A CLINICAL AND PHARMACOKINETIC TRIAL OF SIX DOSES OF ARTEMETHER-LUMEFANTRINE FOR MULTIDRUG-RESISTANT PLASMODIUM FALCIPARUM MALARIA IN THAILAND

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Abstract. The efficacy-safety and pharmacokinetics of the six-dose regimen of artemether-lumefantrine (Coartem®/Riamet®; Novartis Pharma AG, Basel, Switzerland) were assessed in a randomized trial in 219 patients (≥ 12 years old) with acute, uncomplicated Plasmodium falciparum malaria in Thailand. One hundred and sixty-four patients received artemether-lumefantrine and 55 received the standard treatment combination of mefloquine-artesunate. Both drugs induced rapid clearance of parasites and malaria symptoms. The 28-day cure rates were 95.5% (90% confidence interval [CI] = 91.7, 97.9%) for artemether-lumefantrine and 100% (90% CI = 94.5, 100%) for mefloquine-artesunate. This high-dose regimen of artemether-lumefantrine was very well tolerated, with very good compliance. The most frequent adverse events were headache, dizziness, nausea, abdominal pain, dyspepsia, vomiting, and skin rash. Overall, only 2% of patients in both groups showed QTc prolongations but without any cardiac complication, and no differences were seen between patients with and without measurable baseline plasma levels of quinine or mefloquine. Plasma levels of artemether, dihydroartemisinin, and lumefantrine were consistent with historical data for the same dose regimen, and were higher, particularly for lumefantrine, than those previously observed with the four-dose regimen, explaining the greater efficacy of the six-dose regimen in a drug-resistant setting. These results confirm the excellent safety and efficacy of the six-dose regimen of artemether-lumefantrine in the treatment of multidrug-resistant P. falciparum malaria.

INTRODUCTION

Malaria is a leading cause of morbidity and mortality in developing areas of the world and remains a major health problem in endemic regions. It is estimated that 100 million clinical cases occur annually and that more than two million people die every year from the disease.1,2 Despite considerable efforts to eradicate or control malaria, the disease continues to spread in part due to the development of drug-resistant Plasmodium falciparum strains, which have become unresponsive to almost all available drugs,3 particularly in Southeast Asia. The present standard treatment for uncomplicated falciparum malaria in the drug-resistant setting is a free combination of high-dose mefloquine (25 mg/kg) and artesunate (12 mg/kg over a three-day period),4-6 the efficacy of which remains more than 95%.7 However, as mefloquine resistance has appeared and is spreading (the activity of mefloquine is now only approximately 90% as monotherapy), new efficient antimalarial treatments, in particular drug combinations, which are well tolerated and simple to use are urgently needed. A fixed-dose combination atovaquone-proguanil given as four tablets (250 mg of atovaquone/100 mg of proguanil hydrochloride [Malarone®; Glaxo Wellcome, Inc., Research Triangle Park, NC]) once a day for three consecutive days was shown to give overall cure rates > 98% (100% in 79 patients in Thailand) in more than 500 patients in Africa, South America, The Philippines, and Thailand.8,9 However, most recent guidelines in treating malaria strongly recommend the use of a combination of artemisinin derivatives with other antimalarial agents to avoid the emergence of resistance (World Health Organization [WHO] Model List of Essential Drugs, 1999), and artemisinin combinations are considered a central component of the global Roll Back Malaria initiative as first line treatment.

Artemether-lumefantrine (Coartem®/Riamet®; Novartis Pharma AG, Basel, Switzerland) is a new, oral, fixed-dose combination tablet of 20 mg of artemether, a derivative of artemisinin (qinghaosu), and 120 mg of lumefantrine (previously known as benflumetol), a novel antimalarial synthesized and developed by the Academy of Military Medical Sciences in Beijing, People’s Republic of China. This combination was registered in China in 1992 for the treatment of P. falciparum malaria, and has been subsequently further developed by Novartis Pharmaceuticals (code research number CGP 56697). In Europe, it was first approved in January 1999 in Switzerland (trade name Riamet®), including standby emergency treatment for travelers to regions where malaria is prevalent. To date, Coartem®/Riamet® is registered in nearly 60 countries, mainly in Africa, Asia, Latin America, and Europe.

Artemether is characterized by a rapid onset of schizontocidal action, but has a short elimination half-life (2–3 hr),10-12 and recrudescence is frequent when artemether is used as monotherapy,13 unless high dosages are given over several days.14-16 In contrast, lumefantrine has a longer elimination half-life of up to 10 days10 and is associated with a low recrudescence rate,17,18 but has a slower onset of action. The rationale for the drug combination was to combine the benefits of the fast onset of action of artemether with the long duration of action and high cure rate of lumefantrine in a single oral formulation. Moreover, the short course of treatment with artemether-lumefantrine (over a two- or three-day period) should lead to much better compliance,15 which remains a major problem with long treatment regimens.9,20 Clinical studies conducted in more than 2,000 adult and pediatric patients in China, The Gambia, Tanzania, Thailand, and India, and in travelers returning to Europe with acute falciparum malaria have demonstrated that artemether-lumefantrine is very well tolerated and highly efficacious, even against multidrug-resistant strains of the parasite.7,13,21-24 The
therapeutic dosage regimen in adults consists of four doses of artemether-lumefantrine (80 mg of artemether plus 480 mg of lumefantrine per dose) given over a 48-hr period, starting at the time of onset of symptoms or diagnosis, and then at eight, 24, and 48 hr thereafter. This four-dose regimen was rapidly and highly effective with cure rates > 95%. 24 In areas with high malaria transmission (where patients have some immunity) and where P. falciparum is more drug sensitive. In areas such as Thailand, with low transmission but where the most drug-resistant P. falciparum strains occur, a six-dose regimen given over a three-day period is necessary to achieve similar efficacy to that of the four-dose regimen in other regions. 7 This higher six-dose regimen was chosen based on two dose-optimization trials, 2,21 which showed that cure rates were only suboptimal (approximately 80%) using the four-dose regimen in such areas with drug-resistant strains of the parasite. The six-dose regimen is also recommended for stand-by emergency treatment. 24

