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Sponsor / Company: Sanofi Drug substance(s): SSR103371	Study Identifiers: NCT01378286, UTN U1111-1120-0233 Study code: ARAMF_C_05370
Title of the study: A randomised comparative study to assess the efficacy and tolerability of blood schizonticidal treatments with artesunate amodiaquine WintHrop®/ Coarsucam™ (ASAQ) versus Chloroquine (CQ) for uncomplicated *Plasmodium vivax* monoinfection malaria	
Study center(s): A single center in Manaus, Brazil	
Study period: Date first patient enrolled: 09/Jan/2012 Date last patient completed: 05/Jun/2013	
Phase of development: Phase 3	
Objectives: Primary: To demonstrate the noninferiority of ASAQ versus chloroquine with respect to polymerase chain reaction (PCR)-adjusted adequate clinical and parasitological response (ACPR) at Day 28 (D28). Secondary: To assess noninferiority with respect to ACPR at D28 before PCR-adjusted cure rate and at D14 and D42 before and after PCR-adjusted cure rate.	
Methodology: This was a randomized, open-label, 2 parallel-arm trial comparing ASAQ to chloroquine in adults and children over 6 months old with a symptomatic, biologically confirmed *P. vivax* mono-infection.	
Number of patients:	Planned: 380 patients (190/group) Randomized: 380 patients (190/group) Treated: 380 patients (190/group)
Evaluated:	Efficacy: 379 patients (Intent-to-treat [ITT] population); 337 patients (per protocol [PP] population) Safety: 380 patients
Diagnosis and criteria for inclusion: Adults and children over 6 months old (bodyweight >5 kg), able to be treated by the oral route, with an axillary temperature ≥37.5°C or history of fever during the previous 2 days and a symptomatic biologically-confirmed *Plasmodium vivax* mono-infection, with parasitaemia from 250 to 100 000 asexual parasites /µl of blood.	
Study treatments Investigational medicinal product(s): ASAQ (Artesunate Amodiaquine Winthrop® / Coarsucam™; artesunate+amodiaquine fixed-dose combination) and chloroquine (CQ) (Cloroquina® manufactured by Farmanguinhos in Brazil). Formulation: Tablets	
Route(s) of administration: Oral Dose regimen: Dose adapted to the patient's weight; treatment administered under supervision once a day for 3 days.	
Noninvestigational medicinal product(s) Primaquine (Primaquina® manufactured by Farmanguinhos in Brazil) was prescribed at the end of the study in accordance with local study practice for radical cure of *Plasmodium vivax* infection. In case of repeated reject or vomiting of the investigational medicinal product, rescue medications were artesunate/mefloquine tablets and parenteral artesunate was proposed according to Brazilian guidelines.	

Duration of treatment: 3 days

Duration of observation: 6 weeks

Criteria for evaluation:

Efficacy:

Primary: The proportion of patients achieving ACPR to treatment at D28, after PCR adjustment on species, then on strains.

Secondary: ACPR at D28 before PCR adjusted cure rate.
ACPR at D14 and D42 before and after PCR-adjusted cure.
Proportion of aparasitaemic patients at 24, 48, and 72 hours.
Proportion of afebrile patients at 24, 48, and 72 hours.
Evolution of number of gametocyte carriers during the 42 days of follow-up.
Evolution of the mean number of gametocytes during the 42 days of follow-up.
Proportion of patients with recurrence between D28 and D42.
Evolution of haemoglobin levels for each patient between D0 and D7, D0, and D28.

Safety: Adverse events (AEs) reported by the patient or noted by the Investigator.
Standard haematology and blood chemistry.
Neutropenia and elevated hepatic enzymes were documented as adverse events of specific interest (AESIs).
Electrocardiogram (ECG) data was collected and the data on heart rate and QTc interval evaluated by a cardiologist.

Statistical methods: To demonstrate the noninferiority of ASAQ compared to CQ, the bilateral 95% confidence interval (CI) of the difference between the APCR rates observed in the 2 treatment groups was determined. Noninferiority was considered demonstrated if the lower bound of the bilateral 95% CI was superior to -0.05 (or for a one-sided risk of 2.5% [α/2]). The primary analysis was performed with respect to PCR-adjusted ACPR at D28 in the PP population. If noninferiority was demonstrated, a χ^2 test for superiority was performed at a bilateral significance level of 0.05. A similar approach was taken to evaluate noninferiority with respect to the secondary analyses of ACPR, namely PCR-adjusted ACPR at D28 in the ITT population, PCR-unadjusted ACPR at D14, D28, and D42 in the PP and ITT population, and PCR-adjusted ACPR at D14 and D42 in the PP and ITT population. As a sensitivity analysis in the PP population, patients with a different genotype during the follow-up were considered as missing.

