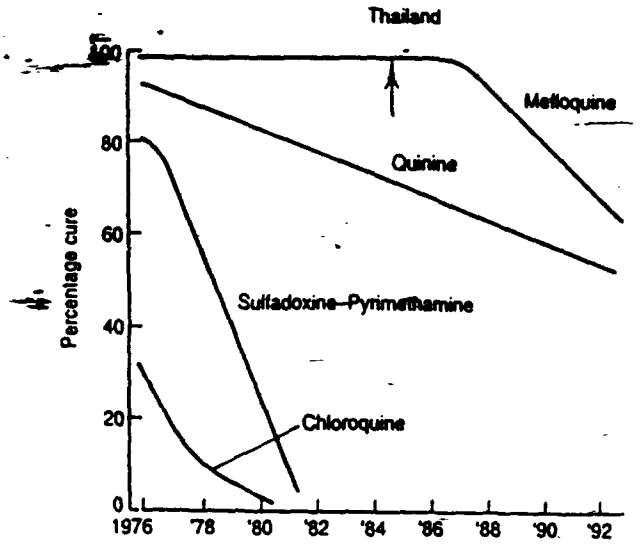
only if travelers will not be visiting such areas. (CDC, Health Information for International Travel, 1995). Studies #115-135 and #115-136, conducted in the Philippines and Peru, respectively, provided an opportunity to prospectively compare the efficacy of MALARONE compared with that of chloroquine. Both of these studies' protocols required amendment because patients treated with chloroquine had unacceptably high failure rates. Inspection of Table 1 shows that in Palawan, an island in the southwest of the Philippine archipelago, cure rates for chloroquine were 30%, and that in northern Peru, cure rates achieved with chloroquine were 8%. In both of these studies, cure rates achieved with atovaquone/proguanil were 100%. Atovaquone/proguanil is an effective antimalarial for treatment of falciparum infection in areas where chloroquine failure rates are unacceptably high, presumably due to resistance.

A similar comparison may be made with amodiaquine efficacy rates in Gabon. Amodiaquine is a congener of chloroquine, believed to offer some efficacy advantage in areas of high chloroquine resistance. Because of liver and bone marrow toxicities and only a limited advantage over chloroquine, this drug has fallen out of use. The NDA for this drug (Camaquin, NDA 6441) was withdrawn in 1994 because the drug had ceased to be marketed in the US. Table 1 also demonstrates the efficacy of atovaquone/proguanil in an area where amodiaquine efficacy is curtailed.

The eastern and western borders of Thailand are regions characterized by some of the most acute problems in malaria resistance in the world. Figure 1, first presented in the MO review of study #115-122 and reproduced here, depicts the diminishing efficacy rates of a number of antimalarials that were previously useful agents in the treatment of *P. falciparum* infection in Thailand. What is particularly striking in this figure is the rapidity with which resistance to some agents developed. Mefloquine, introduced into clinical use in Thailand in the 1980s, was an excellent blood schizonticide and remains one in areas of the world where malaria parasites are susceptible to this drug. Recent observations suggested that mefloquine used alone cures only about 90% of falciparum malaria patients treated in Thailand. The present treatment of choice for falciparum malaria in Thailand is an artemisinin derivative (usually artesunate) plus mefloquine. In the US, mefloquine (Lariam, NDA 19-591, approved 1989) rapidly replaced chloroquine as the antimalarial prophylactic of choice for US travelers. There are no artemisinin derivatives approved for use in the US. The slopes of the curves depicted in Figure 1 suggest that presently available antimalarials may not enjoy as long a lifespan as did chloroquine.

Figure 1. Antimalarial efficacy in Thailand 1970s-1990s



Study #115-122 afforded an opportunity to compare the efficacy of atovaquone/proguanil to that of mefloquine in an area where this drug's efficacy has been observed to decrease sharply over the last decade. The clinical cure rate observed for mefloquine in this study (86%) approximated what has been observed previously in this region. Atovaquone/proguanil demonstrated a high and reproducible 28-day cure rate in this study as well.

A comparison of the efficacy rates for halofantrine in studies #115-130 and #115-131 may also reflect the different environments in which patients were followed. Patients in #130 resided in France and were not exposed to malaria after discharge from the hospital. The Kenyan children studied in # 131 were discharged to an area where there was some background malaria transmission. Reinfections may not account for all of the recurrent parasitemias noted in these patients; it is possible that there is some degree of halofantrine resistance among *P. falciparum* isolates in Kenya. One may speculate that the difference in halofantrine efficacy rates seen in these two studies may be due in part to the difference between no malaria transmission and some malaria transmission in the patient's usual environment. There also may be a diminished susceptibility to halofantrine among the Kenyan isolates of *P. falciparum* that caused the infections seen in this study. There were no *in vitro* data submitted to support such a conclusion.

The controlled clinical trials demonstrated the efficacy of atovaquone/proguanil in a wide range of geographic areas. Efficacy was high and comparable to four approved comparators, pyrimethamine/sulfadoxine, mefloquine, halofantrine, and quinine. Efficacy of atovaquone/proguanil was also demonstrated in areas where there were unacceptable failure rates with chloroquine, amodiaquine, and mefloquine. Efficacy of atovaquone/proguanil was also demonstrated in an area where there was a 10% failure rate for halofantrine. This may have been due in part to reinfection or parasite resistance.

Efficacy as expressed by parasite clearance time

In each of the eight controlled clinical trials, the length of time required to clear the peripheral blood of parasites was measured in hours from the time immediately prior to treatment to the time of the first of two or three negative peripheral smears. Table 2 presents parasite clearance time (PCT) for patients treated with atovaquone/proguanil or comparator in each of these trials. Initial parasite counts were comparable across studies. Inclusion criteria for each of these studies required that patients have no more than 100,000 or 200,000 parasites/µl of blood (in patients with a normal hematocrit, this is equivalent to ~2% or 4% parasitemia). In patients who do not manifest clinical findings of severe or complicated malaria, these parasite counts are consistent with mild to moderate falciparum malaria that is amenable to treatment with an oral agent.

Table 2. Parasite Clearance Times for Patients Treated with Atovaquone and Proguanil Hydrochloride or a Comparator Antimalarial Drug

Study Number	Comparator	Parasite Clearance Time (h) (mean ± sd)	
		ATQ/PGN[a]	Comparator
115-120	Pyrimethamine/sulfadoxine	64.0 ± 21.9	51.4 ± 21.1
115-122	Mefloquine	65.2 ± 17.7	73.8 ± 29.1
115-127	Quinine/tetracycline	55.3 ± 15.3	64.6 ± 22.5
115-130	Halofantrine	63.3 ± 22.2	48.5 ± 14.3
115-131	Halofantrine	64.9 ± 17.4	50.2 ± 13.0
115-134	Amodiaquine	72.1 ± 22.7	66.7 ± 16.1
115-135	Chloroquine Chloroquine plus pyrimethamine/sulfadoxine	46.7 ± 17.5	60.0 ± 32.9 42.8 ± 17.1
115-136	Chloroquine — Pyrimethamine/sulfadoxine	55.7 ± 10.7 44.4 ± 6.8	58.7 ± 25.8 33.6 ± 12.6
Mean (Range)	All	59.1 (46.7-72.1)	55.0 (33.6-73.8)

[a] ATQ/PGN = atovaquone and proguanil hydrochloride

Inspection of Table 2 shows that there was a range of values for PCT for both atovaquone/proguanil and the comparator agents, and comparison of the mean values for these two groups demonstrates comparable PCTs. It should be noted that even agents that did not achieve acceptable 28-day cure rates, such as chloroquine, demonstrated efficacy in clearing the peripheral blood of schizonts in a period of time comparable to that of drugs that did achieve acceptable cure rates such as quinine and tetracycline. Two conclusions may be drawn from such an observation. The first is that PCT can only convey one aspect of drug efficacy, the rapidity with which parasites are cleared from the peripheral blood. Since it has been well established that the peripheral vasculature is only one of several tissue compartments that malaria parasites infect, it is understandable that this marker of drug efficacy is only able to provide information on one aspect of drug efficacy. Nonetheless, one may view all of the agents listed in Table 2 as excellent blood schizonticides; standard WHO criteria define clinical success of an antimalarial (S response) as parasite clearance within 7 days or 168 hours without recurrence during the subsequent 21 days. Even the highest PCT measured for atovaquone/proguanil (72.1 ± 22.7 hours) is well within this limit.

Parasite clearance time is only one of several analyses that can provide information about the rapidity of action of a blood schizonticide. Other parameters that are traditionally useful include time to clear 50% of parasites from the peripheral blood (PC_{50}) and time to clear 90% of parasites (PC_{90}). When considering such measurements, it is important to be

aware of the events of the parasite life cycle during the early stages of human infection. As tissue (pre-erythrocytic) schizonts develop in the hepatocytes, merozoites are released that then invade red blood cells in the peripheral circulation. It is this parasitization of red blood cells and subsequent release of more merozoites that go on to parasitize more red blood cells that is associated with the clinical manifestations of malaria. The administration of a blood schizonticide should interrupt this cyclic parasitization of red blood cells and drug efficacy is manifest by smaller and smaller numbers of parasitized red blood cells over time. However, the erythrocytic life cycle (which is about 48 hours for *P. falciparum*) is not synchronized for all individual parasites; they are emerging from the hepatocytes to invade red blood cells and subsequently multiplying to invade more red blood cells at different times. Because of this dissynchrony peripheral blood parasite counts do not necessarily reflect drug activity in the first 24-48 hours of treatment. Indeed, parasite 'bursts,' acute increases in peripheral parasite count shortly after the initiation of therapy, are commonly observed in the course of treatment of falciparum malaria patients who remain clinically stable and go on to achieve satisfactory parasite clearance and 28-day cures. Quantification of the magnitude or duration of such bursts is not readily found in the medical literature, and could conceivably vary with drug. In one small published series of falciparum patients treated with quinine, increases in peripheral parasite counts as high as 2.5 times the initial value were observed in the first 24 hours of therapy of patients who ultimately cleared parasites within 36 hours (Watt, et al JID 1991; 164:602-4). In the course of the MO review of study # 115-131, which was conducted in Kenyan children, some extraordinary parasite bursts were noted. An example is one patient who was enrolled with a parasite count of 43,000/ul which increased to 380,000 at 12 hours, 800,000 at 24 hours, and 200,000 at 36 hours. The patient was afebrile by 55 hours and cleared his peripheral parasitemia at 60 hours. There were no parasites seen in his peripheral blood for the 28-day period of observation, thus this patient who manifested a peripheral parasitemia at 24 hours that was almost 20x his initial parasite count was cured by standard WHO criteria. This patient was treated with atovaquone/proguanil. Because a number of patients with extraordinary bursts were noted in this treatment arm in study #115-131, the MO undertook an additional analysis of this pediatric study, the study of nonimmune European adults (#115-130), the study of largely nonimmune Thai adults (#115-122), and the study in which atovaquone/proguanil was compared to quinine and tetracycline (#115-127). For each of these studies, serial parasite counts of all evaluable patients were reviewed. The number of patients in each treatment group who manifested a parasite burst that was greater than 3x the initial value within the first 36 hours of treatment was recorded. These were then compared across treatment groups to see if there were any signal suggesting a less robust or slower manifestation of blood schizonticidal activity among patients treated with atovaquone/proguanil. It should be noted that all but two of these patients who demonstrated these extraordinary bursts were cured at 28 days; the two who were not cured had a RI response. Their parasitemia recurred during the 21 days following treatment; they did not fail therapy acutely. These two patients were also followed as out-patients, and thus the possibility of reinfection must also be considered as an explanation for the recurrence of parasitemia. Table 3 demonstrates that no treatment-associated trend was identified.

Table 3. Patients with extraordinary * parasite bursts by treatment group

Study no.	Comparator	Proportion of evaluable patients with extraordinary bursts (%)	
		Atovaquone/proguanil	Comparator
115-131	Halofantrine	7/76 (9.2)	0/75 (0)
115-130	Halofantrine	2/21 (9.5)	2/18 (11.1)
115-122	Mefloquine	4/79 (5.1)	6/68 (8.8)
115-127	Quinine and Tetracycline	1/73 (1.4)	8/76 (10.5)
TOTAL	ALL	14/249 (5.6)	16/237 (6.8)

*Extraordinary bursts were defined as parasite counts >3x initial parasite count within first 36 hours of treatment

Efficacy by patient weight in adult and pediatric populations

The dose of atovaquone/proguanil that was tested in the phase III trials and is the dose recommended in the label was established in the phase II trial undertaken in Thailand, study #115-005. The treatment regimen that was chosen for further study was atovaquone 1000 mg/ proguanil 400 mg daily for three days. It was selected because it was the shortest regimen that achieved the highest efficacy rate (100%). It should be noted that the efficacy of this regimen was established in a group of adults whose mean weight was approximately 50 kg, and that the doses administered were atovaquone 20 mg/kg and proguanil 8 mg/kg. The mean weight of the atovaquone/proguanil treatment group across all phase III studies was 56.9 kg. As a group, these patients received a daily dose of atovaquone 17.6 mg/kg and proguanil 7.0 mg/kg. The efficacy rate observed for this group as a whole was 98.5%. The average adult male in the US is reputed to weigh 70 kg. The possibility exists that patients in this country requiring antimalarial therapy with MALARONE could weigh >70 kg. On a mg/kg basis, such patients would receive less than the recommended doses of atovaquone and proguanil. The MO reviewed the phase III adult study population for patients who weighed >60 kg and patients who weighed >70 kg. Efficacy was assessed for each of these groups. The efficacy rates, expressed as % of evaluable patients with a S response at 28 days, and dosing are presented below.

Table 4. Efficacy rates by patient weight and mg/kg dose of atovaquone/proguanil

	Patients >60 kg	Patients >70 kg
Daily dose of atq/prg (mg/kg)	<16.6 atq / <6.6 prg	<14.2 atq / <5.7 prg
Efficacy rate	125/128 (97.7%)	34/34 (100%)

Table 4 demonstrates that the high efficacy rates observed for Malarone for the treatment of falciparum malaria in the study population as a whole were also seen in the subpopulations who weighed more than 60 kg and therefore received less than atovaquone 20 mg/proguanil 8 g daily for three days. The efficacy of Malarone in the treatment of pediatric malaria was also observed to be consistent across a wide range of daily mg/kg dose. For a full discussion of this subject, the reader is referred to the MO

review of study #115-123. A summary of those results is reproduced here as Table 5. All children represented in this study population (100%) were cured at 28 days.

Table 5: Study #115-123: Mean doses of atovaquone/proguanil administered by pediatric weight class

Weight class	No of evaluable pts	Range of weights (kg)	Mean weight (kg)	Mean dose ATQ administered	Mean dose PRG administered
11-20 kg	15	15-20	17.9	13.9 mg/kg	5.6 mg/kg
21-30 kg	8	21-30	25.2	19.8 mg/kg	7.9 mg/kg
31-40 kg	3	31-35	33.0	22.7 mg/kg	9.0 mg/kg

Efficacy by immune status of the study population

In study #115-136, observations of the high proportion of supposedly malaria-experienced adult patients in Peru who were febrile at presentation prompted speculation regarding different degrees of 'semi-immunity' that may be observed in adult and pediatric patients who reside in malarious areas. That discussion is reproduced below:

This study population, though small, presents an interesting issue regarding the immune status of the patients studied. Those enrolled in the study were described as life-long residents of the malaria-endemic region in which the study was conducted, and some degree of malaria immunity was assumed for this population. Adults who fit such a description are generally referred to as 'semi-immune.' While they can become ill from *Plasmodium* infection, the course of the illness is not as severe as it can be in those individuals with no prior exposure to malaria, the non-immunes. However, the mean IPCs were quite low, and the proportion of patients presenting with fever was quite high. In his discussion of 'pyrogenic density' in malaria, White (in Manson, 20th ed. P. 1108) notes that the parasitemia at which fever occurs can vary widely, and can be regarded as a marker of immunity. Some non-immunes can become febrile before parasites are visible on the peripheral smear, while some (partially) immune adults can be afebrile with peripheral blood parasite counts of up to 100,000 parasites/µl. Thus one might conclude that a population with a low mean IPC and a high rate of fever at presentation does not have 'as much' immunity as a population with either a high mean IPC and high rate of fever at presentation or a high mean IPC and a low rate of fever at presentation. The population of adults in northern Peru enrolled in the present study can be compared other study populations in NDA 21-078. The patients studied in #115-127 were gold miners in Brazilian Amazonia, a region with one of the highest malaria transmission rates in the country. The Brazilian patients presented with comparable mean IPC values (~6000/µl) but only ~60% of patients were febrile at presentation. The Thai adults in study #115-122 presented with mean IPCs of ~18,000/µl and the proportion febrile at presentation was 85-90%, comparable to the patients in the present study in Peru. Many of these patients had received antimalarials prior to enrollment. The Kenyan children enrolled in study #115-131, a population generally considered 'less immune' than adults in malaria-endemic regions, presented with mean IPCs ~30,000/µl; the proportion who were febrile was ~75%. The European adults in study #115-130 presented with a mean IPC ~20,000

and ~90% were febrile. It should be noted that all of the IPC values under discussion here are relatively low; 25,000/µl is approximately a 0.5% parasitemia in patients with a normal hematocrit, and that peripheral parasite counts do not reflect the total body parasite mass, much of which can be sequestered in the microvasculature of various organ systems. Perhaps distinctions between IPCs ≤1% are not clinically meaningful. It is also noteworthy that the intensity of malaria transmission can vary widely in a number of areas in which the disease is 'endemic,' and there is little information in these studies regarding the use of antipyretics prior to presentation. However, the divergent rates of fever at presentation for a given value of IPC observed in these study populations does suggest different host responses among a group generally regarded as 'semi-immune.' A comparison of the highly diverse study populations in this NDA suggests a 'spectrum of immunity' to malaria, even among those individuals who are life-long residents of an endemic region.
If one were to order the study populations presented in this NDA simply based on initial parasite counts and rates of fever at presentation, it might be possible to establish such a spectrum with the truly non-immune patients at one end and those with the most immunologic experience of malaria at the other end.