This trial, conducted in Thailand in patients with acute uncomplicated P. falciparum malaria, aimed to confirm the safety and efficacy of the optimized formulation of artemether-lumefantrine (given as the six-dose regimen), and to assess the pharmacokinetics of the drug. A control arm using the current standard therapy of mefloquine plus artemisunate (MAS) was included, but the trial was not designed to test for a difference or equivalence between artemether-lumefantrine and MAS. The assessment of efficacy of artemether-lumefantrine was done in comparison with a historical control. 2,21

MATERIALS AND METHODS

Patients and trial design. This randomized, open-label, parallel group four-week trial was conducted in Thailand at Bangkok Hospital for Tropical Diseases, Faculty of Tropical Diseases, Mahidol University (Bangkok, Thailand). Male and female patients (≥ 12 years old and ≥ 35 kg body weight) presenting with microscopically confirmed P. falciparum malaria were eligible for the trial, and those who fulfilled all protocol requirements were randomized in a ratio of 3:1 to receive artemether-lumefantrine or MAS.

The trial excluded subjects with signs/symptoms indicative of severe/complicated malaria requiring parenteral treatment, a history of drug hypersensitivity or allergy, heart disease or significant electrocardiogram (ECG) abnormalities, psychiatric disorders (e.g., depression or epilepsy), or severe renal or hepatic impairment (creatinine and/or alanine aminotransferase levels > 2.5 times the upper limit of normal range). Mixed infections were not excluded, and no particular inclusion/exclusion criteria were based on parasite counts. Recent treatment with other antimalarials did not exclude the patient from the trial. Baseline blood samples were taken to determine the presence of quinine, chloroquine, and mefloquine.

The trial was performed in accordance with the Declaration of Helsinki and according to the principles of Good Clinical Practice. The trial protocol and the subject informed consent forms were approved by the Ethical Clearance Committee on Human Rights, Mahidol University (Bangkok, Thailand). All adult participants and parents or guardians of minors gave informed consent prior to participation.

Treatments. Artemether-lumefantrine tablets (Coartem®/Riamet®; Novartis Pharma AG, Basel, Switzerland), each containing 20 mg of artemether and 120 mg of lumefantrine were administered as six consecutive doses (each of four tablets, i.e., 80 mg of artemether and 480 mg of lumefantrine) at 0 and 8 hr on day 1, and twice a day (approximately 8 hr apart) on the following two days.

The MAS regimen was artesunate (50-mg tablets; Guilin Pharmaceutical Factory No. 1, Guilin, People’s Republic of China), 4 mg/kg/day once a day for three days plus mefloquine (250-mg tablets, Lariam®; Hoffman-La-Roche, Basel, Switzerland), 25 mg/kg given as a split dose of 15 and 10 mg/kg on the second and third days. The exact dosage per kilogram of body weight was established to the nearest quarter tablet for the two ingredients.

Patients were encouraged to resume eating normally as soon as food could be tolerated. If the patient vomited any dose (artemether-lumefantrine or MAS) within 1 hr of intake, this dose was replaced. If deterioration of the medical condition occurred, indicating a failure to respond, rescue medication was then initiated according to the investigator’s clinical judgement, and the patient was excluded from the trial. Patients were closely observed until parasite clearance, and then followed weekly until day 29. For any patients with reappearance of parasites during the 28-day trial period, the polymerase chain reaction (PCR) was used to distinguish between recrudescence and re-infection.

Patient monitoring and treatment safety-tolerability assessments. At enrollment, a medical history was obtained, a full baseline physical examination including ECGs was performed, and blood was taken for quantitative parasite counts, PCR (finger prick), routine hematology, and determination of other antimalarials (quinine, mefloquine, chloroquine). After the start of treatments, patients were monitored three times a day for the first three days (or until clearance was reached) for parasitemia and temperature. Electrocardiographic monitoring was performed at baseline, and on days 2, 3, 4, 8, and 29, usually in the morning. A 12-lead ECG was taken for each patient with the patient resting on a bed, and using a paper speed of 50 mm/sec and a voltage of 1.0 mV/cm. The V2 tracing was used to evaluate QTc; therefore at least 4–6 continuous complexes were required for this purpose. This allowed detailed and accurate review of any abnormalities. QTc values were calculated from the QT interval and heart rate given by the machine, after having been reviewed by a cardiologist in a blinded fashion. Patients had full follow-up visits on the fourth, eighth (one week), and 29th day (four week) consisting of evaluations of temperature and blood microscopy (also on the 15th and 22nd days), and ECGs, vital signs, laboratory tests, and any adverse effect or concomitant medication were reported. The end-of-study evaluation was on day 29.

Treatment safety and tolerability were evaluated based on ECG changes in QTc from baseline, significant clinical laboratory changes, and the incidence, severity, and potential drug relationship of adverse events or serious adverse events.

