These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert in the country of prescription.

Sponsor / Company: Sanofi **Drug substance(s):** artesunate plus amodiaquine		**Study Identifiers:** NCT00699920 **Study code:** ARAMF_L_02661
Title of the study:	A randomized study to compare a fixed dose combination of artesunate plus amodiaquine [ASAQ] versus a fixed dose combination of artemether plus lumefantrine [AL] in treatment of repeated uncomplicated *Plasmodium falciparum* malaria attacks occurring during two years of follow-up, in children in Uganda.	
Study centre:	One active centre: Nagongera Health Centre IV, Tororo district - Uganda.	
Study period:	Date first patient enrolled: 02 Jun 2008	Date of first signed informed consent: 02 Jun 2008
	Date last patient enrolled: 29 Oct 2008	
	Date last patient completed: 02 Jun 2010	Date of last patient, last visit: 02 Jun 2010
Phase of development:	IV	

Objectives:

Primary objective:

To demonstrate the non-inferiority of Polymerase chain reaction (PCR) adjusted adequate clinical and parasitological response at D28 (WHO protocol in vivo D28, 2003) of Coarsucam®/ASAQ Winthrop® (artesunate plus amodiaquine) versus Coartem® (artemether plus lumefantrine), based on the first malaria attack of each patient.

Secondary objectives:

For the first attack (directly observed treatment administration):

To compare the two groups of treatment in terms of:

- D42 efficacy
- Parasitological and fever clearance
- Clinical and biological tolerability
- Evolution of gametocyte carriage.

For repeated attacks (non observed treatment administration):

To compare the two groups of treatment in terms of:

- D28 and D42 clinical and parasitological effectiveness
- Clinical and biological tolerability
- Proportion of patients without fever at D3
- Proportion of patients without parasite at D3
- Evolution of gametocyte carriage
- Compliance.

During the total follow-up of the cohort:

To compare the two groups of treatment in terms of:

- Treatment incidence density
- Impact of repeated treatment on clinical and biological tolerability
- Impact on anaemia
- Evolution of Hackett score.

Methodology:	Monocenter, open, randomized, longitudinal comparative study conducted on two parallel groups over a two-year study period. Children received the same treatment for all malaria episodes occurring during the course of the study.	
Number of patients:	**Planned:**	400 patients, 200 per treatment group.
	Randomized:	416 patients (Coarsucam®/ASAQ Winthrop®: 208 / Coartem®: 208)
	Treated:	413 patients (Coarsucam®/ASAQ Winthrop®: 208 / Coartem®: 205)
Evaluated:	**Efficacy:**	Per protocol population (PP): 397 (1st malaria attack) Intent-to-treat population (ITT): 399 (1st malaria attack)
	Safety:	Safety population: 413
	Pharmacokinetics:	Not applicable

Diagnosis and criteria for inclusion:	Inclusion in the cohort: Children aged 6 to 59 months presenting confirmed malaria infection with *Plasmodium falciparum* parasitemia ≥ 2000 asexual parasites / µL of blood and whom parents/legal representative gave written informed consent. Inclusion for each attack: Confirmed *Plasmodium* infection with positive parasitemia. Could not been included: children presenting with at least one danger sign of malaria (e.g. haemoglobin value < 5g/dL), a severe concomitant disease or known disturbances of electrolyte balance (e.g. hypokalaemia or hypomagnesaemia).	
Study treatments:	**Investigational medicinal product: Coarsucam®/ASAQ Winthrop®, fixed-dose combination of artesunate (AS) and amodiaquine (AQ)**	
	Formulation:	Infants tablets: AS 25/AQ 67.5 mg Toddlers tablets: AS 50/AQ 135 mg Children tablets: AS 100/AQ 270 mg
	Route of administration:	Oral route Supervised administration for the first attack Unsupervised administrations for following attacks (except for the 1st intake)
	Dose regimen:	Once daily, dose according to bodyweight range: weight ≥5 and <9kg: 1 tablet of 25/67.5mg; weight ≥9 and <18kg: 1 tablet of 50/135mg; weight ≥18 and <36kg: 1 tablet of 100/270mg;
	Reference therapy: Coartem®, (artemether + lumefantrine - AL)	
	Formulation:	Tablets: 20/120 mg
	Route of administration:	Oral route Supervised administration for the first attack Unsupervised administrations for following attacks (except for the 1st intake)
	Dose regimen:	Twice daily, dose according to bodyweight range: weight <15 kg: 1 tablet/intake; weight ≥15 and <25 kg: 2 tablets/intake; weight ≥25 and <35 kg: 3 tablets/intake.
Duration of treatment:	3 days	
Duration of observation:	Each attack occurring during the 2-year study period was actively followed for 42 days.	
Criteria for evaluation:	**Efficacy Pharmacodynamic**	PCR-corrected and uncorrected clinical and parasitological cure rate at D28 and D42 (WHO classification) For the first attack: fever and parasitological clearance by measuring the axillary temperature and monitoring parasitemia For the following attacks: proportion of apyretic patients at D3 and proportion of patients without parasites at D3 Clinical efficacy : evolution of baseline symptoms (all clinical symptoms were graded) Treatment compliance based on number of residual tablets in blisters Treatment incidence density during the 2 years study period (comparison of the number of malaria attacks between the two arms during the 2 years) Mean delay between 2 attacks during the 2 years study period
	Safety	Clinical tolerability (incidence and intensity of recorded Adverse Event (AE)) Biological tolerability (Haemoglobin, Bilirubin, Alanine Aminotransferase (ALAT), Creatinine, Leukocytes, Neutrophils, and Platelets count)
	Treatment compliance	Tablet count at end-of-treatment visit (D3),

