MALB3002

Title: An open label study to evaluate the safety and efficacy of Malarone (atovaquone, proguanil) as a suppressive prophylactic agent against Plasmodium falciparum malaria in South Africa.

The primary aim was to determine the safety and tolerance of Malarone as a suppressive prophylactic in otherwise healthy non-immune subjects. The secondary objective was to determine the efficacy of Malarone as a suppressive prophylactic in otherwise healthy non-immune subjects at risk of developing *P falciparum* malaria in South Africa.

Setting: The study was conducted between February and July of 1997, the main malaria season in the area. Malaria incidence is seasonal and transmission does not typically occur during the latter part of the year. Four study sites were used (Jozini, Messina, Phalaborwa and Sandriver) all located in the Northeastern region of the country. Incidence rates vary from region to region depending on rainfall and location of groundwater. Messina is regarded as a high risk area for malaria, Jozini intermediate and Phalaborwa low risk as shown in the maps below.

Fig 4: Malaria risk by study site

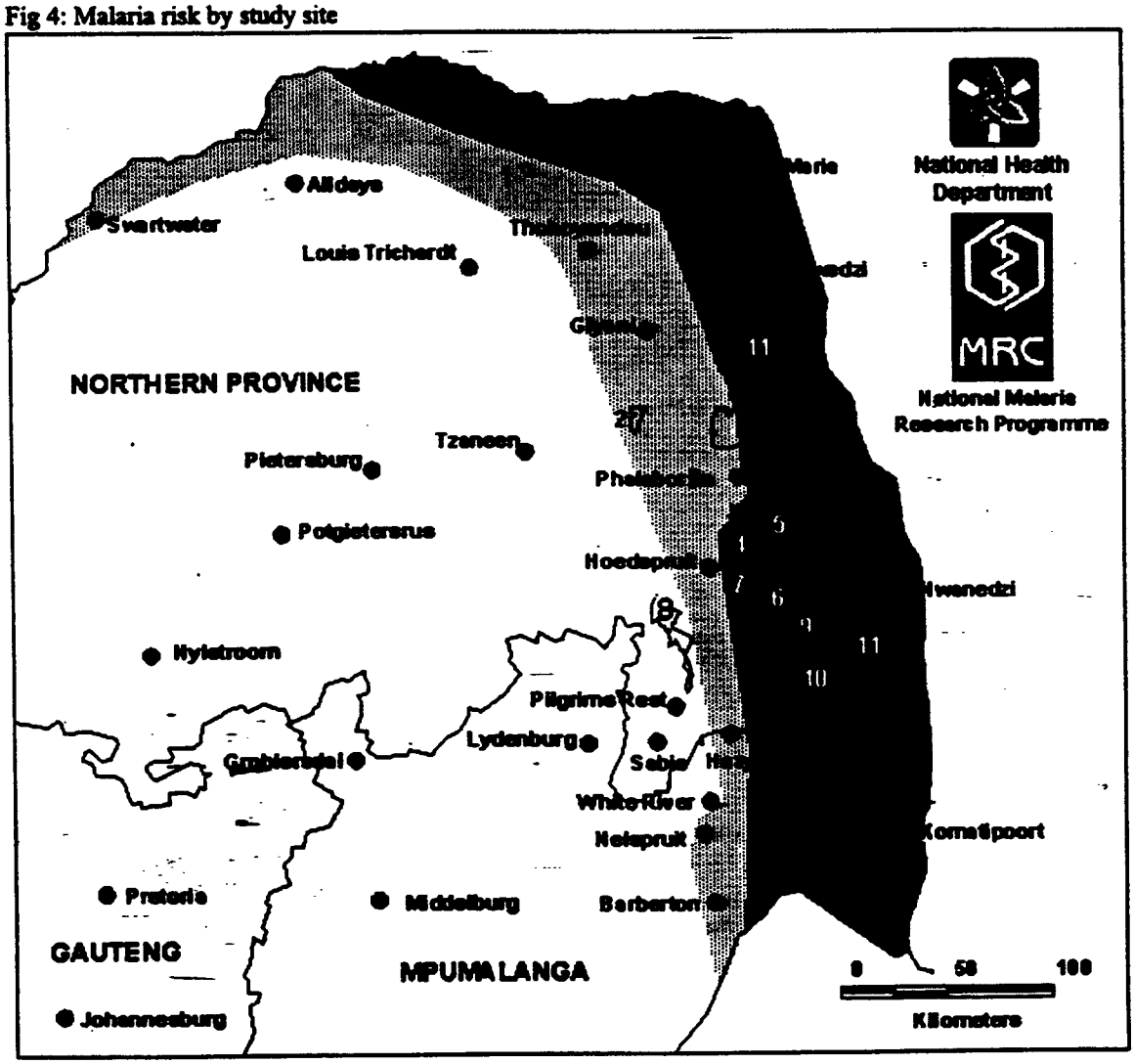
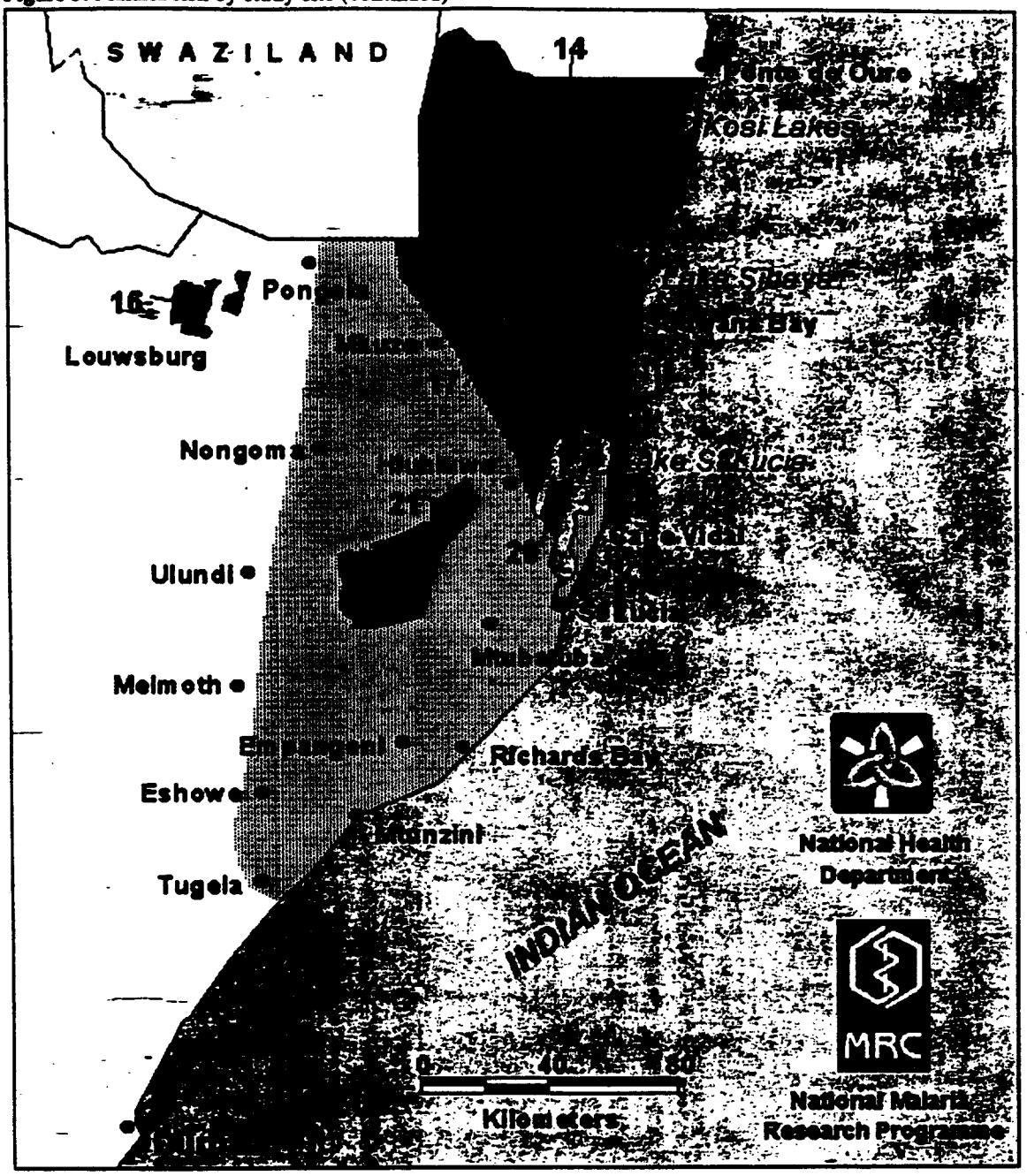
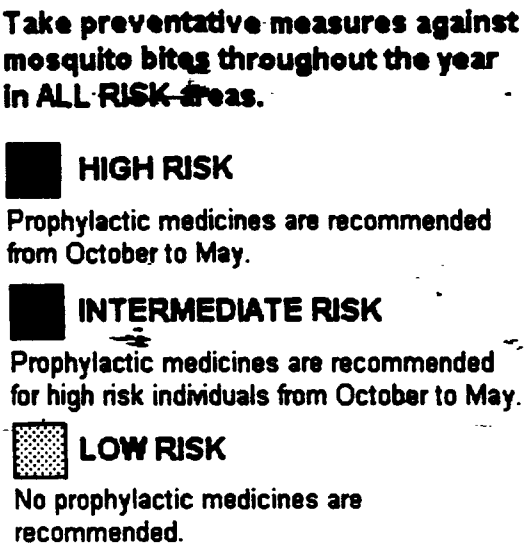


Figure 5: Malaria risk by study site (continued)





Legend to figures 4 and 5

Thus malaria exposure rates differed for the different study sites. Local standards of care mandate the use of either chloroquine /proguanil or mefloquine in individuals sent to these areas. Mosquito repellants and bed nets are also used.

Volunteers deployed for a tour of duty in these malaria areas were given open label chemoprophylaxis with Malarone for 10 weeks. Individuals already resident in these areas were also included provided they had taken either chloroquine/proguanil or mefloquine as prophylaxis during the 28 days preceding allocation to the study drug. This would have reduced the chances that malaria developing on chemoprophylaxis was acquired prior to initiation of Malarone.

Study design
This was an open-label non-comparative study. Subjects were screened and allocated to a 10-week open-label chemo-suppressive phase with Malarone while in a malaria endemic area. Subjects with unresolved abnormalities (eg adverse events or abnormal laboratory results) at the end of 10 weeks were seen for a further 14 days off study drug. During this follow up period the study drug was discontinued though subjects remaining in malaria endemic areas were to be given alternative prophylaxis where appropriate.

Volunteers traveling to a malaria area received one Malarone tablet (atovaquone 250mg/ proguanil 100mg) daily commencing 48 hours prior to entering the endemic area.
Volunteers already residing in an endemic area were required to have been on mefloquine or chloroquine/proguanil for at least 28 days prior to inclusion in the study. Those residing in the area for less than 28 days prior to enrollment were to have been on prophylaxis while they were in the malaria area. The first dose of Malarone was given to these volunteers 2 days before the next dose of chloroquine/proguanil or mefloquine was due.

MO comment: In the latter group of volunteers, depending on the period of residence in the malaria endemic area, some anti-malarial immunity may have been present. Given the long half-lives of chloroquine and mefloquine, a residual effect of these drugs would have been anticipated during the first couple of weeks of prophylaxis with malarone.

The study was conducted in collaboration with the South African Medical Services, South African National Defense Force. The data management was contracted to [redacted] All laboratory assessments were performed by a central laboratory.

Study plan:
At screening demographic information was recorded and a physical examination was performed. Blood was drawn for pregnancy testing where applicable, baseline hematology and clinical chemistry, an ICT malaria P.f. test and malaria smear. Concurrent medications were recorded.

At follow up visits, compliance was checked, adverse events were recorded, concurrent medications were listed, a physical examination was performed and blood was drawn for routine chemistry, hematology and a malaria ICT P.f. test. Blood smears were taken at week 0 and week 10 or any time malaria was suspected.

MO comment: Scheduled follow up visits were at week 5 and 10, allowing extended periods during which self presentation would have been required to detect endpoints. Since these volunteers were military recruits, it is presumed that most such events would have been captured as medical facilities are centralized. Further, concurrent medications would have indicated whether malaria had been treated between visits.

Unscheduled visits: All visits of patients to clinical or to other health care professionals were recorded. At these visits information was obtained on adverse events, concurrent medications, vital signs and malaria blood tests (if performed).

The primary efficacy variable, "patent parasitemia" on blood smear was used to indicate a failure of prophylaxis. Thick smears were evaluated by a central laboratory and parasitemia was confirmed by two technologists.

Table 25: Study plan

	SCREEN VISIT (± -2/52)	WEEK 0 VISIT (0/52)	WEEK 5 VISIT (+5/52)	WEEK 10 VISIT (+10/52)	FOLLOW-UP VISIT[b] (+12/52)
Informed Consent	√				
Inclusion / Exclusion Criteria	√	√			
Medical History / Demography	√				
Physical Examination	√		√	√	√
Vital Signs	√		√	√	√
Hematology /Clinical Chemistry	√			√	√
ICT Malaria P.F. Diagnostic Test	√	√		√	
Malaria Blood Smears[a]	√	√		√	
Pregnancy Test	√				
Adverse Event Review	√	√	√	√	√
Concurrent Medication Review	√	√	√	√	√
Medication	*ISSUED DAILY FROM WEEK 0 VISIT TO WEEK 10 VISIT*				

[a] /or anytime that malaria was suspected

[b] If abnormalities at Week 10 Visit (*i.e.* serious adverse event that was unresolved or abnormal hematology or biochemical values of clinical concern)

Control groups: No control group was included in this trial.

MO comment: The difficulty in providing a meaningful control group is appreciated in settings where the standard of care mandates some form of anti-malarial prophylaxis. In this setting background incidence rates for malaria in communities in the area would give some indication of the malarial risk to study participants. In this non-hyperendemic area, historical data would be affected

by differences in malarial incidences from year to year. Entomologic data showing the prevalence of infected anopheline mosquitoes would give some idea of risk. Without some indicator of risk, the efficacy of prophylaxis cannot be assessed.

Endpoints: The endpoint for efficacy was a positive Malaria P.f. test (ICT), confirmed by a blood smear on microscopy.
Subjects with positive blood smears for malaria were to be withdrawn form the study as treatment failures.

MO comment: The use of the malaria P.f. test as an efficacy endpoint is limited by the sensitivity and specificity of the test. One theoretical disadvantage of this test over smears is the persistance of positive results for several weeks following the successful treatment of malaria, though this is not applicable to this study. Another theoretical difference is the inability of the P.f test to detect parasitemia with non-falciparum malaria. Again, this may not apply to this study since and indication for non-falciparum malaria is not claimed. The validity of the P.f. test as a surrogate for patasitemia has not been established by the FDA. Although significant malaria immunity was not suspected in this population, the unlikely possibility remains that asymptomatic malaria could have occurred and the diagnosis would have limited by the sensitivity of the ICT P.f test.

Inclusion criteria

- Male or female
- In good general health
- At risk of malaria infection
- >= 16 and <= 65 years of age
- Willing and able to give written informed consent and comply with the study protocol.

Exclusion criteria

- Pregnancy
- Lactation
- Being of childbearing potential and in the investigator's opinion not willing or able to avoid pregnancy
- A positive ICT Malaria P.f. test
- Current residence in an area of high transmission without receiving recommended antimalarial prophylaxis (chloroquine/proguanil or mefloquine at the recommended doses) during the 28 days preceding the study. For subjects resident in malaria areas for periods less than 28 days prior to the study, they were required to be on recommended prophylaxis during the time they were in those areas.
- Known hypersensitivity to atovaquone or proguanil
- Clinically significant abnormal baseline hematology or clinical chemistry parameters (Subjects were to be withdrawn at the discretion of the investigator once the results were obtained.)
- Significant renal impairment as evidenced by a creatinine clearance of <30mL/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

Protocol amendments:
Feb 5, 97. This amendment was made prior to recruitment and allowed for volunteers already in an endemic area and on prophylaxis, to be eligible for the trial.

Premature withdrawal

Voluntary withdrawals or withdrawals at the discretion of the investigator were recorded in the case report form and attempts were made to complete post-study assessments including examination and routine laboratory investigations. Subjects remaining in the area were evaluated within two weeks of withdrawal. Volunteers with parasitemia on the screening smear or who developed parisitemia during chemosuppression were withdrawn.

Trial medication:
A single tablet of open label malarone (atovaquone 250mg/proguanil 100mg) was taken daily after food, commencing either 48 hours prior to entering a malaria area, or 2 days before the next due dose of prophylaxis in those already residing in a malaria area. All other malaria prophylaxis was discontinued upon commencing malarone prophylaxis. Study drug was taken daily after food for 10 weeks. Compliance was checked daily. Subjects missing more than 2 consecutive doses were withdrawn as compliance failures.

Volunteers found to have used any other drugs with antimalarial activity during the study were withdrawn. Such drugs included chloroquine, quinine, mefloquine, halofantrine, pyrimethamine/sulfadoxine, proguanil, amodiaquine etc and antibiotics such as co- trimoxazole, tetracycline, doxycycline, rifampin azithromycin and ciprofloxacin.

Safety assessments:
Adverse events were defined as any untoward medical occurrence experienced by a volunteer and included exacerbations of pre-existing illnesses, recurrences of intermittent illnesses, a set of related symptoms or signs or a single symptom or sign.
Serious adverse events included those that were fatal, life threatening, disabling or incapacitating, that required or prolonged hospitalization, congenital anomalies, cancer, and those resulting from drug overdose.

Clinical laboratory testing:
Routine hematology tests included hemoglobin, hematocrit, platelets, white blood cells and a differential count. Clinical chemistry investigations included: sodium, potassium, hepatic transaminases, albumin, alkaline phophatase, calcium, creatinine, creatinine clearance, GGT, glucose, phosphorus, total bilirubin, total protein and urea nitrogen. Pregnancy tests were performed on all females of "childbearing potential".

Intent-to-treat (ITT) analysis
The population for this analysis included all patients who received at least one dose of malarone during chemosuppression and who had a negative malaria screening result (using ICT Malaria P.f. test). This population included all patients lost to follow-up before week 10.

Evaluable successes: These included all subjects who had a negative baseline malaria test and were observed to be negative throughout chemosuppression (weeks 0-10) regardless of missing results before week 10.

Evaluable failures: These included all subjects with a negative baseline malaria test who:
- developed a positive test during chemosuppression (weeks0-10)
- withdrew from the study for a treatment-related adverse event or
- were lost to follow-up
- took concomitant medication with recognized antimalarial activity
- withdrew consent after starting chemoprophylaxis

Per-protocol (PP) analysis:

The population for this analysis included all patients who received at least one dose of Malarone during chemosuppression, who were protocol compliant with taking medication, who did not receive medications that could influence the evaluation of efficacy, who had a negative baseline smear and who were either present at the week 10 visit or were withdrawn prior to week 10 for failure or reasons other than a treatment related adverse event.
Subjects lost to follow-up before week 10 and subjects missing the week 10 visit were excluded.
Evaluable successes included all subjects with negative baseline malaria tests who were observed to have remained negative throughout chemosuppression (weeks 0-10), regardless of missing results before week 10.

Evaluable failures included all subjects who had negative baseline malaria results and at least one positive malaria result during chemosuppression (weeks 0-10) or subjects withdrawn for a treatment-related adverse event.

A negative baseline visit for the ITT population was defined as patients with a negative ICT malaria P.f test at screening. A negative baseline visit for the PP population was defined as a negative malaria smear at screening.