Treatments efficiency assessments. Standard variables for evaluating treatment efficacy were used: the 28-day cure rate was defined as the proportion of patients with clearance of
asexual parasitemia within seven days of initiation of treat-
ment without subsequent recrudescence within 28 days, par-
asite reduction at 24 hr was defined as the percentage re-
duction of parasites per microliter at 24 hr compared with 
baseline, the time to parasite clearance (PCT) was defined 
as the time from the first dose until the first total and con-
tinued (2 days) disappearance of asexual parasite forms, the 
time to fever clearance (FCT) was defined as the time until 
the temperature decreased below and remained below 37.5°C 
for at least two days, and anti-gametocyte activity was de-
fined as the clearance of existing gametocytes without the 
need for further antimalarials. The 28-day cure rate was 
evaluated for both the ITT (intention-to-treat) patients and 
the evaluable patients (excluding 11 patients who were lost 
to follow up before four weeks). Parasite counts (parasite 
density per microliter = [number of parasites × actual white 
blood cells]/number of leukocytes) were determined on Gi-
ems-stained thick blood films.

Polymerase chain reaction. In the case of reappearance 
of parasites during the follow-up period of 28 days, a PCR 
was used to distinguish between re-infection and recrudes-
cence by comparing parasite genotypes of three polymorphic 
loci (merozoite surface protein-1 [MSP-1], MSP-2, and glu-
tamate-rich protein [GLURP]; (Brockman A, SMRU [Shok-
lo Malaria Research Unit] Laboratories, Mae Sot, Thailand, 
unpublished data) to those of baseline samples.

Pharmacokinetic evaluations. The plasma concentra-
tions of artemether, dihydroartemisinin (DHA), and lume-
fantrine were determined in patients treated with artemether-
lumefantrine. Extensive pharmacokinetics (for artemether 
and DHA) was obtained in 25 patients (who gave consent 
to participate in the pharmacokinetic [PK] group), while only 
three samples were collected from each of the remaining 
patients.

Artemether and dihydroartemisinin were measured in the 
25 PK patients, at 0 hr (pre-dosing), and at 1, 2, 3, 4, 6, and 
8 hr following intake of the first and last (sixth) dose of 
artemether-lumefantrine, and at 2 hr following intake of dos-
es 2, 3, 4, and 5. In the remaining patients, they were mea-
sured at 2 hr following intake of doses 1, 3, and 5. Lume-
fantrine was analyzed at 0 hr (pre-dosing), and at 2 hr fol-
lowing intake of each of the six doses of artemether-lume-
fantrine in the 25 PK patients, and at 2 hr following intake of 
doses 1, 3, and 5 in the remaining patients.

Artemether, DHA, and lumefantrine were measured in the 
laboratory of Pr. V. Navaratnam (University Sains Malaysia, 
Penang, Malaysia) as previously described.27,28 The range of 
 intra-assay coefficients of variation for the quality control 
(validation) samples were 9.1–10.3% for artemether, 8.4– 
9.1% for DHA, and 6.4–9.8% for lumefantrine. The limits of 
measurement for the three compounds were 2.5, 1.25, and 
5 ng/ml, respectively, and concentrations below these limits 
were taken as zero.

The following model-independent pharmacokinetic par-
rameters (WinNonlin Professional, Version 2.0; Pharsight 
Corporation, Mountain View, CA) were determined for ar-
temether and DHA, after both first and last dose intakes of 
artemether-lumefantrine: C_max, the highest observed plasma 
concentration; t_max, the time to reach C_max; t_1/2 is the apparent 
terminal elimination half-life; and AUC_0-inf, the area under 
the plasma concentration-time curve calculated by the trap-
ezooidal method over the time interval 0 hr to the last time 
point (t) with a concentration different from zero. Metabolic 
ratios (DHA/artemether) for C_max and AUC_0-8 hr, after each 
first and last dose application of artemether-lumefantrine 
were calculated. No pharmacokinetic analysis was per-
formed for lumefantrine; only summary statistics on plasma 
concentrations are displayed.

Statistical analysis. Sample size for the artemether-lu-
meфантрине arm was calculated based on the 28-day cure rate. 
Since the cure rate in Bangkok is generally lower than in 
any other region in Thailand, treatment with artemether-lu-
meфантрине was to be considered effective if the lower limit 
of the 90% confidence interval (CI) for evaluable patients 
exceeded 85%, which was still regarded to be clinically rel-
levant. For MAS treatment, a cure rate of at least 95% was 
assumed based on results from previous studies.

To test whether the 28-day cure rate with the six-dose 
regimen of artemether-lumefantrine was significantly higher 
than 85%, the 90% two-sided CI using exact Pearson-Clopper 
limits was calculated to show that the lower limit ex-
cedes 85%. This gave a sample size of 127 evaluable pa-
tients. To allow for a 15% dropout rate, the number of pa-
tients to be randomized to the artemether-lumefantrine arm 
was fixed at 150. This number of patients was believed to 
be adequate based on previous studies.29 The number of 
patients to be randomized to MAS was fixed at 50. 

The study was not designed to test for a difference or 
equivalence between artemether-lumefantrine and MAS, but 
to compare with historical controls in which MAS was used. 
However, the 90% CI for the difference in cure rate between 
treatments was calculated using normal approximation as-
suming equal variances. Summary statistics were calculated 
for PCT and FCT (using the Kaplan-Meier method) and for 
parasite reduction at 24 hr. No statistical testing was per-
formed for variables other than the 28-day cure rate.

RESULTS

Trial population and adherence to protocol. Between 
September 1998 and the end of January 1999, 219 patients 
were enrolled, 164 received artemether-lumefantrine and 55 
received MAS. Baseline demographic characteristics of pa-
tients were similar in both groups (Table 1).