The number of patients free of parasites and the number of afebrile patients were compared between the 2 groups on D1, D2, and D3 by means of a χ^2 test (or Fisher's exact test as appropriate).

The cumulative risk of developing gametocytaemia and the cumulative risk of recurrence of malaria were analysed through Kaplan-Meier survival analysis. Incidence rates for developing gametocytaemia with their associated 95% CI were estimated at D28 ± 2 and D42 ± 2 and recurrence rates estimated at D42 ± 2. Survival curves were also generated and the 2 treatment groups compared by means of the logrank test.

Gametocyte density was also calculated in terms of person-weeks and compared between treatment groups by use of a general estimating equation (GEE) model for binary data to take into account between-measure correlations within individual patients.

Absolute and relative changes in haemoglobin levels between D0 and D7, and between D0 and D28 were calculated for each patient and compared between the two groups by means of the Wilcoxon test.

Analysis of safety data was purely descriptive.

Summary:

Population characteristics: In the ITT population, the majority of patients enrolled in the study were adults with 10% of patients aged less than 14 years and 3.7% aged less than 6 years.

	ITT population		**PP population**	
	ASAQ group (N = 189)	CQ group (N = 190)	ASAQ group (N = 165)	CQ group (N = 172)
Age (years)				
Mean ± SD	35.7 ± 16.4	34.7 ± 15.9	36.1 ± 16.8	34.8 ± 16.3
Median [Min ; Max]	35.0 1.0 ; 68.0	34.5 1.0 ; 74.0	36.0 1.0 ; 68.0	34.0 1.0 ; 74.0
<6 years 9 – 14 years ≥14 years	7 (3.7%) 10 (5.3%) 172 (91.0%)	7 (3.7%) 14 (7.4%) 169 (88.9%)	7 (4.2%) 9 (5.5%) 149 (90.3%)	7 (4.1%) 14 (8.1%) 151 (87.8%)
Gender	*N = 189*	*N = 189*	*N = 165*	*N = 171*
Male	136 (72.0%)	144 (75.8%)	122 (73.9%)	131 (76.2%)
Female	53 (28.0%)	46 (24.2%)	43 (26.1%)	41 (23.8%)

The presence of *Plasmodium* species and of *P. vivax* in particular, was detected in blood smears from all patients at inclusion. This was confirmed by PCR in all patients except 3 (1 in the ASAQ group and 2 in the CQ group), for whom PCR failed to identify any parasite. One patient had a mixed infection (*P. vivax* and *P. falciparum*). This patient was excluded from the ITT and PP populations. In the safety population (all enrolled patients), thick blood smears revealed a mean parasite density of 2954 ± 3501 parasites/µL, this being somewhat higher in the patients in the ASAQ group compared to those in the CQ Group. Gametocytes were detected in 220 patients overall (57.9%), at a mean density of 60.4 ± 115.1 parasites/µL.

	ITT population		PP population	
	ASAQ group (N = 189)	CQ group (N = 190)	ASAQ group (N = 165)	CQ group (N = 172)
At least one *Plasmodium* spp.	189 (100.0%)	190 (100.0%)	165 (100.0%)	172 (100.0%)
P. vivax confirmed by PCR	188 (99.5%)	188 (98.9%)	164 (99.4%)	170 (98.8%)
Mean parasite density (µl) ± SD	3243 ± 4023	2669 ± 2884	3379 ± 3817	2796 ± 2948
Gametocyte density >0 Mean ± SD	105 (55.6%) 54.0 ± 77.5	114 (60.0%) 66.8 ± 143.2	95 (57.6%) 56.6 ± 79.0	103 (59.9%) 70.2 ± 149.6
Axillary temperature ≥37.5 °C Mean ± SD	85 (45.0%) 37.2 ± 1.3	77 (40.5%) 37.1 ± 1.3	72 (43.6%) 37.2 ± 1.3	72 (41.9%) 37.1 ± 1.3

Efficacy results:

Primary efficacy analysis

The ACPR rate at D28 after adjustment by PCR in the PP population was 100% (165/165 patients) in the ASAQ group and 93.6% (161/172 patients) in the CQ group. The difference in ACPR rate between the 2 groups was 6.40% (95%CI: 2.74% to 10.05%). Since the lower bound of the 95% CI was superior to the prespecified noninferiority threshold of -0.05, noninferiority of ASAQ with respect to CQ was demonstrated. The 11 treatment failures in the CQ group corresponded to 4 patients in late clinical failure and 7 patients in late parasitological failure. There were no cases of early treatment failure. The proportion of patients achieving ACPR at 28 days was significantly higher in the ASAQ group (p = 0.002), demonstrating superiority over the CQ group.