Results:

One hundred-and-seventy-five volunteers were screened and enrolled into the trial.
Most enrolled patients were young males. The demographic characteristics of this study population are shown below:

Table 26: Demographic characteristics of ITT population

Demographic Characteristics and Disposition of Patients Enrolled into the Study

Characteristic	MALARONI n = 175
Male/Female	149/26
Age (yrs)	
Males	
Mean (SD)	29 (6.5)
Range	18–52
Females	
Mean (SD)	34 (7.2)
Range	24–48
Weight (kg)	
Males	
Mean (SD)	76 (13.4)
Range	55–124
Females	
Mean (SD)	71 (12.3)
Range	48–95
Height (cm)	
Males	
Mean (SD)	175 (7.9)
Range	154–196
Females	
Mean (SD)	164 (7.9)
Range	150–180

All subjects were already residing in the malaria areas prior to the start of the study. The period that each participant had resided in the malaria area prior to the study was not provided. Nor was information provided in each participant on the history of previous malaria attacks. The domicile of participants was not described to confirm the "non-immune" state. A listing of concurrent medical conditions indicated that one patient with hepatosplenomegaly gave a history of previous malaria.

Concurrent medication included the antimalarial prophylaxis being taken by the subjects at the time of enrollment. Consequently all 175 subjects were recorded as taking concurrent antimalarials. Ten of these subjects listed in table 28 received drugs with antimalarial activity during the period of chemoprophylaxis and were analyzed by the FDA as treatment failures in the ITT analysis.

Other frequently-used concurrent medications included analgesics and anti-pyretics (19%) systemic antibacterials (15%) ophthalmologicals (13%) and non-steroidal anti-inflammatory agents (13%).

Treatment compliance: Forty patients (23%) in the ITT population were deemed non-compliant with their medications either because they were lost to follow-up or because they missed more than 2 sequential days of medication.

Patient accountability is described below.

Table 27: patient accountability

Population Subjects	Completed / Reason for discontinuation	Malarone
Safety	N	175
	Study Completers (%)	119 (68)
	Prematurely Discontinued (%)	56 (32)
Safety, Prematurely Discontinued	N	56
	Lack of Efficacy	1
	Adverse Event	8
	Consent Withdrawn	1
	Lost to Follow-up	28
	Protocol Violation	12
	Other	6
Intent-to-treat	N	175
	Study Completers (%)	119 (68)
	Prematurely Discontinued (%)	56 (32)
ITT, Prematurely Discontinued	N	56
	Lack of Efficacy	1
	Adverse Event	8
	Consent Withdrawn	1
	Lost to Follow-up	28
	Protocol Violation	12
	Other	6
Per-protocol	N	113
	Study Completers (%)	108 (96)
	Prematurely Discontinued (%)	5 (4)
PP, Prematurely Discontinued	N	5
	Lack of Efficacy	0
	Adverse Event	3
	Consent Withdrawn	0
	Lost to Follow-up	0
	Protocol Violation	2
	Other	0

Ten subjects received concurrent drugs with antimalarial activity and are described below.

Table 28: Summary of patients withdrawn because of current antimalarial use.

Patient #	Date at start of study prophylaxis	Date of concurrent antimalarial use	Reason (if provided)	Drug
459	12 Mar 97	23 Apr 97	URTI	Bactrim
475	12 mar 97	14 Mar 97	-	Proguanil
476	12 Mar 97	14 Mar 97	-	Nivaquine
479	12 Mar 97	14 Mar 79	-	Nivaquine
629	11 Apr 97	"pre-trial and post		Nivaquine

		-trial"		
675	9 Apr 97	13 May 97	"flu"	Septran
676	9 Apr 97	11 Jun 97	Acne	Doxycycline
709	14 Apr 97	Pre trial till 13 May -	-	Nivaquine/ Paludrine
715	7 Apr 97	Pre trial till 16 Apr	-	Nivaquine/ Paludrine
760	10 Apr 97	16 May 31	Gonorrhea	Doxycycline/ ciprofloxacin

MO comment: These ten subjects were regarded by the FDA as treatment failures in the ITT analysis. They were excluded from the population in the PP analysis. There was no indication that patients receiving concurrent drugs with antimalarial activity were receiving these for symptoms of malaria.
One patient in the ITT population developed parasitemia with *P falciparum*. This patient was reported as non-compliant with his medication. He was regarded as a failure in the ITT population and was excluded by the sponsor from the PP analysis.

Review of the patient with parasitemia:
This was a 23 year old black male, wt 77.5kg. He presented for an unscheduled visit on day 28 of the study with a temperature of 38.8C and was found to be parasitemic with *P falciparum*. He had not been present for any scheduled study visits beyond the week 0 visit and was regarded as a withdrawal for non-compliance. The case narrative stated that he had missed study medication for approximately four days. (The dates that medication was missed were not provided.) On this basis he was excluded from the PP analysis.

In the ITT analysis, 175 subjects were included in the ITT population.

Evaluable failures included:
56 patients referred to above (table 27)
(1 patient with malaria
8 patients with adverse events
1 patient who withdrew consent
28 patients lost to follow-up
12 patients with protocol violations
6 listed as "other" for which details were not supplied)

as well as 10 patients who took concomitant medications with antimalarial activity.

Evaluable successes
109 patients

FDA calculated the success rate in the ITT population as shown below.
Table 29: ITT analysis

ITT population	**175**
Evaluable successes	**109**
Evaluable failures	**66**
Success rate	**62%**

Of the 175 subjects in the ITT population 113 were included in the PP population. Details of the 62 patients excluded from the PP population are shown below:

Table 30: Subjects excluded from the PP population

Exclusion Reason	Number
Failure to return	51
Non-compliance	1
Took antimalarials concurrently	10
Total	62

MO comment: The submission does not indicate the reasons that the 51 patients referred to above failed to return. From the context, it appears that they included patients who were "prematurely discontinued" in the ITT analysis (56) minus those included as "prematurely discontinued" in the PP population (5). Presumably they incorporated subjects withdrawn for non-treatment-related adverse events, consent withdrawals, protocol violations other than concurrent anti-malarial use, subjects non-compliant with treatment and patients lost to follow-up. The description of the 12 protocol violations that were included in the ITT population and the 2 protocol violations included in the PP analysis were not provided. The large number of patients lost to follow-up in this community of military recruits was unexpected.

Three subjects were withdrawn for treatment-related adverse events.
The sponsor assessed the efficacy in the ITT population as "successful" in 69%. In the per-protocol analysis the success rate was calculated at 97%.

Table 31: Efficacy of prophylaxis in ITT and PP populations

	ITT Analysis n = 175	PP Analysis n = 113
Failure of Chemoprophylaxis		
Parasitemia	1	0
Withdrawn (treatment-related)[a]	3	3
Withdrawn (other reasons)	51	–
Total	55	3
Success Rate (95% CI[b])	69% (61–75%)	97% (92–99%)

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

[b] Confidence Interval

MO comment: The above efficacy rates were more a reflection of tolerability than efficacy since the risk of malaria in this population is not known. A record of the number of patients who contracted malaria while on standard prophylaxis prior to the start of the study would have been helpful in establishing a comparative efficacy.

Table 32: FDA analysis of PP population:

PP population	**113**
Evaluable successes	**110**
Evaluable failures	**3**
Success rate	**97%**

MO commnent: The above per-protocol analysis cannot be relied upon as a primary efficacy analysis in view of the large number of poorly characterized withdrawals excluded from this PP population.

Safety:

Exposure: One hundred and seventy five subjects received at least one dose of malarone. Malarone was prescribed as one tablet daily for at least 70 days. The mean exposure time to Malarone was 8.9 weeks.

Events of unusual frequency:

Of all adverse events both attributed and not attributed to the study drug, headache (10%) and flu syndrome (7%) were most common. The most common adverse event attributed to the study drug was headache (7%). Other commonly attributed AE's included abdominal pain (2%) increased cough (2%) "skin disorder (2%). Mouth ulceration was reported in one patient. Table 33 describes all adverse events and drug attributed adverse events.

Table 33: All adverse events and drug-attributed adverse events during chemosuppression

Adverse Experience	Malarone N = 175		Malarone N = 175	
	n1	(%)	n2	(%)
Headache	12	(7)	18	(10)
Flu syndrome	0		12	(7)
Abdominal pain	4	(2)	6	(3)
Pain	2	(1)	6	(3)
Infection	0		6	(3)
Cough increased	3	(2)	4	(2)
Diarrhea	1	(<1)	4	(2)
Accidental injury	0		4	(2)
Skin disorder	3	(2)	3	(2)
Acne	1	(<1)	3	(2)
Eye pain	1	(<1)	3	(2)
Pharyngitis	0		3	(2)
Upper respiratory infection	0		3	(2)
Nausea	2	(1)	2	(1)
Gastritis	1	(<1)	2	(1)
Pain in extremity	1	(<1)	2	(1)
Rash	1	(<1)	2	(1)
Sinusitis	1	(<1)	2	(1)
Bronchitis	0		2	(1)
Skin benign neoplasm	0		2	(1)
Vesiculobullous rash	0		2	(1)
Abscess	1	(<1)	1	(<1)
Allergic reaction	1	(<1)	1	(<1)
Dizziness	1	(<1)	1	(<1)
Increased appetite	1	(<1)	1	(<1)
Liver tenderness	1	(<1)	1	(<1)
Mouth ulceration	1	(<1)	1	(<1)
Arthralgia	0		1	(<1)
Asthenia	0		1	(<1)
Back pain	0		1	(<1)
Bone pain	0		1	(<1)
Burning sensation skin	0		1	(<1)
Cellulitis	0		1	(<1)
Dyspepsia	0		1	(<1)
Dysuria	0		1	(<1)
Ecchymosis	0		1	(<1)
Eye disorder	0		1	(<1)
Fever	0		1	(<1)

N = Number of subjects with data on the database
n1 = Number of subjects reporting adverse experiences possibly attributable to the study drug
n2 = Number of subjects reporting adverse experiences irrespective of attributability
% = Percentage of subjects reporting adverse experiences

Adverse Experience	Malarone N = 175		Malarone N = 175	
	n1	(%)	n2	(%)
Fungal dermatitis	0		1	(<1)
Furunculosis	0		1	(<1)
Gum disorder	0		1	(<1)
Lymphadenopathy	0		1	(<1)
Malaise	0		1	(<1)
Myalgia	0		1	(<1)
Myopathy	0		1	(<1)
Otitis externa	0		1	(<1)
Peptic ulcer	0		1	(<1)
Pericarditis	0		1	(<1)
Rhinitis	0		1	(<1)
Sore throat	0		1	(<1)
Tenosynovitis	0		1	(<1)
Urinary incontinence	0		1	(<1)
Urticaria	0		1	(<1)
Non-grouped AEs	0		3	(2)
No. of subjects >=1 AE	29	(17)	75	(43)

N = Number of subjects with data on the database
n1 = Number of subjects reporting adverse experiences possibly attributable to the study drug
n2 = Number of subjects reporting adverse experiences irrespective of attributability
% = Percentage of subjects reporting adverse experiences

Events of unusual severity

There were no deaths.

Only one serious adverse event was reported, namely the single case of malaria described above. This event was not attributed to the study drug.

Treatment-limiting adverse events were reported in six subjects and included respectively headache, nausea and dizziness, headache, a sexually transmitted disease, flu syndrome and malaria. The former three were considered attributable to the study drug,

Review of three patients with drug-attributed treatment-limiting AE's:

- This was a 42 year-old 48kg white female with hepatosplenomegaly and a reported history of previous malaria. She had experienced headaches on Chloroquine. Headaches developed on the day medication was started and continued for 13 days, reportedly resolving when the medication was stopped.
- This was a 26 year-old 65kg black male who developed nausea and dizziness on study day 13. The medication was stopped the day symptoms developed and the nausea resolved the same day and the dizziness the following day. Hematology and clinical chemistry tests at the time were normal and there was no re-challenge.
- This 45 year-old 91kg white male developed a treatment limiting headache on day 2 of study medication which lasted 4 days and appears to have resolved 5 days before the medication was stopped. This adverse event might not be attributable to the study drug.

Events of unusual character:
No events revealed in toxicology studies (wasting and death in dogs) were observed in these human subjects. Neutropenia and liver disfunction associated with other DHFR inhibitors was not observed.

Laboratory results:
Mean Hb fell from 14.8 +/- 1.25 g/dL at screening to 14.5 +/- 1.31 g/dL at week 10. At follow-up (after cessation of therapy) mean Hb was 14.9+/-1.03 g/dL
Mean PCV fell from 44.1 +/-3.97 % at screening to 42.7 +/-3.22 % at week 10. At follow-up (after cessation of therapy) mean PCV was 44 +/-2.95%.

Table 34: Treatment emergent abnormalities of Hemoglobin and PCV

	Hb (Mean) g/dL	PCV (mean) %	% abnormally low PCV
Screening	14.8	44.1	1% (n=161)
Week 10	14.5	42.7	3% (n=35)
Follow-up	14.9	44	2% (n=46)

Table 35: Treatment emergent abnormalities of white cell count

	WBC * 10^9/l	% Abnormally low
Screening	5.9 +/- 1.52	7% (n=168)
Week10	5.2 +/- 1.61	17% (n=54)
Follow-up	6.5 +/- 1.76	2% (n=46)

MO comment The data suggest a tendency for a mild treatment related anemia to develop during the study. Similar findings were observed in the Kenyan (MALB2001) and Zambian (MALB3001) studies. In all three studies, the small decline in PCV did not appear clinically significant.

No significant treatment emergent changes were observed for any of the clinical chemistry parameters that were examined.

MO comment:
This open-label uncontrolled study in military recruits in South Africa failed to provide useful information on the efficacy of Malarone. The incidence of malaria in the areas where the study was conducted was not determined. The prevalence of malaria varied between study sites, and the risk for malaria among subjects could not be established. Large numbers of patients were withdrawn as "protocol violations" or were lost to follow-up. This was a further impediment to the quality of the data. The exposure of participants to malaria prior to the study was not known. All had been resident in malaria areas when the study was initiated, and had been on other forms of prophylaxis. Since the incidence of malaria in the area was not known and the duration of exposure of study

subjects was not recorded, the level of malaria immunity this group of patients was unknown. The single case of malaria diagnosed during this study occurred in a patient who was described as "missing approximately 4 days of treatment". The sponsor excluded this patient from the per-protocol analysis on the basis of non-compliance. While this is technically correct according to the protocol, missing 4 days of treatment in the course of several weeks of prophylaxis strongly suggests a failure of prophylaxis.
Adverse event profiles were similar to MALB2001 and MALB3001. There were no significant safety concerns among the patients in this study although large numbers of patients were lost to follow-up or withdrawn for protocol violations. This again diminished the strength of the conclusions on safety.

MalB3003

Title: A randomized double-blind placebo-controlled parallel group study to evaluate the suppressive prophylactic activity of Malarone (atovaquone/proguanil) in children at risk of developing *Plasmodium falciparum* infection.

Aim: The aim of the study was to establish the efficacy of Malarone compared with placebo in the prophylaxis of P falciparum malaria among children.

Setting: The study was conducted at a single site, the Albert Schweitzer Hospital, Lamberene Gabon, during the peak malaria transmission season between January and July of 1997. Participants were children between the ages of 4 and 16 years who live in the area. These children do not normally receive prophylaxis for malaria, allowing for the ethical inclusion of a placebo control arm.

Study design: The study comprised 3 phases, an initial 3 day curative phase during which all subjects were given treatment doses of Malarone to eradicate any existing malaria. Subjects who were successfully treated were then randomized to receive either prophylactic doses of Malarone or matching placebo, given daily over 12 weeks. Prophylactic doses of Malarone were based on body weight as described below under "dosing of study medications".
All drugs were given daily for at least 12 weeks.

Following prophylaxis subjects were followed for a further 4 weeks.

Endpoints: The primary efficacy endpoint was the development of parasitemia while on prophylaxis. When a positive smear was observed and confirmed by a second microscopist, a second slide was taken from the patient. (If the confirmatory slide taken within 24-72 hours was negative the patient was not considered a prophylactic failure.)

MO comment: The primary endpoint was parasitemia by any species of plasmodium. I regarded this as an unsuitable endpoint for a study supporting the indication as a prophylactic agent for infection with *P falciparum*. Further, a prolonged period of follow-up would be required to confirm the prevention of relapsing malaria. In a setting where patients remained at risk for new infections with non-falciparum malaria following chemprophylaxis it would not be possible to distinguish relapses from new infections. Thus this study design did not allow a conclusive statement on the efficacy of malarone in preventing relapsing malaria. On this basis I elected to use parasitemia with *P falciparum* as the primary efficacy endpoint.

In patients developing parasitemia, IC50's for atovaquone, proguanil and cycloguanil were measured if a viable isolate was obtained.

Statistical methods: Prophylactic success was evaluated by comparing the proportions of patients among placebo and study drug recipients who did not develop parasitemia during the prophylactic period. Patients were stratified by weight into one of the four categories listed above and analyzed using the Mantel-Haenzsel test using exact methods. Heterogeneity across strata was also checked. Point estimates with 95% confidence limits were calculated for the percent efficacy.

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

Study plan. The study schedule is show below

Table 36: Schedule of 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	17	18
Week	-2/52	-1/52	0/52	1/52	2/52	3/52	4/52	5/52	6/52	7/52	8/52	9/52	10/52	11/52	12/52	13/52	14/52	15/52	16/52
Day	121,-17	-3	0	7	14	21	28	35	42	49	56	63	70	77	84	91	98	105	112
Written Informed Consent	√					√													
Inclusion/ Exclusion Criteria	√	√																	
Medical History/ Demographics	√																		
Physical Examination	√																		
Vital Signs	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Haematology/Clinical Chemistry[a]	√								√						√				
Malaria Blood Smears[b]		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Adverse Event Review		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Concomitant Medication Review		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Medication Issued: Radical Cure/ Chemosuppression[d]		√	√	√	√	√	√	√	√	√	√	√	√	√	√				
Pregnancy Test[e]	√								√						√				
Drug Dispensing Log Checked		√	√	√	√	√	√	√	√	√	√	√	√	√	√				
Pharmacokinetic Blood Sample[f]									√						√				
Blood Sample for in vitro Sensitivity Testing	Asexual malaria infection develops																		

[a] √ at time of withdrawal
[b] √ at any time that malaria was suspected
[c] During the Radical Cure Phase of the trial, medication was issued daily for three days, under supervision of the Field Worker
[d] During the Chemosuppressive Phase of the trial, medication was issued daily under supervision of the Field Worker. The Chemosuppression Phase followed directly on from the Curative Phase
[e] If symptomatic
[f] √ at time of withdrawal
[g] If positive, volunteer would continue to Visit 2. If positive at Visit 4 or thereafter, volunteer was withdrawn

Subjects were screened 14 days before initiation of the curative phase of therapy. Immediately prior to initiation of curative treatment, (week –1) a malaria smear was obtained, the results of clinical chemistry and hematology tests were reviewed and concomitant medications were recorded. Patients were allocated to one of four dosing groups according to body weight (11-20kg, >20-30kg, >30-40kg, >40kg). A maximum of 80 patients were allocated to each group. The patients were then treated with Malarone in curative doses daily for three days. The treatment was supervised by a field worker.
On completion of treatment (week 0), patients were randomized to receive either malarone or placebo as daily prophylaxis. They were seen daily for supervised administration of study medication and data were recorded weekly for the 12 weeks of prophylaxis. At each weekly visit, malaria thick blood smears were checked (additional smears were performed if patients presented at unscheduled visits with symptoms compatible with malaria) and concurrent medications were recorded. At week 6 and week 12 blood samples were drawn for hematology and clinical chemistry testing and levels of atovaquone, proguanil and cycloguanil were measured. Following completion of chemoprophylaxis, patients were seen off medication, weekly for a further four weeks during which malaria blood smears were obtained.