Adherence to the protocol was generally good, although 
some of the patients left the hospital after one or two weeks 
and only returned to the clinic for the four-week follow-up 
visit. All scheduled doses of trial medication were given un-
der close supervision of the hospital staff ensuring full com-
pliance. None of the patients discontinued treatment pre-
maturely. Two patients taking artemether-lumefantrine vom-
ited the first dose, which was replaced, and one patient tak-
ing MAS vomited the second dose and the mefloquine 
tablets were replaced. More than 90% of the patients had 
eaten light or normal meals during the course of treatments. 
Only three patients did not eat before doses 1 and 2 of ar-
temether-lumefantrine.

Safety and tolerability. At enrollment, patients in both 
treatment groups showed common malaria symptoms such as 
headache, asthenia, fatigue, fever, dizziness, nausea, my-
algia, and anorexia. Other less commonly observed symp-
toms/signs included rigors, arthralgia, vomiting, sleep dis-
orders, hepatomegaly/splenomegaly, and abdominal pain. As anticipated, the malaria symptoms disappeared rapidly within 2–5 days in most of the patients in both treatment groups. Most (nearly 90% in both treatment groups) recorded treatment emergent symptoms/signs (TESS) that occurred during the trial period were rated mild or moderate in severity, and were symptoms typical of malaria, e.g., abdominal pain, dyspepsia, nausea, vomiting, diarrhea, anorexia, constipation, and were reported in 18.3% and 21.8% of the patients on artemether-lumefantrine and MAS, respectively. Headache, dizziness, and sleep disorder were reported in 27.4% and 16.4% of the patients, respectively. Skin reactions (mild severity) were reported in eight patients taking artemether-lumefantrine (pruritus, rash, urticaria), and two taking MAS (pruritus, urticaria). Only one adverse event (vomiting after taking MAS on day 2) was assessed by the investigator as related to trial drug.

At baseline, the median QTC was 408 msec (range = 340–500 msec). At this time, no clinically relevant overall increase from baseline in QTC values was seen. The mean absolute (percent) changes in QTC interval on days 2, 3, 4, 8, and 29, were −2.2 msec (−0.4%), −2.3 msec (−0.4%), −1.7 msec (−0.2%), −2.5 msec (−0.4%), and +0.3 msec (+0.3%), respectively, on artemether-lumefantrine. They were −1.3 msec (−0.2%), −1.5 msec (−0.2%), +3.0 msec (+0.9%), −0.3 msec (−0.1%), and +2.7 msec (+0.9%), respectively, on MAS. Only 2% of patients in each treatment group showed QTC prolongations of potential relevance but related to trial drug.

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As expected, several baseline laboratory parameters were affected by disease status (Table 2). More than 60% of the patients had a baseline hematocrit value below the normal range. After three days, an expected slight worsening of anemia occurred in both treatment groups, but by day 29 more than 50% of the patients had a normal hematocrit. Nine patients (7 taking artemether-lumefantrine and 2 taking MAS) had severe (National Institutes of Health grade 4) thrombocytopenia at baseline, but this improved rapidly. Liver function test results were only slightly abnormal at baseline and did not show any significant changes, other than those related to the disease resolution. All parameters normalized over the course of treatment. In three patients, an adverse event of jaundice was noted after treatment with artemether-lumefantrine. All these patients had elevated serum bilirubin at baseline and resolution occurred on follow-up. The results

<table>
<thead>
<tr>
<th>Characteristics of the patients</th>
<th>Artemether-lumefantrine (n = 164)</th>
<th>Leflunomide plus artesunate (n = 55)</th>
<th>Total (n = 219)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex (Males)</strong></td>
<td>No. (%)</td>
<td>115 (70%)</td>
<td>41 (75%)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>Median</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td><strong>Weight (kg) (rounded)</strong></td>
<td>Median</td>
<td>50</td>
<td>52</td>
</tr>
<tr>
<td><strong>Height (cm) (rounded)</strong></td>
<td>Median</td>
<td>160</td>
<td>160</td>
</tr>
<tr>
<td>**Hematocrit (%)</td>
<td>Median</td>
<td>35.9</td>
<td>35.5</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure (mm Hg)</strong></td>
<td>Median</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td><strong>Systolic blood pressure (mm Hg)</strong></td>
<td>Median</td>
<td>50–100</td>
<td>40–80</td>
</tr>
<tr>
<td><strong>Hepatomegaly (%)</strong></td>
<td>No. (%)</td>
<td>54 (33%)</td>
<td>20 (36%)</td>
</tr>
<tr>
<td><strong>Splenomegaly (%)</strong></td>
<td>No. (%)</td>
<td>53 (32%)</td>
<td>21 (38%)</td>
</tr>
<tr>
<td><strong>Temperature (°C)</strong></td>
<td>Median</td>
<td>37.5</td>
<td>37.6</td>
</tr>
<tr>
<td><strong>Previous malaria infection within 3 months</strong></td>
<td>No. (%)</td>
<td>23 (14%)</td>
<td>11 (20%)</td>
</tr>
</tbody>
</table>

**Antimalarials detected in blood at baseline**

| Quinine                          | No. (%)                          | 34 (21%)                          | 8 (15%)        | 42 (19%)      |
| Melloquine                       | No. (%)                          | 9 (5%)                            | 5 (9%)         | 14 (6%)       |
| Parasite density (μl)            | Median                           | 1,608                             | 5,130          | 3,540         |
| Geometric mean                   | Range                            | 2,063                             | 3,329          | 2,326         |
| **<5,000**                       | No. (%)                          | 93 (56.7%)                        | 27 (49.1%)     | 120 (54.8%)   |
| **5,000 to 15,000**              | No. (%)                          | 93 (56.7%)                        | 27 (49.1%)     | 120 (54.8%)   |
| **<50,000**                      | No. (%)                          | 93 (56.7%)                        | 27 (49.1%)     | 120 (54.8%)   |
| **≥50,000**                      | No. (%)                          | 93 (56.7%)                        | 27 (49.1%)     | 120 (54.8%)   |
of the other laboratory tests performed (renal function, serum electrolytes, glucose, total serum protein, serum albumin, urine tests), showed no relevant changes after baseline in either group.

