

Treatment of Acute Uncomplicated *Falciparum* Malaria with Artemether-Lumefantrine in Non-immune Populations: A Safety, Efficacy, and Pharmacokinetic Study

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Abstract. The efficacy and safety of artemether-lumefantrine for the treatment of malaria in non-immune populations are not well defined. In this study, 165 non-immune patients from Europe and non-malarious areas of Colombia with acute, uncomplicated falciparum malaria or mixed infection including *P. falciparum* were treated with the six-dose regimen of artemether-lumefantrine. The parasitologic cure rate at 28 days was 96.0% for the per protocol population (119/124 patients). Median times to parasite clearance and fever clearance were 41.5 and 36.8 hours, respectively. No patient had gametocytes after Day 7. Treatment was well tolerated; most adverse events were mild to moderate and seemed to be related to malaria. There were few serious adverse events, none of which were considered to be drug-related. No significant effects on ECG or laboratory parameters were observed. In conclusion, the six-dose regimen of artemether-lumefantrine was effective and well tolerated in the treatment of acute uncomplicated falciparum malaria in non-immune patients.

INTRODUCTION

The vast majority of cases of malaria occur in endemic countries in Africa, Asia, and Latin America. Imported malaria, however, remains a significant problem in industrialized countries and in non-malarious areas of endemic countries. Travelers from such regions lack the partial immunity to malaria that is considered to develop in residents of endemic areas after repeated infections. The non-immune individuals fall into two broad categories: those who, by virtue of being native to a non-endemic area, have never been exposed to malaria, and those who may originally have lived in endemic areas but subsequently have settled in non-malarious areas and have lost the partial immunity they previously had. Immigrants from endemic areas who have become resident in non-malarious areas are an important group because they may visit endemic areas for professional or personal reasons.¹

The authors are aware of the fact that there is no standard definition of non-immune status. Travel to malaria-endemic areas places non-immune individuals at risk of infection with *Plasmodium falciparum* and of complications of malaria. This is particularly the case where chemoprophylaxis is not used or is ineffective. As a result, a significant number of patients return from travel with imported malaria. It has been estimated that ~16,000 cases of imported malaria occur in Europe each year.² Deaths from falciparum malaria also occur; for example, in the United Kingdom, > 2,000 cases of imported malaria are reported annually, with an average of 9 cases being fatal.³

A number of treatments are currently used in cases of imported malaria in industrialized countries. A survey in France in 2001² found that, even for uncomplicated falciparum malaria, intravenously quinine was the most commonly used

treatment in 41% of cases. Mefloquine (in 18% of cases) and atovaquone-proguanil (Malarone), used in 14% of cases, were the next most commonly used therapies. Quinine and mefloquine have both been associated with potentially severe side effects. Quinine causes highly unpleasant adverse effects, and mefloquine is associated with severe neuropsychological problems,⁴ especially when used at a curative dose. Discontinuation because of adverse reactions has been reported in 11% of patients receiving mefloquine for the treatment of imported uncomplicated falciparum malaria in France.² Atovaquone-proguanil, whereas effective and well tolerated as prophylaxis and in the treatment of falciparum malaria in endemic countries, has been relatively little studied in the treatment (rather than prophylaxis) of malaria in non-immune travelers, and there are few data on its effectiveness against other *Plasmodium* species.⁵

Against this background, there remains a need for additional effective, well-tolerated treatments for imported uncomplicated falciparum malaria. Artemether-lumefantrine (co-artemether) is the first artemisinin-based combination therapy registered in industrialized countries. This fixed combination treatment has been extensively studied in endemic countries, mainly in Southeast Asia^{6–9} and sub-Saharan Africa,^{10–13} and the six-dose regimen has been shown to be associated with high parasitologic cure rates and rapid clearance of parasites and resolution of fever in these settings. However, experience with the six-dose regimen of artemether-lumefantrine in non-immune patients is limited. Here we report the results of a multicenter, open-label, non-comparative study in which adult non-immune travelers with imported uncomplicated falciparum malaria (or mixed infections including *P. falciparum*) were treated with the six-dose regimen of artemether-lumefantrine.

