Atovaquone-Proguanil versus Mefloquine for Malaria Prophylaxis in Nonimmune Travelers: Results from a Randomized, Double-Blind Study

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Concerns about the tolerability of mefloquine highlight the need for new drugs to prevent malaria. Atovaquone-proguanil (Malarone; GlaxoSmithKline) was safe and effective for prevention of falciparum malaria in lifelong residents of malaria-endemic countries, but experience in nonimmune people is limited. In a randomized, double-blind study, nonimmune travelers received malaria prophylaxis with atovaquone-proguanil (493 subjects) or mefloquine (483 subjects). Information about adverse events (AEs) and potential episodes of malaria was obtained 7, 28, and 60 days after travel. AEs were reported by an equivalent proportion of subjects who had received atovaquone-proguanil or mefloquine (71.4% versus 67.3%; difference, 4.1%; 95% confidence interval, −1.71 to 9.9). Subjects who received atovaquone-proguanil had fewer treatment-related neuropsychiatric AEs (14% versus 29%; $P = .001$), fewer AEs of moderate or severe intensity (10% versus 19%; $P = .001$), and fewer AEs that caused prophylaxis to be discontinued (1.2% versus 5.0%; $P = .001$), compared with subjects who received melfoquine. No confirmed diagnoses of malaria occurred in either group. Atovaquone-proguanil was better tolerated than was mefloquine, and it was similarly effective for malaria prophylaxis in nonimmune travelers.

Growing international travel and the continued spread of resistance to antimalarial drugs increase the risk of malaria for travelers. As many as 30,000 travelers from industrialized countries develop malaria each year, with record numbers of imported cases of malaria reported in many North American and European countries [1, 2].

Most cases of imported malaria are preventable, but many travelers fail to use or comply with appropriate chemoprophylaxis [3]. An important factor contributing to this failure is the concern about side effects associated with antimalarial chemoprophylaxis. Mefloquine is highly effective in preventing malaria, but articles in the medical and lay press that highlight the neuropsychiatric side effects of mefloquine have caused many travelers to use less-effective alternatives or to avoid chemoprophylaxis altogether [4–8].

Previous studies of lifelong residents of malaria-

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Appropriate informed consent was obtained and clinical research was conducted in accordance with guidelines for human experimentation as specified by the authors' institutions.

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endemic areas have shown that a fixed-dose combination of atovaquone and proguanil hydrochloride (Malarone; GlaxoSmithKline) is highly effective for prophylaxis of malaria caused by *Plasmodium falciparum* and has a safety profile similar to placebo [9–11]. In addition, both atovaquone and proguanil have causal prophylactic activity against the hepatic stages of *P. falciparum* [12, 13], and, therefore, prophylaxis can be stopped 7 days after travel [14].

We conducted a randomized, double-blind, controlled clinical trial to compare the safety and efficacy of atovaquone-proguanil with the safety and efficacy of mefloquine in nonimmune travelers. The prospectively defined hypothesis was that the frequency of adverse events (AEs) in subjects who were to receive atovaquone-proguanil would not be higher than the frequency of AEs in subjects who were to receive mefloquine. Frequency of treatment-limiting AEs and efficacy of prophylaxis were secondary end points.

METHODS

Subjects were enrolled in study MAL30010 at 15 travel clinics in The Netherlands, Germany, the United Kingdom, Canada, and South Africa. Enrollment criteria and study conduct were as described elsewhere [15], except that subjects were ≥3 years of age, weighed ≥11 kg, and were randomized to receive either atovaquone-proguanil (plus placebo for mefloquine) or mefloquine (plus placebo for atovaquone-proguanil; figure 1). In brief, nonimmune subjects who traveled to a malaria-endemic area for up to 28 days were evaluated 7, 28, and 60 days after return to obtain information about a targeted list of AEs and potential episodes of malaria.