**Efficacy, 28-day cure rate.** Eleven patients (9.5%) taking artemether-lumefantrine and 2 (4%) taking MAS could not be evaluated for the 28-day cure rate because they had no follow-up slide at least four weeks after start of treatment. The 28-day cure rates [90% CI] for the evaluable patients were 95.5% [91.7, 97.9] for those taking artemether-lumefantrine (and thus significantly higher than 85%) and 100% [94.5, 100] for those taking MAS (Table 3). The 90% CI for the difference in cure rates between MAS and artemether-lumefantrine was −0.2, 9.2%. Thus, the two treatment groups were not significantly different with this number of patients \((P = 0.195\), by Fisher’s exact test, two-sided) although this trial was not designed to test this hypothesis. Of the 208 evaluable patients, seven patients (4.5%) taking artemether-lumefantrine had a reappearance of *P. falciparum* parasites (RI failure; WHO classification), and only one case was classified as a new infection by PCR. No reappearance was observed in those taking MAS. Of the six patients with recrudescence, three had no normal meal (only light meals) with two of them showing no detectable levels of lumefantrine at any of the sampling times. All failures had lumefantrine plasma levels less than 4,000 ng/ml after dose 5, whereas the overall mean was greater than 20,000 ng/ml. The median parasite density at baseline in these failures (24,440/µl) was much higher than the overall median (1,608/µl). The 5% failure cases with lumefantrine plasma levels less than 4,000 ng/ml after dose 5, whereas the overall mean was greater than 20,000 ng/ml. The median parasite density at baseline in these failures (24,440/µl) was much higher than the overall median (1,608/µl). Of the 21 evaluable patients taking artemether-lumefantrine who had a parasite density ≥ 50,000/µl at baseline, 19 were cured (90.5%), whereas 98.9% of patients with less than 5,000 parasites/µl were cured.

**Time to parasite clearance.** Both treatments cleared the

| Table 2 | Mean hematologic and clinical chemistry parameters at baseline and on day 29 |
|---|---|---|---|---|---|---|---|
| | Artemether-lumefantrine (n = 164) | Mefloquine plus artesunate (n = 55) |
| | Baseline | Day 29 | Baseline | Day 29 |
| Hemoglobin (g/L) | 116 | 124 | 115 | 122 |
| Hematocrit (%) | 35.9 | 38.5 | 35.5 | 38.1 |
| Red blood cells \((×10^{12}L)\) | 4.4 | 4.7 | 4.4 | 4.7 |
| White blood cells \((×10^{12}L)\) | 5.8 | 7.5 | 5.5 | 7.4 |
| Platelets \((×10^{12}L)\) | 130 | 242 | 111 | 248 |
| Total bilirubin (µmol/L) | 23.9 | 10.2 | 22.8 | 8.8 |
| Alkaline phosphatase (U/L) | 98.4 | 93.2 | 111 | 114 |
| AST (U/L) | 48.2 | 30.2 | 39.6 | 30.2 |
| ALT (U/L) | 44.1 | 32.7 | 37.0 | 29.7 |
| Albumin (g/L) | 39.8 | 43.8 | 39.1 | 43.8 |
| Creatinine (µmol/L) | 88.1 | 76.6 | 83.7 | 76.7 |
| BUN (mmol/L) | 4.9 | 3.5 | 4.8 | 3.5 |

\(\text{AST} = \text{aspartate aminotransferase}; \text{ALT} = \text{alanine aminotransferase}; \text{BUN} = \text{blood urea nitrogen}\).

**Table 3**

<table>
<thead>
<tr>
<th>28-day cure rate [90% CI]</th>
<th>Artemether-lumefantrine (n = 164)</th>
<th>Mefloquine plus artesunate (n = 55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention-to-treat patients</td>
<td>90.2% [85.6, 93.8]</td>
<td>96.4% [89.0, 99.4]</td>
</tr>
<tr>
<td>Evaluable patients</td>
<td>95.5% [91.7, 97.9]</td>
<td>100% [94.5, 100]</td>
</tr>
<tr>
<td>Time to parasite clearance (intention-to-treat patients)</td>
<td>29 hr [26, 32]</td>
<td>31 hr [26, 32]</td>
</tr>
<tr>
<td>25–75th percentiles</td>
<td>18–40 hr</td>
<td>24–35 hr</td>
</tr>
<tr>
<td>Median [95% CI]</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>25–75th percentiles</td>
<td>99.0–100%</td>
<td>99.8–100%</td>
</tr>
<tr>
<td>Time to fever clearance (evaluable patients)</td>
<td>29 hr [23, 37]</td>
<td>23 hr [15, 30]</td>
</tr>
<tr>
<td>25–75th percentiles</td>
<td>8–51 hr</td>
<td>15–31 hr</td>
</tr>
<tr>
<td>Median [95% CI]</td>
<td>72 hr [34, 163]</td>
<td>85 hr [46, 160]</td>
</tr>
<tr>
<td>25–75th percentiles</td>
<td>32–320 hr</td>
<td>46–320 hr</td>
</tr>
</tbody>
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\(\text{CI} = \text{confidence interval}\).
parasites rapidly, and there was no difference between the treatment groups. No RII or RIII failures were seen. The median time to parasite clearance was 29 hr (range = 7–64 hr) for artemether-lumefantrine and 31 hr (range = 7–57 hr) for MAS (Table 3). All patients cleared their parasites within 64 hr after start of treatment. An analysis using Cox’s proportional hazard regression showed that the only baseline characteristics that affected the PCT was parasite density at baseline, the lower the estimated probability to reach parasite clearance. The patients taking artemether-lumefantrine with a parasite density < 500/μl at baseline had a median PCT of 17 hr (n = 65), patients with a parasite density ≥ 500/μl but less than 5,000/μl had a median PCT of 27 hr (n = 28), and for the other categories (see Table 1) above this threshold, no large difference was seen with median PCTs of 39, 40, and 41 hr. The same pattern was seen for patients taking MAS.

