

## EFFICACY AND ACCEPTABILITY OF ORAL ARTEMETHER (ARTEMOS™) FOR THE TREATMENT OF ACUTE UNCOMPLICATED MALARIA IN GHANA

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### SUMMARY

We studied the efficacy and acceptability of an oral artemether, Artemos™ for the treatment of uncomplicated *Plasmodium falciparum* malaria in adults attending outpatient clinic at the Navrongo War Memorial Hospital. A total of 128 patients were recruited, treated and followed up on days 1,2,3,5,7 and 14 to document changes in their treatment outcomes (resolution of clinical signs and symptoms, and parasite clearance). Of the 118 patients who completed the study, 97.5% (95% CI 92.7, 99.5) had adequate clinical response. The proportion of patients having complete parasite clearance on days 5,7 and 14 were 93.2%, 95.8% and 94.2% respectively. There was no significant difference in treatment outcome in both intention to treat and evaluable data analysis. Acceptability of Artemos™ was supported by the absence of vomiting during and after drug ingestion. There were also no reported adverse effects after drug treatment and follow-ups. Artemos™ is acceptable and has a very high cure rate against acute *P. falciparum* malaria in Ghana.

**Keywords:** Efficacy, acceptability, oral artemether, acute malaria.

### INTRODUCTION

Increasing spread of resistance to the existing frontline antimalarial drugs; chloroquine and sulfadoxine-pyrimethamine in Ghana poses one of the greatest challenges to the malaria control strategies<sup>1,2,3</sup>. Despite this, prompt and effective treatment will remain the mainstay of malaria control until perhaps malaria vaccines become a reality<sup>4</sup>. In resource-poor, malaria-endemic countries, lack of comprehensive information on antimalarial drugs efficacy often results in sub-optimal antimalarial treatment or policy change based on limited data, often with mixed successes<sup>5</sup>. Relevant research is therefore a necessity to inform policy and practice. Currently, the artemisinin and its deriva-

tives are novel drugs with most rapidly acting antimalaria activity yet known, they are effective in treating malaria both in children and adults and against all forms of human plasmodia<sup>6</sup>. The artemether derivative has good solubility in lipids as well as aqueous media with quick tissue penetration, fast onset of action and rapid parasite clearance through the action of its endoperoxide ring. It has the ability to reduce the gametocyte carriage rate and hence reduce disease transmission<sup>7-9</sup>.

Several oral artemether generics are in Ghana, however a new formulation in soybean oil and soft gel capsule (Artemos™)<sup>10</sup> is purported to be very effective; a high cure rate, easy to swallow, no bitter or nauseating taste and increased compliance. To determine its efficacy and as a potential component of future malarial combination treatment in Ghana, we evaluated Artemos™ in patients with acute uncomplicated falciparum malaria. To explore acceptability we analysed by "intention-to-treat" and by "evaluable" to compare the clinical and parasitological cure rates, and resolution of clinical signs and symptoms.

### METHODS AND MATERIALS

#### Study Site

The study was carried out at the outpatient department of the Navrongo War Memorial Hospital (NWMH) located in the Kassena-Nankana District (KND) of Ghana from May 2003 to December 2003. The site was chosen based upon its malaria endemicity and quantified epidemiology<sup>11,12</sup>, and regularly updated demographic surveillance system<sup>13</sup>. The district is semi-arid, has a mixture of rural and urban communities and an estimated population of 151,000 people<sup>14</sup>.

#### Study design, recruitment and sampling

Consecutive patients presenting with symptoms suggestive of acute uncomplicated falciparum malaria and a positive blood smear at the NWMH

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were referred to the study team after individual informed consent has been obtained and patient assessed for eligibility using the following study selection criteria: age over 14 years, *Plasmodium falciparum* mono-infection of density  $\geq 200$  asexual parasites/ $\mu\text{L}$ , axillary temperature  $\geq 37.5^\circ\text{C}$  and/or history of fever in the previous 48 hours, absence of signs and symptoms of severe and complicated malaria, absence of known allergy to drugs, provision of informed consent and continuous residency in KND for the two weeks' following treatment with study drugs. Pregnant women were exempted from this study, so were children who were 14 years of age or below and those who were unable to swallow the drug. Recruited patients were interviewed about their symptoms and a physical examination was performed; weight and axillary temperature measured using electronic weighing scale and thermometer respectively. The participants were consecutively recruited until the required sample size that was based on the expected cumulative treatment failures by day 14 was obtained. For a population of 151,000 people given a worst treatment failure of 4.5-10% at 95% confidence level, the number of cases required will be 114. Adjusting for 10% withdrawals, and loss to follow ups, the number required was estimated at 130 cases.