Without knowledge of treatment assignment, and after discussion with the subject, each investigator assessed whether there was a reasonable possibility that each AE was caused by the study drug. An AE was treatment emergent if it started while the subject was taking the study drug. Serum samples collected before and 4 weeks after travel were tested for antibodies to a malaria circumsporozoite protein [16] (to define the minimum number of subjects exposed to malaria-infected mosquitoes) and, in subjects with a potential diagnosis of malaria, for antibodies to blood-stage malaria parasites [17] (to confirm or reject the diagnosis).

Compliance with study drug use was assessed at the 4-week follow-up visit by interviewing the subject, reviewing a diary card, and counting unused pills. Blood samples for routine tests of hematology (hemoglobin level, WBC count, and platelet count) and chemistry (levels of creatinine and alanine aminotransferase) were obtained before and 4 weeks after travel from all subjects at 1 site. The primary study end point was the overall frequency of AEs, regardless of attributability to study drug, assessed 7 days after leaving the malaria-endemic area and analyzed in the intent-to-treat population of all subjects who were randomized and who received at least 1 dose of study drug. Noninferiority was assessed by comparing the 2-sided 95% CI for the AE proportion difference against the noninferiority range (−100%, +10%). The target sample size of 1000 subjects had >80% power to detect a 10% difference in AE proportions [18]. Secondary study end points were the frequency of treatment-limiting AEs and the efficacy of prophylaxis. Proportions of subjects with AEs were compared by means of the Yates' corrected χ^2 test. Because the *P* values are unadjusted and multiple comparisons will inflate the type I error, care should be taken when interpreting these comparisons.

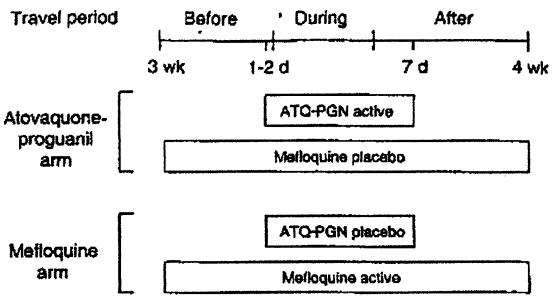

Figure 1. Study drug dosing regimens. ATQ, atovaquone; d, day; PGN, proguanil; wk, week.

Atovaquone-proguanil or matching placebo was supplied as full-strength Malarone tablets (GlaxoSmithKline), which contain 250 mg of atovaquone and 100 mg of proguanil hydrochloride, and Malarone Pediatric tablets (GlaxoSmithKline), which contain 62.5 mg of atovaquone and 25 mg of proguanil hydrochloride. Subjects were instructed to take atovaquone-proguanil (active or placebo) daily, starting 1–2 days before entering a malaria-endemic area and continuing until 1 week after leaving the malaria-endemic area. The daily dose was based on body weight: 1, 2, or 3 Malarone Pediatric tablets for subjects weighing 11–20, 21–30, or 31–40 kg, respectively, and 1 full-strength Malarone tablet for subjects weighing >40 kg [10].

Mefloquine (250 mg tablets; Lariam; F. Hoffman La-Roche) or matching placebo was administered according to standard recommendations of the World Health Organization [19]. Subjects were instructed to take mefloquine (active or placebo) weekly, starting at least 1 week and preferably 2–3 weeks before entering a malaria-endemic area, and continuing until 4 weeks after leaving the malaria-endemic area. The weekly dose was based on body weight: one-fourth of a tablet, for subjects weighing 11–12 kg; one-half of a tablet, for subjects weighing 13–24 kg; three-fourths of a tablet, for subjects weighing 25–35 kg; and 1 tablet, for subjects weighing >35 kg [19].

RESULTS

From April through September 1999, 1013 subjects were randomized to receive atovaquone-proguanil ($n = 508$) or mefloquine ($n = 505$). Thirty-seven subjects did not receive their first dose of study drug because they did not travel to a malaria-endemic area ($n = 20$), were lost to follow-up ($n = 7$), withdrew consent ($n = 5$), or other reasons ($n = 5$). Of the 976 subjects who received ≥1 dose of study drug, 966 (99%) completed the trial (figure 2).

