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<b>Sponsor/company:</b>	sanofi-aventis	<b>ClinialTrials.gov Identifier:</b>	NCT00316329																	
<b>Generic drug name:</b>	Coarsucam	<b>Study Code:</b>	PM_L_0164																	
		<b>Date:</b>	21/Apr/2008																	
<b>Title of the study:</b>	Multinational, randomised, comparative study of the efficacy and safety of three therapeutic regimens: Coarsucam™ (artesunate+amodiaquine fixed-dose combination) administered in 1 or 2 daily intakes per day versus Coartem® (artemether+ lumefantrine) in the treatment of uncomplicated <i>Plasmodium falciparum</i> malaria (PM_L_0164)																			
<b>Investigator(s):</b>	O. Gaye, parasitology department, UCADDakar, Senegal; Ph. Basseur, IRD, Dakar, Senegal; A. Same-Ekobo, FMSB/CHU, Yaounde, Cameroon; I. Sagara, MRTC, Bamako, Mali; M. Randrianariveolojosa, Pasteur Institute of Madagascar.																			
<b>Study center(s):</b>	5 active sites in Senegal (2 sites), Mali, Cameroon, and Madagascar																			
<b>Publications (reference):</b>	None at the time of report writing																			
<b>Study period:</b>			<b>Phase of development:</b>																	
Date first patient enrolled:	15-Mar-2006 (Date of first signed informed consent)		III																	
Date last patient completed:	06-Jan-2007 (Date of last patient last visit)																			
<b>Objectives:</b>	<p><b>Primary objective:</b> To demonstrate the non-inferiority, in terms of clinical and parasitological efficacy on D28 (<i>WHO in vivo protocol D28 2003</i>), of administration of Coarsucam™ as a single daily dose, compared with administration of Coartem®</p> <p><b>Secondary objectives:</b> To compare the 3 treatment groups in terms of:</p> <ul style="list-style-type: none"> <li>- clinical and parasitological efficacy on D14 and D28 in the global population and in the subpopulations of children aged under 5 years and patients aged 5 years and over</li> <li>- time to parasite clearance</li> <li>- time to fever resolution</li> <li>- evolution of gametocytaemia</li> <li>- impact on anaemia</li> <li>- clinical and laboratory safety</li> </ul>																			
<b>Methodology:</b>	Multicentre, randomised, comparative, blinded, phase III study																			
<b>Number of patients:</b>	Planned: 1032	Randomized: 941	Treated: 940																	
<b>Evaluated:</b>	<table border="1"> <thead> <tr> <th>Study Population</th> <th>Coarsucam™ 1 daily intake</th> <th>Coarsucam™ 2 daily intakes</th> <th>Coartem®</th> </tr> </thead> <tbody> <tr> <td>Safety<sup>a</sup></td> <td>313</td> <td>315</td> <td>312</td> </tr> <tr> <td>ITT<sup>b</sup></td> <td>310</td> <td>315</td> <td>311</td> </tr> <tr> <td>PP<sup>c</sup></td> <td>283</td> <td>285</td> <td>289</td> </tr> </tbody> </table> <p><sup>a</sup> with patients who had a double rejection at the first administration.  <sup>b</sup> without patients who had a double rejection at the first administration.  <sup>c</sup> ITT population with no major protocol deviations.</p>				Study Population	Coarsucam™ 1 daily intake	Coarsucam™ 2 daily intakes	Coartem®	Safety <sup>a</sup>	313	315	312	ITT <sup>b</sup>	310	315	311	PP <sup>c</sup>	283	285	289
Study Population	Coarsucam™ 1 daily intake	Coarsucam™ 2 daily intakes	Coartem®																	
Safety <sup>a</sup>	313	315	312																	
ITT <sup>b</sup>	310	315	311																	
PP <sup>c</sup>	283	285	289																	

