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Sponsor / Company: Sanofi **Drug substance(s):** SSR103371	**Study Identifiers:** NCT01023399 **Study code:** ARAMF_L_04314

Title of the study: A nested open-labeled study to compare the effectiveness and safety of a fixed-dose combination of artesunate plus amodiaquine (ASAQ Winthrop®) in the unsupervised treatment of uncomplicated *Plasmodium falciparum* malaria attacks in two patient groups enrolled at two year-intervals in a pilot district of Côte d'Ivoire

Study center(s): 1 active centre– in Republic of Côte d'Ivoire

Study period:

Date first patient enrolled: 1st period: 20/Nov/2009; 2nd period: 11/Mar/2013

Date last patient completed: 1st period: 04/Jun/2010; 2nd period: 28/Oct/2013

Phase of development: Phase 4

Objectives:

Primary: To demonstrate the non-inferiority in terms of clinical and parasitological efficacy after Polymerase Chain Reaction correction (PCRc) at Day 28 (D28) (PCRc Adequate clinical and parasitological response-World Health Organization [ACPR-WHO] protocol 2005) of ASAQ WINTHROP® between 2 groups of patients included in the study in 3 years of interval (instead of 2 as initially planned).

Secondary: To evaluate in both patient-groups and to compare them if relevant:

- The clinical and biological safety.
- The evolution of gametocyte carriage.
- The proportion of apyretic patients at D3.
- The proportion of patients free from parasite at D3.
- The treatment compliance.
- The mean value of blood haemoglobin at inclusion.
- The susceptibility of parasite to monodesethylamodiaquine (MDAQ), the active metabolite of amodiaquine (in vitro testing) (*this last objective was not evaluated*).

Methodology: Monocentre open comparative study between 2 patient-groups enrolled in 2 years of interval.

Number of patients**:**	Planned: 580 (290 patients enrolled at each period)
	Treated: 574 (period 1: 288 patients ; period 2: 286 patients)
Evaluated:	Efficacy: 574 (period 1: 288 patients ; period 2: 286 patients)
	Safety: 580 (290 patients enrolled at each period)

Diagnosis and criteria for inclusion: Children (≥5 kg body weight) and adult patients presenting monospecific infection to *Plasmodium falciparum* with parasitemia >2000/µL (blood smears), axillary temperature ≥37.5°C at inclusion or within the past 24 hours and without severe concomitant disease. Patients (or parents) having signed informed consent, capable of receiving oral treatment. Females of child-bearing age with negative pregnancy test prior to treatment initiation.

Study treatments

Investigational medicinal product(s): ASAQ WINTHROP® (fixed-dose combination of artesunate [AS] + amodiaquine [AQ]).

Formulation: AS 25 mg /AQ 67.5 mg or AS 50 mg /AQ 135 mg or AS 100 mg /AQ 270 mg

Route(s) of administration: oral

Dose regimen: One tablet per day during 3 days (D0, D1, and D2), 3 tablets/blister - dose according to patient's age	**Infants 2-11 months**: AS 25 mg /AQ 67.5 mg **Young children 1-5 years:** AS 50 mg /AQ 135 mg **Children 6-13 years:** AS 100 mg /AQ 270 mg
Two tablets per day during 3 days (D0, D1 and D2) 6 tablets/blister	**Adults ≥ 14 years:** AS 100 mg /AQ 270 mg

Duration of treatment: 1 daily intake of 1 or 2 tablets per day according to patient's age over 3 days (D0, D1, and D2).

Duration of observation: each malaria episode was followed up for 28 days (D28). The patients' enrollment during the 2nd period started 3 years after the start of the 1st period.

Criteria for evaluation:

Efficacy: **Primary criterion:** treatment response after PCR correction according to the WHO 2005 guidelines.

Secondary criteria:

- Proportion of apyretic patients at D3 (axillary temperature <37.5°C).
- Proportion of Adequate Clinical and Parasitological Response (ACPR) at D28 before PCR correction.
- Proportion of ACPR at D14 and D21 before and after PCR correction.
- Proportion of patients free from parasites at D3 (negative thick smear).
- Evolution of the number of gametocyte carriers over the study follow-up.
- Evolution of the mean number of gametocytes per patient over the study follow-up.
- Evolution of the mean level of blood haemoglobin at inclusion and over the study follow-up.
- Evolution of haemoglobin levels between D0 and D7, and D0 and D28.
- Evolution of biomolecular markers of resistance on D0 and on any day of clinical recurrence during follow-up.
- Evolution of the compliance of treatment.

Safety: Adverse events reported by the patient or noted by the Investigator. Standard hematology and blood chemistry over the follow-up.

Evolution of clinical signs and symptoms over the study follow-up, as reported.

Statistical methods:

The primary efficacy endpoint compared the rate of adequate parasitological and clinical response after PCR correction at D28 between the 2 period groups. Non inferiority of ASAQ WINTHROP® during the 2nd period compared to the 1st period was tested by calculating the 95% confidence interval (CI) of the difference observed in the success rates between both period groups in the per protocol (PP) population, with a 2.5% (one-sided α/2) significance level and a β risk of 20% (non-inferiority - Δ = -5%).

As secondary efficacy endpoints, similar analyses than the primary one were performed to compare the parasitological and clinical response after PCR correction at D28 in the intent-to-treat (ITT) population, before PCR correction at D28 in the ITT and PP populations, and after and before PCR correction at D14 and D21 in the ITT and PP populations.

Both period groups were compared regarding the proportion of apyretic patients at D3, proportion of patients free from parasite at D3, the number of gametocyte carriers during the 28-day follow-up and the mean counts of gametocytes, the evolution of clinical signs and symptoms at each visit, the mean blood haemoglobin at inclusion and evolution over the follow-up, the evolution of biomolecular markers of resistance, the evolution of compliance. Tests to compare means between period groups were performed when relevant (Student-T, Mantel Hanszel, Chi², Kruskal-Wallis or Wilcoxon rank tests).

