

**CENTER FOR DRUG EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**21-078 / S-003**

**MEDICAL REVIEW**

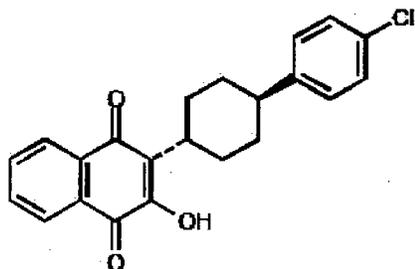
**Medical Officer Review of NDA 21-078/S-003**  
**Malarone™**  
**(Atovaquone and Proguanil hydrochloride)**

**NDA number:** 21-078 /S-003  
**Submission date:** October 5, 2001  
**Stamp date:** October 9, 2001  
**Review complete:** June 21, 2002.

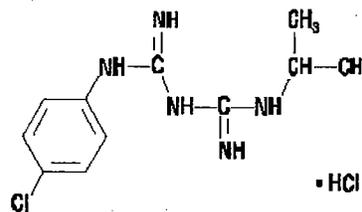
**Applicant:** GlaxoSmithKline  
One Franklin Plaza  
PO box 7929  
Philadelphia PA 19101-7929

**Drug:** Trade: Malarone™  
Generic: Atovaquone and proguanil hydrochloride

**Atovaquone**



**Proguanil hydrochloride**



**Therapeutic category:** Antimalarial

**Dosage form:** Tablet

**Route of administration:** Oral

**Contents of submission:** Two clinical study reports.

**Purpose of submission:** To support revised labeling reflecting the tolerability and efficacy of malarone for malaria prophylaxis in non-immune travelers

**Reviewer:** Leonard Sacks, Medical Officer  
Division of Special Pathogen and Immunologic Drug Products  
HFD-590

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## Executive summary

Malarone was approved for the treatment and prophylaxis of malaria caused by *P falciparum* in 2000. The approval was based predominantly on studies performed in malaria endemic areas and participating subjects were at least partially immune to malaria. The prophylactic efficacy of malarone in malaria naïve subjects was not well studied and for this reason, phase 4 studies were requested in malaria naïve subjects. The applicant performed two such studies (MAL 30010 and MAL 30011) and on the basis of the results, has proposed labeling changes to reflect the tolerability and efficacy in these studies.

Both studies were conducted in healthy travelers to malaria endemic areas. The studies differed primarily in the comparator used (mefloquine in 30010 and chloroquine/proguanil in 30011) and the fact that children >3 years were included in 30010 and subjects greater than 14 years were included in 30011.

In both studies the aim was to include malaria naïve subjects travelling to malaria endemic areas. This was largely accomplished since 4% of the participants in study 30010 and 1.5% of the participants in study 30011 had a history of malaria, a mean of 12.2 years and 17 years previously respectively.

The number of patients eligible for intent-to-treat analysis in each study, and relevant demographic characteristics are shown below.

**Table 1: Description of study populations**

	30010		30011	
	Malarone (n=493)	Mefloquine (n=483)	Malarone (n=511)	Chloroquine/ proguanil (n=511)
Age (mean, range)	33 (4-79)	33.6 (5-80)	36 (13-72)	35 (13-74)
% female	47	43	51	46
White	90	89	97	95
Previous malaria (% yes)	4	4	2	1
Years since malaria episode (mean, range)	10.9 (3-38)	13.6 (3-37)	19.7 (2-60)	14 (2-30)
Duration of trip (mean, range) days	18.8 (3-38)	18.6 (3-37)	16.9 (2-32)	17.6 (3-34)

Both studies comprised predominantly adult white subjects. The demographic characteristics for both arms in both studies were very similar. Both studies were performed on travelers from Canada, Europe and South Africa.

The treatment regimens in each of the studies are shown below:

**Figure 1: Treatment regimens**

### Study 30010

Placebo	-7 days	Malarone Period of Travel	+7 days	Placebo
-21 days		Mefloquine Period of Travel	+28 days	

### Study 30011

Placebo	-2 days	Malarone Period of Travel	+7 days	Placebo
-7 days		Chloroquine/proguanil Period of Travel	+28 days	

Adverse events:

**Table 2: Frequency of all treatment-emergent, drug related adverse events occurring from the first to the last dose of study medications (study 30010)**

Malarone	Mefloquine
203/493 (41%)	205/483 (42%)

**Table 3: Frequency of all treatment-emergent drug-related adverse events occurring from the first to the last dose of study medications (study 30011)**

Malarone	Chloroquine/proguanil
136/511 (27%)	142/511 (28%)

Despite similarities in study design, reporting rates for all adverse events and for drug-related adverse events were substantially higher for malarone users in study 30010 than for malarone users in study 30011. This is unlikely to be due to the slightly longer duration of Malarone treatment in study 30010. The reason for this difference is unclear. In study 30010, subjects suspecting they were on mefloquine may have been more inclined to report adverse events given the prevailing public opinion that mefloquine is poorly tolerated.

Treatment limiting adverse events (AE):

**Table 4: Numbers of subjects with treatment limiting adverse events**

	30010		30011	
	Malarone (n=493)	Mefloquine (n=483)	Malarone (n=511)	Chloroquine/proguanil (n=511)
Treatment limiting AEs	13*	24	11**	15

\*Eight of these were receiving placebo only at the time

\*\*Four of these were receiving placebo only at the time

Individual adverse events

For the period that subjects received active drug, neurological complaints (insomnia, dizziness, headache, dreams, anxiety, and depression) were more common in Mefloquine-treated subjects than in malarone-treated subjects. Oral ulcers were more common in malarone treated subjects. Gastro-intestinal complaints (diarrhea, nausea, abdominal pain and vomiting) were more common in chloroquine/proguanil-treated subjects than in malarone-treated subjects. The frequency of other adverse events was numerically similar between the arms.

Some adverse events, such as diarrhea, are common in travelers and may be less specifically drug-related. The targeted nature of questioning is likely to have increased the reporting of these events compared to non-targeted events.

Reporting rates for individual adverse events were determined during the period that subjects received active drug and differed between the arms of the study. Hence the period of adverse event data collection for mefloquine data was approximately 5 weeks longer than that for malarone and the period of adverse event data collection for chloroquine/proguanil was approximately 3 weeks longer than for malarone. While a more equitable analysis would reflect adverse event rates from 1 week before travel to 1 week after travel in both arms, the above analysis effectively describes the adverse event rates attributable to the regimen in each arm.

Notably, in the case of individual adverse events, the frequency was very similar in the malarone arms of both studies.

Serious adverse events:

There were no deaths in either study.

Serious adverse events (SAE) were reported in both studies but none was attributed to study drug.

**Efficacy:**

Neither of the two studies was designed to test comparative efficacy. This was because extremely large numbers of participants would be needed to provide adequate statistical power, given the low risk of malaria in travelers and the even lower risk of prophylactic failure in those patients who are bitten by an infected mosquito.

In study 30010, there were 3 patients diagnosed with laboratory confirmed *P falciparum* malaria- all in the chloroquine/proguanil arm of the study. Published literature has reflected the poor efficacy of this regimen in regions of chloroquine resistance.

One patient in the malarone arm developed *P ovale* malaria 40-55 days after travel

In study 30011, four suspected cases of malaria were reported. None was confirmed by slides at the central laboratory and malaria antibodies were negative in all four. The reviewer considered two of these cases "possible"- both in the mefloquine arm. The other two cases (one in the malarone arm and one in the mefloquine arm) were considered unlikely.

In an intent-to-treat analysis where individuals lost to follow up were regarded as prophylactic failures, the prophylactic efficacy of each arm in the 2 studies was as follows.

- In study 30010, 3 subjects in the Malarone group and 5 in the mefloquine group did not have 60 day follow up data. The applicant calculated the prophylactic efficacy of both Malarone and mefloquine as 99%.
- In study 30011, 5 subjects in the malarone group and 2 in the chloroquine/proguanil group did not have 60-day efficacy data available. The prophylactic efficacy in this ITT analysis was 99% for both arms

Since the studies were not powered to demonstrate efficacy, the actual exposure to malaria was unknown, and the subjects lost to follow up had a low probability of developing malaria, this analysis is not a rigorous reflection of the true prophylactic efficacy. The results suggest that all regimens used in the studies are effective for malaria prophylaxis.

Based on actual cases of malaria identified, chloroquine/proguanil appears to be the only regimen associated with confirmed prophylactic failure.

