Original Article

Efficacy of generic Artémether -Lumefantrine versus originator Artémether -Lumefantrine in the treatment of uncomplicated malaria in Libreville: randomized, single-blind controlled phase 3 trial

Mfoumou Essono AF[1,2*], Akendengue B[2], Tsoumbou Bakana G[1,2], Agbanrin AA[3], Pongui B[3], Mawili-Mboumba DP[2,3], Kouna Ndouongo P[1,2], Bouyou Akotet M[2,3], Boguikouma JB[1,2]

[1] University Hospital Center of Libreville, Gabon
[2] University of Health Sciences, Libreville-Gabon
[3] Biomedical Research Center in Infectious Pathologies and Associated Pathologies Nkembo hospital - Gabon

Keywords: *Sartem - L forte ; Coartem® ; Efficiency.*

Abstract

Background: In 2005, artemether -lumefantrine was approved as a first-line drug for the treatment of uncomplicated malaria in Gabon. Due to the high cost of the original drug, the National Health Insurance and Social Guarantee Fund (CNAMGS) promotes the prescription of generic medicines. Sartem - L forte from the GSEZ- Nkok Pharmaceutical Health laboratory is a generic manufactured in Gabon. This prospective equivalence study aimed to determine the effectiveness of Sartem - L forte compared to the innovative product Coartem®.

Methods: Participants aged 12 to 59 years with uncomplicated malaria were recruited and randomized to receive Sartem - L forte or Coartem ® as a control. They were expected to return to the study site for follow-up in accordance with World Health Organization recommendations. At each visit, thick and thin blood smears, thick dried blood films, hemoglobin concentrations, and temperature were performed and documented.

Results: Of 30 participants recruited, 22 met the inclusion criteria. The cure rate was, on day 3, 81.18% for Sartem - L forte and 100% for Coartem® and no early treatment failure was observed in both treatment arms. Both drugs showed good early clearance of parasites, with no participant experiencing significant peripheral parasitemia on day 3. Fever reduction was also excellent in both arms. No participant had a temperature >37.5°C on day 3.

Conclusion: The results of this study indicate that Sartem - L forte and Coartem® are equivalent and effective in the management of uncomplicated malaria in adolescents and adults in Gabon.

1. Introduction

Despite the efforts made in recent years to combat malaria, this disease remains the main endemic in the world[1,2]. Indeed, according to the latest report on malaria in the world, there were 247 million cases of malaria in 2021 compared to 245 million in 2020[1]. The number of malaria deaths decreased from 625,000 to 619,000 from 2020 to 2021, but remained higher than the estimated 568,000 deaths in 2019 [1]. The African Region of the WHO (World Health Organization) continues to bear a disproportionate share of the global malaria burden: in 2021, there were 95% of all malaria cases and 96% of deaths due to this disease. disease[1].

Faced with this problem, global health authorities have gradually modified the different control strategies to adapt them to the needs of the moment. This is how, for almost 20 years, Artemisinin-based Therapeutic Combinations (ACT) have become the treatment of choice in the management of uncomplicated *Plasmodium falciparum malaria* in malaria-endemic countries[1,2]. Gabon, like these countries, has adhered to this therapeutic strategy since 2005 with a therapeutic regimen which recommends the artemether-lumefantrine combination. in the management of uncomplicated malaria[3].

In Gabon, the cost of access to health care has improved significantly in recent years thanks to the creation of the National Health Insurance and Social Guarantee Fund (CNAMGS) in 2007. This insurance covers a large part of the economically weak Gabonese population. To reduce the costs of therapeutics, the CNAMGS promotes the prescription of generic drugs. It is with this in mind that many generics are added to the list of medications reimbursed by this insurance. On the Gabonese drug market, apart from the original drug, several generics of artemether-lumefantrine exist. These products are authorized without bioequivalence tests being necessarily carried out in Gabon. Thus, we decided to look at a generic artemether -lumefantrine manufactured in Gabon.

Will this generic give results similar to those of the originator in terms of effectiveness and tolerance? To confirm our hypothesis, we conducted a therapeutic equivalence trial by comparing the effectiveness and safety of generic artemether-lumefantrine to those of original artemether-lumefantrine in adolescents and adult subjects

***Corresponding Author:**

Mfoumou Essono AF

University Hospital Center of Libreville, Gabon

Email: *.annickfloremfoumou@gmail.com*

suffering from non-malaria. complicated. If the effectiveness and tolerance of the generic are comparable to those of the original drug, this will have a positive impact on the cost of treating uncomplicated malaria in Gabon.

2. Patients And Methods

2.1. Study population

These were patients with uncomplicated P. falciparum malaria, aged 12 to 59 years. All participants signed a form indicating their informed consent (or assent) to participation in the study. The Artemether 80 mg/ Lumefantrine 480 mg form being the one we chose for this study, we therefore targeted adolescents and adults. Subjects over 60 years of age were not included in order to minimize reactions that could be mistaken for adverse events and were in fact age-related. For this therapeutic equivalence trial in per-protocol analysis, the number of subjects to be recruited will therefore be 100 but the sponsor was only able to finance a treatment for 30 people.

2.2. Physical examination

All participants were clinically assessed. A standard medical examination was performed at baseline (day 0 before administration of the first dose). At the first visit (day 0), medical history was noted including medications taken before the visit and those in use, general characteristics (temperature, age, weight, blood pressure).

Tympanic temperature (thermo flash) was measured at different site visits. At baseline (on day 0 before administration of the first dose), and on D3. At home, on days 1, 2, 14, 28 or when necessary, participants were recommended to take it axillary, using a mercury thermometer with an accuracy of 0.1°C (which was given to them when they did not have it). If the result was lower than 36°C, the recommendation was to repeat the measurement. Weight was measured using an electronic device as well as blood pressure. The participants were then agreed on D3±1 day (2nd visit=V2), D28±1 day (3rd visit=V3). During these visits, a complete clinical examination was also carried out, the temperature was taken, the thick blood film taken and the possible adverse events were recorded.