European adults < Peruvian adults<Thai adults <Kenyan children ~Filipino adults~ Gabonese adults ~ Zambian adults.

It should be recognized that initial parasite counts and rates of fever at presentation are rough tools for assessing a study population for immunologic experience of malaria. The spectrum above is presented simply to develop the concept that the patients studied in the phase III trials of Malarone are a diverse group immunologically and represent the wide range of patients who can require treatment for acute falciparum malaria. That efficacy rates for atovaquone/proguanil were high and comparable across these studies (see Table 1) suggests that this combination antimalarial can be used in the treatment of both malaria-naïve and malaria-experienced patients.

Efficacy in the treatment of non-falciparum malaria

The studies conducted in Gabon and in Thailand provided a limited opportunity to assess the efficacy of atovaquone/proguanil in the treatment of non-falciparum malaria. A summary of these findings is presented in Table 6.

Table 6. Parasitological Response in Patients with Non-falciparum Malaria Treated with Atovaquone and Proguanil Hydrochloride

Study	Species	Total enrolled	Number blood film negative / Number evaluable			
			Day 7	Day 14	Day 21	Day 28
115-005	*P. vivax*	25	21 / 23	19 / 19	15 / 18	6 / 19
115-134	*P. ovale*	4	4 / 4	2 / 2	3 / 3	3 / 3
	P. malariae	3	3 / 3	3 / 3	3 / 3	3 / 3

The efficacy of MALARONE in the treatment of the erythrocytic phase of non-falciparum malaria was assessed in a small number of patients. Of 23 patients in Thailand infected with *P. vivax* and treated with atovaquone/proguanil 1000 mg /400 mg daily for three days, parasitemia cleared in 21(91.3%) at 7 days. Parasite relapse occurred commonly when *P. vivax* malaria was treated with MALARONE alone. Seven patients in Gabon with malaria due to *P. ovale* or *P. malariae* were treated with atovaquone/proguanil 1000 mg /400 mg daily for three days. All six evaluable patients (3 with *P. malariae*, 2 with *P. ovale*, one with mixed P. *falciparum* and *P. ovale*) were cured at 28 days. *P. vivax* and *P. ovale* infections are both characterized by hypnozoite stages against which MALARONE has no demonstrated activity.

These data are preliminary and do not support a change in the INDICATIONS proposed by the applicant in the draft label. However, they do provide information regarding drug activity against less common species that cause human malaria. Such information can be reassuring to the physician managing the newly presented malaria patient. Accurate speciation of malaria parasites by microscopy is a rare skill that is only maintained with constant practice. Very few clinical laboratories in the US are staffed with individuals who possess such skills. The first question to be addressed in the newly diagnosed malaria patient is whether or not *P. falciparum*, the species most likely to result in death of the patient, is present. If one can be certain that one is not treating falciparum malaria, the question still remains whether or not a given agent is active against the acute stage of the non-falciparum species. Some approved antimalarials such as mefloquine (Lariam, NDA 19-591) are specifically labeled to state that there are insufficient data to support activity against *P. ovale* and *P. malariae*. Others such as pyrimethamine-sulfadoxine (Fansidar, NDA 18-557) make no mention of non-falciparum species. Information such as that provided in Table 6, though limited, and requiring caveats regarding the need for prophylaxis against relapse, can be useful to the clinician.

Future development of Malarone

The applicant submitted the following list of planned studies of treatment with Malarone. These include

A description of these studies is presented in Table 7.

WITHHOLD 1 PAGE (S)

SAFETY REVIEW
INTEGRATED SUMMARY OF SAFETY
INTRODUCTION

Safety data for this NDA were presented in two separate parts. The first part of the Integrated Summary of Safety (ISS) included data from pharmacokinetic, bioequivalence, treatment, and challenge studies, the second included data from prophylaxis studies. This review is limited to the data from the pharmacokinetic, bioequivalence, treatment, and challenge studies. The reader is referred to the MO review of Dr Leonard Sacks for a discussion of the safety data from the prophylaxis studies.

There were 17 completed pharmacokinetic, bioequivalence, treatment, and challenge studies in the ISS, and these studies enrolled a total of 1577 subjects or patients. In this population, there were 148 healthy volunteers and 1429 malaria patients. A total of 841 healthy volunteers and malaria patients received oral atovaquone and proguanil in single or multiple daily dosing regimens ranging from one to seven days of exposure. Among the healthy volunteers, 126 received atovaquone and proguanil in combination. Among the malaria patients, 602 received the recommended daily treatment dose of 1000 mg atovaquone and 400 mg proguanil or an equivalent dose adjusted by body weight in children. Of the 602 patients treated with atovaquone and proguanil, there were 486 adults and 116 children. Table 1 presents the numbers of patients in the various study populations.

Table 1. Subjects in MALARONE Pharmacokinetic, Bioequivalence Treatment and Challenge Trials

Study Population	Treatment	Number of Subjects
		Completed Studies
Healthy Volunteers n=148	ATQ alone	32[a]
	PRG alone	21[a]
	Placebo	5
	ATQ + PRG	126
Adults with Malaria n=1229	ATQ alone	94
	PRG alone	18
	ATQ + PRG - recommended dose[b]	486
	ATQ + PRG - other doses	113
	ATQ + Other Drugs	86
	Comparator	432
Children with Malaria n=200	ATQ + PRG - recommended dose[b]	116
	Comparator	84
Total for ATQ + PRG - All doses		**841**
Total Subjects		1577[c]

ATQ = atovaquone, PRG = proguanil hydrochloride

[a] 36 of these 53 subjects also received ATQ + PRG and are counted in that treatment total.

[b] Recommended treatment dose in adults is 1000 mg atovaquone and 400 mg proguanil hydrochloride once daily for 3 days. In children, this dose is adjusted for body weight.

[c] Excludes 36 healthy volunteers who also received ATQ or PRG alone in the crossover study. Includes 3 patients with malaria who were retreated with the same treatment and assigned new patient numbers.

The applicant reported that safety data collected in the clinical studies that comprise this NDA included evaluations of physical examinations, vital signs, adverse experiences, hematology and clinical chemistry parameters, and urinalyses. No changes in physical exam findings, vital signs, or urinalyses were noted in the clinical studies that were believed to be attributed atovaquone/proguanil. Data from physical exams, vital signs, and urinalyses were not summarized in the ISS, but were presented in the individual study reports. The focus of the ISS was data on adverse experiences and clinical laboratory parameters.

MO COMMENT: Physical exam findings, including vital signs, and urinalysis data were reviewed by the MO as part of the safety reviews for each study report. The MO agreed that there were no changes in physical exam or urinalysis data that were suggestive of an adverse effect due to atovaquone/proguanil. For

additional comment on urinalysis results from individual studies, the reader is referred below to the discussion of G6PD deficient patients in the section entitled LABORATORY STUDIES.

ADVERSE EVENTS

Adverse event reporting in adults/adolescents and in pediatric patients will be discussed separately below.

Adult and adolescent AEs

The applicant summarized all adverse experiences reported by more than 10% of adults and adolescents in the seven controlled phase III studies. Because many of these signs and symptoms can be part of the clinical presentation of acute malaria, these results are presented in Table 2 and compared with the rates of the same AEs considered attributable to study drugs by investigators.

MO COMMENT: For the purposes of safety reporting, the applicant grouped adults and adolescents (individuals aged 12-16 years) together. Some of the phase III treatment trials of malaria in adults included patients as young as 12 years. Studies #115-120, 115-122, 115-130, 134, 135, and 136 included patients aged 12-16 years.

Table 2. Common adverse experiences reported by >10% of adult and adolescent patients treated with 1000 mg atovaquone and 400 mg proguanil in controlled clinical treatment trials

Adverse Experience	Percentage of Patients with Common Adverse Experiences (Percentage of patients in whom AE was considered attributable to study drug by investigator)							
	Study 115-120		Study 115-122		Study 115-134		Study 115-135	
	A+P[a] n=82	PYR+S[b] n=81	A+P n=91	MFQ[b] n=91	A+P n=76	ADQ[b] n=71	A+P n=55	C±PYR+S[b] n=55
Abdominal pain	35 (28)	42 (21)	2 (0)	1 (0)	29 (21)	18 (8)	15 (11)	9 (0)
Headache	46 (28)	37 (31)	0 (0)	2 (1)	13 (3)	15 (7)	5 (0)	9 (0)
Vomiting	12 (12)	15 (15)	10 (0)	2 (0)	26 (26)	30 (25)	18 (9)	13 (2)
Nausea	7 (7)	16 (14)	1 (1)	5 (2)	30 (29)	24 (21)	7 (5)	4 (2)
Diarrhea	26 (16)	16 (11)	5 (0)	2 (0)	24 (16)	20 (7)	0 (0)	2 (2)
Asthenia	28 (24)	19 (16)	1 (0)	0 (0)	5 (0)	24 (3)	0 (0)	4 (0)

Adverse Experience	Percentage of Patients with Common Adverse Experiences (cont'd) (Percentage of patients in whom AE was considered attributable to study drug by investigator)							
	Study 115-127		Study 115-130		Study 115-136			Total A+P n=436
	A+P[a] n=87	QN+TCN[b] n=88	A+P n=25	HLF[b] n=23	A+P n=20	PYR+S n=9	C[b] n=14	
Abdominal pain	52 (30)	38 (26)	12 (4)	9 (0)	25 (10)	22 (0)	14 (0)	26 (17)
Headache	47 (22)	27 (9)	16 (0)	4 (0)	10 (0)	22 (0)	43 (0)	22 (10)
Vomiting	8 (6)	11(9)	44 (44)	4 (4)	35 (15)	22 (11)	0 (0)	17 (12)
Nausea	23 (16)	32 (28)	20 (16)	9 (9)	25 (20)	11 (0)	7 (0)	15 (12)
Diarrhea	15 (8)	18 (13)	12 (12)	17 (9)	5 (5)	11 (0)	7 (0)	14 (8)
Asthenia	36 (14)	36 (18)	8 (4)	4 (0)	0 (0)	0 (0)	5 (0)	14 (8)

[a] A+P = atovaquone and proguanil hydrochloride

[b] PYR+S=pyrimethamine and sulfadoxine, MFQ=mefloquine, ADQ=amodiaquine, QN+TCN=quinine and tetracycline, HLF=halofantrine, C=chloroquine.

MO COMMENT: Table 2 presents data from seven studies in which there was a wide range of values reported for the frequencies of the AEs listed. Study #115-122, conducted in Thai adults, and study 115-135, conducted in Filipino adults, had remarkably low rates of the most common AEs, while studies #115-130 and #115-134, conducted in European adults and Gabonese adults, respectively, had remarkably high rates for the AEs listed. Rather than provide additional information about the investigational agent, this disparity suggests different methods of AE data collection at different study centers, or, perhaps, cultural differences in AE reporting.

MO COMMENT: The frequency of attributable AEs most closely approximated the frequency of all AEs for nausea and vomiting. This was fairly consistent

among patients in the atq/prg treatment groups across all studies. Thus most investigators considered nausea and vomiting most likely attributable to study drug, despite reporting differences noted between treatment centers. Because acute falciparum malaria can be a potentially life-threatening infection, the reliability of oral drug bioavailability is particularly important. The observation that vomiting is a common attributable AE in patients treated with atovaquone/proguanil deserves comment. While this was a common AE observed in patients in NDA 21-087 treated with atq/prg, so it was in patients treated with pyrimethamine/sulfa, amodiaquine, and, most importantly, patients treated with quinine and tetracycline, the drug of choice for acute falciparum malaria in many regions including the US. Atovaquone/proguanil may be best utilized if the prescribing physician is aware of the likelihood that patients may vomit this oral treatment. The draft label appropriately lists vomiting as a common AE and provides instructions to repeat dosing if the patient vomits within one hour of drug administration. It may also be useful to inform the prescribing physician that 15.3% adult patients and 0% of pediatric malaria patients who were treated with atq/prg received antiemetics during that part of the study period that they were taking atovaquone/proguanil, and that concurrent administration of an antiemetic may be warranted. This may be best accomplished in the PRECAUTIONS section, General subsection with the replacement of the current wording on lines 172-174 with the text presented in the section MEDICAL OFFICER'S SAFETY CONCLUSIONS.

'Absorption of atovaquone may be reduced in patients with diarrhea and vomiting. If MALARONE is used in these patients, parasitemia should be closely monitored and the use of an antiemetic considered. In the controlled clinical trials of Malarone for the treatment of falciparum malaria, 15.3% adults and 0% children who were treated with atovaquone/proguanil received an antiemetic during that part of the study period during which they received the antimalarial regimen. In patients with severe or persistent diarrhea or vomiting, alternative therapy should be considered.'

MO COMMENT: Adverse events are more commonly reported as those that occur in >2% of patients. The MO reviewed tables reporting all adverse events and attributable adverse events for adults and adolescents in phase III studies (tables 17, 18, vol 56, NDA 21-078). Attributable events that occurred in >2% of patients were the following: pruritis (3%), myalgia (3%), anorexia (5%), dizziness (5%), diarrhea (8%), asthenia (8%), headache (10%), nausea (12%), vomiting (12%), abdominal pain (17%). In the draft label proposed by the applicant, the section ADVERSE REACTIONS lists those adverse events that occurred in of adults in treatment studies, regardless of attributability. These are the AEs listed in Table 2 above. This list accurately reflects most of the clinically noteworthy AEs attributed to atovaquone/proguanil in the treatment studies. Because many of these AEs are seen in the patient with acute malaria, it may be more informative for the prescribing physician if the list of attributable AEs seen in >2% of patients is substituted for the current statement in the ADVERSE REACTIONS section of the label.

MO COMMENT: In the course of the MO review of Tables 17 and 18 referenced above, certain inconsistencies in event frequency reporting were noted. This was brought to the attention of Regulatory Affairs at GlaxoWellcome on May 18, 1999. Following internal review of these tables, GlaxoWellcome determined that the contents of some individual cells within these tables had been shifted in the process of transferring data between the original spreadsheets and the final document. On May 21, 1999, GlaxoWellcome provided the MO with corrected versions of Tables 17 and 18 that were derived from the original spreadsheets. These tables were reviewed and compared to those provided in the original NDA submission. All data presented and discussed above follow review of these corrected tables.

Pediatric AEs

The applicant summarized all adverse experiences reported by more than 10% children in the two phase III pediatric studies. Because many of these signs and symptoms can be part of the clinical presentation of acute malaria, these results are presented in Table 3 and compared with the rates of the same AEs considered attributable to study drugs by investigators.

Table 3. Common adverse experiences reported by >10% of pediatric patients treated with the recommended dose of atovaquone and proguanil

Adverse Experience	Percentage of Patients with Common Adverse Experiences (Percentage of patients in whom AE was considered attributable to study drug by investigator)			
	Study 115-131		Study 115-123	Total A+P n=116[b]
	A+P[a] n=84	HLF[a] n=84	A+P n=32[b]	
Coughing	12 (0)	17 (0)	45 (0)	21(0)
Headache	10 (2)	18 (5)	45 (0)	19 (2)
Vomiting	15 (13)	8 (2)	19 (0)	17 (11)
Abdominal pain	10 (2)	23 (8)	26 (0)	14 (2)
Anorexia	4 (1)	10 (5)	39 (3)	13 (2)

[a] A+P= atovaquone and proguanil hydrochloride, HLF = halofantrine

[b] No adverse event data were collected for one subject in Study 115-123.