#### Drug administration and follow-up

Enrolled patients were treated with artemether given orally in the standard regimen consisting of 80mg (2 capsules) loading dose followed by 80mg in 8 hours and 80mg daily for 4 days. Initial dose was given at the hospital under the direct supervision of a study nurse and the rest at home under supervision of a field assistant. Patients were always observed for at least 30 minutes after each drug ingestion. Those who vomited the drug once within thirty minutes had repeated dose and those who vomited twice were withdrawn and given parenteral medication. All treatment failures and infection on day 14 were alternatively treated. Paracetamol was permitted for the control of pain and fever during the study period. There were active follow-ups for all study participants on days 1,2,3,5,7 and 14.

#### Clinical and laboratory assessment

On each follow-up day, participants were evaluated clinically and data collected on signs and symptoms. Thick and thin blood films were made, (thin film fixed with methanol) and both thin and thick films stained with giemsa were examined on day 0, or 5,7, and 14 for parasites. Parasite density was estimated as the number of parasites per 200

leucocytes on a thick film, assuming a total leucocyte count of 8,000 per micro-litre of blood. As an in-built quality control measure ten percent of all slides were randomly selected and assessed by a second independent microscopist. Two hundred thick film fields were always examined at X1000 magnification before assigning a negative result. Haemoglobin levels were estimated using an automated haemocue machine on days 0 and 14. The primary endpoint was treatment failure or day 14 adequate clinical response as defined for anti-malarials by World Health Organization (WHO 2002). Secondary endpoints were parasite and fever clearance times. Study completion was reaching a primary endpoint and necessary follow-ups.

#### Data management and analysis

A structured case record form was used to capture all data, double entered and verified. Analysis for treatment outcomes involved two processes: "intention-to-treat" using all subjects who took at least one dose and the "evaluable" analysis using those subjects who completed the study. Point and interval estimates using proportions, means, medians and confidence interval were calculated for the baseline demographic characteristics, relevant signs and symptoms and treatment responses. Also proportions and 95% confidence intervals of parasitaemia levels on days 5, 7 and 14 were estimated.

#### Ethical issues

Risks compared to the benefits in the study were minimal. Potential risks included pain and blood loss on the finger and infection of the fingers during laboratory tests. Benefits included enhanced clinical care, free treatment during study participation and follow-up, and benefit to future generation. These notwithstanding, individual informed consents were obtained and approval sought from the institutional review board.

## RESULTS

#### Baseline characteristics

Of the total 480 patients who were screened, 175 were positive for *Plasmodium falciparum* parasitaemia and 128 satisfied the study selection criteria. Fifty seven percent (73/128) of those enrolled were females. The mean age of the study participants was 29.6 years (range 15-75) while the average weight was 56.8 kilograms (SD 14.6). The proportion of patients presenting with axillary temperature of  $37.5^\circ\text{C}$  or higher was 26.6%. The mean blood haemoglobin and geometric mean parasite density were 13.1g/dl (SD: 2.17) and 897 (Range: 200-120000) respectively (Table 1). The frequencies of symptoms reported at enrolment

were headache 91.4% (85.1, 95.6), fever 73.4% (64.9, 80.9), dizziness 46.7% (37.6, 56.0), myagia 44.5% (35.7, 53.6), abdominal pains 34.4% (26.2, 43.3) and vomiting 18.0% (11.7, 25.7).

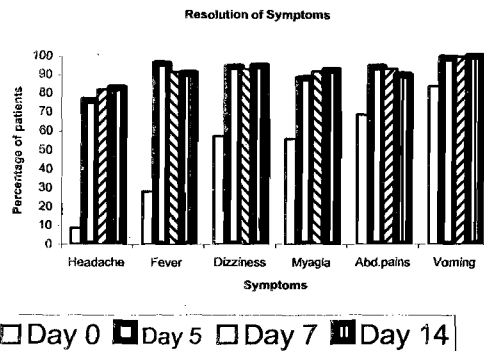
(Figure 1). No significant difference in symptoms or signs between the “intention-to-treat group” and the “evaluables” group was detected.

