From field experience to the discovery of antimalarials:

Partnerships in action

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PARTNERSHIPS IN ACTION

Review of clinical experience with the artesunate-amodiaquine fixed-dose combination "ASAQ FDC" (Coarsucam®)

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Simplified 3-Day Dose Regimen of ASAQ

	Artesunate-amodiaquine fixed-dose combination 3 dosage strengths available	Co-blistered non-fixed AS+AQ Artesunate-amodiaquine
		AS: 50 mg; AQ 153 mg
Infants (4.5-8 kg)	AS: 25 mg AQ: 67.5 mg	
Young Children (8-17 kg)	AS: 50 mg AQ: 135 mg	
Children (17-35 kg)	AS: 100 mg AQ: 270 mg	
Adults (≥36 kg)	AS: 100 mg AQ: 270 mg	

Artesunate-amodiaquine Fixed-Dose Combination (ASAQ FDC)

Optimized 2.7 AS:AQ ratio to prevent over- and under-dosing. Taylor et al. *Bulletin of the WHO*. 2006; 84; 956-964.

Age- or weight-based dosing

Fewer tablets, once-a-day treatment regimen

Soluble tablets

ASAQ FDC versus loose association (AS+AQ) for uncomplicated *P. falciparum* malaria (Burkina-Faso study)

ASAQ FDC versus AL FDC for uncomplicated *P. falciparum* malaria (ATAQ EASY study)

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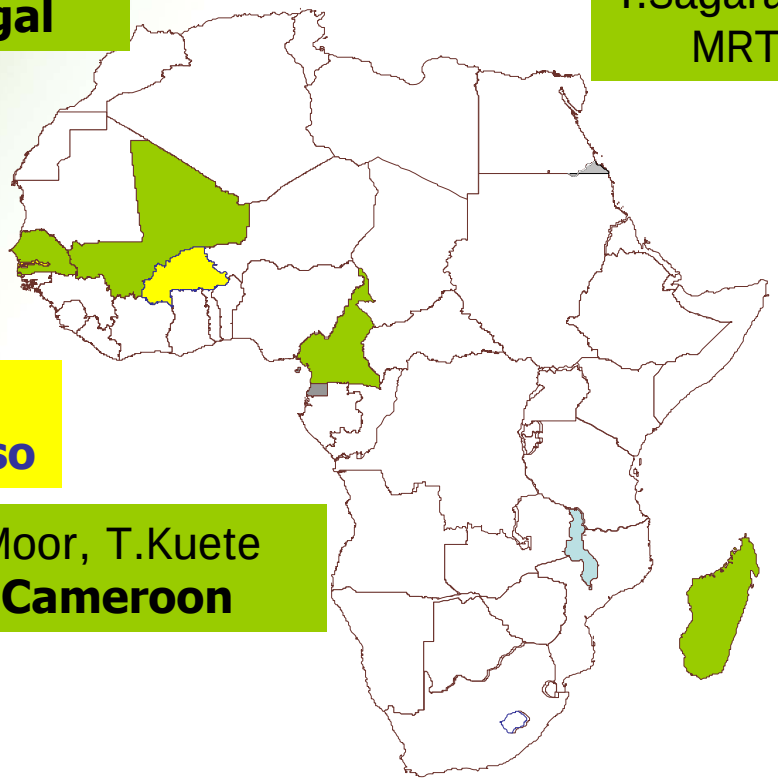

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Burkina Faso Study

Objectives, Burkina Faso Study

Primary objective :

–to demonstrate the non inferiority of ASAQ FDC versus AS+AQ loose association (WHO protocol, 28 day follow-up)

Secondary objectives :

–Parasitological and fever clearances,

–clinical and biological tolerability

Methods, Burkina-Faso study

Open randomized controlled trial (Oct 2004 – Feb 2006)

2 arms:

- ASAQ FDC, one intake a day
- AS+AQ loose association, one intake a day

750 children aged 6 to 59 months, ≥5 kg

Acute uncomplicated *P. falciparum* malaria
(parasitemia >1000 /µl)

Dosage according to age range

Efficacy results, Burkina-Faso study

Dataset	ASAQ FDC	Loose AS+AQ
PP	N=342	N=340
D28 Cure Rate	**92.11%**	**92.06%**
(Δ = - 0.0005; 95% CI [-0.0345; 0.0335]		
mPP	N=329	N=326
D28 Cure Rate	**95.74%**	**96.01%**
(Δ = - 0.0005; 95% CI [-0.0345; 0.0335]		

Non-inferiority of fixed-dose ASAQ versus AS+AQ demonstrated in all datasets (ITT included)

