Public Assessment Report for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

Riamet (Artemether/Lumefantrine)

UK/W/0096/pdWS/001

Marketing Authorisation Holder: Novartis

Rapporteur:	UK
Finalisation procedure (day 120):	06 February 2017

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Riamet
INN (or common name) of the active substance(s):	Artemether and Lumefantrine
MAH:	Novartis Europharm Limited
Currently approved Indication(s)	RIAMET/COARTEM is indicated for the treatment, including stand-by emergency treatment of adults, children and infants (weighing 5 kg or more) with acute, uncomplicated infections due to Plasmodium falciparum or mixed infections including Plasmodium falciparum
Pharmaco-therapeutic group (ATC Code):	P01BF01
Pharmaceutical form(s) and strength(s):	20/120 mg tablets

I. EXECUTIVE SUMMARY

Riamet (Co-artemether; artemether and lumefantrine) is registered and commercially available in several countries under the trade names Riamet® or Coartem®. It is indicated for treatment, including stand-by emergency treatment of adults, children and infants (weighing 5 kg or more) with acute, uncomplicated infections due to *Plasmodium falciparum* or mixed infections including *P. falciparum*.

Globally, Riamet is available as:

- An immediate release (IR) 20/120 mg tablet
- A dispersible 20/120 mg tablet
- A high dose 80/480 mg tablet (not registered in EU).

The MAH conducted a systematic review to identify potential recently completed and older Novartis-sponsored studies qualifying for Article 46 submission. Four CSRs were submitted concerning three studies (one of the four reports covers an extension study) that enrolled paediatric patients (aged < 18 years).

No SmPC and PL changes are proposed by the MAH based on these studies.

II. RECOMMENDATION

The submission is acceptable. There are no questions to be addressed. It is agreed that no additions to the SmPC or PL are required as a result of these new data.

III. INTRODUCTION

On 6 October 2016 the MAH submitted four reports on three completed paediatric studies (one report concerns an extension study) for Riamet in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Riamet and that there is no consequential regulatory action.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the studies

All tablets (conventional and dispersible) contain 20 mg Artemether and 120 mg Lumefantrine. The daily dose is achieved by using 1-4 tablets b.i.d depending on weight.

IV.2 Clinical aspects

1. Introduction

The MAH submitted final reports for:

Study CCOA566A2417:
An open-label, randomised, single–centre, parallel group study of the effects of artemether-lumefantrine (Coartem®), atovaquone-proguanil (Malarone®) and artesunate mefloquine on auditory function following the treatment of acute uncomplicated *Plasmodium falciparum* malaria in patients 12 years of age or older

Study CCOA566B2306:
An open-label, single-arm study to evaluate the efficacy, safety and PK of artemether-lumefantrine dispersible tablets in the treatment of acute uncomplicated *Plasmodium falciparum* malaria in infants <5 kg body weight. CCOA566B2306 is part of the Paediatric Investigation Plan (PIP) (EMEA-000777-PIP01-09-M05, EMA decision: 05 June 2015) for Artemether/Lumefantrine (dispersible tablet).

Study CCOA566B2401 and study CCOA566B2401E1:
A cluster randomised, single-centre, controlled, parallel, 12-month prospective study and additional 12-month follow-up in Africa of malaria incidence in a community setting following systematic treatment of *P. falciparum* asymptomatic carriers with artemether-lumefantrine (Coartem® / Coartem® dispersible).

2. Clinical studies

Study Number	Study Title	Key Objective	Paediatric exposure (< 18yr)	Paediatric results (< 18yr)	Efficacy results	Safety results	LPLV/LO	CSR date
CCOA566A2417	An open-label, randomized, single-center, parallel group study of the effects of artemether-lumefantrine (AL), atovaquone-proguanil (AP) and artesunate mefloquine (AM) on auditory function following the treatment of acute uncomplicated *Plasmodium falciparum* malaria in patients 12 years of age or older.	Assess the auditory safety of artemether-lumefantrine by auditory brainstem response (ABR) measurements.	265 patients were enrolled including 90 adolescents. 51 were treated with AL, 21 with AP and 18 with AM.	Paediatric results not presented separately.	PCR corrected cure rates (95% confidence interval) in the full analysis set: - AL: 98.7% (95.5-99.8) - AP: 98.1% (89.9-100.0) - AM: 98.1% (89.9-100.0).	This study was planned to evaluate the effects of AL on auditory brainstem pathway function in patients with acute *Plasmodium falciparum* malaria. No clinically significant effect on ABR was found in any of the treatment groups.	22-Nov-2008	15-Dec-2009

➢ **Methods**

- Objectives

The primary objective was to assess the auditory safety of artemether-lumefantrine after 3 days of treatment in patients with acute, uncomplicated falciparum malaria by testing the null hypothesis that the rate of auditory brainstem pathway abnormalities as assessed by auditory brainstem response (ABR) at Day 7 is ≥ 15% in such patients. An "auditory brainstem pathway abnormality" was defined as >0.30 msec change in Wave III latency from baseline to Day 7.

Secondary objectives were:

- To evaluate the safety of artemether-lumefantrine after 3 days of treatment in patients with acute, uncomplicated *P. falciparum* malaria by determining the descriptive changes from baseline in auditory function, evaluated by audiometric measurements at Day 3, 7, 28, and 42 following initiation of treatment.
- To evaluate PCR adjusted malaria cure rates of the three treatment regimens at Days 14, 28 and 42, defined as the proportion of patients with clearance of asexual parasitaemia within 7 days of initiation of trial treatment, without recrudescence within 14, 28 and 42 days, respectively, after initiation of treatment.

Exploratory objectives were:

- To explore the general safety and tolerability of the 3 treatment regimens by analysing incidence rates of adverse events;
- To explore any relationship between audiometric changes and drug exposure;
- To collect data on changes in auditory brainstem pathway latencies via ABR with a non-ACT antimalarial (Malarone®, atovaquone-proguanil) and another ACT combination (artesunate-mefloquine) to be used in potential further studies.

- Study design

See the table above. This was a parallel-group, single-centre, open-label randomised study. Patients included in the study were adults or adolescents (age ≥ 12 years) with acute uncomplicated falciparum malaria or mixed infections including *P. falciparum*. Patients were excluded if: they had signs/symptoms indicative of severe/complicated malaria; had a medical or family history of QTc prolongation; were taking drugs that were associated with QTc prolongation; had other medical conditions or were using other drugs that could interfere with study assessments.

- Study population /Sample size

It was planned to randomise 265 patients (159 to artemether-lumefantrine, 53 to atovaquone-proguanil and 53 to artesunate-mefloquine).

- Treatments

Patients were randomised in a 3:1:1 ratio to artemether-lumefantrine, atovaquone-proguanil or artesunate-mefloquine.

Coartem tablets containing 20 mg artemether and 120 mg lumefantrine were from batch numbers X0145, KN 3748761.005 and X0154, KN 3748761.013. Six doses were given over 60 hours as per the SmPC and according to weight as follows:

Body weight range (kg)	No. of tablets per dose
15 to ≤25	2
25 to ≤35	3
>35	4

Malarone tablets (250 mg atovaquone and 100 mg proguanil; see batch details below) were administered according to body weight as follows:

Body weight range (kg)	No. of tablets per dose
11-20	1
21-30	2
31-40	3
>40	4

Artesunate-mefloquine was administered using Plasmotrim and Mephaquin tablets as shown in the table. Artesunate was dosed at 4 mg/kg/day while mefloquine was dosed as 15 mg/kg on day 2 and 10 mg/kg on day 3.

Reference therapy:

Product	Dosage Form	Strength	KN	Batch Number
Malarone®	Film-coated tablets	250 mg	6002144.001	5L004
Plasmotrim®	Tablets	50 mg	6002335.001	0651437
Mephaquin	Tablets	250 mg	6002327.001	0651209

All treatments were given for 3 days and were to be taken with chocolate milk.

- Outcomes/endpoints

Efficacy was a secondary objective in this study. Parasitological cure rates at 14, 28 and 42 days, corrected for re-infection by PCR genotyping were the key efficacy parameters.

The primary objective of the study was to assess the auditory safety of artemether-lumefantrine as assessed by ABR measurements at Day 7. In addition the changes in pure-tone threshold and ABR assessment at Days 3, 7, 28 and 42 were determined.

Safety was also evaluated in terms of adverse events, vital signs, and clinical laboratory assessments of haematology parameters.

Blood samples were taken for the assessment of plasma levels of:
- Lumefantrine, artemether and DHA levels for all artemether-lumefantrine-treated patients
- Mefloquine, artesunate and DHA levels for all artesunate-mefloquine-treated patients

In the artemether-lumefantrine group, 5 samples per patient were taken for lumefantrine measurement (at pre-treatment, and in each of the following time windows: 0-48, 49-72, 73-120, 121-240 hours post first dose). One sample per patient (1 h after last dose) was taken for artemether and DHA measurement. Lumefantrine PK analysis was done using a model population pharmacokinetic method (NONMEM).

In the artesunate-mefloquine group, 7 blood samples per patient were taken for mefloquine measurement (at 0, 6, 14, 24, 38, 96 and 672 hours post dose). One sample per patient (1 h after last dose) was taken for artesunate and DHA measurement. Mefloquine PK analysis was done using a noncompartmental method (WinNonlin Pro).

No blood samples were taken in the atovaquone-proguanil group.

The relation between drug exposures and audiometric changes (as measured by ABR change from baseline) was explored graphically and by regression methods.

- Statistical Methods

The primary endpoint was the rate of ABR Wave III latency changes of > 0.3 msec. This was analysed for the Safety per-protocol set, defined as all randomised patients who took at least 80% of the entire recommended dose regimen, had a valid baseline and Day 7 ABR Wave III latency evaluation and did not use any medication having an ototoxic effect.

The null hypothesis being tested was that the proportion of patients with ABR Wave III latency changes in the artemether-lumefantrine group is ≥ 15% utilising a level of significance of 5%. The test was performed using a one-sided, exact test for a single proportion.

➢ **Results**

- Recruitment/ Number analysed

The actual number randomised was exactly as planned, i.e. 265 patients (159 artemether-lumefantrine, 53 atovaquone-proguanil and 53 artesunate-mefloquine). All randomised patients took all their planned doses. The Day 7 Safety per-protocol set (blinded review) comprised 246 patients (151 artemether-lumefantrine, 50 atovaquone-proguanil and 45 artesunate-mefloquine).

- Baseline data

The three treatment groups were comparable in terms of their demographic data and baseline characteristics.

There were 90 patients (about one third of the total) aged < 18 years.

Table 7-4 Baseline demographic summary (Safety set)

Variable	Artemether-lumefantrine (N=159)	Atovaquone-proguanil (N=53)	Artesunate-mefloquine (N=53)	Total (N=265)
Age (yrs)				
Mean ± SD	25.6 ± 11.60	25.1 ± 11.16	25.2 ± 11.26	25.4 ± 11.40
Median	23.0	23.0	22.0	23.0
Range	12 - 56	12 - 53	12 - 56	12 - 56
Age category - n (%)				
<18 years	51 (32.1)	21 (39.6)	18 (34.0)	90 (34.0)
18-<65 years	108 (67.9)	32 (60.4)	35 (66.0)	175 (66.0)
≥65 years	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sex - n (%)				
Male	96 (60.4)	34 (64.2)	31 (58.5)	161 (60.8)
Female	63 (39.6)	19 (35.8)	22 (41.5)	104 (39.2)

All patients were Black (~80%) or Hispanic (~20%).

About 90% had a fever ≥ 37.5^{0}C at baseline but <10% had a fever ≥39^{0}C. All had *P. falciparum* only and < 10% had gametocytes detected. Baseline parasite counts are shown below.

Variable	Artemether-lumefantrine (N=159)	Atovaquone-proguanil (N=53)	Artesunate-mefloquine (N=53)	Total (N=265)
Parasite density asexual forms (/µL)				
Median	3925	3864	4620	3950
Range	1008 - 44744	1030 - 31124	1012 - 35112	1008 - 44744
n (%)				
<1,000 /µL	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1,000-<5,000 /µL	93 (58.5)	32 (60.4)	29 (54.7)	154 (58.1)
5,000-<15,000 /µL	45 (28.3)	17 (32.1)	17 (32.1)	79 (29.8)
15,000-<50,000 /µL	21 (13.2)	4 (7.5)	7 (13.2)	32 (12.1)
≥50,000 /µL	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

- Efficacy results

PCR-corrected parasitological cure rates are shown for the FAS set using a worst case analysis, in which patients with missing or unclear results are counted as treatment failures.

