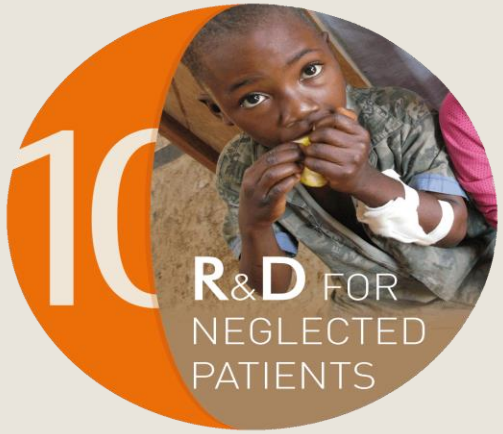

Efficacy, Safety and Population-Pharmacokinetics of Artesunate-Mefloquine combination for the Treatment of Uncomplicated P. falciparum Malaria in African children versus Artemether-Lumefantrine

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CNRFP
KEMRI
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Background

Artemisinin-based combination therapies (ACTs) are recommended by WHO to treat uncomplicated *P. falciparum* malaria. In 2010, WHO asked to reconsider the use of AS+MQ in Africa.

DNDi and Farmanguinhos developed the first **Artesunate-Mefloquine Fixed Dose Combination (FDC) :**

- Simplified 3 day regimen (once a day; MQ: 8 mg/kg/day)
- Paediatric tablet strength (25mg AS / 55mg MQ)
- Technology transfer to Cipla completed in 2009
- WHO pre-qualification since 2012
- Approved in Brazil (2008), India, Myanmar, Malaysia, Vietnam, Tanzania and Niger

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Rationale

Artesunate (AS) and Mefloquine (MQ), in loose or fixed-dose combination (ASMQ), was the first ACT used extensively in Asia and Latin America but in Africa there is limited data in children <5years who are the primary victims of malaria in the continent .

Tolerance of mefloquine in children: perceived barrier to the use of ASMQ in treatment of malaria in Africa.

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Objectives

- **Principal Objective**: To evaluate efficacy of ASMQ fixed-dose combination in children < 5years with uncomplicated falciparum malaria, by determining the proportion of patients achieving a negative parasitaemia without recrudescence by 63 days.

- **Secondary Objectives**

  - As per WHO recommendations, to perform a secondary survival analysis to compare the efficacy of ASMQ and AL
  - To evaluate cure rate at 28 and 42 days
  - To evaluate the safety of ASMQ (incidence and severity of adverse events, vomiting frequency)
  - To evaluate the population-pharmacokinetics of ASMQ and AL (Artemether-Lumefantrine) in children < 5 years (sub-study as poster ASTMH 2013, full results in 2015)

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Methods

Study design:	Phase IV, open-label, randomized, controlled, non-inferiority clinical trial
Main efficacy endpoint	PCR corrected Day 63 cure rate
Non inferiority margin	5% (power 90%, alpha 2.5% using a one-sided test)
Sample size:	940
Drug allocation:	1:1 (ASMQ : AL)
Treatment:	3-day observed oral regimen ASMQ 1x daily; AL 2x daily
Rescue treatment:	Treatment of the other arm (ASMQ => AL; AL=> ASMQ)
Follow up:	1st follow-up period: 63 days (once a week after treatment). And additional follow-up after rescue treatment (63 days or until day of 2nd recurrence)

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Eligibility Criteria

Inclusion criteria

- Age between 6 and 59 months
- Presence of acute uncomplicated malaria with *P. falciparum* mono-infection confirmed by :
  - Axillary Temperature ≥ 37.5˚ C
  - Parasite density between 2000 and 200 000 asexual parasites/µl
- Informed consent from parent/legal representative

Exclusion criteria

- Signs and symptoms of severe/complicated malaria
- Weight < 5 kg
- Inability to tolerate oral medication
- Mixed Plasmodium infection
- Presence of febrile conditions caused by diseases other than malaria
- Known hypersensitivity to mefloquine, quinine, quinidine, artesunate or other artemisinins.
- History of use of any antimalarial agent in previous 2 weeks (4 weeks for mefloquine and piperaquine).
- Prior participation to a therapeutic trial within 3 months

