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Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00445796
		Study Code:	PM_L_0164
Generic drug name:	ARSUCAM®	**Date:**	03/Aug /2007

Title of the study:

Randomised, comparative study of the efficacy and safety of Arsucam® administered as a single daily intake versus two daily intakes in the treatment of *Plasmodium falciparum* malaria attack

Principal investigators/study centres:

- Prof. Ph. Brasseur: Dispensaire Saint Joseph, Mlomp, Département d'Oussouye, Senegal
- Prof. O. Gaye: District sanitaire de Sédhiou, BP 42, Région de Kolda, Senegal
- Prof. A. Samé-Ekobo: FMSB/CHU, Yaoundé, Cameroon

Studied period:	**Development phase:**
Date of the first visit by the first patient included: 27 June 2005 Date of the last visit by the last patient included: 7 October 2005	Phase IV

Objectives:

Primary endpoint:

To demonstrate the non-inferiority, in terms of clinical and parasitological efficacy on D14, of administration of Arsucam® as a single daily intake versus two daily intakes.

Secondary endpoints:

To compare the clinical safety of the two treatment regimens.

Methodology:

This was a randomised, comparative, open-label; multicentre study in 2 groups (Arsucam® as a single daily intake versus two daily intakes). This trial was conducted in Senegal and in Cameroon.

Any suspected uncomplicated malaria attacks occurring in a subject attending a health facility taking part in the trial gave rise to active management, after obtaining consent and verifying inclusion criteria, comprising a 3-day treatment period and 14-day follow-up period (if malaria attack was confirmed by parasitemia). Six visits were scheduled for each patient during which a physical examination was carried out, together with evaluation of clinical safety, measurement of vital signs, and parasitological tests.

Number of patients (included and analysed):

Three hundred (300) patients were to be included. 316 patients were actually included and analysed in the present study: 161 in the Arsucam® single daily intake group and 155 in the Arsucam® two daily intakes group.

Diagnosis and criteria for inclusion/exclusion:

Inclusion criteria:

- adults or children,
- weighing = 10 kg,
- residing in the area covered by the investigating centre throughout the entire follow-up period,
- able to receive oral treatment,
- axillary temperature = 37.5 degrees Celsius or history of fever within the previous 24 hours
- *P. falciparum* density in the blood ranging from 1000 to 100,000 asexual forms per cubic millimetre,
- signed informed consent from each participant or parents (guardians) for the children.

Diagnosis and criteria for inclusion/exclusion (cont.):

Exclusion criteria:

- presence of at least one sign of severe malaria or clinical danger sign : prostration, consciousness disorders, recent and repeated convulsions , respiratory distress, inability to drink, uncontrollable vomiting, macroscopic haemoglobinuria, jaundice, haemorrhagic shock, systolic BP < 70 mmHg in adults or < 50 in children, spontaneous bleeding, inability to sit or stand,
- serious concomitant disease,
- allergy to one of the investigational medicinal products,
- pregnant women (reported, clinically visible pregnancy or pregnancy identified by immunological tests detecting ß-hCG hormone marketed as G Test® or BB Test®) or breast-feeding women. The pregnancy test was carried out after having obtained specific preliminary freely-given written informed consent. If the test was negative, consent to take part in the study was then obtained. If the test was positive, the patient was not included in the study and received treatment with quinine, in compliance with the current therapeutic protocol recommended by the Malaria National Control Program ,
- documented intake of an antimalarial at a suitable dosage within seven days prior to inclusion.

Test product, dose, and mode of administration.:
Investigational product: ARSUCAM® in a coblister containing artesunate and amodiaquine (tablet containing 50 mg of artesunate and tablet containing 153 mg of amodiaquine base). The dosage was adjusted on the basis of the following weight ranges :

- Weight ≥10 kg and < 21 kg: 1 tablet of each product per day ;
- Weight ≥21 and ≤ 40 kg: 2 tablets of each product per day;
- Weight > 40 kg: 4 tablets of each product per day.

Dosage regimen: Dose administered as 2 daily intakes (morning and evening)

Mode of administration: oral use

Reference product: ARSUCAM® in a coblister containing artesunate and amodiaquine (tablet containing 50 mg of artesunate and tablet containing 153 mg of amodiaquine base). The dosage was adjusted on the basis of the weight ranges indicated above.

The daily dosages, batch numbers and expiry dates were identical to the investigational product.

Dosage regimen: Dose administered as a single daily intake (morning)

Mode of administration: oral use

Duration of treatment: 3 days

Criteria for evaluation:

- The primary endpoint was clinical and parasitological cure on D14
- The secondary endpoint was based on the incidence and severity of adverse events.

Statistical methods:

Primary endpoint: adequate response to treatment on D14 (clinical and parasitological response). An adequate response to treatment was defined as the absence of parasitaemia on Day 14, irrespective of axillary temperature, without any signs of early treatment failure or late clinical or parasitological failure (in compliance with WHO definitions).

The non-inferiority of Arsucam® as two intakes versus Arsucam® as a single intake was studied on the basis of the adequate response to treatment on D14.

In order to do so, the two-sided 90% confidence interval of the difference in the proportions of responders on D14 between the two treatment groups was calculated.