Table 9-1 PCR-corrected 14-, 28-, and 42-day cure rates (Full analysis and Evaluable set)

Analysis set	Time point	Statistic	Artemether-lumefantrine	Atovaquone-proguanil	Artesunate-mefloquine
Full analysis set	Day 14	N	159	53	53
		n (%) cured	158 (99.4)	53 (100.0)	52 (98.1)
		95% CI [a]	(96.5 - 100.0)	(93.3 - 100.0)	(89.9 - 100.0)
	Day 28	N	159	53	53
		n (%) cured	157 (98.7)	52 (98.1)	52 (98.1)
		95% CI [a]	(95.5 - 99.8)	(89.9 - 100.0)	(89.9 - 100.0)
	Day 42	N	159	52	53
		n (%) cured	155 (97.5)	51 (98.1)	52 (98.1)
		95% CI [a]	(93.7 - 99.3)	(89.7 - 100.0)	(89.9 - 100.0)
Day 28 Evaluable set	Day 28	N	157	52	52
		n (%) cured	157 (100.0)	52 (100.0)	52 (100.0)
		95% CI [a]	(97.7 - 100.0)	(93.2 - 100.0)	(93.2 - 100.0)

[a] Using Pearson Clopper limits.

The PCR corrected 14-, 28-, and 42-day cure rates were very high and comparable between all treatment groups. With such high rates there were no important differences seen between subgroups with BMI < and ≥ 25 kg/m^2.

Rapid clearance of asexual parasite forms was observed with artemisinin-containing treatments. At 48 hours 98.1% in the artemether-lumefantrine group, 63.5% in the atovaquone-proguanil group and 100% in the artesunate-mefloquine group had negative slides. There were only 3 patients (all in the atovaquone-proguanil group) with a parasite reduction by < 75% at 48 hours. The mean percent parasite reduction at 24 hours after the first dose was higher in the artemether-lumefantrine group (-94.5%) and the artesunate-mefloquine group (-97.5%) compared to the atovaquone-proguanil group (-50.2%).

P. falciparum gametocytes after Day 8 were observed in all three treatment groups, but were less frequent in the artemether-lumefantrine group (3 patients, 1.9%) and the artesunate-mefloquine group (1 patient, 1.9%) than in the atovaquone-proguanil group (6 patients, 11.3%). No schizonts were observed at any time in any group.

A rapid clearance of fever was observed and all patients had no fever by Day 4.

At Day 28, ACPR rates were 98.7% in the artemether-lumefantrine group, 94.3% in the atovaquone-proguanil group and 98.1% in the artesunate-mefloquine group. All "treatment failures" in the artemether-lumefantrine and artesunate-mefloquine groups were in fact unknown outcomes since these patients were withdrawn early.

- Safety results

The null hypothesis being tested (the proportion of subjects with ABR Wave III latency changes in the artemether-lumefantrine group is ≥ 15 %) was rejected (one-sided exact test for a single proportion, p-value <0.0001). In the artemether-lumefantrine treatment group based on the "blinded review" the observed rate was 2.6 % (95% CI: 0.7 – 6.6).

Review	Statistics	Artemether-lumefantrine	Atovaquone-proguanil	Artesunate-mefloquine
Blinded	N	151	50	45
	n (%) with change [a]	4 (2.6)	0 (0.0)	0 (0.0)
	Two-sided 95% CI [b]	(0.7 - 6.6)	(0.0 - 7.1)	(0.0 - 7.9)
	One-sided 95% CI [b]	(0.0 - 6.0)	(0.0 - 5.8)	(0.0 - 6.4)
	p-value [c]	<.0001	not applicable	not applicable
Initial	N	145	49	46
	n (%) with change [a]	2 (1.4)	0 (0.0)	0 (0.0)
	Two-sided 95% CI [b]	(0.2 - 4.9)	(0.0 - 7.3)	(0.0 - 7.7)
	One-sided 95% CI [b]	(0.0 - 4.3)	(0.0 - 5.9)	(0.0 - 6.3)
	p-value [c]	<.0001	not applicable	not applicable

[a] Increase in ABR Wave III latency between baseline and Day 7 of >0.3 ms.

[b] Exact confidence intervals according to the Pearson-Clopper method.

[c] For the one-sided null hypothesis that the incidence rate of ABR Wave III latency changes is ≥ 15% (artemether-lumefantrine group only).

Table 10-4 Treatment group differences in incidence rate of ABR Wave III latency changes on Day 7 (Safety per-protocol set [blinded and initial review])

Review	Treatment group difference	%	95% CI [b]
Blinded	Artemether-lumefantrine minus atovaquone-proguanil	2.6	(-4.7 - 6.6)
	Artemether-lumefantrine minus artesunate-mefloquine	2.6	(-5.4 - 6.6)
	Artesunate-mefloquine minus atovaquone-proguanil	0.0	(-7.1 - 7.9)
Initial	Artemether-lumefantrine minus atovaquone-proguanil	1.4	(-6.0 - 4.9)
	Artemether-lumefantrine minus artesunate-mefloquine	1.4	(-6.4 - 4.9)
	Artesunate-mefloquine minus atovaquone-proguanil	0.0	(-7.3 - 7.7)

[a] Increase in ABR Wave III latency between baseline and Day 7 of >0.30 ms.

[b] Using Wilson score limits.

On days 3, 28 and 42 the rates of ABR Wave III latency changes were as shown below.

Table 10-5 Incidence rate of ABR Wave III latency changes on Days 3, 28, and 42 (Safety per-protocol set [initial review])

Time point	Statistics	Artemether-lumefantrine	Atovaquone-proguanil	Artesunate-mefloquine
Day 3	N	145	50	45
	n (%) with change [a]	4 (2.8)	0 (0.0)	0 (0.0)
	Two-sided 95% CI [b]	(0.8 - 6.9)	(0.0 - 7.1)	(0.0 - 7.9)
	One-sided 95% CI [b]	(0.0 - 6.2)	(0.0 - 5.8)	(0.0 - 6.4)
Day 28	N	143	50	46
	n (%) with change [a]	6 (4.2)	1 (2.0)	0 (0.0)
	Two-sided 95% CI [b]	(1.6 - 8.9)	(0.1 - 10.6)	(0.0 - 7.7)
	One-sided 95% CI [b]	(0.0 - 8.1)	(0.0 - 9.1)	(0.0 - 6.3)
Day 42	N	138	49	47
	n (%) with change [a]	4 (2.9)	0 (0.0)	1 (2.1)
	Two-sided 95% CI [b]	(0.8 - 7.3)	(0.0 - 7.3)	(0.1 - 11.3)
	One-sided 95% CI [b]	(0.0 - 6.5)	(0.0 - 5.9)	(0.0 - 9.7)

[a] Increase in ABR Wave III latency between baseline and the corresponding day of >0.30 ms.

[b] Using Pearson Clopper limits.

Since the Safety per-protocol set is defined separately for each analysis time point, the number of patients included may differ between time points.

Changes in ABR Wave III latency (msec) from baseline to day 7 are shown below.

Table 10-6 ABR Wave III latency (ms) changes from baseline to Day 7 (Safety per-protocol set [blinded review])

Ear	Artemether-lumefantrine		Atovaquone-proguanil		Artesunate-mefloquine	
Time point	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)
Right ear						
Baseline	151	3.86 (3.83 - 3.90)	50	3.89 (3.84 - 3.94)	45	3.86 (3.80 - 3.93)
Change						
Day 7	151	0.01 (-0.01 - 0.03)	50	-0.01 (-0.04 - 0.02)	45	-0.04 (-0.08 - 0.01)
Left ear						
Baseline	151	3.85 (3.82 - 3.88)	50	3.88 (3.84 - 3.93)	45	3.82 (3.77 - 3.88)
Change						
Day 7	151	0.01 (-0.01 - 0.03)	50	-0.01 (-0.04 - 0.02)	45	-0.03 (-0.07 - 0.00)

Summary statistics showed no changes in ABR Wave I and V latencies.

Table 10-8 Incidence rate of ABR Wave I and Wave V latency changes on Days 3, 7, 28, and 42 (Safety per-protocol set [blinded and initial review])

Wave/ Time point	Statistic	Artemether-lumefantrine	Atovaquone-proguanil	Artesunate-mefloquine
Wave I				
Day 3 (initial)	N	145	50	45
	n (%) with change [a]	2 (1.4)	0 (0.0)	0 (0.0)
	Two-sided 95% CI [b]	(0.2 - 4.9)	(0.0 - 7.1)	(0.0 - 7.9)
Day 7 (blinded)	N	151	50	45
	n (%) with change [a]	2 (1.3)	0 (0.0)	0 (0.0)
	Two-sided 95% CI [b]	(0.2 - 4.7)	(0.0 - 7.1)	(0.0 - 7.9)
Day 7 (initial)	N	145	49	46
	n (%) with change [a]	2 (1.4)	1 (2.0)	1 (2.2)
	Two-sided 95% CI [b]	(0.2 - 4.9)	(0.1 - 10.9)	(0.1 - 11.5)
Day 28 (initial)	N	143	50	46
	n (%) with change [a]	2 (1.4)	0 (0.0)	0 (0.0)
	Two-sided 95% CI [b]	(0.2 - 5.0)	(0.0 - 7.1)	(0.0 - 7.7)
Day 42 (initial)	N	138	49	47
	n (%) with change [a]	1 (0.7)	1 (2.0)	1 (2.1)
	Two-sided 95% CI [b]	(0.0 - 4.0)	(0.1 - 10.9)	(0.1 - 11.3)
Wave V				
Day 3 (initial)	N	145	50	45
	n (%) with change [a]	13 (9.0)	2 (4.0)	3 (6.7)
	Two-sided 95% CI [b]	(4.9 - 14.8)	(0.5 - 13.7)	(1.4 - 18.3)
Day 7 (blinded)	N	151	50	45
	n (%) with change [a]	14 (9.3)	4 (8.0)	3 (6.7)
	Two-sided 95% CI [b]	(5.2 - 15.1)	(2.2 - 19.2)	(1.4 - 18.3)
Day 7 (initial)	N	145	49	46
	n (%) with change [a]	14 (9.7)	2 (4.1)	1 (2.2)
	Two-sided 95% CI [b]	(5.4 - 15.7)	(0.5 - 14.0)	(0.1 - 11.5)
Day 28 (initial)	N	143	50	46
	n (%) with change [a]	16 (11.2)	1 (2.0)	1 (2.2)
	Two-sided 95% CI [b]	(6.5 - 17.5)	(0.1 - 10.6)	(0.1 - 11.5)
Day 42 (initial)	N	138	49	47
	n (%) with change [a]	16 (11.6)	2 (4.1)	2 (4.3)
	Two-sided 95% CI [b]	(6.8 - 18.1)	(0.5 - 14.0)	(0.5 - 14.5)

[a] Increase in ABR Wave I/V latency between baseline and the corresponding day of >0.30 ms.

[b] Using Pearson Clopper limits.

Since the Safety per-protocol set is defined separately for each analysis time point, the number of patients included may differ between time points.

No significant changes in pure-tone air conduction thresholds were apparent.

Table 10-9 Pure-tone air conduction threshold average (dB) over time (Safety per-protocol set [initial review])

Ear		Artemether-lumefantrine		Atovaquone-proguanil		Artesunate-mefloquine
Time point	n	Mean (95% CI)	n	Mean (95% CI)	n	Mean (95% CI)
Right ear						
Baseline	148	12.2 (11.4 - 13.0)	51	12.0 (10.5 - 13.6)	47	12.7 (11.2 – 14.2)
Change						
Day 3	145	-2.5 (-3.1 - -1.9)	50	-2.4 (-3.6 - -1.2)	45	-1.9 (-3.0 - -0.7)
Day 7	143	-2.2 (-2.9 - -1.5)	49	-2.6 (-4.0 - -1.1)	46	-2.6 (-3.9 - -1.3)
Day 28	143	-2.7 (-3.5 - -1.9)	50	-2.6 (-4.2 - -1.0)	46	-3.6 (-4.8 - -2.3)
Day 42	138	-3.0 (-3.8 - -2.2)	49	-3.3 (-4.9 - -1.7)	47	-3.1 (-4.2 - -1.9)
Left ear						
Baseline	148	11.4 (10.5 - 12.3)	51	11.3 (9.9 – 12.7)	47	12.5 (10.8 – 14.3)
Change						
Day 3	145	-1.2 (-1.8 - -0.5)	50	-1.5 (-2.6 - -0.3)	45	-1.2 (-2.2 - -0.1)
Day 7	143	-1.7 (-2.4 - -0.9)	49	-1.3 (-2.8 - 0.2)	46	-1.4 (-2.8 - -0.1)
Day 28	143	-2.0 (-2.8 - -1.1)	50	-1.8 (-3.0 - -0.5)	46	-2.5 (-4.3 - -0.7)
Day 42	138	-1.5 (-2.7 - -0.4)	49	-2.1 (-3.5 - -0.6)	47	-3.0 (-4.7 - -1.3)

The pure-tone average is defined as the average of the pure-tone thresholds for the frequencies 500 Hz, 1000 Hz, 2000 Hz, and 3000 Hz.

