The results of laboratory studies were also examined for patients who developed clinically significant results at any time following treatment. The criteria used and the numbers of patients with abnormal results are shown in Table 6. Most of these abnormalities are commonly seen in evolving malaria.

Table 6. Clinically significant laboratory abnormalities

Test	Criteria	Atovaquone/Proguanil			Halofantrine		
		Number (%) Developing Abnormality		Number Abnormal at 28 Days	Number (%) Developing Abnormality		Number Abnormal at 28 Days
Hematocrit	< 25%	8	(9.6%)	0	11	(13.1%)	0
Hemoglobin	< 7.5 g/dl	11	(13.1%)	0	12	(14.3%)	1
White Cell Count	< 3000 /µl	1	(1.2%)	0	0		0
Neutrophil Count	< 1000 /µl	10	(11.9%)	3	7	(8.3%)	0
Eosinophil Count	> 1000 /µl	2	(2.4%)	1	0		0
Platelet Count	< 50 /nl	0		0	1	(1.2%)	0
Glucose	< 50 mg/dl	10	(11.9%)	2	13	(15.5%)	2
BUN	> 25 mg/dl	0		0	3	(3.6%)	0
Creatinine	> 2.0 mg/dl	0		0	0		0
Albumin	< 3.0 g/dl	38	(45.2%)	7	44	(52.4%)	14
Bilirubin	> 2.0 mg/dl	2	(2.4%)	1	0		0
ALAT	> 100 U/l	3	(3.6%)	2	4	(4.8%)	2
ASAT	> 100 U/l	4	(4.8%)	1	5	(6.0%)	2
Proteinuria	2+ or greater	0			0		
Hematuria	2+ or greater	0			0		

REVIEWER'S COMMENTS

This comparative trial of atovaquone/proguanil and halofantrine in a population of children in the highlands of Kenya demonstrated that cure rates achieved with atovaquone/proguanil were high and comparable to those achieved with an approved comparator. Another assessment of the efficacy of atovaquone/proguanil compared with halofantrine in the treatment of malaria in European travelers can be found in the review of study #115-130. Differences in cure rates in these two studies may be due in part to reinfection of the Kenyan patients discharged to home in a malaria endemic area after seven days of in-patient care.

Study #115-122

Comparative clinical trial of a combination of atovaquone and proguanil with mefloquine in the treatment of acute *P. falciparum* malaria in adults in Thailand

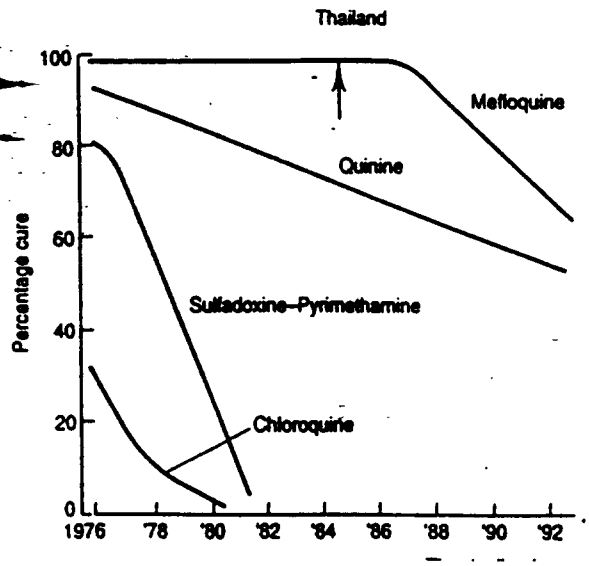
STUDY OBJECTIVES AND DESIGN

This was an open-label, randomized, controlled trial of two multidose regimens for the treatment of adults with falciparum malaria. The principle investigator was Professor Somchai Looareesuwan, Department of Clinical Tropical Medicine, Mahidol University, Bangkok, Thailand. All patient care took place at the Hospital for Tropical Diseases, Bangkok. The study was conducted in accordance with the provisions of the Declaration of Helsinki. It received approval from the Ethics Committee of Mahidol University.

PROTOCOL OVERVIEW

This study was conducted from August 1993 to July 1994. It enrolled 182 patients aged 16-65 years who presented to one of the teaching hospitals of Mahidol University, Bangkok. Malaria due to *P. falciparum* has become increasingly resistant to previously effective antimalarial agents in many parts of the world. The most severe forms of drug resistance have been observed in SE Asia. In Thailand, treatment of acute falciparum malaria is becoming more difficult due to increasing resistance to all available antimalarials. Quinine, long the gold standard for treatment of falciparum malaria, must be used in combination with tetracycline to achieve adequate cure rates. Mefloquine, which was developed for use in resistant falciparum malaria, has been found to be curative in only about 90% of cases when used alone. Figure 1, (from White, NJ in Manson, 20th ed, p 1124) presents antimalarial efficacy in Thailand as a function of time. While Thailand is endemic for both falciparum and vivax malaria, neither is transmitted within metropolitan Bangkok. Patients enrolled in the study under review had acquired their malaria outside the capital city.

Figure 1. Antimalarial efficacy- Thailand



The study population, study procedures, evaluability criteria, efficacy endpoints, and safety monitoring in #115-122 were similar to those described for #115-127. The reader is referred to that review for a detailed description. Study #115-122 differed from #115-127 in that the patients who received the comparator agent were treated with mefloquine 750 mg followed by 500 mg 6 hours later. Patients in #122 could have had initial parasite counts that ranged from 1000 to 200,000 parasites/ µl rather than 1000-100,000/ µl. The study report for #122 stated that all patients agreed to remain in the hospital or in Bangkok, where malaria transmission does not occur, for the full 28 days of the study. The calculation of cure rates for study #122 also differed in that patients who were withdrawn (W) were considered unevaluable and were excluded from the calculation of 28-day cure rates. Cure rates were calculated from the ratio
#S responses/# total S+RI+RII+RIII. Safety data collection was different in study #122 in that AEs were recorded for the first 10 days of the study rather than the first 7 days.

MO COMMENT: Mefloquine (Lariam, NDA 19-591) was approved by the FDA for the treatment of falciparum malaria in 1989. The US label states that the treatment dose is 1250 mg taken as a single dose. Many sources advocate using a split regimen as described above to avoid vomiting.

MO COMMENT: Patients who are hospitalized for the entire duration of the study or patients who are discharged to an area where no malaria transmission occurs following treatment for acute malaria provide a study population in whom recurrent parasitemia can be regarded as recrudescence of prior infection rather than reinfection. Such a population permits a more accurate assessment of drug efficacy.

RESULTS
DEMOGRAPHICS

There were 182 Asian patients enrolled in this study; 91 were treated with A/P and 91 with MFQ. Demographic characteristics of both treatment groups are presented in Table 1.

Table 1. Demography

Group	Sex (M/F)	Mean Age (yrs)	Mean Weight (kg)	G6PD Deficient (%)	Mean IPC /µl	Fever at presentation	Splenomegaly at presentation
ATQ/ PRG	71/20	27.9	52.9	9.0	18,372	82/91 (90.1%)	12/91 (13.2%)
MFQ	74/17	23.7	51.5	9.0	18,859	77/91 (84.6%)	17/91 (18.7%)

IPC=Initial Parasite Count

Table 1 demonstrates that the two treatment arms were well matched for age, weight, initial parasite count, and rates of fever and splenomegaly during presentation. Of interest

is the high rate of fever and low rate of splenomegaly at presentation for Thai adults presenting with falciparum malaria. When these parameters, used as rough indicators of a population's experience with malaria, are compared with those for Brazilian adults in Amazonia (study #115-127) and with European adults traveling to malaria endemic areas (study #115-130), it is noteworthy that the mean IPC, % with fever at presentation, and % with splenomegaly at presentation for Thai adults is more similar to those measurements for European travelers. It was noted in the discussion of the study population that there is no malaria transmission in Bangkok. The study report also noted that some of those patients lost to follow-up came from the Thai-Burmese border where there is considerable malaria transmission. Thus it seems possible that the population under study was mixed regarding prior experience with malaria. The rates of fever and splenomegaly at admission are perhaps most accurate as measures of immunologic experience of malaria when the former is low and the latter is high.

EVALUABILITY AND EFFICACY

Applicant assessment

Evaluability

The applicant's analysis of patient evaluability is presented in Table 2.

Table 2. Patient evaluability per applicant

	ATQ/PRG	MFQ
Total patients enrolled	91	91
Evaluable patients for cure rate	79 (87%)	79 (87%)
Patients lost to follow-up	11 (12%)	11 (12%)
Withdrawn patients	1 (1%)	1 (1%)

The applicant reported that 11 patients in each treatment group were well when allowed to go home, but did not return for follow-up examinations. Two patients were withdrawn from the study. Patient 103, randomized to the A/P group, was found to have shigellosis and tuberculosis shortly after admission. Patient 153, randomized to the MFQ group, experienced a deterioration in his clinical condition during the first 12 hours and was withdrawn and treated with artesunate.

> MO COMMENT: The MO reviewed pertinent line listings for all dropouts. All had cleared their parasitemia two or more days prior to leaving the study. None had any AEs recorded within two days prior to leaving the study.