**Conclusions:**

- These studies demonstrate good tolerability of Malarone compared to Mefloquine and to chloroquine/proguanil. Malarone resulted in a lesser frequency of neurological adverse events than mefloquine and a lesser frequency of gastrointestinal adverse events than chloroquine/proguanil. While adverse event rates were more common in younger than older subjects, too few pediatric subjects were included to allow an evaluation of pediatric safety. Females treated with malarone were found to have higher overall adverse event rates in only one of the two studies. No specific other subpopulation was identified at increased risk for adverse events.
- Compliance was better with malarone than with the comparator drugs, largely as a result of the shorter prophylactic regimen.
- The efficacy of study drugs could not be rigorously determined. Confirmed prophylactic failures were only identified among subjects treated with Chloroquine/proguanil. The findings were restricted to predominantly white subjects.
- The findings support labeling describing the tolerability of Malarone however the reviewer recommends the reporting periods be reflected in both arms of each study so the reader is clear that the duration of therapy (and hence the period that adverse events were reported) was longer on comparator than on Malarone.

## Background

Malarone was approved for the treatment and prophylaxis of *P falciparum* malaria in 2000. The original NDA supporting malarone prophylaxis, relied on clinical studies performed in Kenya, Zambia, Gabon and South Africa. These areas are endemic for malaria and study subjects were presumed to have varying degrees of malaria immunity, based on previous exposure, a high prevalence and incidence of malaria in placebo- treated arms, and the prevalence of splenomegaly.

Subjects with malaria immunity are partially protected against malaria and in cases of active infection they tolerate levels of parasitemia that would normally cause fever and symptoms in naïve subjects. As such, malaria immune subjects may rely less on the efficacy of antimalarial drugs than malaria naïve subjects. Since travelers from the US are almost universally malaria naïve, it is important to confirm the efficacy of prophylactic regimens in these individuals. However prophylactic studies of malaria in travelers are fraught with difficulties. Malaria exposure in travelers varies with the geographic regions that they visit, seasonal changes in malaria prevalence, the types of activities they perform while traveling and the duration of travel. Placebo arms cannot ethically be employed in such patients, so that malaria exposure in these travelers cannot be reliably estimated. Very large active controlled studies may potentially demonstrate drug efficacy in this setting.

On this basis, phase 4 studies were required in malaria naïve travelers, following the initial approval of malarone. This information together with the information from malaria challenge studies in malaria naïve volunteers on prophylaxis reflects drug efficacy in non-immune individuals.

A challenge study in malaria naïve subjects was submitted in the initial NDA. This study employed atovaquone alone rather than the combination of atovaquone and proguanil and good antimalarial activity was demonstrated. This study also indicated that atovaquone was effective as a “causal prophylactic” and that the prolonged suppressive regimen usually required with other comparable products after leaving a malaria area, was not necessary with atovaquone. A further phase 4 study was requested to confirm these findings using malarone rather than atovaquone. This study was not submitted as part of this NDA.

The other available agents approved for malaria prophylaxis in the US include chloroquine, mefloquine and doxycycline. In most parts of the world, *P falciparum* is resistant to chloroquine. Chloroquine has been used together with proguanil in some countries to enhance its efficacy, although prophylactic failures are well recognized with this regimen. Resistance to mefloquine is rare, but adverse events related to the use of mefloquine (particularly of a neuropsychiatric nature) are frequent and pose an important obstacle to compliance. The efficacy of doxycycline has not been rigorously compared to other agents, it is contraindicated in children, and causes photosensitivity and gastro-intestinal intolerance. In view of the disadvantages with these alternatives, it is also important to characterize the comparative safety of malarone, allowing for a “risk benefit” evaluation when selecting drugs for malaria prophylaxis.

This submission includes 2 studies of malarone prophylaxis in malaria naïve travelers. The object of this submission is to support a labeling change reflecting the efficacy and tolerability of Malarone in non-immune travelers.

A DSI inspection was not requested as this NDA does not support any new indication or any new population for intended use, and no inconsistencies in the data between study centers were evident.

## **MAL 30010: An international randomized double blind study to compare the safety and efficacy of malarone versus mefloquine for chemoprophylaxis against malaria in non-immune travelers.**

Primary objective: To compare the safety of malarone with mefloquine  
Secondary objective: To compare the efficacy of malarone with mefloquine

### **Study design**

This was a randomized, double-blind, active-controlled, multicenter study performed in non-immune travelers using malarone or mefloquine for prophylaxis. Subjects were randomized to receive malarone or mefloquine in a blinded fashion at a screening visit 1-4 weeks prior to travel. A single follow up visit was scheduled 4 weeks after returning home, and the investigators conducted two additional telephone interviews.

The estimated risk of developing malaria in East Africa without taking prophylaxis was 1.2% per month (Weiss et al, J infect Dis 1995; 171:1569-75) In this situation, the applicant claims that to establish equivalence with a comparator where predicted efficacy was 90% would require 120,000 subjects. The present study does not aim to demonstrate equivalent prophylactic efficacy to Mefloquine. However the applicant attempted to identify subjects who were bitten by malaria infected mosquitos while on prophylaxis, which would allow a more realistic evaluation of efficacy. Since individuals bitten by malaria infected mosquitoes while on prophylaxis often develop antibodies to the circumsporozoite (CS) antigen of *P falciparum*, paired sera were collected on all participants before and after travel in an attempt to confirm exposure.

*MO comment: The methodology, sensitivity and specificity of the CS antibody test have not been validated. However in the absence of a feasible alternative study design, such information will be regarded as supportive. Potential drawbacks include unconfirmed specificity and the possibility that remote exposure may still give a positive result, for example in African expatriates returning to visit family. The sensitivity is not known, and low inocula may result in negative antibody tests.*

### **Study population**

The study was performed on malaria naïve travelers from 15 centers in Canada, Europe and South Africa. The length of stay in a malaria area was not to exceed 28 days.

*MO comment: A minimum stay was not stipulated and very short stays would diminish the chances of contracting malaria. However, since the aim of the study was to prove safety and not efficacy, even short stays required several doses of study drugs, and provided acceptable safety information.*

### Inclusion criteria:

- Informed consent
- Male and female volunteers >3 years of age and >11kg
- Females of childbearing potential must employ effective measures to prevent pregnancy.
- Good health on history and physical examination
- Travel to an area with substantial risk for *P falciparum*.
- Stay in the malaria area for <28 days
- Telephone contact 7 and 60 days after leaving the malaria area and a clinic visit 4 weeks after leaving the malaria area.

### Exclusion criteria:

- Hypersensitivity to atovaquone, proguanil or mefloquine
- History of seizures or psychiatric disorders
- Alcoholism

- Significant renal or hepatic impairment, cardiac dysfunction, neurological or hematological disorders
- Pregnancy or lactation
- Active malaria within the 12 months prior to the study
- Visit to a malaria area within the previous 60 days

Subjects who discontinued study drug prematurely because of an adverse event were to be followed at all protocol scheduled visits.

### Treatment arms

**Table 30010-1: Treatment regimens**

Malarone arm		Mefloquine	
Drug and dosage	Regimen	Drug and dosage	Regimen
Malarone (atovaquone/proguanil)	1 to 2 days before entering malaria area till 7 days after leaving	Malarone placebo	1 to 2 days before entering malaria area till 7 days after leaving
Mefloquine placebo	Once weekly, 1-3 weeks before entering malaria area till 4 weeks after leaving	Mefloquine	Once weekly, 1-3 weeks before entering malaria area till 4 weeks after leaving

Malarone adult tablets (batch T98/070A) contained 250mg atovaquone and 100mg proguanil hydrochloride. Malarone pediatric tablets (batch T98/088A) contained 62.5mg atovaquone and 25mg proguanil hydrochloride. Mefloquine tablets (batch T98/118A) contained 250mg mefloquine base. Double dummies were provided.

### Dosing:

**Table 30010-2: Dosing of study drugs**

Malarone		Mefloquine	
Adults	1 full strength tablet daily	Adults	1 tablet weekly
11-20kg	1 pediatric tablet daily	11-12kg ¼ tab	¼ tab weekly
21-30kg	2 pediatric tablets daily	13-24	½ tab weekly
31-40kg	3 pediatric tablets daily	25-35kg	¾ tab weekly
>40kg	1 full strength tablet daily	>35kg	1 tab weekly

Compliance was monitored subject diaries, review of returned medication and interview.