Safety per-protocol patients who had a valid ABR at baseline and on the specified day were included. Since the Safety per-protocol set is defined separately for each analysis time point, the number of patients included may differ between time points.

In order to describe thoroughly the cases of ABR changes observed, latency shifts occurring in Wave III and Wave V were taken into consideration. Wave I was not likely to be considered clinically significant because it is generated by the auditory nerve, whereas Waves III and V are thought to be generated primarily in the brainstem.

The time pattern for all patients with Wave III or Wave V changes from baseline > 0.30 msec present at patient's last study visit was described. Clinically relevant ABR latency shifts from baseline of >0.30 msec were considered to be those that occurred after the patient had received the full course of treatment, were sustained and were not reversible during the study. An additional analysis showed that 12 patients (artemether-lumefantrine 10; atovaquone-proguanil 1; artesunate-mefloquine 1) fulfilled these criteria, as shown in the table below. As shown in the table, the 95% CIs were wide and overlapped.

Table 10-10 Number and percent of patients with a sustained change in ABR latency from baseline >0.30 msec, by treatment (Baseline and Day 3 or Day 7 safety per-protocol set, initial or blinded review)

Statistic	Artemether-lumefantrine	Atovaquone-proguanil	Artesunate-mefloquine
N	158	53	49
n (%) with change	10 (6.3)	1 (1.9)	1 (2.0)
Exact two-sided 95% CI	(3.1 – 11.3)	(0.0 – 10.1)	(0.1 – 10.9)
Exact one-sided (upper) 95% CI	(0.0 – 10.5)	(0.0 – 8.6)	(0.0 – 9.3)
Asymptotic two-sided 95% confidence interval	(2.5 – 10.1)	(0.0 – 5.5)	(0.0 – 6.0)
p-value [a]	0.0006	not applicable	not applicable

Safety per-protocol patients who had a valid ABR (initial and/or blinded) at baseline and at day 3 and/or day 7 were included.

A patient is considered to have a sustained ABR change if in either Wave III, or Wave V, or both a change from baseline >0.30 msec is observed on day 3 and/or 7 (irrespective of initial or blinded reading) that is sustained at all available subsequent readings.

Exact confidence intervals were calculated according to the Pearson-Clopper method.

[a] For the null hypothesis that the incidence rate of sustained ABR changes is ≥ 15% (artemether-lumefantrine group only).

The patients with ABR Wave III latency changes on Day 7 and/or sustained change in ABR latency III or V tended to have rather low baseline ABR latencies. The MAH proposed that the observed latency changes from baseline may contain an element of regression to the mean. It is

noteworthy that the 10 patients treated by artemether-lumefantrine with a sustained change in ABR latency from baseline >0.30 msec had no change in their pure tone threshold.

There were no deaths in the study. One SAE was reported in the artesunate-mefloquine group (respiratory distress syndrome on day 4). Adverse events leading to study drug discontinuation or requiring dose adjustment or study drug interruption were not reported.

The overall incidence rate of adverse events was lower in the artemether-lumefantrine group (28.9%) compared to the atovaquone-proguanil group (47.2%) and the artesunate-mefloquine group (67.9%). The difference between the artemether-lumefantrine and other treatment groups was mainly due to a lower incidence of gastrointestinal AEs (7.5% vs. 22.6% and 35.8%) and nervous system disorders, such as dizziness and headache (8.2% vs. 20.8% and 35.8%). Most of the reported adverse events were of mild intensity.

Table 10-1 **Number (%) of patients with most frequent AEs (>2 patients in any treatment group) by primary system organ class and preferred term (Safety set)**

	Artemether-lumefantrine	Atovaquone-proguanil	Artesunate-mefloquine
Patients studied			
Total no. of patients	159	53	53
Total no. of patients with AEs	46 (28.9)	25 (47.2)	36 (67.9)
System organ class/AE [a]			
Blood and lymphatic system disorders	6 (3.8)	1 (1.9)	3 (5.7)
Anaemia	6 (3.8)	1 (1.9)	2 (3.8)
Gastrointestinal disorders	12 (7.5)	12 (22.6)	19 (35.8)
Abdominal pain	3 (1.9)	2 (3.8)	4 (7.5)
Diarrhoea	3 (1.9)	2 (3.8)	7 (13.2)
Vomiting	2 (1.3)	9 (17.0)	15 (28.3)
General disorders and administration site conditions	7 (4.4)	4 (7.5)	2 (3.8)
Pyrexia	6 (3.8)	4 (7.5)	2 (3.8)
Infections and infestations	12 (7.5)	6 (11.3)	5 (9.4)
Nervous system disorders	13 (8.2)	11 (20.8)	19 (35.8)
Dizziness	9 (5.7)	5 (9.4)	14 (26.4)
Headache	5 (3.1)	7 (13.2)	7 (13.2)
Psychiatric disorders	0 (0.0)	0 (0.0)	5 (9.4)
Insomnia	0 (0.0)	0 (0.0)	4 (7.5)
Respiratory, thoracic and mediastinal disorders	3 (1.9)	1 (1.9)	2 (3.8)
Cough	3 (1.9)	1 (1.9)	0 (0.0)

AEs considered drug-related were reported for 3.1% in the artemether-lumefantrine group compared to 11.3% for Malarone and 28.3% for artesunate-mefloquine. The most common of these was vomiting (in 0%, 9.4% and 17%).

All adverse events after baseline suspected to be study drug-related,
by preferred term and treatment
Safety set

Preferred term	Co-artemether N=159 n	(%)	Atovaquone-proguanil N=53 n	(%)	Artesunate-mefloquine N=53 n	(%)
Any adverse event	5	(3.1)	6	(11.3)	15	(28.3)
Dizziness	3	(1.9)	1	(1.9)	8	(15.1)
Abdominal pain	1	(0.6)	0	(0.0)	2	(3.8)
Abdominal pain upper	1	(0.6)	1	(1.9)	2	(3.8)
Anxiety	0	(0.0)	0	(0.0)	2	(3.8)
Diarrhoea	0	(0.0)	2	(3.8)	3	(5.7)
Dyspnoea	0	(0.0)	0	(0.0)	1	(1.9)
Gastritis	0	(0.0)	0	(0.0)	1	(1.9)
Headache	0	(0.0)	0	(0.0)	1	(1.9)
Insomnia	0	(0.0)	0	(0.0)	3	(5.7)
Mood swings	0	(0.0)	0	(0.0)	1	(1.9)
Nausea	0	(0.0)	0	(0.0)	2	(3.8)
Vomiting	0	(0.0)	5	(9.4)	9	(17.0)

No between-group differences of note were observed for haematological parameters and vital signs.

The full PK report is not provided but the CSR states that the graphical exploration as well as linear regression analysis of the PK data showed no significant trend in the relation between exposure to lumefantrine, artemether or DHA and continuous ABR change (blinded day 7 assessment, Wave III). The four patients in the artemether-lumefantrine group with an ABR change above 0.3 msec from baseline were spread in the normal exposure range for model-based lumefantrine Cmax and AUC, as well as for the observed lumefantrine Cmax, artemether and DHA concentrations. No evidence of a relationship between artesunate, DHA or mefloquine exposure and ABR changes was found in the artesunate-mefloquine-treated patients (there was no patient with ABR changes from baseline above 0.30 msec in this group).

Study Number	Study Title	Key Objective	Paediatric exposure (< 18yr)	Paediatric results (< 18yr)	Efficacy results	Safety results	LPLV/LO	CSR date
CCOA566B2306	An open-label, single-arm study to evaluate the efficacy, safety and PK of artemether-lumefantrine (AL) dispersible tablet in the treatment of acute uncomplicated *Plasmodium falciparum* malaria in infants <5 kg body weight.	Efficacy of a 3-day regimen of Co-artemether in infants <5 kg of body weight using the polymerase chain reaction (PCR)-corrected 28-day parasitological cure rate. Evaluation of safety and PK of Co-artemether in infants <5 kg of body weight.	20 children > 28 days and <5kg both male and female were enrolled and treated with a dispersible tablet containing 20mg artemether/120 mg lumefantrine twice daily during 3 days.	Paediatric study.	100% cure rate at day 28 in the per protocol population. The mean exposure to artemether and DHA was 2- to 3-fold greater than that in infants weighing ≥5 kg and children up to 12 years of age.	No new safety signal was identified. A neuro-development al assessment 12 months post-dose did not reveal any significant findings. Given the observed neurotoxic potential of high serum concentration s of artemether in animal studies, and inability to reduce the dose with the existing formulation, a second cohort of patients aged ≤28 days were not recruited.	08-Jul-2014	20-Nov-2014

➢ Methods

- Objectives

The primary objective was to evaluate the efficacy of a 3-day regimen of artemether-lumefantrine dispersible tablet in infants of <5 kg body weight with acute uncomplicated *P. falciparum* malaria using the PCR-corrected 28-day parasitological cure rate.

Secondary objectives were:

To evaluate the efficacy of a 3-day regimen of artemether-lumefantrine dispersible tablets in infants <5 kg with acute uncomplicated *P. falciparum* malaria using:

- The PCR-corrected parasitological cure rate at Day 14 and Day 42 and the parasitological uncorrected cure rate at Day 3, Day 7, Day 14, Day 28 and Day 42;
- The percent parasite reduction at 24 hours after treatment initiation;
- The number of patients with parasitaemia at 72 hours after treatment initiation ≥ 25% of count at baseline and the number of patients with parasitaemia at 48 hours after treatment initiation greater than at baseline;
- The time to parasite clearance (PCT), time to fever clearance (FCT) and time to gametocyte clearance (GCT) as well as gametocyte carriage over time.

To evaluate the safety of a 3-day regimen of artemether-lumefantrine dispersible tablets in infants <5 kg with acute uncomplicated *P. falciparum* malaria based on SAEs, AEs and laboratory assessments.

To investigate the PK of artemether-lumefantrine during and following treatment.

- Study design

This was an open-label and uncontrolled study conducted at 3 sites in Benin and Burkina Faso between 2012 and 2014. Two sequential age cohorts were initially planned:

i) at least 15 infants >28 days of age (Cohort 1) and, following DMC review,
ii) at least 15 term neonates ≤28 days of age (Cohort 2).

Patients in Cohort 1 entered a 3-day treatment period, followed by a core follow-up period up to Week 6 (i.e. Day 42). Patients then attended a visit at 12 months of age to assess their neurodevelopment. Visits to assess safety and efficacy were scheduled at regular intervals during the 6-week core follow-up period. The assessment to address the primary objective was performed at Day 28.

- Study population/Sample size

It was planned to recruit 20 patients into Cohort 1 to obtain 15 evaluable neonates/infants for the primary endpoint.

Eligible patients for Cohort 1 were male and female infants aged >28 days with a body weight <5 kg and with microscopically confirmed acute uncomplicated P. falciparum malaria or mixed infections with asexual P. falciparum parasitaemia of >1,000 and <100,000 parasites/µL.

Patients with severe malaria, with apnoea-bradycardia, sustained bradycardia, tachycardia, desaturation, hypotension, hypothermia or other severely deteriorated general condition, a family history of congenital QTc prolongation or sudden death, any clinically significant neurological condition, or clinically significant abnormalities of the hepatic and renal systems were excluded. Patients who sustained a significant blood volume loss, who were unable to swallow or drink properly, who had a history of malabsorption or previous gastrointestinal surgery, or disturbances of electrolyte balance were also excluded.

- Treatments

All patients received one 20 mg artemether/120 mg lumefantrine dispersible tablet twice daily for 3 consecutive days. Each tablet was dispersed in water (approximately 10 mL) and given orally. Administration was followed whenever possible by food/drink such as milk. Study medication was given under hospital staff supervision.

- Outcomes/endpoints

The primary efficacy variable was the PCR-corrected 28-day parasitological cure rate, defined as the proportion of patients with clearance of asexual parasites within 7 days of initiating study treatment without recrudescence at Day 28, corrected for re-infection by PCR assay. Parasitaemia results were taken from the central microscopy reading.

Safety assessments up to Study Day 42 consisted of monitoring and recording all AEs and SAEs, monitoring of haematology and blood chemistry tests and regular measurement of vital signs (pulse rate, blood pressure and physical examination). Patients were assessed by an age-appropriate neurodevelopmental scale (Shoklo Malaria Research Unit Assessment) at 12 months of age.