Efficacy

Overall cure

As noted above, cure was defined as elimination of parasite within 7 days with no recrudescence by day 28. The applicant's assessment of cure rates is presented in Table 3.

Table 3. Cure rates per applicant

	ATQ/PRG	MFQ
Total patients randomized	91	91

Evaluable patients	79	79
Cured ('sensitive' or S)	79 (100%)	68 (86.1%)
Not cured ('resistant' or RI, RII, RIII)	0 (0%)	11 (13.9%)
Unevaluable patients	12	12

The 95% CI around the difference in cure rates was [5.0, 22.8]. ATQ/PRG efficacy was equivalent to or better than that of mefloquine in the applicant's analysis.

MO COMMENT: The MO reviewed pertinent line listing on the 11 patients who were treated with mefloquine and were not cured. The mean total weight-adjusted dose of mefloquine administered to all patients who were treated with mefloquine was 24.7 mg/kg. Mean total weight adjusted-dose calculated for the population who failed (n=11), was 23.9 mg/kg, suggesting that the population who failed were unlikely to have been underdosed when treated with the standard 1250 mg regimen. It should be pointed out, however, that mefloquine blood levels following a single dose can be highly variable and, even if adequately dosed, drug bioavailability can vary widely in a given population. Testing for mefloquine blood levels was not performed in this study. It was also noted that 3 of the 11 patients who failed mefloquine treatment were enrolled with vomiting that lasted between 20 and 107 hours. Vomiting may also have contributed to lower drug levels in patients receiving a regimen that was administered over a 6-hour interval. It should be noted, however, that the 86% cure rate observed for mefloquine in this study approximates the 90% efficacy observed for mefloquine in Thailand in other recent series. This has generally been attributed to parasite resistance. There were no data reported from this study regarding *in vitro* susceptibility testing of clinical isolates.

PCT and FCT

The applicant did not note any differences in PCT or FCT between treatment arms. These results are presented in Table 4.

Table 4. PCT and FCT per applicant

	PCT (hrs)			FCT (hrs)		
Treatment group	No.	Median	Mean	No.	Median	Mean
ATQ/PRG	90	66.5	65.2	84	53.5	58.9
MFQ	90	65.0	73.8	88	50.0	50.9

MO COMMENT: The FCT as an indicator of drug efficacy is problematic in that about 90% of patients received an antipyretic at some point in the study.

MO assessment

Evaluability and efficacy

Evaluability and efficacy were assessed by the MO using a sampling technique. A random sample of 61/182 (33.5%) patients was generated. Individual CRTs and pertinent line listings for each of these patients was reviewed by the MO for agreement between

the MO and applicant regarding patient evaluability and outcome. The MO reclassified three patients who were considered evaluable and cured by the applicant. The MO considered each of these patients unevaluable. One of these patients was #062 who was randomized to atovaquone/proguanil; the MO reclassified this patient as unevaluable because he missed the follow-up visits on days 14 and 21. The other two patients reclassified by the MO were #080 and #102, both of whom were randomized to mefloquine. The MO reclassified #080 as unevaluable because he missed the follow-up visits on days 21 and 28. The MO reclassified #102 as unevaluable because he received norfloxacin, a fluoroquinolone antimicrobial, from days 7-21 of the study for possible typhoid. While efficacy of fluoroquinolones as definitive treatment for malaria has not been demonstrated in clinical trials, there are several published accounts of *in vitro* data and clinical experience that suggest that some drugs in this class, norfloxacin among them, have antimalarial activity. Efficacy of mefloquine alone in patient #102 could not be assessed. The reclassification of patients by the MO analysis was then evaluated with a bootstrap technique, and the agreement between MO and applicant classification of patients in the sample was sufficient to accept the applicant's assessments of evaluability and efficacy. These are presented in Tables 2, 3, and 4 above.

SAFETY

The applicant's discussion of safety was divided into two parts: adverse experiences and laboratory abnormalities.

Adverse Experiences

Signs and symptoms first appearing or increasing in severity within 10 days of initiation of treatment are recorded in Table 5. The number in parentheses is the number possibly attributed to study drug by the investigator.

Table 5. Adverse experiences

	Atovaquone/Proguanil		Mefloquine	
	Number	Percent	Number	Percent
Sore throat	7	7.7%	7	7.7%
Vomiting	9	9.9%	2	2.2%
Diarrhea	5	5.5%	2	2.2%
Nausea	1 (1)	1.1%	5 (2)	5.5%
Insomnia	1	1.1%	3	3.3%
Abdominal Pain	2	2.2%	1	1.1%
Abscess	1	1.1%	1	1.1%
Anorexia	0	0.0%	2 (1)	2.2%
Dizziness	0	0.0%	2	2.2%
Headache	0	0.0%	2 (1)	2.2%
Chest Pain	1	1.1%	0	0.0%
Chills/Rigors	1	1.1%	0	0.0%
Cough	0	0.0%	1	1.1%
Sore Eye	1	1.1%	0	0.0%
Hepatomegaly	1	1.1%	0	0.0%
Neck Pain	0	0.0%	1	1.1%
Pruritus	1	1.1%	0	0.0%
Rhinitis	0	0.0%	1	1.1%
Splenomegaly	1	1.1%	0	0.0%
Tremors	0	0.0%	1	1.1%

Vomiting was more frequent in patients receiving atovaquone and proguanil. Eight of the nine patients with increasing vomiting after administration of atovaquone and proguanil required readministration of the drugs. There were no patients who received mefloquine that required readministration of the drug. The investigator attributed this difference to the large number of tablets (eight) required for each dose of atovaquone and proguanil.

Laboratory results

Examination of means and/or medians for chemistry, hematology, and urinalysis values showed a noteworthy trend in ALAT and ASAT values on days 3 and 7. There was a significant elevation in these tests in patients receiving atovaquone/proguanil. Clinically significant elevation of ALAT and ASAT occurred more than twice as frequently in patients receiving atovaquone/proguanil as in patients receiving mefloquine. These results are presented in Table 6.

Table 6. Clinically significant laboratory abnormalities

		Atovaquone/ Proguanil			Mefloquine		
		No.	(%)	No.	No.	%	No.
Test	Criteria	Developing Abnormality		Abnormal at 28 Days	Developing Abnormality		Abnormal at 28 Days
Hematocrit	< 25%	6	(6.6%)	0	8	(8.8%)	1
Hemoglobin	< 7.5 g/dl	4	(4.4%)	0	7	(7.7%)	2
Red Cell count	< 3.0 /pl	8	(8.8%)	0	14	(15.4%)	1
White Cell Count	< 3000 /µl	3	(3.3%)	0	3	(3.3%)	0
Neutrophil Count	< 1000 /µl	4	(4.4%)	0	2	(2.2%)	0
Eosinophil Count	> 1000 /µl	38	(41.7%)	32	54	(59.3%)	37
Platelet Count	< 50 /nl	3	(3.3%)	0	3	(3.3%)	0
Glucose	< 50 mg/dl	0		0	0		0
BUN	> 25 mg/dl	0		0	1	(1.1%)	0
Creatinine	> 2.0 mg/dl	0		0	1	(1.1%)	0
Albumin	< 3.0 g/dl	6	(6.6%)	0	4	(4.4%)	0
Bilirubin	> 2.0 mg/dl	6	(6.6%)	0	1	(1.1%)	0
ALAT	> 100 U/l	15	(16.5%)	2	6	(6.6%)	1
ASAT	> 100 U/l	12	(13.2%)	3	6	(6.6%)	0

MO COMMENT: The line listings of patients with abnormal transaminase values (ALAT and ASAT) were reviewed. The highest abnormal values in patients receiving atovaquone/proguanil were ALAT 242 IU and ASAT 227 IU. The highest abnormal values in patients receiving mefloquine were ALAT 349 IU and ASAT 404 IU.

The applicant speculated that this higher rate of transaminase elevations could be due to atovaquone/proguanil, or, alternatively, could be related to exacerbations of chronic hepatitis, which is common in Thailand.

REVIEWER'S COMMENTS

This comparative trial of atovaquone/proguanil and mefloquine in a population of Thai adults demonstrated that cure rates achieved with atovaquone/proguanil were high and better than those achieved with mefloquine. It is noteworthy that mefloquine, though an approved drug for the treatment of falciparum malaria, has long been noted to be associated with declining efficacy rates in SE Asia, presumably due to parasite resistance. The observed efficacy rate of mefloquine (86%) in the present study is comparable to the 90% efficacy reported in the literature for the treatment of falciparum malaria in Thailand. There was some increase in vomiting associated with administration of atovaquone/proguanil, as has been observed in other studies. Safety data from this study also suggested a possible association between atovaquone/ proguanil and transaminitis.

Study # 115-120

Comparative clinical trial of a combination of atovaquone and proguanil versus Fansidar in the treatment of acute *P. falciparum* malaria in adults in Zambia

STUDY OBJECTIVES AND DESIGN

This was an open-label, randomized, controlled trial of two multidose regimens for the treatment of adults with falciparum malaria. The principle investigator was Dr JMK Ekue FRCP, WHO Clinical Pharmacologist, Tropical Diseases Research Centre, Ndola, Zambia. The study was conducted in accordance with the provisions of the Declaration of Helsinki. It received approval from the Ethical Committee of the Tropical Diseases Research Centre, Ndola, Zambia.