Concurrent medication was recorded at all study visits and telephone contacts.

### Randomization:

Randomization was stratified by center and body weight ( $\leq 40$ kg or  $> 40$ kg)

### Study schedule:

Screening visit	1-4 weeks prior to entering malaria area
Telephone contact	1- 7 days after leaving malaria area
Follow-up visit	4 weeks after leaving malaria area
Telephone contact	2- 60 days after leaving malaria area
Unscheduled visits	

At each contact, subjects were asked about 15 symptoms:  
 fever, nausea, vomiting, abdominal pain, diarrhea  
 mouth ulcers, itching  
 headache, insomnia, strange or vivid dreams, dizziness,  
 anxiety, depression,  
 visual difficulties and seizures

*MO comment: Active questioning, specifically about the above symptoms, is likely to increase their frequency compared to unsolicited adverse events. Since this was performed in both arms, the comparative frequency of adverse events will still be evident.*

Other reported symptoms were recorded.

Symptoms were graded as:

- mild (neither interfering with daily activities nor requiring medical advice),
- moderate (interfering with daily activities),
- severe (where medical advice was sought)
- treatment-limiting events (those that resulted in permanent drug discontinuation)

Hematology and clinical chemistry tests were performed at one site on screening and 4 weeks after returning.

Adverse events (AE) included exacerbations of previous illnesses, and conditions diagnosed after starting the study drug, even if present before.

Medical or surgical procedures themselves and overdoses without signs or symptoms were not regarded as AE's

The disease being studied was not regarded as an AE unless more severe than expected.

*MO comment: Many of the anticipated adverse events were similar to those symptoms typical of malaria. The controlled study design should eliminate differences between the arms that are the result of malaria rather than study drug.*

Severe adverse events (SAE) included:

Death, life threatening events, hospitalization or prolongation of hospitalization, disability, congenital anomalies in offspring, and others that are judged medically serious on their merit.

**Measures of efficacy:**

Participants were asked at 7 days, 4 weeks and 60 days after returning from travel whether malaria was diagnosed.

In cases of malaria, information was requested on malaria species, date of symptoms and confirmation of diagnosis, and dates that chemoprophylaxis was taken.

**Sample size:**

Five hundred subjects were to be randomized to each treatment arm. The applicant calculated the 400 evaluable patients per arm had an 82% power to detect non-inferiority of malarone if the overall proportion of adverse events were 40%. The 95% confidence bounds for non-inferiority (Malarone AE proportion – mefloquine AE proportion) was -100% to +10%.

The applicant examined AEs both while on any study drug and while on active drug only reflecting respectively all adverse events and drug attributable adverse events.

The primary endpoint was AE rates from treatment start till 7 days post travel.

*MO comment: The reviewer concurs with this endpoint, as including the entire period of therapy selectively increases exposure to mefloquine and should result in inflated AE rates. It is noted that even under these circumstances exposure to mefloquine will have been greater than to malarone since active mefloquine will have been taken 2-3 weeks before active malarone. However eliminating the initial treatment period would potentially lose many AEs from mefloquine to which patients accommodate with time.*

Similar analyses were performed up to 28 days post travel.

**Analysis populations**

**Safety:** All participants who received at least 1 dose of study drug and had at least one opportunity to report an AE.

**Intent to treat (ITT)** As for the safety population, but subjects who did not enter a malaria area for reasons other than adverse events or loss-to-follow-up were excluded *but subjects who never entered a malaria endemic area were excluded.*

**Per Protocol (PP)**

All subjects randomized and compliant with assigned therapy, remaining blinded to therapy and for whom 60-day efficacy data were available

Adverse events reported by subjects discontinued prematurely were included. After discontinuation, the applicant assumed that no further adverse events occurred in such subjects

**Exposure:**

Duration of exposure was recorded as the interval from first to last dose of study medications.

Compliance was reported as the ratio of number of doses taken/(number of doses taken plus number of doses missed).

**Efficacy:**

The diagnosis of malaria was classified as “definite” if parasites were documented on a blood smear returned to the central laboratory and/or PCR on whole blood or filter paper in the central laboratory was positive.

*MO comment: PCR technology has not been validated in this context. The reviewer will rely on smears for confirmation as “definite” positives. Patients with positive PCR results will be considered in a secondary analysis.*

The diagnosis was “possible” if a diagnosis of malaria was recorded on the case report form based on information from a health care provider, but confirmatory laboratory specimens were not provided.

A diagnosis of malaria was considered “negative” if malaria was recorded on the CRF but smears and parasite DNA analysis by the central laboratory were negative or were missing and antibodies to blood stage parasites were negative.

*MO comment: Antibodies to blood stage parasites have not been validated as confirmatory. They may be residual from remote exposure, and their sensitivity is not well characterized. Patients with such equivocal “negative” results will be assessed by the reviewer on a case by case basis, paying attention to symptoms, response to treatment etc.*

To determine minimum efficacy, the number of patients with malaria over the number who developed anti-CS antibodies and for whom 60 day efficacy data were available, was calculated. If the post travel CS test was not available, it was assumed to be negative.

To calculate maximum efficacy, the denominator was the number of subjects for whom 60-day efficacy data were available.

Percent efficacy was calculated as  $100 \times [1 - (\text{number of subjects with malaria}) / (\text{number of subjects at risk})]$   
The ITT analysis was to regard subjects without 60-day efficacy data as though they had malaria.

**Study results**

Between April 1999 and August 1999, 508 subjects from 15 sites were randomized to receive malarone and 505 to receive mefloquine

The fate of the 1013 participants is summarized below:

Thirty-seven discontinued *before taking the first dose of study drug*, 15 in the Malarone arm and 22 in the mefloquine arm. The reasons are shown below:

Did not travel to malaria area	20
Lost to follow up	7
Withdrew consent	5
Other reasons	5

Ultimately, 493 subjects received Malarone and 483 received mefloquine. The study was completed by 966/976 (99%) of these subjects.

Ten subjects *who received at least one dose of study drug* failed to complete the study because of protocol violations, loss-to-follow up or failure to travel.

*MO comment: There is no indication that subjects were excluded from study or from evaluation because of adverse events or drug failure. Completion rates for this study were high.*

Of those subjects that completed the study, premature drug discontinuations are shown below.

**Table 30010-3: Premature discontinuations**

	Malarone	Mefloquine
Adverse events	16	26
Protocol violations (most commonly: lost study drug)	8	10
Other reasons (Most commonly: non-compliance)	40	40
Total	64	76

*MO comment: Premature discontinuations were more common for adverse events in the mefloquine arm.*

The blind was broken for two subjects in the malarone arm and three in the mefloquine arm who lost their study drugs while traveling and needed to continue prophylaxis after returning.

Eight malarone-treated subjects and seven mefloquine- treated subjects were suspected to have taken the wrong treatment. The details of these 15 subjects were not provided.

**Populations analyzed:**

Safety-all subjects excluding those who never took study drug

ITT- all "safety" subjects. Those never entering a malaria area (for reasons other than loss-to-follow-up or treatment-related adverse events) were excluded

Per protocol-All ITT subjects except those who failed to meet inclusion exclusion criteria or who did not provide 60-day efficacy data.

**Table 30010-4: Number of subjects in each population**

	Safety	Intent to treat	Per protocol
Malarone (508 randomized)	493	463	356
Mefloquine (505 randomized)	483	451	368

*MO comment: There were more exclusions from the per protocol population in the malarone arm. Most of this difference was due to failure of compliance with Malarone (75 patients on malarone versus 44 on mefloquine) where daily dosing was required compared with weekly dosing for mefloquine.*

### Demographics

The demographic characteristics of both study arms were very similar as shown below.

**Table 30010-10: Demographic characteristics**

	<b>Malarone (n=493)</b>	<b>Mefloquine (n=483)</b>
Age (mean, range)	33 (4-79)	34 (5-80)
% female	47	43
Race: Asian	2	3
Black	6	7
White	90	89
Other	1	1
Previous malaria (% yes)	4	4
Years since malaria episode (mean, range)	10.9 (3-38)	13.6 (3-37)
Duration of trip (mean, range) days	18.8 (3-38)	18.6 (3-37)

*MO comment: The study population comprised predominantly white adults. Very few pediatric patients were included (11 subjects between the ages of 4 years and 10 years in the mefloquine arm and 8 in the malarone arm). The other demographic features were balanced between the arms. The adverse event profile may differ in other racial groups. This has been seen with other antimalarials. For example primaquine is not tolerated in racial populations with a high prevalence of G6PD deficiency.*

Seventy eight percent of subjects traveled to Africa.