Summary statistics were to be provided for the maximum concentration observed in the individual patient based on the limited number of samples (two for artemether and DHA [1 and 2 h after the first dose] and four for lumefantrine [6h after doses 5 and 6, then 24 h and 7 days]).

- Statistical Methods

This was not a confirmatory study and no hypothesis testing was planned.
Exact Pearson-Clopper two-sided 95% confidence limits were constructed for the Day 28 PCR-corrected parasitological cure rate.

The primary analysis was conducted on the Evaluable patient set (EPS). Categorical data were presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum and maximum were presented, with 25th and 75th percentiles as appropriate. In addition, Kaplan Meir Median was presented for time to event parameters where estimable.

After completion of the 6-week core study period by Cohort 1, an interim analysis was to be performed including safety, efficacy and PK data. This was stated in the protocol.

It was planned that the existing Novartis PK database would be enriched with data from Cohort 1. Thus the lumefantrine data from Cohort 1 were to be analysed using the existing model to assess if the exposure in infants <5 kg BW but >28 days of age was similar or different from that in infants/children ≥5 kg BW. For artemether and DHA, plasma level data from Cohort 1 were to be analysed descriptively and compared to historic data in infants/children of BW ≥5 kg.

Based on results from the core 6-week follow-up in Cohort 1 patients (PK as well as efficacy and safety results), the DMC would make a decision whether to proceed (a) with enrolling cohort 2 (infants <5 kg BW and ≤28 days old) and (b) with either the same dose regimen, or, if required, with a modified regimen.

The final analysis was to be performed after Cohort 1 patients completed their follow-up visit at 12 months of age.

➢ Results

- Recruitment/ Number analysed

The study enrolled 20 patients into Cohort 1 for the Safety and Full analysis sets, 16 of whom had a Day 28 cure status and were included in the Evaluable patients set (EPS). Also, 17 of the 20 patients attended a long-term follow-up visit at 12 months of age.

	Cohort 1 N=20 n (%)
Completed 6-week follow-up phase	19 (95.0)
Discontinued prior to completion of 6 week follow-up phase	1 (5.0)
Primary reason for discontinuation	
Adverse event	1 (5.0)
Completed follow-up at 12 months of age	17 (85.0)
Did not attend the follow-up at 12 months of age	3 (15.0)
Primary reason for not attending the follow-up at 12 months of age	
Death	2 (10.0)
Loss to follow-up	1 (5.0)
Subject less than 12 months of age	0

Following an interim database lock and review after Cohort 1 had completed the 6-week core follow-up period (i.e. Day 42), a joint DMC recommended not to continue with the initiation of Cohort 2 (≤ 28 days of age). The study therefore concluded when all Cohort 1 patients (>28 days of age) completed their follow-up visit at 12 months of age or had discontinued.

- Baseline data

The mean age of patients at baseline was 99 days, ranging from 37 days to 214 days. The cohort was equally split between males and females, all of African origin. Mean weight was 4.3 kg and mean height was 57 cm.

All 20 patients in Cohort 1 had confirmed *P. falciparum* asexual forms, with a median parasite density of 7273/µL. Over half (60%) had a parasite density >5000/µL. Eight patients had a baseline body temperature of ≥37.5 °C, with one patient with a body temperature ≥39.0 °C. One patient had a co-infection with another species (*P. ovale*).

Four patients from the same site (Benin) were excluded from the EPS and PPS datasets as they did not have microscopy at Day 7 or at any time beyond that time point. These patients were conservatively classified as treatment failures in the FAS dataset.

- Efficacy results

All Cohort 1 patients in the EPS and PPS population sets and 80% in the FAS met PCR-corrected 28-day parasitological cure. In all cases, recurrence of parasitaemia was due to reinfection and not recrudescence.

Table 11-4 Summary of parasitological cure rates for Cohort 1

	Cohort 1		
	EPS N=16 n (%) [CI]	PPS N=16 n (%) [CI]	FAS N=20 n (%) [CI]
PCR-corrected 28-day parasitological cure rate	16 (100) [79.4, 100]	16 (100) [79.4, 100]	16 (80) [56.3, 94.3]
PCR-corrected 14-day parasitological cure rate	16 (100) [79.4, 100]	16 (100) [79.4, 100]	16 (80) [56.3, 94.3]
PCR-corrected 42-day parasitological cure rate	16 (100) [79.4, 100]	16 (100) [79.4, 100]	16 (80) [56.3, 94.3]
3-day parasitological uncorrected cure rate	16 (100) [79.4, 100]	16 (100) [79.4, 100]	20 (100) [83.2, 100]
7-day parasitological uncorrected cure rate	16 (100) [79.4, 100]	16 (100) [79.4, 100]	16 (80) [56.3, 94.3]
14-day parasitological uncorrected cure rate	16 (100) [79.4, 100]	16 (100) [79.4, 100]	16 (80) [56.3, 94.3]
28-day parasitological uncorrected cure rate	10 (62.5) [35.4, 84.8]	10 (62.5) [35.4, 84.8]	10 (50.0) [27.2, 72.8]
42-day parasitological uncorrected cure rate	7 (43.8) [19.8, 70.1]	7 (43.8) [19.8, 70.1]	7 (35.0) [15.4, 59.2]
Subjects with parasitemia count at 48 hours > count at baseline	0	0	0
Subjects with parasitemia count at 72 hours ≥25% of baseline count	0	0	0

Parasitemia results were taken from the central microscopy reading.
CI: Exact Pearson-Clopper two-sided 95% confidence limits.

The uncorrected cure rate at Day 28 was 63% for patients in the EPS, and 50% for patients in the FAS. The uncorrected cure rate at Day 42 was 44% for the EPS and 35% for the FAS.

After 24 hours, mean parasite count had decreased by 99% from baseline for both the EPS and for the FAS. The mean time to parasite clearance was 29 hours for the FAS and 31 hours for the EPS, with a KM median of 24 hours.

Most of the subjects (90% FAS, 87.5% EPS) had gametocyte clearance at Day 1 (8 hours). All patients had gametocyte clearance by Day 14. The mean time to gametocyte clearance was 36 hours for the FAS and 44 hours for the EPS, with a KM median duration of 7.9 hours.

No patients met the definitions of early treatment failure. Seven patients in both the FAS (35%) and in the EPS (44%) had an absence of parasitaemia still on Day 42, meeting the definition of an adequate clinical and parasitological response.

- Safety results

There were no deaths or SAEs reported for Cohort 1 during the core follow-up period of the study. Two patients died during the long-term follow-up period up to 12 months of age. One patient died from dehydration due to acute diarrhoea. The second had experienced a one day history of anorexia on the day of death but the cause of death was unknown.

A further patient had reported an SAE during the long-term follow-up period (meningitis, cerebral malaria and anaemia, with the meningitis and cerebral malaria having resolved with treatment).

One patient discontinued study medication during the core study period for an AE (vomiting of moderate severity), which was not suspected to be related to the study drug by the investigator.

Most AEs reported during the core period reflected the underlying disease of the patients, with anaemia reported for 35%, bronchitis for 30%, pyrexia for 25% and vomiting for 20% of patients. Most AEs were moderate in severity (in 55% of patients), with mild events reported for 15% of patients and severe events for 15% of patients. Severe AEs included anaemia, diarrhoea, cerebral malaria, meningitis and death of unknown aetiology and these were all SAEs reported during the long-term follow-up period. AEs suspected to be related to the study drug by the investigator were reported for 5 patients (25%), including anaemia and vomiting (each reported for 3 patients, 15%). Laboratory parameters did not show clinically meaningful changes from baseline during the study.

The neurodevelopmental assessment (at the Shoklo Malaria Research Unit) was performed at the long-term follow-up visit at 12 months of age. There were no significant findings in the very small sample studied.

- Bioanalytical results

Mean Cmax of artemether and DHA were 509 and 107 ng/mL, respectively, after the first dose. Mean lumefantrine Cmax was 6.38 µg/mL and the mean Day 7 concentration was 0.815 µg/mL. The graphical displays (see below table) show very considerable inter-individual variability.

Table 11-7 Artemether, DHA and lumefantrine Cmax in infants less than 5 kg treated with 6-dose regimen of artemether-lumefantrine dispersible tablets

	Cohort 1 Mean ± SD (CV%)
Artemether Cmax (ng/mL)* (N=18)	509±309 (60.7%)
DHA Cmax (ng/mL)* (N=18)	107±71.7 (67.1%)
Lumefantrine Cmax (µg/mL)** (N=19)	6.38 ±3.38 (53.0%)

*Cmax represents higher concentration between the two concentration time points (at around 1 hour and 2 hours) after first dose
**Cmax represents highest concentration among four concentration time points (at around 6 hours after dose 5 and at 6 hours after dose 6 on Day 3, 24 hours after dose 6, and on Day 7)

Figure 11-3 Individual plasma concentrations of artemether and DHA in infants (less than 5 kg) treated with 6-dose regimen of artemether-lumefantrine dispersible tablets by actual time in hours

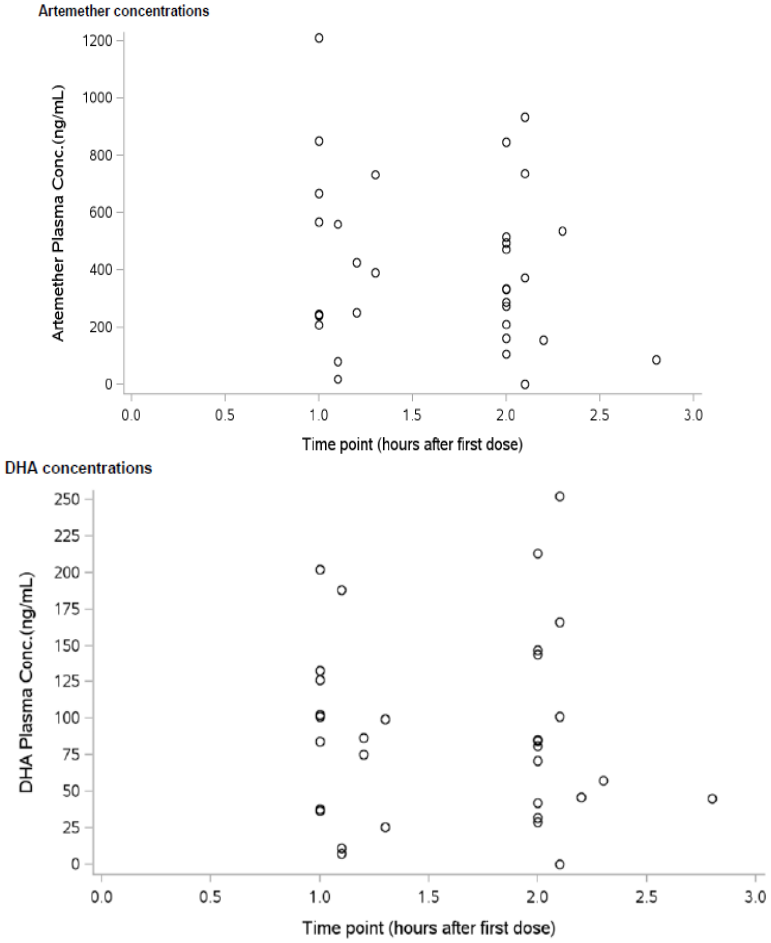
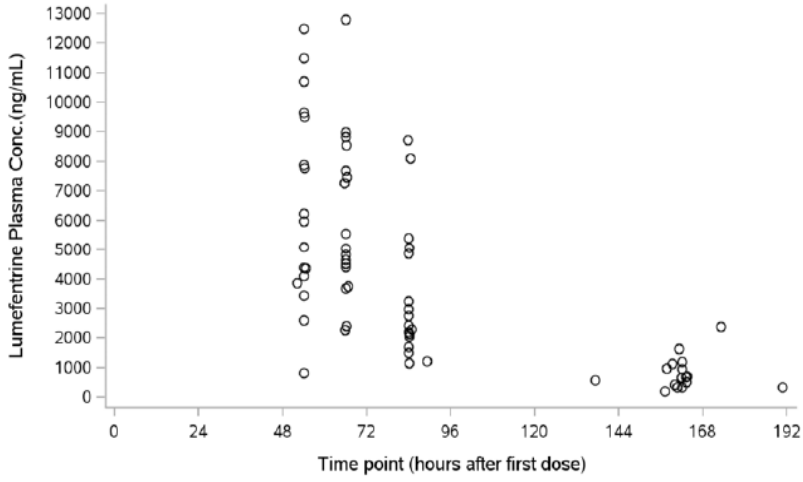


Figure 11-4 Individual plasma concentrations of lumefantrine in infants (less than 5 kg) treated with 6-dose regimen of artemether-lumefantrine dispersible tablets by actual time in hours