MATERIALS AND METHODS

The study protocol and amendments were approved by the ethics committees of all participating institutions, and all pa-

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tients gave written informed consent before participating in the study. Patients were eligible to enter the study if they were at least 18 years of age and had microscopically confirmed acute uncomplicated *Plasmodium falciparum* malaria or mixed infections including *P. falciparum*. Patients who had received prior antimalarial prophylaxis (but not artemisinin derivatives within the previous 7 days) could enter the study. In the initial inclusion criteria for the study, it was simply stated that patients had to be non-immune. After a protocol amendment (implemented after 80 of the 165 patients had been recruited), a precise definition of non-immune status was introduced (i.e., not having spent either the first 5 years of their life or long periods during the 5 years before the study in a malaria-endemic area and not having had acute *P. falciparum* malaria diagnosed during the past 5 years).

Key exclusion criteria were signs/symptoms indicative of severe/complicated malaria (as defined by the World Health Organization¹⁴); known hypersensitivity to the study medication; having received artemisinin derivatives within the previous 7 days; and concurrent use of other treatment/prophylaxis for malaria.

Methods. This was an open-label, non-comparative study performed at 16 centers in Europe and Colombia. The single center in Colombia was in Villavicencio, in an area without endemic malaria. This center had a history of treating non-immune patients, typically patients from non-endemic areas who had to move to endemic areas either in search of employment or as a result of conflict.¹⁵ It was included in the study after a protocol amendment (the original protocol included only European centers) to accelerate recruitment of patients, which before the amendment had been slower than anticipated.

Treatment. Doses of 80 mg artemether and 480 mg lumefantrine (four tablets, each containing 20 mg artemether and 120 mg lumefantrine) were given on diagnosis and at 8, 24, 36, 48, and 60 hours. Patients were followed up for 28 days after diagnosis. Most patients took their medication with fat-containing food.

Efficacy evaluations. Efficacy was assessed in terms of parasitologic cure rates at 7 and 28 days, time to fever clearance, time to parasite clearance, and the proportion of patients with *P. falciparum* gametocytes at each evaluation on days 0, 1, 2, 3, 7, and 28. Confidence intervals on proportions were calculated using the exact Pearson-Clopper method. Time to fever and parasite clearance were analyzed using Kaplan-Meier estimation (with appropriate censoring for patients lost to follow-up). The original sample size was chosen on the basis that, assuming at most a 10% recrudescence rate and requiring a precision of $\pm 5\%$ (95% CI), ~140 patients would be needed.

Pharmacokinetics. It was planned for one 2-mL blood sample to be collected from all patients on Day 3, 4–10 hours after the last dose of study medication, for determination of lumefantrine and desbutyl-lumefantrine. In addition, it was planned to take a blood sample from any patient with treatment failure to assess drug levels. The blood sample was drawn by venipuncture into a heparinized tube. Blood was centrifuged without delay at 1,000 rpm for 15 minutes, and the plasma was transferred in polypropylene tubes and stored at -70°C until shipment for analysis. Samples were shipped to the analytical center packed with dry ice. In practice, samples were available for 27 patients, and only 1 patient with treat-

ment failure had a sample for determination of lumefantrine and desbutyl-lumefantrine.

A subset of 15 patients (recruited at the Colombian center after closure of the main study) had more extensive blood sampling for pharmacokinetic analysis. In these patients, samples were taken pre-dose and 2–4 hours after study medication doses 2, 3, 4, and 5 on Day 3 (72 hours after first dose), Day 4 (96 hours after first dose), and on Day 7 (168 hours after first dose). Lumefantrine and desbutyl-lumefantrine plasma concentrations were measured using liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods at Novartis Pharma, BAPK-F, Rueil-Malmaison, France. These methods were developed by the sponsor and were fully validated. The lower limit of quantitation (LLOQ) of the methods was 50 ng/mL for lumefantrine and 5 ng/mL for desbutyl-lumefantrine. Pharmacokinetic parameters (derived from extensive samplings in the subset of 15 patients) were determined using model-independent methods (WinNonlin Pro., Version 4.0.1; Pharsight Corp., Mountain View, CA).

Safety assessments. Safety was assessed in terms of adverse events and laboratory parameters. Adverse events were summarized in terms of all adverse events occurring after baseline and in terms of treatment-emergent signs and symptoms (TESS; i.e. adverse events occurring after baseline but before re-appearance of asexual parasites in the blood).