*MO comment: This does not interfere with the analysis of safety, but efficacy in other parts of the world is not well reflected.*

### Concomitant medications

Sixty percent of subjects in the malarone group and 58% in the mefloquine group took concomitant medications. Most commonly, these included analgesics, antibiotics, vaccines, anti-diarrheal drugs and oral contraceptives.

Non-study anti-malarial medications were taken by 22 subjects (10 in the malarone arm and 12 in the mefloquine arm) for the following reasons:

Suspected malaria	4
Intolerance of study drug	9
Losing study drug	8
Protocol violation	1

For the purposes of the safety evaluation, these subjects were regarded as premature discontinuations of study drug. For the purposes of the efficacy determination, the 4 subjects with suspected malaria are discussed in the section on efficacy. The remaining cases were included as prophylaxis successes in the ITT analysis.

*MO comment: The small number of subjects receiving other antimalarials for reasons other than malaria were balanced between the arms. Since they had received some treatment with the study drug, they were evaluated as successes for the time they were on assigned treatment. (Excluding these subjects did not make a significant difference in the ITT evaluation of efficacy.)*

**Treatment compliance**

Mean duration of treatment was 28 days for malarone and 53 days for mefloquine reflecting the longer recommended treatment regimen for mefloquine.

The proportion of subjects taking at least 80% of treatment doses in each study phase is shown below.

**Table 30010-11: Proportion of subjects taking > 80% of treatment doses**

	Malarone	Mefloquine
Pre-travel	95%	96%
During travel	95%	93%
Post travel	88%	70%*

\*may reflect difficulty in complying with the 4 week post-travel requirement for mefloquine versus 1 week for malarone.

Compliance between the arms was similar before and during travel but differed after travel.

**Table 30010-12: Compliance**

	Malarone	Mefloquine placebo	Mefloquine	Malarone placebo
Mean number of tablets taken SD	27±9	9±2	8±2	26±9

**Table 30010-13: Exposure to active drug:**

	Malarone	Mefloquine
2-4 weeks	226 (46%)	
4-6 weeks	230 (47%)	
6-8 weeks		146 (30%)
>8 weeks		261 (54%)

*MO comment: the prolonged mefloquine regimen compared with malarone may in and of itself result in more adverse events from mefloquine than from malarone.*

**Adverse events**

The overall frequency of adverse events is reflected in the 3 analyses below. The analyses attempt to address the different durations of active drug administration for the two arms as shown in the schematic diagram.

**Figure 30010-1: Periods of drug therapy**

Placebo	Malarone -7 days	Malarone Period of Travel	Mefloquine +7 days	Placebo
Mefloquine -21 days		Mefloquine Period of Travel	Mefloquine	+28 days

All adverse events, drug-related and unrelated

**Table 30010-14: Frequency of adverse events occurring after start of study drug or placebo till 7 days after leaving malaria area.**

Malarone	Mefloquine	95% CI for the difference (malarone- mefloquine)
352/493 (71.4%)	325/483 (67.3%)	-1.7 to 9.9

**Table 30010-15: Frequency of adverse events occurring after start of active drug till 7 days after leaving malaria area.**

Malarone	Mefloquine	95% CI for the difference (malarone- mefloquine)
318/493 (64.5%)	324/483 (67.1%)	-8.5 to 3.4

*MO comment: This analysis selectively removes the placebo control from the first few weeks of mefloquine exposure resulting in an unfair assessment for mefloquine.*

**Table 30010-16: Frequency of adverse events occurring after start of study drug or placebo till 28 days after leaving malaria area.**

Malarone	Mefloquine	95% CI for the difference (malarone- mefloquine)
367/493 (74.4%)	347/483 (71.8%)	-3 to 8.2

*MO comment: The 10% increase in adverse events in the malarone arm from 7 days to 28 days after leaving the malaria area (during which these subjects received placebo alone) suggests that a substantial proportion of adverse events in this study are not drug attributable. The 5% increase in adverse events in the mefloquine arm from 7 days to 28 days after leaving the malaria area probably also reflects a substantial placebo effect.*

Drug related adverse events:

**Table 30010-17: Frequency of all treatment-emergent, drug-related adverse events occurring from the first to the last dose of study medications (study 30010)**

Malarone	Mefloquine	95% CI for the difference
203/493 (41%)	205/483 (42%)	

**Treatment emergent adverse events over the entire study period:**

**Table 30010-18: Most frequent adverse events (% of subjects) over entire study period while patient was on active medication**

	All events		Drug attributed events	
	Malarone	Mefloquine	Malarone	Mefloquine
Diarrhea	38	36	8	7
Nausea	14	20	3	8
Abdominal pain	17	16	5	5
Headache	12	17	4	7
Dreams	7	16	7	14
Insomnia	5	16	3	13
Dizziness	5	14	2	9
Fever	9	11	<1	1
Vomiting	8	10	1	2
Oral ulcers	9	6	6	4
Pruritis	4	5	2	2
Visual difficulties	2	5	2	3
Anxiety	1	5	<1	4
Depression	<1	5	<1	4

*MO comment: Neurological complaints (insomnia, dizziness, headache, dreams, anxiety, and depression) were more common in mefloquine-treated subjects. Oral ulcers were more common in malarone treated patients. The frequency of other adverse events was numerically similar between the arms. Some, such as diarrhea are common in travelers and may be less specifically drug-related. The targeted nature of questioning is likely to have increased the reporting of these events compared to non-targeted events. However the expectation would be that the increase would occur equally in both arms owing to the blinded design of the study.*

*The above analyses reflect the frequencies of adverse events while on active drug. Hence the period for collecting comparator data is 5 weeks longer than that for malarone treatment. A more equitable analysis to assess adverse events due to the drug rather than due to the regimen, would*

reflect adverse event rates from 1 week before travel to 1 week after travel in both arms. The above analysis reflects the adverse event rates for the regimen rather than the drug.

#### Serious adverse events:

No deaths occurred in the study.

Serious adverse events were reported in 4 subjects in the malarone arm and 10 in the mefloquine arm.

**Table 30010-19: Serious adverse events**

Drug	AE	While on study drug	Drug attributed
Malarone day 20	Diarrhea	Yes	No
Malarone ~ week 4	"viral illness", fever	Yes	No
Mefloquine ~ week 7	Pyelonephritis	Yes	No
Mefloquine	Pregnancy	No	No
Mefloquine ~ week 7	Meningoencephalitis	Yes	No
Mefloquine ~ week 9	Schistosomiasis	Yes	No
Mefloquine	Enteritis	No	No
Malarone	Cerebral ischemia	No	No
Mefloquine ~ week 7	Cellulitis	No	No
Malarone	Amebiasis	No	No
Mefloquine	"Anaphylactic reaction"? food allergy	No	No
Mefloquine	Malaria	No	No
Mefloquine	Sinusitis	No	No
Mefloquine	Fractured femur	No	No

*MO comment: The reviewer concluded that none of the serious adverse events were attributable to study drug.*

#### Treatment limiting adverse events:

These occurred in 13 subjects randomized to receive malarone and 24 randomized to receive mefloquine. Eight of the 13 subjects in the Malarone arm were only receiving placebo at the time of the reported treatment-limiting event.

**Table 30010-20: Number of treatment-limiting events, regardless of relationship to drug, that occurred in more than one patient (In each arm, events reported during treatment with active drug or with placebo are shown separately)**

Event	Malarone arm		Mefloquine arm	
	Malarone	Placebo	Mefloquine	Placebo
Subjects with at least one adverse event	10	7	23	3
Nervous system	5	4	17	3
Insomnia	2	3	11	0
Anxiety	1	1	7	1
Dizziness	1	0	7	1
Dreams	1	3	5	0
Depression	0	2	3	0
Visual disturbances	0	2	3	0
Disturbed concentration	0	0	2	1
Exacerbation of anxiety	0	0	1	1
Digestive system	6	2	6	2
Abdominal pain	5	0	3	1

Event	Malarone arm		Mefloquine arm	
	Malarone	Placebo	Mefloquine	Placebo
Diarrhea	3	1	3	2
Nausea	2	2	3	1
Vomiting	1	1	2	1
Skin	3	0	2	1
Rash	2	0	0	0
Body as a whole	3	2	6	3
Headache	2	2	4	3
Fever	2	0	1	1

*MO comment: Overall, treatment-limiting events were more common while on mefloquine than malarone. In particular, it was neurological events such as insomnia, anxiety, dizziness, dreams and depression that accounted for the difference. The incidence of treatment-limiting gastrointestinal and dermatological events was similar for both arms.*

Drug-related treatment-limiting events occurred in 13 subjects on the malarone arm, (8 of whom were receiving placebo only at the time of the event), and 24 patients in the mefloquine arm.

