2000

A Randomized Controlled Trial of Artemotil (B-Arteether) in Zambian Children With Cerebral Malaria

Philip Thuma  
*Messiah College, pthuma2@jhu.edu*

G. J. Bhat

G. F. Mabeza

C. Osborne

G. Biemba

*See next page for additional authors*

Follow this and additional works at: [https://mosaic.messiah.edu/bio_ed](https://mosaic.messiah.edu/bio_ed)

[Part of the Biology Commons](https://mosaic.messiah.edu/bio_ed)

Permanent URL: [https://mosaic.messiah.edu/bio_ed/154](https://mosaic.messiah.edu/bio_ed/154)

**Recommended Citation**

[https://mosaic.messiah.edu/bio_ed/154](https://mosaic.messiah.edu/bio_ed/154)

Sharpening Intellect | Deepening Christian Faith | Inspiring Action

Messiah College is a Christian college of the liberal and applied arts and sciences. Our mission is to educate men and women toward maturity of intellect, character and Christian faith in preparation for lives of service, leadership and reconciliation in church and society.
Authors

This article is available at Mosaic: https://mosaic.messiah.edu/bio_ed/154
A RANDOMIZED CONTROLLED TRIAL OF ARTEMOTIL (β-ARTEETHER) IN ZAMBIAN CHILDREN WITH CEREBRAL MALARIA

PHILIP E. THUMA, GANAPATI J. BHAT, G. FUNGAI MABEZA, CONNIE OSBORNE, GODFREY BIEMBA, G. M. SHAKANKALE, PIERRE A.M. PEEETERS, BEREND OOSTERHUIS, CHARLES B. LUGT, AND VICTOR R. GORDEUK

Department of Natural Sciences, Messiah College, Grantham, Pennsylvania; Department of Paediatrics and Child Health, University of Zambia School of Medicine, University Teaching Hospital, Lusaka, Zambia; Macha Hospital Malaria Research Institute, Choma, Zambia; NV Organon, Oss, The Netherlands; Pharma Bio-Research International BV, Zuidlaren, The Netherlands; ARTECEF BV, Maastricht, The Netherlands; Center for Sickle Cell Disease, Howard University, Washington, D.C.

Abstract. The efficacy and safety of intramuscular artemotil (ARTECEF) was compared to intravenous quinine in African children with cerebral malaria. This prospective block randomized open-label study was conducted at two centers in Zambia. Subjects were children aged 0 to 10 years of age with cerebral malaria and a Blantyre Coma Score of 2 or less. Ninety two children were studied; 48 received artemotil and 44 quinine. No significant differences in survival, coma resolution time, neurologic sequelae, parasite clearance time, and fever resolution time were seen between the two regimens. Rates for negative malaria smears one month after therapy were similar in both groups. Artemotil was a well-tolerated drug in the 48 patients in this study. It appears to be at least therapeutically equivalent to quinine for the treatment of pediatric cerebral malaria. It has the advantage of being able to be given intramuscularly once daily for only five days.

INTRODUCTION

Malaria continues to be a major cause of childhood morbidity and mortality in sub-Saharan Africa, and with the increasing resistance of Plasmodium falciparum to standard drugs, effective new drugs to treat malaria and its complications are urgently needed. One promising group of drugs is derived from the plant Artemisia annua (qinghaosu) in 1972, various compounds have been developed by chemical modification; four of these have now reached the stage of pharmaceutical development for use in humans. One of these compounds, a semi-synthetic beta-ethyl ether derivative of artemisinin originally known as β-arteether, but now renamed artemotil (ARTECEF), has been developed collaboratively. The purpose of this program was to provide an alternative drug for the treatment of severe malaria, especially in areas where resistance is developing to intravenous quinine, the standard treatment for cerebral malaria. Using public funds for much of the drug’s development, it was anticipated that the final cost of any registered drug would be within the financial reach of those in the poorer and less developed countries of the world.