Blood samples to assess clinical laboratory parameters (hematology: hematocrit; hemoglobin; red blood cell count; white blood cell count; platelet count; and biochemistry: glucose; bilirubin; creatinine [serum]; ALT [SGPT]; and alkaline phosphatase) were taken at baseline and Day 28. Laboratory values were analyzed in terms of summary statistics for changes from baseline, shift tables based on the normal ranges, and shift tables based on National Cancer Institute Common Toxicity Criteria (NCI CTC) where these were available.

At baseline and Days 1, 2, and 3 (e.g., 6–10 hours after last dose), a standard 12-lead ECG (25 mm/s) was recorded followed by a tracing for rhythm evaluation using standard ECG recording equipment. The ECGs were analyzed qualitatively and quantitatively including measurements of the PQ- and QT-interval and the duration of the QRS-complex. QTc-interval was calculated by using the formulae of Bazett¹⁶ and Fridericia.¹⁷ ECGs were reviewed in a blinded manner by cardiologists at a Clinical Research Organization (eResearch Technology, Philadelphia, PA) to guarantee the quality and homogeneity of the interpretation of these data.

RESULTS

Patient population. A total of 165 patients entered the study, 118 from Europe and 47 from Colombia, of whom 154 completed the 3-day treatment period (and received the full course of treatment, although 3 of these patients took a replacement dose after vomiting the first dose) and 135 completed the study. The most common reasons for discontinuation were loss to follow-up and protocol violations, and the most common major protocol violation being incomplete documentation of parasite counts up to Day 7 (19 patients) and on Day 28 after parasite clearance on Day 7 (14 patients).

Demographic and disease characteristics at baseline are shown in Table 1. Patients were predominantly men (69%) and young to middle-aged (median, 37 years). Median body

TABLE 1
Baseline characteristics (all treated patients)

Variable	Statistic	Treated patients (N = 165)
Age (years)	Mean (\pm SD)	37.7 (\pm 12.44)
	Median (range)	37.0 (17–66)
Sex—n (%) patients	Male	113 (68.5)
	Female	52 (31.5)
Race—n (%) patients	White	80 (48.5)
	Black	40 (24.2)
	Other	45 (27.3)
Body weight (kg) ^a	Mean (\pm SD)	72.9 (\pm 13.72)
	Median (range)	73.0 (41–119)
Body weight categories— n (%) patients	\leq 65 kg	55 (33.3)
	> 65 kg	107 (64.8)
Parasitological diagnosis, n (%) patients	<i>P. falciparum</i>	162 (98.2)
	Other species	8 (4.8)
	<i>P. vivax</i>	2 (1.2)
	<i>P. malariae</i>	6 (3.6)
Parasite density per 1,000 red cells [†]	Mean \pm SD	6.2 \pm 9.45
	Median (range)	2.4 (0–70)
Body temperature ($^{\circ}$ C)	Mean (\pm SD)	38.1 \pm 1.29
	Median (range)	38.0 (35.1–40.7)
Time since diagnosis (days) at study entry	Distribution, n (%) patients	
	1 day	150 (90.9)
	2 days	14 (8.5)
	\geq 3 days	1 (0.6)
Time since return from most recent travel (days)	Mean \pm SD	15.2 (\pm 20.77)
	Median (range)	12.0 (1–240)

^a Body weight was not reported for three patients.

[†] For 51 (30.9%) patients, parasite density was reported in other units, and is not included in the statistics given here.

weight was 73.0 kg (range, 41–119 kg), with 65% of patients weighing > 65 kg (including 20 patients, 12.1%, who weighed > 90 kg). Most patients had pure falciparum malaria, with only 5% having mixed infections. Other *Plasmodium* species detected on admission were *P. vivax* (in two patients) and *P. malariae* (in six patients), but were not found subsequently. In another three patients, *P. vivax* was first detected at their final evaluation (Day 28, Day 13, and Day 15).