PROTOCOL OVERVIEW

This study was conducted from December 1993 to May 1994. It enrolled 163 patients aged 12-65 years with acute, uncomplicated falciparum malaria and parasite counts of 100-200,000/µl who presented to the Central Hospital of Ndola and outlying clinics. The patients were cared for at the Tropical Diseases Research Centre, a 50-bed research facility situated within the Central Hospital. In Africa, *P. falciparum* has become increasingly resistant to the previously effective, safe, and affordable antimalarial agent chloroquine. This drug was reliably effective in the treatment of falciparum malaria in Zambia. Declining cure rates for chloroquine were demonstrated in the WHO/CHEMAL

studies conducted at the Ndola Tropical Diseases Research Centre (TDRC) in the 1980s. Data from Ndola in 1985-6 showed that the cure rate for chloroquine was 56%. In 1989-90, chloroquine cured 37% of cases of falciparum malaria at Ndola. Despite the poor efficacy of chloroquine, current government policy in Zambia recommends a 3-day treatment course with chloroquine for falciparum malaria because of the high cost of alternative drugs. Other antimalarial agents have been studied at Ndola and found to be effective. In 1986, a combination of mefloquine and Fansidar (Fansimef) was compared with Fansidar, the comparator agent in the present study. Both drugs were 100% effective. The efficacy of halofantrine was found to range from 96-100% in dose-ranging studies conducted at the Ndola TDRC in 1989-90. The anticipated cure rate for Fansidar in the present study was 100%.

The study population, study procedures, evaluability criteria, efficacy endpoints, and safety monitoring in #115-120 were similar to those described for #115-127. The reader is referred to that review for a detailed description. Study #115-120 differed from #115-127 in that the patients who received the comparator agent were treated with Fansidar (pyrimethamine-sulfadoxine) 25mg-500 mg , three tablets administered in a single dose. Patients in #120 could have had initial parasite counts that ranged from 1000 to 200,000 parasites/ µl rather than 1000-100,000/ µl. The study report for #120 stated that all patients agreed to remain in the hospital, where malaria transmission does not occur, for the full 28 days of the study. Some patients in #120 did attend school or go to work during the daytime hours, but returned to the hospital for dinner and slept in the hospital during the hours when anopheline mosquitoes bite. The calculation of cure rates for study #120 also differed in that patients who were withdrawn (W) were considered unevaluable and were excluded from the calculation of 28-day cure rates. Cure rates were calculated from the ratio #S responses/# total S+RI+RII+RIII. Safety data collection was different in study #120 in that AEs were recorded for the first 10 days of the study rather than the first 7 days.

MO COMMENT: Pyrimethamine-sulfadoxine (Fansidar, NDA 18-557) was approved by the FDA for the treatment of falciparum malaria in 1981. The US label states that the treatment dose is two to three tablets of pyrimethamine 25 mg/sulfadoxine 500 mg taken together as a single dose. The FDA approved label does not provide instructions for determining whether a patient should receive two or three tablets.

MO COMMENT: Patients who are hospitalized for the entire duration of the study or patients who are discharged to an area where no malaria transmission occurs following treatment for acute malaria provide a study population in whom recurrent parasitemia can be regarded as recrudescence of prior infection rather than reinfection. Such a population permits a more accurate assessment of drug efficacy.

RESULTS
DEMOGRAPHICS

There were 163 black African patients enrolled in this study; 82 were treated with A/P and 81 with Fansidar (P/S). Demographic characteristics of both treatment groups are presented in Table 1.

Table 1. Demography

Group	Sex (M/F)	Mean Age (yrs)	Mean Weight (kg)	G6PD Deficient (%)	Mean IPC /µl	Fever at presentation	Splenomegaly at presentation
ATQ/ PRG	80/2	25.9	56.3	11.0	14,799	52/82 (64.2%)	29/82 (35.4%)
P/S	79/2	24.9	56.3	14.8	18,112	60/81 (74.1%)	24/81 (29.6%)

IPC=Initial Parasite Count

Table 1 demonstrates that the two treatment arms were well matched for age, weight, initial parasite count, and rates of fever and splenomegaly during presentation.

EVALUABILITY AND EFFICACY
Applicant assessment
Evaluability
The applicant's analysis of patient evaluability is presented in Table 2.

Table 2. Patient evaluability per applicant

	ATQ/PRG	P/S
Total patients enrolled	82	81
Evaluable patients for cure rate	80 (97.6%)	80 (98.8%)
Patients lost to follow-up	0 (0%)	1 (1.2%)
Withdrawn patients	2 (2.4%)	0 (0%)

Patient #003 was found to have tuberculosis three days after completion of his treatment with A/P and was withdrawn from the study by the investigator. The father of patient #153 withdrew his consent after two days of A/P without explanation. Patient #012 left the ward eight days after treatment with P/S and did not return. The remaining 160 patients stayed in the hospital for the full duration of the follow-up. No patients died and no patients were withdrawn due to an adverse event.

MO COMMENT: The MO reviewed the CRTs and pertinent line listings for patients #003, 153 and 012. Patient #003 was a 30 year old man admitted with an IPC of 10, 324/µl. He cleared his peripheral parasitemia at 84 hours, and had no noteworthy adverse events. He was diagnosed with tuberculosis and withdrawn on day 6. Patient #153 was a 22 year old man who was enrolled with an IPC of 36, 419 and considered to have mild malaria. The last parasite count recorded for

this patient was at 42 hours, at which time he had 26,031 parasites/µl. There were no adverse events recorded for this patient. He received no concomitant medications. The reason for his withdrawal is not stated. Patient #012 was a 25 year old man admitted with an IPC of 5391/µl. His peripheral parasitemia cleared at 42 hours. One adverse event was noted for this patient; he experienced excessive salivation approximately 18 hours after dosing. On study day 8, the patient left the ward and did not return. There was no explanation for his departure.

Efficacy

Overall cure

As noted above, cure was defined as elimination of parasite within 7 days with no recrudescence by day 28. The applicant's assessment of cure rates is presented in Table 3.

Table 3. Cure rates per applicant

	ATQ/PRG	P/S
Total patients randomized	82	81
Evaluable patients Cured ('sensitive' or S) Not cured ('resistant' or RI, RII, RIII,)	80 80 (100%) 0 (0%)	80 79 (98.8%) 1 (1.2%)
Unevaluable patients	2	1

The 95% CI around the difference in cure rates was [-2.43, 4.93]. Atovaquone/proguanil efficacy was equivalent to that of pyrimethamine/sulfadoxine in the applicant's analysis.

PCT and FCT

The applicant noted a significant difference between treatment arms for the median values of both PCT and FCT. Patients treated with A/P had a shorter FCT, and patients treated with P/S has a shorter PCT. These results are presented in Table 4.

Table 4. PCT and FCT per applicant

	PCT (hrs)			FCT (hrs)		
Treatment group	No.	Median	Mean	No.	Median	Mean
ATQ/PRG	81	72.0	64.0	67	23.0	30.4
P/S	81	48.0	51.4	77	48.0	44.9

MO COMMENT: The FCT can only provide limited information about drug efficacy. Approximately 70% of patients received an antipyretic at some point in the study.

MO assessment

Evaluability and efficacy

Evaluability and efficacy were assessed by the MO using a sampling technique. A random sample of 61/163 (37.4%) patients was generated. Individual CRTs and pertinent line listings for each of these patients was reviewed by the MO for agreement between

the MO and applicant regarding patient evaluability and outcome. The MO concurred with the applicant's assessment of evaluability and efficacy in 100% of the patients sampled. This was sufficient to accept the applicant's assessments of evaluability and efficacy of the total study population. These are presented in Tables 2, 3, and 4 above. The cure rate achieved with Fansidar approached the 100% expected, and the cure rate achieved with atovaquone/proguanil was shown to be equivalent to that of an approved comparator.

SAFETY

The applicant's discussion of safety was divided into two parts: adverse experiences and laboratory abnormalities.

Adverse Experiences

Signs and symptoms first appearing or increasing in severity within 10 days of initiation of treatment which occurred at a frequency >2% are recorded in Table 5. The study report noted that the frequency and variety of symptoms was greater than that seen in other centers because symptoms were elicited by non-direct questioning.

