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Sponsor/company:	sanofi-aventis	**ClinicalTrials.gov Identifier:**	NCT00452907
		Study Code:	ARTEN_L_00848
Generic drug name:	Artesunate	**Date:**	26 January 2010

Title of the study:	Assessment of the Public Health Benefit of Artemisinine based combination therapies for uncomplicated Malaria treatment in Mali ARTEN_L_00848
Investigator(s):	Dr Abdoulaye DJIMDE, PharmD, PhD; Pr Ogobara Doumbo, MD, PhD; Bakary Fofana, MD; Bakary Sidibe, MD; Amadou Togo MD, Sekou Toure, BSc; Issaka Sagara, MD, MSPH
Study center(s):	Dispensary of Bougoula-Hameau, Sikasso – MRTC, Bamako, Mali
Publications (reference):	N/A

Study period: Date first patient enrolled: 25-Jul-2005 Date last patient completed: 25-Jun-2007	**Phase of development:** Phase IV study

Objectives:	Specific objective 1. To test the hypothesis that repeated administration of Artesunate/Amiodaquine (AS/AQ), Artesunate/Sulfadoxine-Pyrimethamine (AS/SP) and Arthemeter-Lufemantrine (AR-L) for the treatment of consecutive episodes of uncomplicated malaria reduces the incidence of uncomplicated *falciparum* malaria and anemia. Primary endpoint was the incidence density of uncomplicated malaria over the study period. Secondary end point was the incidence of anemia in each arm. Specific objective 2. To measure the impact of the repeated administration of AR-L, AS/AQ, and AS/SP on malaria transmission and antimalarial immunity. Primary end point was gametocyte prevalence and infectivity. Secondary endpoints: antimalarial immunity as measured by antibody titers using ELISA. Specific objective 3. To assess the treatment efficacy, clinical and biological safety in each treatment arm.

Methodology:	This was an open randomized clinical trial comparing three different artemisinin-based combination treatments: *AR-L, AS/AQ, and AS/SP* Patients, age >=6 months with uncomplicated malaria were randomized to receive AR-L, AS/AQ, or AS/SP. New episodes of malaria were retreated with the same combination therapy that the subject was initially randomized to receive. Once subjects have been assigned to a given group, in the event of subsequent malaria episodes, they were re-treated with that same treatment regimen. Patients were closely followed both clinically and biologically to record any adverse event. In case of treatment failure or development of severe malaria, patients were treated with quinine or hospitalized if necessary.		
Number of Version 01:	Planned: 780	Randomized: 780	Treated: 780
Evaluated:	Efficacy: - Treatment outcomes were classified as Early treatment failure (ETF), late clinical failure (LCF), Late parasitological failure (LPF) and adequate clinical and parasitological response (ACPR) according to WHO latest protocol (WHO, 2003). - Incidence of clinical malaria by treatment arm. - Impact of the repeated administration of AS/AQ, AS/SP and AR-L on malaria transmission and antimalarial immunity.	Safety: The incidence of clinical adverse events (AEs) related or not to study drugs was reported by severity, causality and by study arm. The severity of lab abnormality was defined using grading scale	
Diagnosis and criteria for inclusion:	Subjects with the following characteristics were included in the study. Age at least 6 months, weight at least 5 kg, residing in Bougoula-Hameau, Sikasso, Mali able to receive oral treatment, having an axillary body temperature of more than 37.5 °C for the first randomization, Suffering from a *Plasmodium sp.* infection with a parasite density between 2,000 and 200,000 asexual forms per microliter of blood. A written informed consent was obtained, either from themselves (adults) or from their respective parent/legal guardian (minors). Furthermore, Subsequent malaria episode was defined as the presence of malaria signs or symptoms (Chills, headaches, vomiting… irrespective of axillary temperature >= 37.5^{o}C) with *Plasmodium sp.* infection with parasite density not null. Severe malaria cases were treated with quinine and re-enrolled for the subsequent uncomplicated malaria with the same study treatment arm.		
Investigational product:	Artesunate, Amodiaquine, sulfadoxine/pyrimethamine, Arthemether-lumefantrine		