	ASAQ group (N = 165)	CQ group (N = 172)	Risk difference [95%CI]
PCR-adjusted ACPR in the PP population at Day 28	165 (100.0%)	161 (93.6%)	6.40% [2.74% to 10.05%]

Other analyses of the primary efficacy endpoint

Noninferiority of the PCR-adjusted ACPR rate at D28 in the ASAQ group compared to the CQ group was also demonstrated in the ITT population (risk difference: 3.12% [95%CI: -2.3% to 8.55%]) and in both the PP and ITT populations. The proportion of patients achieving ACPR at 28 days was significantly higher in the ASAQ group (p = 0.003) in the ITT population, demonstrating superiority over the CQ group.

A sensitivity analysis in which patients with strain mismatches between D0 and D28 were considered as missing was also performed. In both the PP and ITT populations, noninferiority was demonstrated (risk difference 6.47% [95%CI: 2.77% to 10.17%] in the PP population and 3.23% [95%CI: -2.23% to 8.68%] in the ITT population).

	ASAQ group	CQ group	Risk difference [95%CI]
PCR-adjusted ACPR in the ITT population at Day 28	177 (93.7%)	172 (90.5%)	3.12% [-2.30% to 8.55]
Sensitivity analysis in the PP population at Day 28	165 (100.0%)	159 (93.5%)	6.47% [2.77% to 10.17%]
Sensitivity analysis in the ITT population at Day 28	177 (93.7%)	170 (90.4%)	3.23% [-2.23% to 8.68%]

Secondary efficacy analyses

Other analyses of the ACPR

Analyses were also carried out of the PCR-unadjusted ACPR at D28 and the PCR-adjusted and unadjusted ACPR at D14 and D42 in both the PP and the ITT populations. Noninferiority of ASAQ with respect to CQ was demonstrated in both populations for the PCR-unadjusted ACPR at D28. The proportion of patients achieving ACPR at 28 days was significantly higher in the ASAQ group (p <0.001) in PP population and (p = 0.001) in ITT population, demonstrating superiority over the CQ group.

At the earlier time-point of D14, all patients from both treatment groups in the PP population fulfilled the ACPR criteria both for the adjusted and for the unadjusted measure. In the ITT population it was not possible to demonstrate non-inferiority of ASAQ with respect to CQ due to loss to follow-up of 8 patients in the ASAQ group and 3 patients in the CQ group, who for this reason failed to fulfil the ACPR criteria.

At the later time-point of D42, non-inferiority of ASAQ with respect to CQ was demonstrated for both PCR-adjusted and unadjusted ACPR in both the ITT and PP populations.

	ASAQ group	CQ group	Risk difference [95%CI]
PCR-unadjusted ACPR in the PP population at Day 28	165 (100.0%)	159 (92.4%)	7.56% [3.61% to 11.51%]
PCR-unadjusted ACPR in the ITT population at Day 28	177 (93.7%)	170 (89.5%)	4.18% [-1.40% to 9.76%]
PCR-adjusted ACPR in the PP population at Day 14	165 (100.0%)	172 (100.0%)	-
PCR-unadjusted ACPR in the PP population at Day 14	165 (100.0%)	172 (100.0%)	-
PCR-adjusted ACPR in the ITT population at Day 14	181 (95.8%)	187 (98.4%)	-2.65% [-6.03% to 0.72%]
PCR-unadjusted ACPR in the ITT population at Day 14	181 (95.8%)	187 (98.4%)	-2.65% [-6.03% to 0.72%]
PCR-adjusted ACPR in the PP population at Day 42	151 (97.4%)	129 (77.7%)	19.71% [12.90% to 26.51%]
PCR-unadjusted ACPR in the PP population at Day 42	149 (96.1%)	122 (73.5%)	22.64% [15.27% to 30.00%]
PCR-adjusted ACPR in the ITT population at Day 42	162 (85.7%)	136 (71.6%)	14.14% [6.01% to 22.26%]
PCR-unadjusted ACPR in the ITT population at Day 42	160 (84.7%)	129 (67.9%)	16.76% [8.37% to 25.16%]

Parasite clearance and fever abatement

In PP population, 99.4% of patients in the ASAQ group and 80.2% of those in the CQ group were free of parasites by D3. The proportion of patients free of parasites was significantly higher (p <0.001) in the ASAQ group than in the CQ group at D1, D2 and D3. Similar results were observed in the ITT population.