#### Events of moderate/severe intensity:

Moderate events were those interfering with daily activities

Severe events were those requiring medical advice

Moderate or severe events occurred in 51 subjects (10%) on the malarone arm 93 subjects (19%) on the mefloquine arm.

The most common severe events attributed to drug were diarrhea (7 for malarone, 6 for mefloquine, insomnia (2 and 10 respectively), abdominal pain (4 and 3 respectively) and dizziness (1 and 5 respectively).

#### Clinical laboratory values over time :

Hemoglobin, platelet count, total white blood cells (WBC), ALT and creatinine were obtained on approximately 100 patients in each treatment group at the screening and follow-up visits. There were no significant differences in the mean values before and after treatment in either of the groups. Maximum and minimum values were similar before and after treatment.

#### Special populations

**Age:** Few pediatric patients were included in the study (19 patients between the ages of 4 and 10 years). Although the overall incidence of adverse events was more frequent in younger patients than in older patients (see statistical review), the small number of pediatric patients does not allow an adequate evaluation of pediatric safety.

Very few geriatric subjects were included in the study population. There was no indication of an increase in adverse events with increasing age (see statistical review) but true geriatric patients were insufficient to allow an evaluation of geriatric safety.

**Race:** There was no difference in adverse event rates for different racial groups, though the study population was predominantly white.

**Gender:** Adverse event rates were significantly higher in females (76% of malarone-treated subjects, 71% mefloquine-treated subjects) than in males (68% of malarone-treated subjects, 65% of mefloquine-treated subjects).

#### MO safety conclusions:

- Among the 976 evaluable patients in the study, no adverse events resulting in prolonged incapacity or death occurred.
- The tolerability of the Mefloquine regimen appeared poorer than that for malarone even after taking into account the longer duration of mefloquine treatment. This was mainly the result of neurological

*toxicity (insomnia, dizziness, abnormal dreams, anxiety and depression). This was reflected in a slightly higher overall incidence of drug related adverse events in this arm, and a higher rate of treatment limiting events. Nausea was also more common in mefloquine treated subjects though other gastrointestinal complaints occurred at a similar frequency in both treatment arms.*

- *Since many of the adverse events were actively solicited, the absolute frequency of these solicited events may be somewhat inflated although the relative prevalence for the arms is instructive.*
- *The prolonged duration of therapy on the Mefloquine arm resulted in significantly poorer compliance among mefloquine-treated subjects during the post-travel period.*
- *Adverse events were more common in females than males for both treatment groups*

### Efficacy

A diagnosis of malaria was considered in 4 subjects. Serological testing for the development of antimalarial antibodies was negative in all 4.

**Table 30010-21: Summary of suspected malaria cases**

Treatment arm	destination	Clinical description	Study confirmation	FDA evaluation
Malarone	Ghana	Fever, nausea vomiting, 3 days after arrival in Ghana	Malaria antibodies negative No slides	Unlikely
Mefloquine	Uganda	Diagnosed locally on slides 16 days after arrival	Malaria antibodies negative. No slides submitted to central lab	Possible based on diagnosis at local lab
Mefloquine	Angola	Diagnosed locally on slides 10 days after arrival	Malaria antibodies negative. No slides submitted to central lab	Possible based on diagnosis at local lab
Mefloquine	Ghana	Fever headache 7 days after arrival	Malaria antibodies negative No slides	Unlikely

*MO comment: The reviewer considered two cases as possible cases of malaria. Both were in the mefloquine arm. Without knowing the risk for being bitten by a malaria infected mosquito while on the study, no conclusions on comparative efficacy can be made.*

In an intent-to-treat analysis performed where subjects lost to follow-up were regarded as prophylactic failures. Three subjects in the Malarone group and 5 in the mefloquine group were lost to follow up. The applicant calculated the prophylactic efficacy of both Malarone and mefloquine as 99%.

*MO comment: Since the study was not powered to demonstrate efficacy, the actual exposure to malaria was unknown, and the subjects lost to follow up had a low probability of developing malaria this analysis is not a rigorous reflection of the true efficacy for either regimen. The results suggest that both drugs are effective for malaria prophylaxis.*

Of 966 subjects with complete 60 day efficacy data, 915 had paired samples available for CS antibody testing. CS antibodies developed in 10 (1.1%).

*MO comment: The development of CS antibodies was very rare which would suggest a very low risk of malaria infection in the study population. However the sensitivity of this test in determining malaria exposure is unknown*

## MAL 30011: An international randomized double blind study to compare the safety and efficacy of malarone versus chloroquine and proguanil hydrochloride for chemoprophylaxis against malaria in non-immune travelers.

Primary objective: To compare the safety of malarone with chloroquine and proguanil  
 Secondary objective: To compare the efficacy of malarone with chloroquine and proguanil

### Study design

As for study 30010, this was a randomized, double-blind, active-controlled, multicenter comparative study performed in healthy, non-immune travelers. It differed in that subjects were randomized to receive malarone or chloroquine and proguanil for malaria prophylaxis in a blinded fashion, at a screening visit 1-4 weeks prior to travel. One clinic follow-up visit was scheduled 4 weeks after leaving the malaria endemic area. In addition, two telephone interviews were conducted, one 7 days after leaving the malaria endemic area and one 60 days after leaving the malaria endemic area.

As described for study 30010, extremely large numbers of participants would be needed to demonstrate prophylactic equivalence to the comparator drug, given the low risk of malaria in travelers not taking prophylaxis. For this reason efficacy was determined as a secondary endpoint and safety was deemed the primary endpoint. As before, paired sera were collected on all participants before and after travel in an attempt to confirm exposure by measuring antibodies to the circumsporozoite (CS) antigen of *P. falciparum*.

### Study population

The study was performed on malaria naïve travelers from 21 centers in Canada, Europe and South Africa. The length of stay in a malaria area was not to exceed 28 days.

*MO comment: As in study 30010, a minimum stay was not stipulated and very short stays would diminish the chances of contracting malaria.*

A study amendment excluded travelers to areas where treatment with chloroquine and proguanil was inappropriate.

*MO comment: This exclusion effectively limits the evaluation of malarone's efficacy to malaria that is sensitive to chloroquine and proguanil. The companion study (30010) using mefloquine as a comparator will be taken into account to reflect the efficacy of malarone in areas where chloroquine/proguanil is inappropriate.*

### Inclusion and exclusion criteria:

These were identical to those in study 30010 except that this study population included male and female volunteers >14 years of age and >50kg in weight (compared with >3 years of age and >11kg in weight for protocol 30010). Patients with generalized psoriasis were excluded from this study but not from study 30010.

Subjects who discontinued study drug prematurely because of an adverse event were to be followed at all protocol scheduled visits.

### Treatment arms

**Table 30011-1: Treatment arms and dosing of study drugs**

Malarone arm		Chloroquine arm	
Drug and dosage	Regimen	Drug and dosage	Regimen
Malarone (atovaquone 250mg/proguanil 100mg) (batch # T98/070A)	1 full strength tablet daily, 1 to 2 days before entering malaria area till 7 days after leaving	Malarone placebo	1 tablet daily, 1 to 2 days before entering malaria area till 7 days after leaving
Chloroquine placebo	2 tablets weekly, 1 week	Chloroquine 250mg*	2 tablets weekly, 1 week

Malarone arm		Chloroquine arm	
Drug and dosage	Regimen	Drug and dosage	Regimen
	before entering malaria area till 4 weeks after leaving	equivalent to 155 mg chloroquine base –	before entering malaria area till 4 weeks after leaving
Proguanil placebo	2 capsules daily 1 to 2 days before entering malaria area till 4 weeks after leaving	Proguanil 100mg* Batch T98/092A.	2 capsules daily 1 to 2 days before entering malaria area till 4 weeks after leaving

Double dummies were provided

Compliance was monitored subject diaries, review of returned medication and interview.

Concurrent medication was recorded at all study visits and telephone contacts.