	Pharmacokinetics	Not applicable
Pharmacokinetics/Pharmacodynamics sampling times and bioanalytical methods: not applicable		
Statistical methods:	**Number of patients:**	With a non-inferiority margin (Δ) chosen at 5 %, $\alpha/2$=2.5%, and β =20%, and the hypothesis of 97.5% of success rate with Coartem®, 192 patients were requested; taking into account less than 10% of lost for follow-up, 208 patients were needed per treatment group.
	Statistical considerations	All statistical analyses were performed on SAS software (version 8.2 for PC). All statistical tests were bilateral and performed at a 5% significance level except for the non-inferiority analysis (unilateral confidence interval)
	Efficacy analysis	The non-inferiority of PCR- adjusted adequate clinical and parasitological response at D28 (WHO protocol in vivo D28 2003) of Coarsucam®/ASAQ Winthrop® (artesunate plus amodiaquine) versus Coartem® (artemether plus lumefantrine), based on the first malaria attack of each patient was studied using the 95% one-sided confidence interval on ITT and Per Protocol populations.

Summary:

Population characteristics:

416 children were included in the study for a 1st episode of uncomplicated *P. falciparum* malaria and 413 were exposed either to Coarsucam®/ASAQ Winthrop® (208) or Coartem® (205).

At 1st malaria attack inclusion, treatment groups did not differ regarding baseline demographic, clinical and biological characteristics.

Malaria episodes monitored:

Over the 2-year study period, a total of 6033 episodes were monitored (6027 exposed to study treatment); table below shows number of patients by episode

E1	**E2**	**E3**	**E4**	**E5**	**E6**	**E7**	**E8**	**E9**	**E10**	**E11**	**E12**	**E13**
413	397	396	393	389	383	378	367	356	346	334	315	290
E14	**E15**	**E16**	**E17**	**E18**	**E19**	**E20**	**E21**	**E22**	**E23**	**E24**	**E25**	**E26**
261	231	192	160	130	97	73	54	38	20	13	6	1

Between Episode 2 and 26, children were mainly infected by *Plasmodium Falciparum.*

Insecticide Impregnated bednets supervised distribution 13 months after the beginning of the study did not have a measurable impact on the incidence of malaria episodes in the cohorts.

Treatment compliance:

Except for a few children included in the Coartem® group, full treatment compliance was observed after unsupervised administration and did not statistically differ between study treatments.

Efficacy results- 1st malaria attack primary criterion:

The main efficacy criterion was defined as the treatment response after PCR correction at D28 for the 1st attack of uncomplicated *P. falciparum* malaria according to WHO 2003 guidelines (confirmed 2009).

PP population		**Coarsucam®/ASAQ Winthrop® N=197**	**Coartem® N=200**	**Total N=397**
Efficacy evaluation after PCR correction	LCF	0 (0.0%)	3 (1.5%)	3 (0.8%)
	LPF	5 (2.5%)	3 (1.5%)	8 (2.0%)
	ACPR	192 (97.5%)	194 (97.0%)	386 (97.2%)

LCF: late clinical failure - LPF: late parasitological failure - ACPR : adequate clinical and parasitological response