MO COMMENT: Among pediatric patients, vomiting was the most common attributable AE among patients who received atovaquone/proguanil.

MO COMMENT: The MO reviewed tables 20 and 21 (vol 56, NDA 21-078) which listed all AEs reported in phase III pediatric patients and attributable AEs reported in phase III pediatric patients. Attributable AEs that occurred in >2% of pediatric patients were rash (3%), splenomegaly (3%), pruritis (6%), and vomiting

(11%). Again, as with adults, it may be informative to include the list of attributable AEs that occurred in >2% of patients in the label. Splenomegaly can be seen in acute malaria; it can also be seen in children raised in areas of high malaria transmission. A causal relationship between three days' treatment with atovaquone/proguanil and splenomegaly cannot be established with the data available here.

Deaths

One death was reported during the conduct of the 17 studies under discussion in this section of the safety review. This patient's course was summarized in the safety review for study #115-012. He was a young Zambian man with a psychiatric history whose malaria was treated with atovaquone 750 mg q 8 hours for 7 days. The patient cleared his parasitemia on day 4 and began exhibiting unusual behavior on day 5. He was transferred to a psychiatric ward on day 10 and treated with a number of psychotropic drugs. On day 13, he became drowsy, experienced a respiratory arrest and died before resuscitation was initiated. The MO review of this patient's CRF determined that this patient might also have been taking traditional remedies for his psychiatric disease. While the patient's antecedent delusions and agitation may have been attributable to atovaquone, his death was unlikely to have been related to atovaquone/proguanil. The reader is referred to the MO review of study #115-012 for further details.

Serious AEs

In addition to the one patient who died, there were nine patients who experienced serious adverse events. Of these nine, one was treated with atovaquone alone, five with atovaquone and proguanil, and three with a comparator. Four of the ten patients (9 SAE + 1 death) reported central nervous system events, four reported nausea and/or vomiting, one each reported an anaphylactic reaction, congestive heart failure, hemolysis, dental abscess, and cytomegalovirus. Events for two patients were attributable to study medication. These were anaphylactic reaction (atovaquone/proguanil) and delusions and agitation prior to sudden death (atovaquone alone).

The MO reviewed the narrative accounts of each of the patients who experienced a serious adverse event. Of particular interest were those patients treated with atovaquone alone or atovaquone/proguanil. A second patient in study #115-012 experienced depression and crying while being treated with atovaquone alone. The patient reported alcohol and marijuana use shortly before study entry. His symptoms resolved while treatment with atovaquone continued. This event was not considered treatment-related. A Kenyan child with a history of seizures enrolled in study #115-131 experienced a seizure after two days of treatment with atq/prg. This event was not considered treatment-related. An adult patient in study # 115-136 experienced a seizure 15 hours after her third and final dose of atq/prg. This patient was found to be hyponatremic and the event was not considered treatment-related. A 15 year old patient in study #115-134 had an anaphylactic reaction to atovaquone/proguanil; this event was treatment-related. One patient in study #115-130 was diagnosed with a dental abscess and cytomegalovirus

infection; neither event was related to treatment with atq/prg. One patient in study #115-130 reported nausea and vomiting which was not thought to be related to treatment with atq/prg, though the patient was withdrawn from the study. For further discussion of these patients, the reader is referred to the MO reviews of the individual studies.

Treatment-limiting AEs

Treatment-limiting adverse events for adult and pediatric patients are summarized in Table 4.

Table 4. Treatment-limiting adverse events in pharmacokinetic and treatment studies

Study	Patient Number	Treatment & Dose[b]	Adverse Event	AE Drug Related	Outcome
115-132	26	1000mg ATQ+ 400mg PRG once	headache	No	withdrawn
115-133	103	1000mg ATQ+ 400mg PRG q24hx3	viral gastro-enteritis	No	withdrawn
	216	1000mg ATQ+ 400mg PRG q24hx3	nausea vomiting	Yes	withdrawn
MALB1002	1690	500mg ATQ+ 400mg PRG by Weiders	microscopic hematuria left loin pain	unlikely unlikely	withdrawn
115-003	302	500 mg ATQ	vomiting	NA	withdrawn
115-122	1153	1250 mg MFQ	vomiting nausea	No No	withdrawn
115-127	036	QN + TCN	hemolysis (black water fever)	No	resolved
115-130	044	1000 mg ATG +400 mg PRG	vomiting nausea	No No	withdrawn
	086	1000 mg ATQ + 400 mg PRG q24hx3	vomiting	Yes	withdrawn
	095	1000 mg ATQ + 400 mg PRG q24hx3	vomiting	Yes	withdrawn
115-131	051	20mg/kg ATQ+ 8mg/kg PRG q24hx3	vomited medicine	Yes	malaria cured, withdrawn
115-134	062	1000mg ATQ+ 400mg PRG q24hx3	anaphylactic reaction	Yes	withdrawn
115-136	002	1000mg ATQ+ 400mg PRG q24hx3	seizures confusion	No	resolved, withdrawn

MO COMMENT: Noteworthy treatment-limiting AEs that occurred in patients treated with atovaquone and proguanil included nausea and vomiting attributed to study drug observed in a healthy volunteer in study #115-133 and vomiting in

three patients enrolled in study #115-130 and one patient enrolled in #115-131. The treatment-limiting vomiting was attributed to atq/prg in three of these patients. Analysis of the treatment-limiting AEs underscores the potential effects of treatment-related vomiting in-patients treated with atovaquone/proguanil. Benefit from this drug will be maximized with appropriate labeling that identifies this potential problem and provides the prescribing physician with information regarding ways to improve bioavailability with repeat dosing and the possible use of antiemetics.

MO COMMENT: Though treatment-related vomiting was a common attributable adverse event in patients who were treated with atovaquone/proguanil (12%), it should be noted that only 3/436 (0.7%) patients experienced treatment-limiting vomiting. As the optimal use of this drug is considered, it should be borne in mind that 15.3% of adults who were treated with atovaquone/proguanil received an antiemetic. That vomiting due to atq/prg was common and treatment-limiting vomiting was not may be related to the use of antiemetics. Proposed labeling changes that address this issue are presented below in the section entitled MEDICAL OFFICER'S CONCLUSIONS.

Adverse events from sources other than clinical trials

Malarone was first marketed in Switzerland in August 1997. As of the safety cutoff date of October 1, 1998 for NDA 21-078, it had been approved in 25 countries. There have been two spontaneous reports of adverse events. One of these was an allergic reaction and the other an episode of elevated liver enzymes.

LABORATORY STUDIES

The applicant's discussion of laboratory data was divided into two parts. These were 1) data from pharmacokinetic and phase II studies, and 2) data from phase III treatment studies.

Of note in the pharmacokinetic and phase II data was one malaria patient in study #115-005 who was treated with atovaquone and proguanil and experienced severe hemolysis and hemoglobinuria requiring blood transfusion. The applicant reported that this patient was one of 71 who were deficient in the red blood cell enzyme glucose-6-phosphate-dehydrogenase (G6PD) who were treated with atovaquone/proguanil (n=52) or atovaquone alone (n=19). According to the applicant's analysis, none of the other 70 patients had evidence of 'anemia out of proportion to the severity of their malaria infection.'

MO COMMENT: It is difficult to establish specific criteria that define 'anemia out of proportion to the severity of malaria infection' among a population of patients with uncomplicated falciparum malaria. The occurrence of severe hemolysis in a patient with G6PD deficiency who was treated with atovaquone/proguanil suggests that the study population in this safety database be analyzed for any signals suggestive of hemolysis associated with

atovaquone/proguanil treatment in patients with this enzyme deficiency. Such a MO analysis is presented below. Before proceeding, however, it should be noted that atovaquone and proguanil, both previously approved and marketed drugs, have not been associated with hemolysis in patients who are G6PD deficient. It should also be noted that there was one other patient among those in the pharmacokinetic, bioequivalence, treatment, and challenge studies who experienced severe hemolysis and hemoglobinuria, or blackwater fever, a well recognized complication of falciparum malaria. This patient (noted in Table 4 above) was treated with quinine and tetracycline and was not G6PD deficient.

The MO evaluation of hemolytic events in patients with G6PD deficiency was limited to the population of patients in phase II and phase III trials in which G6PD testing was conducted. These were the patients enrolled in studies numbered 115-005, 115-012, 115-120, 115-122, 115-123, 115-127, 115-130, and 115-131. Only patients who were treated with atovaquone and proguanil or a regimen that contained one of these two drugs were included in the analysis. In an attempt to limit the confounding effect of hemolysis seen in patients with falciparum malaria, patients were included in this analysis only if 1) they had a sensitive (S) response to atq/prg treatment, and 2) they did not have hemoglobinuria at the time of enrollment. There were 477 patients who fulfilled these criteria; 51 of these patients were G6PD deficient and 426 had normal levels of G6PD. Because anemia from many causes can be a common finding in poorly nourished patients in developing countries, and because it is commonly seen in acute malaria, changes in hemoglobin and/or hematocrit were thought to be too insensitive an indicator for hemolysis. The population of 477 patients described above was analyzed for the number of patients who had hemoglobinuria at any time after enrollment during the first seven days of study. Among the patients who were G6PD deficient, 4/51 (7.8%) had hemoglobinuria during the first seven days of study. Among patients who were G6PD normal, 21/426 (4.9%) did. Using Fisher's exact test, p= 0.327; the difference between these rates was not statistically significant.

The applicant analyzed laboratory data from all phase III treatment studies by treatment group. Changes in mean values for laboratory tests and the percentage of patients with abnormal laboratory values were reported for the atovaquone/proguanil and the comparator treatment groups. These results for adults and children are presented in Table 5 below.

Table 5. Hematology and chemistry summary data in treatment studies

Red Blood Cells (/pL)		Phase II		Phase III Adult Studies				Children (Phase III)			
				A+P[a]		Control[b]		A+P[a]		HLF[a]	
	Day	Mean	Sd[a]	Mean	Sd[a]	Mean	Sd[a]	Mean	Sd[a]	Mean	Sd[a]
	0	4.4	0.8	4.3	.08	4.3	0.8	4.5	0.9	Not	
	3	4.1	0.7	4.1	.08	4.1	0.7	3.9	0.9	Done	
	7	4.1	0.7	4.1	.07	4.1	0.7	3.7	1.0		
	14	4.3	0.6	4.3	.06	4.2	0.6	4.2	0.9		
	28	4.6	0.6	4.5	.06	4.5	0.6	4.7	0.9		
Total number		348		272[c]		273		32			
No. markedly abn[a]		19		14		19		9			
% markedly abn		5.5%		5.1%		7.0%		28.1%			
Markedly abn < 3.0 / pL											

Hemoglobin (g/dL)		Phase II		Phase III Adult Studies				Children (Phase III)			
				A+P[a]		Control[b]		A+P[a]		HLF[a]	
	Day	Mean	Sd[a]	Mean	Sd[a]	Mean	Sd[a]	Mean	Sd[a]	Mean	Sd[a]
	0	12.0	2.2	12.5	2.4	12.3	2.4	11.3	2.0	10.3	2.6
	3	11.1	2.0	11.8	2.3	11.7	2.2	9.9	1.8	9.7	2.3
	7	11.2	1.8	12.0	2.0	11.9	2.1	10	1.7	10.3	2.1
	14	11.8	1.5	12.5	1.8	12.2	1.8	11.2	1.3	10.9	1.6
	28	12.6	1.5	12.9	1.7	12.9	1.8	12.2	1.4	12.1	1.5
Total number		348		349		344		116		84	
No. markedly abn[a]		11		9		14		14		12	
% markedly abn		3.2%		2.6%		4.1%		12.1%		14.3%	
Markedly abn < 7.5 g/dL											

Hematocrit (%)		Phase II		Phase III Adult Studies				Children (Phase III)			
				A+P[a]		Control[b]		A+P[a]		HLF[a]	
	Day	Mean	Sd[a]	Mean	Sd[a]	Mean	Sd[a]	Mean	Sd[a]	Mean	Sd[a]
	0	36.2	6.6	38.6	6.6	38.1	6.9	33.5	5.6	34.0	7.4
	3	33.4	6.0	36.8	6.6	36.8	6.5	30.9	5.9	32.7	7.1
	7	33.5	5.6	37.5	6.0	37.4	6.4	33.6	5.9	34.8	6.0
	14	35.5	4.6	38.5	5.1	38.3	5.4	35.0	4.8	36.6	4.4
	28	38.1	4.4	40.8	4.9	40.4	4.9	38.5	4.7	39.8	3.8
Total number		348		436		432		116		84	
No. markedly abn[a]		25		14		15		16		11	
% markedly abn		7.2%		3.2%		3.5%		13.8%		13.1%	
Markedly abn < 25%											

White Blood Cells (/nL)		Phase II		Phase III Adult Studies				Children (Phase III)			
				A+P[a]		Control[b]		A+P[a]		HLF[a]	
	Day	Mean	Sd[a]	Mean	Sd[a]	Mean	Sd[a]	Mean	Sd[a]	Mean	Sd[a]
	0	6.1	2.2	6.0	2.5	6.0	2.4	8.0	3.9	8.6	3.5
	3	5.6	1.7	5.3	1.9	5.4	1.9	6.5	2.3	7.7	3.2
	7	7.2	2.2	6.5	2.3	6.3	2.3	7.4	2.4	7.2	2.8
	14	7.7	2.1	6.6	2.2	6.6	2.5	6.7	2.1	6.2	1.7
	28	8.2	2.2	6.6	2.3	6.5	2.3	7.1	2.5	6.5	2.3
Total number		348		436		432		116		84	
No. markedly abn[a]		7		35		36		2		0	
% markedly abn		2.0%		8.0%		8.3%		1.7%		0%	
Markedly abn < 3.0 / nL											

Platelets (/nL)		Phase II		Phase III Adult Studies				Children (Phase III)			
				A+P[a]		Control[b]		A+P[a]		HLF[a]	
	Day	Mean	Sd[a]	Mean	Sd[a]	Mean	Sd[a]	Mean	Sd[a]	Mean	Sd[a]
	0	Not		198	110	196	113	163	80	191	92
	3	Done		220	107	224	107	215	99	238	107
	7			313	99	322	111	325	146	379	120
	14			308	103	333	110	312	104	349	122
	28			281	103	290	106	280	99	314	95
Total number				429		426		116		84	
No. markedly abn[a]				6		5		2		1	
% markedly abn				1.4%		1.2%		1.7%		1.2%	
Markedly abn < 50 /nL											

Total Bilirubin (mg/dL)		Phase II		Phase III Adult Studies				Children (Phase III)			
				A+P[a]		Control[b]		A+P[a]		HLF[a]	
	Day	Mean	Sd[a]	Mean	Sd[a]	Mean	Sd[a]	Mean	Sd[a]	Mean	Sd[a]
	0	1.5	1.2	1.3	1.2	1.3	1.2	1.2	1.0	1.2	0.9
	3	0.8	0.9	0.8	0.7	0.7	0.7	0.7	0.5	0.5	0.3
	7	0.6	0.4	0.6	0.3	0.5	0.5	0.5	0.4	0.4	0.2
	14	0.7	0.4	0.6	0.3	0.5	0.3	0.5	0.3	0.4	0.2
	28	0.7	0.3	0.6	0.3	0.5	0.3	0.5	0.4	0.4	0.2
Total number		348		429		430		116		84	
No. markedly abn[a]		14		9		4		5		0	
% markedly abn		4.0%		2.1%		0.9%		4.3%		0%	
Markedly abn >2.0mg/dL											

AST (U/L)		Phase II		Phase III Adult Studies				Children (Phase III)			
				A+P[a]		Control[b]		A+P[a]		HLF[a]	
	Day	Mean	Sd[a]	Mean	Sd[a]	Mean	Sd[a]	Mean	Sd[a]	Mean	Sd[a]
	0	38.9	25.0	30.2	30.3	29.5	27.3	48.1	42.1	59.9	59.6
	3	37.7	30.0	29.9	35.8	27.2	33.5	40.9	43.7	43.4	30.6
	7	35.7	23.4	26.1	22.1	29.1	42.0	40.7	97.3	42.3	21.8
	14	34.5	20.2	25.0	21.2	24.9	15.9	31.0	15.4	35.6	14.1
	28	31.0	24.2	23.4	18.4	22.9	14.8	30.3	17.9	42.6	53.3
Total number		348		433		427		116		84	
No. markedly abn[a]		20		18		13		6		5	
% markedly abn		5.7%		3.2%		3.0%		5.2%		6.0%	
Markedly abn > 100 U/L											