Patients with negative smears at week 0 or negative smears at week 1 following positive or missing smears at week 0 were not withdrawn as treatment failures. This allowed for delayed parasite clearance. Based on this criterion, patients with positive baseline results were excluded from efficacy evaluations.
MO comment:The "reporter period" for prophylaxis efficacy should begin approximately two weeks after initiation of prophylaxis (roughly the incubation period for new cases of malaria) and should end one to two weeks after prophylaxis has stopped (before new infection off prophylaxis has presented). Cases occuring early (1-2 weeks) into the follow-up period should be regarded as failures of causal prophylaxis though not necessarity failures of suppressive prophylaxis.

Protocol amendments:

Jan 14 1997: This ammendment prior to recruitment increased the sample size from 300 to 320 and the dosing period from 70 to 84 days.
August 20 1997. This amendment made after commencing recruitment but before unblinding, identified the ITT population as the primary population for analysis. Patient with positive or missing smears at days 0 whose smears were negative at week 1 were included in both PP and ITT populations as having a negative baseline smear.

Inclusion criteria
Males of females in good general health >=4years and <= 16 years of age who were at risk for malaria infection and able to give informed concent and comply with the protocol.

Exclusion criteria:
Pregnancy
Lactation
Being of childbearing potential iand in the investigator's opinion, not willing or able to avoid pregnanacy.
Received antimalarial drugs or other drugs with antimalarial activity within the previous week.
Known hypersensitivity to atovaquone or proguanil
Clinicly significant abnormal baseline hematology or clinical chemistry parameters (when results were obtained volunteers were withdrawn at the discretion to the investigator
Significant renal impariment as evidenced by a creatinine clearance of <30mL/min.
Splenectomy
Laboratory evidence of hapatitis as defined by a three fold increase above the normal upper limit in alanine transaminase (ALT) for this volunteer population.

Criteria for premature discontinuation:
Voluntary withdrawals or withdrawals at the discretion of the investigator were to be recorded together with the reasons and an attempt was made to follow-up those patients after 2 weeks with a clinic visit. Patients with parasitemia any time from week 1 of chemoprophylaxis to the end of follow-up were withdrawn. Those with parasitemias between week 1 and the end of chemoprophylaxis were regarded as treatment failures.

Patients who vomited after receiving Malarone during the 3-day radical curative phase were to be withdrawn.

MO comment: withdrawing patients who vomited would select against a population unable to tolerate the drug.

Dosing of study medications:

Curative doses of Malarone were extrapolated from adult curative doses and were divided into four weight categories as shown in table 37 below.

Table 37: Daily dosage of Malarone during the Radical cure phase

Study Phase	Treatment Group	Stratum	Weight (kg)	Daily Dosage – atovaquone/proguanil	Dosing Period
Radical Cure	MALARONE	Stratum 1	11–20	250 mg/100 mg once daily (*i.e.* four ¼–strength MALARONE tablets)	3 days
		Stratum 2	>20–30	500 mg/200 mg once daily (*i.e.* two full–strength MALARONE tablets)	3 days
		Stratum 3	>30–40	750 mg/300 mg once daily (*i.e.* three full–strength MALARONE tablets)	3 days
		Stratum 4	>40	1000 mg/400 mg once daily (*i.e.* four full–strength MALARONE tablets)	3 days

Patients randomized to receive malarone during the prophylaxis phase were dosed as shown below:

Table 38: doses of Malarone for chemosupression

Study Phase	Stratum	Weight (kg)	Treatment Group	Daily Dosage – atovaquone/proguanil	Dosing Period
Chemosuppression	Stratum 1	11 – 20	MALARONE OR placebo	62.5 mg/25 mg once daily (one ¼–strength MALARONE tablet) OR 1 placebo tablet	at least 12 weeks (84 days)
Chemosuppression	Stratum 2	>20 – 30	MALARONE OR placebo	125 mg/50 mg once daily (two ¼–strength MALARONE tablets) OR 2 placebo tablets	at least 12 weeks (84 days)
Chemosuppression	Stratum 3	>30 – 40	MALARONE OR placebo	187.5 mg/75 mg once daily (three ¼–strength MALARONE tablets) OR 3 placebo tablets	at least 12 weeks (84 days)
Chemosuppression	Stratum 4	>40	MALARONE OR placebo	250 mg/100 mg once daily (one full– strength MALARONE tablet) OR 1 placebo tablet	at least 12 weeks (84 days)

Randomization to treatment or placebo was performed in blocks of four.

Compliance:

Treatment compliance was checked using daily pill counts by a field worker as study participants presented to the drug distribution sites. Patients missing more than 2 sequential days of medication were withdrawn as compliance failures.

Concurrent therapy.

Subjects developing infections during the study were treated where possible with anti-infective agents not known to have antimalarial activity. Volunteers treated with agents with antimalarial activity (either inside or outside the study were withdrawn. Such agents included known antimalarials (chloroquine, quinine,

mefloquine, halofantrine, pyrimethamine/sulfadoxine, proguanil, amodiaquine etc) and other antimicrobials (co-trimoxazole, tetracycline, doxycycline, rifampicin, azithromycin and ciprofloxacin).

Safety
Adverse events were defined as all untoward medical occurrences experienced by a volunteer and included a disease, exacerbation of a previous illness, recurrence of an intermittent illness or other signs or symptoms. Serious adverse events included those that were fatal, life-threatening, disabling or incapacitating, those that required or prolonged hospitalization. They included cancer, congenital anomalies in the progeny of patients and the consequences of drug overdose

Sample size calculation:
A malaria attack rate of 22% was assumed for the placebo arm and 1.5% for the malarone arm. To detect a 10% difference in attack rates with a 5% level of significant and a power of 80%, at least 132 patients were needed per arm.

Populations for analysis:
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, patients with a positive smear for non-falciparum malaria.
Evaluable failures: Included patients with a positive smear for *P falciparum* anytime after the week 1 visit, up to and including the week 12 visit, patients receiving other drugs with anti-malarial activity, patients withdrawn for an adverse event or non-compliance during that period, patients lost to follow-up during that period and patients missing week 12 blood results.
Evaluable successes: Included patients compliant with study medication who were present at the end of the prophylactic period (week 12) with blood smears negative for *P falciparum* at all scheduled and unscheduled visits following the week 1 visit up to and including the week 12 visit. Subjects with missing smears were included in this population provided a negative baseline and week 12 smear were available.

Per protocol analysis
The population for this analysis was defined as patients who
- had negative baseline smears
- received at least one dose of chemoprophylaxis
- were compliant with the protocol
- did not receive medications that might have interfered with the efficacy analysis.
- were either present at week 12 of the study or had failed or were withdrawn for treatment-related adverse events during the chemoprophylaxis phase.

Patients excluded from this population included those
- lost to follow-up
- withdrawn for reasons other than treatment-related adverse events including non-compliance or use of other antimalarials
- patients with a missing week 12 blood smear

In this population, the following categories of patients were distinguished:

Non evaluable: Patients with no results of a baseline smear, patients with non-falciparum malaria and 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 1 visit, up to and including the week 12 visit and patients withdrawn for a treatment-related adverse event during that period.
Evaluable successes: Included patients compliant with study medication who were present at the end of the prophylactic period (Week 12) with blood smears negative for *P falciparum* at all scheduled and unscheduled visits following the week 1 visit up to and including the week 12 visit. Subjects with missing smears were included in this population provided a negative baseline and week 12 smear were available.

Safety population included all patients who received at least one dose of the study medication. Adverse events were coded using COSTART terms.

Results:

Three hundred and nineteen volunteers were screened and enrolled into the 3-day curative treatment phase of the study. Two hundred and sixty five completed the radical phase.
Of the 54 subjects who did not complete radical therapy, 43 were withdrawn because of vomiting.
Nine withdrew consent, 1 was lost to follow-up and 1 was withdrawn for other reasons.
Those withdrawn in the radical cure phase for adverse events included 1 patient <20kg, 5 patients >=20kg and <30kg, 21 >=30kg and<40 kg and 16>40kg.
MO comment: The large number of early withdrawals for vomiting raises concerns about the tolerability of malarone in this pediatric population. Subjects qualifying for the chemoprophylaxis phase were pre-selected on the basis of their tolerance for Malarone. Most of the patients withdrawn because of vomiting during the treatment phase came from the higher dose strata, raising questions about the appropriate dose and regimens for patients over 30 kg in weight. The tolerance of prophylactic doses in such patients is not known.

At week –1, 36% of 319 volunteers had positive malaria smears. *P falciparum* was present in 76 patients, *P malariae* in 14 and *P ovale* in 1. One patient had a mixed infection with *P falciparum* and *P ovale*.

The distribution of positive smears at screening is shown below:

Table 39: Positive malaria slides at screening, week 0 and week 1

Study Week	Number of Subjects with Positive Smears			
	P. falciparum	*P. malariae*	*P. ovale*	*P. falciparum* + *P. malariae*
Week –1	76	14	1	1
Week 0	5	11	0	0
Week 1	0	0	0	0

Parasite clearance times were longer for *P malariae* than for *P falciparum*.
All subjects were negative for parasitemia at week 1.

MO comment: The patients withdrawn prior to entering the prophylaxis phase included 20/54 (37%) cases with *P falciparum* at screening. The patients entering the prophylaxis phase included 76/265 (29%) with *P falciparum* at screening. The higher percentage of malaria in the "withdrawals" at baseline than in the "non-withdrawals" suggests that the symptoms of malaria itself may have led to some of the withdrawals prior to randomization to prophylaxis, rather than drug-related adverse events alone.

The ITT population included 264 of the 265 patients randomized to one of the treatment arms. (One randomized patient was lost to follow-up before a baseline smear was obtained, and was excluded from the ITT analysis.)

Of the 264 patients included in the ITT population 17 were excluded from the PP population for the reasons shown below:

Table 40: Reasons for exclusion from PP population.

Reason for Discontinuation	Chemoprophylaxis Treatment Group	
	Placebo	Malarone
Lost to follow-up	6	10
Protocol violation[a]		1
Total	6	11

[a] Subject No. 909 took an antimalarial drug concurrently

Of the 16 patients excluded from the PP analysis because of loss to follow-up, 9 were recorded as lost to follow-up in the ITT analysis. Details on the remaining 7 were not provided. The available information on 14 withdrawn patients is shown below.

Table 41: Reasons for withdrawal from PP population

Patient number	Treatment arm	Reason for withdrawal
879	Placebo	LTF (though was seen 13 days after withdrawal)
943	"	LTF
1040	"	Consent withdrawn
902	Malarone	LTF
1097	"	LTF
909	"	Violation (took chloroquine)
1045	"	LTF
1061	"	LTF
1086	"	LTF
1160	"	Protocol violation (no details)
858	"	AE (vomiting) withdrawn day –1 excluded from ITT and PP
916	"	Violation (no details)
920	"	LTF
1147	"	LTF

MO comment: It is unclear why 11 of these withdrawals occurred in the malarone arm and only 3 in the placebo arm. Adverse events were not listed in records of the withdrawn patients to suggest drug intolerance. No clinical features to suggest malaria were recorded around the time that patients were withdrawn.

The details of patient accountability are shown below.

Table 42: Patient accountability

Population Subject#	Completed / Reason for discontinuation	Placebo	Malarone	RC Only
Safety	N	140	125	54
	Study Completers (%)	101 (72)	112 (90)	0
	Prematurely Discontinued (%)	39 (28)	13 (10)	54 (100)
Safety, Prematurely Discontinued	N	39	13	54
	Lack of Efficacy	36	2	0
	Adverse Event	0	1	43
	Consent Withdrawn	1	0	9
	Lost to Follow-up	2	7	1
	Protocol Violation	0	3	0
	Other	0	0	1
Intent-to-treat	N	140	124	
	Study Completers (%)	101 (72)	112 (90)	
	Prematurely Discontinued (%)	39 (28)	12 (10)	
ITT, Prematurely Discontinued	N	39	12	
	Lack of Efficacy	36	2	
	Adverse Event	0	0	
	Consent Withdrawn	1	0	
	Lost to Follow-up	2	7	
	Protocol Violation	0	3	
	Other	0	0	
Per-protocol	N	134	113	
	Study Completers (%)	98 (73)	111 (98)	
	Prematurely Discontinued (%)	36 (27)	2 (2)	
PP, Prematurely Discontinued	N	36	2	
	Lack of Efficacy	36	2	
	Adverse Event	0	0	
	Consent Withdrawn	0	0	
	Lost to Follow-up	0	0	
	Protocol Violation	0	0	
	Other	0	0	

Table 43: Distribution of patients between the study populations:

	Radical cure 319	
Withdrawn	55 (vomiting 43, withdrew consent 9, other 3)	
	Malarone	Placebo
ITT	124	140
Withdrawn	11 (10 LTF, 1 violation)	6 (6 LTF)
PP	113	134

The number of patients in each weight stratum within each population are shown below

Table 44: Numbers of patients in each population by weight category:

Analysis Population	Stratum 1 (11–20 kg)		Stratum 2 (>20–30 kg)		Stratum 3 (>30–40 kg)		Stratum 4 (>40 kg)	
	Placebo	MALARONE	Placebo	MALARONE	Placebo	MALARONE	Placebo	MALARONE
Safety	40	37	35	36	30	26	35	26
ITT	40	37	35	36	30	25	35	26
PP	37	35	34	31	30	22	33	25

Demographic characteristics of the ITT population are shown below.

Table 45: Demographic characteristics of patients randomized to placebo and to malarone

Characteristic	Placebo n = 140	Malarone n = 125
Male/Female	67/73	65/60
Age (yrs)		
Males		
Mean (SD)	10 (2.8)	10 (2.8)
Range	5–16	5–15
Females		
Mean (SD)	10 (3.0)	9 (3.1)
Range	5–15	5–15
Weight (kg)		
Males		
Mean (SD)	30 (10.0)	30 (10.7)
Range	15–60	15–60
Females		
Mean (SD)	33 (14.3)	29 (11.7)
Range	13–71	14–56
Height (cm)		
Males		
Mean (SD)	136 (17.0)	135 (17.2)
Range	105–175	107–174
Females		
Mean (SD)	137 (19.5)	132 (17.7)
Range	105–174	102–162

The patients were evenly matched across treatment groups for age, sex, weight and height. This was an older pediatric population with a mean age of 10 years and a minimum age of 5 years.
MO comment: The minimum age was five years and only a proportion of the pediatric population was covered. This limitation should be reflected in the label.
Concurrent medical conditions at screening included a prepoderance of skin rashes.
Comparable rates of splenomegaly were reported in each treatment arm; 10/124 in placebo-treated patients and 14/140 in malarone-treated patients. The 9% prevalence of spenomegaly in this community presumably reflects substantial malaria exposure.

Concurrent therapy:
Concurrent therapies were similar for both study arms. Overall, 70% of placebo recipients and 68% of Malarone recipients received concurrent medications. Most common were anti-emetics given during the curative phase of the study. In particular, anti-helminthics were used in 18 and 13 placebo and Malarone treated patients respecitvely, antiprotozoals in 1 and 2 respectively and antimalarials in 1 and 1 respectively. Skin preparations including insect repellants were used in 5 and 2 patients respectively.

Table 46: Concurrent medications

Medication Groups	Placebo N		Malarone N		RC Or N
Number of patients	140		125		54
Number of patients with concomitant medication	98	(70%)	85	(68%)	6
ANALGESICS					
Any medication	23	(16%)	23	(18%)	0
Other analgesics and antipyretics	23	(16%)	23	(18%)	0
ANTHELMINTICS					
Any medication	18	(13%)	13	(10%)	0
Antinematodal agents	18	(13%)	13	(10%)	0
ANTIANEMIC PREPARATIONS					
Any medication	1	(<1%)	0		0
Iron preparations	1	(<1%)	0		0
Vitamin b12 and folic acid	1	(<1%)	0		0
ANTIBACTERIALS FOR SYSTEMIC USE					
Any medication	11	(8%)	10	(8%)	0
Aminoglycoside antibacterials	1	(<1%)	0		0
Beta-lactam antibacterials, penicillins	9	(6%)	8	(6%)	0
Other antibacterials	1	(<1%)	2	(2%)	0
ANTIBIOTICS AND CHEMOTHER. FOR DERMATOLOGICAL USE					
Any medication	2	(1%)	2	(2%)	0
Antibiotics for topical use	1	(<1%)	0		0
Chemotherapeutics for topical use	1	(<1%)	2	(2%)	0
ANTIDIARR.,INTEST. ANTIINFL./ANTIINFECT. AGENTS					
Any medication	1	(<1%)	0		0
Intestinal antiinfectives	1	(<1%)	0		0
ANTIFUNGALS FOR DERMATOLOGICAL USE					
Any medication	1	(<1%)	0		0
Antifungals for topical use	1	(<1%)	0		0
ANTIPROTOZOALS					
Any medication	2	(1%)	3	(2%)	0
Agents against amoebiasis and other protozoal dis.	1	(<1%)	2	(2%)	0
Antimalarials	1	(<1%)	1	(<1%)	0

Medication Groups	Placebo N		Malarone N		RC Or N
ANTISPAS. AND ANTICHOLINERGIC AGENTS AND PROPULSIV					
Any medication	75	(54%)	66	(53%)	5
Belladonna and derivatives, plain	3	(2%)	2	(2%)	0
Propulsives	73	(52%)	65	(52%)	5
CARDIAC THERAPY					
Any medication	1	(<1%)	1	(<1%)	0
Cardiac stimulants excl. cardiac glycosides	1	(<1%)	1	(<1%)	0
COUGH AND COLD PREPARATIONS					
Any medication	1	(<1%)	7	(6%)	0
Cough suppressants and expectorants, combinations	0		1	(<1%)	0
Expectorants,excl combinations with cough suppr.	1	(<1%)	6	(5%)	0
ECTOPARASITICID.,INCL SCABICID.,INSECT. AND REPELL					
Any medication	5	(4%)	2	(2%)	0
Ectoparasiticides, incl scabicides	5	(4%)	2	(2%)	0
GYNECOLOGICAL ANTIINFECTIVES AND ANTISEPTICS					
Any medication	1	(<1%)	2	(2%)	0
Antiinfectives/antisept.,excl comb with corticost.	1	(<1%)	2	(2%)	0
OPHTHALMOLOGICAL AND OTOLOGICAL PREPARATIONS					
Any medication	1	(<1%)	0		0
Antiinfectives	1	(<1%)	0		0
OPHTHALMOLOGICALS					
Any medication	3	(2%)	2	(2%)	0
Antiinfectives	3	(2%)	2	(2%)	0
OTOLOGICALS					
Any medication	1	(<1%)	0		0
Antiinfectives	1	(<1%)	0		0
STOMATOLOGICAL PREPARATIONS					
Any medication	3	(2%)	2	(2%)	0
Stomatological preparations	3	(2%)	2	(2%)	0
THROAT PREPARATIONS					
Any medication	1	(<1%)	0		0
Throat preparations	1	(<1%)	0		0

Medication Groups	Placebo N		Malarone N		RC Only N
VACCINES					
Any medication	1	(<1%)	2	(2%)	0
Bacterial vaccines	1	(<1%)	2	(2%)	0
VITAMINS					
Any medication	5	(4%)	4	(3%)	0
Multivitamins, combinations	5	(4%)	4	(3%)	0
NON-CLASSIFIED DRUGS					
Any medication	3	(2%)	2	(2%)	1
Non-grouped Drugs	3	(2%)	2	(2%)	1

The two patients treated with antimalarials are described below.
#909 This 9 year old male with parasitemia at screening, developed a fever on day 35 of the study and was treated with chloroquine. A study visit the following day showed a temperature of 38.9C, and a negative malaria smear. This subject was included by the sponsor as a success in the ITT population but excluded from the PP population. The patient was in the Malarone arm.
MO Comment: Since this withdrawal was contingent on a treatment emergent adverse event (fever where malaria was not conclusivly excluded on the day of treatment) the patient was regarded as a treatment failure in the ITT analysis and was excluded from the PP analysis.
#1058 This 7 year old female with a parasitemia at screening, developed a fever on day 25 of study and was given chloroquine. A visit on the following day confirmed parasitemia on smear. This patient was regarded as a treatment failure in both ITT and PP populations. The patient was in the placebo arm.