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Study Sites

Banfora & Balonghin
CNRFP
PI: Dr Sirima
N= 390

Kisumu, KEMRI
PI: Dr Ogutu
N=347

Korogwe, NIMR
PI: Dr Lusingu
N=113

Bagamoyo, IHI
PI: Dr Mtoro
N=55

Kilosa, NIMR
PI: Dr Mrango
N=40

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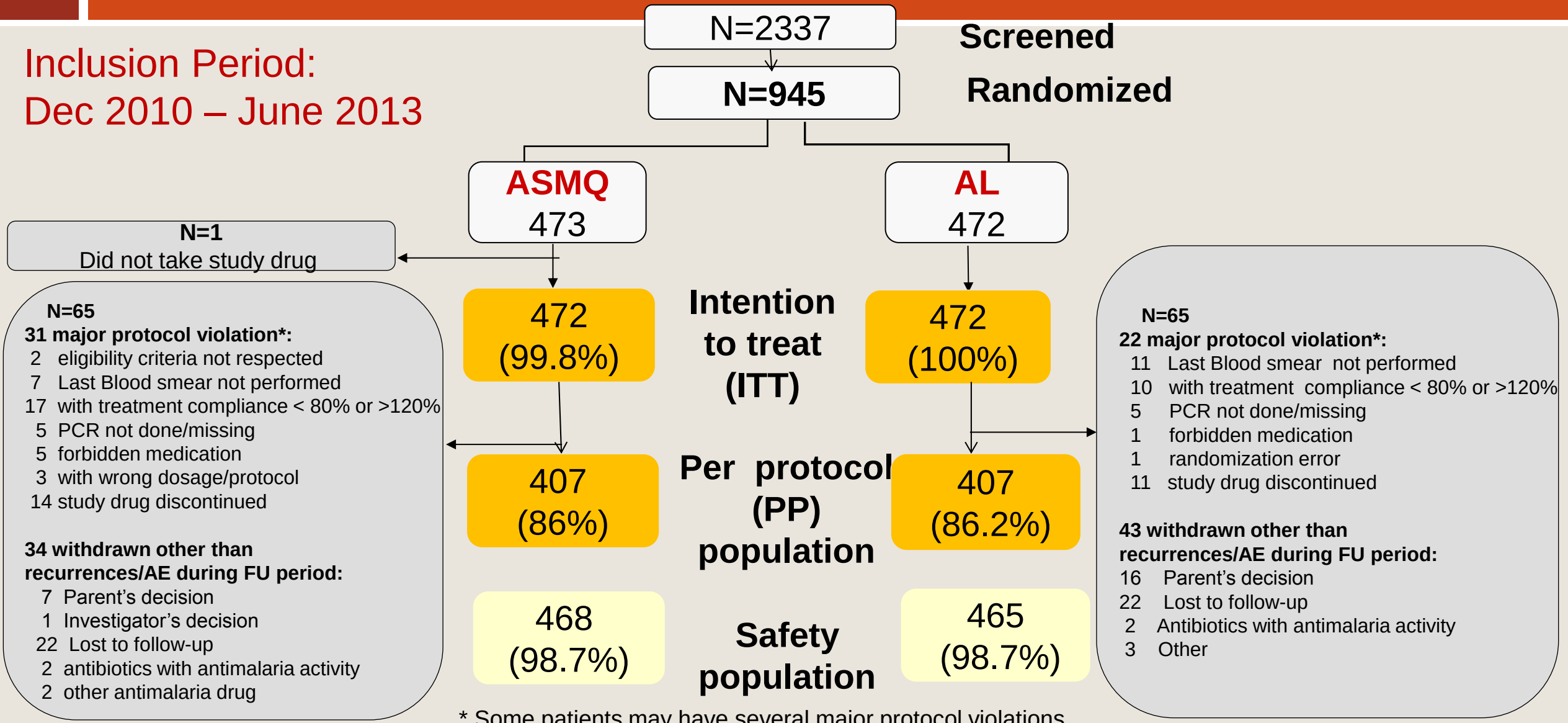
Disposition of Patients

Inclusion Period:
Dec 2010 – June 2013



* Some patients may have several major protocol violations

Results- Baseline Characteristics (ITT)