Parasite reduction at 24 hr. At approximately 24 hr after the start of treatments (i.e., day 2), more than 40% of intention-to-treat patients had cleared their parasitemias, and on day 3 nearly 95% of the patients in both treatment groups were free of parasites. Apart from four patients (3 taking artemether-lumefantrine and one taking MAS), all patients had reduced their baseline parasitemias within the first 24 hr after start of treatment, and all except 11 patients had a reduction of more than 90%. The median reduction at 24 hr for the evaluable patients was 100% for both treatments (Table 3).

Time to fever clearance. Only 105 of the 219 patients were evaluated for FCT; the remaining 114 patients had a baseline temperature of ≤ 37.5°C. Median FCT was 29 hr with artemether-lumefantrine versus 23 hr with MAS (Table 3).

Time to gametocyte clearance. Nearly 10% of all patients had gametocytes detected on their pre-treatment slide. During the first 72 hr, gametocytes were detected in 26 (15.9%) patients taking artemether-lumefantrine and 10 (18.2%) taking MAS. These patients rapidly cleared their gametocytes. The median time to gametocyte clearance was 72 hr for artemether-lumefantrine and 85 hr for MAS (Table 3). Only three patients (1 taking artemether-lumefantrine and two taking MAS) who were negative for gametocytes at baseline had gametocytes detected later during the follow-up only on one slide.

Plasmodium vivax infections. Twenty-three (10.5%) patients (16 [9.8%] taking artemether-lumefantrine and 7 [12.7%] taking MAS) had mixed infections including *P. vivax* at baseline. All of these patients rapidly cleared these parasites within the first 42 hr of treatment, more than half of them within 24 hr. During the 28-day trial period, *P. vivax* reappeared in six patients taking artemether-lumefantrine. Three of them also had *P. vivax* at baseline and reappearance was seen between days 24 and 29. The other three patients showed the appearance of these parasite forms on days 19, 21, and 25. These six patients received chloroquine for two or three days followed by two weeks of primaquine.

Pharmacokinetics. Artemether–DHA. Mean plasma concentrations of artemether and DHA measured in the 25 PK patients are shown in Figure 1, and the pharmacokinetic parameters are listed in Table 4. Artemether showed time-dependent pharmacokinetics with peak plasma concentrations progressively decreasing with successive dose intakes, while those of DHA increased. C_{max} and AUC(0–8 hr) after last (sixth) dose intake of artemether-lumefantrine were reduced significantly by 61% and 64%, respectively, compared with those obtained after first dose.

Dihydroartemisinin appeared rapidly in plasma, reaching peaks 2–3 hr after dosing. C_{max} and AUC(0–8 hr) after last dose intake of artemether-lumefantrine were increased by 103% and 89%, respectively, compared with those after first dose.

### Table 4

<table>
<thead>
<tr>
<th></th>
<th>Artemether</th>
<th>Dihydroartemisinin</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>After last dose</td>
<td>After last dose</td>
</tr>
<tr>
<td>C_{max} (ng/ml)</td>
<td>186 ± 125</td>
<td>66.2 ± 54.3</td>
</tr>
<tr>
<td>C_{ss} (ng/ml)</td>
<td>13.5 ± 11.4</td>
<td>6.7 ± 8.5</td>
</tr>
<tr>
<td>t_{1/2} (hr)</td>
<td>2.0 [1–8]</td>
<td>2.0 [1–8]</td>
</tr>
<tr>
<td>AUC(0–8 hr) (ng·hr/ml)</td>
<td>535 ± 272</td>
<td>211 ± 108§</td>
</tr>
<tr>
<td>t_{1/2} (hr)</td>
<td>1.6 ± 0.3#</td>
<td>2.2 ± 1.0#</td>
</tr>
</tbody>
</table>

* AUC = area under curve.
† Mean of individual ratios of C_{max} (or AUC) after last dose/C_{max} (or AUC) after first dose.
‡ Median [range].
§ n = 22.
¶ n = 7.
# n = 12.
Elimination of artemether and DHA was rapid (t½ = 1.6–2.2 hr).

The mean ± SD metabolic ratios of DHA:artemether calculated for AUC after first and last dose intakes of artemether-lumefantrine were 0.7 ± 0.3 (range = 0.06–1.4) and 3.5 ± 1.7 (range = 1.2–7.6), respectively. They were 0.6 ± 0.3 (range = 0.07–1.2) and 3.8 ± 1.9 (range = 1.0–8.5), respectively, for Cmax. This increase was the result of a decreased exposure to artemether combined with an increased production of DHA. The plasma values obtained in the remaining patients confirmed these findings.