Parasite density was generally relatively low, with a mean of 6.2 asexual forms per 1,000 erythrocytes. Median body temperature was 38.0 $^{\circ}$ C. More than 30% of patients had a baseline temperature of at least 39 $^{\circ}$ C, and 37% were afebrile (body temperature < 37.5 $^{\circ}$ C). More than 90% of patients entered the study within 1 day of diagnosis. Median time since return from most recent travel (as reported by the patients) was 12.0 days, but the range was very wide (1–240 days). Most of the patients from the European centers had recently returned from traveling in sub-Saharan Africa (most commonly Ghana, Cameroon, or Kenya, but including a wide range of countries). All patients at the Colombian center had traveled in other parts of Colombia. Of the 80 patients enrolled before the protocol amendment, 20% had used antimalarial prophylaxis within 7 days of study entry. Of the 85 patients recruited once the protocol amendment was in force, 17.6% had used antimalarial prophylaxis within 4 weeks of study entry. The sub-analyses of various subgroupings of the study cohort, especially with regard to the Colombian patients, did not reveal any difference.

Efficacy. Efficacy results are shown in Table 2. Results are presented for the per protocol (PP) population (defined as all patients who completed the study and did not have major protocol violations). It was originally planned to analyze efficacy primarily on the intention-to-treat (ITT) population

TABLE 2
Efficacy results (per protocol population)

Parameter statistic	PP population (N = 126)
28-day parasitologic cure rate n/M (%) patients (95% CI*)	119/124 (96.0 [90.8, 98.7])
7-day parasitologic cure rate n/M (%) patients (95% CI*)	123/125 (98.4 [98.4, 99.8])
Time to parasite clearance (hours)	
Median [95% CI]	41.5 [40.0, 42.6]
Time to fever clearance (hours)	
Median [95% CI]	36.8 [24.5, 40.0]
n (%) patients with parasite clearance by time after initiation of therapy	
PCT \geq 24 h	30 (23.8)
PCT > 24– \leq 48 h	62 (49.2)
PCT > 48 h	32 (25.4)
Parasite clearance not achieved	2 (1.6)
n/M (%) patients with gametocytes by time window	
Days 0–3 [‡]	26/126 (20.6)
Day 4 to day 7 [‡]	7/113 (6.2)
Day 8 to day 42 [‡]	0/122 (0.0)

* Using Pearson Clopper limits.

[†] Percentage of patients with at least one positive slide between baseline and 72 hours after start of treatment.

[‡] Percentage of patients with positive slide at the weekly follow-up visits evaluated by time window.

For time to parasite clearance and time to fever clearance, patients who had no or parasites or fever (as appropriate) at baseline were censored at the time-point hour = 0.

M = number of patients with observations.

(all patients with confirmed malaria who received at least one dose of study drug). The pre-specified ITT analysis, however, counted patients who had incomplete documentation of parasite counts after parasite clearance as treatment failures. An unexpectedly high proportion of patients in the study had incomplete documentation of parasite counts after parasite clearance, most commonly because of discontinuation before the Day 28 visit. This would have led to an underestimation of the parasitologic cure rate in the ITT population. The PP population was therefore considered to provide the most relevant parasitologic cure rates.

At 7 days, the parasitologic cure rate was 98.4%, with Pearson-Clopper 95% CIs of 94.3%, 99.8%. Of the two patients who were not cured at Day 7, one did not clear parasites until Day 10, and the other was withdrawn from the study because of unsatisfactory therapeutic effect after the second dose of study medication. This latter patient was successfully treated with quinine and doxycycline.

The parasitologic cure rate at 28 days was 96.0% (95% CI, 90.8%, 98.7%). In addition to the two patients who did not clear parasites by Day 7, three patients had late re-appearance of parasites (at Days 22, 24, and 28). All three of these patients were treated successfully with atovaquone-proguanil (Malarone), and one patient also received chloroquine. All three patients had been infected in sub-Saharan Africa, but in different countries: Kenya, the Gambia, and either Rwanda or Angola.

Subgroup analysis according to body weight category in the PP population showed 28-day parasitologic cure rates of 100% (95% CI, 92.5%, 100.0%) in patients of body weight \leq 65 kg and 93.4% (95% CI, 85.3%, 97.8%) in patients weighing > 65 kg. The median weight of the five patients with treatment failure was 85 (range, 73–97 kg) versus 70.5 kg (range, 47–115 kg) in the 119 patients who were successfully cured.

The effects of age on treatment outcome were not examined by subgroup analysis (there were very few patients > 60 years of age in the study); the patients in the PP population who had treatment failure ranged between 21 and 62 years of age.

Of the three patients who vomited and replaced doses of artemether-lumefantrine, two were cured at Day 28, and the other was discontinued from the study because of a protocol violation (incomplete documentation of parasite counts after clearance). This latter patient also violated the protocol by only taking three doses of study medication.