*MO comment: Since proguanil 100mg is a component of malarone, this study effectively compares the substitution of the atovaquone component of malarone with chloroquine. The comparative safety of proguanil cannot be determined from this study since proguanil is used in both arms, (albeit twice the dose in the chloroquine arm). Proguanil alone is not currently approved for use in the USA. However it is used extensively in combination with chloroquine for malaria prophylaxis in other parts of the world and may be obtained by US travelers while out of the USA. Given the very limited options for malaria prophylaxis the choice of comparator is acceptable when evaluated in conjunction with study 30010 where mefloquine is used as the comparator.*

**Study schedule:**

Screening visit	1-4 weeks prior to entering malaria area
Telephone contact	7 days after leaving malaria area
Follow-up visit	4 weeks after leaving malaria area
Telephone contact	60 days after leaving malaria area
Unscheduled visits	

At each contact, subjects were asked about the same 15 symptoms stipulated in protocol 30010. Hematology and clinical chemistry monitoring were undertaken "if appropriate". One study site performed hematology and clinical chemistry tests at screening and at the 4 week follow up visit.

*MO comment: As for study 30010, active questioning, specifically about the above symptoms is likely to increase their frequency in both treatment arms compared to unsolicited adverse events. In the absence of protocol defined monitoring of blood tests, no rigorous comparison of clinical laboratory results is possible between the study arms.*

Symptoms were graded as:

- mild (neither interfering with daily activities nor requiring medical advice),
- moderate (interfering with daily activities),
- severe ( where medical advice was sought)
- treatment-limiting events (those that resulted in permanent drug discontinuation)

The definition of adverse events (AE) was the same as that in study 30010.

*MO comment: Many of the anticipated adverse events were similar to those symptoms typical of malaria. The controlled study design should eliminate differences between the arms that are the result of malaria rather than study drug.*

**Measures of efficacy:**

Participants were asked at 7 days, 4 weeks and 60 days after returning from travel whether malaria was diagnosed.

In cases of malaria, information was requested on malaria species, date of symptoms and confirmation of diagnosis, and dates that chemoprophylaxis was taken.

Blood smears obtained at the time of malaria diagnosis were reviewed at the reference laboratory of the Toronto hospital and DNA was extracted for PCR determination. Antibodies to each of the 4 species of malaria parasite were measured and a positive result was defined by a titer  $\geq 1:64$  following a negative baseline or a  $\geq 16$ -fold increase in titer over baseline.

Serum was collected from all subjects at baseline and at the 4-week follow-up visit, for measurement of circumsporozoite antibodies, in an attempt to identify patients who were infected with malaria but did not develop clinical illness. A positive result was defined by an optical density greater than 2 standard deviations above the mean for negative control sera and more than 2 standard deviations above the baseline result.

*MO comment: The test for circumsporozoite antibodies has not been validated and is regarded as exploratory.*

A diagnosis of malaria was considered

- Definite – if parasite DNA was detected by PCR or parasites were seen on the smear sent to the reference laboratory.
- Possible- if the CRF recorded a diagnosis of malaria but smears and DNA analysis were negative or missing and antibodies to blood stage parasites were missing
- Negative- if the CRF recorded a diagnosis of malaria but smears and DNA analysis were negative or missing and antibodies to blood stage parasites were negative.

*MO comment: The negative predictive value of antibodies to blood stage parasites is not clear. On this basis FDA will regard cases defined in "c)" above as "possible"*

**Sample size:**

Five hundred subjects were to be randomized to each treatment arm. The applicant calculated the 400 evaluable patients per arm had an 82% power to detect non-inferiority of malarone if the overall proportion of adverse events were 40%. The 95% confidence bounds for non-inferiority (Malarone AE proportion – chloroquine/proguanil AE proportion) was -100% to +10%.

Periods of drug exposure were as follows:

**Figure 30011-1: Periods of drug exposure**

Placebo	Malarone -2 days	Malarone Period of Travel	Malarone +7 days	Placebo
Chloroquine/proguanil -7 days		Chloroquine/proguanil Period of Travel	Chloroquine/proguanil	+28 days

The applicant selected the period from 7 days prior to travel to 7 days after return for the primary analysis of Malarone safety. The reviewer concurs with this approach.

**Analysis populations**

Definitions of populations for analysis:

Safety- all subjects who received at least one dose of study drug and had the opportunity to report an adverse event

Intent-to-treat (ITT): As for safety population but subjects who did not enter a malaria area for reasons other than adverse events or loss-to-follow-up were excluded

Per protocol: All treatment compliant patients who completed 60 days of follow-up. Those lacking 60-day efficacy data were excluded

Compliance was checked by counting the tablets returned.

Non-inferiority for the primary endpoint of adverse events up to day 7 post treatment was defined if the 95% confidence bound for Malarone AE%-chloroquine/proguanil AE%= (-100%, 10%)

#### Efficacy

This was evaluated in terms of the number or definite, possible or negative results for malaria as defined previously. Efficacy was expressed for the ITT population and an estimate of minimum efficacy was also calculated using the population with positive CS antibodies as the denominator.

Percentage efficacy was expressed as  $[1 - (\# \text{ subjects with malaria} / \# \text{ subjects at risk for malaria})] \times 100$

### Study results

There were 1085 participants who were screened at 21 sites in Canada, Denmark, South Africa, France, Germany, the Netherlands and the United Kingdom.

540 were randomized to receive malarone and 543 to receive chloroquine and proguanil.

The disposition of screened participants is reflected below.

**Table 30011-2: Discontinuations prior to starting study drug**

		Malarone	Chloroquine/ proguanil
Screened		540	543
Discontinued before taking first dose	Never started on study	4	10
	Protocol violation	0	1
	Lost to follow up	6	3
	Withdrew consent	4	3
	Adverse event	0	1
	“Other reasons”	15	14
	Total	29	32

Of those who were randomized and received study drug, outcomes were as follows.

**Table 30011-3: Discontinuations after starting study drug**

		Malarone	Chloroquine/ proguanil
Randomized		511	511
Discontinued from study prematurely	Lost to follow up	2	1
	Did not travel	2	2
	Adverse event	1	1
	Protocol violation	1	-
	Malaria diagnosed	1	-
	Lost study medication	1	-
	Could not swallow placebo tablet	1	-
	Withdrew consent	1	-
	Total	10 (2%)	4 (<1%)
Completed study but discontinued study drug prematurely	Adverse events	11	16
	Withdrew consent	1	
	Protocol violation	9	6
	Other (most commonly did not travel)	28	21
	Total	49	43

**Table 30011-4: Composition of ITT population**

		Malarone	Chloroquine/proguanil
Randomized		540	543
Excluded	not treated	29	32
	did not travel	26	26
Total ITT		507	506

**Table 30011-5: Composition of per-protocol population**

		Malarone	Chloroquine/proguanil
Randomized		540	543
Excluded	Not treated	29	32
	Did not travel	27	26
	Missed telephone contact 2	32	26
	Failed compliance criteria	44	60
	Incorrect treatment	7	6
	Failed inclusion/exclusion	6	6
	Broken treatment blind	6	3
Total PP		448	437

*MO comment: Subjects excluded from the ITT and PP populations were balanced between the arms except for those who failed compliance criteria. This difference is probably the result of the longer treatment regimen in the chloroquine/proguanil arm.*

### Demographics

The demographic characteristics of participants are described below.

**Table 30011-6: Demographic data**

	Malarone (n=511)	Chloroquine/proguanil (n=511)
Mean age (range)	36 (13-72)	35 (13-74)
Males	49%	54%
White race	97%	95%
Mean height [cm] (range)	173 (150-203)	173 (148-197)
Mean weight [Kg] (range)	71 (49-145)	72 (50-118)

*MO comment: The study population comprised predominantly white adults. The demographic features were balanced between the arms. The adverse event profile may differ in other racial groups. This has been seen with other antimalarials. For example primaquine is not tolerated in racial populations with a high prevalence of G6PD deficiency. Therefore the adverse event data may not necessarily reflect the risk for all travelers. There were no patients in this study younger than 13 years and pediatric conclusions on safety cannot be made.*

Previous malaria was reported in 16 study participants, an average of 17 years previously. 63% of participants traveled to Africa. Past malaria history and malaria exposure during the study are shown below.