**Lumefantrine.** The mean plasma concentrations of lumefantrine measured in the 25 PK patients are shown in Figure 2. Plasma concentrations of lumefantrine increased after each of the six artemether-lumefantrine doses, reaching Cmax (mean = 25.7 μg/ml) after the last dose intake. Individual plasma levels after last dose intake ranged between 2.1 and 62.9 μg/ml. The same figure was obtained in the other remaining patients. Two patients had non-measurable levels of lumefantrine after the first, third, and fifth dose of artemether-lumefantrine; they both showed recrudescence. These two patients had taken only light meals. In four patients, lumefantrine was measurable only after the fifth dose of artemether-lumefantrine (range = 0.04–14 μg/ml); they were cured except for one who recrudesced (this patient had the highest baseline parasite density: 422,400/μl compared with the others: range = 273–81,650/μl). Individual plasma values are shown in Figure 3 in comparison with previous data from 14 Thai patients given the four-dose regimen (the clinical findings of this four-dose regimen were previously published and the plasma values were also previously reviewed). The six-dose regimen gave higher concentrations than the four-dose regimen, which explains the higher efficacy observed in the present trial.

**Co-medications and analysis of drug-drug interactions.** Approximately 25% of the patients had antimalarials detected in blood at enrollment (baseline tests): 42 patients (19.2%) had detectable quinine and 14 (6.4%) had detectable mefloquine. For quinine, the plasma levels ranged from 120 to 21,000 ng/ml (median = 4,050 ng/ml), and for mefloquine from 300 to 5,500 ng/ml (median = 1,815 ng/ml).

Overall, 45.2% of the patients received antipyretics to treat fever prior to the start of the trial, and 81.7% received them during the trial (133 taking artemether-lumefantrine and 46 taking MAS). The medication was mostly paracetamol, but in eight cases on artemether-lumefantrine, intramuscular metamizole sodium (Novalgin; Hoechst Marion Roussel Ltd., Bangkok, Thailand) was given for two to three days. Of the 219 patients, 86.6% taking artemether-lumefantrine and 43.6% taking MAS received concomitant medications other than antipyretics or antimalarials. These co-medications were most frequently glucose plus sodium chloride solution, dimenhydrinate, aludrox, ranitidine, amoxicillin, bromhexine hydrochloride, and chlorphenamine.

The analysis of drug-drug interactions did not reveal any difference in safety parameters (adverse effects and ECGs) between the patient population who received co-medications, in particular other antimalarials, and patients who did not. Special attention was given to ECGs, and no difference was seen in the incidence of QTc prolongations between patients taking artemether-lumefantrine with or without quinine or mefloquine detected at baseline (Table 5). Similarly, the analysis did not reveal any major differences in efficacy in these patients. The cure rate was 86.7% in patients (n = 30) with quinine detected and 100% in patients (n = 9) with mefloquine detected versus 97.4% in patients (n = 116) with no quinine or mefloquine detected.

**DISCUSSION**

Artemether-lumefantrine (Coartem®/Riamet®) is a new oral antimalarial drug that consists of a fixed-dose combination of artemether and lumefantrine given as a four- or six-dose regimen over a two- or three-day period. The four-dose regimen of artemether-lumefantrine has demonstrated 28-day cure rates of more than 95% in patients from China, Africa, and India with known immunity to malaria or with non-drug resistant infections, but gave inferior cure rates (approximately 85%) in Thailand compared with the stan-
recommended for standby emergency treatment in non-immune travelers. 18,24 This trial was conducted in Thailand using the six-dose regimen to confirm the safety/tolerability and efficacy of the optimized formulation of artemether-lumefantrine against highly multidrug-resistant *P. falciparum* infections, and to further characterize the pharmacokinetics of artemether, DHA, and lumefantrine. A control arm with the current standard therapy of mefloquine-artesunate was used as a comparator to bridge with historical data.

The two treatments were very well tolerated, and none of the patients discontinued the trial. The adverse events starting or worsening after baseline, i.e., TESS, were primarily considered for assessing the tolerability/safety profile of artemether-lumefantrine compared with MAS. Even so, there appeared to be a high degree of confounding of the TESS with the typical symptomatology of malaria/concurrent infections as shown by more than half of the patients in both treatment groups reporting adverse events (fever, headache, and viral/bacterial infections constituted the vast majority of TESS), mostly mild in intensity and unlikely to be drug-related. The cases of skin reactions and dyspepsia are more likely to be drug-related. Overall, artemether-lumefantrine did not differ from MAS in terms of severity or incidence of adverse events. It is reassuring to note that neither artemether-lumefantrine nor MAS induced any significant renal, hepatic, or hemopoietic dysfunction.