Following pre-clinical studies, artemotil was formulated in a sesame oil base for use as an intramuscular injection. Phase I studies of the drug in healthy adult volunteers in The Netherlands demonstrated its tolerability, safety, and pharmacokinetics (Jonkman JHG and others, unpublished data). Phase II studies in Thai adults with uncomplicated and severe malaria showed safety and efficacy when used over a five-day period with an initial loading dose (Peeters PAM and others, unpublished data). Subsequently, a Phase III, multicenter, open label, randomized comparative efficacy study was proposed in African children with cerebral malaria. The primary objective of the study was to compare the efficacy of intramuscular artemotil versus intravenous quinine in the treatment of cerebral malaria in children in terms of survival. Secondary objectives included comparison of other indicators of treatment response such as parasite clearance time (PCT), fever clearance time (FCT), and coma recovery time (CRT). The presence of parasites at the 7th, 14th, 21st and 28th day post-treatment visits, and prevalence of neurologic sequelae were also to be determined. In addition, the study was designed to assess safety and tolerability of the regimens. This report presents the results of this Phase III study from two of the three centers that studied this drug in African children with cerebral malaria.

MATERIALS AND METHODS

The study was conducted in accordance with the rules of Good Clinical Practice and in compliance with the Declaration of Helsinki revised in 1989. It was approved by the Research and Ethics Committee of the University of Zambia (Lusaka, Zambia) and the Secretariat of the Committee for Research Involving Human Subjects, World Health Organization (Geneva, Switzerland). Informed written consent for all participants was obtained from the parent or parents. The project was undertaken at two centers in Zambia located in communities in which malaria is endemic; the Macha Mission Hospital near Choma and the University Teaching Hospital in Lusaka. The study was monitored at both sites by Pharma Bio-Research International, B.V. (Zuidlaren, The Netherlands), contracted as the study and safety monitor.

Enrollment and treatment. The study was carried out between January 1996 and May 1997. Children aged 0–10 years presenting to either hospital with asexual P. falciparum parasitemia and a Blantyre coma score of 2 or less with no other cause for coma (normal cerebrospinal fluid, normoglycemic, more than 30 minutes since last convulsion) were eligible for enrollment. Patients were excluded if there was a prior history of any chronic illness, a clinical condition compatible with chemical intoxication from traditional medicine, or black water fever (frank hemoglobinuria). Eligible patients were then assigned a treatment group by opening a sealed coded envelope that contained the results of a computer-generated block randomization schedule. Baseline as-
sessments were performed including a complete physical examination, cerebrospinal fluid analysis, ECG, complete blood count, glucose, renal and liver function tests, urinalysis, and blood culture. Following Standard Operating Procedures for all patients, each child was initially given intravenous physiologic saline 10–15 mL/kg over 30 minutes for rehydration, intramuscular phenobarbitone 10 mg/kg for seizure prophylaxis, and whole blood (screened for HIV and Hepatitis B) 15–20 mL/kg over 4 hours if the hematocrit was less than 15%. Depending on the randomization code, patients were given either 5 days of intramuscular artemotil with an initial loading dose of 3.2 mg/kg and subsequent daily doses of 1.6 mg/kg or intravenous quinine dihydrochloride using a loading dose of 20 mg/kg in 5% dextrose over 4 hours followed by 10 mg/kg in 5% dextrose given over 2 hours every 8 hours. Treatment with oral quinine sulfate (10 mg/kg every eight hours) was commenced instead of the intravenous quinine when the patient was able to take oral medicine and had received a minimum of three intravenous doses. The quinine therapy was continued for a total of 7 days. Patients were treated using established guidelines with intensive nursing care including the determination of vital signs, coma score, and peripheral glucose every four hours with malaria smears every eight hours.

Assessment and laboratory studies. The primary response variable was survival rate. Secondary response variables were coma recovery time (CRT), defined as the time at which a Blantyre coma score of 5 was first attained and maintained for 24 hours; fever clearance time (FCT) defined as the time at which the first axillary temperature of ≤37.5°C was recorded preceding a 24 hour period in which the temperature did not exceed this level; and parasite clearance time (PCT) defined as the first negative malaria smear with no subsequent positive smears in the following 24 hour period. Patients were assessed on a twice-daily basis with a detailed physical and neurological examination and a daily detailed symptom review to determine any adverse effects of the drugs. Hematological and biochemical parameters were assessed on Days 0, 3, and 7. Following discharge at Day 7, patients were seen at weekly intervals up to Day 28 for physical and neurological exams, hematological and biochemical tests and a review of symptoms.