	ASMQ	AL
Patients N (%)	472	472
Age (mean month) (SD)	30.35 (14.76)	29.72 (14.33)
Sex ratio (male : female)	0.95	1.16
Pf parasite count (/ ul), Mean (SD)	66205.5 (55126.32)	66078.92 (53420.44)
Pf parasite count (/ ul), Median (range)	47368 (237-268787)	50925 (1935-199928)
Gametocytes, Median (range)	0 (0-1380)	0 (0-384)
Hemoglobin (g/dl), Mean (SD)	9.51 (1.72)	9.47 (1.9)
Neutrophils (10^3/ ul) Mean (SD)	5.15 (2.85)	5.18 (2.76)
Platelets (10^3/ ul), Mean (SD)	176.25 (102.78)	174.30 (102.77)
Leukocytes (10^3/ ul), Mean (SD)	9.70 (3.90)	9.80 (3.93)
Headache, n (%)	59 (12.5%)	65 (13.8%)
Vomiting, n (%)	71 (15.1%)	46 (9.7%)
Gastrointestinal disorders, n (%)	2 (0.4%)	3 (0.6%)
Loss of appetite/anorexia, n (%)	139 (29.5%)	146 (30.9%)

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End of study breakout reasons (ITT)

Description	ASMQ (N=472)	AL (N=472)
Completed	204 (**43.2**)*	202 (**42.8**)*
Early treatment failure (ETF)	2 (**0.4**)	0 (**0.0**)
Late Treatment Failure (LTF)	214 (**45.4**)	211 (**44.7**)
- reinfections	173 (80.8)**	165 (78.2)**
- recrudescences	15 (7)**	18 (8.5)**
- Undetermined/missing	26 (12.2)**	28 (13.3)**
Adverse events	8 (**1.7**)	4 (**0.8**)
Serious adverse event	0 (0.0)	2 (0.4)
Parent/guardian's decision	12 (2.6)	21 (4.5)
Other antimalarial drugs	2 (0.4)	0 (0.0)
Antibiotics with antimalarial activity	2 (0.4)	2 (0.4)
Investigator's decision	1 (0.2)	0 (0.0)
Lost to follow up	25 (5.3)	24 (5.1)
Other	2 (0.4)	6 (1.3)***

* : 1 patient/arm completed the study but parasitaemia not done at the last visit => failure and not completer in the efficacy analysis
**: % calculated on patients with recurrences
** *: 1 patient as protocol violation, but a PCR at the last visit concluded to reinfection

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Primary Efficacy criterion: Adequate Clinical and Parasitological Response (ACPR) **PCR Corrected on D63**

Populations	Statistics	ASMQ	AL	% ASMQ - % AL [95%CI]
PP	N	407	407	
	n (%) / Yes	370 (**90.9**)	365 (**89.7**)	1.23% [-2.84 , 5.29]
	n (%) / No	37 (9.1)	42 (10.3)	Non-inferiority limit=-5% p=0.0013*
ITT	N	472	472	
	n (%) / Yes	376 (**79.7**)	367 (**77.8**)	1.91% [-3.31 , 7.13]
	n (%) / No	96 (20.3)	105 (22.2)	Non-inferiority limit=-5% p=0.0048*

