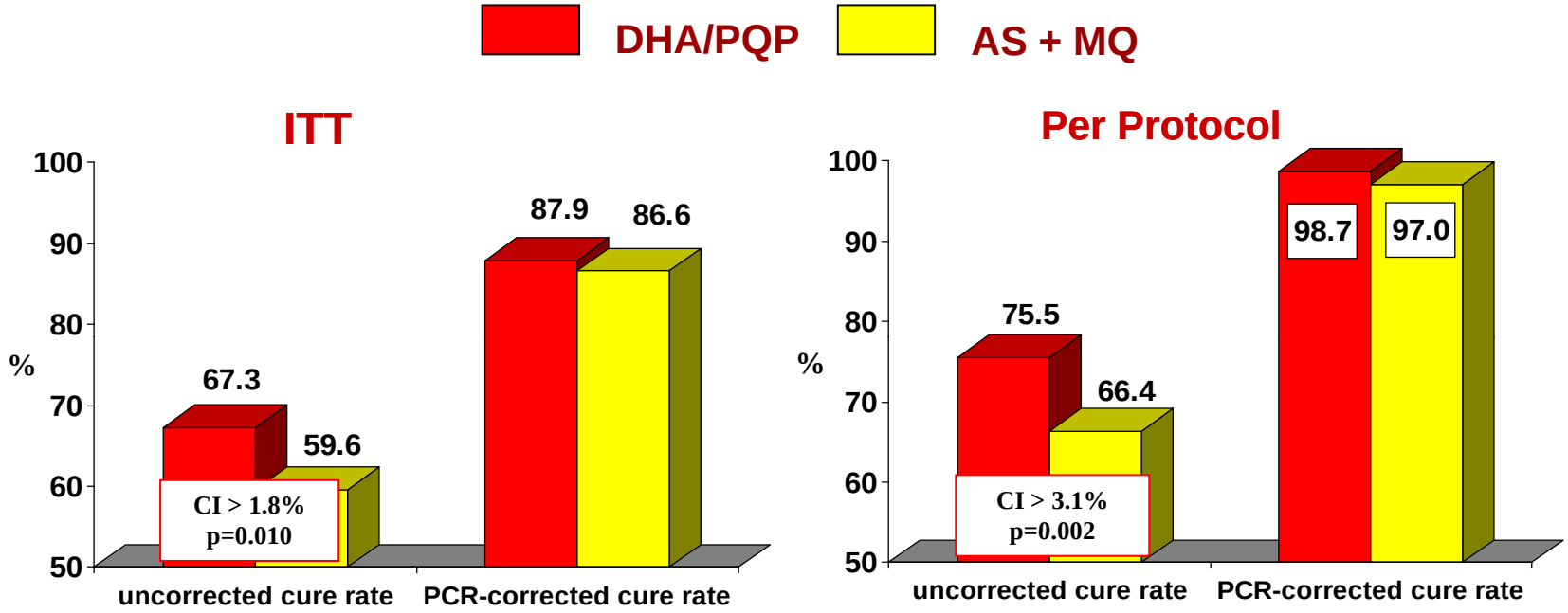
Results: D63 PCR corrected (primary endpoint) and uncorrected ACPR



- **No difference in PCR corrected cure rates between treatments**
- **In all the populations, the difference between the two treatment uncorrected cure rates was statistically significant**
- **D63 results (PP, PCR corrected) met the WHO criteria (>95%)**