**Table 30011-7: Past and present exposure to malaria**

	Malarone (n=511)	Chloroquine/proguanil (n=511)
Previous history of malaria	2%	1%
Mean years since last malaria episode (range)	19.7 (2-60)	14 (2-30)
Mean duration of trip [days] (range)	16.9 (2-32)	17.6 (3-34)

*MO comment: Previous malaria could result in a persistently positive antibody test. Nevertheless, this did not confound the diagnosis, since cases reported in the CRF were diagnosed on the basis of symptoms and the 4 cases ultimately diagnosed in this study were confirmed by parasite smears or DNA.*

*There was slightly more exposure to malaria in the chloroquine/proguanil arm based on the duration of travel.*

### Concomitant medications

- Concomitant medications were taken by 59% of patients in the malarone arm and 58% in the chloroquine/proguanil arm. Most were analgesics, antibiotics, vaccines, anti-diarrheal drugs and oral contraceptives.

*MO comment: While concurrent medication might affect the adverse event profile, the use of concurrent therapy was balanced between the arms allowing a valid comparison of adverse event rates*

- Concurrent antimalarials: These were taken by 12 subjects, four of whom were suspected to have malaria and are discussed further in this review. The remaining 8 discontinued study drug early, and were given alternative antimalarial drugs for prophylaxis. The reasons for premature discontinuations in these individuals included adverse event (3), withdrawn consent (1), losing study drug (2), unplanned return to malaria area (1) and "protocol violation"

*MO comment: Since patients on alternative antimalarials were all captured as premature discontinuations or malaria cases, the fact that they received alternative agents does not affect the evaluation of the study drugs.*

### Treatment compliance

The mean duration of therapy with malarone was 26 days, chloroquine 48 days and proguanil 45 days, reflecting the differences in the respective prophylactic regimens.

Compliance before, during and after travel is shown below.

**Table 30011-8: Percentage of subjects taking >80% of prescribed doses before, during and after travel**

	Malarone	Chloroquine Placebo	Proguanil placebo	Chloroquine	Proguanil	Malarone placebo
Before	95	93	93	94	90	94
During	96	92	94	91	94	96
After	93	78	85	80	87	95

*MO comment: Compliance before and during travel was similar for all arms. However after travel, compliance with an additional four weeks of weekly (chloroquine) or daily (Proguanil) therapy was poor compared with one week of daily therapy (malarone).*

### Exposure

Exposure to active drug is shown below.

**Table 30011-9: Duration of exposure to active drug**

	Malarone	Chloroquine	Proguanil
% patients treated for 2-4 weeks	51%	1%	3%
% patients treated for 4-6 weeks	40%	12%	26%
% patients treated for 6-8 weeks	<1%	54%	57%
% patients treated for >8 weeks	0%	30%	11%
Mean duration of therapy [days]	26	48	45

*MO comment: duration of treatment was substantially shorter for malarone than for either of the comparator drugs*

### Adverse events

The overall frequency of all adverse events is reflected in the 3 analyses below. The analyses attempt to address the different durations of active drug administration for the two arms as shown in the schematic diagram.

**Figure 30011-2: Periods of drug therapy**

Pre travel		Period of travel	Post-travel	
Placebo	Malarone -2 days	Malarone Period of Travel	Malarone +7 days	Placebo
Chloroquine/proguanil -7 days		Chloroquine/proguanil Period of Travel	Chloroquine/proguanil +28 days	

**Table 30011-10: Frequency of adverse events occurring after start of study drug or placebo till 7 days after leaving malaria area.**

Malarone	Chloroquine/proguanil	95% CI for the difference
311/511 (60.9%)	329/511 (64.4%)	-9.5 to 2.4

*MO comment: In this analysis, active drug is received by comparator-treated patients for 5 days longer than for malarone treated patients. It is the analysis that allows the greatest overlap between the study arms in the use of active drug. Since comparator is received for longer, the comparator arm may demonstrate higher AE rates purely as a result of increased exposure. This effect is unlikely to be large.*

**Table 30011-11: Frequency of adverse events occurring after start of active drug till 7 days after leaving malaria area.**

Malarone	Chloroquine/proguanil	95% CI for the difference
296/511 (57.9%)	329/511 (64.4%)	-12.4 to -0.5

*MO comment: This analysis selectively removes the placebo control from the first few days of chloroquine/ proguanil exposure resulting in an unfair assessment for chloroquine/ proguanil.*

**Table 30011-12: Frequency of adverse events occurring after start of study drug or placebo till 28 days after leaving malaria area.**

Malarone	Chloroquine/proguanil	95% CI for the difference
328/511 (64.2%)	340/511 (66.5%)	-8.2 to 3.5

*MO comment: The increase in adverse events in the malarone arm from 7 days to 28 days after leaving the malaria area (during which these subjects received placebo alone) suggests that a substantial proportion of adverse events in this study are not drug attributable.*

Drug related treatment emergent adverse events over the entire study period:

**Table 30011-13: Frequency of drug-related adverse events over the entire study period**

Malarone	Chloroquine/proguanil	95% CI for the difference
136/511 (27%)	142/511 (28%)	-9.5 to 2.4

*MO comment: The reviewer regarded the safety analysis from start of study drug to 7 days after returning from travel as the most accurate comparison between the study arms for adverse events related to drug. The frequency of all adverse events was determined to be equivalent between the arms. The frequency of drug attributed adverse events over the entire study period was also found to be equivalent. This latter analysis reflected the adverse event rate due to the regimen rather than the drug. Drawbacks in the study design include the specific solicitation of selected adverse events which may have weakened spontaneously reported signals.*

**Table 30011-14: Most frequent adverse events (% of subjects) over entire study period**

	All events		Drug attributed	
	Malarone	Chloroquine/ proguanil	Malarone	Chloroquine/ proguanil
Diarrhea	37	39	5	7
Nausea	12	18	2	7
Abdominal pain	15	22	3	6
Headache	16	15	4	4
Dreams	6	7	4	3
Insomnia	5	6	2	2
Dizziness	8	8	3	4
Fever	9	8	<1	<1
Vomiting	9	14	0	2
Oral ulcers	6	7	4	5
Pruritis	4	2	1	<1
Visual difficulties	3	3	2	2
Anxiety	<1	1	<1	<1
Depression	<1	1	<1	<1

*MO comment: Since the entire study period is reflected here, adverse event rates are likely to be higher in the comparator arm since these subjects received 3 more weeks of active drug than those in the Malarone arm. The results (not shown) were similar when adverse event rates were compared for both arms until 7 days after returning from travel (during which period both arms received active drug).*

*Similar clusters of symptoms (headache, nausea and diarrhea) were frequently reported in both study arms. Gastro-intestinal complaints (diarrhea, nausea, abdominal pain and vomiting) were more common in chloroquine/proguanil-treated subjects. The frequency of other adverse events was numerically similar between the arms. Some, such as diarrhea are common in travelers and may be less specifically drug-related. The targeted nature of questioning is likely to have increased the reporting of these events compared to non-targeted events.*

**Events of unusual severity:**

There were no deaths on the study

Serious adverse events were reported in 6 subjects in the malarone arm and 6 in the comparator arm.

**Table 30011-15: Serious adverse events**

Drug	AE	Drug attributed
Malarone	Diarrhea	No
	Fever	No
	Fever	No
	Shigella dysentery	No
	Wolff-Parkinson- White	No
	Pituitary tumor	No
Chloroquine/proguanil	Malaria	No
	Malaria	No
	Malaria	No
	Pneumonia	No
	“Chest virus”	No
	Depression	No

*MO comment: The reviewer concurred that none of the serious adverse events shown above was attributable to study drug.*

**Treatment limiting adverse events:**

These occurred in 11 subjects randomized to receive malarone and 15 randomized to receive chloroquine/proguanil. Four of the subjects in the Malarone arm were only receiving placebo at the time of the alleged treatment-limiting event.

**Table 30011-16: Number of treatment-limiting events, regardless of relationship to drug.**

	Malarone	Chloroquine/Proguanil
Fever	2	1
Headache	1	2
Malaria	0	3
Allergic reaction	1	0
Burning pharynx	0	1
Colic	0	1
Dengue	1	0
Epigastric pain	0	1
Pituitary neoplasm	1	0
Diarrhea	2	5
Nausea	0	6
Abdominal pain	1	4
Vomiting	0	3
Constipation	0	1
Dysphagia	0	1
Esophageal reflux	0	1
Heartburn	0	1
Oral ulcers	0	1
Dizziness	2	3
Anxiety	0	1
Visual difficulty	0	1
Pneumonia	1	0
Sore throat	1	0
Rash	2	0
Costal chondritis	0	1
WPW	1	0

*MO comment: Gastrointestinal complaints were more common in the chloroquine/proguanil arm. Other treatment limiting events were not distinctive for either arm.*

Since treatment regimens did not overlap, there were periods before and after travel where individuals received Chloroquine/proguanil or placebo but no malarone or placebo. Adverse events leading to permanent discontinuation of drug occurred in 1 subject on active malarone, 10 on active chloroquine/proguanil and 3 on chloroquine proguanil placebo.