The fact that artemether and arteether, given in high intramuscular doses, prolonged the QTc-interval in rats and dogs, 30 and that lumefantrine has structural similarities to halofantrine, an antimalarial liquid formulation, may have resulted in a potential for a quinine-artemether-lumefantrine interaction is consistent with historical data, 10,12 and showed that the six-dose regimen can correct the antiplasmodial drug-induced QTc prolongations with both artemether-lumefantrine and MAS may have been caused by malaria itself or electrolyte disturbances. Mefloquine is not known to commonly or significantly affect cardiac depolarization. Thus, it is noteworthy that artemether-lumefantrine behaved similarly in this trial. These results are consistent with those of a previous study comparing these two antimalarial agents. 12,29 Twenty-five percent of the patients in this trial had quinine or mefloquine detected in their blood when receiving the trial medication. The median quinine levels (4,050 ng/ml) and those of mefloquine (1,815 ng/ml) were sufficiently high to allow meaningful evaluation of the potential for a drug-drug interaction. No difference in either the pattern or severity of adverse events, or in the frequency of QTc prolongations, was observed between the patients who had quinine/mefloquine detected in their blood at baseline compared with those in whom no antimalarials were detected. This suggests that the potential for a quinine-artemether-lumefantrine interaction is limited. Overall, the data from this trial confirm that even with this high-dose regimen, artemether-lumefantrine was very well tolerated and compliance was very good.

Artemether-lumefantrine induced rapid clearance of parasites and malaria symptoms. There was no clinical significant difference in efficacy between artemether-lumefantrine and the combination of MAS. Since antipyretics were frequently given, the effect of both drugs on the time taken for resolution of fever should be interpreted with caution. An important observation was that all seven patients taking artemether-lumefantrine who recrudesced had low to non-measurable levels of lumefantrine, which most probably was a reflection of no or low food intake, resulting in poor absorption of lumefantrine. These patients were then given quinine (3 × 200 mg/day) and tetracycline (4 × 250 mg/day) for one week. These findings were in accordance with pharmacokinetic-pharmacodynamic relationship evaluations showing that cure rate is dependent on lumefantrine systemic exposure. 17,39 Three cases of parasite reappearance were observed in patients who did not eat during the treatment period. This, however, is known with generally lipophilic antimalarial drugs given via the oral route. Thus, patients with high parasite density and low food intake should be observed closely. Nevertheless, the six-dose regimen can correct the non-tolerance of food or a high parasite density at baseline in most of the patients. Furthermore, it is encouraging that these failures can be successfully retreated with artemether-lumefantrine as shown in a study in African children. 44 Efficacy of treatment with MAS was similar to previous data also obtained in Thailand. 29

Plasma levels of artemether, DHA, and lumefantrine were consistent with historical data. 10,12 and showed that the six-

### Table 5

<table>
<thead>
<tr>
<th></th>
<th>QTc increase &gt; 60 msec No. (%)</th>
<th>QTc increase &gt; 30 msec and QTc &gt; 450/470 No. (%)</th>
<th>QTc increase &gt; 30 msec and QTc &gt; 450/470 No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mefloquine plus artemate</td>
<td>55 (1.8%)</td>
<td>3 (5.5%)</td>
<td>1 (1.8%)</td>
</tr>
<tr>
<td>Artemether-lumefantrine</td>
<td>164</td>
<td>0 (3.0%)</td>
<td>3 (1.8%)</td>
</tr>
<tr>
<td>No other antimalarial detected</td>
<td>121</td>
<td>0 (2.5%)</td>
<td>1 (0.8%)</td>
</tr>
<tr>
<td>Quinine detected</td>
<td>34</td>
<td>2 (5.9%)</td>
<td>2 (5.9%)</td>
</tr>
<tr>
<td>Mefloquine detected</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
dose regimen produced higher plasma levels, particularly of lumefantrine, than the four-dose regimen, explaining the higher efficacy. The time-dependent pharmacokinetics of artemether was confirmed in this trial in patients. However, since both artemether and DHA are parasiticidal, this change in metabolite:drug ratios during a treatment course does not impact efficacy.

Administration of mefloquine prior to artemether-lumefantrine in healthy subjects was shown to lower plasma concentrations of lumefantrine by 30–40%, but this was considered not to be clinically relevant, given the wide therapeutically range of lumefantrine plasma levels observed in clinical studies. The present findings confirm these predictions since the nine patients taking artemether-lumefantrine who had mefloquine in their blood at enrollment were all cured.

Overall, and including the present trial, four studies in malaria patients have been conducted in Thailand using the four- or six-dose regimen of artemether-lumefantrine, three of them using MAS as a comparator. These studies were 1) a large randomized study of the four-dose regimen (n = 309) versus MAS (n = 308), 2) a randomized dose-optimization study comparing the four-dose regimen (n = 120) with two six-dose regimens given over a three- (n = 118) or five-day period (n = 121), 3) a randomized study evaluating the six-dose regimen (n = 150) in comparison with a smaller MAS treatment arm (n = 50), and the current trial. These studies showed that the six-dose regimen of artemether-lumefantrine (cure rates = 95.5–99.1%) was more effective than the four-dose regimen (cure rates = 81–83.3%), and was as effective as the current standard treatment of mefloquine-artesunate (cure rates = 94–100%) in multidrug-resistant \( P. falciparum \) malaria, and was overall better tolerated than MAS. Of particular importance is that these large studies, which included high-dose regimens, all provided strong evidence against a systematic effect of therapeutic doses of artemether-lumefantrine on cardiac conduction or repolarization. These findings further support previous reports demonstrating the excellent safety profile of the combination artemether-lumefantrine.

In conclusion, this study confirmed the excellent efficacy and safety/tolerability profile of the combination artemether-lumefantrine (Coartem®/Riamet®) given as a six-dose regimen of the optimized formulation in the treatment of highly multidrug-resistant \( P. falciparum \) malaria in Thailand. Coartem®/Riamet® proved to be as effective as the current standard therapy of MAS, with no relevant effects on electrocardiographic parameters. Fast parasite clearance and good compliance due to fixed-dose combination and short treatment duration are additional advantages of Coartem®/Riamet®.

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