Table 5. Adverse experiences

	Atovaquone/Proguanil		Fansidar	
	Number	Percent	Number	Percent
Headache	38	46.3%	30	37.0%
Abdominal Pain	29	35.4%	34	42.0%
Weakness	23	28.0%	15	18.5%
Diarrhea	21	25.6%	13	16.0%
Myalgia	11	13.4%	12	14.8%
Splenomegaly	12	14.6%	11	13.6%
Vomiting	10	12.2%	12	14.8%
Coughing	13	15.9%	8	9.9%
Orthostatic Hypotension	6	7.3%	14	17.3%
Chills/Rigors	6	7.3%	13	16.0%
Nausea	6	7.3%	13	16.0%
Diaphoresis	8	9.8%	9	11.1%
Arthralgia	9	11.0%	7	8.6%
Dizziness	6	7.3%	9	11.1%
Hepatomegaly	6	7.3%	9	11.1%
Chest Pain	9	11.0%	5	6.2%
Anorexia	7	8.5%	6	7.4%
Back Pain	7	8.5%	6	7.4%
Pruritus	7	8.5%	6	7.4%
Herpes Labialis	3	3.7%	7	8.6%
Palpitations	9	11.0%	1	1.2%
Rhinitis	5	6.1%	4	4.9%
Insomnia	1	1.2%	5	6.2%
Epistaxis	3	3.7%	2	2.5%
Neck Pain	3	3.7%	2	2.5%
Toothache	2	2.4%	3	3.7%
Dyspepsia	2	2.4%	2	2.5%

Of note is that diarrhea and palpitations were reported with increased frequency in patients treated with atovaquone/proguanil. It is difficult to know how to interpret the rates of diarrhea reported. This symptom can be associated with malaria. Of the patients examined (83% of study population), 28% had one or more enteric parasites, including ascariasis, hookworm, schistosomiasis, and giardiasis. Of the 38 patients found to have one or more enteric parasites, 14 (17% of treatment group) received atovaquone/proguanil and 24 (30% of treatment group) received Fansidar. The rate of intestinal parasitism does not appear to explain the differences observed in the rates of diarrhea between the two treatments. Interestingly, vomiting, another gastrointestinal AE that has been quite prominent in the atovaquone/proguanil group in other studies, was not more frequent in patients treated with atovaquone/proguanil in the present study. The higher rate of reporting of palpitations noted in the patients treated with atovaquone/proguanil has not been reported in other studies in this application.

Laboratory results

Examination of means and/or medians for chemistry, hematology, and urinalysis values showed statistically significant differences between treatment groups for the tests presented in Table 6. None of these differences was clinically significant.

Table 6. Laboratory results with statistical significance between groups

Lab Test	Day	Treatment Group		95% CI for Difference
		Atovaquone/ Proguanil	Fansidar	
Lymphocytes	7	54.0	59.0	2.0 to 9.0 %
Creatinine	3	86.0	98.5	8.0 to 19.0 mol/l
Creatinine	7	85.0	101.0	9.0 to 20.0 mol/l
Creatinine	14	85.0	98.0	8.0 to 18.0 mol/l
Total Bilirubin	3	11.0	6.0	2.0 to 6.0 mol/l
Total Bilirubin	7	6.0	4.0	1.0 to 3.0 mol/l
Total Bilirubin	14	7.0	5.0	1.0 to 2.0 mol/l

REVIEWER'S COMMENTS

This comparative trial of atovaquone/proguanil and pyrimethamine/sulfadoxine in a population of Zambian adults demonstrated that cure rates achieved with atovaquone/proguanil were high and equivalent to those achieved with an approved comparator with established efficacy in this part of Africa. Safety data of note included a higher rate of diarrhea but a lower rate of vomiting in patients who received atovaquone/proguanil compared with patients who received comparator. There was also a higher rate of palpitations noted in patients in the atovaquone/proguanil treatment group.

Study 115-135

Comparative clinical trial of a combination of atovaquone and proguanil versus chloroquine in the treatment of acute *P. falciparum* malaria in adults and children in the Philippines

STUDY OBJECTIVES AND DESIGN

This trial was planned as an open-label, randomized, controlled trial of two multidose regimens for the treatment of falciparum malaria. After less than half of the patients were enrolled, it was found that those patients in the chloroquine treatment group had a cure rate of ~35% and it was thought to be unethical to proceed with further treatment with chloroquine alone. The protocol was amended to include the concurrent administration of Fansidar (pyrimethamine/sulfadoxine) with chloroquine. The principle investigator was Dr Dorina G Bustos, Research Institute for Tropical Medicine, Manila and Palawan Provincial Hospital, Puerto Princesa, Palawan, Philippines. The study was conducted in accordance with the provisions of the Declaration of Helsinki. It received approval from the Institutional Review Board, Research Institute for Tropical Medicine, Manila.

PROTOCOL OVERVIEW

This study was conducted from October 1994 to March 1995. It enrolled 110 patients aged 12-65 years with acute, uncomplicated falciparum malaria and parasite counts of 100-200,000/µl who presented to the Palawan Provincial Hospital. Palawan is located in the southwest of the Philippine archipelago. Malaria is transmitted throughout the island, and infections with *P. vivax* and *P. falciparum* occur in a ratio of about 7:3. Transmission is reported to not occur within 6 km of Puerto Princesa, the main city. As early as 1971, a 47% rate of R1 and R2 resistance to chloroquine was documented on this island. Since 1987, *in vitro* resistance to Fansidar has been documented in several parts of the Philippines. Clinical studies with Fansidar with 28-day follow-up have not been reported. In the judgement of individual Philippine investigators, Fansidar cure rates have been thought to exceed 90%. Although not marketed in the Philippines, mefloquine has been shown to be 100% effective in previous clinical trials. Halofantrine demonstrated a 100% cure rate in a small study of 30 adults with falciparum malaria in 1989. Chloroquine remains the standard antimalarial treatment in this area, is the first line agent for the Malaria Control Service of the Philippines Department of Health. Fansidar and quinine are used increasingly frequently as second-line agents when chloroquine fails. Chloroquine is readily available to the general population. The study report stated that most patients would have had some treatment prior to being seen at the hospital.

The study population, study procedures, evaluability criteria, efficacy endpoints, and safety monitoring in #115-135 were similar to those described for #115-127. The reader is referred to that review for a detailed description. Study #115-135 differed from #115-127 in that the patients who received the comparator agent were treated first with chloroquine, 600 mg x 1, 300 mg 6 hr later, then 300 mg per day x 2 days (patients #1-40). Patients weighing less than 40 kg received a weight adjusted dose. Because of a 35% cure rate among these patients treated with chloroquine alone, subsequent patients in the control group received chloroquine and Fansidar (pyrimethamine-sulfadoxine) 25mg-500 mg, three tablets administered in a single dose. Patients weighing less than 50 kg received two tablets in a single dose. Patients in #135 could have had initial parasite counts that ranged from 1000 to 200,000 parasites/ µl rather than 1000-100,000/ µl. The study report for #135 stated that all patients agreed to remain in the hospital, where malaria transmission does not occur, for the full 28 days of the study. Some patients in #135 did attend school or go to work during the daytime hours, but returned to the hospital by 10 pm when anopheline mosquitoes were reported to start biting. The calculation of cure rates for study #135 also differed in that patients who were withdrawn (W) were considered unevaluable and were excluded from the calculation of 28-day cure rates. Cure rates were calculated from the ratio #S responses/# total S+RI+RII+RIII. Safety data collection was different in study #135 in that AEs were recorded for the first 10 days of the study rather than the first 7 days.

MO COMMENT: Chloroquine (Aralen, NDA 6-002) was approved by the FDA for the treatment of malaria in 1949. The treatment dose in the FDA approved label is the same as the regimen described for the study under review. Pyrimethamine-sulfadoxine (Fansidar, NDA 18-557) was approved by the FDA for the treatment of falciparum malaria in 1981. The US label states that the treatment dose is two to three tablets of pyrimethamine 25 mg/sulfadoxine 500 mg taken together as a single dose. The FDA approved label does not provide instructions for determining whether a patient should receive two or three tablets.

MO COMMENT: Patients who are hospitalized for the entire duration of the study or patients who are discharged to an area where no malaria transmission occurs following treatment for acute malaria provide a study population in whom recurrent parasitemia can be regarded as recrudescence of prior infection rather than reinfection. Such a population permits a more accurate assessment of drug efficacy.

The study report also stated that pretreatment isolates were examined for susceptibility to a battery of standard antimalarial agents. Satisfactory growth occurred in approximately 30 of these; the results of susceptibility testing will be discussed below.

RESULTS
DEMOGRAPHICS

There were 110 Filipino (Malay) patients enrolled in this study; 55 were treated with atovaquone/proguanil (A/P), 23 with chloroquine alone (C), and 32 with chloroquine and Fansidar (C/P/S). Demographic characteristics of all treatment groups are presented in Table 1.

Table 1. Demography

Group	Sex (M/F)	Mean Age (yrs)	Mean Weight (kg)	Mean IPC /μl	Fever at presentation	Splenomegaly at presentation
A/P	39/16	28.6	53.7	18,042	51/55 (92.7%)	2/55 (3.6%)
C	16/7	32.8	50.7	16,814	15/23 (65.2%)	1/23 (4.3%)
C/P/S	21/11	28.0	51.5	12,133	25/33 (78.1%)	0 (0%)

IPC=Initial Parasite Count

Table 1 demonstrates that the treatment arms were well matched for age, weight, initial parasite count, and splenomegaly at presentation. A higher proportion of patients who received A/P was febrile at presentation. When overall severity, recorded at presentation by the individual investigator, was assessed for each treatment arm, it did not appear that the A/P group enrolled patients with more severe disease. Overall assessment was comparable for the three treatment groups except that those 23 patients who received chloroquine alone had a slightly higher rate with moderate rather than mild disease. Table 2 presents overall clinical assessment at enrollment by treatment group.