2.3. Phone calls

Trial participants also received telephone calls from the investigation center on D0, D1, D2, D14 after initiation of treatment. These telephone calls made it possible to ensure good compliance with treatment, to identify possible adverse events, and to minimize the number of people lost to follow-up and premature withdrawals from the study.

2.4. Biological Analysis

Blood samples were taken in an appropriate room by a nurse assigned solely to this task.

The thick film (using the Lambaréné method) and a blood smear for the count of plasmodia were taken during screening, on day 0, to confirm compliance with the inclusion and exclusion criteria. For each participant, the thick film was also examined on day 3 or any other day if the participant returned spontaneously and if a parasitological re-evaluation was necessary. The labeling of the samples was anonymous. The screening number or the patient's inclusion number, the date and day of follow-up were noted either on the frosted part of the slide or on the glass using an indelible marker.

Other biological analyzes were also carried out in order to identify or not a possible criterion for non-inclusion in the study. These were: blood count, C- Reative protein (CRP), aspartate aminotransferases (AST) , alanine aminotransferases (ALT), uremia, creatinemia and pregnancy blood test.

Women of childbearing age were asked to take a serum pregnancy test before recruitment into the study because artemether - lumefantrine is contraindicated during the first trimester of pregnancy.

2.5. Drugs

Medicines directly involved in the protocol were the following: Sartem - L forte produced by La Santé Pharmaceutique de GSEZ-Nkok (Gabon). It came in the form of a blister pack of 6 tablets containing 80 mg of artemether and 480 mg of Lumefantrine. According to the instructions, the chemical composition would be similar to that of the original drug.

The original drug was Coartem ® under license from the pharmaceutical company Novartis. The medicine came in the form of a blister pack of 6 tablets containing 80 mg of artemether and 480 mg of lumefantrine.

All antimalarials were stored in a cool, dry place. All drug doses were administered under the supervision of a qualified agent designated by the principal investigator. Participants remained under observation for a period of 30 minutes after drug administration in case any adverse reactions occurred. Any participant experiencing vomiting during this period received the same dose of medication again and remained under observation for an additional 30 minutes. If vomiting started again, the participant was removed from the study and offered replacement treatment. The rest of the treatment was taken at home. The investigator called the participant on the telephone every day (at the appointed time) to ensure that the medication was actually taken.

2.6. Rescue treatments

If a participant vomited twice, they were taken to emergency care to receive parenteral treatment with injectable artesunate, as were those with signs of severe or complicated malaria. The artesunate dose was 2.4 mg/kg (0.24 ml of reconstituted solution for injection per kg of body weight) by intravenous (IV) injection at 0, 12 and 24 hours. After at least 24 hours (3 doses) of treatment with artesunate, switching to the oral route was considered.

Participants who met one of the criteria for therapeutic failure received treatment with quinine at a dose of 24 mg/kg/day for 7 days.

2.7. Other authorized treatments

A fever above 38°C was treated with paracetamol. However, instructions were given to the participants.

Adverse events requiring treatment were managed according to best available local practice. The treatments to treat adverse events linked to the drugs targeted by the study were noted in the patient's individual file: the name of the additional drug, its dosage and the date and time of administration.

2.8. Treatments not recommended

The use of herbal medicines was discouraged for the duration of the study, and participants were encouraged to come to the study site if they were feeling unwell, so that they could receive treatment.

2.9. Type of study

This surveillance study constitutes a 2-arm prospective evaluation of clinical and parasitological responses to treatment of uncomplicated malaria with direct observation of treatment. People with uncomplicated malaria, who met the inclusion criteria in the study, were recruited and treated with generic artemether-lumefantrine (Sartem - L forte) versus Artémether -Lumefantrine originator (Coartem ®), and did subject to monitoring for 28 days. Follow-up

consisted of a series of scheduled follow-up visits and telephone calls and clinical assessments and laboratory examinations. Based on the results of these assessments, patients were classified as having treatment failure (early or late) or adequate response.

This is a therapeutic trial of a generic drug, randomized, simple blinded and controlled by an originator drug to evaluate the equivalence on the negativation of the thick blood drop of the generic in uncomplicated malaria in adults. Participants were selected individually and then randomly received either the generic drug or the original drug. Depending on the medication they had received, they were divided into 2 arms (Sartem - L forte and Coartem ®).

2.10. Study site, period and duration

The study took place at the Estuaire - Mélen Regional Hospital (HREM) precisely at the Biomedical Research Center in Infectious Pathologies and Associated Pathologies (CREIPA). This is a sentinel center for the diagnosis and treatment of malaria in Gabon and authorization to recruit patients was obtained in advance by the director of HREM. The period selected for this study is 2 months and 15 days, from August 10, 2023 to October 25, 2023.

2.11. Inclusion, non-inclusion and exclusion criteria

Any participant aged 12 to 59 years old, man or woman, benefiting from health insurance, in particular CNAMGS, and meeting the following criteria: Weight ≥ 35 kg; An axillary or tympanic temperature ≥ 37.5°C; A positive thick drop; Parasitemia of between 500 and 200,000 trophozoites/µl of blood; Naïve to any treatment for malaria within 30 days prior to study inclusion; with informed and signed consent; A signed pregnancy test consent.