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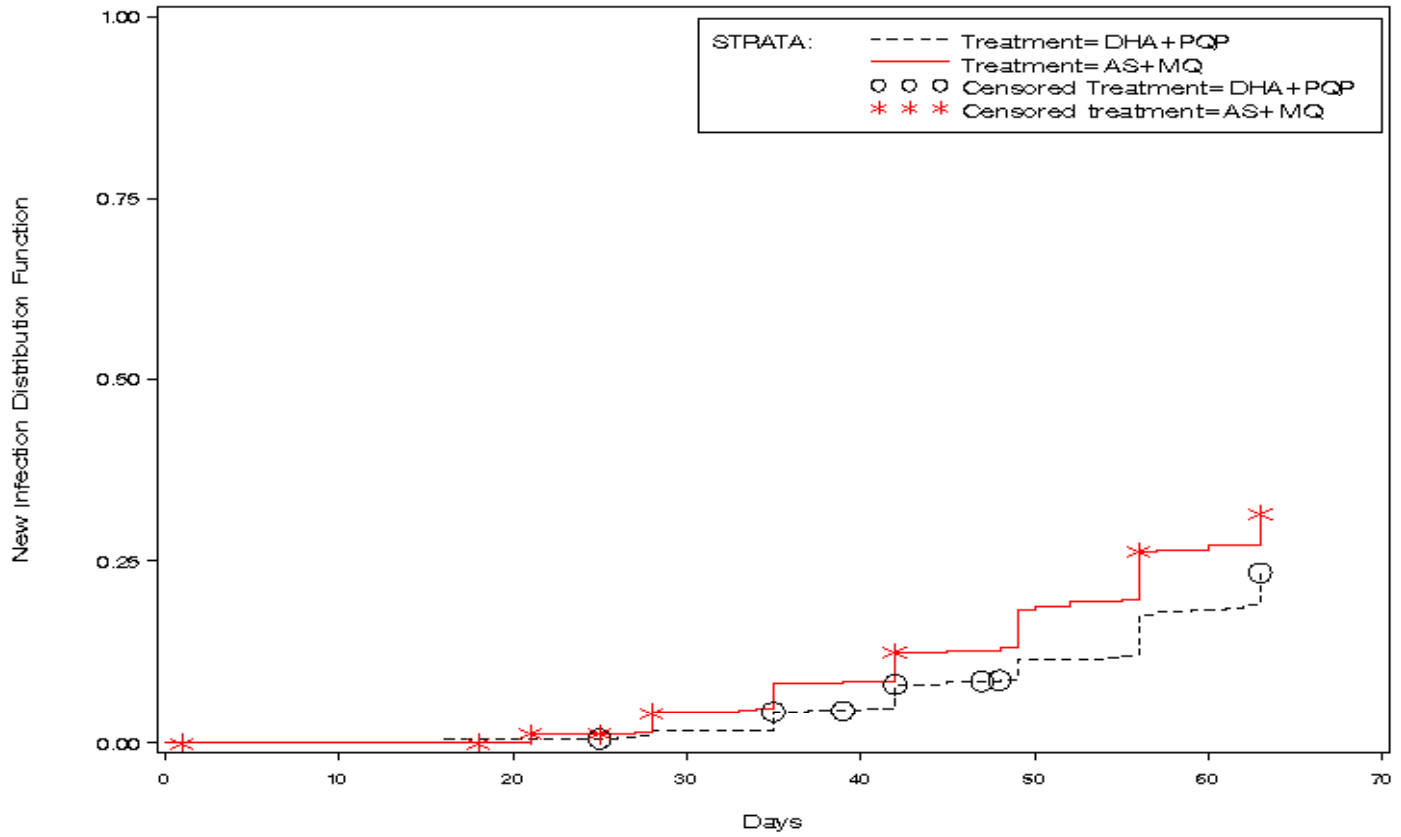
Results: New infections up to D63, PP population

Table 11.4.11c.2: Log-Rank, p= 0.0039 testing the survival distribution function



- **More new infections in the AS + MQ group**
- **Better post treatment prophylactic effect for DHA/PQP**

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Conclusions: Asian study

- **The study demonstrated that DHA/PQP was non-inferior to AS + MQ on the PCR-corrected cure rate at Day 63 (primary end-point).**
- **Since performance of AS + MQ is consistent with expectations, this also demonstrates that DHA/PQP is efficacious.**
- **The study showed superiority of DHA/PQP vs AS + MQ on the uncorrected cure rate at Day 63. DHA/PQP reduced the rate of new infections in a statistically and clinically significant way as compared to AS + MQ.**
- **The two treatment groups showed a very similar efficacy and safety profile as for the other considered end-points.**

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Three additional trials requested by EMA

1. **Thorough QTc trial**
2. **PK in Caucasian and Asian healthy subjects**
3. **Food Interaction**