<b>Inclusion criteria:</b>	Patients presenting uncomplicated Plasmodium falciparum malaria (parasite density ranging from 1000 to 200,000 asexual forms per $\mu$ L). Patients (or parents) having signed informed consent, capable of receiving oral treatment. Females of child-bearing age with negative pregnancy test.	
<b>Investigational product:</b>	<b>Coarsucam™</b> (artesunate (AS) + amodiaquine (AQ) fixed-dose combination )	
Dose:	AS 25/AQ 67.5 mg tablets AS 50/AQ 135 mg tablets Dosage adjusted according to body weight range; completed if necessary with placebo tablets for blinding	
Administration:	Oral administration, 1 or 2 daily intakes per day	
<b>Duration of treatment:</b> 3 days per patient	<b>Duration of observation:</b> 28 days per patient	
<b>Reference therapy:</b>	<b>Coartem®</b> (artemether + lumefantrine)	
Dose:	Tablet containing 20/120 mg Dosage adjusted according to body weight range	
Administration:	Oral administration, in 2 daily intakes per day	
<b>Criteria for evaluation:</b>		
Efficacy:	Parasitological and clinical efficacy on D28 (Monitoring antimalarial drug resistance, WHO/HTM/RBM/2003.50). Assessment of parasitaemia, gametocytaemia, axillary temperature and clinical symptoms	
Safety:	Adverse events and clinical symptoms reported by the patient or noted by the investigator. Standard haematology, blood chemistry and vital signs.	
<b>Statistical methods:</b>	The primary efficacy endpoint corresponded to parasitological and clinical response after PCR correction on D28 for the Coarsucam™ 1 daily intake/day and Coartem® groups. It was described by treatment group, age group and overall and was evaluated in the ITT and PP populations. The main analysis corresponded to the ITT population. Non inferiority was tested with the BINOMIAL procedure (STATXACT) with a 5% (one-sided) significance level (non-inferiority delta of 5%). Tests to compare means between treatment groups were performed when relevant (ANOVAs). Tests to compare percentages were performed when relevant (Chi-2 test or Fisher non parametric test when the number of patients was insufficient).	
<b>Summary:</b>	Overall, 941 patients were enrolled at 5 investigative sites. Of these patients, 1 discontinued the study before treatment initiation. Therefore, 940 patients aged 0.9 to 65 years were treated. The 3 patient groups displayed similar demographic characteristics and clinical symptoms at inclusion. Overall, 42 patients were withdrawn from the study (15, 17, and 10 in the Coarsucam™ 1 daily intake, Coarsucam™ 2 daily intakes and Coartem® groups respectively) including 20 patients who discontinued during the treatment period. The main reason for discontinuation was consent withdrawal (2, 8 and 4 in Coarsucam™ 1 daily intake, Coarsucam™ 2 daily intakes and Coartem® groups, respectively) or loss to follow up (3, 5 and 2 in the Coarsucam™ 1 daily intake, Coarsucam™ 2 daily intakes and Coartem® groups, respectively).	

## Efficacy results

ACPR in the ITT population on Day 28 after PCR correction were 95.2% in the Coarsucam™ one daily dose group (n=310), 94.9% in the Coarsucam™ two daily doses group (n=315) and 95.5% in the Coartem® group (n=311) respectively. Results calculated in the PP population were 98.9% in the Coarsucam™ one daily dose group (n=283), 100% in the Coarsucam™ two daily doses group (n=285) and 98.6% in the Coartem® group (n=289) respectively. Statistical analyses performed in both ITT and PP populations demonstrated the non-inferiority of administering Coarsucam™ 1 daily intake versus Coartem®, in terms of clinical and parasitological efficacy on D28 (2 sided 90%CI= [-0.03; 0.03] in the ITT population; = [-0.02; 0.01] in the PP population).

In children less than 5 years, ACPR in the ITT population on day 28 after PCR correction were 94.4% (n=143) in the Coarsucam™ one daily dose group, 95.9% (n=148) in the Coarsucam™ two daily doses group and 93.7% (n=142) in the Coartem® group; while in the PP population ACPR on D28 were 98.5% (n=134), 100% (n=137) and 97% (n=133), respectively. The non inferiority of administering Coarsucam™ 1 daily intake versus Coartem® was also confirmed in the subpopulation of children less than 5 years (2 sided 90%CI=[-0.06; 0.04] in the ITT population, =[-0.0526; 0.0181] in PP population).

The non-inferiority of administration of Coarsucam™ 2 daily intakes versus Coartem® and Coarsucam™ 1 daily intake was also demonstrated, in terms of clinical and parasitological efficacy on D28.

On D14, similar adequate responses to treatment after PCR correction were obtained for the 3 treatment regimens in both ITT and PP populations.

Parasite clearance was also comparable in the 3 treatment groups. Around 35% of patients showed negative parasitaemia on D1 and around 99% on D3 without any significant difference between treatment groups at each time.

The number of gametocyte-carrier patients markedly decreased during the study (43 patients at inclusion and 3 patients at D28); it was significantly higher in the Coarsucam™ 2 daily intakes group at D14 (p=0.027) and D28 (p=0.04). The mean values for gametocytaemia were halved between D1 and D14; the number of gametocytes carriers was null from D21 in the Coarsucam™ 1 daily intake group and from D14 in the Coartem® group.

A favourable evolution of baseline symptoms was observed for the 3 patient groups during the study:

- All patients had an axillary temperature = 37.5°C or a history of fever within the 24 previous hours on inclusion. After 3 days of treatment, more than 99% of patients were apyretic, irrespective of the treatment regimen.