Compliance was confirmed by a field worker as study subjects presented to the drug distribution center each day. Two subjects in the Malarone arm were recorded as "not having taken their medicine according to the protocol" but not missing more than 2 consecutive doses.

Efficacy:

Parasitemia developed in 25 subjects treated with placebo and none of the subjects treated with malarone. Six subjects treated with placebo and 10 treated with malarone were withdrawn prior to week 12. The sponsor calculated the prophylaxis success rate in the Malarone arm as 92% for the ITT population and 100% for the PP population.

Table 47: Efficacy results as reported by sponsor (all species of malaria)

	ITT Analysis		PP Analysis	
	Placebo n = 140	MALARONE n = 124[a]	Placebo n = 134	MALARONE n = 113
Failure of Chemoprophylaxis				
Parasitemia	25	0	25	0
Withdrawn (treatment-related)[b]	0	0	0	0
Withdrawn (other reasons)	6	10	-	-
Total	31	10	25	0
Success Rate	78%	92%[c]	81%	100%[d]
Efficacy Rate[e]	-	64%	-	100%
(95% CI[f])	-	(19–88%)	-	(65–100%)

[a] One subject received a single dose of study drug but withdrew before a baseline smear was obtained and thus is included in the safety population but excluded from the ITT population

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

[c] P = 0.002, Mantel–Haenszel Test, versus Placebo

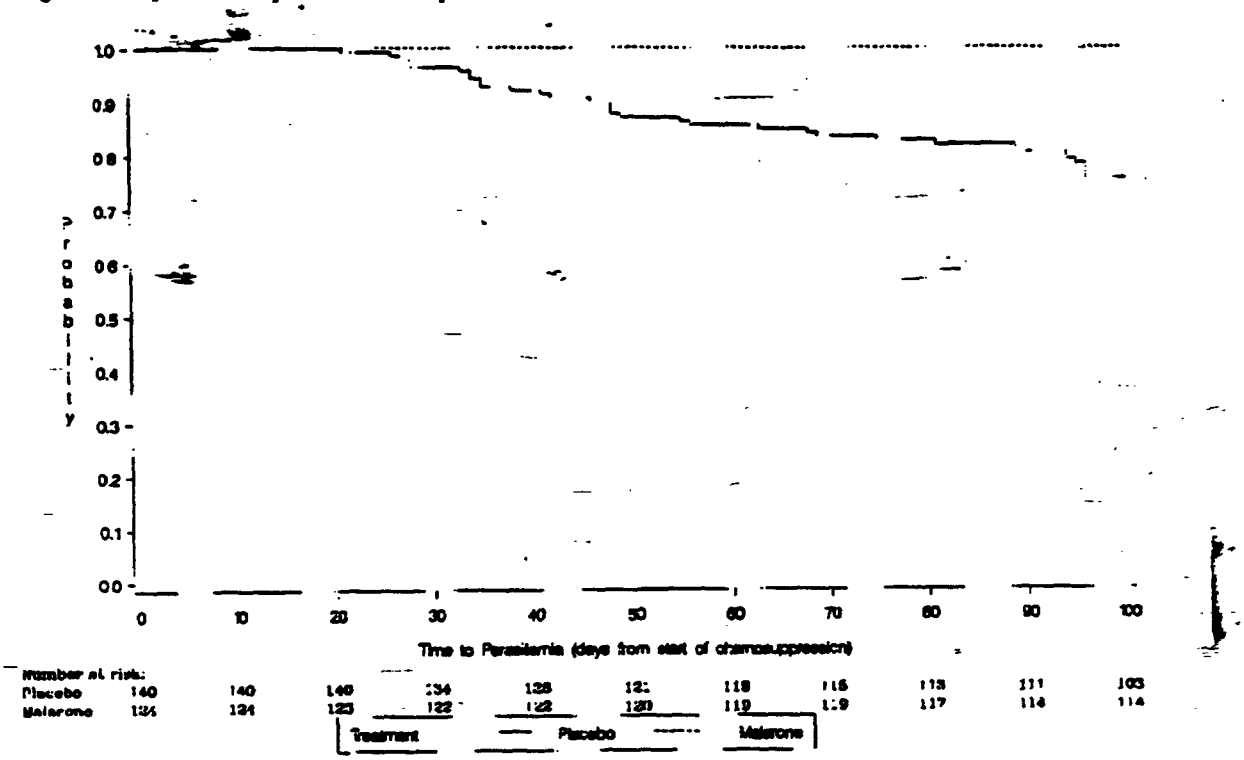
[d] P < 0.001, Mantel–Haenszel Test, versus Placebo

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

[f] Confidence Interval

The proportion of placebo and Malarone treated patients remaining malaria free during the study was charted in the Kaplan-Meier curve below.

Figure 6: Kaplan Meier plot for time to parasitemia



Two cases of non-falciparum malaria occurred among placebo recipients during the study period, one case of *P ovale* and one of *P malariae.*

MO comment: The efficacy for malarone was adjusted using *P falciparum* parasitemia as the primary efficacy endpoint and one patient in the ITT population treated as a success by the sponsor was regarded as a failure.

Table 48: Sponsor reported success rates for *P falciparum*

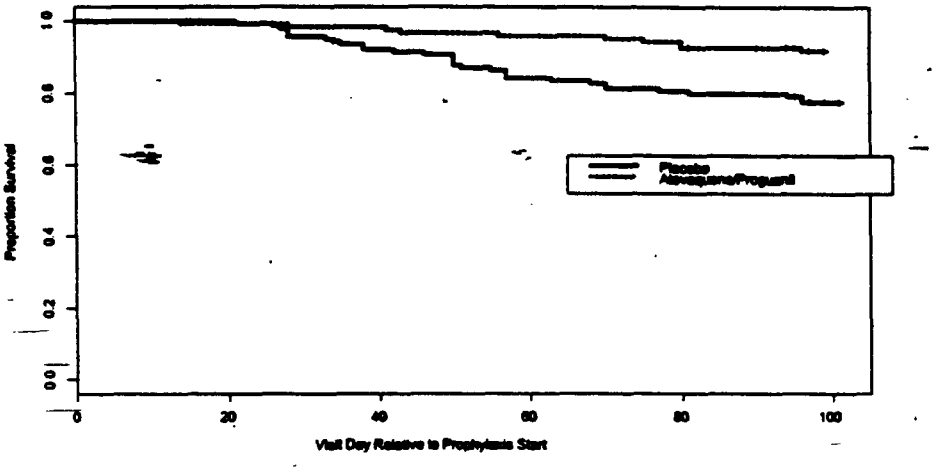
Population	Prophylaxis Result	Total	Placebo	Malarone	Exact Mantel Haenszel Test P value (**)	Homogeneity Test P value (**)	Prophylactic Success Odds Ratio (95% CI) (**)
Intent-To-Treat	Failure	41 (16%)	31 (22%)	10 (8%)			
	Success	223 (84%)	109 (78%)	114 (92%)	0.002	0.532	0.31 (0.13 , 0.68)
	N	264	140	124			
Per-Protocol (*)	Failure	23 (9%)	23 (17%)	0			
	Success	222 (91%)	109 (83%)	113 (100%)	<0.001	.	0 (0 , 0.17)
	N	245	132	113			

Table 49: Efficacy as determined by FDA

	ITT		PP	
	Placebo (n=140)	Malarone (n=124)	Placebo (n=134)	Malarone (n=113)
Evaluable successes	109	113	109	113
Evaluable failures	29	11	23	0
Unevaluable	2 (non-falciparum)	0	2	0
Success rates	109/138 (79%)	113/124 (91%)	109/132 (83%)	113/113 (100%)

Since the point estimates of success rates did not capture the longitudinal characteristics of the data, a "survival analysis" was performed on the data (described in detail in the statistical review) reflecting the proportion of successes over time as shown below.

FIGURE 7: STUDY MALB-3003: TIME TO PROPHYLAXIS FAILURE IN ITT SUBJECTS



Parasitemia during the four week follow-up period
Parasitemia occurred in 12 of 112 evaluable subjects who were treated with placebo and 3 of 114 who were treated with Malarone. The latter 3 cases occurred at weeks 15, 15, and 16 respectively.

MO comment: the fact that the three cases in the Malarone treated arm occurred 3 or more weeks after stopping prophylaxis suggests that these were new infections rather than failures of causal prophylaxis.

In vitro sensitivity:
In vitro sensitivity was tested for three isolates obtained from placebo treated patients who developed infection during the prophylaxis phase. The available results revealed IC_{50}'s comparable with cited IC_{50}'s from other published studies where the isolates were regarded as drug sensitive (Table 50)

Table 50: Drug sensitivity results on 3 isolates from placebo treated patients who developed malaria

Subject Number	IC_{50} Values (nM)		
	Atovaquone	Proguanil	Cycloguanil
986	10.9	11030	6.9
991	2.7	No Data	No Data
1027	No Data	1380	55.6
Mean	6.8	6205	31.3
Range	2.7–10.9	1380–11030	6.9–55.6
Historical Mean[a]	1.73	10405	23.8
Cited Median Data[b]	1.61		
Cited Geometric Mean Data[c]	0.90		

[a] Data from Study MALB2001 (RM1997/00697/00)

[b] Gay F, Bustos D, Traore B, *et. al. In vitro* response of *Plasmodium falciparum* to atovaquone and correlation with other antimalarials: comparison between African and Asian strains. Am J Trop Med Hyg 1997; 56: 315–317.

[c] Basco LK, Ramiliarisoa O and Le Bras J. *In vitro* activity of atovaquone against the African isolates and clones of *Plasmodium falciparum*. Am J Trop Med Hyg 1995; 53:388–391.

MO comment: Since the three patients reflected here were only treated with Malarone for three days, the possibility of drug resistance developing following treatment is not adequately addressed by these data.

Safety results:

Drug exposure:

Three hundred and nineteen patients received a three day curative regimen consisting of malarone and 125 of these receive malarone in daily prophylactic doses for a mean of 11.1 weeks. Doses were as shown in tables 37 and 38.

Adverse events:

Events of unusual frequency:

Regardless of causality, the most commonly reported adverse events during chemosuppression were abdominal pain (33%), headache (19%), fever (6%), increased coughing (9%), flu syndrome (9%) and vomiting (7%). These were equally frequent in malarone and placebo treated patients.

Overall, 42% malarone treated patients and 41% placebo treated patients reported at least one drug-related adverse event. The most commonly reported adverse events possibly related to drug included abdominal pain (31%), headache (14%) and vomiting (7%).

MO comment: Forty-three of the 319 patients (13%) enrolled in the curative phase were withdrawn for vomiting. The remaining population proceeding to chemoprophylaxis was enriched for patients less likely to vomit. Thus vomiting in the general population treated prophylactically with Malarone may be more frequent than the 7% reported above.

The most frequently reported adverse events possibly related to study drug are listed below.

Table 51: Most frequently reported adverse events at least possibly related to study drug

	Placebo (n=140)	Malarone (n=125)
Abdominal pain	40 (29%)	39 (31%)
Headache	19 (14%)	17 (14%)
Vomiting	8 (6%)	9 (7%)
Diarrhea	2 (1%)	0
Vertigo	2 (1%)	0
Nausea	1 (<1%)	1 (<1%)
Pruritis	1 (<1%)	0

Adverse events of unusual character:
Adverse events that might be anticipated due to this class of medications included leukopenia, and anemia as with other DHFR inhibitors (see section on laboratory results.)
Proguanil is known to cause alopecia and mouth ulcers though neither of these complaints were represented in the AE database for this study.

Adverse events of unusual severity:
No deaths occurred during the study period.
No treatment limiting adverse event occurred in either the placebo or the malarone treated groups during the chemosuppression phase. During the radical cure phase, 44 subjects vomited or experienced abdominal pain and were withdrawn. One placebo-treated patient with symptomatic malaria was erroneously recorded as having a treatment limiting adverse event during the chemoprophylaxis phase and one malarone recipient withdrawn during radical cure for vomiting was mistakenly given a dose of study medication. This event was documented as treatment limiting.

Two pregnancies occurred in patients during the study. Both subjects were allocated to the placebo arm of the study. In one the outcome was not known and in the other an abortion was performed for socio-economic reasons.

Clinical laboratory evaluations
Routine hematology investigations included hemoglobin, hematocrit, white cell count and platelet count. Routine clinical chemistry tests included ALT, albumin, alkaline phosphatase, creatinine, GGT, postassium, sodium, total bilirubin and urea. Results were reported at screening, week 6, week 12 and at withdrawal. At each time-point, mean values, medians, maximum and minimum values were compared for malarone and placebo treated patients. Within each treatment group, differences between successive samples were examined using the same statistical parameters. No treatment emergent effects were found for any of these laboratory investigations.
Mean and minimum platelet counts (and possibly mean and minimum hemoglobin levels) were anticipated to be lower in placebo treated patients than in malarone treated patients at the withdrawal visit (owing to the effects of malaria). This was confirmed for platelet counts but not for hemoglobin as shown in the following two tables.
Table 52: Platelet counts for Malarone and placebo treated patients

Platelets (10**9/L)

Visit	Statistic	Placebo	Malarone
Screening	N	140	125
	Mean	238	233
	Std.Dev.	76.3	75.0
	Median	234	226
	Minimum		
	Maximum		
	H/L est.		-6
	H/L 95% CI		(-24,13)
Week 6	N	129	122
	Mean	242	246
	Std.Dev.	81.8	78.1
	Median	239	248
	Minimum		
	Maximum		
	H/L est.		4
	H/L 95% CI		(-16,23)
Week 12	N	112	115
	Mean	254	268
	Std.Dev.	83.4	76.5
	Median	243	267
	Minimum		
	Maximum		
	H/L est.		16
	H/L 95% CI		(-4,37)
Withdrawal	N	34	3
	Mean	206	327
	Std.Dev.	68.0	56.0
	Median	211	296
	Minimum		
	Maximum		
	H/L est.		126
	H/L 95% CI		(50,211)

Table 53: Hemoglobin levels for Malarone and placebo treated patients

Hemoglobin (g/dL)

Visit	Statistic	Placebo	Malarone
Screening	N	140	125
	Mean	10.6	10.5
	Std.Dev.	1.25	0.99
	Median	10.4	10.4
	Minimum		
	Maximum		
	H/L est.		0
	H/L 95% CI		(-0.2,0.3)
Week 6	N	129	122
	Mean	11.3	11.2
	Std.Dev.	1.07	1.18
	Median	11.4	11.1
	Minimum		
	Maximum		
	H/L est.		-0.2
	H/L 95% CI		(-0.4,0.1)
Week 12	N	112	115
	Mean	11.3	11.2
	Std.Dev.	0.95	1.01
	Median	11.4	11.1
	Minimum		
	Maximum		
	H/L est.		-0.2
	H/L 95% CI		(-0.4,0.1)
Withdrawal	N	34	3
	Mean	11.2	10.7
	Std.Dev.	1.10	1.42
	Median	11.4	10.2
	Minimum		
	Maximum		
	H/L est.		-0.7
	H/L 95% CI		(-2.0,1.0)

MO comment: Vomiting was identified as a significant adverse event from curative doses of Malarone in pediatric patients. There were no significant abnormalities identified on routine laboratory examinations in pediatric patients receiving prophylactic doses of malarone.

Clinical pharmacology results:
Drug plasma levels were measured for atovaquone, proguanil and cycloguanil at week 6 and week 12 as shown in the table below.

Table 54: Plasma drug levels of atovaquone, proguanil and cycloguanil at week 6 and week 12.

	Week 6			Week 12		
	ATQ (µg/mL)	PGN (ng/mL)	CGN (ng/mL)	ATG (µg/mL)	PGN (ng/mL)	CGN (ng/mL)
Mean (SD[a])	3.5 (1.9)	18.8 (10.7)	9.1 (4.1)	2.6 (1.4)	21.3 (21.1)	8.9 (4.1)
Median	3.2	15.5	8.8	2.3	14.4	7.5
Range						

Abbreviations: ATQ = atovaquone; PGN = proguanil hydrochloride; CGN = cycloguanil

[a] Standard Deviation

MO comment: Ranges for proguanil appeared broader than the ranges for atovaquone. The shorter half-life of atovaquone may have contributed to this finding.

MO comment: This study in older children (>5years) demonstrated good per-protocol efficacy of Malarone against *P falciparum* over a 12 week period. Chloroquine resistance was not addressed in this study. The patients in this study probably had substantial malarial immunity. This was suggested by the high prevalence of malaria at screening (36%), and high rates of splenomegaly (9%). Thus this population may differ in response when compared to malaria naïve children. Malarone was not tested in children below five years of age. Used in therapeutic doses as a radical cure, malarone was associated with a high incidence of vomiting (43/319). This was more common in the larger children receiving higher doses. In recommended prophylactic doses, Malarone was well-tolerated.

MALB 2002

Title of study:
Prophylactic antimalarial activity of atovaquone in volunteers challenged with *Plasmodium falciparum*.

Setting: This volunteer challenge study was conducted at the Johns Hopkins School of Medicine in Baltimore on healthy American volunteers between Sept 1996 and October 1997.

Study objective: To evaluate the causal prophylactic activity of orally administered atovaquone in subjects challenged with *P faciparum* infection

Rationale: Two dosing regimens of atovaquone were selected and administered in a manner to reflect causal prophylaxis, that is they were designed to provide therapeutic levels until the end of the hepatic phase, but not into the erythrocytic phase of the infection. Blood was taken for parasite culture at day 7 to detect prepatent erythrocytic forms that might have escaped causal prophylaxis. Extended follow-up allowed for the possibility of delayed patency resulting from sub-therapeutic suppressive levels of drug in the post-hepatic phase.

Study design:
The prophylactic efficacy of Atovaquone was examined in a double-blind placebo-controlled study on healthy volunteers challenged with a chloroquine sensitive laboratory strain of *P falciparum*. The prophylactic efficacy, pharmacokinetics and safety of atovaquone were investigated in this setting.

Outpatient volunteers were screened over a period of approximately 2 months. Recruits were subjected to prophylaxis and challenged over a period of seven days and were then followed up for a period of 3 months.
Three treatment groups were included:

a) high dose atovaquone (750mg once daily for 7 days commencing the day before challenge),
b) low dose atovaquone (250mg of drug the day before challenge),
c) placebo

The NF54 strain of chloroquine sensitive *P falciparum* was used to infect *Anopheles stephensi* mosquitoes. Efficacy was assessed by examining the peripheral blood for parasites using four independent detection methods.

Volunteers were sought by advertisement .