The non-inclusion criteria were as follows: Malaria severity criteria; Pregnant woman; Hemoglobin < 8g/dl; Mixed infestation or monospecific infestation with another Plasmodium species, detected by microscopic examination; Febrile condition due to illnesses other than malaria or other known chronic or serious underlying illnesses (heart, kidney or liver disease, HIV/AIDS); Regular taking of medications, which could interfere with the pharmacokinetics of the antimalarial drug; History of hypersensitivity to any of the drugs tested or used as replacement therapy, or contraindication to these drugs; Patient unable or unwilling to perform a pregnancy test.

The criteria for withdrawal from the study will be as follows for the per-protocol analysis: Refusal to continue the study; Movement of the participant outside the study area; Difficulty complying with the study protocol; Participation in another clinical trial and lost to follow-up;

2.12. Screening and recruitment

Patients with a febrile state (temperature > 35.5° C) or a recent history of fever were sought from outpatient consultations in the Emergency, Medicine and Pediatrics departments. Sequential numbers were assigned to all patients who met the recruitment criteria during screening; these patients were then subject to further evaluation by the principal investigator.

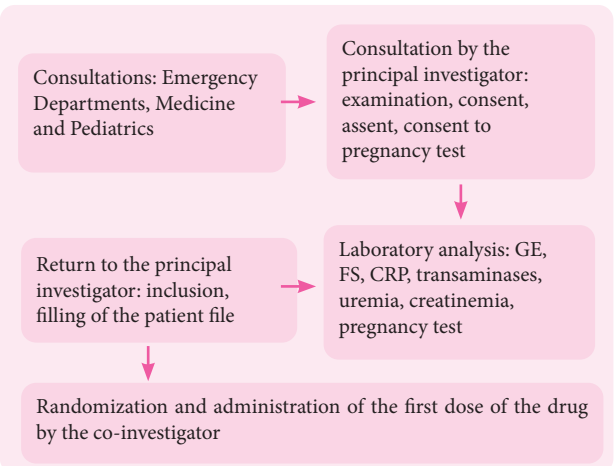
The screening form (Appendix 3) was used to record general information and clinical observations regarding each patient examined. If the patient met the clinical criteria, a search for parasitemia was carried out. If the patient met all the recruitment criteria, all the information relating to the study was explained to them through a leaflet that they kept in their possession. After these explanations, he asked her to give and sign her informed consent, consent to the pregnancy test for the woman of childbearing age and assent for the minor. The participant was then sent to the laboratory for other biological analyzes including blood count, CRP, transaminases (AST, ALT), uremia and creatinemia.

2.13. Randomization

Participants were included in the study by the investigator. They were assigned an identification number and then recorded using this number in the patient file. The treatment was assigned by drawing lots to one or the other of the 2 therapeutic groups. The draw, carried out by 2 investigators other than the principal investigator, was carried out from a basket containing 2 types of envelopes of different colors (white and yellow). The envelopes contained a white sheet with the name of the group (S or C) written on it. In the white envelopes, there was group S (Sartem arm - L forte) and in the yellow envelopes, group C (Coartem arm). Once the draw was made, the first dose of the drug was administered by the investigator and the box was given to the participant in the corresponding envelope. At the second visit (day 3 of treatment), the participant had the duty to return the empty medication blister in its envelope. These envelopes remained out of sight of the principal investigator until the end of recruitment.

2.14. Study drug administration protocol

The tablets were to be swallowed with a glass of water (twice-daily daily dose) for 3 days at mealtimes. On D0, the first dose was given by the investigator on site and the second dose 8 hours later. The treatment was continued for the next 2 days at home in unsupervised mode (in the morning at 8 am and in the evening at 8 pm).



GE: Thick Drop ; FS: Blood Smear; CRP: C-Reactive Protein

Figure 5: *Participants' circuit during the study*

2.15. Monitoring and evaluation criteria of the study

Participants were called on site on D3, D14 and D28 for a complete clinical examination and performance of a control GE. They also received telephone calls 8 hours after the first dose of the drug and every 8 am and 8 pm for the following 2 days to ensure treatment compliance and to record and evaluate adverse events. The telephone calls continued on D7, D21 in order to be able to objectively the appearance of late adverse events or detect symptoms of malaria reinfestation.

An individual file (Appendix 4) and a serious adverse event reporting form (Appendix 7) were used to record general information and clinical observations for each study participant. The consultation schedule, times for taking medications at home and taking temperatures were clearly explained and recorded on a sheet which was given to each participant.

A personal identification number (patient study number) was assigned to patients who met all criteria; they only received the treatment when the study was fully explained to them and they had freely given their consent. Anyone who decided not to participate in the study was examined, treated and monitored by the principal

investigator, in accordance with the standards of care established by the Ministry of Health.

Age was expressed in completed years. Sex was a binary qualitative variable (male, female), temperature in degrees Celsius (°C), parasite density in parasites per microliter (parasites/µl), side effects were a qualitative variable, CRP in milligrams per liter (mg/l) , transaminases (AST and ALT) in international units per liter (IU/l), uremia in millimoles per liter (mmol/l) and serum creatinine in micromoles per liter (µmol/l). The questionnaire included three sections, namely sociodemographic, clinical and paraclinical parameters.

2.16. Efficacy, tolerance and therapeutic compliance

The primary endpoint was the reduction in parasitemia by at least 90% after 3 days of treatment. The generic is considered as effective as the original drug by tolerating a difference in reduction of parasitemia of 5% with the original drug. The secondary endpoints were: the tolerance of the generic, determined by the low frequency of adverse effects, up to 28 days after initiation of treatment; the time for the fever to disappear on D1 , D2 and D3 after initiation of treatment.

The assessment of safety was the first secondary endpoint. It was based on the search for adverse effects during questioning (appendix 6) and during clinical examination. These were: abdominal pain, asthenia, cough, diarrhea, dizziness, fever, headache (headache), muscle and joint pain, loss of appetite, rash, nausea, vomiting .