Peripheral smears for parasite quantification were obtained from a fingerstick sample of blood from which both a thick and thin smear were made on clean glass slides. The slides were coded, stained with Giemsa stain and read in a blinded fashion by two skilled microscopists. Results were determined independently by counting and calculating the percentage of parasitized red blood cells on a thin smear. If parasitemia was less than 1%, the number of asexual parasites per 200 white blood cells on a thick smear were counted. The results from the two microscopists were averaged and multiplied by the appropriate red blood cell or white blood cell count to determine the parasite density per microlitre of blood. Full blood count was determined by an automated counter (Cobas Micros, Roche Diagnostics, RSA) and biochemical parameters by using spectrophotometric kits (SIGMA Chemical, St. Louis, MO) with a spectrophotometer (Spectronics 20D, Milton Roy, NY). ECG was determined before the start of therapy and on the last day of therapy.

**Statistical analysis.** Malaria parasite concentrations showed a log normal distribution and were logarithmically transformed for statistical analysis. Data analysis was performed with the Systat 7.0 (SPSS Inc., Chicago, IL) statistical program using Student’s t-test for parametric and Mann-Whitney U test for non-parametric continuous data and Fisher’s exact or Pearson’s chi-square test for proportions. All tests were two-sided. Kaplan-Meier plots were determined for primary and secondary variables. A logistic regression model for the effect of treatment on survival was developed using LogXact 2.1 (SPSS, Inc.), by first examining the effect of the individual baseline variables on mortality. Those that had a significance level of <0.1 were then incorporated into a multivariate model, followed by a stepwise procedure removing all covariates that no longer had a significance level <0.1 in the multivariate model.

The original multicentre study was designed to demonstrate a lack of difference in the survival rate among artemotil recipients compared to recipients of the standard quinine treatment. A survival rate of at least 85% was considered the approximate survival rate in children with cerebral malaria who receive standard treatment. Based on this assumption, we planned to recruit a total of 480 patients assuming an estimated rate of 15% withdrawals and post-enrollment exclusions.

**RESULTS**

A total of 95 children were enrolled in the study at the two Zambian sites; 46 at the rural Macha Mission Hospital and 49 at University Teaching Hospital in Lusaka. As shown in Figure 1, the three who died before therapy was begun were excluded from analysis, leaving 44 in the quinine group and 48 in the artemotil group. The comparison of baseline clinical and demographic variables between those who received quinine and those who received artemotil showed adequate randomization (Table 1). Although children randomized to the quinine group had a significantly increased rate
of seizures before admission as well as higher mean baseline parasitemia counts, other indicators of more severe malaria were not more common in the quinine group. Children at the rural hospital were more likely to be younger and sicker with higher parasite counts than those at the urban hospital but were adequately randomized between the two drug study groups.

**Survival rates.** Table 2 shows survival rates for patients from both centers and for the combined treatment groups. There was no difference in survival rates between the two treatment groups. Those children receiving treatment with quinine had a survival rate of 80% (95% C.I., 67% to 92%) while those receiving artemotil had a survival rate of 79% (95% C.I., 67% to 91%) ($P=0.964$). Figure 2 demonstrates the remarkable similarity of the Kaplan-Meier survival curves between artemotil and quinine. A logistic regression model was developed with stratification by study site using covariates of age, history of seizures, log of malaria parasites at Time 0, and duration of coma prior to treatment. With this model, the adjusted odds ratio for death in those receiving artemotil was 0.89 the odds in the quinine group (95% C.I., 0.3 to 3.0, $P=0.96$).

**Other indicators of efficacy.** Secondary variables for this study were PCT, FCT, and CRT among survivors. Results are shown in Table 3. For 9 survivors (6 receiving artemotil and 3 receiving quinine), coma resolution times could not be calculated due to persistent severe neurologic sequelae lasting for more than 7 days. For these patients, the coma recovery time was censored at 168 hours and this result was used for statistical analysis purposes. One patient did not have adequate recording of parasite counts to enable determination of a PCT and two patients had no fever after admission, thus preventing calculation of FCT. While those treated with quinine had a shorter mean CRT (44 hours versus 61 hours) and a shorter mean PCT (34 hours versus 50 hours) neither of these were statistically significant differences. The mean PCT was only marginally different (not significant), being 57 hours for the quinine treatment group and 53 hours for the artemotil treatment group.