ALT (U/L)		Phase II		Phase III Adult Studies				Children (Phase III)			
				A+P[a]		Control[b]		A+P[a]		HLF[a]	
	Day	Mean	Sd[a]	Mean	Sd[a]	Mean	Sd[a]	Mean	Sd[a]	Mean	Sd[a]
	0	34.0	29.7	27.4	109.3	23.5	36.3	29.2	33.3	47.4	91.2
	3	36.0	32.8	25.4	59.8	21.6	29.6	26.3	51.1	33.9	38.0
	7	41.6	30.9	30.1	40.1	31.6	47.8	27.7	78.5	32.3	22.6
	14	40.3	33.6	27.1	32.2	27.3	28.2	21.1	17.2	24.1	12.5
	28	35.8	44.3	21.0	24.6	21.1	21.7	21.0	19.9	34.5	77.4
Total number		348		433		428		116		84	
No. markedly abn[a]		37		21		15		3		4	
% markedly abn		10.6%		4.8%		3.5%		2.6%		4.8%	
Markedly abn > 100 U/L											

Glucose (mg/dL)		Phase II		Phase III Adult Studies				Children (Phase III)			
				A+P[a]		Control[b]		A+P[a]		HLF[a]	
	Day	Mean	Sd[a]	Mean	Sd[a]	Mean	Sd[a]	Mean	Sd[a]	Mean	Sd[a]
	0	113	28	111.0	29.8	112.2	34.5	109	38	102	33
	3	105	24	101.6	29.2	101.9	27.8	95	25	94	27
	7			91.8	17.7	90.8	22.8	87	24	84	24
	14			90.5	23.1	89.0	21.3	84	20	79	17
	28	94	27	92.3	27.0	91.9	21.6	85	19	77	16
Total number		315		429		427		116		84	
No. markedly abn[a]		0		3		3		12		13	
% markedly abn		0%		0.7%		0.7%		10.3%		15.5%	
Markedly abn <50 mg/dL											

Creatinine (mg/dL)		Phase II		Phase III Adult Studies				Children (Phase III)			
				A+P[a]		Control[b]		A+P[a]		HLF[a]	
	Day	Mean	Sd[a]	Mean	Sd[a]	Mean	Sd[a]	Mean	Sd[a]	Mean	Sd[a]
	0	1.1	0.3	1.1	0.4	1.2	0.5	1.0	0.4	0.9	0.5
	3	1.0	0.2	1.1	0.4	1.1	0.6	0.8	0.3	0.8	0.5
	7	1.0	0.2	1.0	0.3	1.0	0.4	0.7	0.3	0.8	0.3
	14	1.0	0.2	1.0	0.3	1.0	0.3	0.7	0.2	0.7	0.3
	28	1.0	0.2	1.0	0.2	1.0	0.3	0.7	0.2	0.7	0.3
Total number		348		433		428		116		84	
No. markedly abn[a]		0		8		9		0		0	
% markedly abn		0%		1.8%		2.1%		0%		0%	
Markedly abn >2 mg/dL											

[a] A+P = atovaquone + proguanil hydrochloride, HLF = halofantrine, SD= standard deviation, abn = abnormal.

[b] Adult Controls = combined data from treatment with pyrimethamine and sulfadoxine in study 115-120, mefloquine in study 115-122, halofantrine in study 115-130, amodiaquine in study 115-134, chloroquine, with or without pyrimethamine and sulfadoxine, in study 115-135, quinine and tetracycline in study 115-127, and pyrimethamine and sulfadoxine in 115-136.

[c] For Day 0

Table 5 shows that the comparison of mean laboratory values between treatment groups for adults and children did not reveal any treatment associated differences in laboratory values that were clinically significant. Examination of the means for each treatment group does show the anemia, leukopenia, and mild abnormalities of liver function and renal function that can be seen in acute malaria.

Examination of the percentages of adult patients in each treatment group with markedly abnormal laboratory values shows that patients who were treated with atq/prg had a higher rate of markedly abnormal total bilirubin (2.1% v. 0.9%) and ALT (4.8% v. 3.5%) levels. Hyperbilirubinemia was also more common in pediatric patients treated with atq/prg compared to controls, though this was not the case with transaminase (ALT or AST) values among children studied. The applicant pointed out that the most marked elevations of transaminases and the most marked differences between atq/prg treatment group and control were seen in studies #115-122, which was conducted in adults in Thailand, and in study #115-130, which was conducted in adults in France. In study # 115-122, marked elevations of ALT or AST were seen in 21% atq/prg patients compared

with 9% control (mefloquine) patients. The applicant speculated that the observations made in Thailand might have been the result of the high rate of chronic hepatitis B infection. However, if that were the case, one would expect to see such patients equally represented between the two treatment groups. In almost all instances, abnormal liver function tests did return to normal by the end of the 28-day study period.

MO COMMENT: In an attempt to better characterize the liver function test abnormalities noted in patients treated with atovaquone/proguanil, the MO performed an additional analysis on the patients in study # 115-122, the study in which there was a large difference between treatment groups in the number of patients with markedly abnormal liver function tests. In an attempt to limit the confounding effect of acute *Plasmodium falciparum* infection on total bilirubin, ALAT, and ASAT, only patients with normal values for these tests at enrollment were analyzed by treatment arm and by study day. The proportion of patients with an abnormal value for each of these tests was determined for each day of the study on which blood was drawn after day 0. These results are presented in Table 6.

Table 6. Liver function test abnormalities by treatment arm and by study day in patients with normal values at enrollment in study #115-122

	No. of patients with elevated Tbili (%)		No. of patients with elevated ASAT (%)		No. of patients with elevated ALAT (%)	
Study day	A/P	Mef	A/P	Mef	A/P	Mef
Day 3	3/46 (6.5)	2/51 (3.9)	24/59 (40.7)	6/57 (10.5)	7/60 (11.7)	3/62 (4.8)
Day 7	1/46 (2.1)	1/53 (1.8)	10/59 (16.9)	5/58 (8.6)	16/60 (26.7)	10/64 (15.6)
Day 14	0	1/49 (2.0)	7/55 (12.7)	8/56 (14.3)	14/57 (24.6)	13/61 (21.3)
Day 28	0	0	4/48 (8.3)	4/49 (8.2)	7/49 (14.3)	9/51 (17.6)

A/P = atovaquone/proguanil; Mef= mefloquine

Table 6 shows that adult malaria patients treated with atovaquone/proguanil and mefloquine both exhibited early elevations in total bilirubin that resolved within 4 weeks. There was little difference in the rates or duration of total bilirubin abnormalities between treatment groups. Hemolysis due to red blood cell parasitization and sequestration of parasite in the microvasculature of the liver might be mechanisms by which *Plasmodium* infection causes elevations in the total bilirubin. Further examination of Table 6 shows that elevations in transaminases (ASAT and ALAT) occurred more commonly and lasted longer in both treatment groups studied in #115-122. It is noteworthy that a larger proportion of patients treated with atovaquone/proguanil had early (day 3) elevations in both ASAT and ALAT (40.7% v. 10.5% and 11.7% v. 4.8%, respectively). This trend persisted in each treatment group at day 7, when atovaquone/proguanil-treated patients were again observed to have a higher rate of transaminase elevations than mefloquine-treated patients (16.9% v. 8.6% and 26.7% and 15.6%). None of these transaminase elevations was more than 5x the upper limit of normal (200 IU). When transaminase elevations were analyzed at later points in the study (days 14 and 28), there were few differences noted between treatment groups. Both had a small proportion of patients who had elevated transaminase levels at the conclusion of the study.

The high rates of early elevations of transaminase values in patients treated with atovaquone/proguanil are noteworthy when one considers that the population analyzed in Table 6 was limited to patients who had normal values for these tests at enrollment. The natural history of falciparum infection suggests that, because of sequestration of parasites in microvasculature, there may be a lag between parasite clearance from the peripheral blood and normalization of some liver function tests. However, in a randomized trial such as this one, the proportion of patients manifesting this lag would be evenly distributed between treatment groups. Similarly, the suggestion made in the study report for #115-122 that high rates of chronic hepatitis B infection in Thai adults might explain the liver function test abnormalities seen here does not seem applicable to a randomized study population. These abnormalities did not persist for the duration of the study, nor were they particularly severe abnormalities. Examination of the mean values for these liver function tests in the entire phase III population (Table 5) does not reflect the differences between treatment groups seen in #115-122. It may be useful to inform the prescribing physician that mild elevations of transaminase levels can persist up to 4 weeks following treatment for malaria with atovaquone/proguanil.

MO COMMENT: The draft label includes a statement that describes the liver function test abnormalities noted in the patients in the phase III trials. It is presented below:

[redacted]

The applicant should consider the addition of wording that informs the prescribing physician about the nature and duration of these abnormalities.

Also noteworthy in the pediatric patient population was the higher rate of hypoglycemia seen in atq/prg and comparator-treated children (10.3% and 15.5%, respectively) when compared with adults (0.7% and 0.7%, respectively). Rather than suggest an association with treatment, this more likely represents the differences between adult and pediatric malaria.

DRUG INTERACTIONS

The applicant reported that no formal drug interaction studies have been performed with atovaquone/proguanil and drugs likely to be administered with them during the treatment of malaria.

MO COMMENT: The draft label includes statements about potential interactions between Malarone and tetracycline, metoclopramide, and rifampin. The label states,

Concomitant treatment with tetracycline has been associated with [redacted] plasma concentrations of atovaquone.

MO COMMENT: An explanation for the conclusion regarding metoclopramide should be provided. The Biopharmaceutics review of NDA 20-259, atovaquone tablet (MEPRON), included a comparison of steady-state concentrations (Css) of atovaquone achieved during the concomitant administration of other drugs. When all patients were considered (n=191), the Css for atovaquone was 13.9 mcg/ml. Patients who received concomitant metoclopramide (n=6) achieved a Css of atovaquone of 5.8 mcg/ml. A possible mechanism proposed for this lowered concentration was that metoclopramide-induced stimulation of the GI tract may have resulted in reduced absorption of atovaquone. The reader is referred to the section MEDICAL OFFICER'S SAFETY CONCLUSIONS for proposed wording for this section of the label.

MO COMMENT: Earlier MO COMMENTS have suggested the applicant add a statement to the label that acknowledges the relatively high rate of nausea and vomiting attributed to Malarone and advises early use of an antiemetic in patients who are candidates for oral antimalarial therapy with Malarone. Such a statement should include a reference to the The reader is referred to the section MEDICAL OFFICER'S SAFETY CONCLUSIONS for proposed wording for this section of the label.

MEDICAL OFFICER'S SAFETY CONCLUSIONS

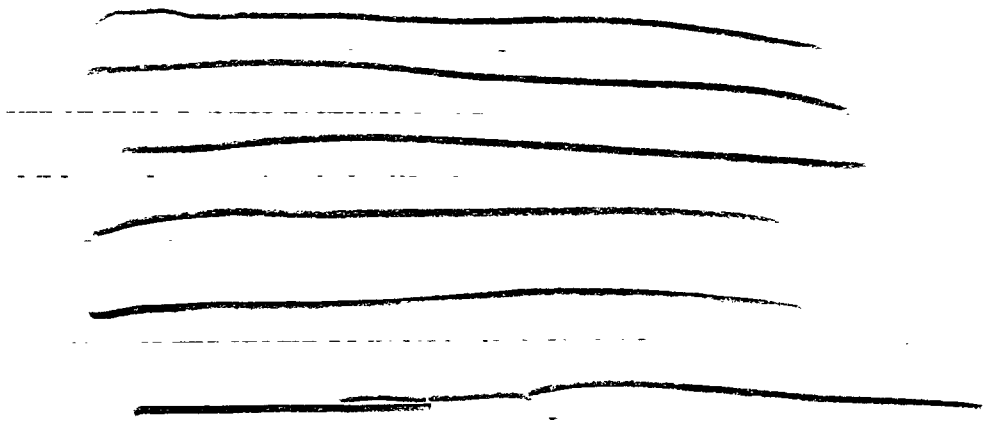
The safety data submitted with NDA 21-078 for pharmacokinetic, bioequivalent, treatment, and challenge studies support the safety of the combination of atovaquone and proguanil when given for the treatment of uncomplicated falciparum malaria.

The following labeling changes are recommended. All label references are to the draft dated May 13, 1999:

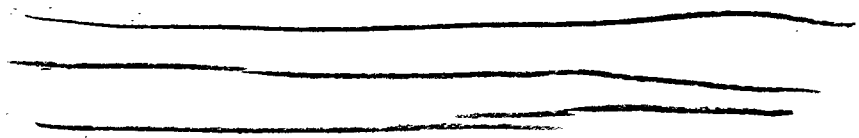
1. Atovaquone/proguanil may be best utilized if the prescribing physician is aware of the likelihood that patients may vomit this oral treatment. The draft label appropriately lists vomiting as a common AE and provides instructions to repeat dosing if the patient vomits within one hour of drug administration.

   It may also be useful to inform the prescribing physician that 15.3% patients in controlled treatment trials received antiemetics during that part of the study period that they were taking atovaquone/proguanil, and that concurrent administration of an antiemetic may be warranted. Analysis of the treatment-limiting AEs underscores the potential effects of treatment-related vomiting in patients treated with

atovaquone/proguanil. Benefit from this drug will be maximized with appropriate labeling that identifies this potential problem and provides the prescribing physician with information regarding ways to improve bioavailability with repeat dosing and the possible use of antiemetics. This may be best accomplished in the PRECAUTIONS section, General subsection with the replacement of the current wording on lines 172-174 with the following:



2. Adverse events are more commonly reported as those that occur in >2% of patients. The MO reviewed tables reporting all adverse events and attributable adverse events for adults and adolescents in phase III studies (tables 17, 18; vol 56, NDA 21-078). Attributable events that occurred in >2% of patients were the following: pruritis (3%), myalgia (3%), anorexia (5%), dizziness (5%), diarrhea (8%), asthenia (8%), headache (10%), nausea (12%), vomiting (12%), abdominal pain (17%). In the draft label proposed by the applicant, the section ADVERSE REACTIONS lists those adverse events that occurred in — of adults in treatment studies, regardless of attributability. These are the AEs listed in Table 2 above. This list accurately reflects most of the clinically noteworthy AEs attributed to atovaquone/proguanil in the treatment studies. Because many of these AEs are seen in the patient with acute malaria, it may be more informative for the prescribing physician if the list of attributable AEs seen in — of patients is substituted for the current statement in the ADVERSE REACTIONS section of the label. The following statement should be substituted for the current wording on lines 236-239 in the draft label:



3. Attributable AEs that occurred in >2% of pediatric patients were rash (3%), splenomegaly (3%), pruritis (6%), and vomiting (11%). Again, as with adults, it may be informative to include the list of attributable AEs that occurred in — of patients in the label. Splenomegaly can be seen in acute malaria; it can also be seen in children raised in areas of high malaria transmission. A causal relationship between

three days' treatment with atovaquone/proguanil and splenomegaly cannot be established with the data available here. The following statement should be substituted for the current wording on lines 240-242 in the draft label:

4. The applicant should consider the addition of the following sentence at the end of the sentence on line 245:

5. The applicant should include a statement in both the CLINICAL PHARMACOLOGY section, Drug Interactions subsection and in the PRECAUTIONS section, Drug Interactions subsection that explains how and in what population(s) conclusions were drawn regarding interactions between atq/prg and metoclopramide, tetracycline, and rifampin.

120-DAY SAFETY UPDATE
TREATMENT AND PROPHYLAXIS OF MALARIA

On April 27, 1999, the applicant submitted to NDA 21-078 the required update on safety reporting that included the period from the original safety cutoff, October 1, 1998 to February 26, 1999. During this period there were no new data for the completed studies presented in the original NDA. Also during this period,

e

WITHHOLD 3 PAGE (S)

CONCLUSION TO MEDICAL OFFICER'S REVIEW OF TREATMENT INDICATION FOR NDA 21-078

Malarone, a fixed combination of atovaquone and proguanil, is safe and effective in the treatment of acute uncomplicated falciparum malaria. Efficacy of this drug has been demonstrated in a wide range of geographic settings. It has been shown to have high efficacy rates comparable to approved comparators, and it has been shown to have better efficacy rates than drugs with unacceptable failure rates that are presumably due to drug resistance. Efficacy has also been demonstrated in adults and children across a wide range of weight classes and doses and in populations that demonstrate widely varying degrees of immunity or non-immunity to malaria. Preliminary evidence suggests that Malarone may have activity against the erythrocytic phases of non-falciparum malaria as well.

I recommend approval of this drug for the treatment of acute uncomplicated falciparum malaria.