Compliance with treatment was assessed at the 2nd visit (D3) after the start of treatment. The patient was considered compliant if all of the tablets contained in the box (secondary packaging) of the medication were consumed.

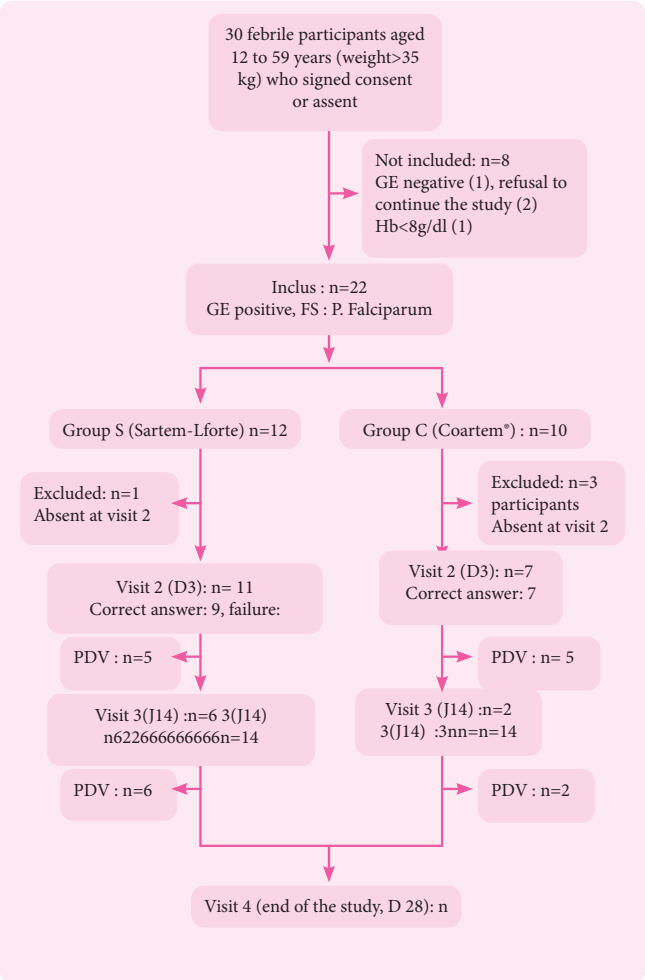
2.17. Ethical and legal aspects

The trial was conducted in accordance with the guidelines of the International Conference on Harmonization Good Clinical Practice and the principles of the Declaration of Helsinki. The protocol was approved by the National Ethics Committee and the regulatory authorities of our country. Informed consent was obtained from the participants. Participant data required for analysis was entered/ transmitted into a validated database and is stored in a secure location. The minimum retention period will be 15 years by default. In all cases, the principal investigator is responsible for the study data.

2.18. Statistical analysis

The data were entered into an Excel table then exported into RStudi software for analysis. The statistical analyzes consisted of the descriptive analysis of the study population: frequency and percentage for the qualitative variables and the means and standard deviations for the quantitative variables. The bivariate analysis consisted of comparing the means for the quantitative variables using the Wilcoxon-Mann Witheney test and for the qualitative variables using the Fisher exact test and Chi2. The significance threshold was set a priori at 5%. Only data from participants who had at least 2 visits were used.

Thirty participants consented to our study. After counting, the white envelopes were assigned to group S and the yellow ones to group C. Group S corresponded to the participants who received Sartem - Lforte and group C to those who received Coartem ®. Of the 30 participants who consented to our study, 22 had met the inclusion criteria (12 from group S and 10 from group C), 4 were lost to follow-up at the second visit (1 from group S and 3 from group C) . No participants were present at visit 4 (D28).



P: plasmodium ; GE: Thick Drop ; POV: Lost to sight; FS: Blood smear. Hb: Hemoglobin

Figure 4: *Flowchart of the study registration and follow-up procedure*

3. Results

3.1. Socio-demographic data

All participants in the study, both in the Sartem - L forte arm and in the Coartem ® arm, were of Gabonese nationality. The average age in the Sartem - L forte arm is 15.6± 4.3 years and that of the Coartem ® arm, 16.4± 5.3 years. There were 5 men out of 12 participants in the Sartem - L forte group and 3 out of 10 in the Coartem ® arm. The number of women was equal in both arms.

3.2. General settings

The general parameters of the participants at inclusion are presented in Table 1. The average temperature was 37.9 ±1.4°C in the Sartem - L forte arm . Systolic blood pressure averaged 114 mmHg in the Sartem - L forte arm and 111 mmHg in the Coartem ® arm. The mean diastolic blood pressure was 76.1 mmHg in the S group and 71.8 mmHg in the Coartem ® arm. The heart rate was 99.5 cycles/min in the Coartem ® arm. Eight out of 12 participants in the Sartem - L forte arm presented polyarthralgia and 70% in the Coartem ® arm had a lack of appetite at baseline.

Table 1: Distribution of participants according to general parameters

general settings	Sartem-Lforte 2 (40 mg) / 6 (480 mg) N=12	Coartem ® _ 2 (40 mg) / 6 (480 mg) N=10	p
Systolic BP (mmHg)	114 ±14.5	111.5 ±10.5	0.62
Diastolic BP (mmHg):	76.1 ±12.9	71.8 ±7.7	0.37
HR (cycles/min)	96.6 ±21.4	99.5 ±18.3	0.74
Temperature (°C)	37.9 ± 1.4	37.6±1.2	0.53
Asthenia: n (%)	12 (100.0)	10 (100.0)	
Polyarthralgia: n (%)	8 (66.7)	5 (50.0)	
Lack of appetite: n (%)	6 (50.0)	7 (70.0)	

PA: Blood Pressure; HR: Heart Rate; A: Artemether; L: Lumefantrine ; n: number of participants

3.2.1. Parameters at I

The average parasite density was 30450.6 parasites/µl in the arm which was to be treated with Sartem - L forte and 21552.3 parasites/µl in the arm which was to be treated with Coartem ®. The average hemoglobin level was 11.4 ± 0.9 g/dl in the Sartem - L forte arm compared to 10.9 ± 1.2 g/dl in the Coartem ® arm. The other biological parameters of the participants at study inclusion are presented in Table 2.