Study Number	Study Title	Key Objective	Paediatric exposure (< 18yr)	Paediatric results (< 18yr)	Efficacy results	Safety results	LPLV/LO	CSR date
CCOA566B2401	A cluster randomized, single-center, controlled, parallel,12-month prospective study and additional 12-month follow-up in Africa of malaria incidence in a community setting following systematic treatment of *P. falciparum* asymptomatic carriers with artemether-lumefantrine (Coartem® / Coartem® dispersible).	Evaluate at the community level whether treatment of asymptomatic carriers (ACs) of *Plasmodium falciparum* was associated with:- a lower rate of symptomatic malaria episodes over a 12-month follow-up in infants and children (<5 years of age) - an improvement in haemoglobin level after 28 days in ACs >6 months old.	This was a cluster randomized study; a total of 14,075 subjects were recruited of which 6268 children <15yrs. 3023 in the intervention group and 3245 in the control group.	The results reported are those in paediatric patients.	The efficacy results of this study showed no significant difference between the intervention and control arms with respect to rates of symptomatic malaria episodes in infants and children (<5 years of age). On the other primary objective, a statistically significant difference between the two study arms was observed in changes in hemoglobin levels at CSC1 Day 28 in ACs (>6 months of age), but the magnitude of the difference was not clinically meaningful.	Safety data did not reveal any unexpected findings. Rates of AEs and SAEs were low and similar in both study arms.	15-Feb-2012	22-Aug-2012
CCOA566B2401E1	A cluster randomized, single-center, controlled, parallel, 12-month prospective study and additional 12-month follow-up in Africa of malaria incidence in a community setting following systematic treatment of *Plasmodium falciparum* (*P. falciparum*) asymptomatic carriers with artemether-lumefantrine (Coartem®/Coartem® dispersible).	To assess and compare the incidence of symptomatic malaria episodes associated with a parasite density >5000/µL (overall and in the population <5 years) over the 1-year extension and core study plus extension in the intervention versus the control arm.	A total of 12226 subjects were enrolled into the extension phase, the number of paediatric patients is not reported.	Not separately reported.	This study was a 1-year extension to the core study COA566B2401 and was terminated due to the unfavourable results of the core study which did not show a reduction in malaria episodes .	Safety data did not reveal any unexpected findings. Rates of AEs/SAEs were moderate overall and were more prevalent in subjects with SMRCs from the control arm than those from the interventional arm.	26-Jul-2012	22-Feb-2013

➢ Methods

The following applies to the design of the initial study; the extension study was terminated early.

- Objectives

Primary objectives were to evaluate at the community level whether treatment of asymptomatic carriers (ACs) of *P. falciparum* was associated with:

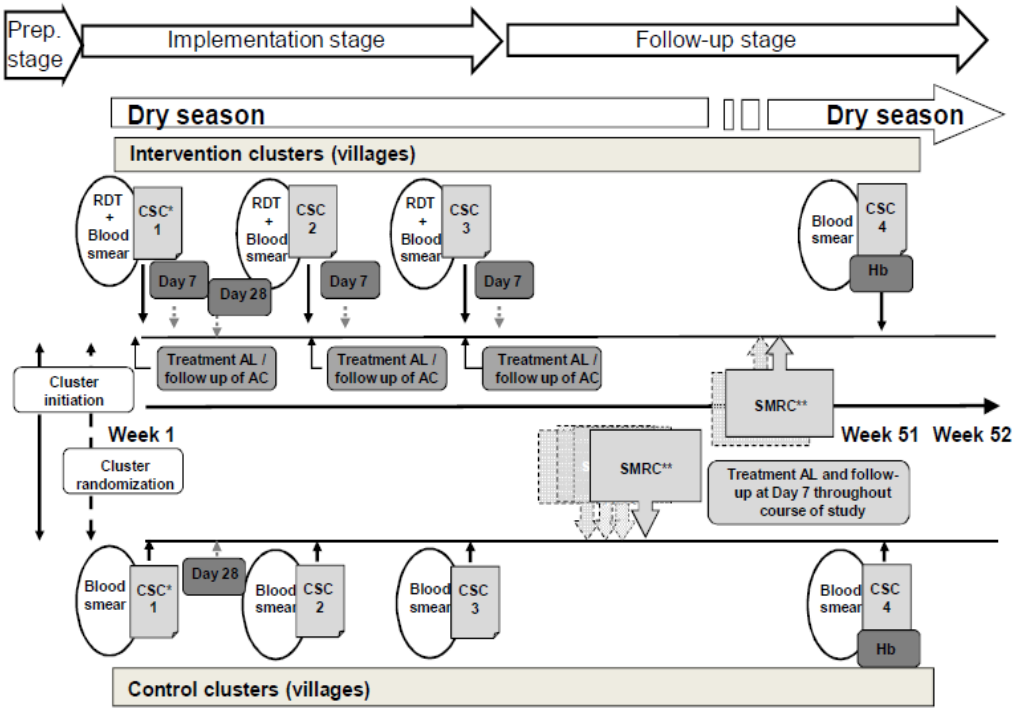
1. A lower rate of symptomatic malaria episodes over a 12-month follow-up in infants and children (<5 years of age)
2. An improvement in haemoglobin level after 28 days in ACs >6 months old

Key secondary objectives were to assess and compare, between the intervention and control arms, the prevalence of gametocyte carriage and asymptomatic carriage; haemoglobin levels in children; and the incidence of symptomatic malaria episodes in all subjects.

- Study design

This was a cluster randomised, single-centre (in Burkina Faso), controlled, parallel group study conducted initially over 12 months with an additional 12-month follow-up (extension study). The study design and planned visits are shown in the figure.

Figure 9-1 Study design



- Study population/Sample size

Consented adults and children were eligible for the intervention arm if they had been diagnosed as ACs of *P. falciparum* by RDT or had a symptomatic malaria episode. To be eligible for the control arm subjects had to have a symptomatic malaria episode. Subjects could not be treated with AL if they had body weight <5 kg, had known hypersensitivity to study medication, had signs and symptoms of severe malaria, were in the first trimester of pregnancy or had any predisposition to prolonged QTc interval.

In the intervention arm, ACs were identified in a series of four community screening campaigns (CSCs). In control clusters a 40% randomly selected subset of subjects was screened by microscopy for delayed reading. CSC1, 2 and 3 were performed approximately 1 month apart over the course of 3 months at the beginning of the study, prior to the start of the malaria

season. CSC4 was performed at the end of the follow-up stage, approximately 1 year after CSC1.

There were 18 clusters (9,000 – 14,000 subjects in total) planned.

- Treatments

  - In CSC1-3 all ACs identified in the intervention clusters were treated with AL. No treatment was administered in the control clusters.
  - In CSC4 no treatment was given in either the intervention or the control clusters.
  - All symptomatic malaria episodes at any time in both arms were treated with AL.

AL tablets and AL dispersible tablets (20/120 mg) were used. Dose and formulation were determined by body weight as shown below.

Table 9-2 Artemether-lumefantrine dosing recommendation

Total body weight	Formulation	Treatment regimen	Number of tablets taken daily	Number of days of treatment
5 to <15 kg	Dispersible tablets	6 doses of 1 tablet	1 b.i.d.	3
15 to <25 kg	Dispersible tablets	6 doses of 2 tablets	2 b.i.d	3
25 to <35 kg	Tablets	6 doses of 3 tablets	3 b.i.d	3
≥35 kg	Tablets	6 doses of 4 tablets	4 b.i.d	3

- Outcomes/endpoints

The primary efficacy endpoints were the number of RDT-confirmed symptomatic malaria episodes with parasitaemia ≥5000/µL (SMRC5000s) per person-year in infants and children (i.e. <5 years of age) and the change in haemoglobin levels from Day 1 of CSC1 to Day 28 of CSC1 for all microscopy-confirmed ACs >6 months of age.
Secondary efficacy endpoints included the prevalence of microscopy-confirmed gametocyte carriers (GCs), the prevalence of microscopy-confirmed ACs, haemoglobin levels at end of study (CSC4) in children (aged >6 months to <5 years) and incidence of SMRC5000s in the study population as a whole.

Adverse events were collected for 7 days after the start of treatment for ACs in the intervention arm and all SMRCs in both arms) and SAEs were collected during the entire study in both treatment arms.

- Statistical Methods

Analyses focused on cluster level, i.e. cluster was considered as an experimental unit and observations were based on individual subjects in each cluster. The primary variables were the number of SMRC5000 per person-year in infants and children <5 years of age during the whole study duration and mean change from Day 1 to Day 28 in haemoglobin level for ACs at CSC1.
One-sided t-test of equal means was conducted to a significance level of 0.05 for both primary variables. No adjustments for multiplicity were performed.

➢ **Results**

- Recruitment/ Number analysed

There were 14,075 subjects recruited and analysed. Patient disposition was as shown below.

- Baseline data

The intervention and control arms were similar in terms of baseline demographic characteristics. Age range was very wide, but with a median of approximately 16 years in both arms. Approximately 53% were female and ethnicity in both arms was Mossi in > 90%.

Based on individual data, 17-18% of subjects were aged < 5 years at the time of enrolment.

Table 10-1 Overall subject disposition by study arm (Randomized clusters set)

Category	Disposition/reason	Statistics	Intervention	Control
Overall-C		N	9	9
	Cluster initiation completed	Mean-pct (SD)	100 (0.00)	100 (0.00)
	Born after cluster initiation	Mean-pct (SD)	2.2 (0.30)	1.9 (0.69)
	Immigrant during the study	Mean-pct (SD)	5.4 (2.22)	2.7 (1.33)
	Completed	Mean-pct (SD)	86.5 (4.22)	89.5 (2.63)
	Discontinued	Mean-pct (SD)	13.5 (4.22)	10.5 (2.63)
	Primary reason for discontinuation			
	Lost to follow-up	Mean-pct (SD)	12.3 (4.37)	9.4 (2.60)
	Subject withdrew consent	Mean-pct (SD)	0.5 (0.18)	0.6 (0.41)
	Protocol deviation	Mean-pct (SD)	0.0 (0.00)	0.0 (0.00)
	Death	Mean-pct (SD)	0.7 (0.25)	0.6 (0.31)
Overall-I		N	6817	7258
	Cluster initiation completed	n (%)	6817 (100)	7258 (100)
	Born after cluster initiation	n (%)	151 (2.2)	128 (1.8)
	Immigrant during the study	n (%)	349 (5.1)	207 (2.9)
	Completed	n (%)	5897 (86.5)	6510 (89.7)
	Discontinued	n (%)	920 (13.5)	748 (10.3)
	Primary reason for discontinuation			
	Lost to follow-up	n (%)	837 (12.3)	661 (9.1)
	Subject withdrew consent	n (%)	35 (0.5)	43 (0.6)
	Protocol deviation	n (%)	0	0
	Death	n (%)	48 (0.7)	44 (0.6)

Table 11-1 Analysis sets by study arm (Randomized clusters set)

Analysis Set	Statistics	Intervention	Control	Total
Overall-C	N	9	9	18
Consenting inhabitants	Mean-pct (SD)	100 (0.00)	100 (0.00)	100 (0.00)
<5 years*	Mean-pct (SD)	18.5 (1.90)	17.7 (2.99)	18.1 (2.46)
≥5 years*	Mean-pct (SD)	78.9 (1.99)	80.6 (2.96)	79.7 (2.59)
Asymptomatic carriers at CSC1**	Mean-pct (SD)	34.6 (5.03)	42.8 (7.64)**	38.7 (7.57)**
Safety analyzable asymptomatic carriers	Mean-pct (SD)	56.1 (6.04)	NA	56.1 (6.04)
Safety analyzable symptomatic carriers	Mean-pct (SD)	34.5 (4.39)	30.1 (7.08)	32.3 (6.15)
Overall-I	N	6817	7258	14075
Consenting inhabitants	n (%)	6817 (100)	7258 (100)	14075 (100)
<5 years*	n (%)	1255 (18.4)	1235 (17.0)	2490 (17.7)
≥5 years*	n (%)	5385 (79.0)	5892 (81.2)	11277 (80.1)
Asymptomatic carriers at CSC1**	n (%)	2397 (35.2)	1138 (42.4)[1]	3535 (37.2)[2]
Safety analyzable asymptomatic carriers	n (%)	3819 (56.0)	NA	3819 (40.2)[2]
Safety analyzable symptomatic carriers	n (%)	2320 (34.0)	2275 (31.3)	4595 (32.6)

Category	Parameter	Statistics	Intervention	Control
Overall-I	Age group at CSC1/Day 1	n	6258	6810
	≤6 months	n (%)	130 (2.1)	100 (1.5)
	>6 months - <5 years	n (%)	933 (14.9)	965 (14.2)
	5 - 9 years	n (%)	990 (15.8)	1131 (16.6)
	10 - 14 years	n (%)	970 (15.5)	1039 (15.3)
	≥15 years	n (%)	3235 (51.7)	3575 (52.5)
	Age (years) at CSC1/Day 1	n	6258	6810
		Mean	24.06 (21.173)	23.42 (20.371)
		Median (range)	15.67 (0.13-102.61)	16.28 (0.09-103.66)
	Age group at post CSC follow-up	n	6640	7127
	<5 years	n (%)	1255 (18.9)	1235 (17.3)
	≥5 years	n (%)	5385 (81.1)	5892 (82.7)
	Age (years) at post CSC follow-up	n	6640	7127
		Mean (SD)	23.41 (21.026)	22.86 (20.218)
		Median (range)	15.56 (0.01-102.81)	15.84 (0.00-103.85)
	Sex	N	6817	7258
	Male	n (%)	3161 (46.4)	3442 (47.4)
	Female	n (%)	3656 (53.6)	3816 (52.6)

Overall-C: overall based on cluster level summary data.
Overall-I: overall based on individual subject data.
% is based on the number of subjects present in randomized clusters set.
*Age is calculated at start of post CSC follow-up.
**Applicable for about 40% randomly selected subjects of the control clusters. Denominators for percentages and Mean-pct in the control clusters are based on this subset of patients.
[1]Percentage is based on denominator of 2684 control subjects who were randomly selected for testing for asymptomatic carriage of *P. falciparum*.
[2]Percentage is based on denominator of 9501 subjects (6817 intervention + 2684 control) who were tested for asymptomatic carriage of *P. falciparum*.

