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Prescribing decisions should be made based on the approved package insert in the country of prescription

Sponsor/company:	sanofi-aventis	**ClinialTrials.gov Identifier:**	NCT00540410
		Study Code:	ARAMF_L_02873
Generic drug name:	Artesunate + amodiaquine	**Date:**	22 June 2010

Title of the study:	Randomized study comparing artesunate+amodiaquine and artemether + lumefantrine administered for the repeated treatment of recurrent uncomplicated *Plasmodium falciparum* malaria in Senegal in a cohort followed-up for 2 years
Investigator:	Pr O. Gaye, parasitology department, UCAD Dakar, Senegal.
Study center:	1 active site in Senegal
Publications (reference):	None
Study period: Date first patient enrolled: 26-Sep-2007 (Date of first signed informed consent) Date last patient completed: 11- Feb-2009 (Date of last patient last visit)	**Phase of development:** IV
Objectives:	**Primary objective**: To demonstrate the non-inferiority, in terms of clinical and parasitological efficacy after PCR (polymerase chain reaction) correction at D28 (PCR corrected ACPR (adequate clinical and parasitological response) of Coarsucam™ (fixed dose combination of artesunate+amodiaquine) compared with Coartem® (fixed dose combination of artemether + lumefantrine) for the first episode of uncomplicated *Plasmodium falciparum* malaria occurring within the study duration. **Secondary objectives**: - **For the 1st episode of uncomplicated *Plasmodium falciparum* malaria** (treatment administration supervised), to compare both treatment groups in terms of: o clinical and parasitological efficacy on D14 o time to parasite clearance o time to fever resolution o clinical and biological safety o auditory (audiometry) and cardiac safety (QTc) in patients aged 12 years or more - **For the 2nd and following episodes**, to compare both treatment groups in terms of: o treatment efficacy at D14 and D28 (PCR corrected ACPR) without keeping a watch over treatment administration o proportion of apyretic patients at D3 o proportion of patients free from parasite at D3 o clinical and biological safety o auditory (audiometry) in patients aged 12 years or more o treatment compliance - **For the whole study duration**: o To determine the impact of the repeated administration of each study treatment on malarial morbidity and clinical, laboratory and auditory safety - **Particular conditions**: o Women of childbearing potential: Women with positive pregnancy test at D0 were not included Women with positive pregnancy test at D28 were withdrawn from the cohort but followed at least up to delivery All patients were advised to come back to the center as soon as symptoms that could correspond to a new episode of malaria appeared.

Methodology:	Monocenter, randomized, comparative, open-label, phase IV study on 2 parallel groups.		
Number of patients:	Planned: 400 (200: <12 years ; 200: ≥12 years)	Randomized: 366	Treated: 366
Evaluated:	ITT population: 366 PP population:365	Safety: 366	Pharmacokinetics: not applicable
Diagnosis and criteria for inclusion:	Children (> 5kg body weight) and adult patients presenting uncomplicated *Plasmodium falciparum* malaria (axillary temperature ≥ 37.5C° at inclusion or within past 24 hours, parasite density > 1000 asexual parasites/µL). Patients (or parents) having signed informed consent, capable of receiving oral treatment. Females of child-bearing age with negative pregnancy test prior each treatment initiation.		
Investigational product: Dose: Administration:	**Coarsucam**™ (artesunate (AS) + amodiaquine (AQ) fixed-dose combination) Dosage adjusted according to body weight range. Adult patients: AS 100 mg / AQ 270 mg per bi-layer tablet Children: AS 50 mg / AQ 135 mg per bi-layer tablet Pediatric dose: AS 25 mg / AQ 67.5 mg per bi-layer tablet Oral administration, 1 daily intake. 1st episode treatment administration watched over, recurrent episodes treatment administration not watched over unless 1st dose.		
Duration of treatment: **Duration of observation:**	3 days per patient for each episode occurring over the 2-year study period 28 days per patient for each episode		
Reference therapy: Dose: Administration:	**Coartem®** (artemether (A) + lumefantrine (L) fixed-dose combination) Tablet containing: A 20mg / L 120 mg - Dosage adjusted according to body weight range Oral administration, in 2 daily intakes per day. 1st episode treatment administration watched over, recurrent episodes treatment administration not watched over unless 1st dose.		
Criteria for evaluation: Efficacy:	Parasitological and clinical efficacy on D28 for the 1st episode of uncomplicated malaria. Assessment of parasitaemia, axillary temperature and clinical symptoms (PCR corrected ACPR).		
Safety:	Adverse events and clinical symptoms reported by the patient (or parents) or noted by the investigator. Standard haematology, blood chemistry, vital signs, Auditory safety (audiometry in patients aged ≥ 12 years). Cardiac safety at 1st episode for patients aged ≥ 12 years (QTc).		
Statistical methods:	The primary efficacy endpoint compared the parasitological and clinical response after PCR correction on D28 for the 1st uncomplicated malaria episode between the Coarsucam™ and Coartem® groups. Non inferiority of Coarsucam™ compared to Coartem®, was tested by calculating the 95% confidence interval of the difference observed in the success rates between both treatment groups in the ITT and PP populations, with a 2.5% (one-sided) significance level (non-inferiority delta of 5%). The main analysis corresponded to the ITT population.		
Statistical methods (cont'd):	Tests to compare means between treatment groups were performed when relevant (Student-T test or Wilcoxon rank test when distribution was not normal). Tests to compare percentages were performed when relevant (Chi-2 test or Fisher non parametric test when the number of patients was <5). Repeated measure analysis was performed to explain the success and failure of treatment, including the rank of the episode and treatment group in the model, as well as the episode rank and treatment group interaction. The mean time elapsed between 2 episodes of malaria was analyzed using survival curve methods for both treatment groups.		