Inclusion criteria 18-45 years of age

- Within 25% of ideal body weight
- Demonstrated understanding of malaria and of the study
- Able to provided a responsible person to assist with follow-up
- Blood type A or O that supported the growth of *P falciparum in vitro*

Exclusion criteria:

- History of malaria or residence in a malaria area
- Glucose-6-P-dehydrogenase deficiency or sickle cell trait or disease
- Clinically significant medical problems on history, physical examination or laboratory tests
- Chronic use of any drugs
- Women of childbearing potential
- Allergy to mosquito bites
- Intolerance of antimalarial drugs
- Use of any anti-infective drug or quinine-containing drink during the week before atovaquone administration

Administration of medication:
The day prior to challenge, study drug was given with a breakfast containing 0.7 gm fat.

This low level of fat intake was designed to ensure that plasma levels in the low dose arm remained below therapeutic levels at day six when erythrocytic forms normally appear.
On days 0-5 study drug was given daily with 11.1g fat
Patients in the atovaquone groups received either one tablet of atovaquone and two placebo tablets or three atovaquone tablets on day -1. Three tablets of atovaquone or placebo were administered daily for the remaining 6 days. A summary of dosing is shown below.

Table 55: Dosage regimens

Study day	-1	0	1	2	3	4	5
Dose No.	1	2	3	4	5	6	7
Regimen		challenge ⇓					
High Dose	D	D	D	D	D	D	D
Low Dose	d	p	p	p	p	p	p
Placebo	p	p	p	p	p	p	p

D= 750 mg atovaquone; d= 250 mg atovaquone; p= placebo

MO comment: Several differences between this experimental population and the general population likely to require malaria prophylaxis were identified. Weight, age and blood type were restricted. Concurrent medications were not permitted. The active drug did not contain proguanil. It was administered under ideal conditions with controlled fat intake. The malaria challenge was restricted to a single strain of chloroquine sensitive parasites.

Challenge:
Colony reared *Anopheles stephensi* mosquitoes were infected with the NF54 strain of *P falciparum* by pre-feeding on co-cultured gametocytes. Infection of the batch of mosquitoes was confirmed prior to infection of patients and individual mosquitoes biting volunteers were dissected to confirm infection in these. Five mosquitoes were used on each patient to maximize the chances of biting and infecting.
NF54 is a well-characterized strain of chloroquine sensitive *P falciparum*. IC50 values for atovaquone are 0.19 ng/ml and for chloroquine are 2.3 ng/ml.

The sponsor planned to recruit 19 volunteers, allowing at least 16 volunteers, (12 drug and 4 placebo) to be challenged.
All concurrent medications taken during the study period were recorded

Recruitment:
Volunteers were sought by advertisement and initially screened by phone. Potential recruits were then seen at several screening visits to acquaint them with the protocol and to evaluate reliability.
Individuals were screened with routine hematology and clinical chemistry tests. Blood grouping was performed, G-6-P-D and hemoglobin S were measured. Serology was performed for HIV and hepatitis B and C.
Monitoring: Malaria PCR was performed on day 1 and day 5.
Atovaquone levels were to be measured on day –1, 0, 1, 3, 5, 7, 9, 11, 14, 17, 21, and at the time of parasitemia.

Patient visits (See schedule below):
- Daily from day 6 to 21
- Every other day from day 23-33
- Weekly weeks 6-12
- Once 12 months after challenge

At each visit, blood was drawn for Quantitative Buffy Coat (QBC), thick smear and malaria PCR. Positive QBC's and positive smears were confirmed by two observers. *P falciparum* culture was performed on days 7, 8, and at the time malaria presented itself. An initial positive result for the QBC would lead to initiation of treatment.

Table 56: Schedule of study visits

	Procedure											
	Clinical Eval'n[a]	Heme[b]	Lytes	Chem Panel[c]	Other	Dose[d]	Challenge	QBC and Smear	PCR	Culture[e]	Biopsy	Drug Levels
Screening	X	X	X	X	X[f]							
-2 wk	X	X	X	X	X[g]							
Treatment and Challenge												
-1	X			X		A/P			X			X[h]
0	X					A/P	X					X[h]
1	X					A/P			X			X
2	X					A/P						
3	X					A/P						X
4	X					A/P						
5	X					A/P			X			X
Follow-up												
6	X				X[i]			X	X		X	
7	X	X	X	X				X	X	X	X	X
8	X							X	X	X	X	
9	X							X	X			X
10	X							X	X			
11	X							X	X			X
12-13	X							X	X			
(Patient)	X	X	X	X		CQ		X	X	X[j]	X	X
14	X	X	X	X				X	X			X
15-16	X							X	X			
17	X							X	X			X
18-20	X							X	X			
21	X	X	X	X				X	X			X
Alternate days D22-35	X							X				
Weekly wks 6-12	X							X				

[a] Complete history and physical at screening, otherwise non-directed interview for symptoms, and oral temperature.
[b] Hemoglobin, hematocrit, white cell count and differential, platelet count, PT, PTT
[c] AST, ALT, total bilirubin, albumin, creatinine
[d] A/P = atovaquone or placebo; CQ = chloroquine
[e] AST, ALT, blood for malaria culture
[f] ABO and Rh, G6PD screen, HgbS screen, HIV, Hepatitis BsAg and CAb, urinalysis, malaria screen
[g] Malaria lecture and exam; written consent; HCG for women
[h] Blood samples just prior to dosing
[i] Random urine for drug screen
[j] Sensitivity to atovaquone

MO comment: The following definitions were used to evaluate outcome:
Primary endpoint: A positive PCR and/or QBC and/or culture and /or smear for *P falciparum*.
Evaluable failure: A patient compliant with medication, developing the primary endpoint up to 12 weeks following challenge where concurrent medications with antimalarial activity were not taken

Evaluable success: A patient compliant with medication, with negative tests for the primary endpoint at all visits till week 12, with sequential blood tests available at least weekly during the study, where concurrent medications with antimalarial activity were not taken.
Unevaluable: patients taking concurrent medications with antimalarial activity, those non-compliant with medication, and those with less than one malaria blood investigation per week (including patients lost to follow up).

Adverse events: These included any untoward medical occurrence regardless of the relationship to drug. Serious adverse events included fatal events, life threatening events, permanently disabling events, those causing prolonged hospitalization, congenital anomalies, cancer and overdoses.

Results:
One hundred and eighty-three subjects responded to advertisements to participate in the study. Of these, 152 failed the telephone interview, 7 failed laboratory tests, one was overweight, three chose not to continue and one failed the malaria quiz. The remaining 19 were enrolled of which 16 proceeded to malaria challenge.
Treatment assignment:
Nineteen volunteers were randomized in a single block; 7 to receive high dose atovaquone, 7 to receive low dose atovaquone and 5 to receive placebo. After the first dose of drug but before challenge three subjects were withdrawn.

Table 57: Treatment groups

	Total recruited 19		
	High dose atovaquone	Low dose atovaquone	Placebo
	7	7	5
Withdrawn before challenge	1	1	1

Demographic characteristics: The majority of the subjects were young white males as shown below.

Table 58: demographic characteristics of study volunteers

Characteristic	Placebo n = 5	Atovaquone 250 mg x1 n = 7	Atovaquone 750 mg/ day x7 n = 7
Male/Female	4/1	7/0	7/0
Age (yrs)			
Mean (SD)	29 (7.5)	31 (9.0)	30 (5.7)
Range	24–42	22–44	23–40
Weight (kg)			
Mean (SD)	77 (7.4)	81 (9.8)	81 (7.4)
Range	69–88	75–100	70–91
Height (cm)			
Mean (SD)	176 (9.9)	184 (6.2)	182 (5.2)
Range	162–186	172–191	174–188

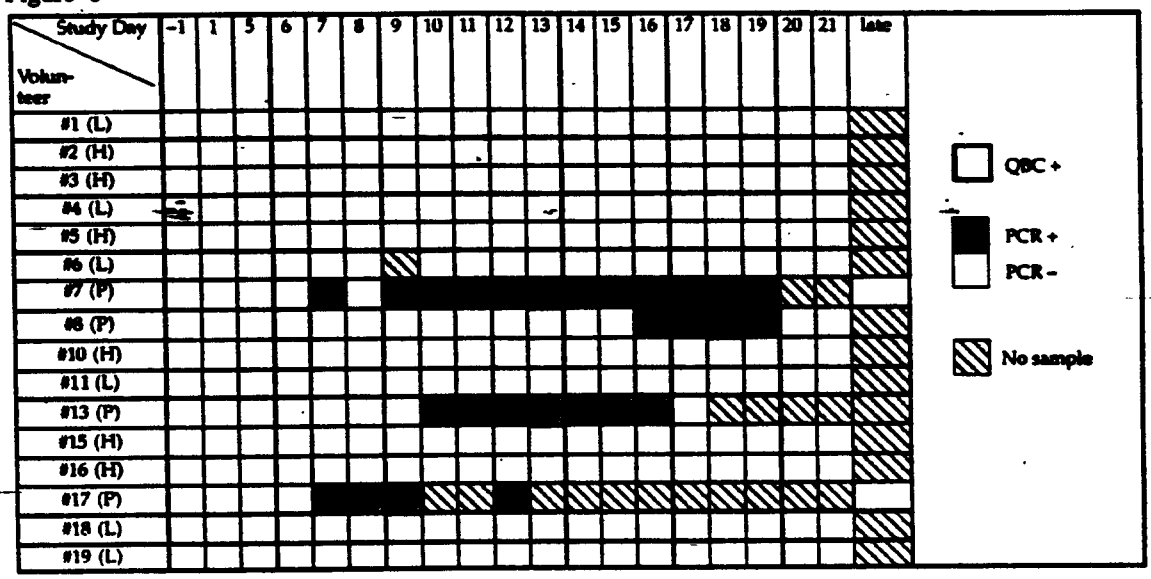
Subject No.'s 9, 12 and 14 were withdrawn from the study prior to challenge.

Compliance on the study was recorded as 99.5%. Only three study visits were missed, all by the same volunteer who was then admitted for supervision. Average bite frequencies for placebo, low dose and high dose atovaquone groups were 5.5, 5.8 and 5.3 bites respectively.

The infection of the mosquitos was recorded using a mean salivary gland index. For the respective study arms, the mean index was 3.5, 3.2, and 3.4. (For methodology see: Collins et al. J Parasitol 1977;63:52-6)

Parasitemia was documented at various time points, either by PCR, QBC or thick smears as shown in the figure below.

Figure 8



H=high dose atovaquone, L = low dose atovaquone, P= placebo
Numbers in boxes indicate the number of days *in vitro* before cultures were judged positive.

All 4 placebo recipients developed malaria as confirmed by PCR, culture and QBC. (Cultures were done on days 7,8 and at the time the QBC become positive.) Surprisingly, none of the subjects was found to have visible parasites on thick smear. PCR was the first test to become positive, between 2 and 6 days prior to a positive QBC. All positive QBCs were confirmed by a positive malarial culture. Three of the four subjects were symptomatic at the time of the positive QBC. One never developed symptoms.

Thick smears and QBC remained negative for all drug-treated patients through 12 weeks of follow-up. None of these patients was reported to have taken any concurrent antimalarials.
The efficacy results are summarized below:

Table 59: Efficacy results according to treatment group

	placebo	Low dose atovaquone	High dose atovaquone
N	4	6	6
Evaluable successes	0	6	6
Evaluable failures	4	0	0
Success rate	0/4	6/6	6/6

PCR appears to have been a sensitive and specific technique with no false positives for detecting the single experimental isolate used in this study. Based on the PCR results, the pre-patent period for these experimental infections ranged between 7 and 16 days. Clinical and laboratory follow-up was continued on alternative days from days 23-33 and weekly for weeks 6-12 following challenge. This would have been sufficient to detect delayed parasitemias in the high dose prophylaxis arm.

At the time that malaria cultures were positive, all isolates were reported as atovaquone sensitive (IC_{50} 0.46-0.9 nM, see microbiology review for methods).

MO comment: According to the sponsor, atovaquone given as a 250mg dose 24 hours before challenge prevented experimental malaria in 6/6 volunteers supporting the causal prophylactic efficacy of this agent. On the basis of this information (admittedly limited to 6 study subjects infected with a chloroquine and atovaquone sensitive strain), it is unclear why the proposed prophylactic regimen in the label requires continuation of drug for seven days after leaving a malaria area.

Safety results

Exposure: Among the fourteen subjects receiving atovaquone in this study, six received 750mg daily for seven days, seven received a single dose of 250mg and one received a single dose of 750mg.

Symptoms of malaria in placebo treated patients:
Three of the four placebo recipients were symptomatic at the time of microscopic parasitemia. Abnormal findings included headache, myalgia, chills, sweats and fever (37.9C), thrombocytopenia in 2 subjects and leukopenia and proteinuria in 1 subject each.
One subject with confirmed malaria remained asymptomatic.

MO comment: The relative paucity of symptoms and modest temperature elevations probably reflect the benefits of very early intervention. There is no reason to suspect underlying immunity to malaria in these subjects.

Events of unusual frequency:

The most commonly reported adverse event regardless of causality was headache. Adverse events were more common in the high dose atovaquone group than the low dose or placebo groups.
Of the adverse events attributed to the drug, headache and nausea were most common as shown below.

Table 60: Adverse events possibly related to study drug occurring in >= 2% of subjects during prophylaxis

Adverse Event	Placebo n = 5	Atovaquone 250 mg x1 n = 7	Atovaquone 750 mg/ day x7 n = 7
Nausea	0	0	1 (14)
Headache	0	0	1 (14)

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

Overall, adverse events were reported in 15/19 participants. The majority of these adverse events were not attributed to medication as shown below:

Table 61: Summary of adverse events by attributability during the treatment and follow-up phase

Adverse Experience	Placebo N = 5		ATV 250 N = 7		ATV 750 N = 7		Placebo N = 5		ATV 250 N = 7		ATV 750 N = 7	
	n1	(%)	n1	(%)	n1	(%)	n2	(%)	n2	(%)	n2	(%)
Headache	0		0		1	(14)	4	(80)	3	(43)	5	(71)
Anemia	0		0		0		2	(40)	1	(14)	2	(29)
Infection ...	0		0		0		1	(20)	1	(14)	2	(29)
Rhinitis	0		0		0		1	(20)	0		2	(29)
Somnolence	0		0		0		0		0		2	(29)
Myalgia	0		0		0		3	(60)	1	(14)	1	(14)
Flu syndrome	0		0		0		0		1	(14)	1	(14)
Fever	0		0		0		2	(40)	0		1	(14)
Nausea	0		0		1	(14)	1	(20)	0		1	(14)
Leukopenia	0		0		0		1	(20)	0		1	(14)
Bilirubinemia	0		0		0		0		0		1	(14)
Dizziness	0		0		0		0		0		1	(14)
Hyperglycemia	0		0		0		0		0		1	(14)
Asthenia	0		0		0		1	(20)	1	(14)	0	
Pharyngitis	0		0		0		1	(20)	1	(14)	0	
Rash	0		0		0		0		1	(14)	0	
Chills	0		0		0		3	(60)	0		0	
Thrombocytopenia	0		0		0		2	(40)	0		0	
Sgot increase	1	(20)	0		0		1	(20)	0		0	
Albuminuria	0		0		0		1	(20)	0		0	
Depersonalization	0		0		0		1	(20)	0		0	
Diarrhea	0		0		0		1	(20)	0		0	
Dyspepsia	0		0		0		1	(20)	0		0	
Pain back	0		0		0		1	(20)	0		0	
Sgpt increase	0		0		0		1	(20)	0		0	
Sinusitis	0		0		0		1	(20)	0		0	
Sweat	0		0		0		1	(20)	0		0	
Non-grouped AEs	0		0		0		0		0		1	(14)
No. of subjects >=1 AE	1	(20)	0		2	(29)	4	(80)	4	(57)	7	(100)

N = Number of subjects with data on the database
n1 = Number of subjects reporting adverse experiences possibly attributable to the study drug
n2 = Number of subjects reporting adverse experiences irrespective of attributability
% = Percentage of subjects reporting adverse experiences

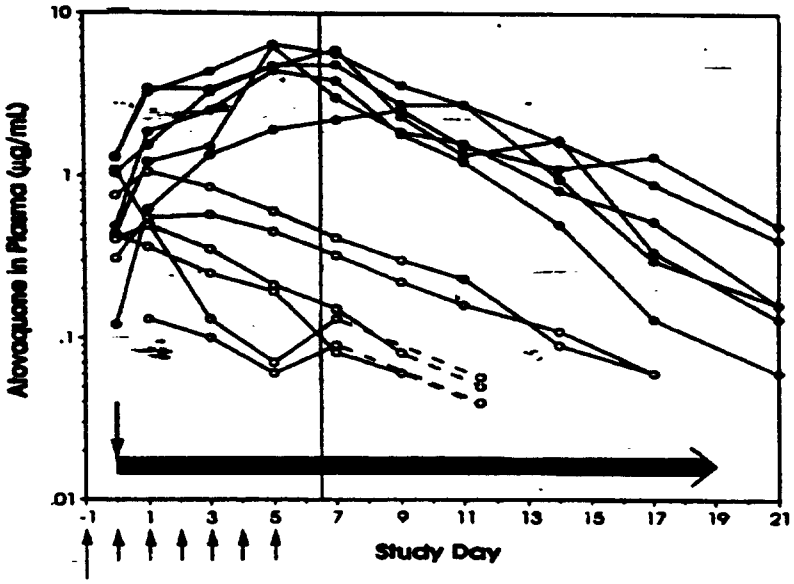
Events of unusual severity:
There were no deaths, serious or treatment-limiting adverse events during the period of study.

Laboratory abnormalities:
No significant treatment-emergent abnormalities were detected on routine hematology testing (RBC, Hb, PCV, WBC, platelets and differential counts) or routine clinical chemistry testing (AST, ALT, alkaline phosphatase, BUN, creatinine, electrolytes, glucose, albumin and prothrombin time).

MO comment: No safety issues were identified on the two study regimens (low and high dose atovaquone). The very small number of study subjects, pre-selected on the basis of excellent health and no concurrent medications is a limitation on the broader applicability of these data.

Clinical pharmacology results:
The figure below illustrates the clinical pharmacology of atovaquone in relation to the hepatic and erythrocytic phases of experimental infection.

Figure 9: Plasma levels of atovaquone according to low and high dose study regimens



Plasma Levels of Atovaquone Relative to the Earliest Appearance of Circulating Parasites.
At the indicated times plasma samples were collected for atovaquone determinations from subjects in the high (●) and low (○) dose groups. High dose data are depicted through day 21 only; dotted lines indicate extrapolated values, which fall below the lower limit of detection (0.05 µg/mL); coefficient of variation in the assay was ≤15%. All volunteers were challenged on day 0 (downward pointing arrow). Bar indicates site of ensuing infection, with the shortest prepatent period (6.5 days) followed by parasitemia. Large upward pointing arrow denotes single 250 mg dose in low dose regimen, or first 750 mg dose in high dose regimen; small arrows denote subsequent 750 mg doses in high dose regimen.