A similar reduction in the prevalence and intensity of anorexia, dizziness, chills, perspiration, pain, jaundice, hepatomegaly, splenomegaly, pruritus, skinfold, skinrash was observed in the 3 patient groups among the population who presented these symptoms at baseline.

- The prevalence of headaches decreased in the 3 groups from 82.2% at baseline to 5.9% at D3. A significant difference was only observed at D3 (p=0.03): 11.0% of patients in the Coarsucam™ 1 daily intake, 7.3% in the Coarsucam™ 2 daily intakes and 3.3% in the Coartem® groups reported headache.

- The prevalence of asthenia decreased in the 3 groups from 87.1% at baseline to 11.1% at D3; a significant difference was observed only at D2 (p=0.03): 20.9% of patients in the Coarsucam™ 1 daily intake, 24.5% in the Coarsucam™ 2 daily intakes and 16.7% in the Coartem® groups reported asthenia.

- The prevalence of vomiting decreased during the study (from 48.9% at baseline to 2.8% at D3). The proportion of patients who vomited outside the centre was higher at D1, in the Coarsucam™ 1 daily intake (23.4%) than in the 2 other groups (13.2% in the Coarsucam™ 2 daily intakes and 12.3% in the Coartem® groups; p=0.0178). No difference was observed on this parameter after D1 between treatment groups.

- A reduction in the number of patients suffering from diarrhoea was also observed in the 3 groups (from 2.1% at baseline to 0.3% at D3).

Safety results:

	<b>Coarsucam™ 1 daily intake n=313</b>	<b>Coarsucam™ 2 daily intakes n=315</b>	<b>Coartem® n=312</b>
Any EAEs	105 (33.5%)	85 (27.0%)	85 (27.2%)
Any ESAEs	1 (0.3%)	0	0
All deaths	1 (0.3%)	0	1 (0.3%)
Withdrawals due to AE	3 (1.0%)	0	0

EAE=emergent adverse event; ESAE=emergent serious adverse event

Two patients died during the study: 1 patient in the Coarsucam™ 1 daily intake experienced lung infection and anaemia on D3 and 1 patient in the Coartem® experienced a coma on D1 from unknown cause. These events were not attributed to the treatment by the investigators. One other serious AE was noted for one patient in the Coarsucam™ 1 daily intake who experienced treatment-related severe anaemia 5 days after the last intake of treatment; he recovered after hospitalisation.

Three patients in the Coarsucam™ 1 daily intake group discontinued the study due to treatment-related AEs of severe intensity (persistence of severe vomiting, fatigue and vertigo and asthenia); All patients recovered.

Rejection or vomiting during the first half-hour after drug administration was observed in 13.0% of treated patients, with no significant difference between treatment groups. An equivalent dose of treatment was re-administered in each case. The number of patients having at least one vomiting or rejection episode in the half hour after the administration was statistically significantly higher in the subgroup of patients aged less than 5 years, compared with older patients (  $p < 0.01$ ).

Some symptoms not present at inclusion appeared under treatment: vomiting (7.4%), pain (2.5%), anorexia (1.8%), pruritus (1.7%), diarrhoea (1.3%), asthenia (0.9%), headache (0.6%), and chills (0.4%), without differences between the treatment groups.

The number of treatment-related AEs was lower in the Coartem® group than in the 2 others, with a significant difference between the treatment groups (Chi<sup>2</sup> test,  $p = 0.01$ ). Somnolence related to treatment was reported in 11 patients receiving Coarsucam™ 1 daily intake, and in 6 patients treated by Coarsucam™ 2 intake, all except 2 graded moderate were graded mild. Of note, all somnolence cases were reported in the Madagascar study site. Excluding these somnolence cases, there is no significant difference between the treatment groups (Chi<sup>2</sup> test,  $p = 0.18$ ).

Overall, hematological and biochemical parameters had a similar evolution during the study between the 3 treatment groups. Except for neutrophils (1.8% of patients with abnormal values at baseline to 8.4% at D28, without difference between treatment groups at each time), the number of patients who had abnormal laboratory results as well as the toxicity grade decreased during the study whatever the treatment group. No statistically significant difference between the treatment groups was observed in the number of patients having abnormal laboratory values for hemoglobin, neutrophils, platelets, ALT and creatinine at D7 and D28. Anaemia was reported as an AE for 7 patients during the study (5 in the Coarsucam™ 1 daily intake, 1 in the Coarsucam™ 2 daily intakes and 1 in the Coartem® groups). Neither thrombopenia nor neutropenia was reported as AE during the study.

Vital signs had a similar evolution during the study between the 3 treatment groups. Overall, the three treatments were well tolerated.

**Date of report:**

23 October 2007