* : statistically significant

ASMQ non inferior to AL

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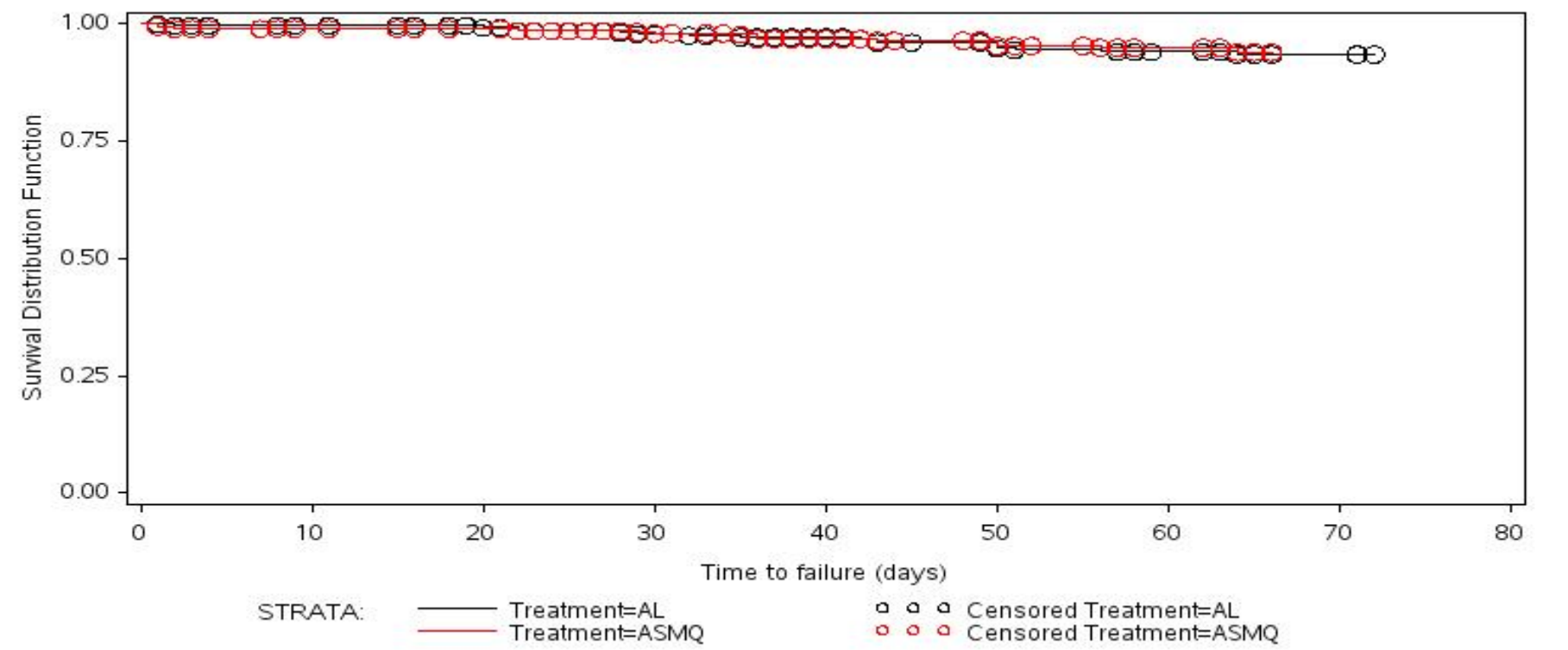
Survival Analysis (Kaplan Meier-mITT)



Timepoint	Treatment	Number Failed	Number Left	Survival	Failure	Test	Chi-Square	DF	Pr > Chi-Square
At 20 days	ASMQ	4	434	0.9909	0.00905	.	.	.	.
	AL	3	400	0.9927	0.00725	.	.	.	.
At 40 days	ASMQ	12	327	0.9690	0.0310	.	.	.	.
	AL	10	293	0.9728	0.0272	.	.	.	.
At 60 days	ASMQ	17	237	0.9504	0.0496	Log-Rank	0.0546	1	0.8153
	AL	18	223	0.9410	0.0590		.	.	.

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Secondary efficacy criterion: Cure rate at Day 28 and D42 - **PCR Corrected**

	Day	Statistics	ASMQ	AL	% ASMQ - % AL [95%CI]
PP	D28	N	407	407	
		n (%) / Yes	397 (**97.5**)	385 (**94.6**)	2.95% [0.29 , 5.61]
		n (%) / No	10 (2.5)	22 (5.4)	Non-inferiority limit=-5% p<0.0001*
	D42	N	407	407	
		n (%) / Yes	381 (**93.6**)	375 (**92.1**)	1.47 %[-2.06 , 5.01]
		n (%) / No	26 (6.4)	32 (7.9)	Non-inferiority limit=-5% p=0.0002*
ITT	D28	N	472	472	
		n (%) / Yes	422 (**89.4**)	402 (**85.2**)	4.24% [-0.00 , 8.48]
		n (%) / No	50 (10.6)	70 (14.8)	Non-inferiority limit=-5% p<0.0001*
	D42	N	472	472	
		n (%) / Yes	397 (**84.1**)	384 (**81.4**)	2.75% [-2.06 , 7.57]
		n (%) / No	75 (15.9)	88 (18.6)	Non-inferiority limit=-5% p=0.0008*

* : statistically significant

ASMQ non inferior to AL

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Cure Rate - **PCR Uncorrected at all time points**

		Statistics	ASMQ N=407	AL N=407	% ASMQ - % AL [95%CI]
PP	D28	n (%) / Yes	331 (**81.3**)	289 (**71.0**)	10.32% [4.51 , 16.13]
		n (%) / No	76 (18.7)	118 (29.0)	Non-inferiority limit=-5% p<0.0001*
	D42	n (%) / Yes	253 (**62.2**)	234 (**57.5**)	4.67 %[-2.06 , 11.40]
		n (%) / No	154 (37.8)	173 (42.5)	Non-inferiority limit=-5% p=0.0024*
	D63	n (%) / Yes	201 (**49.4**)	200 (**49.1**)	0.25% [-6.62 , 7.11]
		n (%) / No	206 (50.6)	207 (50.9)	Non-inferiority limit=-5% p=0.0672