*MO comment: Treatment-limiting events were more common in the chloroquine/proguanil arm. However patients on this arm received approximately 4 weeks more therapy than those on the malarone arm*

**Events of moderate/severe intensity:**

Moderate events were those interfering with daily activities

Severe events were those requiring medical advice

Moderate or severe events regardless of attributability occurred in 109 (21%) subjects on the malarone arm 152 subjects (30%) on the mefloquine arm.

There were 5 subjects in the Malarone arm and 11 in the chloroquine proguanil arm with severe events attributed to drug. These are shown below.

**Table 30011-17: Severe adverse events attributed to study drug**

	Malarone	Chloroquine/Proguanil
Diarrhea	1	2
Rash	2	1
Dreams	1	1
Nausea	0	2
Pruritis	0	2
Abdominal pain	0	1
Allergic reaction	1	0
Aphonia	0	1
Burning in pharynx	0	1
Colic	0	1
Dyspepsia	0	1
Edema of lips	0	1
Enlargement of tongue	0	1
Epigastric pain	0	1
Convulsions	0	1
Headache	1	0
Oral ulcers	0	1
Vomiting	0	1
Swelling of eyelids	0	1

**Clinical laboratory values over time:**

Hemoglobin, platelet count, total white blood cells (WBC), ALT and creatinine were obtained on approximately 90 patients in each treatment group at the screening and follow-up visits. There were no significant differences in the mean values before and after treatment in either groups. Maximum and minimum values were similar before and after treatment, except for maximum WBC value in the chloroquine/proguanil group with was 11.5 before treatment and 34.7 on follow-up.

*MO comment: The change in the maximum WBC on chloroquine proguanil probably represents acute infection other than malaria in one individual, since the mean value of the WBC in this group did not change appreciably.*

**Special populations**

**Age:** No patients under 13 years were included in the study. Although the overall incidence of adverse events was more frequent in younger patients than in older patients (see statistical review), no conclusions on pediatric safety can be made.

There was no indication of an increase in adverse events with increasing age (see statistical review) and no evidence of increased toxicity in elderly patients.

**Race:** There was no difference in adverse event rates for different racial groups, though the study population was predominantly white.

**Gender:** There was no significant difference in adverse event rates for males and female treated with malarone in this study.

**Renal or hepatic dysfunction:** No data were provided on patients with renal or hepatic dysfunction.

**MO safety conclusions:**

- *Malarone and Chloroquine/proguanil appear comparably safe. Among the 511 evaluable patients in each arm, no adverse events resulting in prolonged incapacity or death occurred.*
- *The tolerability of the chloroquine/proguanil regimen appeared poorer than that for malarone as a result of gastrointestinal adverse events, even after taking into account the longer duration of this regimen. This was reflected in a slightly higher overall incidence of adverse events in this arm, and a higher rate of treatment limiting events*
- *Since many of the adverse events were actively solicited, the absolute frequency of these solicited events may be somewhat inflated although the relative prevalence for the arms is instructive.*

- *The prolonged duration of therapy on the chloroquine/proguanil arm resulted in significantly poorer compliance among those subjects.*
- *Adverse events were more common in younger patients than older patients. There was no relationship between other special sub-populations and adverse event rates.*

### Efficacy

A diagnosis of malaria was considered in 4 subjects

**Table 30011-18: Summary of suspected malaria cases**

Treatment arm	Destination	Clinical description	Study confirmation	FDA evaluation
Chloroquine/proguanil	Uganda	Headache and fever 11 days after returning from travel	Positive smear for <i>P falciparum</i> , positive PCR, positive antibodies to <i>P falciparum</i>	Definite <i>P falciparum</i>
Chloroquine/proguanil	Nigeria	Fever 6 days after returning from travel	Positive smear for <i>P falciparum</i> , positive PCR, positive antibodies to <i>P falciparum</i>	Definite <i>P falciparum</i>
Chloroquine/proguanil	Mali	Fever 3 days after returning from travel	Positive smear for <i>P falciparum</i> , positive PCR, positive antibodies to <i>P falciparum</i>	Definite <i>P falciparum</i>
Malarone	The Gambia	Headache 40-55 days after returning from travel and 28 days after stopping malarone	Positive smear for <i>P ovale</i> . Positive antibodies to <i>P ovale</i>	Definite <i>P ovale</i>

*MO comment: Among the 511 evaluable participants in the chloroquine proguanil arm, there were 3 confirmed cases of *P falciparum* malaria. Among the 511 participants in the Malarone arm there was one case of *P ovale* malaria. Although the actual exposure of participants in both arms is not known, the results suggest a trend to greater efficacy against *P falciparum* in the malarone arm. Malarone is not approved for the prevention of *P ovale* and appeared to fail against this species in one patient.*

### Circumsporozoite (CS) antibodies and malaria exposure:

A total of 987 subjects had paired sera available to determine the development of CS antibodies. CS antibodies developed in 15 (1.5%). Among these were one of the subjects who developed *P falciparum* and the one subject who developed *P ovale*.

*MO comment: The sensitivity of CS antibodies is probably weak, since 3 patient with confirmed malaria did not develop a positive titer. The extent to which this test reflects true malaria exposure is not known and would require confirmation in suitable challenge studies.*

In an ITT analysis, 5 subjects in the malarone group and 2 in the control group did not have 60-day efficacy data available and were assumed to be prophylactic failures. The prophylactic efficacy in this ITT analysis was 99% for both arms.

A minimum efficacy using the denominator of individuals with positive CS antibodies was 58% for malarone and 54% for chloroquine/proguanil.

*MO comment: The ITT population included many subjects who discontinued drug prematurely for a variety of reasons other than malaria (see table 22). These were analyzed by the applicant as "ITT successes".*

*Among the small number of subjects who were lost to follow-up, the probability of malaria was low, yet these were analyzed by the applicant as "ITT failures".*

*The interpretation of the "minimum efficacy analysis" is unclear without knowing the sensitivity and specificity of the CS test.*

*The above pitfalls weaken the validity of the efficacy analysis. While the results suggest a trend to superior prophylactic efficacy for *P falciparum* in the Malarone arm, these results are not statistically significant, particularly since actual malaria exposure (the number of individuals bitten by an infected mosquito) in the 2 arms remains speculative.*

Among the 3 subjects on the Chloroquine/proguanil arm who developed *P falciparum* malaria 2 had cycloguanil and proguanil levels in the anticipated therapeutic range, and one had low levels. Chloroquine levels were not measured. Drug levels were not obtained on the subject in the malarone arm who developed *P ovale* infection.

*MO comment: The positive drug levels in patients who developed *P falciparum* malaria suggest true drug failure as the cause rather than non-compliance. These findings are consistent with literature reporting the suboptimal efficacy of chloroquine/proguanil prophylaxis in areas of chloroquine resistance.*

**Overall conclusions and recommendations**

*These two studies demonstrate good tolerability of Malarone compared to Mefloquine and to chloroquine/proguanil. Malarone resulted in a lesser frequency of neurological adverse events than mefloquine and a lesser frequency of gastrointestinal adverse events than chloroquine/proguanil. While adverse event rates were more common in younger than older subjects, no specific subpopulation was identified at increased risk for adverse events. Compliance was better with malarone than with the comparator drugs, largely as a result of the shorter prophylactic regimen. The efficacy of study drugs could not be rigorously determined. Confirmed prophylactic failures were only identified among subjects treated with Chloroquine/proguanil.*

*The findings support labeling describing the tolerability of Malarone however the reviewer recommends some changes to the proposed material to give a more equitable representation of comparative safety. Specifically, the text in the proposed label should clarify the periods during which adverse events were reported in each of the study arms, since the periods of reporting were longer for the comparator arms than for the malarone arms.*

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/s/

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Rigoberto Roca  
8/6/02 06:07:50 PM  
MEDICAL OFFICER  
for Leonard Sacks.