- Efficacy results

The cluster level analysis of the primary efficacy endpoints showed that:

- The mean (SD) rates of SMRC5000s per person year in infants and children (<5 years) were 1.69 (0.436) in the intervention arm and 1.60 (0.526) in the control arm (p = 0.3482). The individual level data also showed no difference between arms.

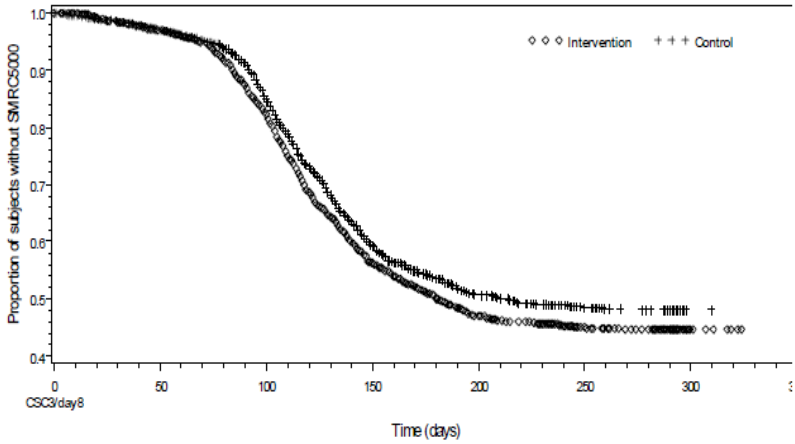
Table 11-4 Number of $SMRC_{5000}$s per person-year in infants and children (<5 years) in post CSC follow-up (Cluster level data, Eligible clusters set)

Statistics	Intervention	Control	P-value
N	9	9	
Mean (SD)	1.69 (0.436)	1.60 (0.526)	0.3482
Median (range)	1.69 (1.0-2.6)	1.69 (0.5-2.4)	

Table 11-5 Number of $SMRC_{5000}$s per person-year in infants and children (<5 years) in post CSC follow-up, by study arm (Individual level data, Eligible clusters set)

Category	Study arm	Number of $SMRC_{5000}$s	Person-year observed	Number of $SMRC_{5000}$s per person-year
Overall-I	Intervention (N=1255)	1468	895.8	1.64
	Control (N=1235)	1461	905.5	1.61

Figure 11-1 **Kaplan-Meier plot of incidence of first $SMRC_{5000}$ in infants and children (<5 years) in post-CSC follow-up, Eligible clusters set**



- The mean (SD) changes in haemoglobin levels in ACs (>6 months) from CSC1/Day 1 to CSC1/Day 28 were +0.53 (0.256) g/dL in the intervention arm and -0.21 (0.266) g/dL in the control arm (p<0.0001). The difference was not considered clinically relevant.

Table 11-6 **Change in hemoglobin level (g/dL) in asymptomatic carriers >6 months of age from CSC1/Day 1 to CSC1/Day 28 by study arm (Asymptomatic carriers at CSC1 analysis set)**

		Intervention			Control*			
Category	Statistics	CSC1/Day 1	CSC1/Day 28	Change	CSC1/Day 1	CSC1/Day 28	Change	P-value
Overall-C	N	9	9	9	9	9	9	
	Mean	11.81	12.33	0.53	12.06	11.86	-0.21	<0.0001
	SD	0.329	0.318	0.256	0.345	0.373	0.266	
	Median	11.95	12.38	0.54	12.14	11.95	-0.26	
	Range	11.1-12.1	11.7-12.7	0.1-1.0	11.5-12.6	11.1-12.4	-0.5-0.3	
Overall-I	n	2387	2116	2107	1136	1091	1089	
	Mean	11.81	12.36	0.62	12.10	11.87	-0.20	
	SD	1.879	1.564	1.396	2.005	1.773	1.374	
	Median	11.90	12.40	0.60	12.20	11.90	-0.20	
	Range	3.8-18.2	5.8-17.6	-6.3-5.8	5.1-18.3	5.4-17.3	-4.7-5.6	

Regarding the key secondary endpoints:
There was a lower prevalence of microscopy-confirmed GCs in the intervention arm than the control arm at CSC2/Day 1 and CSC3/Day 1, but not at CSC4/Day 1. The between-arm difference was statistically significant at CSC2/Day 1 and CSC3/Day 1.

Table 11-9 **Prevalence of microscopy- and qRT-PCR-confirmed gametocyte carriers at CSC4/Day 1 by study arm (Eligible clusters set)**

		Intervention N=1023		Control* N=976	
Category	Result	Microscopy n (%)	qRT-PCR n (%)	Microscopy n (%)	qRT-PCR n (%)
Overall-I	Negative	949 (92.8)	514 (50.2)	915 (93.8)	511 (52.4)
	Positive	61 (6.0)	508 (49.7)	53 (5.4)	462 (47.3)
	Not evaluable	13 (1.3)	1 (0.1)	8 (0.8)	3 (0.3)

Table 11-10 **Prevalence of microscopy-confirmed gametocyte carriers over time by study arm (Eligible clusters set)**

Category	Study Arm	Statistics	CSC1/Day 1	CSC2/Day 1	CSC3/Day 1	CSC4/Day 1
Overall-C	Intervention	N/Mean-pct(SD)	9/9.5 (2.95)	9/0.6 (0.38)	9/0.4 (0.40)	9/4.8 (1.34)
	Control*	N/Mean-pct(SD)	9/10.2 (4.54)	9/5.5 (2.54)	9/5.8 (1.77)	9/5.1 (1.38)
Overall-I	Intervention	n/N (%)	543/5575 (9.7)	33/5680 (0.6)	23/6114 (0.4)	279/5820 (4.8)
	Control*	n/N (%)	246/2472 (10.0)	130/2355 (5.5)	144/2424 (5.9)	113/2249 (5.0)

The prevalence of AC showed a similar pattern to that for GC, such that the between-arm differences were statistically significant at CSC2/Day 1 and CSC3/Day 1.

Table 11-12 Prevalence of microscopy-confirmed asymptomatic carriers over time by study arm (Eligible clusters set)

Category	Study arm	Statistics	CSC1/Day 1	CSC2/Day 1	CSC3/Day 1	CSC4/Day 1
Overall-C	Intervention	N/Mean-pct (SD)	9/42.8 (5.67)	9/4.1 (1.62)	9/2.8 (0.92)	9/34.4 (3.92)
	Control*	N/Mean-pct (SD)	9/47.5 (8.05)	9/35.7 (4.94)	9/32.2 (9.26)	9/37.8 (6.37)
Overall-I	Intervention	n/N (%)	2428/5575 (43.6)	237/5680 (4.2)	171/6114 (2.8)	2023/5820 (34.8)
	Control*	n/N (%)	1153/2472 (46.6)	833/2355 (35.4)	741/2424 (30.6)	815/2249 (36.2)

However, there was no statistically significant difference between treatment arms in SMRC5000 rates per person-year for all subjects with mean rates in the intervention and control arms of 0.45 and 0.39, respectively, p = 0.1032 (individual level analysis).

Table 11-7 Treatment differences in number of $SMRC_{5000}$ per person-year in post CSC follow-up (Eligible clusters set)

Statistics	Intervention	Control	P-value
N	9	9	
Mean (SD)	0.45 (0.123)	0.38 (0.119)	0.1032
Median (range)	0.43 (0.3-0.74)	0.41 (0.1-0.56)	

The day 7 parasitological cure rates for treated episodes of clinical malaria were >95% regardless of baseline parasite count.

The changes in haemoglobin in the age group from 6 months to 5 years are shown below. As for the analysis of change in all subjects from 6 months, the difference between groups was significant for Day 1 vs. Day 28 but it was not considered clinically relevant. There was no significant difference between Day 1 and CSC4.

Table 11-15 Overall summary and change in hemoglobin level (g/dL) from CSC1/Day 1 to CSC1/Day 28 in infants and children (>6 months and <5 years) by study arm (Asymptomatic carriers at CSC1 analysis set)

		Intervention			Control*			
Category	Statistic	CSC1/Day 1	CSC1/Day 28	Change	CSC1/Day 1	CSC1/Day 28	Change	P-value
Overall-C	N	9	9	9	9	9	9	
	Mean	9.83	11.03	1.19	9.68	10.16	0.48	0.0001
	SD	0.411	0.321	0.282	0.409	0.394	0.356	
	Minimum	9.2	10.6	0.7	8.9	9.5	-0.2	
	Median	9.66	10.93	1.26	9.80	10.35	0.48	
	Maximum	10.5	11.5	1.7	10.1	10.6	1.0	
Overall-I	n	432	406	404	179	174	173	
	Mean	9.78	10.95	1.19	9.67	10.17	0.51	
	SD	1.763	1.543	1.520	1.707	1.748	1.308	
	Minimum	4.1	5.8	-6.3	5.1	5.4	-2.0	
	Median	9.80	11.20	1.10	10.00	10.20	0.30	
	Maximum	16.5	14.5	5.7	13.6	15.8	5.6	

Table 11-16 Change in hemoglobin level (g/dL) from CSC1/Day 1 to CSC4/Day 1 in infants and children (>6 months and <5 years) by study arm (Eligible clusters set)

		Intervention			Control*			
Category	Statistics	CSC1/Day 1	CSC4/Day 1	Change	CSC1/Day 1	CSC4/Day 1	Change	P-value
Overall-C	N	9	9	9	9	9	9	
	Mean	10.24	10.99	0.76	10.04	11.13	1.08	0.9318
	SD	0.371	0.267	0.389	0.476	0.360	0.487	
	Median	10.34	11.00	0.88	10.08	10.97	1.16	
	Range	9.7-10.7	10.6-11.4	0.2-1.5	9.3-10.9	10.7-11.7	0.2-1.7	
Overall-I	n	819	827	745	348	321	308	
	Mean	10.20	10.98	0.74	10.09	11.17	1.03	
	SD	1.777	1.550	1.791	1.762	1.586	1.794	
	Median	10.30	11.10	0.70	10.25	11.20	1.10	
	Range	4.0-16.5	4.9-16.0	-5.4-6.3	4.8-16.5	4.7-19.0	-4.2-9.2	

- Safety results

Exposure to tablets and dispersible tablets was as shown below.