Table 2. Overall clinical assessment of severity at enrollment

Clinical assessment	A/P	C	C/P/S
Mild	65.4%	43.5%	62.5%
Moderate	34.6%	56.5%	37.5%
Severe	0	0	0

MO COMMENT: It should be noted that the category 'severe' in Table 2 does not refer to the WHO designation 'severe malaria' which is defined by the occurrence of certain serious complications of falciparum malaria such as cerebral malaria, hypoglycemia, and renal failure, among others. Such patients were specifically excluded from this study since they require parenteral therapy. The use of the term 'severe' here referred to the spectrum of disease seen in uncomplicated malaria and was subjectively determined by the investigator.

EVALUABILITY AND EFFICACY

Applicant assessment

Evaluability

The applicant's analysis of patient evaluability is presented in Table 3.

Table 3. Patient evaluability per applicant

	A/P	C + C/P/S
Total patients enrolled	55	55
Evaluable patients for cure rate	55 (100%)	54 (98.2%)
Patients lost to follow-up	0 (0%)	0 (0%)
Withdrawn patients	1 (1.8%)	0 (0%)

Patient #005 was randomized to A/P and withdrawn on day 8 because he was diagnosed with a urinary tract infection and received trimethoprim-sulfamethoxazole to treat this intercurrent illness. The applicant did not provide information regarding any patient in the comparator group who was not evaluable for cure. No patients died and no patients were withdrawn due to an adverse event.

MO COMMENT: The MO reviewed the CRT and pertinent line listings and electronic databases for patient #005. This patient was a 48 year old man admitted with mild malaria and an IPC of 8800/µl. The patient's parasitemia was 0 at 18 hours, though there were only 2 consecutive negative smears documented for this patient during the acute period. He remained aparasitemic on day 7, and no further smears were recorded. His urinalysis at enrollment showed 20-30 RBC and 5-10 WBC. The patient initially received amoxicillin for a urinary tract infection for days 4-8 of the study. TMP/SMX treatment was started on day 9 for UTI. He had no adverse events recorded at the time of his withdrawal. This patient appeared to have cleared his parasitemia, though the criterion of 3 negative smears was not met. There is no reason provided for this observation. The MO concurs that the patient was appropriately withdrawn because of his need for concomitant treatment with an antimicrobial that has antimalarial activity.

MO COMMENT: The MO reviewed the line listings describing patients' results. There were no patients other than #005 with a 'W' or a 'U' score. The MO review of the applicant's assessment of patient evaluability suggested that the values for each treatment group in the second row of Table 3, Evaluable patients for cure rate, should be reversed.

Efficacy

Overall cure

As noted above, cure was defined as elimination of parasite within 7 days with no recrudescence by day 28. The applicant's assessment of cure rates is presented in Table 4.

Table 4. Cure rates per applicant

	A/P	C	C/P/S
Total patients randomized	55	23	32
Evaluable patients	54	23	32
Cured ('sensitive' or S)	54(100%)	7 (30.4%)	28(87.5%)
Not cured ('resistant' or RI, RII, RIII,)	0 (0%)	16 (69.6%)	4 (12.5%)
Unevaluable patients	1	0	0

The applicant reported that the 95% CI around the difference in cure rates between A/P and chloroquine (C) was [49.8, 89.4]; the 95% CI around the difference in cure rates between A/P and chloroquine/Fansidar (C/P/S) was [3.3, 21.7].

MO COMMENT: This study was not planned as a 3-way comparison and was not powered as such. However the data presented in Table 4 do permit the conclusion that atovaquone/proguanil provides better efficacy than either chloroquine alone or chloroquine/Fansidar. Because chloroquine resistance is widespread in the Philippines, a more meaningful comparison might be made between the A/P group and the C/P/S group. For further discussion of this issue, see MO assessment, Efficacy, *Overall Cure*.

PCT and FCT

The applicant noted no significant difference between treatment arms for the median values of either PCT or FCT. These results are presented in Table 5.

Table 5. PCT and FCT per applicant

	PCT (hrs)			FCT (hrs)		
Treatment group	No.	Median	Mean	No.	Median	Mean
A/P	55	49.3	46.7	51	36.0	38.8
C	19	52.0	60.0	16	47.8	46.8
C/P/S	32	41.7	42.8	27	34.5	34.5

MO COMMENT: The FCT can only provide limited information about drug efficacy. Approximately 90% of patients received an antipyretic at some point in the study.

In vitro data analysis

The applicant reported that 87 of the 110 patients enrolled had pretreatment parasite counts sufficiently large enough to permit *in vitro* drug susceptibility testing. Satisfactory growth occurred in 30 of these parasite strains. All isolates demonstrated *in vitro* susceptibility to atovaquone; *in vitro* resistance to chloroquine was demonstrated in 41% of those strains tested, to quinine in 32% of strains tested, to mefloquine in 29% of strains tested, and to halofantrine in 48% of strains tested.

MO COMMENT: The data presented above highlight the difficulty in correlating results from *in vitro* susceptibility testing with clinical outcome. Though clinical cure rates for a given agent can be highly dependent on the geographic area under study and on the length of time the parasite population has been exposed to that agent, the *in vitro* results presented above do not correlate with observations from earlier clinical trials with mefloquine and halofantrine. It is possible that some level of resistance to these agents has developed since the clinical trials reported above were conducted. These data highlight the importance of ongoing surveillance and the need for susceptibility data in a defined geographic area.

MO assessment

Evaluability and efficacy —

Study #115-135 was planned as a two-armed equivalence trial. Three months into the study, the protocol was amended because the failure rate in the comparator group (chloroquine, C) was unacceptably high. The amendment resulted in the introduction of a third treatment group in which Fansidar (pyrimethamine/sulfadoxine, P/S) was added to chloroquine. The applicant then modified the null hypothesis of the study to state that there was no difference in 28-day cure rates between the three treatment groups. The applicant analyzed efficacy by calculating the 95% CI around the differences in cure rates for each pair of treatment groups. The study may be viewed as supportive of the high efficacy rates observed for atovaquone/proguanil in the randomized, controlled, two-arm trials of the NDA submission.

The MO analysis of the data presented by the applicant included a review of the CRTs and pertinent line listings for all failures in the comparator groups. The MO concurred with the applicant's scoring of these patients' outcomes. The MO analysis next included a review of the evaluability and efficacy outcome of all patients in the atovaquone/proguanil treatment group. All CRTs and pertinent line listings for patients treated with A/P were reviewed. Particular attention was paid to documentation of clearance of acute parasitemia, documentation of weekly smears to study day 28, recorded parasite clearance time, intercurrent adverse events or laboratory values that may represent a worsening of malaria (eg fever/chills, rising creatinine or markedly depressed hemoglobin), and concomitant medications with antimalarial activity. The conduct of the study differed from the planned protocol in that only two negative smears instead of three were required to document clearance of parasitemia. The MO assessment agreed with that of the applicant with the exception of patient #084, who was scored as evaluable and a cure with a parasite clearance time of 5.5 hours. Review of this patient's serial parasite counts showed that there was no documentation of a peripheral smear being performed any time between pretreatment and day 7. It was not possible to verify that this patient had negative smears at hours 6 and 12. For this reason, the MO regarded this patient as unevaluable. Otherwise, the MO concurred with the applicant's assessment of efficacy in the atovaquone/proguanil treatment group. Table 6 presents the MO analysis of evaluability and efficacy for the A/P treatment group.

Table 6. Evaluability and efficacy per MO

Patient Disposition	A/P
Total patients randomized	55
Evaluable patients Cured ('sensitive' or S) Not cured ('resistant' or RI, RII, RIII,)	53 53(100%) 0 (0%)
Unevaluable patients*	2

*The MO considered patient #005 unevaluable because he was withdrawn because he received TMP/SMX, a drug with antimalarial activity, for an intercurrent urinary tract infection. The MO considered patient #084 unevaluable because there was no documentation of peripheral smears showing initial parasite clearance.

There were no data presented on the number of patients who had received antimalarial therapy prior to enrollment. According to the study report, chloroquine is widely available, but data from the study under review suggest that its efficacy is unreliable. Because the 28-day cure rates with atovaquone/proguanil have been high and consistent at all of the study centers participating in these trials, it is difficult to determine what role, if any, prior therapy has played in the cure rates observed in study #135. It is noteworthy that the median PCT reported for patients who received ATQ/PRG in #135 was somewhat shorter (~50 hr) than the value reported from most other study centers (~60hr).

There were seven patients enrolled in this trial who were ≤16 years old. They were patients # 037, 039, 041, 059, 092, 093, and 105. All were between 12 and 16 years old, their weights ranged from 30-48 kg. All were cured.

The MO found that the cure rate for A/P for the treatment of acute falciparum malaria in the Philippines was high and similar to that reported from other study centers in this NDA submission.

SAFETY

The applicant's discussion of safety was divided into two parts: adverse experiences and laboratory abnormalities.

Adverse Experiences

Signs and symptoms first appearing or increasing in severity within 10 days of initiation of treatment which occurred at a frequency >2% are recorded in Table 7. The study report noted that all symptoms except hematemesis were common in patients being treated for malaria. A larger number of gastrointestinal symptoms were thought possibly attributable to A/P than to the other agents.