Median times to parasite clearance and fever clearance were 41.5 (95% CI, 40.0, 42.6) and 36.8 hours (95% CI, 24.5, 40.0), respectively. Between baseline and Day 3, > 20% of the patients had *P. falciparum* gametocytes. No patient had gametocytes after Day 7.

Safety and tolerability. There were no deaths or life-threatening adverse events (AEs) during the study. Six patients had AEs that needed prolonged hospitalization. In three of the patients, the AEs were primarily related to malaria (in two cases to the severity of the signs/symptoms of the initial infection and in the other to recrudescence). The pattern of AEs in two of the remaining three patients (anemia, thrombocytopenia, liver function test abnormalities, hematuria, malaise, and abdominal pain in one patient and hepatocellular damage in the other) also suggests an association with malaria, particularly with one patient who discontinued artemether-lumefantrine treatment after the second dose and received intravenously quinine as antimalarial rescue medication from Day 0 to Day 3 because of complications of malaria. The endocarditis reported in one patient seems to have been a coincidental infection. None of the three patients, including one with reported progression of malaria, who had either hepatocellular damage or liver function test (LFT) abnormalities had serum transaminase levels greater than NCI CTC Grade 2. One patient had NCI CTC Grade 3 serum bilirubin levels at baseline, but at Day 28, this had decreased to NCI CTC Grade 1. Resolution of all of the AEs that needed prolonged hospitalization was reported, with the exception of the malaria (reported on Day 22) in one patient, for which no further information was available.

The most common AEs (those reported in at least 5% of patients) are shown in Table 3. In total, 75% of patients reported at least one adverse event. The most frequent AEs reported were headache, insomnia, diarrhea, vertigo, malaise, and cough. Most of the common AEs, such as headache, malaise, and gastrointestinal disturbances such as diarrhea, nausea and vomiting, together with anorexia and vertigo and chills, were probably related to signs and symptoms of malaria. The proportions of patients experiencing common AEs that were suspected by the investigators to be related to study treatment are also shown in Table 3. It can be seen that insomnia was the most frequently reported adverse event considered to be treatment-related. For the other common adverse events, only a small proportion were considered to be treatment-related. No allergic reactions were reported in any of the patients.

The overall profile of changes from baseline in laboratory parameters (hematology and biochemistry) observed was consistent with the resolution of acute uncomplicated malaria. Both hematology and biochemistry values tended to normalize over the course of the study. None of the patients

TABLE 3

Most frequently reported adverse events (those occurring in at least 5% of patients)

	n (%) with AEs (N = 165)	
	All AEs	Drug-related AEs
Total no. of patients with AEs	124 (75.2)	48 (29.1)
Adverse events ^a		
Headache	48 (29.1)	6 (3.6)
Insomnia	22 (13.3)	11 (6.7)
Diarrhoea	22 (13.3)	5 (3.0)
Vertigo	21 (12.7)	6 (3.6)
Malaise	19 (11.5)	2 (1.2)
Cough	18 (10.9)	2 (1.2)
Anorexia	17 (10.3)	4 (2.4)
Vomiting	14 (8.5)	6 (3.6)
Asthenia	13 (7.9)	1 (0.6)
Nausea	11 (6.7)	5 (3.0)
Chills	11 (6.7)	4 (2.4)
Hyperhidrosis	10 (6.1)	3 (1.8)
Abdominal pain	10 (6.1)	2 (1.2)

^a MedDRA preferred term, presented by descending order of overall frequency.

had shifts from baseline to NCI CTC Grade 3 or 4 for any parameter. Four patients had anemia reported as an AE, one of whom also had reported microcytic anemia and thrombocytopenia. In all of these patients, the hemoglobin level, hematocrit, and platelet count were all within NCI CTC grade 0 by Day 28. Also, nine patients had liver function test abnormalities (elevated transaminases and/or bilirubin) reported as AEs. In most cases, the AEs were reported between the two scheduled sampling times for laboratory analysis. In all but three cases, all LFT values were within the normal range by Day 28. In the remaining cases, SGPT was elevated outside the normal range, to NCI CTC Grade 1 (i.e., up to 2.5 times upper limit of normal [ULN]); in one case, this was a slight worsening from the baseline value.