Table 12-1 Number (%) of asymptomatic carriers exposed to study medication at CSCs (Safety analyzable asymptomatic carriers set)

CSC	AC Status	AL n (%)	AL dispersible n (%)	Both n (%)	Total n (%)
CSC1 (N=3490)	CSC1 only	1594 (45.7)	1042 (29.9)	0 (0)	2636 (75.5)
CSC2 (N=3477)	CSC2 only	359 (10.3)	86 (2.5)	0 (0)	445 (12.8)
CSC3 (N=3621)	CSC3 only	214 (5.9)	96 (2.7)	0 (0)	310 (8.6)
CSC1,2 (N=3367)	CSC1 and CSC2	63 (1.9)	294 (8.7)	17 (0.5)	374 (11.1)
CSC2,3 (N=3323)	CSC2 and CSC3	6 (0.2)	11 (0.3)	0 (0)	17 (0.5)
CSC1,3 (N=3310)	CSC1 and CSC3	8 (0.2)	14 (0.4)	0 (0)	22 (0.7)
CSC1,2,3 (N=3231)	CSC1, CSC2 and CSC3	1 (0.0)	11 (0.3)	0 (0)	12 (0.4)
CSC3 (N= 0)	After CSC3*	0 (0)	0 (0)	0 (0)	0 (0)

There were 92 subjects (0.65%) who died during the study (see table below). Of these, 69 had not received study medication and 14 died more than 30 days after their last dose. The 9 remaining subjects died within 30 days of receiving AL. Causes of death were malaria in two cases and one case each due to respiratory tract infection, sepsis, gastroenteritis, asthmatic crisis and pelvic fracture. Two subjects died within 30 days of receiving AL for unknown reasons.

SAEs within 30 days of receiving AL occurred in 9 ACs. Malaria, bronchitis and pneumonia were the most common SAEs; no other SAE occurred in more than one AC. SAEs were reported in 47 (1.0%) of subjects treated with AL for symptomatic malaria episodes. Vomiting was the most common SAE (0.6%), followed by malaria (0.2%) and pneumonia (0.1%). No other SAE occurred in more than one subject.

Table 12-6 Deaths occurring within 30 days of last dose of study medication

	Age/Sex/	Day of	Day of	Cause of death	
Subject ID	Ethnicity	last dose	death	Reported term	Preferred term
Intervention arm					
2/00550	0/F/Mossi	1	6	Death – cause of death is unknown	Death
4/00566	69/F/Mossi	1	4	Pelvis fracture	Pelvic fracture
4/00979	0/F/Mossi	77	79	Malaria	Malaria
6/00242	0/M/Mossi	1	5	Severe malaria	Malaria
6/00662	0/F/Fulani	32	61	Respiratory tract infection	Respiratory tract infection
10/00151	52/M/Mossi	1	26	Acute gastroenteritis	Gastroenteritis
18/00120	46/M/Mossi	300	304	Asthma crisis	Asthmatic crisis
Control arm					
11/00323	17/M/Mossi	1	9	Septicemia	Sepsis
11/00387	2/F/Mossi	158	159	Death – cause of death is unknown	Death

Table 12-8 **Number (%) of artemether-lumefantrine-treated $SMRC_{5000}$ subjects with SAEs within 30 days after treatment initiation by treatment episode (Safety analyzable symptomatic carriers set)**

Primary system organ class Preferred term	Treatment Episode 1 N=2554 n (%)	Treatment Episode 2 N=1006 n (%)	Treatment Episode 3 N=469 n (%)	Overall N=2554 n (%)
Any primary system organ class				
Total	15 (0.6)	9 (0.9)	1 (0.2)	27 (1.1)
Gastrointestinal disorders				
Total	11 (0.4)	7 (0.7)	1 (0.2)	21 (0.8)
Vomiting	11 (0.4)	7 (0.7)	1 (0.2)	21 (0.8)
Infections and infestations				
Total	3 (0.1)	2 (0.2)	0	5 (0.2)
Malaria	3 (0.1)	2 (0.2)	0	5 (0.2)
Pneumonia	2 (0.1)	0	0	2 (0.1)
Nervous system disorders				
Total	1 (0.0)	0	0	1 (0.0)
Somnolence	1 (0.0)	0	0	1 (0.0)

A total of 0.3% of ACs treated with AL experienced AEs during the 7 days after initiation of treatment. The most common AEs were infections, notably malaria, bronchitis and pneumonia. No specific AE was reported in more than 0.1% of treated subjects. Of subjects who received AL treatment for symptomatic malaria episodes, a total of 0.6% had at least 1 AE within 7 days of initiation of treatment. Vomiting (in 0.5% of subjects) was the most common AE.

Table 12-4 **Number (%) of artemether-lumefantrine-treated $SMRC_{5000}$ subjects with AEs within 7 days after treatment initiation by treatment episode, by primary system organ class and preferred term (Safety analyzable symptomatic carriers set)**

Primary system organ class Preferred term	Treatment Episode 1 N=2554 n (%)	Treatment Episode 2 N=1006 n (%)	Treatment Episode 3 N=469 n (%)	Overall N=2554 n (%)
Any primary system organ class				
Total	9 (0.4)	5 (0.5)	1 (0.2)	16 (0.6)
Gastrointestinal disorders				
Total	8 (0.3)	4 (0.4)	1 (0.2)	14 (0.5)
Vomiting	8 (0.3)	4 (0.4)	1 (0.2)	14 (0.5)
Infections and infestations				
Total	1 (0.0)	1 (0.1)	0	2 (0.1)
Malaria	1 (0.0)	1 (0.1)	0	2 (0.1)
Pneumonia	1 (0.0)	0	0	1 (0.0)

In the extension study

There were 12226 (of 14075 in the core study) enrolled into the 1-year extension phase. No efficacy data are reported. Since the extension was a non-interventional study, the safety data pertain to the use of AL to treat SMRCs during the 1-year extension in both arms (interventional and control). Only the AEs pertaining to the subjects with SMRC episodes within 7 days after initiation of treatment (safety analysable AC set) were reported in both the study clusters.

There were 1871 subjects with symptoms of malaria of which 852 had a positive RDT (intervention 466, control 386) and 831 were treated with AL.

A total of 87 AEs (all SAEs and including 14 deaths) were reported. Percentages with AEs were 0.6% (39/6372) for control subjects vs. 0.4% (23/5854) for intervention subjects. The most commonly affected SOCs were infections and infestations (malaria, pneumoniafollowed by gastrointestinal disorders (abdominal pain, diarrhoea, vomiting) and pregnancy, puerperium and perinatal conditions (abortion, complications of delivery). The SAEs observed were not considered to be unusual in this population and no SAEs related to study drug were reported.

Of 14 deaths, 6 were in the intervention arm and 8 in the control arm but none received AL during the extension study. The number included 5 infants or children ≤5 years of age (2 intervention and 3 control arm).

Table 12-1 Deaths reported during the study

Subject ID	Age/Sex/ Ethnicity	Day of death	Cause of Death Preferred term
Intervention arm			
4/00361	76/M/Mossi	477	Indeterminate disease
4/00961	0/F/Mossi		Diarrhea, fever, conjunctival paleness
4/00979	75/F/Mossi	413	Pneumonia and parasitosis
8/00027	94/F/Mossi	479	Unknown cause of mortality
14/00268	66/F/Mossi	482	Fever of unspecified origin
14/00303	0/M/Mossi		Malaria
Control arm			
5/00774	84/M/Mossi	426	Hypertension
12/00477	63/F/Mossi	439	Disorder of the nervous system
13/00113	1/F/Mossi	440	Pneumonia
13/00272	90/F/Mossi	445	Acute diarrheal disease
13/00398	77/M/Mossi	447	Severe abdominal pains
13/00757	1/M/Mossi	415	Bacterial infection
16/00407	5/F/Mossi	488	Unknown cause of mortality
17/00831	70/M/Mossi	502	Acute diarrheal disease

3. Discussion on clinical aspects

Study CCOA566A2417

This study aimed to evaluate the effects of artemether-lumefantrine on auditory brainstem pathway function in patients with acute, uncomplicated falciparum malaria by testing the null hypothesis that the rate of auditory brainstem pathway abnormalities is ≥ 15% in the population treated with artemether-lumefantrine, as assessed by ABR at Day 7 following initiation of treatment compared with their baseline values. An "auditory brainstem pathway abnormality" was defined in this study as a > 0.30 msec change in Wave III latency from baseline to Day 7. The study was designed in such a way that if >15% of patients had a Wave III latency change > 0.30 msec, then it would be reasonable to suspect that at least some of these cases represented auditory function impairment.

The primary study objective was met based as the proportion of patients with ABR wave III latency changes of > 0.30 msec on day 7 is statistically significantly below 15% in the artemether-lumefantrine treatment group (one-sided exact test for a single proportion, p-value <0.0001) based on the "blinded review" and confirmed by the supportive analysis based on the "initial review". The actual proportion of patients with ABR Wave III latency changes at day 7 observed in the artemether-lumefantrine treatment group was 2.6% (95% CI: 0.7 – 6.6) for the "blinded review" and 1.4% (95% CI: 0.2 – 4.9) for the "initial review".

Incidence rates of ABR Wave III latency changes on Days 3, 28, and 42 were low. Absolute ABR Wave III latency (ms) changes from baseline to Day 7 as well as to later visits were very small in all three treatment groups, with no differences of note between treatment groups.

Small reductions in the order of 2-3 dB in pure-tone air conduction threshold average were observed in all treatment groups, with no differences of note between treatment groups and no consistent trends.

Only a few other studies have investigated the effect of ACTs on auditory function in malaria patients.

- McCall et al (2006) performed audiometric assessments (pure tone audiometry and ABR) in 15 volunteers experimentally infected with malaria who then received artemether-lumefantrine. No effects on hearing loss nor any auditory pathway damage deemed to be caused by drug treatment were found ten days after start of treatment or later.
- In a case-control study along the Thailand-Myanmar border, Hutagalung et al (2006) performed audiometry and ABR in 68 subjects treated with artemether-lumefantrine within the previous five years and found no evidence of auditory brainstem impairment attributable to artemether-lumefantrine.
- Gürkov et al (2008) performed pure tone and ABR audiometry in malaria patients in Ethiopia. Pure tone audiometry revealed transient significant cochlear hearing loss in patients treated with quinine but not in those treated with artemether-lumefantrine or atovaquone-proguanil. There was no evidence of drug-induced brain stem lesions by ABR measurements.
- Carrara et al (2008) studied malaria patients receiving oral artesunate-mefloquine on the Thai-Burmese border. At Day 7 after treatment they did not find any pure-tone threshold change exceeding 10 dB at any tested frequency, and no patient showed a shift in ABR Wave III peak latency change >0.30 msec.

These studies report a lack of evidence of impairment of either the auditory brainstem pathway or the auditory function in malaria patients treated with artemisinins.

The PCR corrected 14-, 28-, and 42-day cure rates were very high and comparable between treatment groups and above 95% at Day 14, 28 and Day 42. Also the adverse event profile of artemether-lumefantrine was favourable when compared to atovaquone-proguanil and artesunate-mefloquine.

In conclusion
This was a study conducted predominantly in young adults (median age 23 years) in which 90 patients were aged between 12 and <18 years. The safety and efficacy data are not shown separately for the adolescents. Nevertheless, efficacy was so high that no difference by age would be detectable and the safety profile was clearly different between treatments even though the same proportion in each group was in the adolescent age range.

The concern that was to be addressed in this study goes back to the nonclinical data presented in the original application dossier. In addition, since that time there have been publications reporting possible effects of ACTs on hearing, although a review of the literature was unable to conclude that a relationship was undoubtedly demonstrated.

The audiometry was overseen by a specialised unit (House Ear Institute, Los Angeles). The CSR justifies the pre-defined primary analysis of the study by stating that based on clinical and experimental experience, a 15% incidence rate of subjects showing auditory brainstem pathway abnormalities was considered by external consultants (expert otologist at HEI) to represent a reasonable and clinically relevant threshold incidence rate for suspicion of systematic damage to the auditory brainstem, irrespective of potential technical issues with data acquisition.

The results do show clear numerical differences between the artemether-lumefantrine group and the control treatments, including the group that also received an artemisinin-based regimen, for the Wave III latency changes from baseline to various time points and for sustained changes as defined by the MAH. In contrast, there was no differential effect of artemether-lumefantrine on the pure-tone air conduction thresholds. The MAH concludes that there were no clinically significant adverse effects on the auditory system.

In reality, the study is not so very helpful even though it suggests that the lipid-soluble artemether does indeed reach and impact on the ABR findings. The main concern regarding possible effects of artemisinins on hearing pertains to repeated use and to use in young children. Data are still lacking to determine the real risk of various ACTs in his regard. From the current study it can only be stated that there was a clear differentiation between artemether-lumefantrine and the other 2 regimens in terms of ABR findings but it is not known whether the results have any clinical implications.

Study COA566b2306

EU paediatric experts previously considered that an unmet medical need exists in the population of neonates and infants <5 kg of body weight with acute uncomplicated *P. falciparum* malaria. This study was therefore requested under the EU PIP for Riamet to evaluate the PK, efficacy and safety of artemether-lumefantrine dispersible tablets in the treatment of acute uncomplicated *P. falciparum* malaria in neonates and infants <5 kg of body weight for two sequential age cohorts: term age >28 days (Cohort 1) and term age ≤28 days (Cohort 2).