The 2 groups were well balanced with respect to baseline demographics, history of malaria, travel destination, and duration of travel (table 1). Thirty-three subjects were ≤12 years old, and 23 were ≥65 years old. Forty-two subjects (4.3%) reported a previous episode of malaria a median of 9 years before enrollment. The average duration of travel was ~2.5 weeks, and 79% of subjects traveled to Africa.

All subjects and study personnel remained blinded to treatment assignment with 5 exceptions. Two subjects in the atovaquone-proguanil group and 3 in the mefloquine group lost their study drug during their return trip from a malaria-endemic area, and the investigator broke the blind to enable completion of postexposure prophylaxis with active drug.

The mean duration of treatment ± SD was 28 ± 8 days for subjects who received atovaquone-proguanil and 53 ± 16 days for those who received mefloquine. The proportions of subjects in the atovaquone-proguanil group who took at least 80% of prescribed doses in the pretravel, travel, and posttravel periods, were 95%, 95%, and 88%, respectively; for the mefloquine group, the proportions were 96%, 93%, and 70%, respectively. In the posttravel period, the difference between groups was significant ($P = .001$).

At 7 days after returning from a malaria-endemic area, ≥1 AE, regardless of potential relationship to study drug, was reported in 352 (71.4%) of 493 subjects in the atovaquone-proguanil group and 325 (67.3%) of 483 subjects in the mefloquine group. The difference in frequency of AEs in the intent-to-treat population was 4.1% (95% CI, −1.7 to 9.9). The total number of AEs reported was 1037 (38.4 per 100 person-weeks) in the atovaquone-proguanil group and 1163 (43.4 per 100 person-weeks) in the mefloquine group.

Because of the different recommended pretravel dosing regimens, subjects randomized to receive atovaquone-proguanil started receiving mefloquine placebo up to 3 weeks before starting atovaquone-proguanil. There were also 3 subjects in the mefloquine group who started receiving atovaquone-proguanil placebo before starting active mefloquine. Excluding events that occurred while subjects were receiving only placebo, AEs were reported in 318 (64.5%) of 493 subjects who received atovaquone-proguanil and 324 (67.1%) of 483 subjects who received mefloquine. The difference in frequency of AEs in the population who received active treatment was −2.6% (95% CI, −8.5 to 3.4).

Of the 2120 treatment-emergent AEs, 1310 (62%) were considered by the investigator to be unrelated to the study drug. Treatment-emergent AEs attributed to study drug occurred in a significantly higher proportion of subjects who received mefloquine, compared with those who received atovaquone-pro-

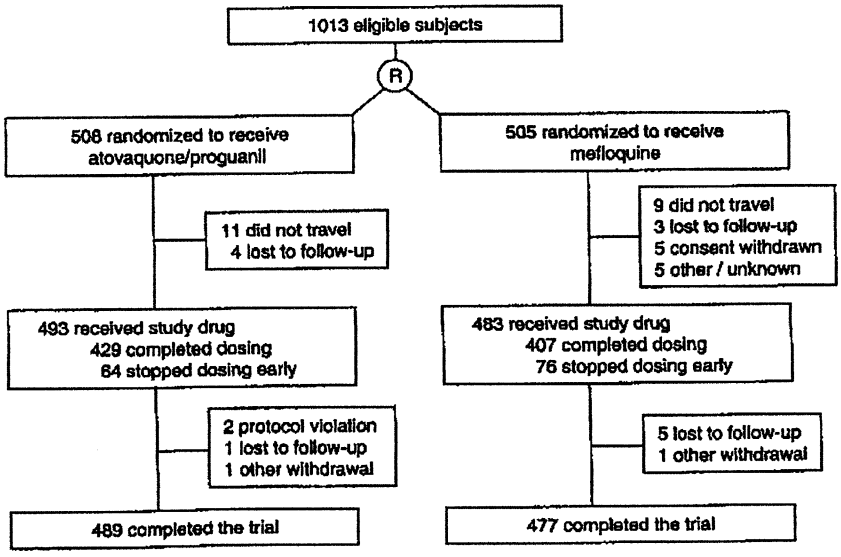

Figure 2. Flow diagram of subject accountability during the trial. R, randomized.