ECG evaluations revealed only very small and clinically irrelevant changes in mean and median QTc, as calculated using either Bazett's or Fridericia's formula. The proportions of patients with predefined QTc signal values are shown in Table 4. The majority of patients had QTc increases from baseline of < 30 ms. There were no patients with absolute QTc values (using either formula) of > 500 ms, and none of the patients had QTc increases from baseline of > 60 ms according to both formulae. One patient had an increase from baseline of > 60 ms in QTc interval calculated using Bazett's formula from 393 ms at baseline to 456 ms at Day 2. Two

TABLE 4

Number (%) of patients with signal QTc values or signal QTc increases from baseline

QTc increase (ms)	QTc increases from baseline to highest post-baseline value [n (%) patients] (N = 147)	
	Bazett's formula	Fridericia's formula
≤ 0	38 (25.9)	25 (17.0)
> 0–< 30	62 (42.2)	56 (38.1)
30–60	16 (10.9)	34 (23.1)
> 60	1 (0.7)	2 (1.4)
Baseline ECG not done	30 (20.4)	30 (20.4)

Percentages are calculated using the total number of patients with post-baseline visit day 3 as denominator.

Bazett's formula: $QTc = QT/(RR \times 1/2)$. Fridericia's formula: $QTc = QT/(RR \times 1/3)$.

TABLE 5

Pharmacokinetic variables for lumefantrine and desbutyl-lumefantrine

Variable	Lumefantrine	Desbutyl-lumefantrine
C_{\max} ($\mu\text{g}/\text{mL}$) – mean \pm SD (CV%)	5.72 \pm 2.91 (50.8%)	0.0193 \pm 0.0079 (40.7%)
t_{\max} (h) – median [range]	52.42 [12.08–93.50]	62.67 [50.00–93.50]
$AUC_{(0-t)}$ ($\mu\text{g} \cdot \text{h}/\text{mL}$) – mean \pm SD (CV%)	272 \pm 159 (58.4%)	0.905 \pm 0.738 (81.5%)
AUC_{∞} ($\mu\text{g} \cdot \text{h}/\text{mL}$) – mean \pm SD (CV%)	335 \pm 196* (58.5%)	NA

* $N = 8$.

NA, not available.

patients had an increase from baseline of > 60 ms in QTc interval calculated using Fridericia's formula. One patient had an increase of 71 ms from baseline to Day 2 (from 331 to 402 ms). The only AE reported by this patient was mild vertigo from Day 2 to Day 3. The other had a QTc increase of 64 ms from 401 ms to 465 ms at Day 1. Days 2 and 3 QTc values were both within the normal range, at 420 and 427 ms, respectively. This patient reported mild vertigo on Day 1 but otherwise experienced no AEs.

Pharmacokinetics. Lumefantrine concentrations could be determined from single samples in 27 patients (body weight range, 49–115 kg) drawn between 5:30 AM and 11:00 AM after the last dose of treatment. Concentrations ranged from 0.457 to 17.6 $\mu\text{g}/\text{mL}$. Median value for patients sampled at similar time-points (i.e., between 5.50 and 6.92 hours, likely to reflect time at which C_{\max} occurs) was 5.58 $\mu\text{g}/\text{mL}$ (mean \pm SD: 6.55 \pm 4.81 $\mu\text{g}/\text{mL}$). Descriptive and linear regression analyses both suggested that exposure was not directly related to body weight (e.g., the patient with the highest body weight [115 kg] showed a concentration of 5.59 $\mu\text{g}/\text{mL}$ 6 hours after dose). The linear regression showed only a very weak negative correlation ($R^2 = 0.09$, $P = 0.20$) between log-transformed lumefantrine concentrations and body weights. Lumefantrine concentration was available for one patient who had treatment failure. This was the patient described above with polymerase chain reaction–confirmed recrudescence at Day 28. This patient had the lowest lumefantrine plasma concentration observed (0.457 $\mu\text{g}/\text{mL}$, at 5.5 hours, expected to be close to t_{\max}), which was indicative of a very low absorption of the drug in this patient. His body weight was 85 kg. Because

lumefantrine concentration was only available for one patient with treatment failure, no meaningful evaluation of any correlation between parasitologic cure and lumefantrine levels was possible.