The first cohort of infants (>28 days old) consisted of 20 infants aged between 37 and 214 days. They were treated using the regimen approved for children with a body weight of 5 to 15 kg, i.e. 1 dispersible tablet (20 mg artemether/120 mg lumefantrine) BID for 3 days. The first dose was given at the time of initial diagnosis and was followed by five additional doses of one dispersible tablet given at 8, 24, 36, 48 and 60 hours thereafter.

This first cohort successfully completed the 6-week core follow-up period (i.e. Day 42) with no new or unexpected safety findings and with PCR-corrected 28-day parasitological cure rate of 100% for the EPS and PPS and 80% for the FAS (20% of FAS patients did not have a Day 28 cure status). Secondary efficacy measures were supportive of the primary endpoint.

No patients met the definitions of early treatment failure. Seven patients (35%) in the FAS met the definition of an adequate clinical and parasitological response.

A PK sampling schedule similar to that used in older infants and children in a previous study (Study COA566B2303) was applied for cross-study comparison.

The mean plasma lumefantrine concentrations in infants <5 kg were comparable to those observed in infants/children 5 to <15 kg in Study COA566B2303 at the same dose level (i.e. mean Cmax was 6.13 and 5.16 µg/mL for the crushed and dispersible tablet groups, respectively in infants/children of 5 to <15 kg). However, the mean plasma lumefantrine concentration on Day 7 was higher (0.815 µg/mL) compared to Study COA566B2303 (0.410 and 0.296 µg/mL, respectively). This observation (higher concentration only on Day 7) could be due to a complex phenomenon of reduced absorption and reduced clearance in infants. Lumefantrine is a lipophilic compound that needs bile and food for good absorption, and it is majorly excreted unchanged in faeces with minimal metabolism. The biliary system is not fully matured in infants, which would reduce both the absorption and clearance (with minimal contribution from reduced metabolism). During dosing, these two factors balance out, and concentrations are in the range that was observed in older infants/children. Once dosing is stopped, reduced clearance takes over, and concentrations on Day 7 are higher due to this.

Mean plasma concentrations of artemether were 2- to 3-fold greater in infants <5 kg compared to historical concentrations in infants and children 5 to <15 kg of body weight in Study COA566B2303 at the same dose level. Individual concentrations of artemether and DHA generally overlapped with the range of those observed in Study B2303 but with a trend toward or higher than the upper limit of this range. Artemether exposure was consistently high in infants <3 months and <5 kg and infants with the lowest weight and age had the highest exposure. Artemether undergoes high first pass metabolism and is predominantly metabolised by CYP3A4, which is present in gut and liver and is reported to have significantly lower activity in infants <12 months of age. Hence, higher artemether exposure in infants appears to reflect immature CYP3A4 activity.

Concentrations of DHA increased to a lesser extent compared with artemether, probably due to different metabolic pathways, and its relatively lower first pass effect. DHA undergoes glucuronidation, predominantly by UGT1A9 and UGT2B7, which are mostly hepatic and appear to have no substantial difference in their activity from 1 to 12 months of age. However, below 1 month of age there could be significantly lowered activity of these metabolic enzymes and hence increased DHA exposure.

Based on these findings, it is anticipated that artemether and DHA exposure in neonates ≤28 days of age given the same artemether-lumefantrine dose would be even higher than has been observed in Cohort 1 because of lower body weight and immature clearance.

As artemether-lumefantrine dispersible is a fixed-dose combination of artemether and lumefantrine, there is no practical way to adjust the dose, which still maintains a 1:6 ratio of artemether and lumefantrine dose and exposure.

Published data suggest that the neurotoxic drug exposure time (time spent over the lowest observed neurotoxic effect level) is the most important parameter related to neurotoxicity of artemisinins, whereas short-term peak concentrations have not been shown to be a major factor.

Literature also supports the hypothesis that accumulation of artemisinins when administered as intramuscular injection in oily vehicle extends the drug exposure time and hence the potential for neurotoxicity. Higher exposures (Cmax and AUC) after single administration of artemether have been observed with decreasing age of rat pups. Greater systemic toxicity was observed in the younger animals (mortality along with microscopic changes in the brain in Day 7-13 pups started at 30 mg/kg/day but no mortality in older pups was observed at this dose). The results in the older juvenile rats and adult rats were consistent. Neither mortality nor clinical neurotoxicity was seen in adult rats at equivalent/higher exposures of artemether administered for a longer duration. Therefore, there could be concern that younger infants with body weight <5 kg may also be at particular risk for toxicity not observed in older children or adults. The neonatal brain may be more vulnerable to drugs/toxins and neurologic lesions may affect development, but will likely not become apparent until later.

Additionally, falciparum malaria can increase blood brain permeability to artemether or other substances. The aforementioned factors may render neonates more vulnerable to artemether toxicity, especially to neurotoxicity.

On the basis of these considerations the study did not proceed to dose Cohort 2 with half the dose currently recommended for >5 kg children. The half quantity of artemether and lumefantrine cannot be guaranteed with half a dispersible tablet (it is not suitable for splitting; no score) or half an aliquot of the dispersion (not a homogeneous solution). Hence there is a risk of under-treatment and lack of efficacy, or over-treatment and risk of toxicity. Although the protocol had considered possible dose adjustment with 1 dispersible tablet administered once daily for 3 days, this would not reduce the risk of potential artemether and DHA toxicity because the exposure of a particular dose would remain elevated. Moreover, therapeutic efficacy may be reduced in this case because of inadequate lumefantrine exposure. Based on these results and discussion above, it was appropriate that the DMC recommended that the study should not proceed with the second cohort (infants ≤28 days of age).

The Shoklo assessment was used in a previous observational study (Study COA566A2407) conducted in Zambia. It was selected because it focused on coordination and concentration which were the expected CNS adverse effects of artemisinins. The mean and median behavior scores were close or equal to the maximum possible value. However, unlike Study A2407, the present study could not provide a baseline for comparison between different ages, nor data from a comparative arm. It is interesting to note that median and lower limit of range scores for coordination, or behaviour milestones at 12 months were not lower than those for the Karen ethnic minority on the Thai-Burmese border or London cohorts, while the same variables were slightly higher for tone milestones in the present study. In summary, although the Shoklo test was developed specifically for countries with limited healthcare resources, the limitations of the present study mean these results must be viewed with caution.

<u>In conclusion</u>
Although there were no new or unexpected safety signals and the PCR-corrected 28-day cure rate was 100% of evaluable patients there is concern that the mean exposure to artemether and DHA was 2- to 3-fold greater than that in infants weighing ≥5 kg. It cannot be ruled out that the higher exposures may lead to neurotoxicity/other toxicities which were not observed in older infants/children and there is no sound basis for dose adjustment criteria. Also, there are too few data to provide reassurance that could support use in children < 5 kg but >28 days of age.

Study COA556b2401 and E01

The study showed no significant difference between the intervention and control arms with respect to rates of SMRC5000 in infants and children (<5 years of age) in post-CSC follow-up. A statistically significant difference between the two study arms was observed in changes in haemoglobin levels at CSC1 Day 28 in ACs (>6 months of age) but the magnitude of the difference was not considered to be clinically meaningful.

Asymptomatic carriage of *P. falciparum* and gametocyte carriage showed greater decreases in the intervention arm than the control arm at CSC2 and CSC3 but there was no difference between study arms at CSC4. There were no differences between arms in changes at CSC4 in haemoglobin levels or anemia status in infants and children (>6 months and <5 years of age); improvements were observed in both study arms.

Demographic characteristics did not show major differences that might explain the observed lack of difference between study arms on most efficacy parameters. Subject disposition data did show a greater degree of immigration into the intervention clusters than the control clusters, however, together with a greater proportion of subjects lost to follow-up.

This study was not intended to assess the efficacy of AL in treating symptomatic malaria episodes although several thousand malaria episodes were effectively treated during the course of the study, and decreases in rates of asymptomatic carriage and gametocyte carriage were observed by microscopy in the intervention arm from CSC1-3.

The CSR discusses potential methodological shortcomings of the study, for example:

- Greater isolation of villages, although obviously difficult to implement, could potentially have increased the effects of the interventions in the study. Immigration of villagers into the intervention arm villages introduces the possibility of diluting the effect of the screening campaign interventions, and there were several villages that were not participating in the study that were adjacent to study villages.
- An 8-fold greater sensitivity of qRT-PCR versus microscopy reading was observed in gametocyte detection. It is possible that by using RDT and subsequent microscopic confirmation a significant proportion of GCs were undetected.
- Improvement in anaemia status in untreated ACs in the control arm between CSC1 and CSC4 may have resulted from general medical attention received by control subjects merely due to their participation in the study.
- It is also possible that clearance of asymptomatic carriage may have increased the risk of contracting symptomatic malaria. It has been suggested that asymptomatic carriage might be a form of tolerance to *P. falciparum* infection, which could protect against the development of clinical episodes. Kaplan-Meier analysis suggested that at later time points in the study, the incidence of first symptomatic malaria episodes was higher in the intervention than the control group.

Safety data did not reveal any unexpected findings.

<u>In conclusion</u>
Treatment of ACs with AL did not reduce the rate of SMRC5000 in infants and children (<5 years of age) in the community. AL treatment of ACs led to a small improvement in their haemoglobin levels that was statistically significant but not clinically relevant. Asymptomatic carriage of gametocytes and asexual forms of *P. falciparum* showed greater decreases in the intervention arm than the control arm at CSC2 and CSC3, but this effect was not sustained until CSC4. The results do not impact on the approved indication for AL.

V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

Study CCOA566A2417

This study aimed to evaluate the effects of artemether-lumefantrine on auditory brainstem pathway function in patients with acute, uncomplicated falciparum malaria by testing the null hypothesis that the rate of auditory brainstem pathway abnormalities is ≥ 15% in the population treated with artemether-lumefantrine, as assessed by ABR at Day 7 following initiation of treatment compared with their baseline values. The study included 90 patients aged between 12 and <18 years. The safety and efficacy data are not shown separately for the adolescents. Nevertheless, efficacy was so high that no difference by age would be detectable and the safety profile was clearly different between treatments even though the same proportion in each group was in the adolescent age range.

In reality, the study is not so very helpful even though it suggests that the lipid-soluble artemether does indeed reach and impact on the ABR findings. The main concern regarding possible effects of artemisinins on hearing pertains to repeated use and to use in young children. Data are still lacking to determine the real risk of various ACTs in his regard. From the current study it can only be stated that there was a clear differentiation between artemether-lumefantrine and the other 2 regimens in terms of ABR findings but it is not known whether the results have any clinical implications.

Study COA566b2306

This study was requested under the EU PIP for Riamet to evaluate the PK, efficacy and safety of artemether-lumefantrine dispersible tablets in the treatment of acute uncomplicated *P. falciparum* malaria in neonates and infants <5 kg of body weight for two sequential age cohorts: term age >28 days (Cohort 1) and term age ≤28 days (Cohort 2). Although there were no new or unexpected safety signals and the PCR-corrected 28-day cure rate was 100% of evaluable patients there is concern that the mean exposure to artemether and DHA was 2- to 3-fold greater than that in infants weighing ≥5 kg. It cannot be ruled out that the higher exposures may lead to neurotoxicity/other toxicities which were not observed in older infants/children and there is no sound basis for dose adjustment criteria. Also, there are too few data to provide reassurance that could support use in children < 5 kg but >28 days of age.

Study COA556b2401 and E01

The study showed no significant difference between the intervention and control arms with respect to rates of SMRC5000 in infants and children (<5 years of age) in post-CSC follow-up. A statistically significant difference between the two study arms was observed in changes in haemoglobin levels at CSC1 Day 28 in ACs (>6 months of age) but the magnitude of the difference was not considered to be clinically meaningful. Asymptomatic carriage of *P. falciparum* and gametocyte carriage showed greater decreases in the intervention arm than the control arm at CSC2 and CSC3 but there was no difference between study arms at CSC4. There were no differences between arms in changes at CSC4 in haemoglobin levels or anaemia status in infants and children (>6 months and <5 years of age); improvements were observed in both study arms. The results do not impact on the approved indication for AL.

- **Recommendation**

There are no implications for the SmPC. This very clearly states that use is from 5 kg body weight and there are no statements of lack of information in patients of < 5 kg in 4.4 or 5.2 that would need to be corrected or amended.

Whilst it could be argued that it could be useful to convey the PK findings in children < 5 kg body weight as documented in study COA566b2306 to discourage off label use of Riamet in this subset the assessor considers that there are too few data on PK and too large an inter-individual variability to add anything useful. Since Riamet is not indicated for use at < 5 kg there is no reason to add safety data to the SmPC.

Therefore no regulatory action is considered to be necessary or appropriate.