* : statistically significant

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Adverse Events Summary (D0 – D63 or study termination)

Item	Statistics	ASMQ (N=468)	AL (N=465)
At least one AE	n (%)	381 (81.4)	367 (78.9)
At least one AE leading to treatment discontinuation	n (%)	10 (2.1)	4 (0.9)
At least one AE≥ severe	n (%)	16 (3.4)	14 (3.0)
At least one AE (possibly/ probably/ definitely) related to treatment	n (%)	46 (9.8)	49 (10.5)
At least one SAE	n (%)	8 (1.7)	10 (2.2)
At least one SAE leading to treatment discontinuation	n (%)	2 (0.4)	0 (0.0)

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Adverse Events leading to Treatment Discontinuation

	Statistics	ASMQ (N=468)	AL (N=465)
ALL		10 (2.1%)	4 (0.9%)
Malaria/ Anaemia/ sepsis	n (%)	1 (0.2%)	0 (0.0%)
Malaria/sepsis	n (%)	1 (0.2%)	0 (0.0%)
Vomiting	n (%)	8 (1.7%)	4 (0.9%)

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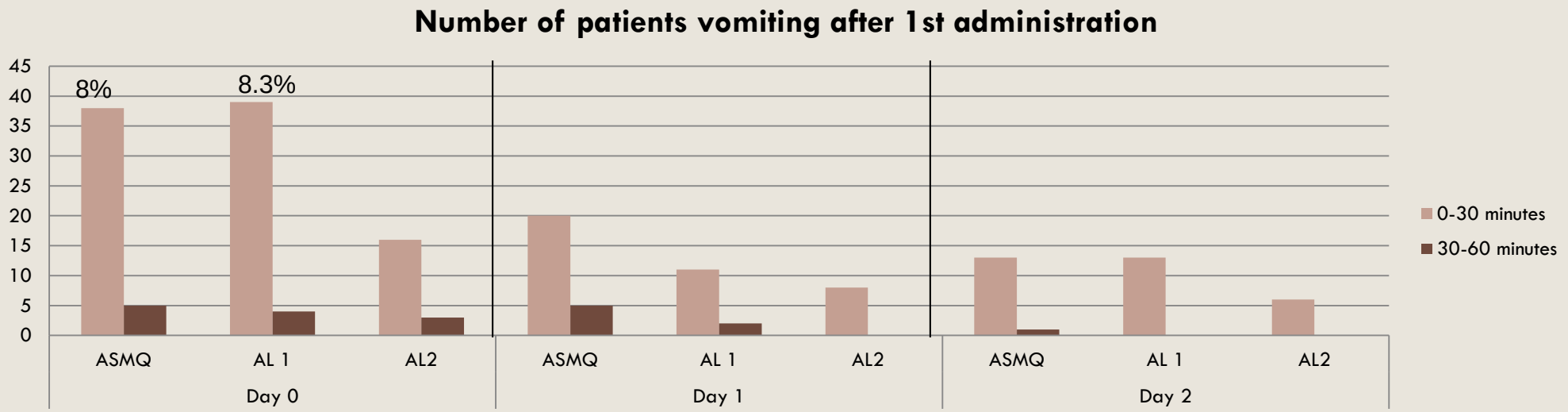
Early Vomitings (max 1 hour after administration)



Number of patients vomiting after readministration:

7 patients in ASMQ (1.5%) and 4 patients in AL (0.8%)