Table 7. Adverse experiences (the number in parentheses denotes the number possibly attributable to study drug by the investigator)

	Atovaquone/Proguanil		Chloroquine		Chloroquine/Fansidar	
	Number	Percent	Number	Percent	Number	Percent
Vomiting	10(5)	18.2%	4(1)	17.4%	3	9.4%
Abdominal Pain	8(6)	14.5%	4	17.4%	1	3.1%
Anorexia	6(3)	10.9%	3(1)	13.0%	0	
Headache	3	5.5%	4	17.4%	1	3.1%
Nausea	4(3)	7.3%	2(1)	8.7%	0	
Insomnia	3	5.5%	3	13.0%	0	
Dizziness	1	1.8%	3(1)	13.0%	0	
Myalgia	2	3.6%	1	4.3%	1	3.1%
Chills/Rigors	1	1.8%	1	4.3%	1	3.1%
Coughing	2	3.6%	0		0	
Weakness	0		2	8.7%	0	
Diarrhea	0		1(1)	4.3%	0	
Hematemesis	0		1	4.3%	0	
Tinnitus	0		1(1)	4.3%	0	

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Laboratory results
Examination of means and/or medians for chemistry, hematology, and urinalysis values showed statistically significant differences between treatment groups for the tests presented in Table 8. None of these differences was clinically significant.

Table 8. Laboratory results with statistical significance between groups

Lab Test	Day	Atovaquone/ Proguanil	Chloroquine	Chloroquine/ Fansidar
Lymphocytes (%)	3	54.0	48.0	49.5
Total Bilirubin (m/l)	7	12.1	14.2	7.0

REVIEWER'S COMMENTS

This trial of atovaquone/proguanil, chloroquine, and chloroquine and pyrimethamine/sulfadoxine in a population of Philippine adults and children demonstrated that cure rates achieved with atovaquone/proguanil were high and similar to those achieved with this combination in other study centers in Asia, Africa, and South America. While the study was not designed to assess equivalence with the population who received chloroquine and Fansidar, inspection of cure rates suggests that the efficacy of atovaquone proguanil is comparable to that of chloroquine/Fansidar in this part of the Philippines. There was a slightly higher rate of gastrointestinal adverse events thought to be attributable to atovaquone/proguanil as compared to chloroquine and chloroquine/Fansidar treatment.

Study #115-134
Comparative clinical trial of a combination of atovaquone and progūanil versus amodiaquine in the treatment of acute *P. falciparum* malaria in adults in Gabon

STUDY OBJECTIVES AND DESIGN

This was an open-label, randomized, controlled trial of two multidose regimens for the treatment of out-patient adults with falciparum malaria. The principle investigator was Dr Peter Kremsner MD, International Research Laboratory, Albert Schweitzer Hospital, Lambaréné, Gabon. All patients enrolled had presented to Albert Schweitzer Hospital and were cared for as out-patients by serial visits to that facility throughout the course of the

study. The study was conducted in accordance with the provisions of the Declaration of Helsinki. It received approval from the Chairman of the International Fund of the Albert Schweitzer Hospital.

PROTOCOL OVERVIEW

This study was conducted from July 1994 to March 1995. It enrolled 148 patients aged 10-80 years who presented to the Albert Schweitzer Hospital with acute malaria. The study was initially designed to evaluate atovaquone/proguanil for the treatment of falciparum malaria only. The protocol was amended in December 1994 to include patients with malaria due to *P. ovale* and *P. malariae* as well. Worldwide, these two species of *Plasmodium* are less common causes of human malaria, and are generally susceptible to chloroquine. The investigators amended the protocol because they noted about 5% of patients presenting for treatment had malaria due to *P. ovale* or *P. malariae*, and viewed the study under discussion as an opportunity to assess the potential of atovaquone/proguanil as alternative therapy, particularly in patients with mixed infections, or in patients whose *Plasmodium* species cannot be readily identified.

> MO COMMENT: The geographic range of *Plasmodium ovale* is largely limited to West/Central Africa; it is also occasionally found in the Western Pacific. *P. malariae*, like *P. falciparum*, is found throughout the tropics, but, of the four *Plasmodium* species known to infect humans, is the least common cause of malaria. The inclusion of data on even a small series of patients infected with these two species can be very helpful in the management of the patient with malaria in a setting, such as most US hospitals, where there is limited experience speciating malarial parasites from peripheral smears.

Recent data regarding cure rates in the treatment of falciparum malaria in Gabon show limited efficacy for standard therapies. Studies in the 1990s have shown 28-day cure rates for chloroquine of 9% in children and 36% in adults. Short-course quinine (3 days) only cured 32% of Gabonese children. Amodiaquine, a 4-aminoquinoline and congener of chloroquine, is prescribed in Gabon as a replacement for chloroquine. Recent data from Gabon demonstrate a cure rate for amodiaquine of 65%. Fansidar (pyrimethamine/sulfadoxine) is generally used for recrudescences, and is thought to have an efficacy rate $\geq$ 95%. Other agents studied in this part of Africa include halofantrine, which cured 100% of patients, and the combination of chloroquine plus clindamycin, which cured 97% of adults. The protocol was amended a second time in December 1994 to increase the total number of patients to be enrolled in the study. The reason for this amendment was that the investigators observed a higher than expected cure rate for amodiaquine (81%) and a higher than expected drop-out rate (15% rather than 10%).

> MO COMMENT: Discordant results have been noted in certain regions of the world between efficacy rates and/or *in vitro* susceptibility testing for antimalarial agents studied prior to the clinical trials conducted for NDA 21-078, and efficacy rates observed for the same agents in the clinical trials performed to support this NDA (see MO Review of studies #115-120, Zambia and #115-112, Zambia). Accurate information about clinical efficacy of antimalarials other than atq/prg is

important to establishing the efficacy of atq/prg in regions where there is thought to be resistance to these other agents. The applicant's draft label makes specific claims for atq/prg efficacy in infections caused by *P. falciparum* strains resistant to many other agents. For drugs for which such discordant results have been observed, the data obtained in the clinical trials of NDA 21-078 in which direct comparisons of atq/prg and such comparator agents were made will be given considerable weight when assessing Malarone activity against resistant organisms.

The study population, study procedures, evaluability criteria, efficacy endpoints, and safety monitoring in #115-134 were similar to those described for #115-127. The reader is referred to that review for a detailed description. Study #115-134 differed from #115-127 in that the patients who received the comparator agent were treated with amodiaquine given at 24-hour intervals. The first two doses were each 600 mg base, the third 400 mg base. Patients in #134 could have had initial parasite counts that ranged from 200 to 100,000 parasites/ µl rather than 1000-100,000/ µl. Patients in #134 were not hospitalized at all; they were followed as out-patients. They remained in the clinic 2-4 hours following the first dose of study drug, and then returned for serial follow-up visits. As a result, clinical evaluations and peripheral smears were performed at 12-hourly intervals in study #134 until patients were afebrile and aparasitemic. The calculation of cure rates for study #134 also differed in that patients who were withdrawn (W) were considered unevaluable and were excluded from the calculation of 28-day cure rates. Cure rates were calculated from the ratio #S responses/# total S+RI+RII+RIII. Safety data collection was different in study #134 in that AEs were recorded for the first 10 days of the study rather than the first 7 days.

MO COMMENT: Amodiaquine has been described in standard texts (Bruce-Chwatt, Goodman and Gilman) as a congener of chloroquine that is more active *in vitro* and *in vivo* against chloroquine-resistant strains of *P. falciparum.* It has been used for both treatment and prophylaxis of malaria. The treatment dose described in Goodman and Gilman (6^{th} ed) is somewhat lower than the one used in this protocol, it is 24 hourly doses of 600 mg-400 mg-400 mg. One of the metabolites of amodiaquine, a quinoneimine, can cause hepatotoxicity and potentially lethal agranulocytosis (1 in 2000 taking a prophylactic regimen). Because of the risks and limited therapeutic advantage over chloroquine, the use of amodiaquine for prophylaxis and treatment has been discouraged by WHO. There are some authors who consider this action premature. Amodiaquine is still used in some countries, as noted above.

MO COMMENT: Amodiaquine hydrochloride (Camaquin, Parke-Davis NDA 6441) was approved for marketing by the FDA in 1948. The NDA was one of 91 withdrawn by the commissioner on April 1, 1994 because the drug had ceased to be marketed in the US. The Federal Register notice of March 2, 1994 (docket no. 94N-0044) in which this withdrawal was announced stated that this action was being taken at the manufacturer's request.

MO COMMENT: Patients who are not hospitalized for the entire duration of the study provide a study population in whom recurrent parasitemia cannot be regarded as recrudescence of prior infection rather than reinfection. This should be kept in mind when comparing efficacy rates of either treatment group in the present study to efficacy rates among patients who remain in an area of no malaria transmission for the duration of the study.