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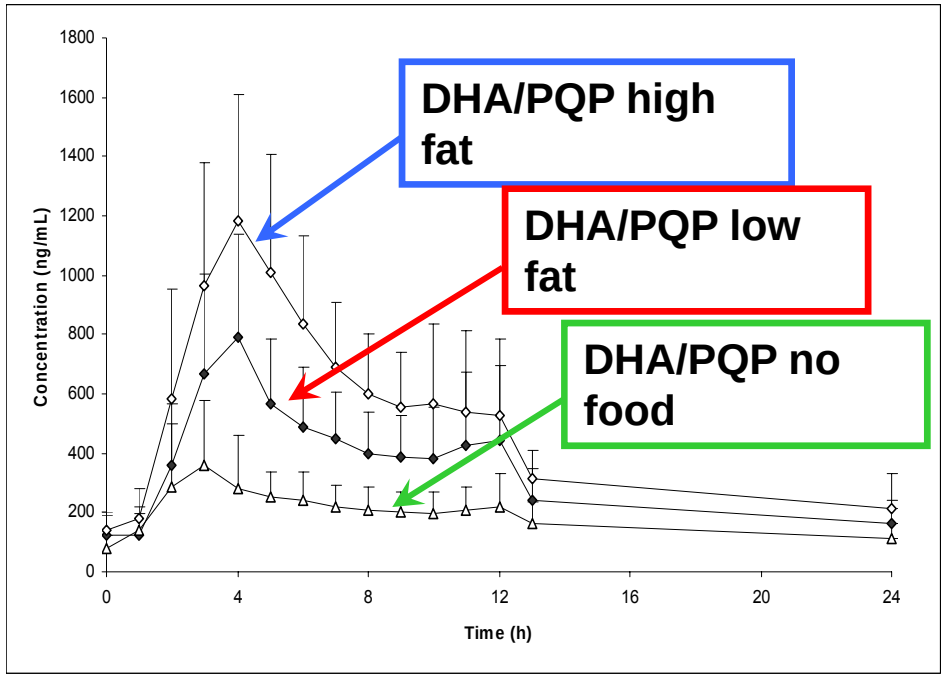
1. Thorough QTc trial in 268 healthy subjects

[Full dose (three days) of AL or DHA/PQP according to body weight]

Maximum time-matched changes in QTcF (ms)

5 groups	QTcF prolongation
Placebo (no food)	+ 10 ms
Riamet/ (400 Kcal with 20g fat)	+ 20 ms
Eurartesim (no food)	+ 33 ms
Eurartesim (400 Kcal with 20g fat)	+ 46 ms
Eurartesim (1,000 Kcal with 75g fat)	+ 56 ms



PQP levels, 24h after last (third) administration

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Analysis of maximum time-matched actual values and changes from baseline for QTcF

QTcF (ms)	Placebo (N=60)	AL (N=64)	DHA/PQP (N=40)
	n (%)	n (%)	n (%)
>450 ms	0 (0.0)	2 (3.1)	4 (10.0)
>480 ms	0 (0.0)	0 (0.0)	0 (0.0)
>500 ms	0 (0.0)	0 (0.0)	0 (0.0)
>60 ms (post vs pre)	0 (0.0)	0 (0.0)	0 (0.0)

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QTc study conclusions

- The effect of DHA/PQP on QTc interval is directly related to the levels of PQP in blood, which positively correlates with fat co-administration. This further supports the standard recommendation of giving DHA/PQP apart from food.
- It is equivalent to that produced by choroquine, as reported in literature.
- As for AL no subjects showed QTc >500 ms or prolongations (after- vs pre-dose) > 60 ms.
- The QTc prolongation is a “risk factor”, not an “event” and is common to most highly effective antimalarials.

No cardiac events were observed during this trial, nor have they ever been reported at the current dosage in the treatment of uncomplicated malaria.