For the 15 patients who provided more detailed pharmacokinetic data, plasma concentration-time profiles for lumefantrine and its metabolite desbutyl-lumefantrine are shown in Figure 1. Pharmacokinetic parameters for both compounds are shown in Table 5. The metabolite-to-parent ratio was 0.36% \pm 0.15% (C_{\max}) and 0.33% \pm 0.19% ($AUC_{(0-t)}$). Linear regression analyses of log-transformed pharmacokinetic parameters (C_{\max} and $AUC_{(0-t)}$) against body weight did not show any significant relationship between body weight and the pharmacokinetic parameters ($R^2 = 0.22$, $P = 0.078$ for C_{\max} and $R^2 = 0.13$, $P = 0.182$ for $AUC_{(0-t)}$ for lumefantrine and $R^2 = 0.08$, $P = 0.303$ and $R^2 = 0.002$, $P = 0.866$, respectively, for desbutyl-lumefantrine). All 15 patients achieved parasite clearance without recrudescence and with no gametocytes present at end of study. This was despite a large range of individual exposure levels to lumefantrine (C_{\max} from 2.12 to 11.2 $\mu\text{g}/\text{mL}$ and $AUC_{(0-t)}$ from 98.8 to 761 $\mu\text{g} \cdot \text{h}/\text{mL}$) and desbutyl-lumefantrine (C_{\max} from 0.006 to 0.034 $\mu\text{g}/\text{mL}$ and $AUC_{(0-t)}$ from 0.276 to 2.76 $\mu\text{g} \cdot \text{h}/\text{mL}$). Therefore, no relationship between drug exposure levels and parasite clearance could be established. Neither descriptive analysis nor linear regression analyses of QTc changes from baseline (calculated using either the Bazett or Fridericia formula) showed any significant relationship between the pharmacokinetic parameters and QTc changes from baseline.

DISCUSSION

This study, which included a total of 165 patients, is (to our knowledge) probably the largest prospective clinical trial performed to date on imported falciparum malaria in non-immune patients. Originally intended to be conducted in centers in Germany and Switzerland, slow recruitment (because of decreasing numbers of patients returning to these countries with imported malaria) led to the inclusion of centers in other countries through amendments to the protocol. The patient population described here were non-immune, defined as not having spent either the first 5 years of their life or for long periods during the 5 years before the study in a malaria-endemic area and not having had acute *P. falciparum* malaria diagnosed during the past 5 years. Whereas there are no malarious regions in Western Europe, the disease is endemic in

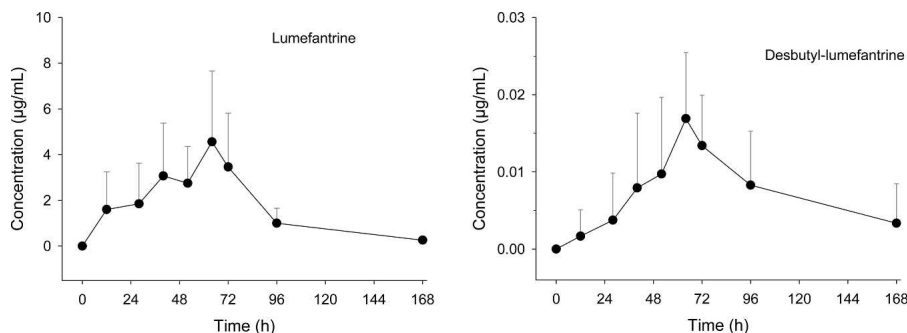


FIGURE 1. Mean \pm SD plasma concentration--time profiles of lumefantrine and desbutyl-lumefantrine.

some areas of Colombia. The patients recruited at the Colombian center were from non-malarious areas of the country and had, at most, infrequent travel to malarious regions, in addition to satisfying the definition of non-immunity given above.