Parasite clearance was also evaluated by graphing the percent change in parasites from the start of therapy and calculating 50% and 95% clearance times for each patient. The mean 50% clearance time was similar for both treatments: 14.9 hours for quinine and 15.4 hours for artemotil. The mean 95% clearance time was 31.9 hours for quinine and

---

**Table 1**  
Baseline characteristics of study patients (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Quinine</th>
<th>Artemotil</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>44</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Female (%)</td>
<td>17 (39)</td>
<td>28 (58)</td>
<td>0.770</td>
</tr>
<tr>
<td>Age in months</td>
<td>39.5 ± 21.8</td>
<td>46.9 ± 27.28</td>
<td>0.152</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>12.0 ± 3.4</td>
<td>12.8 ± 4.3</td>
<td>0.353</td>
</tr>
<tr>
<td>Onset of coma before therapy (hr)</td>
<td>15.5 ± 16.3</td>
<td>16.3 ± 16.9</td>
<td>0.739</td>
</tr>
<tr>
<td>History of seizures (%)</td>
<td>43 (98)</td>
<td>41 (85)</td>
<td>0.032</td>
</tr>
<tr>
<td>History of prior treatment (%)</td>
<td>24/33 (73)</td>
<td>30/35 (86)</td>
<td>0.194</td>
</tr>
<tr>
<td>Blantyre Coma score</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>43 (98)</td>
<td>42 (88)</td>
<td></td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>37.8 ± 1.0</td>
<td>37.8 ± 1.3</td>
<td>0.869</td>
</tr>
<tr>
<td>Pulse (per min)</td>
<td>143 ± 15</td>
<td>142 ± 17</td>
<td>0.9</td>
</tr>
<tr>
<td>Respirations (per min)</td>
<td>42 ± 9</td>
<td>45 ± 10</td>
<td>0.175</td>
</tr>
<tr>
<td>White blood cell count ($\times 10^3$/mm$^3$)</td>
<td>11.4 ± 6.3</td>
<td>13.6 ± 10.3</td>
<td>0.215</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>22 ± 7</td>
<td>19 ± 7</td>
<td>0.096</td>
</tr>
<tr>
<td>Platelet count ($\times 10^3$/mm$^3$) (n = 71)</td>
<td>135 ± 80</td>
<td>130 ± 81</td>
<td>0.784</td>
</tr>
<tr>
<td>Blood glucose (mg/ml)</td>
<td>87 ± 38</td>
<td>95 ± 78</td>
<td>0.763</td>
</tr>
<tr>
<td>Parasitemia ($\times 10^3$/mm$^3$) (geometric mean; range)</td>
<td>43.9 (0.02–749)</td>
<td>18.6 (0.149–915.6)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

---

**Table 2**  
Survival rates

<table>
<thead>
<tr>
<th></th>
<th>Quinine (%)</th>
<th>Artemotil (%)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macha</td>
<td>16/22 (73)</td>
<td>19/23 (83)</td>
<td>0.425</td>
</tr>
<tr>
<td>UTH</td>
<td>19/22 (86)</td>
<td>19/23 (76)</td>
<td>0.368</td>
</tr>
<tr>
<td>Both</td>
<td>35/44 (80)</td>
<td>38/48 (79)</td>
<td>0.964</td>
</tr>
</tbody>
</table>

---

$SD$ = standard deviation.

---

**Figure 2.** Kaplan-Meier plot showing survival curve of 92 patients receiving quinine or artemotil.
29.2 hours for artemotil, with no significant difference between the two treatment modalities. It should be noted that the higher mean baseline parasite counts in the quinine group makes interpretation of the data difficult.

For both regimens, the rates for having a negative malaria smear were calculated at 7, 14, 21 and 28 days after beginning therapy, and were not significantly different. At Day 7, 32/35 (91%) of those receiving quinine had a negative malaria smear compared to 34/38 (90%) in the artemotil group. Patients were not discharged to a malaria-free transmission zone, and most did not have access to malaria preventive measures such as mosquito nets or chemoprophylaxis, so that a subsequent positive malaria smear did not differentiate between recrudescence or a re-infection. The proportion of negative smears in the artemotil group was greater than that of the quinine group at every point after Day 7, but this was not a significant difference.