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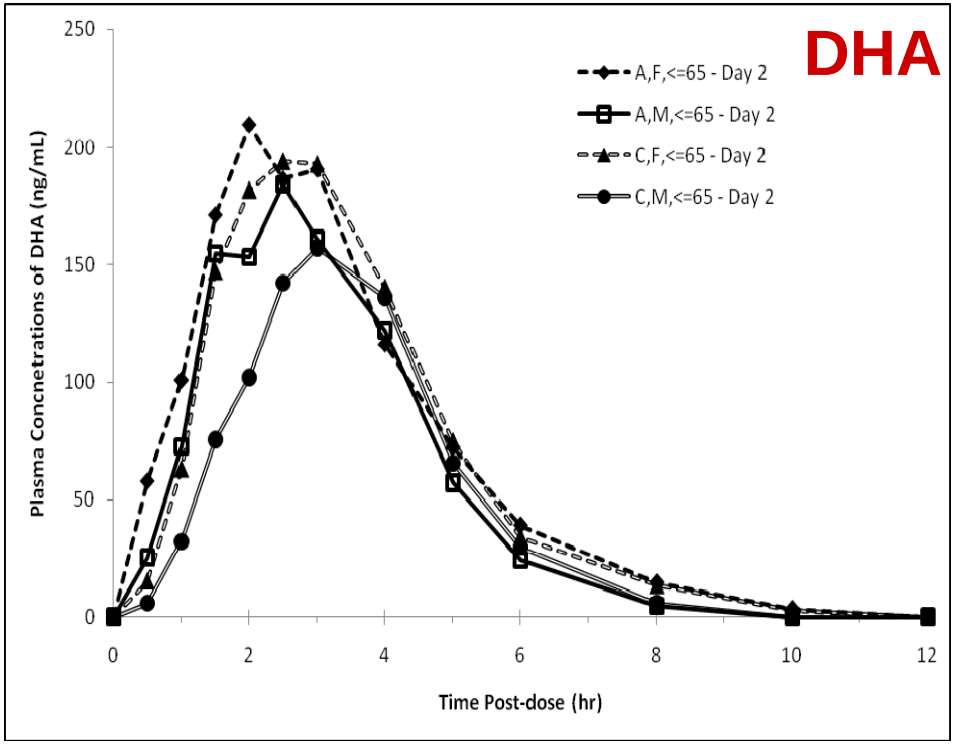
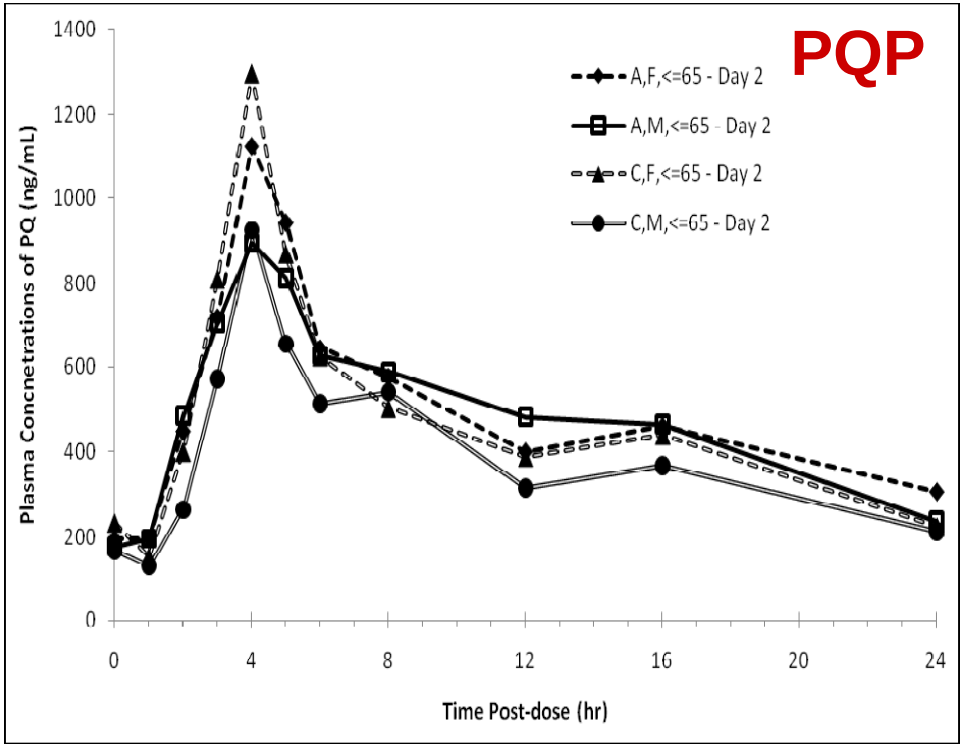
2. Phase I, PK trial in healthy Asian and Caucausian volunteers

- 72 healthy subjects stratified by ethnicity, gender and body weight
- Eurartesim given p.o after a light breakfast. Full dose (three days) according to body weight