By D1, 99.4% of patients in the ASAQ group and 89.5% of those in the CQ group in the PP population were no longer febrile. After D2, none of the ASAQ patients were febrile. By D3, only one patient (in the CQ group) remained febrile. The proportion of afebrile patients was significantly higher (p <0.001) in the ASAQ group than in the CQ group on D1, but not thereafter, indicating more rapid resolution of fever. Qualitatively similar findings were obtained in the ITT population.

PP population	ASAQ group (N = 165)	CQ group (N = 172)	*P*
Patients parasite-free by Day 1	33 (20.0%)	4 (2.3%)	<0.001
Patients parasite-free by Day 2	144 (87.3%)	77 (44.8%)	<0.001
Patients parasite-free by Day 3	164 (99.4%)	138 (80.2%)	<0.001
Patients without fever on Day 1	164 (99.4%)	154 (89.5%)	<0.001
Patients without fever on Day 2	165 (100.0%)	170 (98.8%)	0.499
Patients without fever on Day 3	165 (100.0%)	171 (99.4%)	1.000

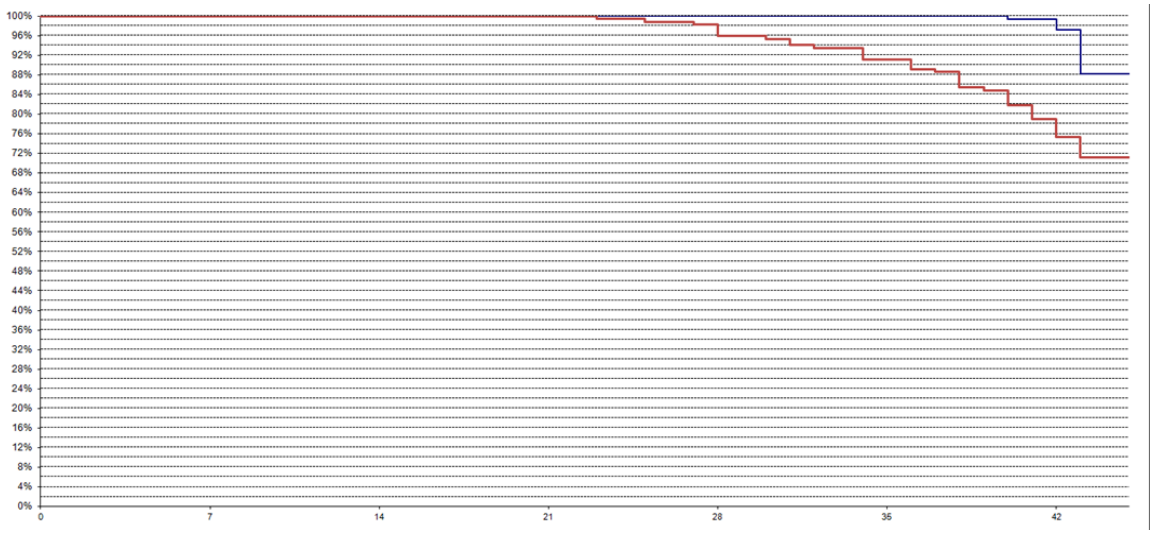
Evolution of the number of gametocyte carriers

After D7, positive gametocytaemia associated with asexual parasitaemia was identified at least once in 4 patients in the ASAQ group (2.6%) and in 25 patients in the CQ group (15.1%) from the PP population. This proportion was significantly higher in the CQ group compared to the ASAQ group (p <0.001). In patients without gametocytaemia at D0, the cumulative risk of developing gametocytaemia at D7, D14, D28 and D42 was approximately two-fold lower in the ASAQ group compared to the CQ group (p <0.001; logrank test). Qualitatively similar findings were obtained in the ITT population.

Cumulative risk of developing gametocytaemia PP population	ASAQ group (N = 70)	CQ group (N = 69)	*P*
Day 7	21.43% [13.52% - 33.00%]	49.28% [38.24% - 61.56%]	<0.001
Day 14	21.43% [13.52% - 33.00%]	49.28% [38.24% - 61.56%]	
Day 28	21.43% [13.52% - 33.00%]	50.72% [39.63% - 62.94%]	
Day 42	23.88% [15.21% - 36.32%]	56.21% [44.64% - 68.43%]	

Recurrence of malaria

The cumulative probability of recurrence-free survival was determined by Kaplan-Meier survival analysis. This was significantly higher in the ASAQ group than in the CQ group (p <0.001; logrank test). The median time to recurrence was 42 days in the ASAQ group and 38 days in the CQ group. Qualitatively similar findings were obtained when PCR-unadjusted recurrence was considered, as well as in the ITT population.