Table 2: Distribution of participants according to biological parameters at inclusion

Biological parameters	Sartem-Lforte 2 (40 mg) / 6 (480 mg) N=12	Coartem ® _ 2 (40 mg) / 6 (480 mg) N=10	p
Negative pregnancy test n (%)	7(58.3)	7(70)	
Uremia (mmol/l)	3.5±1.0	3.5±0.8	0.86
Creatinemia (µmol/l)	68.2±12.7	65.4±7.2	0.58
ASAT(IU/l)	24.4 ± 7.6	23.5±13.0	0.84
ALAT (IU/l): average	18.7±5.5	13.3	0.03
Hemoglobin (g/dl): average	11.4 ± 0.9	10.9±1.2	0.24
Parasite Density (parasite/µl)	30450.6	21552.3	0.61

ASAT: Aspartate aminotransferases; ALT: Alanine aminotransferases; 2 : Artemether; 6 : Lumefantrine

3.2.2. Clinical response

On D1, 2 participants in the Sartem - L forte arm were febrile and 3 in the Coartem ® arm. On D3 and D4, no participant had a temperature > 35.5°C (Table 3).

Table 3: Distribution of participants according to clinical response to Sartem - L forte treatment versus Coartem ® on D0, D1, D2 and D3 : temperature ≥37.5°C

	Sartem-Lforte 2 (40 mg) / 6 (480 mg) N=12	Coartem 2 (40 mg) / 6 (480 mg) N=10	p
	not(%)	not(%)	
Day 0 (n=22)	12(100.0)	10(100.0)	
Day 1 (n=5)	2(22.0)	3(30.0)	0.52
Day 2 (n=0)	-	-	
Day 3 (n=0)	-	-	

n: number of feverish participants;-: No participants; 2 : Artemether; 6 : Lumefantrine

3.2.3. Parasitological response

A total of 18 participants benefited from the second on-site visit, including 11 from the S Sartem - L forte arm and 7 from the Coartem ® arm. The parasitological response at 72 hours of treatment was adequate in 9 participants in the Sartem - L forte arm. The cure rate was 100% in the Coartem ® arm (Table 4). The parasitic stage found at FS in the 2 participants in the Sartem - L forte arm was the trophozooids for one and the gametocytes for the other. Their parasite densities were 140 and 250 parasites/µl of blood, respectively.

Table 4: Parasitological response (GE and FS) to treatment with Sartem - L forte versus Coartem ® on D3

	Sarten-Lforte (N=11)	Coartem ® A 40 mg/L 480 mg (N=7)	p
GE on D3: n (%)	2 (18.2)	-	0.49
FS on D3: n (%)			
Trophozooids	1 (8.3)	-	
Gametocytes	1 (8.3)	-	

n: positive number of participants; GE: Thick Drop ; FS: Blood Smear; -: No participants; A: Artemether; L: Lumefantrine

3.3. Adverse events

Two participants experienced adverse events and both were in the Sartem - L forte arm. It was abdominal pain on the one hand, which appeared on D2 of treatment and which disappeared on D5 of treatment with the administration of a painkiller, namely paracetamol (1gram three times a day). The second side effect was a hives-like skin rash, which appeared on day 1 of treatment and disappeared on day 5 on antihistamine (Loratidine 10 mg/day in one dose).

II.2.6. Participation in the second phase of the study.

Sartem - L forte arm were present at the second site visit and 7 from the Coartem ® arm. On D14, the participation rate was 50% in the Sartem arm and 20% in the Coartem ® arm. The overall participation rate in the study was 81.9% at the second visit (D3), 63.7% at the third visit (D14 by telephone). and no participation at D28 (Table 5).

Table 5: Distribution of populations according to participation in the study from D3 to D28

day	Sartem-Lforte At 40 mg/L 480 mg (N=12)	Coartem ® _ At 40 mg/L 480 mg (N=10)	Total
	not (%)	not (%)	Not (%)
D3	11(91.7)	7 (70)	18 (81.9)
D14	6(50)	2 (20)	8 (36.4)

n: number of participants; A: Artemether; L: Lumefantrine

4. Discussion

After the introduction of Artemisinin-based Therapeutic Combinations (ACT) as treatment of choice in the management of uncomplicated Plasmodium falciparum malaria in malaria endemic countries by the WHO associated with other methods of treatment prevention such as Thanks to insecticide- treated bed nets and indoor spraying, the prevalence of malaria has decreased in many countries[1]. Preserving the effectiveness of ACTs for the treatment of Plasmodium falciparum malaria is among the global public health priorities . The presence of fake and substandard medicines has been reported in many parts of the world, including sub-Saharan Africa[14]. The WHO has identified antimalarials as a group of medicines most at risk of being falsified or of substandard quality, due to high demand, particularly in areas of moderate to high endemicity[15]. Previous studies have reported the presence of poor and substandard antimalarial drugs in the Tanzanian market[14]. Regular monitoring and evaluation of the performance of generic antimalarials through therapeutic effectiveness studies are important for the fight against malaria.

The present study reports a prospective comparison of a generic Artémether - Lumefantrine, Sarten-Lforte to its originator, Coartem®. This is an antimalarial drug recommended as first-line treatment by the Gabonese authorities (PNLP). The comparison was made for their effectiveness and tolerance in the treatment of uncomplicated Plasmodium falciparum malaria in Gabon.