Andrea Meyerhoff MD MSc DTMH
Medical Officer

Concurrence Only:
HFD590/TmLdrMO/Hopkins
HFD-590/DivDir/Goldberger
HFD-104/OfficeDir/Kweder

cc: Original NDA 21-078
HFD-590
HFD-590/MO/Meyerhoff
HFD-590/Chem/SmithJ
HFD-590/Micro/Bala
HFD-590/Pharm/Kunder
HFD-590/Biopharm/Mahayni
HFD-725/Biometrics/Jiang
HFD-590/PM/Dempsey

NDA 21-078
Medical review: Atovaquone/proguanil prophylaxis for malaria

Title: medical officer's review of NDA

NDA number 20-634

Applicant identification:

Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park,
NC 27709
Phone (919) 483-2100

Submission/review dates
Date of submission Dec 29, 1998.
Date review completed June 11, 1999

Medical officer: Leonard Sacks

Drug identification:

Generic name: Atovaquone and proguanil hydrochloride tablets

Trade Name: Malarone

Chemical name: trans-2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthalenedione and 1-(4-chlorophenyl)-5-isopropyl-biguanide hydrochloride

Dosage form: Tablet

Route of administration: Oral

Proposed indication and usage as described in the label:
INDICATIONS AND USAGE:
Prophylaxis of *P falciparum* malaria including ;
DOSAGE AND ADMINISTRATION
Prophylactic treatment with MALARONE should be started 1 or 2 days before entering a malaria-endemic area and
Adults: One malarone tablet (adult strength=250mg atovaquone /100 mg proguanil hydrochloride) per day.
Pediatrics dosed by weight according to the following table

Weight (kg)	Atovaquone/proguanil HCl Total Daily Dose	Dosage regimen
11-20	62.5mg/25mg	One Malarone Pediatric Tablet daily
-30	125mg/50mg	Two Malarone Pediatric Tablets as a single dose daily
-40	187.5mg/75mg	Three Malarone Pediatric Tablet as a single dose daily
>40	250mg/100mg	One Malarone Tablet (adult strength) daily

Table of Contents

NDA 21-078
Medical review: Atovaquone/proguanil prophylaxis for malaria

Background:
Regulatory history:
Malarone has been approved for the treatment of *P falciparum* malaria in the following countries: Argentina, Australia, Austria, Bahrain, Belgium, Brazil, Canada, Chile, Cyprus, Ecuador, France, Gabon, Germany, Italy, Jamaica, Kenya, Kuwait, Luxembourg, Netherlands Antilles, Mauritius, Myanmar, Peru Phillippines, Portugal, Singapore, Sweden, Switzerland, Trinidad and Tobago, UK. Malarone hase been approved for treatment and prophylaxis of *P falciparum* malaria in Denmark. A submission to the Mutual Recognition Procedure of Europe in Dec 1997 was withdrawn in July 1998.

Pre-clinical concerns:
Pharmacology and toxicology studies demonstrated that proguanil was toxic when given to dogs in a dose of 20-160mg/kg. Over 9 weeks, proguanil at this dose resulted in gastritis, vomiting, emaciation and death. (See pharmacology/toxicology review). Over a 26-week study period, proguanil given to dogs alone or in combination with atovaquone resulted in histopathalogical abnormalities of the heart liver and gall bladder. Cardiac lesions in these animals included fibrovascular proliferation. Proguanil 40 mg/kg/day either alone or in combination with atovaquone resulted in the deaths of three beagle dogs, among 8 treated with this regimen.

Novel dosing claim:
Individuals infected with malarial sporozoites from a mosquito normally experience an asymptomatic "prepatent" period during which parasites develop and multiply in the liver. Approximately 6 ½ -10 days after infection, parasites are released from the liver where they infect red cells, producing positive blood smears and symptomatic disease. Antimalarial agents acting on the liver stage of the infection (prior to the appearance of parasites in the blood) have been designated "causal" prophylactics. No antimalarial agent to date has been has been approved as a "causal" prophylactic. Traditionally, antimalarial prophylaxis is continued for 4 weeks beyond the period of malaria exposure, to cover the time during which the parasites are present in the peripheral blood. This application seeks a dosing regimen for malarone prophylaxis, extending only seven days beyond the period of malaria exposure based on the purported activity of atovaquone and proguanil against the hepatic phase of the infection.

Material reviewed:
Clinical trials supporting the indication for the prophylaxis of malaria due to *P falciparum* included five clinical trials as shown below. Four were conducted in Africa. They included two placebo-controlled field trials performed in adults, one in children and an uncontrolled adult study to provide predominantly safety data. In support of Malarone as a "causal prophylactic" a single volunteer challenge study was conducted in the USA using atovaquone alone. Further support for this claim was provided in the form of a reprint of a historic study examining proguanil alone as a causal prophylaxis.

Table 1: Controlled studies of Malarone in the prophylaxis of malaria

Study Number	Document Number	Study Design	Treatments	Number of Subjects	Mean Age in Years (Range)	Duration of Therapy
MALB 2001	RM1997/ 00697	Randomized, double-blind, controlled trial in Kenyan adults	Atovaquone 250 mg and proguanil HCl 100 mg daily Atovaquone 500 mg and proguanil HCl 200 mg daily Placebo	285	30 (18–55)	10 weeks
MALB 2002	RM1997/ 00668	Randomized, double-blind, controlled trial in adult volunteers in the U.S.	Atovaquone 250 mg Atovaquone 750 mg daily Placebo	19	30 (22–44)	1 day 7 days 7 days
MALB 3001	RM1997/ 00687	Randomized, double-blind, controlled trial in Zambian adults	Atovaquone 250 mg and proguanil HCl 100 mg daily Placebo	274	32 (16–44)	10 weeks
MALB 3003	RM1997/ 00686	Randomized, double-blind, controlled trial in children in Gabon	Atovaquone ~5 mg/kg and proguanil HCl ~2 mg/kg daily Placebo	365	10 (5–16)	12 weeks

Table 2: Uncontrolled study of Malarone in the prophylaxis of malaria

Study Number	Document Number	Study Design	Treatments	Number of Subjects	Mean Age in Years (Range)	Duration of Therapy
MALB 2002	RM1997/ 00690	Uncontrolled, open-label trial in non-immune adult South African military personnel	Atovaquone 250 mg and proguanil HCl 100 mg daily	175	20 (18–52)	10 weeks

MALB2001

A Randomised double-blind placebo controlled parallel group study to determine the chemosuppressive activity of a fixed dose combination of atovaquone/proguanil in volunteers at risk for developing *P falciparum* malaria in Kenya

Study design: This was a placebo-controlled, double blind, randomized, three arm parallel-group trial. Following screening, all patients received "radical curative treatment" with four tablets of Malarone daily for three days (atovaquone 250mg/proguanil 100mg per tablet). Patients were then randomized to one of three suppressive treatment regimens. These regimens included one Malarone tablet daily, (atovaquone 250mg/proguanil 100mg per tablet), two Malarone tablets daily or placebo daily. A successful radical cure was defined by negative smears at week one or week two following radical curative treatment. Successfully treated patients continued the prophylactic phase of the study for ten weeks. Upon completion of prophylaxis, subjects were followed for a further 4 weeks. Weekly malaria smears were taken and the study endpoint was a positive thick film for any plasmodium species while on prophylaxis. The study was conducted at a single site in the Lwak village of Northern Kenya, during the peak malaria transmission period April to August 1996. The schedule of events is shown in table 3.

Table 3: Schedule of study visits and procedures

	Screening	Radical Cure	Chemosuppression											Follow-up			
Study Visit		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Week Day	-2/52 ±-17/365	-1/52 -3/365	0/52 0/365	1/52 7/365	2/52 14/365	3/52 21/365	4/52 28/365	5/52 35/365	6/52 42/365	7/52 49/365	8/52 56/365	9/52 63/365	10/52 70/365	11/52 77/365	12/52 84/365	13/52 91/365	14/52 98/365
Written informed consent	√																
Inclusion/exclusion Criteria	√	√															
Medical history/ demography	√																
Physical examination[f]	√							√					√				
Vital signs	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Hematology/ Biochemistry[a]	√							√					√				
Malaria blood smears[b]	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Adverse event review			√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Concomitant medicine review		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Medication issued: Radical Cure[c] Chemosuppression[d]		√	√	√	√	√	√	√	√	√	√	√	√				
Pregnancy test	√							√					√				
DRC Issued/ Reviewed/ Collected		√	√	√	√	√	√	√	√	√	√	√	√				
Pharmacokinetic Blood Sample[e]	√							√					√				
Blood sample for *in vitro* sensitivity testing	Anytime malaria develops																

[a] / or at time of withdrawal

[b] / or at any time that malaria was suspected

[c] During the Radical Curative Phase of the trial medication was issued daily for three days, under supervision of the Field Worker

[d] During the Chemosuppression Phase of the trial, medication was issued daily under supervision of the Field Worker. The Chemosuppression Phase followed on directly from the Radical Curative Phase

[e] / or at time of withdrawal

[f] Only done at Visit 16 if any abnormalities were detected at Visit 12

The study was conducted in collaboration with the US army Medical research unit in Kenya and the Kenya Medical Research Institute. Data management and biochemistry and plasma drug level analysis were contracted to

Inclusion criteria:

- Male or female
- In good health
- >=18 and <=65 years of age
- willing and able to give informed consent and able to comply with the protocol

Exclusion criteria:

- Pregnancy
- Lactation
- Of childbearing potential and in the investigator's opinion not willing or able to avoid pregnancy.
- Received antimalarial drugs or other drugs with antimalarial activity within the previous 2 weeks.
- Known hypersensitivity to atovaquone or proguanil.
- Clinically significant abnormal baseline hematology or clinical chemistry parameters (when results were obtained volunteers were withdrawn at the discretion of the investigator)
- Significant renal impairment as evidenced by a creatinine clearance of <30 ml\min
- Splenectomy
- Laboratory evidence of hepatitis as defined by a three-fold increase above the normal upper limit in alanine transaminase (ALT) for this volunteer population
- Clinically significant concomitant medical problems as determined by the investigators.

Criteria for premature discontinuation.
Volunteers could withdraw themselves or could be withdrawn by the investigator at any time if continued participation was considered detrimental. If the reason for withdrawal was an adverse event, then an adverse event form was completed. Subjects were evaluated two weeks after withdrawal if they remained in the study area.

1) Subjects with parasitemia at the end of "radical cure" or during chemo-suppression or follow-up were withdrawn and managed according to the clinical judgment of the attending study clinician.

2) Subjects missing more than 2 days of medication were withdrawn as compliance failures. Compliance was checked by a field worker in the community.

3) Concurrent therapy: Volunteers receiving drugs with anti-malarial activity during the study were withdrawn. Such drugs included chloroquine, quinine, mefloquine, halofantrine, pyrimethamine/sulphadoxine, proguanil and antibiotics such as co-trimoxazole, tetracycline, doxycycline and rifampicin.

Study procedures:
Study drug was administered under the supervision of field workers each day, 45 minutes after food.
Randomization was in blocks of 30.
Investigators assessed patients on weeks –1,0, 5,10 and 14. These visits included a review of inclusion and exclusion criteria, a medical history, physical examinations and additional blood sampling for hematology, biochemistry and pharmacokinetic tests. Field workers performed the rest of the visits during which compliance and concomitant medications were reviewed, adverse events were recorded and blood smears for malaria were obtained.

At the start of chemosuppression, thick blood films were examined.

Subjects developing malaria were treated with pyrimethamine/sulphadoxine and in vitro drug-sensitivity tests were performed and drug levels were measured.

Efficacy assessment:
The primary endpoint was the development of parasitemia with any species of plasmodium during chemoprophylaxis.
Smears regarded as positive by one microscopist were confirmed by a second microscopist, and disagreements were settled by a third senior technologist.
MO comment: Negative smears were not reviewed by a second microscopist compromising the sensitivity of detecting endpoints.

Since the claimed indication is for the prophylaxis of malaria due to *P falciparum*, the primary endpoint should be limited to smears positive for *P falciparum*

IC_{50} values were obtained wherever viable isolates were identified and compared with historical values to identify the development of drug resistance.
MO comment: A historical comparison would not distinguish between development of drug resistance versus initial infection with a resistant parasite.

Safety assessment:
The population analyzed for safety included all patients who received at least one dose of atovaquone/proguanil during chemoprophylaxis. Adverse events were coded using COSTART terms summarized by attributability, intensity, seriousness and action taken.
Treatment-limiting adverse events were defined as events for which the action taken was recorded as "study drug discontinued." Symptomatic malaria was not considered a treatment-related adverse event.

Adverse events were defined as any untoward medical occurrences experienced by the volunteer. They included exacerbation of pre-existing illnesses.

Serious adverse events included deaths, life-threatening events, disabling or incapacitating events, events requiring or prolonging hospitalization, cancer, congenital anomalies, adverse consequences of overdose, and laboratory findings fitting the definition of serious adverse events or other laboratory findings of major clinical concern.

Routine protocol-defined clinical laboratory tests included hematocrit, hemoglobin, platelets, total white blood cells and a lymphocyte count, serum sodium, potassium, albumin, creatinine, urea, total bilirubin, alkaline phosphatase, and alanine aminotransferase.

Sample size calculations:
Eighty to one hundred subjects were to be included in each of the three study arms. If 85% of placebo-treated subjects developed parasitemia, the study would have a power of 80% to detect an 85% efficacy compared to placebo with a confidence of >70%.

Intent-to-treat analysis
The population for this analysis was defined as subjects who:
- Had negative baseline smears
- were randomized
- received at least one dose of study medication.

Patients excluded from this population included
- Subjects withdrawn due to intolerance of "radical cure"
- Subjects lost to follow up before the baseline visit
- Subjects lost to follow up during radical cure

In this population, the following categories of patients were distinguished:
Non evaluable: Patients with no results of a baseline smear, patients not confirmed to have taken at least one dose of study medication.
Evaluable failures: Included patients with a positive smear for *P falciparum* anytime after the week 2 visit, up to and including the week 10 visit, patients receiving other drugs with anti-malarial activity, patients

The protocol was modified to reflect that the chemosuppressive phase of the study would last 10 weeks rather than at least 10 weeks as previously determined. The statistical aim of the study was restated to demonstrate that the chemosuppressive protective efficacy of a fixed dose combination of atovaquone and proguanil against *P falciparum* infection is at least 85% better than placebo with a lower limit of confidence of approximately 70%. The sample size was raised from 64 to 70 per arm to provide a power of 80% to detect an 85% efficacy compared to placebo with a lower limit of confidence of approximately 70% if the placebo infection rate was 85% as expected. In addition, "clinically significant concomitant medical problems" were added to the list of exclusion criteria. Also provision was made to reclassify all patients missing daily medication for more than 2 consecutive days as compliance failures. These patients were to be withdrawn from the study.

April 12 1996

A change in packaging of the study medications was described allowing patients to receive 10 cartons each containing two "tracer packs", one tablet to be taken from each pack per day. During the follow up period of up to 4 weeks, serious or unexpected adverse events would be captured rather than all adverse events.

May 31 1996

An extra physical examination was scheduled for visit 16 to allow for follow-up of physical findings during study.

July 11 1996

An additional blood sample was to be taken during the four weeks of follow-up on patients with a positive malaria smear, to measure concentrations of atovaquone, proguanil and cycloguanil. An interim analysis was scheduled for all patients with positive smears during chemoprophylaxis to determine if all were receiving placebo. This information was to be used to support the use of a single tablet dose in subsequent prophylactic trials.

Results:

Two hundred and sixteen subjects were screened and enrolled for radical curative treatment. Two hundred and five completed the radical cure phase. Randomization resulted in 70 subjects being allocated to the one tablet arm, 67 to the two-tablet arm and 68 to the placebo arm.

Table 4: Patient disposition

216 screened			
205 completed radical cure			
Treatment group	Placebo (n=68)	One tablet (n=70)	Two tablets (n=67)
Loss to follow-up	3	2	2
ITT population	65	68	65
Discontinued during prophylaxis	11	14	11
Per-protocol	54	54	54

The 11 patients who failed to complete radical therapy included 9 who failed to return, one who was withdrawn for repeated vomiting and one who withdrew consent. Seven subjects were lost to follow-up before the baseline visit and were not included in the ITT population. No subjects were excluded on the basis of a positive baseline smear.

MO comment: Visit 1 was not conducted due to resource constraints (see vol 58 p 28 of NDA) According to the report on protocol deviations the week 0 visit was not conducted and week 1 data was used for a baseline. Failures of prophylaxis would only have been detected after two to three weeks and the above procedure is acceptable.

Thirty-six subjects entering the chemo-prophylaxis phase were discontinued as shown below:

Table 5: Reasons for discontinuation

Reason for Discontinuation	Chemoprophylaxis Treatment Group		
	Placebo	1 ATQ/PGN Tab[b] Per Day	2 ATQ/PGN Tabs[b] Per Day
Failure to return	6 (18; 80; 104; 109; 131; 150)	4 (102; 103; 116; 221)	2 (52; 180)
No Week 10 blood smear	2 (15; 86)	6 (72; 93; 114; 169; 172, 227)	7 (77; 94; 101; 134; 151; 212; 214)
Non-compliance	2 (123; 164)	3 (19; 56; 226)	
Refused drawing of blood		1 (65)	
Took antimalarial concurrently	1 (89)		1 (79)
Mistaken entry (violation of inclusion/exclusion criteria)			1 (222)
Total	11	14	11

Withdrawals for reasons other than parasitemia occurred in 11 placebo recipients, 14 patients treated with one tablet of malarone and 11 patients treated with two tablets of malarone.