Results of neurological follow up among survivors and the proportion with no neurologic sequelae or deficits are shown in Table 4. The categories and frequencies of sequelae at follow-up visits are shown in Table 5. No statistically significant differences were seen between the two treatment groups in any of these parameters, although by Day 28, of those who had received quinine, 3/24 (11%) had residual neurologic sequelae compared to 5/34 (15%) of those who had received artemotil. Additional documentation of the time taken after recovery from coma to regain the milestones of eating, drinking, sitting, standing and walking were available from the rural Macha Hospital study site. No significant differences in these parameters were seen between the two treatment groups.

**Adverse events.** Not including death, there were a total of 82 adverse events recorded in 36/48 (75%) of the patients receiving artemotil and 61 adverse events recorded in 34/44 (77%) of the patients receiving quinine. Most of these events were consistent with severe malaria and the expected multi-organ involvement of the illness. Table 6 shows the type and frequency of adverse events in all categories where more than a total of 3 adverse events was recorded. Comparison of hematological and biochemical parameters at Days 0, 3, 7, 14, 21 and 28 between the two treatment groups revealed no significant differences. Pre and post-treatment ECGs were assessed for any arrhythmia or changes in QT interval. No abnormalities were seen.

**DISCUSSION**

This is the first reported clinical trial on the use of artemotil in African children with cerebral malaria. The multicentre study (of which this report is a part) intended to recruit a total of 480 patients; however the two study sites in Zambia were able to recruit only 95 patients. While malaria has been on the increase in this country in recent years, this study defined cerebral malaria as a Blantyre coma score of ≥ 2, excluding many cases of severe malaria. Despite the limited number of patients studied, the results indicate that artemotil is at least as efficacious as standard quinine therapy. The adjusted odds ratio for death in the artemotil group was 0.9 times the odds in the quinine group, with a 95% confidence interval of 0.3 to 3.0 (P = 0.96). The CRT, PCT and FCT were also not significantly different between the two treatment groups.

Various published reports have documented the efficacy of other artemisinin derivatives for the treatment of *P. falciparum* malaria,13,14 including the treatment of cerebral malaria using artemether in children.15,16 While parasite clearance tended to be faster in the present study in the artemotil group as has been reported in other studies of artemisinin derivatives,17 the data from this study did not reach statistical significance. In addition, the higher mean baseline parasite counts in the quinine group make interpretation of the data difficult. This study did not compare artemotil to artemether. It would appear that it has no clear advantage over artemether other than the fact that it is formulated in sesame seed oil rather than peanut oil, theoretically leading to less likely exposure to aflatoxins.

A concern of possible neurotoxicity from artemisinin derivatives18–21 and the wisdom of using this drug in patients

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Table 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coma resolution time, parasite clearance time, and fever resolution time in survivors</strong></td>
<td><strong>Proportion of survivors with no neurologic sequelae</strong></td>
</tr>
<tr>
<td></td>
<td>Treatment group</td>
</tr>
<tr>
<td>No. of Patients</td>
<td>Quinine (survivors with follow-up)</td>
</tr>
<tr>
<td>Mean time (hr) ± SD</td>
<td>Artemotil (survivors with follow-up)</td>
</tr>
<tr>
<td>CRT = coma resolution time; PCT = parasite clearance time; FCT = fever clearance time; QN = quinine; AR = artemotil; SD = standard deviation.</td>
<td></td>
</tr>
<tr>
<td><strong>Table 5</strong></td>
<td><strong>Categories and frequency of neurologic sequelae seen in survivors</strong></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinine Group Day 7 (n = 12)</td>
<td>7</td>
</tr>
<tr>
<td>Quinine Group Day 28 (n = 3)</td>
<td>1</td>
</tr>
<tr>
<td>Artemotil Group Day 7 (n = 15)</td>
<td>11</td>
</tr>
<tr>
<td>Artemotil Group Day 28 (n = 5)</td>
<td>2</td>
</tr>
<tr>
<td><strong>Note:</strong> Some patients had more than one neurologic sequelae.</td>
<td></td>
</tr>
</tbody>
</table>
who are already neurologically compromised by cerebral malaria has been raised. Studies in dogs have shown dose-related damage to certain brain-stem nuclei, especially from arteether and arteether (now called artemotil) when given by intramuscular injection in an oily base. 28 Thus, the present study was designed to monitor the neurological status of each patient carefully, determining the rate of neurological sequelae 22 with one center also documenting the times it took to regain various milestones. Analysis of the data generated from this small study shows no significant difference in neurological sequelae between those receiving artemotil compared to those receiving conventional quinine. While not statistically significant, the finding that at Day 28, of those receiving quinine, only 11% had neurologic sequelae compared to 15% of those receiving artemotil warrants close monitoring in future studies since this may be due to a subtle effect of artemotil therapy. Despite this, these results are in agreement with a recent Cochrane systematic review of published and unpublished randomized studies of artemisinin derivatives compared to quinine used to treat cerebral malaria. No significant difference in neurological sequelae were found. 4