Table 1. Baseline characteristics of the study groups in a comparison of atovaquone-proguanil with mefloquine for malaria prophylaxis.

Characteristic	Patients who received: Atovaquone-proguanil (n = 493)	Patients who received: Mefloquine (n = 483)
Age, years		
Mean ± SD	33.0 ± 13.3	33.6 ± 13.2
Range	4–79	5–80
Sex, % male:% female	53:47	57:43
Race, %[a]		
White	90	89
Black	6	7
Asian	2	3
Other	1	1
Height, mean cm ± SD	174 ± 12.1	173 ± 12.3
Weight, mean kg ± SD	72.0 ± 15.3	71.2 ± 15.2
History of malaria		
Yes, %	4.5	4.1
Time since last episode, median years (range)	8 (1–40)	10 (1–50)
Travel destination, %		
East Africa	37	35
West Africa	24	24
Southern Africa	17	15
Central Africa	4	3
South America	6	7
Other	13	16
Duration of travel, mean days ± SD	18.8 ± 6.9	18.6 ± 7.0

[a] Percentages may not add up to 100 because of rounding.

guanil (42% vs. 30%; $P = .001$). The difference was especially pronounced for neuropsychiatric events (table 2).

Most AEs were mild in intensity. AEs attributable to the study drug were described as moderate (interfered with daily activities) or severe (required medical advice) in 51 (10%) of 493 subjects (96 events) who received atovaquone-proguanil and in 92 (19%) of 483 subjects (194 events) who received mefloquine (difference, 9%; $P = .001$). These events were severe in 19 subjects (4%; 31 events) who received atovaquone-proguanil and in 29 subjects (6%; 55 events) who received mefloquine.

Sixty-four subjects in the atovaquone-proguanil group and 76 subjects in the mefloquine group discontinued use of the study drug prematurely. The reasons for premature discontinuation in the atovaquone-proguanil group versus the mefloquine group were AEs (16 subjects vs. 26 subjects), protocol violation (8 vs. 10), and other (40 vs. 40). Other reasons included the following: the subject did not travel, the study drugs were lost or stolen, and the subject stopped taking the study drug prematurely after returning from travel.

Among subjects who discontinued taking the study drug as a result of an AE, the event was attributed to treatment in 37 subjects. Twenty-eight such events occurred in 13 subjects randomized to receive atovaquone-proguanil, and 79 such events occurred in 24 subjects randomized to receive mefloquine (table 3). In the atovaquone-proguanil group, 16 events in 8 subjects occurred after starting mefloquine placebo but before starting atovaquone-proguanil. Treatment-limiting neuropsychiatric events began in 19 subjects while they were receiving mefloquine, in 5 subjects while they were receiving mefloquine placebo, and in 3 subjects while they were receiving atovaquone-proguanil.

A serious AE occurred in 4 subjects who received atovaquone-proguanil (infectious illnesses in 3 subjects and cerebral ischemia in 1 subject) and in 10 subjects who received mefloquine (infectious illnesses in 7 subjects and breast cancer, anaphylaxis, or fractured femur in 1 subject each). None was considered attributable to treatment with the study drug.

For the 220 subjects who had laboratory safety samples obtained, there were no significant differences in either treatment group between baseline and follow-up values for hematology and clinical chemistry tests. No clinically important laboratory abnormalities were identified.

A potential diagnosis of malaria was entertained in 4 subjects,

Table 2. Treatment-emergent adverse events attributed to the study drug.