4.1. Prevalence

Thirty people with fever consented to our study. Among them, 24 had malaria, or 80% of cases. The prevalence in our study is high compared to studies previously carried out in Gabon (33.5% in 2021, 37.5% in 2020 and 29.6% in 2019)[16] and elsewhere (28%) notably in a systematic review etiologies of febrile states published in 2015[17]. This high prevalence is explained by the difficulty in the recruitment phase. Indeed, even after explanations of the principle of the study, several patients who presented hyperthermia were reluctant to participate in the study. The number of febrile states is therefore probably underestimated.

4.2. Socio-demographic parameters

4.2.1. Age

The study population was largely made up of adolescents, which explains the average age of the participants which was 15.6 years with a standard deviation of 4.3 years in the Sartem group - L forte and 16.4 years with a standard deviation of 5.3 years in the group. These data are in agreement with studies on malaria which target the adult population, particularly that of Mbouloungou . et al in Gabon, in 2017, which found an average age of 16 years with a standard deviation of 17 years in Gabon[8]. This is also the case (15.8±3.4 years) in a meta-analysis carried out in 2017 in Ethiopia[18].

4.2.2. Sex

Women were the majority in this study: 58.3% in group A and 70% in group B. This result is consistent with certain data in the literature, notably a therapeutic trial which was carried out in Tanzania. In this study which compared a generic Artémether – Lumefantrine (Artéfan) to its original product, 53.8% of the population were women in the Artéfan group and 44% in the Coartem ® group. The trend is rather the opposite in other studies found in the literature but these took into account the infant population: This is the case of the work of Adegbite et al in Gabon in 2019[19] and in Uganda, where the ratio varied depending on the region[20].

4.2.3. Nationality

All participants in this study were of Gabonese nationality. This result can be explained by the methodology of the study which wanted as one of the inclusion criteria affiliation to health insurance, in particular ACNAMGS which is a mutual insurance company which mainly covers Gabonese people.

4.3. Clinical and biological parameters at inclusion

4.3.1. Temperature

The average temperature of the participants in this study (37.9°C in the Sartem - L forte arm versus 37.6°C in the Coartem ® arm is similar to those that were found in Uganda in the 3 regions or study had been carried out namely: 37.5°C versus 37.6°C in Apac , 37.9°C versus 37.5°C in Mubende and 37.7°C in the 2 groups in Kamungu . This is a randomized trial which evaluated the effectiveness of Artesunate/ Amodiaquine versus Artemether / Lumefantrine for the treatment of uncomplicated malaria. Other data from the literature show slightly higher temperatures at the inclusion of participants in particular 38.4°C versus 38.5°C in a trial similar to our study[14] and 38.6°C versus 38.1°C in Lambaréné (Gabon) or the effectiveness, tolerability and safety of the Artemether -lumefantrine were studied compared to Artesunate- Amodiaquine for the treatment of uncomplicated *P falciparum malaria*[19]. Several participants in our study presented afebrile in consultation after self-medication with paracetamol, this is probably the origin the slight drop in temperatures compared to these other studies, particularly that of Gabon. But the temperature difference in the comparative groups remains negligible whatever the study considered.

4.3.2. Parasite density

In this study, the parasite density was on average 30450.6 trophozooids /µl in the Sartem - L forte group and 21552.3 trophozooids /µl in the Coartem ® group. This result is higher than that found by the study by Adegbite et al in Lambaréné (Gabon) in 2019. This work found an average parasite mass, upon inclusion of participants, of 13,772 trophozoites/µl of blood in a group and 17648 trophozoites/ µl in another. This discrepancy can be explained by the difference in the type of population in the two studies. Indeed, in this latest study carried out in Gabon in 2019 by Zoleko Manego And al on the parasite density of symptomatic P. falciparum malaria patients[21], it was demonstrated that the highest parasite density was present in schoolchildren and adolescents (47% and 18%). The results of this study suggest a shift in the risk of malaria, from very young children to children of school age, as suggested by the results reported by Mawili-Mboumba et al in 2013, namely that children over 5 years old would now become a population at risk of malaria[9]. This age group was the most represented in this study, so the work of Adegbite et al was targeted only on children (6 months to 12 years) just like that of Tanzania[14]. The parasite density for the latter was much lower (9730.93 parasites/µl in one group and 8754.75 parasites/ µl in another) and the population was also much younger (6 to 59 months).

4.3.3. Anemia

Anemia is a common complication of malaria regardless of the age of the patient or the region of infestation. It is hemolytic and correlates with the severity of the disease. The average hemoglobin level found in this study is 11.4 g/dl in the Sartem-Lforte group and 10.9 g/dl in the Coartem ® group. Severe anemia (hemoglobin level < 8g/dl) is a factor in the severity of malaria and was a criterion for non-inclusion of patients in the study; which can explain these relatively high averages. This result is consistent with other trials in the literature of the same design[14,19,20].

4.4. Therapeutic response

4.4.1. Clinical response

The disappearance of fever was exceptional for both Sartem - L forte and Coartem ® arms. On day 1 (24 hours after the start of treatment, only 2 participants in the Sartem - L forte group had a temperature >37.5° compared to 3 in the Coartem ® group . On days 2 and 3, no participant had a temperature > 37.5° C. This decrease in temperatures was close to that reported in several studies, notably that of Tanzania where there was only one participant with a temperature > 37.5° C in the Artéfan arm and absence of fever in all participants in the Coartem ® arm. These results are consistent with most data regarding the effectiveness of ACTs[17-19].