Cumulative probability of recurrence-free survival (PP population): Blue curve: ASAQ group; red curve: CQ group.

Evolution of haemoglobin levels

Contrary to what has been observed in African patients, serum haemoglobin levels were close to the lower level of normal (130 g/L) at baseline and at each study visit. No obvious differences between treatment groups were observed. Around half the patients in both groups had an abnormal serum haemoglobin level at each visit. None of these abnormalities were considered clinically significant. In the PP population, haemoglobin levels decreased between D0 and D7 by -4.0% (mean value) in the ASAQ group and by -0.9% in the CQ group. Between D0 and D28, they increased by 1.7% (mean value) in the ASAQ group and by 4.0% in the CQ group. Qualitatively similar findings were obtained in the ITT population.

Safety results: Treatment-emergent adverse events (TEAEs) were reported by 79 patients (41.6%) in the ASAQ group and by 85 patients (44.7%) in the CQ group. Serious adverse events were reported in 3 patients in the ASAQ group and AESIs by 8 patients in the ASAQ group and by 9 in the CQ group. No TEAEs leading to death or to treatment discontinuation were reported.

The only individual TEAEs to be reported in more than 5 patients in one or other of the 2 treatment groups (>2.5% of exposed patients) were sinus bradycardia, pruritus, insomnia, gastritis, oral herpes, alanine aminotransferase increased, pyrexia, and diarrhea. Most of the TEAEs were documented at similar frequencies in the 2 treatment groups. However, 2 AEs were reported in a higher proportion (by ≥2%) of patients in the ASAQ group compared to the CQ group. These were sinus bradycardia and diarrhea. On the other hand, pruritus, insomnia, pyrexia, and upper abdominal pain were more frequently encountered in the CQ group. In 5 patients in the CQ group, pyrexia may indicate treatment failure.

TEAEs (Preferred Term)	ASAQ group (N = 190)	CQ group (N = 190)
Sinus bradycardia	34 (17.9%)	20 (10.5%)
Pruritus	14 (7.4%)	21 (11.1%)
Insomnia	8 (4.2%)	12 (6.3%)
Gastritis	9 (4.7%)	6 (3.2%)
Oral herpes	8 (4.2%)	7 (3.7%)
Alanine aminotransferase increased	9 (4.7%)	8 (4.2%)
Pyrexia	1 (0.5%)	7 (3.7%)
Diarrhoea	5 (2.6%)	1 (0.5%)
Upper abdominal pain	None	4 (2.1%)

Five serious adverse events (SAEs) in 3 patients were reported during the course of the study, all in the ASAQ group (1.6% of patients in this group), and all corresponding to patients who required hospitalisation. These corresponded to 1 patient who presented an episode of uncontrollable vomiting and developed an extrapyramidal disorder after infusion of metoclopramide, 1 patient presenting gastritis and 1 patient with nausea and vomiting.

Adverse events of special interest (elevated hepatic enzymes or neutropenia) were reported in 17 patients.

AESIs (Preferred Term)	ASAQ group (N = 190)	CQ group (N = 190)
Any AESIs	8 (4.2%)	9 (4.7%)
Neutropenia	None	1 (0.5%)
ALAT increased (including one case of Herpes simplex infection and one case of chronic hepatitis infection in the ASAQ group and one case of hepatitis steatosis in the chloroquine group)	8 (4.2%)	8 (4.2%)
Pregnancy	1 (0.5%)	

For haematology parameters and blood chemistry parameters other than ALAT, no clinically significant abnormal values were observed and no safety signals detected. The ECG was monitored systematically in all patients aged 10 years and over at baseline, D2 and D28 and globally reviewed by the cardiologist. A higher proportion of patients in the ASAQ group presented sinus bradycardia on D2 and D28 compared to the CQ group, although whether this could be attributed to treatment was unclear. No cases of severe sinus bradycardia were observed and no clinical symptoms that could be a consequence of sinus bradycardia were reported. Regarding the QTc interval, no significant changes in QTcF were observed. No further significant ECG changes were observed in the study and it was concluded that both treatments presented a favourable ECG safety profile.
Issue date: 20-Feb-2015