Dose: Administration:	Arm1 (AR-L)*: For patients < 15 kg, 1 tablet per dose; 15-25 kg, 2 tablets per dose; 25-35 kg, 3 tablets per dose; > 35 kg, 4 tablets per dose. *Treatment is given over 3 days twice a day Arm2 (AS+AQ)*: For patients < 10 kg, ½ tablet AS + ½ tablet AQ; 10-20 kg, 1 tablet AS+ 1 tablet AQ per day 21-40 kg, 2 tablets AS+2 tablets AQ per day; > 40 kg, 4 tablets AS + 4 tablets AQ per day. * Treatment is given over 3 days once a day. Arm3 (AS+SP)* For patients <= 10 kg, ½ tablet AS + ½ tablet SP; 11-20 kg, 1 tablet AS+ 1 tablet SP per day 21-40 kg, 2 tablets AS+2 tablets SP per day; > 40 kg, 4 tablets AS + 3 tablets SP per day * SP is given only the first day while AQ is given over 3 days once a day Oral route	
Duration of treatment: 3 days		**Duration of observation:** 28 days
Criteria for evaluation:		
Efficacy Safety:	Adequate clinical and parasitological response (ACPR) by day 28. Treatment outcomes were classified as early treatment failure (ETF), late clinical failure (LCF), late parasitological failure (LPF) and adequate clinical and parasitological response (ACPR) according to WHO latest protocol (WHO, 2003) Clinical and parasitological cure at day 28. Incidence of clinical adverse events and modification of biological parameters. All subjects who received at least one dose starting from their first episode of malaria were included into the safety and other secondary objectives analysis. All subjects were analyzed using their initial assigned randomization code. Missing data was ignored in this analysis	
Statistical methods:	Data were double entered and validated using MS Access and then analyzed using Stata software version 10.0. For efficacy data, a non-inferiority at 5% alpha significance level is then claimed if the right endpoint of the one-sided 100(1-α) % confidence interval for the efficacy difference does not surpass 5% at day 28 analysis corrected for re-infection between any one treatment arm compared to the others. For the incidence reduction, any significant difference at 5% alpha significance level is considered significant depending on the other objectives outcomes. Demographic variables and baseline, specifically age and sex, parasite density… were tabulated by treatment group and overall during the first episode of malaria. Asexual parasite density, gametocyte density and hemoglobin level were computed and compared between arms during each episode. Baseline characteristics, specifically parasitemia, gametocyte index and anemia frequency were summarized as well. The comparisons were made by treatment group. Chi-square test, Fisher exact statistic, Anova test, and non parametric statistics were computed whereby appropriate for these comparisons as indicated in the table.	

Summary:	
Results on incidence:	Using AR-L arm as reference patients in the AS+AQ and AS+SP arms had 15% and 17% less risk for experiencing uncomplicated malaria, respectively (P < 0.001). The Intention –to-treat (ITT) analysis of *P. falciparum* only before PCR correction showed that AS/SP is significantly more efficacious (89.6%) than AS/AQ (78.6%) which in turn is significantly better than AR-L (62.3%). However, molecular correction showed 95.0%, 95.9, and 98.5 of ACPR respectively with AR-L, AS/AQ and AS/SP. While using the per-protocol (pp) analysis before PCR correction, AS/SP is still significantly (P < 0.001) more efficacious (89.8%) than AS/AQ (79.1%) which in turn is significantly better than AR-L (62.7%). The rates of treatment failure were significantly higher in AS/AQ and AR-L arms than in AS/SP. There was 26% more risk for subject in age category less than 5 years old to get malaria episode compared to subject in age category greater or equal to 5 years old independently to the treatment arm.
Safety results:	Vomiting occurring 3 days after treatment initiation was the most frequent AE. AR-L is significantly (P < 0.001) less associated with vomiting (8.9%) than AS/AQ (21.6%) and AS/SP (23.2%). The incidence rates of the remaining SAEs were comparable between the three treatment regimens. No laboratory adverse event related to any treatment was found. No clinically significant abnormal laboratory toxicity was found with any of the treatment arms. The incidence of abnormal liver enzyme ALAT was similar in all three arms with 0.72, 0.74%, and 1.18% while the incidence of abnormal creatinin was 5.09, 6.33 and 15.19% (which was significantly higher), respectively in AR-L, AS/AQ and AS/SP groups. The occurrence of abnormal leucopenia was similar in the three groups.
Date of report:	22 September 2009