Event	No. (%) of subjects with adverse events who received: Atovaquone-proguanil (n = 493)	No. (%) of subjects with adverse events who received: Mefloquine (n = 483)	P
Any adverse event[a]	149 (30)	204 (42)	.001
Any neuropsychiatric event	69 (14)	139 (29)	.001
Strange or vivid dreams	33 (7)	66 (14)	.001
Insomnia	15 (3)	65 (13)	.001
Dizziness or vertigo	11 (2)	43 (9)	.001
Visual difficulties	8 (2)	16 (3)	.134
Anxiety	3 (<1)	18 (4)	.002
Depression	3 (<1)	17 (4)	.003
Any gastrointestinal event	77 (16)	94 (19)	.159
Diarrhea	37 (8)	34 (7)	.875
Nausea	15 (3)	40 (8)	.001
Abdominal pain	26 (5)	23 (5)	.826
Mouth ulcers	29 (6)	17 (4)	.112
Vomiting	7 (1)	9 (2)	.769
Headache	19 (4)	32 (7)	.040
Itching	12 (2)	15 (3)	.657

[a] Among subjects who reported a drug-related adverse event, the mean number of adverse events (± SD) per subject was 1.9 ± 1.3 for subjects while receiving atovaquone-proguanil and 2.6 ± 2.1 for subjects while receiving mefloquine.

Table 3. Treatment-limiting adverse events attributed to the study drug.

Event	Number of subjects with adverse events who received	
	Atovaquone-proguanil (n = 493)	Mefloquine (n = 483)
Any treatment-limiting event	6[a]	24[b]
Any neuropsychiatric event	3	19[b]
Insomnia	2	12
Anxiety	1	9
Strange or vivid dreams	1	7
Dizziness or vertigo	1	7
Depression	0	3
Visual difficulties	0	3
Concentration impairment	0	3
Other[c]	0	4
Any gastrointestinal event[d]	1	7
Headache	1	6
Other[e]	2	6

[a] One of 6 subjects developed visual disturbance 5 days before starting active atovaquone-proguanil therapy; the subject also developed headache and vertigo 8 days later. All 3 events were considered to be treatment limiting. Seven additional subjects developed a treatment-limiting adverse event while receiving mefloquine placebo before starting active atovaquone-proguanil therapy. These included 5 subjects with neuropsychiatric events (3 subjects with insomnia, 3 with strange or vivid dreams, 2 with depression, 2 with visual difficulties, and 1 with anxiety), gastrointestinal events (1 subject with nausea and 1 with vomiting) or headache (in 2 subjects).

[b] $P = .001$.

[c] Other neuropsychiatric events were irritability, dysarthria, mood disorder, dyspraxia, trembling hands, and hyperventilation, each of which occurred in 1 subject who received mefloquine.

[d] Gastrointestinal events were vomiting, diarrhea, and abdominal pain in 1 subject who received atovaquone-proguanil; and diarrhea (in 4 subjects), abdominal pain (in 3), nausea (in 3), vomiting (in 2), and bloating (in 1) in subjects who received mefloquine.

[e] Other events were urticaria and pruritic rash, each of which occurred in 1 subject while receiving atovaquone-proguanil, and body ache, dry lips, acne, musculoskeletal pain, leg pruritus, night sweats, fever, fatigue, and tachycardia, each of which occurred in 1 subject while receiving mefloquine.

but serologic testing indicated that none of them had malaria. One subject who had received atovaquone-proguanil developed fever, cough, stuffy nose, nausea, and vomiting 3 days after arrival in Ghana. A local physician diagnosed malaria, respiratory infection, or both, and the physician prescribed orally administered antibiotics and a single injection of chloroquine. No blood smears or other diagnostic samples were obtained, and there was no significant increase in blood-stage antibody titers after travel. Two subjects who had received mefloquine had *P. falciparum* malaria diagnosed on the basis of blood smears that were obtained while traveling in Uganda (16 days after arrival) or Angola (10 days after arrival). Both were treated for malaria, but specimens for diagnostic confirmation were not returned to the reference laboratory, and there was no significant increase in blood-stage antibody titers after travel. One subject who had received mefloquine developed fever, headache, abdominal pain, and myalgia 7 days after arrival in Ghana. He was treated for malaria, but no blood smears or other diagnostic samples were obtained, and antibodies to blood-stage parasites were not detected in serum samples obtained at the 4-week posttravel visit.