The recording of adverse events during the study also documented that 10 children experienced aphasia, speech disorders, or deafness during or after treatment in the artemotil group compared to 6 in the quinine group. These adverse events should be carefully monitored in the future to determine whether they are related to the type of therapy. It should also be pointed out that since the current study was not designed to detect subtle neurological effects of the drugs such effects could have occurred without being detected.

The development of resistance by *P. falciparum* to current drugs for malaria makes it imperative to develop new drugs. Artemotil appears to be effective even when *P. falciparum* strains develop resistance to other drugs. 23,24 Although artemisinin derivatives have been used for many years in China, resistance to these drugs has been slow to develop, making it likely that they will have a relatively long usefulness compared to other recently developed drugs such as halofantrine. 25,26 Despite the relative lack of resistance to artemisinin derivatives noted to date, the cure rates using these drugs may be affected by the observed inter-individual variability in drug pharmacokinetics. 27 While there are several reasons for this variability, absorption from an intramuscular injection site may be unpredictable, especially in children who are comatose with little muscle activity. Two of the artemotil deaths in our study had parasitemia at the time of death, one at 38 hours and the other at 140 hours after the start of therapy. Whether this represented resistance to artemotil or poor absorption of the drug is not known since levels of artemotil and its metabolites in the patients’ serum samples were not available. Recrudescence of parasitemia after treatment with artemisinin derivatives is possible if the course of therapy is shorter than 5 to 7 days. Distinguishing between recrudescence and re-infection is difficult without the use of parasite molecular fingerprinting techniques. These were not performed in this study.

Apart from the low incidence of resistance, another potentially important yet underrated benefit of the artemisinin derivatives over more commonly used drugs such as quinine and mefloquine, is their effect on limiting gametocyte production. 28 If artemisinin derivatives were to be used for the treatment of severe malaria in children, it is possible that these children with sometimes extremely high parasite counts and gametocyte carriage rates would no longer be a community source of gametocytes after treatment, and thus lead to a decrease in community transmissibility of malaria. 29

As malaria continues to exert its toll on the lives of children in sub-Saharan Africa, it is imperative that new treatment modalities are found that will decrease the unnecessary suffering and the more than 1 million annual deaths associated with this disease. Artemotil has been shown to be efficacious for the treatment of pediatric cerebral malaria in this study. Its mode of delivery, once-daily intramuscular injections, lends its usefulness to situations that are found in much of rural Africa where access to intravenous delivery of drugs is not available. The use of intramuscular artemotil as an alternative drug to intravenous quinine for pediatric cerebral malaria may be a valuable addition to the limited armamentarium currently available in a large part of Africa. Further studies are indicated to assess this possibility and evaluate its safety as compared to intravenous quinine.

Acknowledgments: We wish to thank the Zambian Ministry of Health for allowing us to perform this study. Special thanks go to S. Zulu, P. Mbachundu, G. Simwanza, H. Mbewe, A. Zulu, M. Chandala, M. Simwinga, C. Chimoga, and P. Muyaya, without whom the study could not have been done. The laboratory services of Macha Mission Hospital and the University Teaching Hospital were indispensable for the study. Development of this drug has been performed collaboratively by the World Bank/World Health Organization Special Programme for Research and Training in Tropical Diseases, the Walter Reed Army Institute of Research, Washington, D.C. and the Dutch pharmaceutical company, ARTECEF BV.

Financial support: This investigation received the financial support of the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR 960370).

REFERENCES


ARTEMOTIL FOR PEDIATRIC CEREBRAL MALARIA

529