4.4.2. Parasitological response

According to the latest WHO guidelines, all patients who have received antimalarial treatment should be classified into one of the following categories: early therapeutic failure, late clinical failure, late parasitological failure or adequate clinical and parasitological response (Annex 2)[22]. Also, the effectiveness of Artémether Lumefantrine has been proven by numerous studies for several years[14,18-20,23]. However, no study evaluating the effectiveness and tolerance of one of its generics compared to the original drug has been carried out in Gabon. A similar study whose generic was Artéfan was carried out in Tanzania (published in 2019) and showed that Artéfan is equivalent to the innovative product Coartem® in the treatment of uncomplicated malaria with undetectable parasite density in both arms. This is also the case for several other studies which have integrated Artémether Lumefantrine in their protocol.

In this study, the therapeutic effectiveness of the generic antimalarial Sartem - L forte and that of the innovative product Coartem ® were compared. The early elimination of parasites for both drugs on day 3 (72 hours after the start of treatment) by microscopy was satisfactory in the Sartem - L forte arm (parasitemia present in 2 participants or 18.2% of cases) and excellent in the Coartem ® arm (no parasites /µl on D3). The parasitemia detected in these 2 participants was not high enough to speak of therapeutic failure. Early therapeutic failure (within 72 hours following the start of treatment) is defined by the WHO by the presence of one or more criteria, namely: signs of danger or serious malaria on day 1, 2 or 3, in the presence parasitemia; parasitemia on day 2 higher than that on day 0, whatever the axillary temperature; parasitemia on day 3 and axillary temperature ≥37.5°C; and parasitemia on day 3 ≥ 25% compared to the count on day 0[22]. Thus for one study participant, the proportion of parasitemia on D3/parasitemia on D0 (140/137900) was 0.1%. The reduction in parasitemia was therefore 99.9%. For the second case, this ratio (280/7443) was 3.8%, i.e. a reduction in parasitemia of 96.2%. This study therefore shows that Sartem - L forte is as effective as Coartem ® in the management of uncomplicated malaria in adolescents and adults but this therapeutic response is not statistically significant (p=. 0.49).

Resistance of P. species to artemisinin has been reported in East and South Asian countries[14], but not yet in Africa. According to the WHO, if 10% of study participants have peripheral parasitemia on day 3, this is an indicator of the emergence of artemisinin resistance to *Plasmodium species*[12]. The presence of non-significant peripheral parasitemia on day 3 in the Sartem - L forte arm and its absence in the Coartem arm may indicate the absence of strains of *P. falciparum* resistant to artemisinin in Gabon. The parasitic stages found on D3 in the patients were trophozooids for one and gametocytes for the other, in agreement with several other studies[18,20]. These are the different stages of the parasite cycle.

4.5. Adverse events

This study identified two cases of adverse events in the Sartem -L forte arm, namely abdominal pain and a urticaria-type hypersensitivity reaction. But neither required hospitalization. These events are side effects listed on the Coartem® leaflet and are also found in other studies which have evaluated the tolerance of Artémether Lumefantrine notably in Uganda[20] and Niger[23,24]. Generally speaking, when adverse events appear following treatment with Artemether -Lumefantrine , they are mild or moderate[23,24,25,26,27], which this study does not contradict. Artémether -Lumefantrine was therefore well tolerated in both arms. There were few adverse events in only one arm with a significant statistical difference (p 0.45 for urticaria and 0.55 for abdominal pain).

4.6. Limitations of the study

The limitations in this study are not negligible. It was designed to mimic the routine standard of care for simple malaria management in Gabon. In this approach, patients are given antimalarial medications with instructions to take the prescribed doses at home. Therefore, information on parasite density during days 1 and 2 after drug administration was not collected. Additionally, compliance with prescribed medications was based on patient, parent or guardian assessments, as well as taking home temperatures. Also, microscopy instead of molecular techniques, such as PCR, has been used to identify Plasmodium species. Therefore, the cure rates reported in both arms of the study are PCR uncorrected. Due to a lack of funding, blood samples could only be taken on days 0 and 3, which made this study incomplete (no participant came to visit the site on day 28 as this had been recommended to them). The interpretation of the results of this study must therefore be cautious, also taking into account its low power in relation to the small sample size.

5. Conclusion

The aim of this work was to compare the effectiveness and safety of a generic antimalarial (Artémether-Lumefantrine) to those of the original drug. The generic was Sarten-Lforte (Artémether 40 mg/ Lumefantrine 480 mg) and the original drug Coartem ® (Artémether 40 mg/ Lumefantrine 480 mg). The evaluation was carried out on adolescents and adults living in Gabon who presented with uncomplicated malaria. It appears that the 2 drugs are equivalent in both effectiveness and tolerance. Due to its low cost and availability (manufactured in Gabon), the use of Sartem - L forte should be advantageous compared to the relatively expensive innovator drug, Coartem . But the limitations of this study linked to a small sample, poor regularity of participants and a biased methodology compared to previous studies of the same size do not allow such conclusions to be drawn. Work will be continued, with improvement in methodology, according to WHO recommendations in therapeutic efficacy trials in uncomplicated malaria.

6. Suggestions

To the health authorities: Study the possibility of requiring therapeutic trials from pharmaceutical industries before granting a drug marketing authorization.

To patients suffering from malaria: Be fully compliant with the prescribed treatment. Adhere more to follow-up, whatever the illness, by respecting appointments.

Funding : This work does not receive any specific grant from public, commercial or associative funding agencies.

Acknowledgments : We would like to thank Service Edition Publication for correcting and proofreading this document.