Low plasma levels were achieved in the low dose arm as shown in table 62

Table 62: Pharmacokinetic results for each subject

	KINETIC PARAMETER			
SUBJECT	$AUC_{0-6.5}$ (µg/day/mL)	$AUC_{6.5-11.5}$ (µg/day/mL)	C_{max} (µg/mL)	$T_{½}$ (day)
High Dose				
#2	18.7	10.6	6.23	3.8
#3	8.51	10.4	2.47	7.4
#5	18.4	11.0	4.34	2.3
#10	24.1	16.6	4.79	4.5
#15	29.5	19.5	6.40	2.6
#16	21.4	15.4	5.92	2.7
mean ± SD	20.1 ± 7.0	13.9 ± 3.8	5.03 ± 1.50	3.9 ± 1.9
Low Dose				
#1	1.77	0.48	1.08	ND
#4	0.56	0.33	0.13	ND
#6	1.67	0.31	0.43	3.1
#11	5.05	1.57	1.05	3.7
#18	3.17	1.17	0.57	4.3
#19	2.13	0.47	0.40	3.1
mean ± SD	2.39 ± 1.55	0.72 ± 0.52	0.61 ± 0.38	3.6 ± 0.6

[a] Plasma levels were drawn prior to each dose of drug/placebo; C_{max} therefore denotes peak concentration in the single (low) dose group, and highest trough concentration in the multiple (high) dose group.

ND denotes insufficient data to calculate.

MO comment on plasma drug levels: Subjects in the low dose arm demonstrated C_{max} plasma levels consistently below 1.08 ug/ml. In subject 4 this peak C_{max} was only 0.13 ug/ml with an AUC during the first 6.5 days of 0.56ug/day/ml; a value well below the 3.7-10.4ug/day/ml quoted to have failed eradicating erythrocytic infections in non-immune travellers (Chiodini et al J Antimicrob Chemother 1995;36:1073-8). This suggests that hepatic phase parasites are more susceptible to atovaquone than erythrocytic parasites, or perhaps that hepatic concentrations of the drug may exceed those in the blood. At the start of the erythrocytic phase in this study (day 6.5) AUC's for 2 low dose subjects still exceeded the lowest AUC seen in one of the low dose subjects at the beginning of the study. Some suppressive activity was presumably present in these two subjects during the erythrocytic phase.

MO concluding comment: This study showed that a single low dose of atovaquone 250mg taken 24 hours before experimental challenge with *P falciparum* was sufficient to protect all of six volunteers from developing disease. Higher and more prolonged doses were also effective. The prophylaxis was effective despite very low blood levels of the drug (well below those needed for treatment). On the basis of the presented data it is not clear whether this was due to greater susceptibility of hepatic forms than erythrocytic forms, higher drug levels in the liver than the blood or whether this single isolate used in the challenge had an unusually low MIC for the drug. Previous quoted studies have shown the rapid development of resistance in malaria treated with atovaquone alone. The sponsor

has suggested that the absence of emergent resistance in this study might be due to combined action on hepatic and erythrocytic stage parasites or to the low parasite burden.

The possibility that the single challenge strain was unusually susceptible to atovaquone (IC50 for NF54 0.19ng/ml) should be considered before the findings of this study can be more generally applied. In this submission two isolates from patients participating in study MALB3003 showed IC50's for atovaquone of 10.9nM (4ng/ml) and 2.7 nM (0.99ng/ml), respectively 21 and 5.2 times the IC50 of the challenge strain. The number of bites was also restricted to five per patient. In the field, larger numbers of bites and higher inocula may also have an impact on prophylactic efficacy.

Mechanisms of chloroquine resistance are diverse and may be as non-specific as calcium channel dependent pumps. The performance of atovaquone against isolates demonstrating this mechanism of drug resistance must be regarded as unproven. The claim that Malarone is active against chloroquine resistant malaria is obviously not supported by this study.

The study provides support for the causal prophylactic activity of atovaquone in this controlled setting, using a single strain of *P falciparum* malaria. The causal prophylactic activity of proguanil has not been tested in this study but quoted literature (Fairley NH. Trans R Soc Trop Med Hyg 1946, 40:105-62) indicates that Progaunil given at a dose of 10mg to 100mg as a single dose on days +3, +4 or +5 following challenge was 100% effective in protecting against experimental malaria. (Proguanil given as a single dose 3 hours before challenge or on days 6,7 or 8 following challenge was not reliably protective.) These historic data were obtained long before chloroquine resistance was documented, the endpoints were determined by less sensitive means (smears only) and the applicability of these data to currently prevalent isolates is unclear.

Integrated summary for safety: prophylaxis studies

Studies employing prophylactic and treatment doses of Malarone have provided two categories of safety data: high-dose short-term use and prolonged low-dose use. The studies using treatment doses are reviewed by Dr Meyerhoff while this section focuses on the prolonged low dose use of Malarone in prophylactic regimens.

Safety information for patients receiving prophylactic doses of Malarone was derived from four prophylactic studies. In these studies Malarone was administered at doses ranging from 250mg to 500mg daily in adults, and dosages for pediatric patients were calculated using weight to extrapolate from the adult 250mg dose. Study periods ranged between 10 and 12 weeks.

Three of the four studies incorporated a curative phase during which all patients received treatment dosages of Malarone for three days. Subjects who failed these treatment doses for reasons of drug intolerance were excluded from the safety population for prophylaxis. Hence the safety population (all individuals receiving at least one prophylactic dose of Malarone) was depleted of individuals reacting badly to initial treatment with Malarone.

The four prophylactic studies reviewed for safety enrolled 1009 patients. Safety data were available for 919 subjects who received either Malarone or placebo. The disposition of these patients is shown in table 63.

Table 63: Disposition of patients participating in Malarone prophylaxis studies.

Study Population	Prophylaxis	Number of Subjects
Adults n=654	ATQ + PRG – recommended prophylaxis dose[a]	381
	ATQ + PRG – other doses	67
	Placebo	206
Children n=265	ATQ + PRG – recommended prophylaxis dose[a]	125
	Placebo	140
Total for ATQ + PRG Prophylaxis at Recommended Dose[a]		**506**
Total for ATQ + PRG Prophylaxis at Other Doses		**67**
Total for Placebo		**346**
Total Prophylaxis Subjects		**919**

[a] Recommended prophylactic dose in adults is 250 mg atovaquone and 100 mg proguanil hydrochloride (1 MALARONE tablet) once daily. In children who are ≤ 40 kg, this dose is adjusted for body weight.

Population for safety:
The database included only subjects who received study medication and who either had adverse events or laboratory data on record.

Safety Data: The safety data collected included evaluations from physical examinations, vital signs, adverse experiences and hematology and clinical chemistry parameters

"Radical cure" safety data: Three of the four studies reviewed here for safety in prophylaxis incorporated a radical cure phase. During this phase all participants were treated with curative doses of Malarone for three days. Safety data from the radical cure phase of the studies best reflected safety concerns due to "treatment regimens" of Malarone rather than prophylactic regimens. Among adverse events reported for individuals

during radical cure, the following were reported in more than 2% of participating adults (see table 65 for details):
dyspepsia
dizziness,
gastritis,
vomiting,
headache,
nausea
abdominal pain
pruritis
asthenia
Among children receiving radical cure, events reported in more than 2% of participants included:
Abdominal pain
Vomiting,
Nausea
Headache.

One serious adverse event and 45 treatment limiting adverse events occurred in patients on "radical cure" and these individuals were excluded from the prophylaxis database.

The recommended adult prophylactic dose of Malarone 250mg/day was employed in three of the five studies, a dose of 500mg/day was also employed in one of these studies.

Drug exposure for each study is shown below.

Table 64: Allocated study drugs during prophylactic phase (ITT patients)

	Malarone 250qd	Malarone 500mg qd	Placebo	Pediatric dosing
MALB2001	70	67	68	0
MALB3001	136	0	138	0
MALB3002	175	0	0	0
MALB3003	0	0	140	124
Total	381	67	346	124

Exposure ranged between 10 and 12 weeks

Of the 448 adults receiving prophylaxis with Malarone, 79% were male. Of the 124 children receiving prophylactic Malarone, 52%were male. Most of the study participants were black.

Table 65: Demographics of patients included in the safety population

Subject Population	Number of Subjects	Gender		Race		Mean Age or Range of Mean Ages (yr)	Mean Body Weight or Range of Mean Body Weights (kg)
		M	F	B	W		
Adults	448	356 (79%)	92 (21%)	402 (90%)	46 (10%)	31	66
Children and Adolescents	125	65 (52%)	60 (48%)	125 (100%)	0	9	29
All Subjects	573	421 (73%)	152 (27%)	527 (92%)	46 (8%)	9–31	29–66

Adverse events:

Adverse experience reporting included spontaneously developing adverse experiences, intercurrent illnesses including malaria and its symptoms, and existing medical conditions which worsened. The experiences reported by the sponsor in this section were confined to those occurring during the prophylactic phase.

Adverse experiences such as malaria (which were not accommodated in the COSTART list of terms) were classified in the "ungrouped" category.

Pooling of adverse experience data:
Adverse experiences occurring in protocols MALB3001, 2001 and 3002 were pooled whereas adverse experience data for pediatric subjects was separately presented.

Serious adverse experiences included those that were fatal, immediately life-threatening, permanently or significantly disabling or that required prolonged hospitalization. Congenital anomalies, malignancies and overdoses were included.

Adverse Experiences reported during chemosuppression:
During the three prophylactic studies of Malarone in adults, (MALB2001, MALB3001, MalB3002) involving 654 subjects, adverse events were reported in 58% (379).

Events of unusual frequency:

The table below summarizes the adverse events occurring in more then 2% of patients in each dosing category. All adverse events and drug-related adverse events are listed for each of four treatment regimens; placebo, Malarone used in placebo controlled trials (A+P:C), Malarone used in controlled and uncontrolled studies (A+P:U) and Malarone administered at 500mg QD (twice the recommended prophylactic dose) (A+Px2:C).

Table 66: All adverse events and drug attributable adverse events during adult prophylactic studies

Adverse Experience	Placebo N = 206		A+P:C N = 206		A+P:C+U N = 381		A+Px2:C N = 67		Placebo N = 206		A+P:C N = 206		A+P:C+U N = 381		A+Px2:C N = 67	
	n1	(%)	n1	(%)	n1	(%)	n1	(%)	n2	(%)	n2	(%)	n2	(%)	n2	(%)
Headache	14	(7)	6	(3)	18	(5)	0		56	(27)	45	(22)	63	(17)	29	(43)
Myalgia	0		0		0		0		23	(11)	24	(12)	25	(7)	23	(34)
Abdominal pain	11	(5)	9	(4)	13	(3)	3	(4)	21	(10)	18	(9)	24	(6)	9	(13)
Pain	2	(<1)	1	(<1)	3	(<1)	0		14	(7)	15	(7)	21	(6)	2	(3)
Upper respiratory infection	8		0		0		0		15	(7)	17	(8)	20	(5)	17	(25)
Back pain	0		0		0		0		8	(4)	16	(8)	17	(4)	8	(12)
Cough increased	1	(<1)	1	(<1)	4	(1)	0		17	(8)	12	(6)	16	(4)	6	(9)
Diarrhea	7	(3)	4	(2)	5	(1)	3	(4)	16	(8)	12	(6)	16	(4)	8	(12)
Flu syndrome	0		0		0		0		3	(1)	4	(2)	15	(4)	2	(3)
Pruritus	2	(<1)	3	(1)	3	(<1)	0		6	(3)	13	(6)	13	(3)	10	(15)
Accidental injury	0		0		0		0		4	(2)	9	(4)	13	(3)	2	(3)
Fever	3	(1)	0		0		0		26	(13)	11	(5)	12	(3)	1	(1)
Rash	0		1	(<1)	2	(<1)	0		6	(3)	10	(5)	12	(3)	2	(3)
Infection	0		0		0		0		3	(1)	4	(2)	10	(3)	1	(1)
Conjunctivitis	0		0		0		0		7	(3)	9	(4)	9	(2)	6	(9)
Gastritis	5	(2)	6	(3)	7	(2)	5	(7)	7	(3)	7	(3)	9	(2)	7	(10)
Chest pain	0		1	(<1)	1	(<1)	0		2	(<1)	8	(4)	8	(2)	3	(4)
Dyspepsia	9	(4)	4	(2)	4	(1)	8	(12)	11	(5)	6	(3)	7	(2)	12	(18)
Sore throat	1	(<1)	1	(<1)	1	(<1)	0		6	(3)	6	(3)	7	(2)	8	(12)
Pharyngitis	0		0		0		0		7	(3)	4	(2)	7	(2)	11	(16)
Asthenia	1	(<1)	0		0		0		10	(5)	5	(2)	6	(2)	5	(7)
Dizziness	1	(<1)	2	(<1)	3	(<1)	1	(1)	5	(2)	5	(2)	6	(2)	2	(3)
Eye pain	0		0		1	(<1)	0		2	(<1)	3	(1)	6	(2)	3	(4)
Rhinitis	0		0		0		0		9	(4)	4	(2)	5	(1)	0	
Urinary tract infection	0		0		0		0		4	(2)	4	(2)	4	(1)	1	(1)
Constipation	0		0		0		0		0		4	(2)	4	(1)	3	(4)
Arthralgia	1	(<1)	0		0		0		10	(5)	3	(1)	4	(1)	3	(4)
Malaise	1	(<1)	0		0		0		6	(3)	3	(1)	4	(1)	0	
Dysuria	0		0		0		0		1	(<1)	3	(1)	4	(1)	0	
Bronchitis	0		1	(<1)	1	(<1)	0		0		2	(<1)	4	(1)	0	
Vomiting	1	(<1)	1	(<1)	1	(<1)	1	(1)	4	(2)	3	(1)	3	(<1)	1	(1)
Anorexia	3	(1)	1	(<1)	1	(<1)	3	(4)	3	(1)	3	(1)	3	(<1)	7	(10)
Neck pain	0		1	(<1)	1	(<1)	0		2	(<1)	3	(1)	3	(<1)	0	
Furunculosis	0		0		0		0		4	(2)	2	(<1)	3	(<1)	1	(1)
Cellulitis	0		0		0		0		2	(<1)	2	(<1)	3	(<1)	2	(3)
Ecchymosis	0		0		0		0		0		2	(<1)	3	(<1)	0	
Nausea	3	(1)	0		2	(<1)	2	(3)	5	(2)	1	(<1)	3	(<1)	3	(4)
Skin benign neoplasm	0		0		0		0		0		1	(<1)	3	(<1)	0	

N = Number of subjects with data on the database
n1 = Number of subjects reporting adverse experiences possibly attributable to the study drug
n2 = Number of subjects reporting adverse experiences irrespective of attributability
% = Percentage of subjects reporting adverse experiences

Adverse Experience	Placebo N = 206		A+P:C N = 206		A+P:C+U N = 381		A+Pm2:C N = 67		Placebo N = 206		A+P:C N = 206		A+P:C+U N = 381		A+Pm2:C N = 67	
	n1	(%)	n1	(%)	n1	(%)	n1	(%)	n2	(%)	n2	(%)	n2	(%)	n2	(%)
Skin disorder	0		0		1	(<1)	0		0		0		3	(<1)	0	
Acne	0		0		1	(<1)	0		0		0		3	(<1)	0	
Gingivitis	0		0		0		0		1	(<1)	2	(<1)	2	(<1)	3	(4)
Skin ulcer	0		0		0		0		1	(<1)	2	(<1)	2	(<1)	2	(3)
Face edema	0		0		0		0		0		2	(<1)	2	(<1)	1	(1)
Herpes zoster	0		0		0		0		0		2	(<1)	2	(<1)	0	
Fungal dermatitis	0		0		0		0		1	(<1)	1	(<1)	2	(<1)	3	(4)
Bone pain	0		0		0		0		1	(<1)	1	(<1)	2	(<1)	0	
Otitis externa	0		0		0		0		1	(<1)	1	(<1)	2	(<1)	1	(1)
Lymphadenopathy	0		0		0		0		1	(<1)	1	(<1)	2	(<1)	0	
Pain in extremity	0		0		1	(<1)	0		1	(<1)	0		2	(<1)	0	
Sinusitis	0		0		1	(<1)	0		0		0		2	(<1)	0	
Vesiculobullous rash	0		0		0		0		0		0		2	(<1)	0	
Edema	0		0		0		0		2	(<1)	1	(<1)	1	(<1)	0	
Otitis media	0		0		0		0		1	(<1)	1	(<1)	1	(<1)	0	
Liver function test abnormal	0		0		0		0		1	(<1)	1	(<1)	1	(<1)	2	(3)
Salpingitis	0		0		0		0		1	(<1)	1	(<1)	1	(<1)	2	(3)
Stomatitis	0		1	(<1)	1	(<1)	0		1	(<1)	1	(<1)	1	(<1)	0	
Urethritis	0		0		0		0		1	(<1)	1	(<1)	1	(<1)	0	
Ulcerative stomatitis	0		1	(<1)	1	(<1)	0		0		1	(<1)	1	(<1)	0	
Ear pain	0		0		0		0		0		1	(<1)	1	(<1)	0	
Hernia	0		0		0		0		0		1	(<1)	1	(<1)	0	
Joint disorder	0		0		0		0		0		1	(<1)	1	(<1)	0	
Kidney pain	0		0		0		0		0		1	(<1)	1	(<1)	0	
Myositis	0		0		0		0		0		1	(<1)	1	(<1)	0	
Psychosis	0		0		0		0		0		1	(<1)	1	(<1)	0	
Abscess	0		0		1	(<1)	0		2	(<1)	0		1	(<1)	1	(1)
Eye disorder	0		0		0		0		1	(<1)	0		1	(<1)	2	(3)
Urticaria	0		0		0		0		1	(<1)	0		1	(<1)	0	
Gum disorder	0		0		0		0		0		0		1	(<1)	1	(1)
Allergic reaction	0		0		1	(<1)	0		0		0		1	(<1)	0	
Increased appetite	0		0		1	(<1)	0		0		0		1	(<1)	0	
Liver tenderness	0		0		1	(<1)	0		0		0		1	(<1)	0	
Mouth ulceration	0		0		1	(<1)	0		0		0		1	(<1)	0	
Burning sensation skin	0		0		0		0		0		0		1	(<1)	0	
Myopathy	0		0		0		0		0		0		1	(<1)	0	
Peptic ulcer	0		0		0		0		0		0		1	(<1)	0	
Pericarditis	0		0		0		0		0		0		1	(<1)	0	

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n1 = Number of subjects reporting adverse experiences possibly attributable to the study drug
n2 = Number of subjects reporting adverse experiences irrespective of attributability
% = Percentage of subjects reporting adverse experiences

Adverse Experience	Placebo N = 206		A+P:C N = 206		A+P:C+U N = 381		A+Pm2:C N = 67		Placebo N = 206		A+P:C N = 206		A+P:C+U N = 381		A+Pm2:C N = 67	
	n1	(%)	n1	(%)	n1	(%)	n1	(%)	n2	(%)	n2	(%)	n2	(%)	n2	(%)
Tenosynovitis	0		0		0		0		0		0		1	(<1)	0	
Urinary incontinence	0		0		0		0		0		0		1	(<1)	0	
Ear disorder	0		0		0		0		3	(1)	0		0		0	
Sweating increased	0		0		0		0		3	(1)	0		0		0	
Asthma	0		0		0		0		2	(<1)	0		0		1	(1)
Pneumonia	0		0		0		0		2	(<1)	0		0		1	(1)
Dyspnea	0		0		0		0		2	(<1)	0		0		0	
Glossitis	1	(<1)	0		0		1	(1)	1	(<1)	0		0		1	(1)
Arthritis	0		0		0		0		1	(<1)	0		0		0	
Chills	0		0		0		0		1	(<1)	0		0		0	
Dysmenorrhea	0		0		0		0		1	(<1)	0		0		0	
Esophagitis	0		0		0		0		1	(<1)	0		0		0	
Hematuria	0		0		0		0		1	(<1)	0		0		0	
Hiccup	0		0		0		0		1	(<1)	0		0		0	
Leukorrhea	0		0		0		0		1	(<1)	0		0		0	
Myasthenia	0		0		0		0		1	(<1)	0		0		0	
Neurosis	0		0		0		0		1	(<1)	0		0		0	
Paresthesia	0		0		0		0		1	(<1)	0		0		0	
Pelvic pain	0		0		0		0		1	(<1)	0		0		0	
Sputum increased	0		0		0		0		1	(<1)	0		0		0	
Tooth disorder	0		0		0		0		1	(<1)	0		0		0	
Vaginal hemorrhage	0		0		0		0		1	(<1)	0		0		0	
Muscle cramps	0		0		0		0		0		0		0		2	(3)
Creatinine increased	0		0		0		0		0		0		0		1	(1)
Insomnia	0		0		0		0		0		0		0		1	(1)
Nasal septum disorder	0		0		0		0		0		0		0		1	(1)
Sepsis	0		0		0		0		0		0		0		1	(1)
Sore mouth	0		0		0		0		0		0		0		1	(1)
Non-grouped AEs	24	(12)	0		0		0		29	(14)	7	(3)	10	(3)	3	(4)
No. of subjects >=1 AE	65	(32)	35	(17)	64	(17)	21	(31)	133	(65)	112	(54)	187	(49)	59	(88)

N = Number of subjects with data on the database
n1 = Number of subjects reporting adverse experiences possibly attributable to the study drug
n2 = Number of subjects reporting adverse experiences irrespective of attributability
% = Percentage of subjects reporting adverse experiences

Headache was the most commonly reported adverse event, attributed to drug in 3 to 5% of subjects. A high incidence of headache (43%), not attributed to drug was seen in the 67 patients on high dose Malarone. As a group, gastro-intestinal symptoms were commonly reported, including abdominal pain (attributed to drug in 3-5% though no different from placebo), diarrhea, gastritis, and dyspepsia.
"Non grouped" adverse events included all diagnoses of malaria.