PK profiles similar between Asians and Caucasians and between males and females

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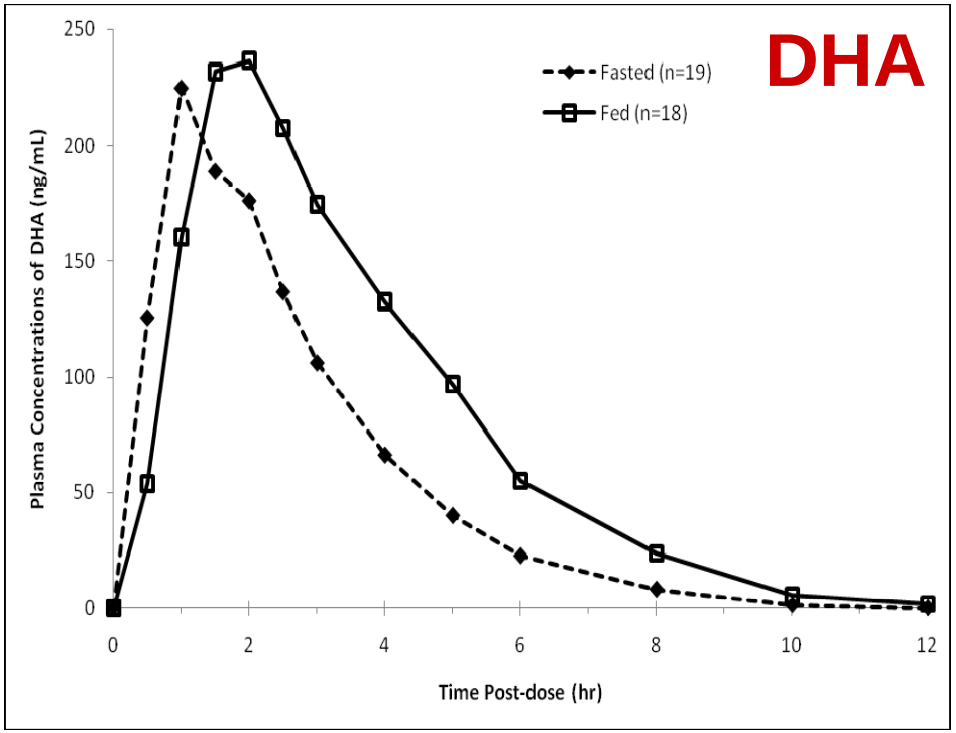
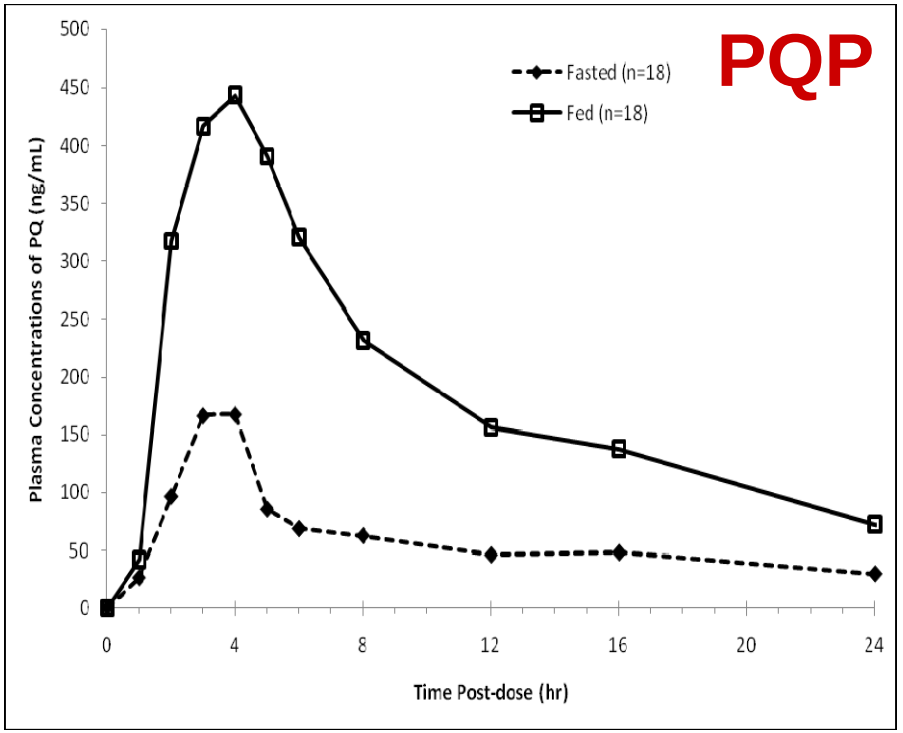
3. Study of the effect of food on the PK of DHA/PQP after single oral administration

- 36 healthy Caucasian males with body weight ≥ 75 kg stratified in two groups (18+18). Standard PK procedures performed
- Two groups: **1)Fasting** and **2)Fed** (high fat, high calorie meal). Only one dose given.





The observed food effect in the PK parametres of both DHA and PQP supports the recommendation that DHA/PQP should be given under fasting conditions

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Conclusions

- A large pool of evidence supports the non-inferiority of DHA/PQP vs. other ACTs for the treatment of acute uncomplicated *P. falciparum* malaria
- DHA/PQP has repeatedly shown good tolerability and safety
- Its dosing (three doses instead of six for artemether/lumefantrine) contributes to a better compliance
- The centralized registration of DHA/PQP with EMA will bring alternatives to developing countries and also allow the availability of an ACT (for the first time) in all the 27 EU Countries.

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“You call us the future, but we are also the present”

Picture of children…

Thank you!

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