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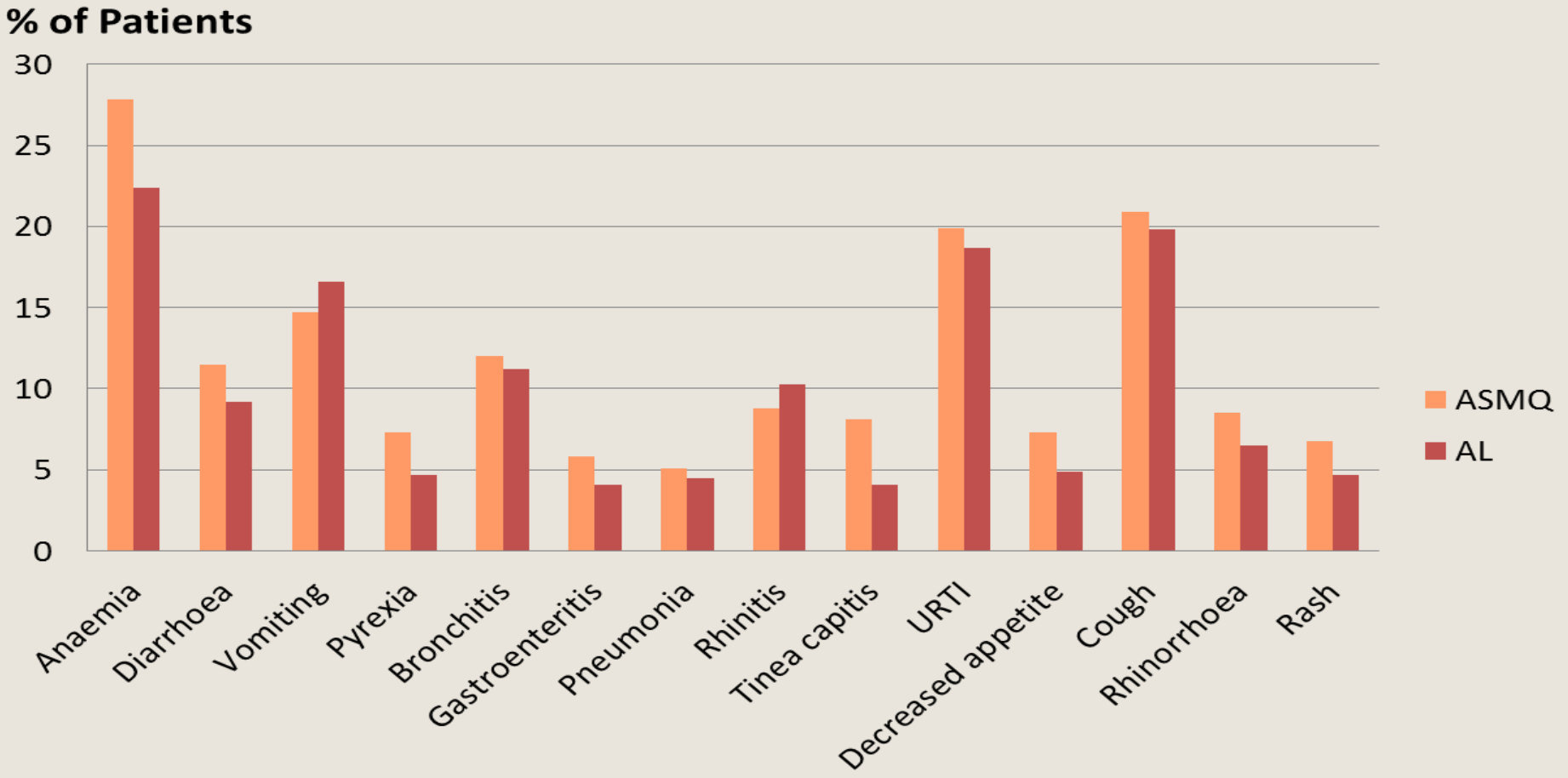
Most frequent Adverse events (≥ 5%)