RESULTS

DEMOGRAPHICS

There were 148 patients enrolled in this study; 141 had acute falciparum malaria, 7 were infected with other *Plasmodium* species. All but four were black Africans. Two were described as Metiose (mixed race, no indication of immune status), and one was described as 'white, non-immune,' and one as Arab (also no indication of immune status). Though the entry criteria specified that patients should be between 15 and 65 years old, five were enrolled with ages outside this range. Patient #081 was 80 years old, #082 was 70 years old, #M2 was 13 years old, #M5 was 73 years old, and #M7 was 10 years old. Demographic characteristics of both treatment groups with falciparum malaria and of those infected with other *Plasmodia* are presented in Table 1.

Table 1. Demography

Group	No.	Sex (M/F)	Mean Age (yrs)	Mean Weight (kg)	Mean IPC /µl	Fever at presentation	Splenomegaly at presentation
ATQ/ PRG	70	33/37	32.1	58.9	4883	32/70 (45.7%)	10/70 (14.3%)
AMO	71	34/37	28.6	60.2	6328	44/71 (62.0%)	13/71 (18.3%)
Other plasmodia	7	6/1	32.4	51.9	3004	-*	-*

IPC=Initial Parasite Count

*These data were not provided for the 'Other plasmodia' group

Table 1 demonstrates that the two treatment arms infected with *P. falciparum* were well matched for age, weight, initial parasite count, and rates of fever and splenomegaly during presentation.

EVALUABILITY AND EFFICACY

Patients infected with *P. falciparum* will be discussed first; a discussion of patients infected with other plasmodia will follow.

Applicant assessment

Evaluability (patients with *P. falciparum* only)

The applicant's analysis of patient evaluability is presented in Table 2.

Table 2. Patient evaluability per applicant

	ATQ/PRG	MFQ
Total patients enrolled	70	71
Evaluable patients for cure rate	63 (90%)	63 (88.7%)
Patients lost to follow-up	5 (7.1%)	7 (9.9%)
Withdrawn patients	2 (2.9%)	1 (1.4%)

The applicant reported that two patients in the ATQ/PRG group were withdrawn, #060 and #062. One patient in the AMO group, #037 was withdrawn. Patient #060 was withdrawn when she refused the first dose of study drugs. Patient #062 was withdrawn for a serious AE, vomiting, urticarial rash, and hypotension. For additional discussion of this patient, please see Efficacy and evaluability, MO assessment below. Patient #037 was withdrawn because she received a 10-day course of trimethoprim for a urinary tract infection during the course of the study.

Efficacy

Overall cure

As noted above, cure was defined as elimination of parasite within 7 days with no recrudescence by day 28. The applicant's assessment of cure rates is presented in Table 3.

Table 3. Cure rates per applicant

	ATQ/PRG	AMO
Total patients randomized	70	71
Evaluable patients Cured ('sensitive' or S) Not cured ('resistant' or RI, RII, RIII,)	63 62 (98.4%) 1 (1.6%)	63 51(81.0%) 12 (19.0%)
Unevaluable patients	7	8

The 95% CI around the difference in cure rates was [5.7, 29.2]. ATQ/PRG efficacy was equivalent to or better than that of amodiaquine in the applicant's analysis.

> MO COMMENT: The one patient who was not cured in the ATQ/PRG group was #075, a 16 year old African boy who weighed 55 kg and was observed to recrudesce at day 28. As noted above, in out-patients residing in a malaria-endemic area, recrudescence cannot be distinguished from reinfection.

PCT and FCT

The applicant did not note any differences in PCT or FCT between treatment arms. These results are presented in Table 4.

Table 4. PCT and FCT per applicant

	PCT (hrs)			FCT (hrs)		
Treatment group	No.	Median	Mean	No.	Median	Mean
ATQ/PRG	67	83.3	72.1	39	12.0	27.4
AMO	71	60.1	65.8	52	12.0	19.8
Other Plasmodia	7		130.3	3		20.0

MO COMMENT: The FCT as an indicator of drug efficacy is of limited use in this study. While about 16% of patients in either treatment group received an antipyretic, 22.5% of patients treated with amodiaquine received prednisolone, mostly for itching. Only 1.4% of patients treated with atovaquone/proguanil received prednisolone. Itching following administration of chloroquine is commonly seen in African patients; it is not surprising that a similar phenomenon was observed in the treatment group receiving a chloroquine congener.

MO assessment

Evaluability and efficacy

Evaluability and efficacy were assessed by the MO using a sampling technique. A random sample of 61/148 (41.2%) patients was generated. Individual CRTs and pertinent line listings for each of these patients was reviewed by the MO for agreement between the MO and applicant regarding patient evaluability and outcome. The MO reclassified one patient. The reclassification of patients by the MO analysis was then evaluated with a bootstrap technique, and the agreement between MO and applicant classification of patients in the sample was sufficient to accept the applicant's assessments of evaluability and efficacy. These are presented in Tables 2, 3, and 4 above.

MO COMMENT: It should be noted that these tables include the patients who were infected with other *Plasmodium* species. There were seven patients infected with species other than *P. falciparum*, and all received atovaquone/proguanil. One of these patients was unevaluable (#M7) because he was lost to follow-up on day 14. Thus there were 6 patients in the ATQ/PRG treatment group who were evaluable though not infected with *P. falciparum*. The applicant reported that all were cured. If cure rates for ATQ/PRG are calculated and these patients with malaria due to other plasmodia are excluded from the evaluable population, the cure rate for ATQ/PRG in patients infected with *P. falciparum* is 56/57 (98.2%).

Review of the sample did not result in the reclassification of patients such that the applicant's data regarding overall cure rates was unacceptable. However, the one reclassification made by the MO warrants mention. Patient #062 was scored by the applicant as withdrawn (W) for a serious adverse event and therefore unevaluable. The MO considered this patient evaluable and not cured (RIII, no significant reduction in parasitemia). The MO reviewed the CRF for this patient. She was a 15 year old girl who was admitted with a mild clinical presentation of falciparum malaria, BP 100/80 mmHg and an IPC of 1000/µl. This patient vomited each day after her dose of atovaquone/proguanil, and was observed to develop an urticarial rash and hypotension to 70/45 mmHg following each dose. She was treated with prednisolone on the first day for

her skin reaction and metoclopramide following the second and third doses of atovaquone/proguanil in an attempt to keep her from vomiting the study drugs. The patient was kept in the clinic throughout day 2 because of her clinical condition. Of note were the patient's parasite counts after a 0 hr value of 1000/µl. At 12 hours, the parasite count had risen to 95,000/µl, at 24 hours 110,000/µl, at 36 hours 120,000/µl, and at 48 hr was 70,000/µl. The patient was withdrawn at 60 hours. While a rise in parasitemia during the first 24-48 hours of treatment is not uncommon in patients with falciparum malaria who are ultimately cured, this is usually quantified as 2.5 to 3x the value noted at the onset of treatment, though it may be somewhat higher in children. Patient # 062 was withdrawn when her parasite count was 70x the value noted at enrollment. Whether it would continue to decrease or increase again cannot be known. Whether patient #062's course was the result of a lack of antimalarial activity of the study drug against the infecting strain of *P. falciparum*, or the result of treatment-induced vomiting and inadequate blood levels of antimalarials cannot be determined. What is noteworthy is that this patient developed signs of anaphylaxis following her first dose of study drug and was repeatedly rechallenged with the same drug. In addition, she remained in the study despite a marked rise in parasite counts and persistent vomiting. Had this patient been withdrawn after the first dose and subsequent vomiting, hypotension, and urticaria, the MO assessment of her outcome would have been in agreement with that of the applicant. That this patient completed a full course of the study regimen despite what appears to have been repeated serious drug reactions and rising parasite counts is a failure of her medical care, including the drugs used to treat her.

Following the completion of the review of the sample discussed above, the MO reviewed all CRTs for patients in either treatment group who were withdrawn or lost to follow-up. The MO agreed with the scoring of all other patients who were withdrawn and who were lost to follow-up.

Other plasmodia

Seven patients who were infected with *P. ovale* or *P. malariae* were included in the study. All were treated with atovaquone/proguanil. As noted above, one of these patients, #M7, was lost to follow-up at day 14. Of the six evaluable patients, three were infected with *P. malariae*, two with *P. ovale*, and one with a mixed infection of *P. falciparum* and *P. ovale*. All six of these patients were cured. The data in table 4 show that the mean parasite clearance time for ATQ/PRG in these 'other plasmodia' infections was almost twice as long as was observed for the same regimen in the treatment of *P. falciparum*.

> MO COMMENT: The MO reviewed pertinent line listings and CRTs for the patients infected with other plasmodia. The MO analysis agrees with that of the applicant. In a small number of patients infected with *P. ovale* or *P. malariae*, atovaquone/proguanil achieved high overall cure rates with somewhat prolonged parasite clearance times. The draft label submitted by the applicant does not include any data regarding MALARONE efficacy in malaria due to *P. ovale* or *p. malariae*. Data on drug efficacy against these two less common malaria pathogens is not readily available. Among those antimalarials more recently approved by FDA, Fansidar and Lariam, there is either no mention of these species (Fansidar),

or an explicit statement of lack of clinical trial data in infections due to these species (Lariam). While the data presented for atovaquone/proguanil do not warrant the expansion of the INDICATIONS and USAGE section to include *P. ovale* and *P. malariae*, information in the label regarding drug efficacy in this small number of patients may be useful to the prescribing physician.