Most withdrawals occurred during the second half of the 10 week chemoprophylaxis period and were equivalent for the groups.

MO comment: Line listings for all withdrawals were reviewed looking for pyrexia, thrombocytopenia, malarial symptoms and treatment with antimalarials at the time of withdrawal. None of the 36 withdrawn patients was documented to have a fever or symptoms of malaria at the time of withdrawal. Significant thrombocytopenia was not evident in any of the subjects at the time of withdrawal.
Two subjects received antimalarials. One (#89) placebo-treated patient with a positive baseline smear received "Fansidar" at the beginning of chemoprophylaxis. One patient in the 2 tablet arm (#79) received intramuscular chloroquine 2 days after the week six visit. Neither fever nor thrombocytopenia were recorded and a malaria smear 2 days prior to the date of discontinuation was negative. It did not appear that any of the withdrawals had evidence of malaria as a cause for discontinuation. Most were withdrawn for reasons of poor follow-up and an absence of blood smears at the end of chemoprophylaxis. No withdrawals occurred as a result of a treatment related adverse event

All 36 withdrawals above were treated as evaluable failures in the ITT analysis.
All 36 withdrawals above were excluded from the PP analysis.

Demographics at screening:
Patient characteristics on enrollment are described in table 6 below.

Table 6: Demographic features of patients at the screening visit

Characteristic	Placebo n = 68	1 ATQ/PGN Tab[a] Per Day n = 70	2 ATQ/PGN Tabs[a] Per Day n = 67
Male/Female	47/21	47/23	41/26
Age (yrs)			
Males			
Mean (SD)	29 (7.8)	32 (9.9)	28 (9.7)
Range	19–55	18–51	17–53
Females			
Mean (SD)	32.0 (12.2)	31 (11.6)	28 (11.0)
Range	18–53	18–51	18–54
Weight (kg)			
Males			
Mean (SD)	63 (7.6)	64 (8.1)	64 (5.9)
Range	45–77	46–84	55–79
Females			
Mean (SD)	65 (10.7)	58 (9.0)	61 (8.7)
Range	45–96	41–75	45–75
Height (cm)			
Males			
Mean (SD)	175 (7.0)	173 (9.8)	176 (5.4)
Range	152–190	136–189	164–188
Females			
Mean (SD)	165 (7.5)	161 (6.2)	165 (7.4)
Range	150–186	150–172	151–176

MO comment: Patients were equally matched between the three arms for sex, age, weight and height. The inclusion of younger women may have been limited because of their childbearing potential.

At screening 34% of randomized subjects had positive malaria smears, 25/68 in the placebo arm, 23/70 in the one-tablet arm and 21/67 in the two-tablet arm. All subjects in the ITT population had negative smears at week 1 or 2 following radical treatment.

MO comment: High rates of parasitemia at screening indicate that this population had substantial malaria exposure prior to prophylaxis with appreciable malaria immunity unlike malaria naïve travelers.

Concurrent illnesses were similar in all three groups. Headache and trauma accounted for a large proportion of these.
Table 7 shows that concurrent therapy during the study was also similar for the groups.

Table 7: Antimicrobials and other most commonly used concurrent medications

	Placebo (n=68)	One tablet (n=70)	Two tablets (n=67)
All medications	57 (84%)	55 (79%)	59 (88%)
Analgesics	52 (76%)	48 (69%)	53 (79%)
Antacids	13 (19%)	17 (24%)	16 (24%)
Antibacterials (any)	41 (60%)	36 (51%)	39 (58%)
Beta lactams	36(53%)	33 (47%)	39 (58%)
Sulphonamides	1 (1%)	0	0
Tetracyclines	7 (10%)	7 (10%)	8 (12%)
Quinolones	4 (6%)	2 (3%)	2 (3%)
Antihistamines	34 (50%)	37 (53%)	39 (58%)
Antiepileptics	20 (29%)	23 (33%)	32 (48%)
Cardiac meds	23 (34%)	35 (50%)	32 (48%)
Antimalarials *	23 (34%)	5 (7%)	6 (9%)

The frequent use of cardiac medications and antiepileptics in all groups was notable. Agents with possible antimalarial activity included sulphonamide/trimethoprim in one placebo recipient, and tetracyclines in 10-12% of each group.

Compliance:
Compliance was supervised each day by a field worker and recorded in a daily record card as study subjects arrived at drug distribution sites. At each weekly visit, daily record cards were collected and compliance records were entered into the case report form. Five subjects were withdrawn for non-compliance, two in the placebo group and 3 in the single tablet group.

Efficacy results:

Parasitemia developed in 28 subjects on placebo and none of the subjects in either of the malarone arms during the chemo-suppressive phase of the study. The degree of parasitemia was not reported.

All parasitemias were identified morphologically as *P falciparum*. Gametocytes were not reported in any of these treatment emergent infections.

Correlation between fever and parasitemia:
A temperature >38C was only recorded in 5 placebo recipients despite the fact that 26 had positive smears at screening and 28 developed malaria during the chemoprophylaxis period.

MO comment: The absence of fever in the majority of patients developing malaria in this study suggests that this population had substantial immunity and their presentation differed from the presentation expected of naïve travelers entering a malaria area for the first time.

To exclude the possibility that cases occurring in the chemoprophylaxis phase were recrudescences following radical cure, I calculated the odds for parasitemia developing during chemoprophylaxis among patients with a parasitemia at the screening visit vs those without parasitemia at the screening visit in patients on the placebo arm. The purpose of this analysis was to determine whether malarone selectively suppressed recrudescences or whether it prevented new infections.

Table 8 Treatment failures among placebo recipients with or without baseline parasitemia

	Treatment failure	No treatment failure
Baseline parasitemia	11	15
No baseline parasitemia	17	22

MO comment: Eleven of 26 patients (42%) who were parasitemic at screening developed malaria during the study as compared with 17 of 39 patients (44%) who were not parasitemic at baseline, (OR 0.95 (CI 0.31-2.91)). A parasitemia at screening did not increase the risk of developing malaria during the study, suggesting that infections in the placebo group were no more likely to be recrudescences than they were to be new infections.

Prophylactic efficacy in the ITT population was determined as follows:
N=198
Table 9: Results in the ITT population

	Placebo	Low dose Malarone	High dose Malarone
Non-evaluable	0	0	0
Evaluable failures	39	14	11
Evaluable successes	26	54	54

Prophylactic efficacy in the PP population was determined as follows:
N=162
Table 10: Results in the PP population

	placebo	Low dose Malarone	High dose Malarone
Non-evaluable	0	0	0
Evaluable failures	28	0	0
Evaluable successes	26	54	54

Calculated efficacy rates are shown in table 11.

Table 11: Prophylactic efficacy in ITT and PP populations as determined by sponsor.

	ITT Analysis			PP Analysis		
	Placebo n = 65	1 ATQ/PGN Tab[a] Per Day n = 68	2 ATQ/PGN Tabs[a] Per Day n = 65	Placebo n = 54	1 ATQ/PGN Tab[a] Per Day n = 54	2 ATQ/PGN Tabs[a] Per Day n = 54
Failure of Chemoprophylaxis						
Parasitemia	28	0	0	28	0	0
Withdrawn (treatment-related)[b]	0	0	0	0	0	0
Withdrawn (other reasons)	11	14	11	-	-	-
Total	39	14	11	28	0	0
Success Rate	40%	79%[c]	83%[c]	48%	100%[c]	100%[c]
Difference in Success Rate (ATQ/PGN-Placebo)	-	39%	43%	-	52%	52%
(95% CI[d])	-	(23–55%)	(26–58%)	-	(35–67%)	(35–67%)
Efficacy Rate[e]	-	66%	72%	-	100%	100%
(95% CI[d])	-	(39–85%)	(46–89%)	-	(77–100%)	(77–100%)

[a] 250 mg atovaquone/100 mg proguanil hydrochloride per tablet

[b] Withdrawn due to a Treatment-Related Adverse Event

[c] P = <0.001, Fisher's Exact Test, versus Placebo

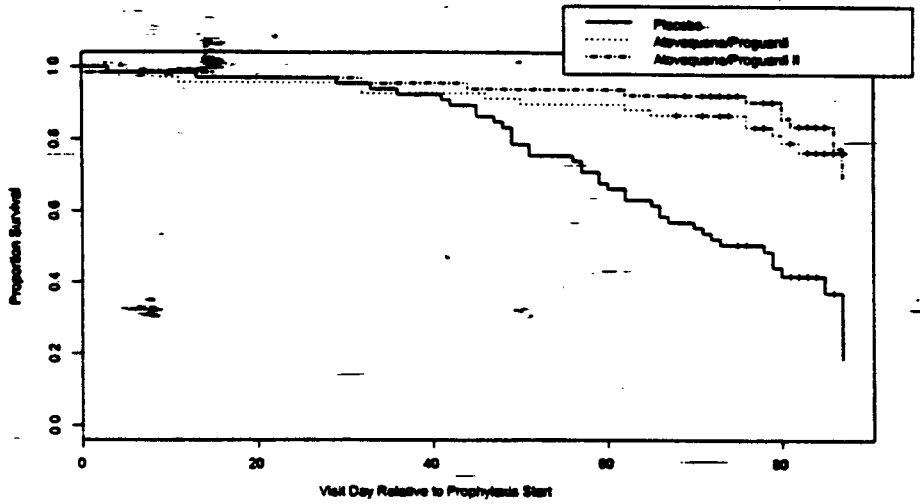
[d] Confidence Interval

[e] Efficacy Rate = 100 x (1-[failure rate in atovaquone/proguanil hydrochloride group/failure rate in placebo group])

Note: seven subjects, 3 in the placebo group, 2 in the low-dose group and 2 in the high-dose group were randomized to treatment but lost to follow-up before they had a baseline smear performed and thus are included in the safety population but excluded from the ITT population.

High rates of withdrawal for reasons other than malaria were seen, complicating interpretation of the calculated efficacy rates. For this reason and the fact that point estimates of success rates did not capture the longitudinal characteristics of the data, a "survival analysis" was performed on the data in the ITT population (described in detail in the statistical review) reflecting the proportion of successes over time as shown below.

FIGURE 1: STUDY MALB-2001: TIME TO PROPHYLAXIS FAILURE IN ITT SUBJECTS



MO comment: The above analysis demonstrates the treatment effect (the divergence of the "placebo" from the "MALARONE" curves), first discernable at day 40 of the study.

Analysis of follow up period
During the four weeks of follow-up after completion of chemoprophylaxis, parasitemia was recorded in six of 29 evaluable subjects in the placebo arm, 2 of 57 evaluable subjects in the low dose arm and 3 of 57 in the high dose arm. Both positive cases in the low dose arm occurred at week 12 (two weeks after completing prophylaxis). Cases in the high dose arm occurred at weeks 11, 13 and 14.
Case summaries for the five patients with parasitemias recorded following active prophylaxis are shown below.

- This patient in the high dose arm with a parasitemia 8 days into the follow up period was a 31 year old female weighing 61kg. She was seen at least weekly during the last 4 weeks of prophylaxis. There was no indication of non-compliance. AE's reported during the last 4 weeks of prophylaxis included myalgia, conjunctivitis, pelvic inflammatory disease and headache. There was no record of vomiting or other complaints potentially affecting absorption. Concomitant medications during this period included indomethicin, paracetamol, amoxacillin, metronidazole, phenobarbital and chlorpheniramine.
- This 22 year-old 58kg male on the high dose arm developed parasitemia 28 days after completing prophylaxis. His attendance at study visits was regular and intercurrent complaints included tonsillitis, pruruitis and gastritis. Concomitant medications were amoxacillin, paracetamol, indomethicin chlopheniramine and penicillin.
- This 23 year 60 kg male developed parasitemia 25 days after completing prophylaxis. Attendance was regular and intercurrent complaints were hedadache, heartburn, stomach upset, URTI and sore throat. Concurrent medications were penicillin, amoxacillin, paracetamol and chlorpheniramine.
- This 37 year-old 65kg male on the low dose arm was seen weekly for the last four weeks of chemoprophylaxis. Parasitemia was recorded sixteen days after stopping prophylaxis. A five day episode of gastroenteritis occurred ending 33 days before the end of the prophylaxis phase. Concomitant medications included amoxacillin, metronidazole, penicillin, paracetamol and chlorpheniramine.
- This 47 year-old 81kg male on the low-dose arm developed parasitemia 27 days after completing prophylaxis. He had missed the appointment prior to completion of prophylaxis. Recorded AE's included pruritis, lumbago and rash, none of them limiting treatment. Concomitant medications included indomethicin, antacids and chlorphenamine.

MO comment: The case occurring early in the follow up period (8 days after completion of prophylaxis) appeared sooner than the anticipated incubation period for a new infection would have predicted. This suggested that infection was acquired during chemoprophylaxis and was not aborted during the hepatic phase implying a failure of causal prophylactic effect, a resistant infection or a

problem in compliance during the treatment phase. Review of individual case histories did not reveal any reasons for drug failure.

Drug sensitivity studies.
In vitro drug sensitivity tests were performed on 8 isolates from patients on placebo who developed malaria following "radical cure". For all these isolates, IC_{50} 's for atovaquone, proguanil and cycloguanil were within the range, reported historically for isolates in other parts of Kenya and Africa. Six of the isolates were resistant to chloroquine in vitro (resistance threshold 45 nM reported by the sponsor-see microbiology review).

Table 12: IC_{50} values for eight isolates from placebo recipients developing malaria following radical cure. Comparative historical data is provided

Subject Number	IC_{50} Values (nM)			
	Atovaquone	Proguanil	Cycloguanil	Chloroquine
002	0.82	10406	59.0	61.9
017	1.96	13233	14.9	119.3
021	0.98	4687	107.6	82.6
082	1.69	3239	22.2	48.2
100	2.34	11392	9.0	6.0
112	0.60	4318	90.3	11.9
156	2.51	8629	28.5	107.8
196	1.25	5927	76.4	71.1
Mean	1.53	7729	51.0	63.6
Median	1.47	7278	43.7	66.5
Range	0.60–2.51	3239–13233	9.0–107.6	6.0–119.3
Historical Mean	1.73	10405	23.8	30.9
Cited Median Data[a]	1.61			34.4
Cited Geometric Mean Data[b]	0.90			25.10

Medical officer comment: Since seven of these patients were not given prophylactic regimens and were only treated for three days, they are not likely to reflect the risk for induction of resistance through prophylaxis. They are almost certainly new infections with isolates unrelated to the original infecting strain. Only one isolate (82) was obtained from a patient who completed prophylaxis and developed malaria during the follow up period. This was also probably a new infection since the interval between prophylaxis and the appearance of this isolate was 16 days. All these cases were treated with pyrimethamine/sulphadoxine and the clinical efficacy of malarone in patients with chloroquine resistant isolates was not specifically investigated. The breakpoint for chloroquine sensitivity has been selected by the sponsor as 45nM. Literature sources demonstrate a range of IC_{50} values characterizing chloroquine sensitive and resistant isolates, and the lowest IC_{50}'s for reported populations of resistant isolates may be higher than 45nM (see microbiology review).
Based on a breakpoint of 45 nM for chloroquine, 75% of the above isolates would be regarded as chloroquine resistant.

Medical officer comment on efficacy: This study demonstrated 100% per protocol efficacy of two doses of malarone in a ten-week prophylactic regimen. The 100% per protocol efficacy in the low dosage arm justified the selection of this dose for further study in subsequent phase 3 studies. Study subjects were from a community where malaria is endemic. They appeared to have significant malarial immunity, with high baseline parasitemia rates, responding to infections with minimal symptoms and no fever.

Causal prophylaxis was not proven as subjects remained in the malaria endemic area after prophylaxis was stopped. Thus it was not possible to determine the probability for infections acquired during prophylaxis to declare themselves in the follow-up period. This would be important to justify 7 days of extended prophylaxis following departure from a malaria area rather than the

traditional 4 weeks required for suppressive prophylactics. One subject developed malaria only eight days after stopping prophylaxis, suggesting that an infection acquired during prophylaxis was not aborted. The drug sensitivity of this isolate was not tested.

Safety

Exposure: 197 patients received 3 days each of 1000mg atovaquone and 400mg proguanil during the treatment phase. 70 subjects then received low dose prophylaxis with atovaquone 250mg/proguanil 100mg daily for a mean of 9.2 weeks, and 67 received high dose prophylaxis with atovaquone 500mg/proguanil 200mg daily for a mean of 9.4 weeks.