Regarding safety, the frequency of reported treatment-emergent adverse events (TEAEs) and abnormal biological values was determined.

An interim descriptive analysis was performed at the end of the 1st period.

Summary:

Population characteristics: 580 patients were included in the study (290 per study period) and 475 (81.7%) completed the study: 1st period 257 (88.6%) and 2nd period 218 (75.2%). At inclusion, the patients' demographic characteristics did not differ between the 1st and 2nd study periods. Patients were slightly more often of male gender (52.1% - p = 0.24), were aged 4.8 ± 6.1 years (p = 0.48) and weighed 15.5 ± 10.3 kg (p = 0.64). Diseases reported according to System Organ Class (SOC) were mainly concomitant diseases in 39.4% of patients and being most often reported during the 2nd study period (Period 1: 22.6% - Period 2: 56.3%).

All patients suffered from *Plasmodium falciparum* infection and 2.1% of patients were gametocytes carriers (period 1: 2.4% versus period 2: 1.7% - p = 0.568). Mean initial parasitemia was significantly higher at inclusion of the 2nd period (71 069.3 ± 85 478 versus 41 555.2 ± 45 491 trophozoites /µL p <0.001). Gametocyte density in gametocyte carriers was also greater at D0 during the 2nd period compared to the 1st period (respectively 967.8 ± 1 290.9 versus 47.1 ± 70.9 gametocytes/µL) and at the limit of the statistical significant threshold (p = 0.051).

No difference in mean number of signs and symptoms of malaria per patient was shown between the 2 period groups, (p = 0.360). A statistically significant difference was shown for the presence at inclusion of chills (Period 1: 21.9% versus Period 2: 42.7%, p <0.001) and jaundice (Period 1: 8.7% versus Period 2: 3.8%, p = 0.017) only.

Blood haematology and biochemistry parameters determined at inclusion were no different, except for a statistically higher mean of hemoglobin observed at inclusion time of the second period (p = 0.008) and a lower mean of platelets and of alanine transaminase (ALT) during this same period (p <0.001). Anaemia was shown in 277 (96.2 %) patients during the 1st period versus 264 (92.3%) patients during the 2nd study period of which 2 patients had values judged clinically significant by the Investigator.

Efficacy results: The primary objective of the study was to assess the non-inferiority of ASAQ WINTHROP® administered during the 2nd study period, compared to the efficacy observed during the 1st study period, ie, at the beginning of the implementation program. The main efficacy criterion was defined as the D28 treatment response after PCR correction in the PP population evaluated according to WHO 2005 guidelines.

In the PP population, the proportion of patients with an ACPR after PCR correction to treatment was similar during the 2nd and 1st period: 96.3% versus 95.7%, respectively. As the lower limit of the 95%CI (-0.029 ; 0.040) was superior to the pre-specified non inferiority margin of -5%, it could be concluded with a 2.5% one-sided α risk error that the efficacy of ASAQ WINTHROP® administered during the 2nd period was non-inferior to that of ASAQ WINTHROP® administered during the 1st period in treating uncomplicated *Plasmodium falciparum* malaria. Such non-inferiority was not confirmed by the secondary ITT analysis of the primary efficacy criterion showing a lower proportion of patients with an ACPR after PCR correction to treatment during the 2nd period than during the 1st period: 90.6% versus 92.7%, respectively (95%CI [-0.067; 0.024]). In the ITT population without patients with visit for efficacy assessment not performed (P1: 7 versus P2: 18), the non-inferiority of ASAQ WINTHROP® when administered during the 2nd study period was seen (95%CI [-0.017; 0.050]).

As well, non-inferiority was not statistically demonstrated on secondary efficacy analyses performed on ACPR rates before PCRc at D28 which were lower during the 2nd period compared to the 1st period: respectively 83.8% versus 87.1% in the PP population (95%CI [-0.095 ; 0.029]) and 78.7% versus 85.1% in the ITT population (95%CI [-0.127 ; -0.001]).

The proportion of patients free from parasite at D3 did not differ between the 1st and 2nd study period groups: 100% and 99.3% of patients respectively (p = 0.244). The proportions of gametocyte carriers decreased similarly during the follow-up of the 1st and 2nd study periods being 2.1% at D0 and D3 (both p = 0.568), 1.8% at D7 (p = 0.991), 0.9% at D14 (p = 0.201), 0.2% at D21 (p = 0.471), and nil at D28.

At D3, the proportion of apyretic patients (axillary temperature <37.5°C) was significantly higher in the 2nd study period population than in the 1st period's one: 98.6% versus 95.4%, respectively (p = 0.046).

Safety results: No death was reported. No adverse event (AE) led to study treatment discontinuation. The frequency of patients with reported AEs was significantly lower during the 2nd period than during the 1st period: in 39.3% and 50.0% patients, respectively (p = 0.010) but no particular difference was observed between the type, intensity, relationship and outcome of AEs reported during both study periods 19 (0.6%) AEs were considered related to the study treatment by the Investigator in 19 (3.3%) patients, were of mild or moderate intensity in 12 cases and of severe intensity in 7 patients; 17 of them resolved favorably and the 2 other cases progressed favorably.

Six serious adverse events were reported in 5 (0.9%) patients: abnormal liver function adverse event of special interest (AESI) in 3 (0.5%) patients, anaemia in 1 (0.2%) patient, dysentery and febrile convulsion in 1 (0.2%) patient.

One case of unrelated and spontaneously recovered extrapyramidal disorder and 1 case of unrelated nystagmus were also reported as AESI.

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