<table>
<tr><td>Summary:</td><td>366 patients were included in the study for a 1st episode of uncomplicated P. falciparum malaria and were randomly assigned to receive either Coarsucam™ (184) or Coartem® (182). Two-hundred and one patients (55%) were less than 12 years' old: 101 and 100 patients were included respectively in the Coarsucam™ and Coartem® groups. Sixty patients (17%) and 4 patients (1%) presented respectively a 2nd episode and 3rd recurrence.</td></tr>
<tr><td>Efficacy results:</td><td>In the ITT population, the rate of adequate clinical and parasitological responses after PCR correction at D28 for the 1st episode of uncomplicated malaria was 98.4% vs 96.2% respectively in the Coarsucam™ and Coartem® groups. The efficacy of Coarsucam™ was non-inferior to that of Coartem® in treating uncomplicated P. falciparum malaria. This non-inferiority was demonstrated whatever the patients' range of age or the number of episodes occurring during the nearly 2-year study duration.</td></tr>
<tr><td>Efficacy results (cont'd):</td><td>
Adequate clinical and parasitological response rates after[a] and before[b] PCRc at D28
<table>
<tr><th>Studied population</th><th>N</th><th>Coarsucam™</th><th>Coartem®</th><th>95% CI</th></tr>
<tr><td>whole population (ITT) [a]</td><td rowspan="2">366</td><td>98.4%</td><td>96.2%</td><td>[-0.011; 0.056]</td></tr>
<tr><td>whole population (ITT) [b]</td><td>96.2%</td><td>94.0%</td><td>[-0.022; 0.067]</td></tr>
<tr><td>whole population (PP) [a]</td><td rowspan="2">365</td><td>98.9%</td><td>96.7%</td><td>[-0.008; 0.052]</td></tr>
<tr><td>whole population (PP) [b]</td><td>96.7%</td><td>94.5%</td><td>[-0.020; 0.065]</td></tr>
<tr><td>Patients < 12 years (ITT) [a]</td><td>201</td><td>97.0%</td><td>95.0%</td><td>[-0.034; 0.074]</td></tr>
<tr><td>Patients ≥ 12 years (ITT) [a]</td><td>165</td><td>100%</td><td>97.6%</td><td>[-0.009; 0.058]</td></tr>
</table>
An adequate clinical and parasitological response was obtained at D28 in the 60 and 4 patients who presented respectively a 2nd and 3rd episode of uncomplicated malaria during the study period.
Time to parasite clearance was 1.7 ± 0.5 days (median 2) in both treatment groups (p = 0.10). Almost all patients (97%) were free from parasite at the 3rd treatment day (D2), no parasite was found in any patient at the end-of-treatment visit (D3). For the 2nd and 3rd episodes of malaria all patients with parasite at D0 were free from parasite at D3.
For the 1st episode, the proportion of gametocyte-carriers in the Coarsucam™ group was higher than that in the Coartem® group at D2 (8.2% vs 2.7% - p = 0.02), D3 (8.2% vs 2.8% -p = 0.02) and D7 (6.6% vs 1.1% - p = 0.01). Irrespective of the assigned treatment, at D28 no gametocyte-carrier was detected.
A greater effect of Coarsucam™ on the evolution of the blood hemoglobin level was observed during 1st and 2nd episodes, resulting in significantly higher level of hemoglobinemia measured one month after the treated episode of malaria.
The patients' distribution according to the number episodes did not differ between the Coarsucam™ and Coartem® groups (p = 0.74), as well as the mean time to first recurrence (181.3 ± 165.2 days - p = 0.35). Recurrence occurred within 15 days following the 1st
episode in 37% of the cases and more than 6 months after the 1st episode in 53% of the total patients. Analyses performed using the Kaplan-Meier survival method to describe time to treatment failure did not show any significant difference between both study treatments (ITT p = 0.20, PP p = 0.15).
Although treatment was home-administered for the 2nd and 3rd episode, the compliance remained excellent.</td></tr>
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Safety results	During the study almost all treatment-related AEs reported in 11.7% of the patients were of mild or moderate intensity, only one neutropenia was severe. No unusual AE occurred, no death was reported and 2 patients withdrew prematurely from the study due to non treatment-related SAEs. Treatment-related AEs were "blood disorders" (5.2% of patients), "gastrointestinal disorders" (4.1%) and "nervous system disorders" (2.5%), other treatment-related SOC disorders were reported in less than 1% of the patients. Treatment-related anemia (3.8% patients) was usually of mild intensity and recovered with or without iron-based treatment. At 1st treated episode, severe neutropenia were observed in 10 (2.7%) patients, all were aged 12 or more years and were considered treatment-related in 5 (1.4%) patients. Recovery was observed in 2 patients at the last follow-up visit of the study (Other patients were followed until recovery). Mild abdominal pain and vomiting were more frequently observed in patients aged 12 years or more and recovered most often within 1 day. Mild hypersomnia or somnolence was mainly reported in less than 12 years' old patients included in the Coarsucam™ group and resolved within 1 or 2 days of occurrence. Emergent treatment-related AEs reported and AE incidences observed during this study were those commonly shown in previous studies. In patients who were treated at least twice, the recurrent administration of Coarsucam™ or Coartem® did not result in major safety issue. Although treatment-related anemia was reported in 3 patients during the 1st treated episode period and was severe in one case, it did not recur at the 2nd treated episode of malaria. A QTc increase was observed in both treatment groups between D0 and D3. It resulted probably from an effect of depolarization, as well as from an interfering artifact due to fever resolution and its subsequent chronotropic effect. Our study results showed the excellent auditory safety profile of both study treatments and whatever the administered dose of Coarsucam™.
Date of report:	11-Jun-2010