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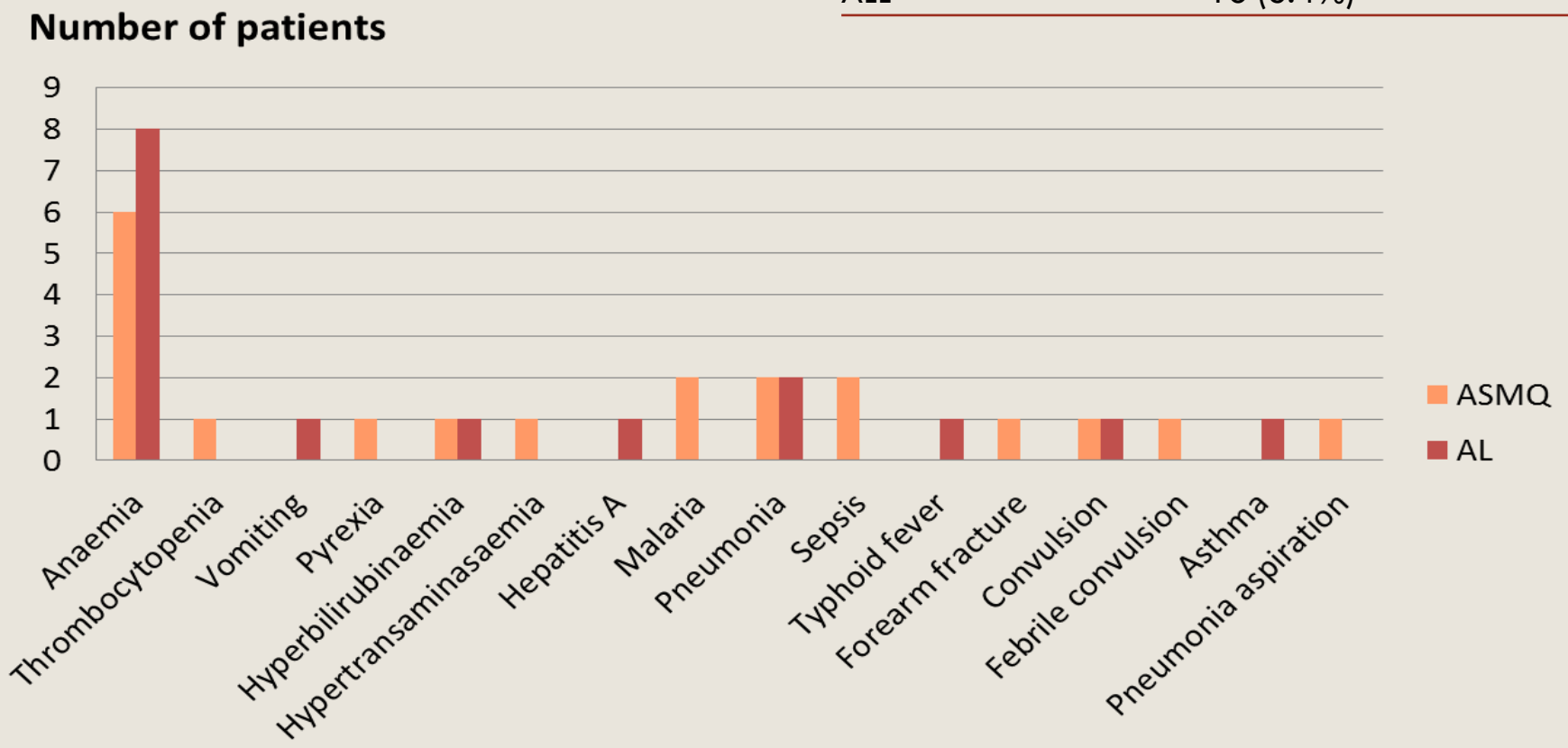
Adverse Events with Intensity ≥ severe (grades 3 & 4*)

	ASMQ (N=468)	AL (N=465)
ALL	16 (3.4%)	14 (3.0%)



*Ony 1 AE with grade 4: Anaemia for 1 ETF patient

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Serious Adverse Events

Item	ASMQ (N=468)	AL (N=465)
ALL	8 (1.7%)	10 (2.2%)
Anaemia	2 (0.4%)	4 (0.9%)
Amoebic dysentery	1 (0.2%)	0 (0.0%)
Hepatitis A	0 (0.0%)	1 (0.2%)
Malaria	2 (0.4%)*	0 (0.0%)
Pneumonia	3 (0.6%)	3 (0.6%)
Sepsis	2 (0.4%) *	0 (0.0%)
Staphylococcal skin infection	0 (0.0%)	1 (0.2%)
Tonsillitis	1 (0.2%)	0 (0.0%)
Urinary tract infection	0 (0.0%)	1 (0.2%)
Thermal burn	0 (0.0%)	1 (0.2%)
Asthma	0 (0.0%)	1 (0.2%)
Pneumonia aspiration	1 (0.2%)	0 (0.0%)

* 2 patients with ETF

No death

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Conclusions

Efficacy

- ASMQ non inferior to AL in all PCR corrected analyses

Tolerability

- Mild to moderate AEs frequent in both treatments
- Very limited cases of vomiting leading to treatment discontinuation in both treatments
- No new event of interest

The results support inclusion of ASMQ treatment in the therapeutic arsenal for children < 5 years in Africa.

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Acknowledgements

Study participants

Sites staff

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THANK YOU

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