Adverse events were reported by 180 (88%) study subjects during the prophylaxis phase regardless of the relation to treatment, 62 (91%) in the placebo group, 59 (84%) in the low-dose and 59 (88%) in the high-dose treatment arms.

Events of unusual frequency:

The most common adverse events during chemoprophylaxis were abdominal pain, back pain, dyspepsia, gastritis myalgia, headache, diarrhea, arthralgia, coughing, sore throat, URTI and pruritis. Those possibly attributed to Malarone included dyspepsia, abdominal pain and gastritis.
Frequent adverse events possibly related to study medication are shown below.
Table 13: Adverse events possibly related to study medication occurring in more than 2% of subjects

Adverse Event	Placebo n = 68	1 ATQ/PGN Tab[b] Per Day n = 70	2 ATQ/PGN Tabs[b] Per Day n = 67
Dyspepsia	9 (13)	4 (6)	8 (12)
Gastritis	5 (7)	6 (9)	5 (7)
Abdominal pain	4 (6)	5 (7)	3 (4)
Nausea	3 (4)	0	2 (3)
Pruritus	0	3 (4)	0
Anorexia	2 (3)	1 (1)	3 (4)
Headache	2 (3)	0	0
Diarrhea	3 (4)	2 (3)	3 (4)

[a] Data reported as number of subjects followed by percentage in parenthesis

[b] 250 mg atovaquone/100 mg proguanil hydrochloride per tablet

Six of the eight most frequent complaints were gastrointestinal in nature. Most were equally common in patients treated with placebo and those treated with both low and high doses of malarone. Dyspesia though common in placebo-treated patients, was seen more frequently in patients on the higher dose of Malarone than the lower dose. Pruritis was seen in three patients treated with low dose Malarone but not in patients treated with placebo.

Events of unusual severity:
No deaths occurred in the study, which included a follow up period of four weeks beyond the discontinuation of prophylaxis.

Hospitalization was required for five subjects. Three receiving placebo were admitted for skin ulceration, shigella dysentery and head, chest and back pain. One on low dose Malarone was hospitalized for cellulitis, and one subject was admitted for frequent vomiting following the "radical treatment" phase.

Laboratory abnormalities:

No significant treatment emergent abnormalities were observed on routine hematology tests. While a trend to decreasing PCV was apparent in the placebo and 250mg dosage groups, this was not observed in the 500mg dosage group. The most marked change was in the placebo group and probably reflects the anemia resulting form malaria.

Table 14: Hematocrit at screening, week 5 and week 10

Parameter = PCV (Hematocrit) (%)

Visit	Statistic or Category	Treatment Group: Placebo	A250P100	A500P200
Screening	N	57	59	57
	Mean	41.3	40.0	39.9
	Std.Dev.	5.06	4.86	5.19
	Median	41.3	40.9	40.9
	Minimum			
	Maximum			
Week 5	N	59	64	63
	Mean	40.9	39.4	39.7
	Std.Dev.	4.58	4.76	4.86
	Median	41.8	40.2	39.9
	Minimum			
	Maximum			
Week 10	N	46	60	61
	Mean	39.7	38.9	39.1
	Std.Dev.	4.95	4.71	4.66
	Median	40.4	39.2	39.5
	Minimum			
	Maximum			

Clinical chemistry testing did not demonstrate treatment emergent effects. High potassium levels and low levels of sodium, albumin and urea were frequently present in both treatment and placebo arms and did not show any trends in relation to treatment. These findings were ascribed to poor storage or transportation.

Events of unusual character;
Animal studies using proguanil have resulted in a fatal wasting syndrome in dogs, with intestinal hyperemia and hypocellular marrow. Wasting was not specifically investigated in the subjects of this trial though gastrointestinal complaints were common. As a member of the class of DHFR inhibitors, proguanil's potential for causing leukopenia, anemia and throbocytopenia was examined. No toxic effects on the white cell count or platelet count were apparent.
Adverse events attributed to the drug included:
Pruritis (3 subjects) diarrhea (5) abdominal pain (8), dyspepsia (12) gastritis (11) anorexia (4) stomatitis (1) ulcerative stomatitis (1) nausea (5) dizziness (1) glossitis (1) vomiting (1).

MALB3001 (Zambia)
Title of study: A Randomized double-blind, placebo-controlled, parallel group study to evaluate the suppressive prophylactic activity of MALARONE (atovaquone/proguanil) in volunteers at risk of developing *P falciparum* malaria in Zambia

Setting: the study was conducted at a single research site in the Mpongwe district, Zambia, during the malaria transmission season from February to July of 1997. Participants in the study were local residents, presumed to have a significant level of immunity to malaria through repeated prior exposure. These individuals did not normally use drugs for malaria prophylaxis, so incorporating a placebo arm in the study was regarded as ethical since it reflected the "standard of care" in the region. High rates of asymptomatic infection in this community mandated the incorporation of an initial radical curative phase prior to the initiation of chemoprophylaxis.

Study design: This was a double blind, placebo controlled, randomized, two-arm, parallel group trial. All enrolled patients were given a 3 day malaria treatment course using 4 malarone tablets a day to effect a "radical cure". This was followed by a period of ten weeks during which chemosuppression or placebo was administered. During this phase, patients either received a single tablet of malarone (atovaquone 250mg/proguanil 100mg) or a single matching placebo daily. Upon completion of chemoprophylaxis subjects were followed for a further 4 weeks off therapy.
Recruitment of 300 subjects was planned, 150 in each prophylaxis arm.

Table 15: Schedule of study visits.

	Screening	Radical Cure	Chemosuppression											Follow-up			
Study Visit		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Week Day	-2/52 ±-17/365	-1/52 -3/365	0/52 0/365	1/52 7/365	2/52 14/365	3/52 21/365	4/52 28/365	5/52 35/365	6/52 42/365	7/52 49/365	8/52 56/365	9/52 63/365	10/52 70/365	11/52 77/365	12/52 84/365	13/52 91/365	14/52 98/365
Written informed consent	√																
Inclusion/exclusion Criteria	√	√															
Medical history/ demography	√																
Physical examination	√							√					√				√
Vital signs	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Hematology/Clinical Chemistry[a]	√							√					√				
Malaria blood smears[b]		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Adverse event review			√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Concomitant medicine review		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Medication issued: Radical Cure[c] Chemosuppression[d]		√	√	√	√	√	√	√	√	√	√	√	√				
Pregnancy test	√							√					√				
Drug Dispensing Log Checked		√	√	√	√	√	√	√	√	√	√	√	√				
Pharmacokinetic Blood Sample[e]								√					√				
Blood sample for *in vitro* sensitivity testing	Anytime malaria develops																

[a] / or at time of withdrawal

[b] / or at any time that malaria was suspected

[c] During the Radical Curative Phase of the trial, medication was issued daily for three days, under supervision of the Field Worker

[d] During the Chemosuppression Phase of the trial, medication was issued daily under supervision of the Field Worker. The Chemosuppression Phase followed on directly from the Radical Curative Phase

[e] / or at time of withdrawal

[f] If positive, volunteer could continue to Visit 3. If positive at Visit 3 or thereafter, volunteer was withdrawn.

The study was conducted in collaboration with the Tropical Diseases Research Center, Ndola Zambia and data management was performed under contract by [redacted]

Inclusion criteria at screening:

- Healthy males or females >=16 years and <= 65 years of age
- willing and able to give informed consent and to comply with the protocol.

Exclusion criteria at screening:

- Pregnancy
- Lactation
- Women of childbearing potential, in the investigator's opinion unwilling or unable to avoid pregnancy
- The use of antimalarial drugs or drugs with antimalarial activity within the previous 2 weeks.
- Subjects who would normally receive malaria prophylaxis during the high transmission season
- Known hypersensitivity to atovaquone or proguanil
- Clinically significant abnormal baseline hematology of clinical chemistry parameters (Volunteers were withdrawn at the investigator's discretion once results were obtained.)
- Significant renal impairment with a creatinine clearance of <30ml/min
- Splenectomy
- Laboratory evidence of hepatitis defined as a more than three fold increase above the normal upper limit in alanine transaminase for this population
- Individuals who sleep under a bed net.

MO comment: This population was weighted against enrolling women of childbearing age.

Criteria for premature discontinuation: Withdrawals at the discretion of the subject or investigator were recorded and the reason for withdrawal was listed. Efforts were made to complete a post study assessment including routine blood testing within two weeks of withdrawal.
Withdrawals for adverse events were recorded on adverse event forms.
Volunteers with parasitemia at the end of radical cure, during the chemosuppression phase or during follow-up were withdrawn and managed by the study clinician.

Trial medications:
Radical cure. All subjects were treated with 4 malarone tablets (equivalent to atovaquone 1000mg/proguanil 400mg) daily for three days given after food.

Chemoprophylaxis: Subjects were randomized to receive 1 tablet of Malarone daily (atovaquone 250mg/proguanil 100mg) or matching placebo for 70 days. Drug administration was supervised by a field worker. Randomization to Malarone or placebo was performed in blocks of four.

Field workers recorded the compliance of subjects daily as they presented to the drug distribution sites. Subjects missing medication for more than 2 consecutive days were withdrawn.

Concurrent therapy:
Subjects receiving drugs with antimalarial activity (other than the study medication were withdrawn. Such drugs included known antimalarials such as chloroquine, quinine amodiaquine etc, co-trimoxazole, tetracycline, doxycycline, rifampicin, azithromycin and ciprofloxacin.

Study procedure:
Investigators performed assessments at screening and weeks –1,0,5,10 and 14
Field workers performed other scheduled visits.
MO comment: It is unclear whether investigators were responsible for the assessment at visits when patients were withdrawn.

Screening
Screening included collection of demographic data, a physical exam, blood tests for pregnancy clinical chemistry and hematology and documentation of concurrent medications.

Radical cure
Following a baseline malaria smear, eligible subjects were treated with malarone 4 tablets daily for 3 days. Patients were seen on each of these three days to record concurrent medications and adverse events.

Chemosuppression
Subjects were randomized to receive daily malarone or placebo for the next 10 weeks. During these ten weeks subjects were seen daily for drug administration. Each week, blood was drawn for malaria thick smears and on weeks 5 and 10 additional blood was drawn for routine clinical chemistry, hematology pregnancy tests and plasma levels of atovaquone, proguanil and cycloguanil. In vitro drug sensitivities were measured on volunteers developing malaria.

Unscheduled visits
The reasons for any unscheduled visits to the study clinic or to other healthcare professionals were recorded.

Endpoints: The primary efficacy endpoint was the development of parasitemia while on chemoprophylaxis. All such parasitemias were confirmed by two microscopists. If both regarded the slide as positive, a second slide was drawn from the patients. The patient was confirmed a treatment failure if both microscopists found this second slide to be positive. Disagreements between microscopists were adjudicated by a senior technologist. Volunteers whose second confirmatory slide was negative continued treatment and were not regarded as treatment failures.

MO comment: Low levels of parasitemia may not be apparent on all slides. However cases with two discordant slides would have declared themselves at a subsequent visit since no new intervention was prescribed. Quantitative reports of parasitemia were not provided.

IC_{50} was measured on all viable isolates from patients who developed parasitemia (>=2000 parasites/µl) during chemoprophylaxis.

Adverse events: These were defined as any untoward medical occurrences experienced by a volunteer. They included a new disease, exacerbation of an existing disease or a recurrence of disease.

Serious adverse events included those that were fatal, life threatening, disabling or incapacitating, that required hospitalization or prolonged current hospitalization, or that resulted from overdosage. They included cancer, congenital anomalies, and any other event that jeopardized the patient.

Routine laboratory testing included hemoglobin, lymphocyte count, hematocrit, platelets, total white cell count, serum ALT, albumin, alkaline phasphatase, creatinine glucose, potassium, sodium, total bilirubin, urea and where indicated GGT.

Samples for pharmacokinetic testing were obtained prior to the daily dose of medication. The time of the previous drug dose and the time of the blood draw were recorded.

Sample size:
To detect a 17% difference in efficacy rates with a power of 80% and a significance level of 5%, 134 subjects were needed in each arm, assuming an attack rate in placebo treated patients of 30% and of 1.5% in Malarone treated patients. To allow for dropouts, 150 volunteers were recruited to each treatment group.

Populations for analysis:
The sponsor identified the intention-to-treat (ITT) population as the primary population and the per-protocol population (PP) as the secondary population for analysis.

Populations and evaluablility criteria for the ITT and PP analyses are identical to those used in study MALB2001 and are described on pages 8 and 9.

Negative baseline smears referred to those patients with a negative smear at week 0, or week 1 if the smear at week 0 was positive.

MO Comment: Excluding patients with positive baseline smears from randomization to prophylaxis would enrich the study cohort for patients likely to respond well to Malarone prophylaxis. (Failures of Malarone treatment are also likely to be failures of Malarone prophylaxis either for reasons of drug resistance, intolerance or altered biometabolism.)

Percent efficacy was calculated as follows.
Percent efficacy = (1-failure rate$_{malarone}$/failure rate$_{placebo}$)*100

Safety analysis:
The population providing safety data included all patients who had received at least one dose of study medication. Adverse events were coded using "Costart" terms and reported in terms of seriousness, intensity, action taken and attributability to the study medication.

Protocol amendments:
14 January 1997: This amendment allowed for additional collection times for concurrent medication data and adverse events.
20 August 1997: This amendment stipulated the method for allocation of randomization numbers to volunteers. In this amendment, the primary population was identified as the ITT population.

Results:
Two hundred and ninety-nine patients were screened and enrolled in the 3-day "radical cure" phase of the study. Two hundred and seventy four (92%) completed this phase. One hundred and thirty-six were randomized to treatment with Malarone and 138 to treatment with placebo. Two were lost to follow up before a baseline smear was obtained leaving 272 patients in the ITT population. Of these, 213 remained in the PP population as shown below.

Table 16: Disposition of patients in MALB3001

Screening 299	
Failed to complete radical cure 25	
Completed radical cure 274	
Malarone 136	Placebo 138
Excluded from ITT 2	Excluded from ITT 0
ITT 272	
Malarone 134	Placebo 138
Excluded from PP 32	Excluded from PP 27
PP 213	
Malarone 102	Placebo 111

Twenty five patients failed to complete the curative phase for the following reasons, protocol violation (9) lost to follow-up (8) consent withdrawn (6) other (2). None were withdrawn due to adverse events.

Two patients completed "radical cure" but did not have a baseline malaria smear, and were excluded from the ITT population.

Table 17: Subjects excluded from the PP population

Reason for Discontinuation	Chemoprophylaxis Treatment Group	
	Placebo	MALARONE
Lost to follow-up	14	16
Protocol violation	8	12
Consent withdrawn	5	4
Total	27	32

MO comment: Of the ITT population, 22% (59) were excluded from the-per protocol population. Protocol violations accounted for 20 of these.
Protocol violators were reviewed for evidence suggestive of malaria at the time of withdrawal. Only one patient from the placebo group (1345) withdrawn at week13 had a temperature (38.5C).
Protocol violations and losses to follow up were slightly more frequent in the Malarone group than the placebo group. Most of the protocol violations were missing medication doses for 2 or more consecutive days.

Baseline demographic data were similar for malarone and placebo groups as seen in table 18.

Table 18: Demographic and physical characteristics of participants

Characteristic	Placebo n = 138	MALARONE n = 136
Male/Female	125/13	119/17
Age (yrs)		
Males		
Mean (SD)	30 (9.2)	29 (10.1)
Range	16–60	17–64
Females		
Mean (SD)	41 (11.8)	47 (12.5)
Range	22–59	24–64
Weight (kg)		
Males		
Mean (SD)	59 (7.0)	59 (6.4)
Range	45–78	40–79
Females		
Mean (SD)	53 (7.3)	53 (10.7)
Range	42–65	37–71
Height (cm)		
Males		
Mean (SD)	169 (7.8)	170 (6.8)
Range	136–190	154–187
Females		
Mean (SD)	163 (14.7)	156 (5.2)
Range	135–190	144–163

Very few females were enrolled in this study.

Review of concurrent medications:
Fifty-nine percent of the placebo treated patients and 42% of the Malarone treated subjects took other medications. Analgesics were taken by 42% and 31% of placebo and Malarone treated patients, beta lactam antibiotics by 19% and14 % respectively and "stomatological preparations" were taken by 17% and 15%. Antimalarials were only used by patients who had failed prophylaxis. Antibiotics used included penicillin, erythromycin amoxacillin, ampicillin, cloxacillin and metronidazole. Tetracycline was used topically as an eye ointment by 4 patients 1 in the placebo group and 3 in the Malarone group.

Efficacy results:
Parasitemia developed in 41 subjects treated with placebo and 2 subjects treated with Malarone
An additional 27 subjects were withdrawn from the placebo arm and 32 were withdrawn from the Malarone arm before week 10. Twenty of these subjects were withdrawn because they missed more than 2 consecutive days of study medication, 8 from the placebo group and 12 from the Malarone group. There were no withdrawals due to a treatment-related adverse event.