A total of 963 subjects completed the 60-day follow-up period and had efficacy information recorded. A total of 915 subjects had paired serum samples available for serological testing, and circumsporozoite antibodies developed in 10 subjects (1.1%). The minimum and maximum observed efficacy of both atovaquone-proguanil and mefloquine was 100% (table 4).

DISCUSSION

This study was designed to compare the AE profiles of atovaquone-proguanil and mefloquine for chemoprophylaxis of malaria in nonimmune travelers. The proportions of subjects who had at least 1 AE was similar in the 2 treatment groups, but evaluation of several parameters indicated that atovaquone-proguanil was better tolerated than was mefloquine. Subjects randomized to receive atovaquone-proguanil had a lower frequency of treatment-related neuropsychiatric AEs, a lower frequency of treatment-emergent AEs of moderate or severe intensity, and a lower frequency of treatment-related events that caused prophylaxis to be discontinued, compared with those randomized to receive mefloquine.

Failure to complete the full course of antimalarial prophylaxis will increase the risk of developing malaria, and neuropsychiatric events are the most important AEs that cause travelers to discontinue mefloquine prophylaxis. Although none of the neuropsychiatric events related to mefloquine were considered serious, 19 such events caused subjects to discontinue prophylaxis. Overall, prophylaxis was discontinued as a result of a drug-related AE in 5% of the subjects who received mefloquine but only 1.2% of the subjects who received atovaquone-proguanil (table 3). In addition, the proportion of subjects who took at least 80% of prescribed doses of study drug in the posttravel period was higher with atovaquone-proguanil than with mefloquine (88% vs. 70%). This may be because the duration of posttravel dosing is shorter with atovaquone-proguanil (7 days) than it is with mefloquine (4 weeks).

The pretravel dosing regimens are also different, and subjects randomized to the atovaquone-proguanil group received mefloquine placebo for up to 3 weeks before starting therapy with atovaquone-proguanil. There were 64 neuropsychiatric events in 44 subjects that occurred after starting mefloquine placebo but before starting active chemoprophylaxis with atovaquone-proguanil. This may represent the background incidence of these events in people planning for international travel. Alternatively, this may be related to widespread publicity about neuropsychiatric side effects associated with mefloquine or infor-

Table 4. Estimates of minimum and maximum efficacy for malaria prophylaxis.

Variable	Subjects who received	
	Atovaquone-proguanil	Mefloquine
Subjects with 60-day efficacy data available, no.	486	477
Subjects who developed circumsporozoite antibodies, no.	5	5
Subjects with confirmed malaria, no.	0	0
Minimum efficacy, % (95% CI)[a]	100 (48–100)	100 (48–100)
Maximum efficacy, % (95% CI)[b]	100 (99–100)	100 (99–100)

[a] Minimum efficacy = 100 × [1 − (no. of subjects with confirmed malaria/no. with circumsporozoite antibodies)].
[b] Maximum efficacy = 100 × [1 − (no. of subjects with confirmed malaria/no. with 60-day efficacy data)].

mation provided during the informed consent process, with a resulting placebo effect in some subjects who think they are receiving mefloquine. A placebo effect could explain the higher frequency of AEs among subjects who received atovaquone-proguanil in the present study compared with a similar study in which subjects who received atovaquone-proguanil were given placebos for chloroquine and proguanil instead of mefloquine [15].

The frequency of AEs in the atovaquone-proguanil group in the previous study compared with the present study was 61% versus 71% for all AEs (regardless of attributability to study drug) and 22% versus 30% for AEs considered to be drug related. In the present study, neuropsychiatric events were reported by a significantly larger proportion of subjects who received mefloquine, compared with those who received atovaquone-proguanil (table 2), which provides convincing evidence that such events are causally related to mefloquine in some people.

The frequency of AEs attributed to mefloquine in the present study (42%) is similar to the frequency in 2 previous studies that used a questionnaire to elicit information about specific side effects. Among 1214 British travelers who received mefloquine and who responded to a postal questionnaire after returning from abroad, 503 (41%) reported side effects that they attributed to mefloquine [7]. Among 183 British soldiers who responded to a questionnaire 2 weeks after starting prophylaxis with mefloquine, 71 (39%) reported AEs considered by the investigators to be side effects of mefloquine [20].