**Table 1** Baseline characteristics of the study participants

Variables	Intention-to-treat (n=128)	Evaluables (n=118)
<b>Age (years):</b>		
Mean (SD)	29.6 (12.6)	28.9(12.1)
<b>Sex:</b>		
Females, %	57.0	57.6
<b>Weight (kg):</b>		
Mean (SD)	56.8(14.6)	55.8(14.5)
<b>Temperature (°C):</b>		
≥37.5 (95% CI)	26.6(19.1,35.1)	22.9(15.6,31.5)
<b>Haemoglobin (g/dl):</b>		
Mean (SD)	13.1(2.17)	13.0 (2.2)
<b>Geometric mean parasite density (µl):</b>		
Range	897 (220-120000)	913 (200-120000)

**Treatment outcome**

The study completion rate was 92.2% (118/128). By intention to treat analysis 89.8% (115/128) had adequate clinical response and 90.6%, 93.7% and 87% respectively had complete parasite clearance on day 5,7 and 14 (Table 2). Per evaluable analysis 97.5% (115/118) had adequate clinical response and 94% (111/118) had complete parasite cure by day 14. The proportion of patients having complete parasite clearance on days 5 and 7 were 93.2% and 95.8% respectively (Table 2). Three patients failed treatment; one was on day 7 and the other two on day 14.



**Figure 1** Resolution of presenting symptoms by day of study

**Table 2** Clinical and parasitologic outcomes of treatment

	Intention-to-treat (n=128) % (95%CI)	Evaluables (n=118) % (95%CI)
<b>Treatment outcomes</b>		
Study completion rate	92.2 (86.1, 96.2)	-
Adequate clinical response	89.8 (83.2, 94.5)	97.5 (92.7, 99.5)
<b>Parasite clearance</b>		
Day 5	90.6 (84.1, 95.1)	93.2 (87.0, 97.0)
Day 7	93.7 (88.0, 97.3)	95.8 (90.3, 98.6)
Day 14	86.7 (79.5, 92.1)	94.1 (88.1, 97.6)

**Symptoms resolution**

All the presenting symptoms at enrolment regressed significantly during follow-up, with no new reported sign, symptom or adverse event

**Withdrawals**

About 8% (10/128) of patients were withdrawn; two patients gave wrong contact addresses, six travelled outside the district, one developed pneu-

monia and one withdrew her consent. All withdrawals were assigned an outcome of treatment failure in the intention to treat analysis.

## DISCUSSION

Resistance of *Plasmodium falciparum* to drug therapy remains a problem despite the availability of wide selection of antimalarial drugs. Though the enthusiasm of using artemisinin-containing combination (ACT) therapy to treat *falciparum* malaria is necessitated<sup>15</sup>, the reality of using these in most endemic countries has to do with the problem of availability, affordability and effectiveness<sup>16</sup>. It has therefore been suggested that anti-malarial policy be country-oriented and take into account factors like parasite distribution, prevailing health care systems and their logistics and drug resistance, availability, cost and compliance<sup>17</sup>. All should be geared at reducing disease burden within the limits of sustainable antimalaria drug policy.

We have sought in this study to provide evidence on the efficacy and acceptability of widely used oral artemether (Artemos<sup>TM</sup>) in Ghana. The medicine was found in this study to be efficacious, in support of other reports<sup>18,19</sup>; resulting in adequate clinical response of 97.5% by day 14 post-treatment. This compared to other front line anti-malarials means that this drug did not adversely affect study participants in terms of treatment outcomes<sup>1,2,3</sup>.

The parasite clearance rate obtained in this study is comparable to similar studies using artemisinin derivatives in other endemic areas<sup>18,19,20</sup>. None of the patients vomited the drug during ingestion, and no adverse effect was elicited during treatment or follow-up.

It must however be stressed that treatment duration over five days raises some concern about compliance in the field. Patients who get well earlier may not complete the full treatment course and given that the artemisinins have short half-life, the risk may be resurgence of infection and clinical malaria. It is therefore desirable to explore the possibility of shortening the treatment duration in order to ensure maximum compliance during routine use. Therefore the current move in prolonging the useful lifespan of antimalarials through the use of artemisinin combination therapy over a shorter period could be the way forward<sup>15</sup>. It may therefore be necessary to explore the possibility of using artemos<sup>TM</sup> in combination with other commonly used antimalarials in Ghana.

In conclusion, Artemos<sup>TM</sup> has a high clinical cure rate, rapid parasite clearance and is tolerable. Such effective and tolerable malaria treatment will help increase cure rate, slow down development of resistance through rapid parasite clearance and help reduce overall malaria transmission if used appropriately.

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