At baseline, patients tended to have relatively low parasite counts. There was a wide range of time between returning from travel and diagnosis of malaria; the median was 12 days, but one patient had apparently been infected for at least 240 days before diagnosis. The majority of infections were pure *P. falciparum*. Mixed infections with other species (*P. vivax* and *P. malariae*) were found in < 5% of patients. Data from Thailand suggest mixed infections (*P. vivax* and *P. falciparum*) cause more anemia, but this fact does not seem relevant in the present context to influence the interpretation of our data.¹⁸

Most patients completed the study as planned, but there was a relatively high rate of premature discontinuation and of protocol violations. This was unexpected on the basis of studies with artemether-lumefantrine in malaria-endemic countries. Most patients who discontinued prematurely were lost to follow-up or did so as a result of protocol violations, specifically as incomplete documentation of parasite counts after initial clearance. It seems that a significant proportion of patients failed to return to the study centers once their malaria symptoms had resolved. This high rate of discontinuation and protocol violations led us to present the efficacy analysis based on the PP population, rather than the planned primary analysis based on an ITT population, providing the most representative parasitologic cure rate.

The original intention to conduct a study comparing the most commonly used drugs such as mefloquine, atovaquone/proguanil, and artemether/lumefantrine proved not to be feasible because of declining numbers of non-immune malaria patients in industrialized countries. In addition, it also became evident that atovaquone-proguanil was used extensively as a chemoprophylactic agent and was therefore less likely to be used as drug of choice for treatment.

Treatment was effective, with a high 28-day parasitologic cure rate. Two patients did not clear parasites by Day 7, and three patients had late re-appearance of parasites (at Days 22, 24, and 28). The observed 28-day parasitologic cure rate was comparable with those seen in trials in endemic countries (ranging from 94% to 97%, although analysis populations were not always defined as in this study),^{6,9,10,12,13} suggesting that treatment is as effective in the non-immune population as in semi-immune patients. Gametocytes also appeared to be cleared rapidly.

The 28-day parasitologic cure rate was chosen as the primary efficacy endpoint on the basis of WHO recommendations in place at the time the study was designed. It is therefore possible that not all cases of recrudescence were detected, because those occurring later than Day 28 would have been missed. A recent publication reporting a comparative study of artemether-lumefantrine and artesunate plus amodiaquine performed in Zanzibar¹² found that the Day 28 and Day 42 parasitologic cure rates for artemether-lumefantrine (uncorrected for re-infection) were 93% and 77%, respectively. This difference was largely caused by re-infection: the adjusted cure rates after polymerase chain reaction analysis to identify new infections were 97% at Day 28 and 92% at Day 42. Re-infection should not be an issue in non-malarious areas, but a 42-day follow-up period would still have been preferable in this study to detect late recrudescence. In practice,

however, a follow-up period of > 28 days would seem to be impracticable in the European setting, as shown by the proportion of patients who were lost to follow-up in this study.

Artemether-lumefantrine was well-tolerated, with most reported AEs appearing to be related to malaria. Laboratory evaluations were consistent with malaria and its resolution. ECG evaluations were performed because of the chemical similarity between lumefantrine and halofantrine, an antimalarial known to be associated with prolongation of the QTc interval.⁸ The possibility of a cardiotoxic effect of lumefantrine has been extensively studied in *in vitro* and *in vivo* studies. These studies unequivocally showed that lumefantrine lacks the cardiotoxicity of halofantrine.^{7,8,19} In this study, no significant effects on cardiac safety in terms of QTc interval were observed; changes in QTc interval and rates of QTc prolongation were low and consistent with those previously observed.

The pharmacokinetic data obtained in this study suggest that lumefantrine and desbutyl-lumefantrine concentrations are not strongly correlated with body weight. No clear relationship between lumefantrine or desbutyl-lumefantrine levels and either parasite clearance or changes in QTc interval were apparent. However, the higher median body weight in patients with treatment failures (although based on very few patients) highlights the need for additional data to ensure that the dose does not need to be adapted in overweight patients. No allergic reactions were seen, although these have been reported elsewhere.²⁰

In conclusion, the six-dose regimen of artemether-lumefantrine is a good choice for treating acute uncomplicated falciparum malaria in non-immune patients, with a high efficacy, a rapid resolution of clinical symptoms, and a good tolerability. It may prove to be the most appropriate option when considering the range of treatments available in industrialized countries, particularly when some alternative therapies such as quinine and mefloquine are associated with tolerability problems. Another alternative, atovaquone-proguanil, although apparently well tolerated, has not been well studied in the treatment of malaria in the non-immune population,^{21,22} but may be as effective as artemether-lumefantrine. The results of this study also underline the fact that all non-immune patients treated for malaria need to be informed about the possibility of re-appearance of parasite and clinical recrudescence for several weeks after treatment.

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