MO comment: Symptoms occurring during malaria include headache, nausea, diarrhea, fever and these symptoms would account for high reporting rates in the placebo treated patients. In this sense, placebo was unhelpful in illuminating these specific adverse events as drug-related.

The five most common adverse events are shown below.

Table 67: Five most commonly reported adverse experiences during prophylaxis (both drug related and unrelated):

Adverse Experience	Percentage of Adults with Common Adverse Experiences During Prophylaxis Phases of Studies MALR2001, MALR3001 and MALR3002								
	MALR2001			MALR3001		MALR3002	Placebo-Controlled		All studies
	Pbo n=68	A+P n=70	A+Px2 n=67	Pbo n=138	A+P n=136	A+P n=175	Pbo n=206	A+P n=206	A+P n=381
Headache	41	37	43	20	14	10	27	22	17
Myalgia	34	34	36	0	0	<1	11	12	7
Abdominal Pain	10	16	13	10	5	3	10	9	6
URI	18	23	25	2	<1	2	7	8	5
Back Pain	9	19	12	1	2	<1	4	8	4
At least one AE	96	84	88	51	39	43	66	54	49

When only drug-attributed events were considered, gastro-intestinal complaints predominated

Table 68: Drug attributed adverse events in adults:

Adverse Experience	Percentage of Adults with Common Attributable Adverse Experiences During Prophylaxis Phases of Studies MALR2001, MALR3001, and MALR3002								
	MALR2001			MALR3001		MALR3002	Placebo-Controlled		All studies
	Pbo n=68	A+P n=70	A+Px2 n=67	Pbo n=138	A+P n=136	A+P n=175	Pbo n=206	A+P n=206	A+P n=381
Abdominal Pain	6	7	4	5	3	2	5	4	3
Dyspepsia	13	6	12	0	0	0	4	2	1
Gastritis	7	9	7	0	0	<1	2	3	2
Headache	3	0	0	9	4	7	7	3	5
Diarrhea	4	3	4	3	1	<1	3	2	1
At least one AE	54	26	31	20	13	17	32	17	17

Prophylaxis in children:
Adverse events were reported in 61% of the 265 children participating in the prophylaxis study as shown below:
Table 69: Six most common adverse event in pediatric subjects (drug-related and unrelated).

Event	Percentage of Children and Adolescents with Common Adverse Experience During Prophylaxis Phase of Study MALR3003									
	11–20 kg		>20–30 kg		>30–40 kg		>40 kg		Total	
	Pbo n=40	A+P n=32	Pbo n=39	A+P n=36	Pbo n=30	A+P n=26	Pbo n=35	A+P n=26	Pbo n=140	A+P n=125
Abdominal Pain	23	38	26	36	43	23	29	31	29	33
Headache	10	14	9	17	33	15	37	35	21	19
Flu Syndrome	3	8	0	8	7	12	17	8	6	9
Vomiting	10	5	6	8	10	8	0	8	6	7
Increase Cough	8	11	0	8	17	12	6	4	9	9
Fever	18	8	0	6	13	0	11	8	11	6
At least one AE	58	70	51	58	77	46	66	62	62	60

Most commonly reported drug-related events reflected the pattern above, though complaints presumbly due to intercurrent upper repiratory tract infections (cough and "flu symptoms") are absent as shown below.

Table 70: Four most common drug-related adverse events in pediatric subjects:

Event	Percentage of Children and Adolescents with Common Attributable Adverse Experience During Prophylaxis Phase of Study MALB3003									
	11–20 kg		>20–30 kg		>30–40 kg		>40 kg		Total	
	Pbo n=40	A+P n=37	Pbo n=35	A+P n=36	Pbo n=30	A+P n=26	Pbo n=35	A+P n=26	Pbo n=140	A+P n=125
Abdominal Pain	20	35	26	36	43	23	29	27	29	31
Headache	3	8	3	11	30	12	23	27	14	14
Vomiting	10	5	6	8	7	8	0	8	6	7
Nausea	0	0	0	0	3	0	0	4	<1	<1
At least one AE	28	43	34	44	60	31	46	46	41	42

Adverse events during follow-up:
Upon completion of prophylactic regimens, study subjects were followed from 2 to 4 weeks after stopping study medication. Data from the follow-up period did not suggest delayed toxicity for Malarone.
Three of 448 adults reported adverse events possibly related to study medication in the follow-up period. These included headache, increased cough, abdominal pain and vomiting. Adverse events were not observed in any of the children during the follow-up period.

Adverse events related to population subgroups:
Gender
Seventy-nine percent of the 356 adults in Malarone prophylaxis studies were male. Despite the smaller number of women, women were more likely to report adverse events than men (59% vs 47%). Abdominal pain was reported in 8% of women and 3% of men, gastritis in 5% and 1%, dizziness in 3% and<1%, headache in 8% and 4%, and diarrhea and dyspepsia in 2% and <1% of women and men respectively. In the pediatric study, drug-related adverse events were equally frequent in girls (42%) and boys (40%). Individual adverse events commonly reported in the pediatric prophylaxis study included abdominal pain (28% of boys and 35% of girls), headache (14% of boys and 13% of girls), vomiting (6% of girls and 8% of boys) and nausea (2% of girls).
Race
All patients in the prophylaxis studies were black except for 46 white subjects in the uncontrolled South African study. These white subjects represented 12% of the 335 patients in the pooled cohort of patients treated with the recommended prophylactic dose of Malarone. Overall, drug-related events were reported in 16% of black subjects and 2% of white subjects. Individual adverse events commonly reported included headache (3% blacks and 15% whites), abdominal pain (4% blacks, 0 whites), and gastritis (2% blacks, 2% whites.) Only headache appeared unequally distributed for race, though the small proportion of white patients may make this conclusion unreliable.

Age
The sponsor examined adverse event reports for patients aged <=30 years and >30 years. The information was derived from the three adult prophylaxis studies, MALB2001, MALB3001 and MALB3002. The most commonly reported adverse events are shown below.

Table 71: Drug-attributed adverse events according to age group

	<=30 yrs (n=278)	>30 yrs (n=170)
Headache	17%	16%
Myalgia	6%	8%
Upper respiratory tract infection	4%	7%

MO comment: No significant differences were evident in adverse event rates for these two age groups. Small numbers of patients and the fact that the extremes of age were not examined limits the value of this data.

Events of unusual severity:
No deaths were reported during any of the prophylaxis studies.

Eight serious adverse events were reported during the prophylaxis studies. None of these was attributed to Malarone. The details of these patients are shown below.

Table 72: Summary of serious adverse events during prophylaxis

Study	Subject Number	Age, Gender, Race	Adverse Event	Frequency	Severity	Relationship	Treatment Group
MALB3001	[redacted]	36, male, black	Malaria	Single episode	Moderate	Possible	Placebo
	47	33, male, black	Infected skin ulcer (worsened)	Single episode	Moderate	Unrelated	Placebo
	118	39, female, black	Complicated cellulitis	Single episode	Severe	Unrelated	250 mg atovaquone/ 100 mg proguanil
	163	55, male, black	Dysentery	Single episode	Severe	Unrelated	Placebo
	183	18, female, black	Abdominal pain	Intermittent	Severe	Possible	1000 mg atovaquone/ 400 mg proguanil (Radical Cure Phase)
			Vomiting	Intermittent	Moderate	Possible	1000 mg atovaquone/ 400 mg proguanil (Radical Cure Phase)
MALB3001	1505	49, female, black	Pneumonia	Single episode	Severe	Not a reasonable possibility	Placebo
	1545	38, female, black	Bronchopneumonia	Single episode	Severe	Not a reasonable possibility	Placebo
MALB3002	737	23, male, black	Malaria	Single episode	Mild	Unrelated	250 mg atovaquone/ 100 mg proguanil
MALB3003	None						

Only two of these events occurred in patients randomized to the Malarone treatment arm. In one of these cases the adverse event was cellulitis, not considered related to study drug. In the second the adverse event was malaria and was not considered drug-related. An 18 year old female, treated first with a "radical cure" regimen was randomized to daily placebo for prophylaxis. Two days into the prophylaxis phase she presented with severe abdominal pain and vomiting. These symptoms were probably not related to the study drug since her last dose of Malarone was given two days before the onset of her adverse event.

Treatment limiting adverse events:
These were defined as events causing the patient to stop medication and withdraw from the study.
Treatment limiting events during the "radical cure" phase (where treatment doses of Malarone were used) were common in the pediatric study. Forty-three of 319 (13.5%) pediatric patients given radical curative doses of Malarone were withdrawn for vomiting or abdominal pain
Treatment limiting adverse events during the prophylaxis phase were less common and are described in the table below:

Table 73: Treatment limiting adverse events in chemoprophylaxis phase

	Malarone	placebo	Adverse event	Treatment related
MALB2001		22	Malaria	No
MALB3001		1	Genital sores	No
MALB3002	2		Headache	Yes
	1		Nausea & dizziness	Yes
	1		STD	No
	1		Flu syndrome	No
	1		Malaria	No
MALB3003		1	malaria	No
	1		Vomiting	No
Total	7	24		

Overall premature discontinuations of Malarone due to treatment related adverse events occurred in 3/381 treated adults and 0/125 children. Seventy-two subjects discontinued prematurely due to an event that was not reported as drug-related. In 24 this event was malaria.

Data from countries where Malarone has been marketed:

Since initial marketing in Switzerland in August 1997, Malarone had been approved in more than 25 countries worldwide. Two adverse experiences were recorded on a spontaneous reporting database; one allergic reaction and one elevation of liver enzymes.
MO comment: This information cannot be regarded as comprehensive without more detail on prescribing patterns and reporting practices.

Long term adverse experiences
The maximum period of exposure to Malarone in treatment and prophylaxis studies was 12 weeks. No data are available for treatment beyond this period.

Clinical laboratory safety data:

Regular hematology and clinical chemistry tests were performed participants in studies MALB2001, MALB3001, MalB3002 and MALB3003. The schedule for hematology tests in each of these studies is given below:

Table 74: Schedule of hematology tests in prophylaxis studies

Parameter	MALB2001			MALB3001			MALB3002[b]		MALB3003		
	S[a]	W5[a]	W10[a]	S	W5	W10	S	W10	S	W6[a]	W12[a]
Hematology											
Hemoglobin	X	X	X	X	X	X	X	X	X	X	X
Lymphocytes	X	X	X	X	X	X	X	X			
Hematocrit	X	X	X	X	X	X	X	X	X	X	X
Platelets	X	X	X	X	X	X	X	X	X	X	X
White Blood Cells	X	X	X	X	X	X	X	X	X	X	X
Red Blood Cells							X	X			
Mean Corpuscular Volume							X	X			
Chemistry											
Sodium	X	X	X	X	X	X	X	X	X	X	X
Potassium	X	X	X	X	X	X	X	X	X	X	X
ALT	X	X	X	X	X	X	X	X	X	X	X
Albumin	X	X	X	X	X	X	X	X	X	X	X
Alkaline Phosphatase	X	X	X	X	X	X	X	X	X	X	X
Creatinine	X	X	X	X	X	X	X	X	X	X	X
Bilirubin	X	X	X	X	X	X	X	X	X	X	X
Urea	X	X	X	X	X	X	X	X	X	X	X
GGT							X	X			

[a] S = Screening visit; W5 = week 5 visit; W6 = week 6 visit; W10 = week 10 visit; W12 = week 12 visit.

[b] For study MALB3002, a full differential was performed and total protein, phosphorus, glucose, creatinine clearance and calcium were measured.

Clinical chemistry tests monitored in the above four studies included sodium, potassium, albumin, bilirubin, urea, serum creatinine, alkaline phosphatase and alanine aminotransferase. Routine glucose was only monitored in studies MALB3001 and 3002.

For routine haematology parameters no significant trends were noted when comparing Malarone-treated individuals given the recommended dose with placebo treated patients in pooled data, either at screening, week 5, week 10, follow-up or withdrawal. No time-related or dose-related trends were evident.

Similar findings applied to the clinical chemistry tests.
It was noted that while the mean potassium levels were normal and did not change according to study visit or treatment allocation, maximum levels in all categories were excessive, pointing to hemolysis and problems in the handling and preservation of specimens as shown below.

Table 75: Serum postassium levels by study visit and treatment group for studies MALB2001, 3001 and 3002
A+P:C= Controlled studies using recommended doses of malarone
A+P:C+U=Controlled and uncontrolled studies using recommended doses of malarone
A+Px2:C=Controlled study using double recommended dose of malarone

Parameter = Potassium (mmol/L)

Visit	Statistic or Category	Treatment Group: Placebo	A+P:C	A+P:C+U	A+Px2:C
Screening	N	172	178	334	51
	Mean	4.8	4.7	4.4	6.7
	Std.Dev.	1.50	1.31	1.04	2.78
	Median	4.4	4.3	4.1	6.0
	Minimum				
	Maximum				
Week 5	N	147	134	259	40
	Mean	4.8	4.6	4.6	4.2
	Std.Dev.	2.55	1.06	1.06	0.84
	Median	4.6	4.4	4.4	4.0
	Minimum				
	Maximum				
Week 10	N	103	131	227	33
	Mean	4.5	4.5	4.4	4.1
	Std.Dev.	0.64	0.59	0.54	0.61
	Median	4.5	4.6	4.4	3.9
	Minimum				
	Maximum				
Follow-up	N			46	
	Mean			4.1	
	Std.Dev.			0.28	
	Median			4.1	
	Minimum				
	Maximum				
Withdrawal	N	39	9	9	
	Mean	4.8	5.1	5.1	
	Std.Dev.	0.60	1.27	1.27	
	Median	4.8	5.0	5.0	
	Minimum				
	Maximum				

Separate comparisons of laboratory data were presented to investigate the impact of differences in age, gender, race. No treatment-related differences in the results were observed when males and females were compared though hemoglobin levels and hematocrits were lower in females at all time points. No treatment related differences in laboratory results were observed when adults <=30 years and > 30 years were compared. Black adults were more likely than adults of other races to have abnormal clinical chemistry and hematology. These abnormal results occurred during screening, chemoprophylaxis and follow-up and were not attributed to the medication. They included elevations of white cell counts, elevations of lymphocyte counts, higher alkaline phosphatase levels and lower hemoglobin levels.

MO comment: racial comparisons were confounded by the very small number of white patients (N=43) compared to black patients (N=302) and the uneven distribution of races across studies and study centers.

In the pediatric study, there was a tendency for hemoglobin levels to increase from screening to week 6 and 12 for both placebo and Malarone treated subjects of all age-groups as shown below.

Table 76: Hemoglobin values for pediatric subjects stratified by weight and study medication

Parameter = Hemoglobin (g/dL)

Visit	Statistic or Category	Treatment/Stratum: Placebo 1	Placebo 2	Placebo 3	Placebo 4	Malarone 1	Malarone 2	Malarone 3	Malarone 4
Screening	N	40	35	30	35	37	36	26	26
	Mean	10.2	10.7	10.6	10.8	10.3	10.3	10.9	10.8
	Std.Dev.	1.33	1.41	1.10	1.06	0.89	1.00	1.09	0.83
	Median	10.1	10.4	10.5	10.7	10.1	10.2	10.9	10.8
	Minimum								
	Maximum								
Week 6	N	38	31	28	32	37	34	25	26
	Mean	11.1	11.6	11.0	11.4	10.9	11.3	11.1	11.6
	Std.Dev.	1.06	0.86	1.17	1.13	1.32	1.23	0.72	1.16
	Median	11.3	11.5	11.3	11.4	10.7	11.4	11.1	11.5
	Minimum								
	Maximum								
Week 12	N	34	26	25	27	35	32	22	26
	Mean	10.9	11.5	11.3	11.5	10.6	11.2	11.3	11.8
	Std.Dev.	0.90	0.84	0.95	1.00	0.83	0.97	0.70	1.13
	Median	10.9	11.7	11.3	11.4	10.5	11.2	11.3	11.9
	Minimum								
	Maximum								
Withdrawal	N	8	10	9	7	2	1		
	Mean	10.7	11.4	11.4	11.3	9.9	12.3		
	Std.Dev.	1.07	1.13	0.98	1.30	0.42			
	Median	10.8	11.4	11.5	11.4	9.9	12.3		
	Minimum				8.6	9.6	12.3		
	Maximum								

(Treatment strata 1-4 refer to the four dosing groups assigned on the basis of body weight. See table 38)

A similar trend was observed for the hematocrit.

MO comment: The improvement in hemoglobin during the study may reflect the beneficial effects of "radical" malaria treatment upon admission and recognition and treatment of other intercurrent conditions causing anemia during the study.

Among pediatric patients, the mean total bilirubin increased between screening and week 12. This was observed equally across treatment groups and weight categories as shown below.

Table 77: Total bilirubin levels by weight category and treatment group

Parameter = Total Bilirubin (umol/L)

Visit	Statistic or Category	Treatment/Stratum: Placebo 1	Placebo 2	Placebo 3	Placebo 4	Malarone 1	Malarone 2	Malarone 3	Malarone
Screening	N	40	35	30	35	37	36	26	26
	Mean	2.4	1.9	2.8	3.0	2.0	2.5	2.2	4.9
	Std.Dev.	2.48	0.81	2.19	3.30	1.41	2.40	1.00	4.24
	Median	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7
	Minimum								
	Maximum								
Week 6	N	38	31	28	32	35	34	25	26
	Mean	2.9	4.1	1.9	2.5	5.7	2.4	2.6	2.9
	Std.Dev.	1.84	4.30	0.69	1.30	15.73	1.39	1.75	2.59
	Median	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7
	Minimum								
	Maximum								
Week 12	N	34	26	25	27	34	32	22	26
	Mean	7.2	8.2	9.0	9.9	8.6	7.8	7.2	10.2
	Std.Dev.	2.57	3.31	1.72	2.71	2.83	1.05	2.25	4.11
	Median	7.0	8.0	8.0	10.0	8.0	7.0	7.0	9.0
	Minimum								
	Maximum								
Withdrawal	N	8	8	9	7	2	1		
	Mean	9.7	8.2	15.5	10.9	14.5	2.0		
	Std.Dev.	5.43	7.30	22.02	8.07	1.54			
	Median	9.5	8.5	8.0	11.0	14.5	2.0		
	Minimum								
	Maximum								

MO comment: The reason for increasing bilirubin levels in pediatric patients in both drug-treated and placebo-treated groups is not clear. This trend was not reflected in adult studies. Changes in bilirubin were not accompanied by elevations of transaminases or alkaline phosphatase.