If the upper limit of the confidence interval was below the acceptance limit (d=3%), the non-inferiority of Arsucam® 2 intakes versus a single intake was demonstrated.

Secondary endpoints: the safety of Arsucam® was evaluated by the presence or absence of adverse events.

Results:

Three hundred and sixteen (316) patients, 42.4% of which were female, aged 2 to 80 years (18.4% children aged under 5 years, 40.5% from 6 to 13 years and 41.1% aged over 14 years) were included in the study. The 2 patient groups displayed similar demographic characteristics and clinical symptoms on inclusion in the study. Seven (7) patients were withdrawn prematurely from the study: 5 patients moved out of the area covered by the investigating centre, one patient withdrew his consent and another patient was withdrawn from the study further to a serious adverse event (bronchopneumopathy on D1). Apart from the latter 2 patients in the Arsucam® single intake group, who were withdrawn from the study and only received treatment for one day, all of the other patients received treatment for 3 days as provided for in the protocol. The patients taking part in the study were followed up for a period of 14 days after inclusion.

Efficacy results:

The adequate responses to treatment were similar for the 2 treatment regimens, and approaching 100% before and after PCR analysis on D14. The statistical analyses conducted on the ITT and PP populations demonstrated the non-inferiority of administering Arsucam® as 2 intakes versus a single daily intake, in terms of clinical and parasitological efficacy on D14.

Parasite clearance was comparable in the two treatment groups. Approximately 70% of patients showed negative parasitaemia on D2 and approximately 90% on D3.

The number of gametocyte-carrier patients showed only minor variation during follow-up (12 patients on inclusion, D7 and D14, and 14 patients on D3). The mean values for gametocytaemia were halved between D1 and D7 in both groups.

A favourable outcome with regard to the symptoms of malaria attack was observed for the 2 patient groups during the study:

- On inclusion, more than 75% of patients had an axillary temperature above 37.5°C. After 3 days of treatment, more than 99% of patients were apyretic, irrespective of the Arsucam® treatment regimen.
- A similar reduction in the incidence and intensity of headache, perspiration, dizziness and chills was observed in the 2 patient groups.
- The incidence of pain also decreased in the two groups.
- The incidence of anorexia decreased during treatment, but remained statistically more frequent in the Arsucam® single intake group (40%) versus the Arsucam® 2 intakes group (30%) on D1 ($p = 0.0389$). This symptom mainly affected patients aged under 7 years in the 2 treatment groups. Moreover, a difference was observed between the Senegalese centres and the Cameroon Centre: the investigators from the latter centre diagnosed more cases of anorexia in their patients during the study than the Senegalese investigators (61% versus 24% on D1).
- The incidence of asthenia was halved after 3 days of treatment in the 2 patient groups.
- Symptoms such as jaundice, skinfold and hepatomegaly were infrequently observed in the study population on inclusion, and little change was observed in the incidence of such symptoms during treatment. No patients presented with skinfold or jaundice at the end of the study.
- A comparable reduction in the number of patients suffering from vomiting or diarrhoea was observed in the 2 groups (46% on inclusion versus 3.5% on D3 for vomiting, and 8.9% on inclusion versus 2.2% on D3 for diarrhoea).

The two treatment regimens used demonstrate comparable efficacy.

Safety results:

During the study, 26 patients presented an adverse event, without any significant differences between the 2 patient groups. Out of the AEs, 14 were mild, 10 moderate and 2 severe. Twenty AEs were perceived by the investigators as treatment-related. These AEs corresponded to gastrointestinal disorders (2.5%) (nausea (1.3%), abdominal pain (0.9%), duodenal ulcer (0.3%)), pruritus (2.5%) and nervous system disorders (1.3%) (drowsiness (0.6%), seizures (0.3%) and dysgeusia (0.3%)). Two serious adverse events (pneumonia and bronchopneumopathy) not related to the study treatment occurred in 2 patients (one in each group) causing one patient to be withdrawn from the study (a patient in the Arsucam® single intake group, due to bronchopneumopathy). With the exception of this case of bronchopneumopathy which improved upon receiving specific treatment, all of the other AEs had resolved prior to the end of the study. No significant changes in vital signs were reported during the study.

Rejection of treatment during the first half-hour after administration was observed in 10 patients, 6 in the Arsucam® single intake group and 4 in the Arsucam® two intakes group, mainly occurring on D0. Out of these 10 patients, 7 were aged 6 to 13 years. No differences were observed between the 2 patient groups. An equivalent dose of treatment was re-administered in each case.

Certain symptoms attributable to malaria but not present on inclusion appeared during treatment: asthenia (5.7%), vomiting (4.7%), anorexia (4.7%), diarrhoea (2.8%), abdominal pain (1.9%) and dizziness (2.2%), without any differences between the treatment groups. Furthermore, although little change was observed in the number of patients with asthenia during treatment, in the majority of patients, the intensity of asthenia increased during treatment, from “mild” on inclusion to “moderate” at the end of treatment, without any differences between the 2 treatment groups. The influence of the number of tablets per intake, or the total quantity of drug substance to be ingested, on the onset of these symptoms was the subject of a descriptive analysis only, owing to the limited

sample size. **Arsucam®** treatment was well tolerated during the study. The 2 treatment regimens showed similar safety profiles **.** ▪
Date of report: Final version dated 22 September 2006