In the United States, the wholesale acquisition price per tablet is $3.92 for Malarone-brand atovaquone-proguanil and $7.55 for Lariam-brand mefloquine (First DataBank, Inc., unpublished data, October 2000). For trips of 1, 7, or 14 days' duration, to use the prophylaxis regimens outlined in figure 1, a traveler would need 9, 15, or 22 Malarone tablets (at a wholesale acquisition price of $36, $59, or $86, respectively) or 7, 8, or 9 Lariam tablets (at a wholesale acquisition price of $53, $60, or $68, respectively). Short-term travelers are likely to have minimal concern about the cost difference between atovaquone-proguanil and mefloquine. Long-term travelers (those who travel for >2 weeks) will need to weigh the higher costs of atovaquone-proguanil against the benefits of improved tolerability compared with mefloquine and the impact that adverse reactions to antimalarial drugs may have on their trip.

We evaluated the efficacy of chemoprophylaxis as a secondary end point. A diagnosis of malaria is often based on the presence of fever in a person who has been potentially exposed to infected mosquitoes or is based on inaccurate interpretation of blood films; experience has shown that such diagnoses are often incorrect. We attempted to collect blood specimens at the time of suspected diagnosis for evaluation in a reference laboratory, as described elsewhere [15], but these attempts were unsuccessful in the 4 subjects for whom a diagnosis of potential malaria was made during travel. Fortunately, measurement of antibodies to blood-stage parasites is an established procedure for confirming a suspected diagnosis of malaria [21]. Blood-stage antibodies generally develop within 3–9 days after onset of patent parasitemia and persist for many months or years [22]. Of the 4 subjects in this study who were considered by a local health care provider to have "malaria" during travel, one had an illness that occurred 3 days after arrival, which is shorter than the minimum prepatent period [23], and none of the 4 developed a significant rise in blood-stage antibodies in serum samples obtained 4 weeks after travel. Thus, there were no cases of confirmed malaria in this study.

Antibodies to the circumsporozoite protein of *P. falciparum* develop in many subjects bitten by an infected mosquito, including people taking no prophylaxis who develop malaria [24] and those taking effective prophylaxis who do not develop malaria [25]. Prospective collection of paired serum samples to measure anticircumsporozoite antibodies allowed us to estimate the minimum efficacy of chemoprophylaxis. Because we obtained only a single postexposure serum sample, the number of subjects in our study with a circumsporozoite antibody response is a minimum estimate of the number actually bitten by a malaria-infected mosquito. Because only 10 subjects de-

v[illegible]oped anticircumsporozoite antibodies, the estimated mini-p[illegible] efficacy has a broad confidence interval (table 4).

In summary, results from this study show that atovaquone-proguanil was better tolerated than was mefloquine, and that it was similarly effective for malaria prophylaxis in nonimmune travelers.

STUDY GROUP MEMBERS

O[illegible] members of the Malarone International Study Team include Suni Boraston and James Salzman (Vancouver, British Columbia) and Dominique Tessier (Montreal, Quebec, Canada); Theo J. L. M. Goud (Rotterdam, The Netherlands); Klaus Fleischer (Würzburg), Manfred Peters (Hamburg), and Berndt Zieger (Dresden, Germany); and Simmy Waner (Johannesburg, South Africa).

GlaxoSmithKline members of the study team include Fatima Ar[illegible]d (Midrand, South Africa); Clare Brennan, Gerri B. Miller, an[illegible] Trevor Scott (Research Park Triangle, North Carolina, United States of America); Corinne Hedgley (Greenford) and Miriam O'Hare (Bournemouth, United Kingdom); Tine Hendrickx, Paul de Jonge, and Sanne van Delft (Zeist, The Netherlands); Raymond Marina (Mississauga, Ontario, Canada); and Heinz Richter (Hamburg, Germany).

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