"Drug-drug" interactions were not specifically investigated. No adverse events reported during the prophylaxis trials were ascribed to the interaction of Malarone with other concomitantly administered drugs

MO comments on overall safety during prophylaxis studies
Prophylactic doses of Malarone given for up to 12 weeks appeared safe. The most common adverse events included headache and gastro-intestinal complaints (abdominal pain, dyspepsia, gastritis, diarrhea, vomiting). These were rarely treatment limiting and appeared not to pose a significant threat to compliance. The fact that patients vomiting during radical cure were excluded from the prophylactic safety database raises the concern that vomiting may be a more common problem in Malarone naïve individuals. No hematological, hepatic or renal toxicity was identified on the prophylactic dosing regimen.

The population studied in this database was limited to young, healthy volunteers with no underlying illnesses. Safety data were not provided for elderly or very young patients, pregnant individuals or those with underlying medical conditions or concomitant medications. Use of Malarone for periods exceeding 12 weeks was also not investigated.
Some of the recognized adverse events associated with proguanil (oral ulceration, alopecia) were not reported in these studies. Techniques for eliciting AE data in these studies may have selectively excluded certain adverse events, particularly those less likely to be perceived as drug related.

120 day safety update, April 27,1999:
No new safety data were presented on the completed prophylaxis studies included in the original submission.

Integrated summary of efficacy:

In the USA, three antimalarial agents are currently recommended for malaria prophylaxis, chloroquine, mefloquine and doxycycline. Each has drawbacks. Chloroquine resistant malaria is ubiquitous rendering chloroquine ineffective in most malaria endemic areas. Mefloquine has been associated with neuropsychiatric side effects and is contraindicated in individuals with underlying psychiatric disease. Doxycycline is contraindicated in children. Thus more antimalarial prophylactic medications are required to cover gaps in the prophylactic armamentarium.

Pooled studies:
The placebo-controlled studies included a total of 744 subjects. All these subjects received treatment doses of Malarone for 3 days to cure pre-existing infection. Ten of these were withdrawn or lost-to follow-up prior to having a baseline smear. The remaining 734 were included in the intent-to-treat population. Of these 734, 73 were lost to follow-up, and 39 were identified as "protocol violations". The remaining 622 were included in the per protocol population. Among these subjects, three dosing regimens were used. The majority of adult patients were given 250mg Malarone daily, children were treated using quarter strength tablets dosed by body weight, and a minority of adults was given Malarone 500mg qd. The distribution of doses is shown below for ITT and PP populations.

Table 78: Subject allocation in placebo-controlled prophylaxis studies

	Placebo		Malarone 500mg		Malarone 250mg		Malarone per wt	
	PP	ITT	PP	ITT	PP	ITT	PP	ITT
MALB2001	54	65	54	65	54	68		
MALB3001	111	138			102	134		
MALB3003	134	140					113	124
Total	299	343	54	65	156	202	113	124

On an intent-to-treat basis, 343 individuals in total were allocated to receive placebo and 391 to receive Malarone. On a per-protocol basis 299 individuals received placebo and 323 received Malarone. During the prophylaxis phase of these studies 94 of the patients allocated to placebo developed malaria. Two patients allocated to receive Malarone developed malaria.

Defining a failure as a confirmed case of malaria (and excluding the other categories of failure in the PP and ITT analyses referred to in each study review, such as drug intolerance, non-compliance, loss-to follow-up), overall efficacy rates (=1-falure rate$_{malarone}$/failure rate$_{placebo}$) were 97.6% in the PP population and 98% in the ITT populations.

Incorporating the analysis changes described in the individual study reviews (including the exclusion of cases of non-falciparum malaria), pooled efficacy results are shown below:

Table 79. Pooled efficacy results for placebo controlled prophylaxis studies

	Total number of patients randomized	Failed to complete study	Developed Parasitemia (*P falciparum)*
Malarone	326	57	2
Placebo	341	44	92

Efficacy in non-immune travelers

For the three studies, incidence rates of malaria in placebo recipients normalized per 10-week study period varied substantially as shown below.

Table 80: Incidence rates of malaria among placebo recipients normalized per 10 week period

	ITT	PP
MALB3003 (pediatric Gabon)	15%	16%
MALB3001 (adult Zambia)	30%	37%
MALB2001 (adult Kenya)	43%	52%

Malaria prevalence rates at screening were (96/319) 30% in the Gabonese study, 7% in the Zambian study and 34% in the Kenyan study.

MO comment: Variations in prevalence and incidence rates of malaria point to geographic and possible temporal differences between study locations. Common to all these study subjects was considerable exposure to malaria prior to commencement of the study. Since even a single attack of malaria may result in some immunity (Gupta et al. Nature med 1999;5:340-343), all these study communities presumably have substantial malaria immunity. This is likely based on high local prevalence and the fact that high fevers were not recorded among subjects with patent malaria during the study period. The prevalence of splenomegaly was not specifically elicited according to each protocol and this might have supported the presence of antimalarial immunity. Limited published data suggest that the protective efficacy of malaria prophylaxis may be lower in non-immune than immune subjects (Taylor et al Clin Infect Dis 1999;28:74-81). In the above three studies, the only 2 prophylaxis failures occurred in the population with the lowest baseline prevalence of malaria (Zambia MALB3001) where malarial immunity might be lowest, though the numbers of

subjects are too small to give statistical strength to this hypothesis. While some reassurance may be derived from a) the high success rates in the above studies, b) the high efficacy of Malarone as a malarial treatment in non-immune travellers, and c) the efficacy of atovaquone in the single challenge study in this submission, the efficacy of Malarone as a prophylactic in non-immune subjects (such as travellers from the USA) may differ.

Efficacy as a "causal prophylaxis":
Some evidence for the efficacy of Malarone as a causal prophylaxis has been provided in this submission. No existing antimalarial prophylaxis has been approved by the FDA for this indication.

a) In the volunteer challenge study on non-immune US volunteers (MALB2002), atovaquone given at a dose of 250mg once, 24 hours prior to experimental challenge with *P falciparum* was effective in preventing malaria in 6/6 subjects whereas 4/4 placebo-treated patients developed malaria. Atovaquone given as a 750mg QD dose for 7 days starting one day prior to experimental challenge with *P falciparum* was also successful in preventing malaria in 6/6 subjects. In this study, only one of the two Malarone components was investigated, and only 6 of the subjects in this study were treated with the dose of atovaquone recommended by the sponsor. A single atovaquone-susceptible strain of malaria was used in this challenge study which may not reflect conditions in the field. With these reservations the low single dose of atovaquone shown to be effective prior to the development of erythrocytic parasites in the volunteers suggests that Malarone may be effective as a causal prophylaxis.
b) The causal prophylactic efficacy of proguanil is claimed on the basis of a historical study (Fairley 1946 Trans Royal Soc Trop Med Hyg 40:105-51). In this study, volunteers were treated with daily doses of proguanil 100mg as shown below. Causal prophylaxis was established if at day 7, subinoculation of whole blood from challenge subjects into healthy volunteers did not cause malaria:

Table 81: Summary of proguanil challenge study (Fairley)

Proguanil dose	Number of subjects	Period of treatment (days pre- and post-challenge)	Number negative at subinoculation on day 7 and subsequently
100mg	3	-1 to +6	3
100mg	3	+7 to +20	0
100mg	1	0 to +1	0
100mg	1	+1 to +2	1
100mg	1	0 to +2	1
100mg	1	0 to +3	1
100mg	1	0 to +4	1
100mg	1	0 to +5	1

MO comment: The above study differed from current conditions in several respects. The proguanil was only one component of Malarone. The product was manufactured under different conditions than the current product and bio-equivalence was not confirmed. Small numbers of subjects were investigated and the number of untreated controls developing malaria is not provided. The methods for parasite detection (sub-inoculation) differed from current methods (PCR, QBC, smears). With these limitations, this study suggests a causal prophylactic effect of proguanil when administered for at least two days, starting one day after experimental challenge. Proguanil given on the day of challenge and the day after challenge failed to prevent malaria in the one reported subject.

c) In vitro: (See microbiology review) Data was provided showing the activity of atovaquone and proguanil/cycloguanil on hepatocyte cultures infected with non-human plasmodia. Proguanil was shown to delay the onset of parasitemia in a rhesus monkey injected with sporozoites of *P cynomolgi* though hypnozoites were observed on liver biopsy.
d) Follow-up: The placebo-controlled field trials in this submission (MALB2001, MALB3001 and MALB3003) included a period of follow-up for four weeks following cessation of prophylaxis. During this period subjects remained in the endemic area and were exposed to new infections. Since the incubation period for malaria ranges between one and two weeks, subjects given prophylaxis who developed malaria within the first 7 to 14 days after stopping prophylaxis may represent failures of causal prophylaxis. (They may also be explained by resistant infection or non-compliance). Cases

developing later in prophylaxis could also represent causal prophylaxis failure where patency has been delayed by the use of prophylaxis. Without genetic testing, such cases cannot be distinguished from new infections. Cases of *P falciparum* developing in the follow-up period among Malarone treated subjects are shown below.

Table 82: Malaria cases developing during follow-up of subjects who received Malarone prophylaxis

Study	Follow-up day at diagnosis
MALB2001 (Adults Kenya)	8
	16
	27
	28
	25
MALB3001 (Adults Zambia)	27
MALB3003 (Pediatric Gabon)	22
	21
	29

MO comment: At least one of these cases (that developing on day 8 of follow-up) appears to be a failure of "causal prophylaxis". No clinical studies in this submission have tested the efficacy of the recommended dosage regimen in travelers after leaving malaria endemic areas. The possibility remains that such individuals may experience delayed attacks of malaria following the recommended seven days of prophylaxis after returning home.

Considering the above information, some causal prophylactic efficacy of Malarone is recognized although the robustness of this claim is not established. In view of the limited alternative prophylactic choices, the benefits in rapidly making this product available outweigh the advantages of delaying approval pending the completion of studies in travelers.

Observations on dosage recommendations:
The mean plasma levels for atovaquone in study subjects is compared with the IC50 for the 8 field isolates tested.

Table 83: Atovaquone Plasma levels and IC50s of clinical isolates

	Plasma levels (µg/ml)		IC50(ng/ml)	
	Mean	Range	Mean	Range
Kenya	-	-	*(1.53nM)* 0.56	
Zambia	2.07		-	-
Gabon 6wk	3.5 -		(6.8nM) 2.50	
Gabon 12wk	2.6			

The most resistant isolates demonstrated IC50s well below the minimum plasma levels seen in study subjects.
An available plasma level of one treatment failure in the Zambian study was [redacted] one week prior to failure. Plasma levels for the second treatment failure were [redacted] at week 5 and [redacted] at the time of withdrawal. Based on the range of IC50s seen, both these patients are unlikely to have failed therapy due to inadequate dosing.

MO comment: These observations suggest that the therapeutic index for the atovaquone component of Malarone at the recommended prophylactic dose is high. However, the total number of isolates tested (10) is small with a wide range of IC50s, and the possibility of atovaquone resistance cannot be excluded in the regions that were studied.

Mean plasma levels of proguanil and cycloguanil were compared with the corresponding IC50s for 10 clinical isolates.

Table 84: Plasma levels of proguanil and cycloguanil and IC50s of clinical isolates

	Mean plasma level (range)		Mean IC50 (range)	
	Proguanil	Cycloguanil	Proguanil	Cycloguanil
Kenya	-	-	1963 ng/ml	12.9ng/ml
Zambia	26.8ng/ml	10.9ng/ml	-	-
Gabon wk6	18.8ng/ml	9.1ng/ml	1576ng/ml	7.9ng/ml
Gabon wk12	21.3ng/ml	8.9ng/ml		

MO comment
Mean IC50 for proguanil in Kenyan isolates was as high as 104 times the mean plasma level of Gabonese study subjects. Since most of the drug activity has been ascribed to the metabolite cycloguanil, the same comparison was performed for cycloguanil levels. The highest mean IC50 for cycloguanil was 1.4 times the lowest mean plasma level of Gabonese subjects. Steady state and mean trough levels of proguanil and cycloguanil appear to be subtherapeutic when compared with the drug's ability to inhibit erythrocytic cultures. It is not known whether the efficacy of such low concentrations is improved by concurrent atovaquone, and by prophylactic rather than therapeutic applications.

MO Concluding statements:

The clinical data regarding Malarone prophylaxis in this submission demonstrate acceptable efficacy when compared to placebo. The extent to which these results can be applied to a projected population of non-immune travelers likely to use the drug in the USA is limited by the following factors.
1) Most studies were conducted in populations resident in malaria endemic areas where malaria immunity was prevalent. The extent to which malarial immunity influenced the efficacy of the medication is not known.
2) All field studies were conducted in Africa. The impact of isolates from other geographic locations is not known.
3) The recommended dosage regimen assumes that Malarone is effective as a causal prophylaxis. This hypothesis was not optimally tested in field studies where study subjects remained in malaria-endemic areas after stopping prophylaxis. Microbiological data showed that Malarone was active against non-human plasmodia in hepatocyte cultures. The single challenge study (using atovaquone alone, a single challenge strain and only 6 appropriately dosed subjects) provided limited reassurance with regard to the efficacy of Malarone as a causal prophylaxis. During the 4 weeks following cessation of prophylaxis in clinical trial participants who remained in malaria endemic areas and were available for evaluation, malaria developed in 24/211 subjects who took placebo and 9/328 who took Malarone. While new infections could not be distinguished from recrudescences, all but one of the infections in Malarone treated patients occurred more than 15 days after stopping therapy, probably representing new infections. The single case occurring on day 8 following cessation of malarone therapy probably represented a failure of malarone causal prophylaxis. The possibility remains that delayed recrudescences may occur with the recommended regimen. I believe the high efficacy rates for Malarone during the time that subjects are taking prophylaxis, and the very low recrudescence rates seen with short course treatment regimens justify this risk rather than delaying approval, at a time when new effective agents are urgently needed. The limited prophylactic alternatives are subject to failure in the face of escalating drug resistance, and emerging adverse event profiles and in this context I believe it would be detrimental to withhold Malarone as a prophylaxis, given the current understanding of its efficacy.

It is not known whether a longer period of prophylaxis after leaving a malaria endemic area (>7 days) would affect overall efficacy. This could potentially increase the risk of drug related adverse events and is not warranted given the present state of knowledge about the product.

No serious safety concerns were identified when Malarone was used as prophylaxis over periods of up to 12 weeks

The existing spectrum of antimalarial prophylaxis is limited and adverse event profiles and other contraindications make some of these products unsuitable for certain individuals. The rise in drug-resistant malaria has resulted in diminishing efficacy among many existing agents. Recognizing the pressing need for new drugs active in the prophylaxis of malaria, I recommend the approval of Malarone for the prophylaxis of *P falciparum*. However, the limitations referred to in this review mandate further study. The phase 4 requirements to satisfy these shortfalls are described below.

- Studies in non-immune travelers:

International, randomized, double-blind studies to evaluate the safety and efficacy of Malarone versus an for the chemoprophylaxis against malaria in non-immune travelers. Three such studies (MAL30010, MAL30011 and MAL 30012) have been described by the sponsor in a letter of May 27,1999.

Pediatric patients should be included in the study population.

These study concepts have been outlined in a submission of May 14, 1999.

Final reports for these studies must be submitted by February 2001.

Labeling recommendations:

I suggest the following changes to the label as initially proposed in the submission of December 29, 1998.

Prevention of malaria:-

MALARONE was evaluated for prophylaxis of malaria in four clinical trials in malaria endemic areas:

Three placebo-controlled studies of 10-12 weeks' duration were conducted among residents of malaria endemic areas in Kenya, Zambia and Gabon. Of a total of randomized patients (including pediatric patients 5-16 years of age), were withdrawn for reasons other than malaria or drug related-adverse events. (Fifty-five percent of these were lost to follow-up and 45% were withdrawn for protocol violations.)

Table Prevention of parasitemia in placebo-controlled clinical trials of MALARONE for prophylaxis of *P. falciparum* malaria

	Total number of patients randomized	Failed to complete study	Developed Parasitemia (*P falciparum*)
Malarone	326	57	2
Placebo	341	44	92

In a 10-week study of 175 South African subjects who moved into malaria endemic areas and were given prophylaxis with one MALARONE tablet daily, parasitemia developed in one subject who missed several doses of medication. Since no placebo control was included, the incidence of malaria in this study was not known. In a malaria challenge study conducted in healthy US volunteers, atovaquone alone prevented malaria in 6/6 individuals whereas 4/4 placebo-treated volunteers developed malaria. Although these data suggest that MALARONE prophylaxis is effective both in malaria-immune and non-immune subjects, differences in the response rates may occur.

Causal prophylaxis: In separate studies with small numbers of volunteers, atovaquone and proguanil hydrochloride were independently shown to have causal prophylactic activity directed against liver-stage parasites of *P falciparum*. Six patients given a single dose of atovaquone 250mg 24 hours prior malaria challenge were protected from developing malaria whereas all 4 placebo-treated patients developed malaria.
During the 4 weeks following cessation of prophylaxis in clinical trial participants who remained in malaria endemic areas and were available for evaluation, malaria developed in 24/211 subjects who took placebo and 9/328 who took MALARONE. While new infections could not be distinguished from recrudescences, all but one of the infections in MALARONE treated patients occurred more than 15 days after stopping therapy, probably representing new infections. The single case occurring on day 8 following cessation of MALARONE therapy probably represented a failure of MALARONE prophylaxis.
The possibility that delayed cases of *P falciparum* malaria may occur some time after stopping MALARONE prophylaxis cannot be ruled out. Hence returning travelers developing febrile illnesses should be investigated for malaria.

INDICATIONS AND USAGE
Prevention of malaria: MALARONE is indicated for the prophylaxis of *P falciparum* malaria

Under **PRECAUTIONS** section, **Information for patients** subsection

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Eighteen of 521 (3.5%) patients with acute malaria presented with a pre-treatment serum creatinine greater than 2.0mg/dl (range 2.1-4.3 mg/dl). All were successfully treated with MALRONE. Seventeen of 18 (94.4%) had normal serum creatinine levels by day 7.

Pediatric use: Safety and effectiveness for the treatment of malaria in pediatric patients

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Concurrence HFD590/MTL/HopkinsR

CC
NDA 21-078
HFD-590/Officedir/KwederS
HFD590-Divdir/GoldbergerM
HFD590/MTL/HopkinsR
HFD-590/MO/SacksL
HFD-590/MO/MeyerhoffA
HFD-590/PM/DempseyM
HFD590/MicroBalaS
HFD-590/Stats/JiangJ
HFD-590/Stats/SillimanS
HFD-590/Biopharm/MahayniH
HFD-590/Biopharm/AjayiF
HFD-590/Pharmtox/KunderS
HFD-590/Pharmtox/HastingsK
HFD-590/Chemistry/SmithJ
HFD-590/Chemistry/SchmuffN