Safety results, Burkina Faso : Withdrawals due to treatment intolerance

	FDC ASAQ n=375	Loose AS+AQ n=374
AE leading to treatment discontinuation (Vomiting/spitting out)	13 (3.5%)	14 (3.7%)

Safety Results, Burkina Faso : Serious Adverse Events

ASAQ FDC, n=6

Severe malaria: 4

Death :1 (severe malaria)

Gastroenteritis:1

Loose AS+AQ, n= 6

Severe malaria: 5

Death:1 (severe malaria)

ATAQ-EASY Study

(Multi-centre, Multi-national ASAQ-FDC)

Methods

Randomized, blinded, multicentre study in Cameroon, Mali Senegal and Madagascar (Mar-Dec 2006)

3 arms

- **Fixed dose ASAQ 1 intake a day (+ placebo)**
- **Fixed dose ASAQ 2 intakes a day**
- **Fixed dose AL 2 intakes a day**

941 adults and children over 10 kg

Uncomplicated *P. falciparum* malaria (parasitemia ≥1000/µl)

Dosage according to bodyweight range

Objectives

Primary objective :

- to demonstrate the non inferiority of ASAQ FDC once daily dose versus AL FDC (WHO 2003 protocol, 28 day follow-up)

Secondary objectives :

- Comparison of efficacy in the 3 arms
- Parasitological and fever clearances,
- clinical and biological tolerability.

Efficacy Results: Primary endpoint

PCR corrected D28 cure rate (PP population)	ASAQ FDC 1 intake n=283	AL FDC 2 intakes n=289
ETF	0	0
LCF	0	1 (0.3%)
LPF	3 (1.1%)	3 (1.0%)
ACPR	**280 (98.9%)**	**285 (98.6%)**

The two-sided 90% CI of the difference in the proportions of ACPR is : [-0.02 ; **0.01**].
Upper limit of CI < 0.05 (non-inferiority delta)

Non-inferiority of ASAQ FDC once a day versus AL FDC demonstrated in all datasets

Efficacy Results: Secondary Endpoints

IC [-0.03 ; 0.00] IC [-0.03 ; 0.00]

PCR corrected D28 cure rate (PP population)	FDC ASAQ 1 intake n=283	FDC ASAQ 2 intakes n=285	FDC AL 2 intakes n=289
ETF	0	0	0
LCF	0	0	1 (0.3%)
LPF	3 (1.1%)	0	3 (1.0%)
ACPR	**280 (98.9%)**	**285 (100.0%)**	**285 (98.6%)**