Table 19: Efficacy analyses for ITT and PP populations

	ITT Analysis		PP Analysis	
	Placebo n = 138	MALARONE n = 134[a]	Placebo n = 111	MALARONE n = 102
Failure of Chemoprophylaxis				
Parasitemia	41	2	41	2
Withdrawn (treatment-related)[b]	0	0	0	0
Withdrawn (other reasons)	27	32	–	–
Total	68	34	41	2
Success Rate	51%	75%[c]	63%	98%[c]
Difference in Success Rate (MALARONE – Placebo) (95% CI[d])		24% (12–36%)		35% (24–46%)
Efficacy Rate[e] (95% CI[d])	– –	49% (25–68%)	– –	95% (79–100%)

[a] Two subjects received a single dose of study drug but withdrew before a baseline smear was obtained and thus were not eligible for the ITT population.

[b] Withdrawn due to a Treatment-Related Adverse Event

[c] $P < 0.001$, Fisher's Exact Test, versus Placebo

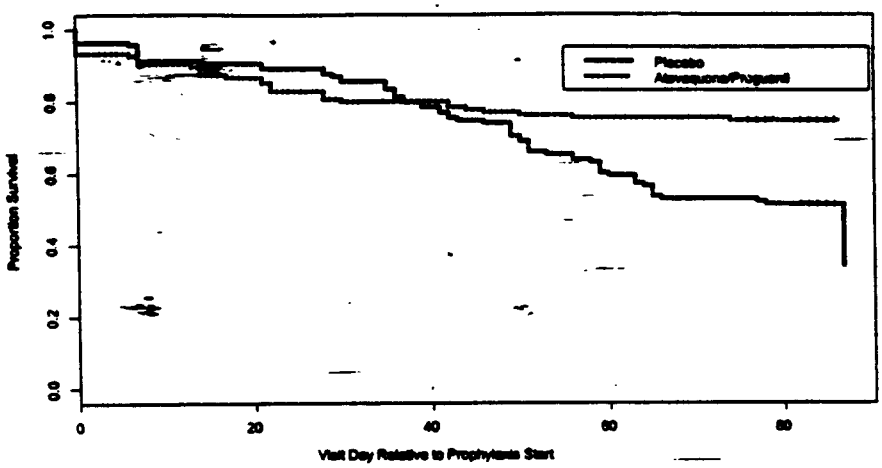
[d] Confidence Interval.

[e] Percent efficacy = 100 x (1–[failure rate in MALARONE group/failure rate in placebo group]).

MO comment: The FDA concurred with the above efficacy rates. While only a small proportion of withdrawals for non-compliance would have developed malaria, (less in the malarone arm than the placebo arm) the ITT analysis assumed that all non-compliant patients were treatment failures. Thus the ITT analysis underestimated the efficacy of the drug. The PP analysis was more representative of the true efficacy when interpreted in the setting of a compliant treatment group.
Success rates of placebo treated subjects in this study were noted to be higher than corresponding success rates in the Kenyan study MALB2001. Based on the higher prevalence of malaria at screening in Kenyans (34%) than Zambians (7%) the difference was probably due to lower attack rates in the Zambian than the Kenyan studies.

As described in the statistical review, a "survival analysis" was performed on the ITT population to reflect the evolution of the data with time. The proportion of patients remaining in the study and malaria free are shown in the figure below.

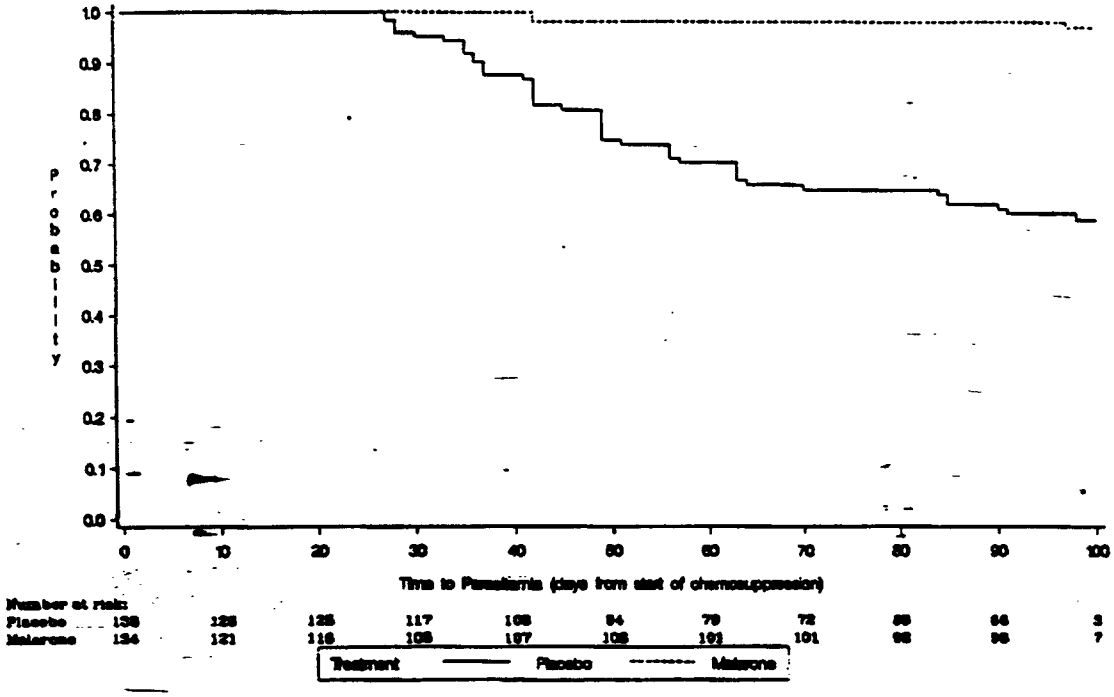
FIGURE 2: STUDY MALB-3001: TIME TO PROPHYLAXIS FAILURE IN ITT SUBJECTS



MO comment: Both arms of the study showed large numbers of withdrawals. A treatment effect was first discernable after day 40. Lower malaria attack rates were seen in this study than the Kenyan study (MALB2001).

A similar result is reflected by the malaria free survival as shown below. Since only confirmed cases of malaria are accounted for, the possibility of malaria occurring in the patients lost to follow-up or withdrawn is not addressed in this anlysis.

Figure 3: Kaplan-Meier curve for malaria free time by treatment group



Evaluation of treatment failures:

Two patients on the Malarone arm of the study developed malaria while on chemoprophylaxis as detailed below.

This 26 year old male, weight 55 kg with a negative malaria smear during screening completed radical cure on March 10, 97. On April 22, after 42 days of chemoprophylaxis, the patient was found to have a parasitemia at his scheduled visit 8. The temperature was recorded as 36.3C. The patient had missed one visit (visit 6) during chemoprophylaxis. No concurrent medications were listed prior to parasitemia. Underlying conditions upon enrollment were recorded as sneezing, running nose, headache, groin abcess and genital sore.

This 22 year old male, weight 54 kg, with a negative screening smear, completed radical cure on March 19, 97. On May 1 at the 8th scheduled visit, he developed a fever of 38.5C and parasitemia 43 days after starting chemoprophylaxis. The patient had attended all visits until the time of parasitemia. Concurrent conditions included "headache" treated with Panadol.

In vitro sensitivity testing was not performed on isolates from either of these patients.

MO comment: There were no apparent reasons for treatment failure in the histories of either of these patients. Compliance with the protocol was good, neither of the subjects were overweight or had a history of vomiting or other complaints to explain the lack of therapeutic effect. Compared with protocol MALB2001 where half the subjects were treated with 2 malarone tablets a day and no failures of prophylaxis occurred, the lower dose of malarone in this study is a possible contributory factor to these failures. The possibility of drug resistance in these patients remains a consideration. Finally parasitemias at screening were much less frequent in this population than the Kenyan study, and there may have been less malarial immunity in this population, with a greater likelihood for the failure of prophylaxis.

Drug levels of atovaquone, proguanil and cycloguanil were evaluated in the two subjects who failed malarone prophylaxis and were compared with the mean trough levels calculated from the pharmacokinetic data in this study. These mean trough values are tabulated below.

Table 20: Summary of trough levels of atovaquone, proguanil and cycloguanil in study MALB3001

Analyte	Mean	SD[b]	Median	Min	Max
Atovaquone (µg/mL)	2.07	1.17	1.99		
Proguanil (ng/mL)	26.8	14.0	24.2		
Cycloguanil (ng/mL)	10.9	5.59	10.0		
Proguanil/ Cycloguanil	2.90	2.05	2.5		

[a] Median trough sampling time 23 hours

[b] Standard Deviation

In the first Malarone failure, a plasma level was not obtained at the time malaria was diagnosed but a steady-state plasma level one week before showed proguanil and cycloguanil levels below the limit of detection despite a C_{ss} for atovaquone of which exceeded the mean C_{ss} for the population.

MO comment: The disparity in levels of the two drugs may reflect the comparatively short half life of proguanil compared to atovaquone. Poor compliance would be reflected first in the levels of proguanil.

The second treatment failure had steady-state levels of atovaquone, proguanil and cycloguanil at week 5 [redacted], and at withdrawal [redacted] which were below the expected mean Css levels for both drugs.

MO comment: Non-compliance or a suboptimal dose should be considered as reasons for treatment failure in these two patients.

Relationship between parasitemia at screening and parasitemia developing during chemoprophylaxis.

Again, to exclude the possibility that cases occurring in the chemoprophylaxis phase were recrudescences following radical cure, I calculated the odds for parasitemia developing during chemoprophylaxis among patients with a parasitemia at the screening visit versus those without parasitemia at the screening visit in patients on the placebo arm. The purpose of this analysis was to determine whether Malarone selectively suppressed recrudescences or whether it prevented new infections.

Table 21: Treatment failures among placebo recipients with or without parasitemia at screening

	Treatment failure	No treatment failure
Parasitemia at screening	5	9
No parasitemia at screening	36	61

MO comment: Five of 14 patients (36%) who were parasitemic at screening developed malaria during the study as compared with 36 of 97 patients (37%) who were not parasitemic at baseline, (OR 0.94 (CI 0.23-3.43) suggesting that infections in the placebo group were equally likely to be new infections or recrudescences.
Parasitemia during follow-up.

During the 4 weeks of follow-up, parasitemia was found in 6 of 70 subjects in the placebo group and 1 of 100 subjects in the Malarone group. The six placebo treated patients developed parasitemias between 14 and 28 days after completing the chemoprophylactic phase. The Malarone treated patient developed parasitemia 27 days after completion of prophylaxis.

Safety

Exposure: Two hundred and ninety-nine subjects received Malarone (atovaquone 1000mg/proguanil 400mg) daily for three days. One hundred and thirty-six of these subjects randomized to the Malarone prophylaxis arm received one tablet of Malarone (atovaquone 250mg/proguanil 100mg) daily for up to 70 days with a mean exposure time of 8 weeks.

Adverse events regardless of causality, were reported during chemoprophylaxis by 124 subjects (45%), 71 (51%) in the placebo group and 53 (39%) in the Malarone group.

MO comment: It is unclear why adverse events were less frequently reported for Malarone treated subjects in this study than for subjects on the same dose in the Kenyan study (MALB2001). Drug – attributed "Gastritis" and "Dyspepsia" were reported in 9% and 6% of Kenyans on the Malarone 250mg dose, but none of the Zambians.

Events of unusual frequency:
The most commonly reported adverse events were headache, fever and abdominal pain.

Table 22: Adverse events possibly related to study medication reported by >=2% of subjects during the prophylaxis phase of the study

Adverse Event	Placebo n = 138	MALARONE n = 136
Headache	12 (9)	6 (4)
Abdominal pain	7 (5)	4 (3)
Diarrhea	4 (3)	2 (1)
Fever	3 (2)	0

[1] Data reported as number of subjects followed by percentage.

Other infrequent adverse events were more common in the placebo treated group than the Malarone treated group. They included malaise, sore throat, asthenia, pruritis, anorexia and glossitis. Dizziness attributed to the drug occurred in 2 patients on Malarone and one on placebo.

In "previous treatment studies" the sponsor reported abdominal pain as an adverse event in 15%, vomiting in 12%, diarrhea in 8% and nausea in 11%. During prophylaxis in this study, these rates were 3% 1% 1% and 0% and during radical cure 1%, 1%, 1%, and 1% respectively. Higher rates in treatment studies suggest that in these, some adverse events were either caused by malaria or by the higher treatment dose. Also, prophylaxis studies excluded patients who did not tolerate radical cure.

Events of unusual severity

There were no deaths during the study period.
During the radical cure phase and the chemosuppression phase there were no serious adverse events in any of the patients. During the four weeks of follow-up off medication, two placebo- treated patients were hospitalized with pneumonia.
Treatment limiting adverse events attributed to the study drug were not observed during the radical cure phase. One placebo treated patient developed treatment limiting "leukorrhea" during chemosuppression.

Clinical laboratory evaluation.

No treatment emergent abnormalities were detected in lymphocyte count, platelets and total white cell count. Hematocrit showed a tendency to fall during the study in both malarone and placebo arms as shown below:

Table 23: Hematocrit values during study period

PCV (Hematocrit) (%)

Visit	Statistic	Placebo	Malarone
Screening	N	138	136
	Mean	42	43
	Std.Dev.	4.2	3.8
	Median	43	43
	Minimum		
	Maximum		
	H/L est.		0
	H/L 95% CI		(-1,1)
Week 5	N	116	107
	Mean	42	42
	Std.Dev.	4.2	4.0
	Median	43	43
	Minimum		
	Maximum		
	H/L est.		0
	H/L 95% CI		(-1,1)
Week 10	N	71	100
	Mean	39	39
	Std.Dev.	4.7	3.7
	Median	40	40
	Minimum		
	Maximum		
	H/L est.		-0.5
	H/L 95% CI		(-2,1)
Withdrawal	N	53	14
	Mean	40	39
	Std.Dev.	3.8	3.1
	Median	40	39
	Minimum		
	Maximum		
	H/L est.		-1
	H/L 95% CI		(-3,2)

Abnormally low PCV was noted with increasing frequency during the study as shown below:

Table 24: Proportion of patients with abnormally low PCV during study period

	Placebo	Malarone
Screening	39/138 (28%)	41/136 (30%)
Week 5	39/116 (34%)	30/107 (28%)
Week 10	46/71 (65%)	68/100 (68%)
Withdrawal	38/53 (72%)	11/14 (79%)

MO comment: There was a slight decrease in mean hematocrit from week 0 to withdrawal among patients treated with Malarone and placebo. In the control group, cases of clinical malaria would have contributed to the tendency for anemia to develop during the study. Similar changes were observed in the Kenyan study (MALB2001), although in this study the mean hematocrit of patients at screening was lower and the change during the course of the study was smaller.

Treatment related changes were not observed for clinical chemistry tests (ALT, Albumin. Alkaline phosphatase, Creatinine, GGGT, Glucose, Potassium, Sodium Total Bilirubin and Urea. Abnormally high serum potassium and low serum glucose were measured in a number of patients both in the malarone and placebo groups. This was ascribed to poor transport conditions with resulting delays in processing and deterioration of specimens.

Events of unusual character:

Recognized adverse events from the class of DHFR inibitors were specifically sought. Apart from anemia, no evidence for leukopenia, or liver function abnormalities were seen. Mouth ulcers and hair loss

(recognized with proguanil) were not reported. Preclinical animal data showing wasting and deaths in dogs were not borne out in this human study where wasting was not documented. Gastrointestinal effects as previously recognized with atovaquone were observed.

MO discussion of results for MALB3001

This study demonstrated good per-protocol efficacy in protecting individuals living in a highly malaria endemic area from developing malaria on blood smear during 10 weeks of prophylaxis (98% success rate for Malarone vs 63% success rate for placebo). A 7% prevalence of malaria at screening, and minimal fever or symptoms at the time malaria developed suggest that this community had substantial antimalarial immunity unlike malaria naive travelers to the area. No specific evidence of efficacy for known chloroquine resistant infection was provided. Efficacy against non-falciparum malaria was not determined. The efficacy of Malarone as a "causal" prophylactic rather than a suppressive prophylactic was not adequately addressed by this study. Too few cases in the follow-up period occurred (only 1 parasitemia in the Malarone group) to allow meaningful differentiation between infections contracted during chemoprophylaxis versus those contracted following completion of prophylaxis. The reasons for failure of prophylaxis in two subjects receiving Malarone were unclear although suboptimal blood levels appeared to play a role. The drug was well tolerated with minor gastrointestinal adverse events, and a suggestion of treatment related anemia.