Conflicts of interest : The authors have no conflicts of interest to declare

Abbreviations :

ACR : American College Rheumatology;
CHUL : Libreville Hospital Center;
CRP : C Reactive protein;
eGFR : estimated glomerular filtration spleen;
Hb : hemoglobin;
SLE : Lupus Erythematosus Disseminate;
THE : Lupus Erythematosus Systematic;
MCHC : Corpuscular hemoglobin concentration;
MCV : Mean Corpuscular Volume

References

1. **WHO.** World malaria report 2022. Geneva: World Health Organization; 2017 [In line] consulted on 24.10.2023 https:// www.who.int › world-malaria-report-2022

2. **Tinto H, Zongo I, Nikiema R, et al.** Study of the therapeutic effectiveness of Artesunate- Lumefantrine combinations versus Artemether-Lumefantrine in unsupervised administration in the treatment of simple Plasmodium falciparum malaria in Burkina Faso. Health Science 2012; 2:230

3. **National Malaria Control Program.** National guidelines for the management of malaria in Gabon, 2013.[In line] Accessed 19.1023 https://platform.who.int › docs › guideline

4. **Charline D.** Malaria in health on the net 2021[Online] consulted on 10/24/2023 https://www.sante-sur-le-net.com

5. **Pastor Institute.** Malaria 2021. [Online] consulted on 10/24/2023 https://www.pasteur.fr

6. **Maghendji-Nzondo S , Nzoughe H , Lemamy GJ *et al* .** Prevalence of malaria, prevention measures, and main clinical characteristics in febrile children admitted to the Franceville Regional Hospital, Gabon. Parasite 2016, 23:32

7. **Bouyou-Akotet MK, Mawili-Mboumba DP, Kendjo E *et al.*** Complicated malaria and other severe febrile illness in a pediatric ward in Libreville, Gabon. BMC InfectiousDiseases 2012;12:216

8. **Mbouloungou A, Koumba AA, Mombo JB *et al.*** Geography of Malaria in the Libreville-Owendo- Akanda region , Gabon. European Scientific Journal,2019,15(27):362-382 .

9. **Mawili Mboumba DP, Bouyou Akotet MK, Kendljo E *et al.*** Increase in malaria prevalence and age of at risk population in different areas of Gabon. Malaria journal 2013, 12: 3

10. **Gabon.Ministry of Health. National Health** Development Plan 2017-2021, Libreville 2013:28[Online]. Accessed on 24.10.2023 https://www.ilo.org › dyn › docs › GAB-111848

11. **Balaji SN, Deshmukh R, Trivedi V.** Severe malaria: biology, clinical manifestation, pathogenesis and consequences. J terminal vector Dis 2020; 57(1):1-13

12. **World Health Organization.** Efficiency test protocol therapeutic.[online]. Accessed 10/24/2023. https://cdn.who. int › template-protocol-for- tet

13. **Manase Kilonzi1 M, Omary Minzi O, Ritah Mutagonda R *et al.*** Comparison of malaria treatment outcome of generic and innovator's anti-malarial drugs containing artemether– lumefantrine combination in the management of uncomplicated malaria amongst Tanzanian children. Malaria Journal 2019, 18:133

14. **World Health Organization.** In developing countries, 1 in 10 medicines are substandard or falsified. Geneva 2017[En line]. https://www.who Accessed 10/17/2023

15. **Lendongo-Wombo JB, Oyegue-Liabagui SL, Biteghe -Bi-Essone JC *et al.*** Epidemiology of malaria from 2019 to 2021 in the town of Franceville, southeastern Gabon. Health public BMC 2022;22(1):2313

16. **Prasad N, Murdoch DR and Reyburn H.** Etiology of serious febrile illnesses in low- and middle-income countries: a systematic review 2015; 10(6):e0127962[pub med]

17. **Mohammed Biset Ayalew M.** Therapeutic efficacy of artemetherlumefantrine in the treatment of uncomplicated Plasmodium falciparum malaria in Ethiopia: a systematic review and meta-analysis yalew . Infectious Diseases of Poverty 2017; 6:157

18. **Adegbite BR, Edoa JR, Honkpehedji YJ *et al.*** Monitoring of efficacy , tolerability and safety of artemether–lumefantrine and artesunate–amodiaquine for the treatment of uncomplicated Plasmodium falciparum malaria in Lambaréné , Gabon: an open-label clinical trial. Malaria Journal 2019; 18:424

19. **Yeka A, Kigozi R, Conrad MD *et al.*** Artesunate/Amodiaquine versus Artemether/Lumefantrine for the treatment of uncomplicated malaria in Uganda: A Randomized Trial. The Journal of Infectious Diseases 2016;213:1134 –1142

20. **Zoleko Manego R, Koehne E , Kreidenweiss A.** Description of Plasmodium falciparum infections in central Gabon demonstrating high parasite densities among symptomatic adolescents and adults. Malaria Journal 2019; 18:371

21. **WHO.** Therapeutic efficacy test protocol. Geneva 2009. [Online] consulted on 10/20/2023

22. **Muhindo MK, Kakuru A, Jagannathan P *et al.*** Early parasite clearance following artemisinin-based combination therapy among Ugandan children with uncomplicated Plasmodium falciparum malaria.Malaria Journal 2014; 13:32

23. **Ibrahima I, Laminou M, Adehossi E.** Study of the therapeutic effectiveness and tolerance of artemether – lumefantrine and artesunate – amodiaquine in Niger. Bull. Soc. Pathol . Exot . 2020; 113:17-23 ·

24. **Egunsola O Kazeem and Oshikoya KA.** Comparative safety of artemether-lumefantrine and other artemisinin-based combinations in children: a systematic review. Malaria Journal 2013; 12:385

25. **Ibrahim ML, Sadou F, Daou M *et al.*** Comparison of the therapeutic effectiveness and tolerance of Arthemether-Lumefantrine and Artesunate- Amodiaquine combinations in Niger. Mali Medical 2016; 31(1)

26. **Whegang Youdom S, Chiabi A , Basco LK.** Monitoring the effectiveness and safety of artemisinin-based combination therapies: review and network meta-analysis of antimalarial therapeutic efficacy trials in Cameroon. Drugs in R&D 2019.