Non-inferiority of ASAQ FDC twice day versus AL FDC demonstrated in all datasets

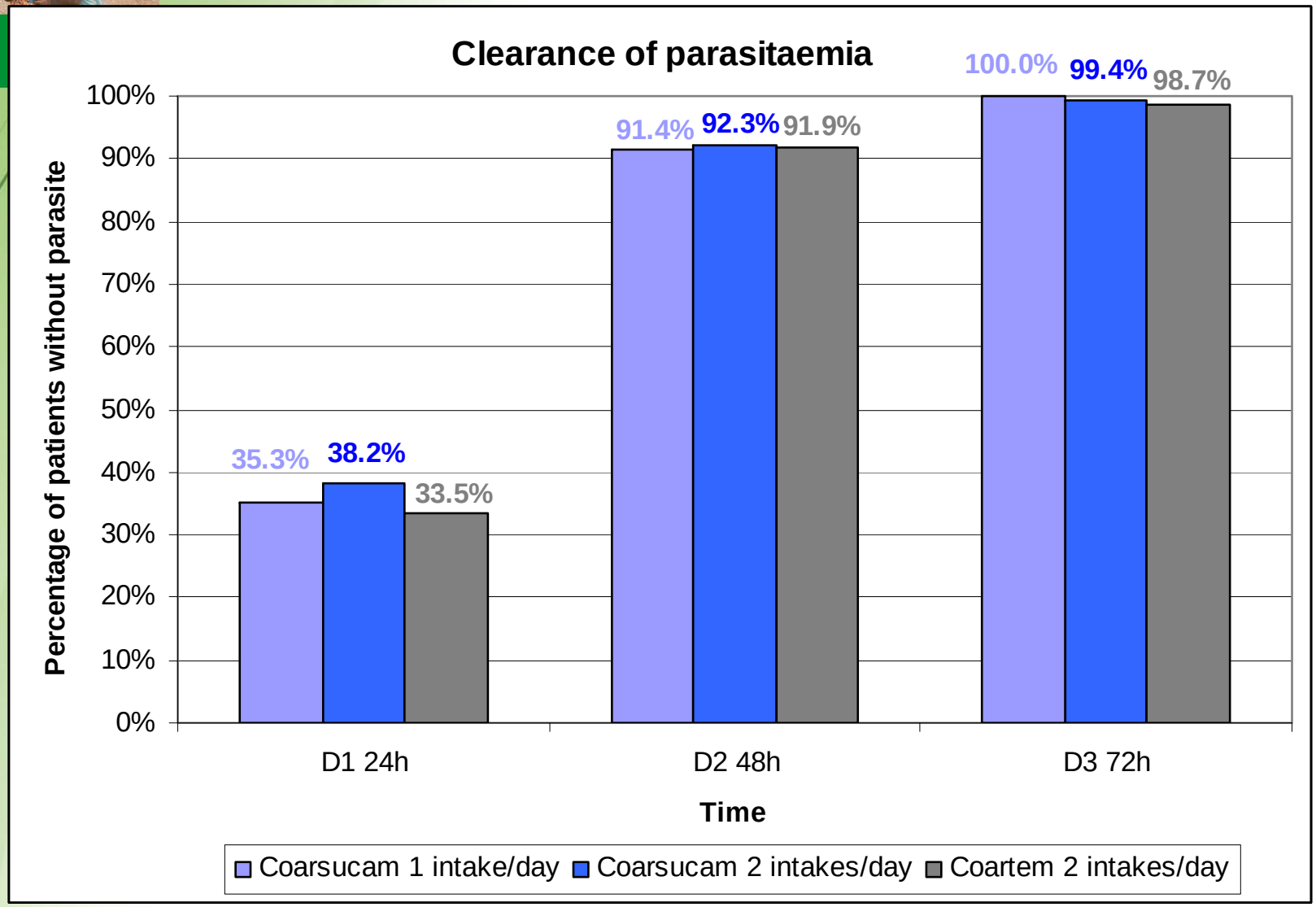
Efficacy Results in children < 5 years

IC:[-0.06 ; 0.04]).

Efficacy evaluation on D28 PCR correction on the ITT population	FDC ASAQ 1 intake n=143	FDC ASAQ 2 intakes n=148	FDC AL 2 intakes n=142
Age < 5 years			
Possible failure	6 (4.2%)	6 (4.1%)	4 (2.8%)
ETF	0	0	0
LCF	0	0	2 (1.4%)
LPF	2 (1.4%)	0	3 (2.1%)
ACPR	**135 (94.4%)**	**142 (95.9%)**	**133 (93.7%)**

Non-inferiority of ASAQ FDC versus AL FDC demonstrated in all datasets

Efficacy Results: parasitological clearance



Safety Results

Rejection or vomiting in the half hour post treatment administration between D0 and D2

Vomiting or Rejection	ASAQ FDC 1 intake n=313	ASAQ FDC 2 intakes n=315	AL FDC 2 intakes n=312
< 5 years	30/146 (20.5%)	30/148 (20.3%)	22/142 (15.5%)
[5; 14[years	10/105 (9.5%)	15/113 (13.3%)	10/112 (8.9%)
≥ 14 years	2/62 (3.2%)	2/54 (3.7%)	1/58 (1.7%)
P-value (Khi² test)	0.0013	0.0115	0.0126

Significant statistical differences between age ranges

No significant difference among treatment groups

Safety Results : Serious Adverse Events

ASAQ FDC once daily, n=2 :

Anemia + lung infection (death)

Anemia (full recovery after hospitalization)

AL FDC twice daily, n=1

Coma (death)

Safety : gastro-intestinal AEs
Incidence of vomiting after Day 0

BURKINA-FASO Study

Nausea and vomiting were < 2% over course of study

Multi-centre, multi-national study

Nausea and vomiting : min 0.3%, max 6% in all groups

No significant difference among treatment groups

Safety : Biological Safety Data

Laboratory Tests

- Hematology:
  - leucocytes, neutrophils, platelets, hemoglobin

- Biochemistry:
  - AST, ALT, bilirubin, and creatinine

No significant difference among treatment groups in either study

Conclusions

Burkina-Faso Study (patients' no. = 750**)**

- Non-inferiority of ASAQ FDC vs loose AS+AQ association
- Comparable clinical and biological safety in the 2 groups of treatment; no unexpected adverse event

ATAQ EASY Study (patients' no. = 941**)**

- Non-inferiority of ASAQ FDC vs AL FDC demonstrated, including in children under 5 years of age
- Comparable clinical and biological safety in the 3 groups of treatment; no unexpected adverse event

ASAQ key post-launch issues

- Efficacy/effectiveness in various geographic areas
- Safety
  - Confirm safety profile in larger numbers of patients
  - Adults
  - Repeated administrations
  - Co-administered treatments
  - Concomitant conditions
  - Safety in first trimester of pregnancy
- Development of parasite resistance
- Compliance and its impact on
  - Efficacy, safety, quality of life, economics ?

Thank you for attention !