Efficacy results - 1st malaria attack primary criterion - cont'd:	As the inferior limit of the 95%CI [-0.028; 0.037] of the difference of the PCRc-ACPR rates between groups was superior to -5%, the non inferiority with a 2.5% one-sided α/2 risk error has been demonstrated. Secondary analyses performed on the Intent to treat (ITT) population confirmed the non inferiority with PCRc-ACPR rates of 97.0% vs 96.5% (95%CI [-0.030; 0.039]). The Kaplan-Meier survival method in both ITT and Per protocol (PP) populations did not show any significant difference between study treatments.
Efficacy results- 1st malaria attack:	For the first episode, success rates at D42 after PCR correction in the ITT and PP populations were respectively 96% and 96.4% in the Coarsucam®/ASAQ Winthrop® and 94.5% and 95% Coartem® groups. ACPR rates observed before PCR correction at D28 in the PP and ITT populations were respectively 52.3% and 52% in the Coarsucam®/ASAQ Winthrop® group vs 52.0% and 51.7% in the Coartem® group. Despite very close cure rates, non-inferiority was not statistically shown; low efficacy rates observed in both groups led to a dramatic decrease in the power of the statistical test, to only 20%. Time to parasitological clearance did not differ between the Coarsucam®/ASAQ Winthrop® and Coartem® groups (respectively: 1.8±0.4 days vs 1.8±0.5 days - p = 0.150). At D1 mean parasite density was significantly lower in the Coarsucam®/ASAQ Winthrop® group than in the Coartem® group (respectively: 986.5 ± 2 400.8 vs 1 214.4 ± 2 381.7 parasites/µL - p = 0.030). This difference was no longer seen at D2 with 97.7% of all treated children free of parasites. No parasite was detected at the D3 and D7-follow-up visits in any child. The number of gametocytes carriers during the follow-up of the 1st malaria attack did not differ between groups, ranging between 12.0% and 17.5% during the first week, and then being less than 5%. Significantly more children were apyretic in the Coarsucam®/ASAQ Winthrop® group than in the Coartem® group at D1 of the first episode (respectively 98.5% vs 86.1% - p <0.001). At D3, no difference was observed between study treatment groups, the proportions of apyretic children in each treatment group were respectively 99.5% and 96.5%.
Efficacy results - subsequent malaria attacks	ACPR rates observed after PCR correction at D28 in the PP population ranged between 80% and 98.9% for subsequent attacks. Although cure rates were often similar between the 2 groups, non inferiority was not demonstrated for some episodes, with no trend in favor of either the Coarsucam®/ASAQ Winthrop® or Coartem® group. ACPR rates remained stable in both treatment groups over time during the 23 months of the study. Children experienced a mean number of 15±5 malaria attacks (min. 1; median 15; max. 26). Children included in the Coarsucam®/ASAQ Winthrop® group presented statistically more malaria attacks (15.7 ± 4.9) than children included in the Coartem® group (14.4 ± 4.9) (p = 0.011). The average duration between 2 attacks was longer in the Coartem® than in the Coarsucam®/ASAQ Winthrop® group: respectively 49 ± 21 days vs 43 ± 18 days (p = 0.002). Whatever the attack and the treatment group, all children were free from parasites at D3-end of treatment showing the consistent susceptibility of parasites to artemisinin derivatives in the study area during the study period. No impact of age on parasitological clearance profile was shown. While more than 10% of the children carried gametocytes at D0 of the 1st malaria attack, this proportion was nil or less than 2.3% at D0 for the following attacks, within only one exception. That is an important feature in terms of transmission. For subsequent malaria attacks 98% or more children were apyretic at D3. This proportion remained stable during the whole study period and never differed between treatment groups
Efficacy results - anaemia - all malaria attacks	Mean haemoglobinemia was below the lower normal limit (<10g/dL) at D0 of the 1st malaria attack, but reached lower normal limit on D0 of the 2nd attack. It was close to or above 11 g/dL between the 4th and 10th attacks and ranged between 10 to 11g/dL at the subsequent attacks without clinically significant differences between groups. Nearly four out five children (79.4%) were anaemic at inclusion for the 1st malaria attack, this proportion decreased dramatically by almost half (42.7%) at the 2nd attack, then ranged between 12.9% and 36.0% from the following attacks.

Efficacy results - disease signs and symptoms all malaria attacks	In nearly 80% of children some subjective malaria clinical symptoms were not assessed; when evaluable, they regressed well under treatment in both groups.
Safety results:	Incidence of AEs (59.8%) and Serious Adverse Events (SAEs) (6.1%) did not differ between treatment groups during the whole study duration. Most frequently reported AEs were general disorders and more particularly pyrexia, concomitant infections and infestations. Most reported SAEs were related to the severity of the malaria attack or to concomitant infection or injuries. One female child died during the course of the study. SAE occurrence rate per malaria attack did not show any specific episode-related distribution, but decreased with the number of treated malaria attacks. Increased ALAT considered as Adverse Events of Special Interest (AESIs), was rarely associated with increased total bilirubinemia, and was most often isolated. It was reported in 11 and 12 children who had received respectively Coarsucam®/ASAQ Winthrop® and Coartem®; one in each group was considered to be related to study treatment. Severe neutropenia or agranulocytosis were recorded, in 4 children and 2 children in the Coarsucam®/ASAQ Winthrop® and Coartem® groups respectively All abnormal results went spontaneously back to normal. All children experiencing AESI were re-administered study treatment for subsequent attacks, with no recurrence of AESI after treatment.
Date of report: 26-Feb-2013	