SAFETY

The applicant's discussion of safety was divided into two parts: adverse experiences and laboratory abnormalities.

Adverse Experiences

Signs and symptoms first appearing or increasing in severity within 10 days of initiation of treatment with a frequency >2% are recorded in Table 5. Vomiting occurred with about equal frequency in both treatment groups. Abdominal pain was twice as frequent in those patients treated with ATQ/PRG.

Table 5. Adverse experiences

	Atovaquone/Proguanil		Amodiaquine	
	Number	Percent	Number	Percent
Pruritus	8	11.4%	35	49.3%
Vomiting	20	28.6%	20	28.2%
Nausea	23	32.9%	16	22.5%
Insomnia	12	17.1%	26	36.6%
Diarrhea	18	25.7%	13	18.3%
Abdominal Pain	20	28.6%	10	14.1%
Dizziness	4	5.7%	19	26.8%
Headache	10	14.3%	11	15.5%
Weakness	4	5.7%	16	22.5%
Anorexia	6	8.6%	13	18.3%
Coughing	3	4.3%	7	9.9%
Myalgia	6	8.6%	4	5.6%
Palpitations	3	4.3%	5	7.0%
Chills/Rigors	3	4.3%	4	5.6%
Gastric Pain	2	2.9%	1	1.4%
Tinnitus	1	1.4%	2	2.8%
Common Cold	2	2.9%	0	
Photophobia	2	2.9%	0	

Laboratory results

Examination of means and/or medians for chemistry, hematology, and urinalysis values did not reveal any clinically significant differences between treatment groups. The numbers of individuals in each treatment group with clinically significant laboratory abnormalities is presented in Table 6. Of note is that changes in liver function tests were uncommon in this study.

Table 6. Clinically significant laboratory abnormalities

		Atovaquone/Proguanil		Amodiaquine	
Test	Criteria	Number (%) Developing Abnormality	Number Abnormal at 28 Days	Number (%) Developing Abnormality	Number Abnormal at 8 Days
Hematocrit	< 25%	0	0	3 (4.5%)	1
Hemoglobin	< 7.5 g/dl	0	0	3 (4.5%)	1
White Cell Count	< 3000 /µl	0	0	2 (3.0%)	0
Neutrophil Count	< 1000 /µl	10 (15.2%)	4	8 (11.9%)	3
Eosinophil Count	> 1000 /µl	18 (27.3%)	16	22 (32.8%)	18
Platelet Count	< 50 /nl	0	0	0	0
Glucose	< 50 mg/dl	0	0	1 (1.5%)	1
BUN	> 25 mg/dl	0	0	2 (3.0%)	0
Creatinine	> 2.0 mg/dl	0	0	0	0
Albumin	< 3.0 g/dl	0	0	0	0
Bilirubin	> 2.0 mg/dl	0	0	0	0
ALAT	> 100 U/l	0	0	0	0
ASAT	> 100 U/l	1 (1.5%)	0	0	0
Proteinuria	2+ or greater	0		0	
Hematuria	2+ or greater	1 (1.4%)		1 (1.4%)	

REVIEWER'S COMMENTS

This comparative trial of atovaquone/proguanil and amodiaquine in a population of Gabonese adults with falciparum malaria demonstrated that cure rates achieved with atovaquone/proguanil were high and better than those achieved with amodiaquine, a chloroquine congener thought to have some activity against chloroquine-resistant strains of *P. falciparum*. Indeed, the protocol for this study was amended to increase the enrollment when efficacy rates with amodiaquine were higher than what was anticipated when the trial was initially designed. The comparison of the prior clinical efficacy data available on antimalarials in Gabon and what was observed for amodiaquine in study #115-134 highlights the difficulty in characterizing antimalarial resistance in a given area. Though the data in the present study demonstrate a higher efficacy rate for amodiaquine than was previously reported (81% v. 65%), both are unacceptably low. Study #115-134 provided adequate evidence to conclude that atovaquone/proguanil is clinically effective in an area where amodiaquine has an unacceptable failure rate, presumably due to parasite resistance. This study also provided a limited amount of efficacy data on atovaquone/proguanil in the treatment of the more infrequent species that cause human malaria, *P. ovale* and *P. malariae*.

Study #115-136

Comparative clinical trial of a fixed formulation of atovaquone and proguanil versus chloroquine in the treatment of acute *P. falciparum* malaria in adults or children in Peru

STUDY OBJECTIVES AND DESIGN

This trial was planned as an open-label, randomized, controlled trial of two multidose regimens for the treatment of falciparum malaria. It was the first trial of atovaquone/proguanil in a fixed combination formulation, and the only one of the phase III trials submitted in NDA 21-078. It was to enroll 50 patients into each of two treatment groups, atovaquone/proguanil or chloroquine. After 29 patients were enrolled, it was found that those patients in the chloroquine treatment group had a cure rate of ~7% and it was thought to be unethical to proceed with further treatment with chloroquine alone. The protocol was amended to change the comparator to Fansidar (pyrimethamine/sulfadoxine). The plan was then to re-randomize treatment assignment and make this second phase of the study independent of the first. However, patient recruitment declined and this second phase of the study was prematurely terminated. The principle investigator was Dr Alejandro Llanos-Cuentas, Alexander von Humboldt Institute of Tropical Medicine, Universidad Peruana Cayetano Heredia, Lima, Peru, and Study House, Piura, Peru. The study was conducted in accordance with the provisions of the Declaration of Helsinki. It received approval from the Institutional Review Board, Universidad Peruana Cayetano Heredia, Lima.

PROTOCOL OVERVIEW

This study was conducted from June 1995 to May 1996. It enrolled 43 patients aged 12-65 years with acute, uncomplicated falciparum malaria and parasite counts of 1000-200,000/µl who presented to clinics around the northern Peruvian city of Piura, which is

located in an area where malaria is endemic and transmission occurs throughout the year. Vivax had previously been the main type of malaria transmitted in this region, but in recent years, the prevalence of falciparum had greatly increased. This has been attributed to the construction of new irrigation systems that have provided breeding sites for anopheline mosquitoes. Standard treatment for malaria in this area has been chloroquine, which was believed cure about 70% of patients. Chloroquine failures have been treated with Fansidar (pyrimethamine-sulfadoxine) which has been thought to be about 90% effective. Patients recruited for this study were agricultural workers who were life-long residents of the area, and therefore considered semi-immune.

The study population, study procedures, evaluability criteria, efficacy endpoints, and safety monitoring in #115-135 were similar to those described for #115-127. The reader is referred to that review for a detailed description. Study #115-136 differed from #115-127 in that the patients who received the comparator agent were treated first with chloroquine, 600 mg x 1, 300 mg 6 hr later, then 300 mg per day x 2 days. Because of a 7% cure rate among these patients treated with chloroquine alone (n=14), subsequent patients in the control group received Fansidar (pyrimethamine-sulfadoxine) 25mg-500 mg, three tablets administered in a single dose, instead of chloroquine. Patients in #136 could have had initial parasite counts that ranged from 1000 to 200,000 parasites/ µl rather than 1000-100,000/ µl. All patients in study #136 were housed in the Piura study house for the entire duration of the study. The calculation of cure rates for study #136 also differed in that patients who were withdrawn (W) were considered unevaluable and were excluded from the calculation of 28-day cure rates. Cure rates were calculated from the ratio #S responses/# total evaluable patients.

MO COMMENT: Chloroquine (Aralen, NDA 6-002) was approved by the FDA for the treatment of malaria in 1949. The treatment dose in the FDA approved label is the same as the regimen described for the study under review. Pyrimethamine-sulfadoxine (Fansidar, NDA 18-557) was approved by the FDA for the treatment of falciparum malaria in 1981. The US label states that the treatment dose is two to three tablets of pyrimethamine 25-mg/sulfadoxine 500 mg taken together as a single dose. The FDA approved label does not provide instructions for determining whether a patient should receive two or three tablets.

MO COMMENT: Patients who are hospitalized for the entire duration of the study or patients who are discharged to an area where no malaria transmission occurs following treatment for acute malaria provide a study population in whom recurrent parasitemia can be regarded as recrudescence of prior infection rather than reinfection. Such a population permits a more accurate assessment of drug efficacy.

RESULTS
DEMOGRAPHICS

There were 43 patients enrolled in this study; all were described as mestizo (mixed race). The study was divided into two phases. Phase I included the population treated with

either atovaquone/proguanil (A/P-I: 15 patients) or chloroquine (C-I: 14 patients). Phase II included the population treated with either atovaquone/proguanil (A/P-II: 5 patients) or Fansidar (P/S-II: 9 patients). Table 1 presents demographic data on all four groups.

Table 1. Demography

Group	Sex (M/F)	Mean Age (yrs)	Mean Weight (kg)	Mean IPC /µl	Fever at presentation	Splenomegaly at presentation
A/P- I	11/4	37.0	59.2	4378	14/15 (93%)	6/15 (40%)
C - I	14/0	32.8	57.7	4091	13/14 (93%)	6/14 (43%)
A/P - II	3/2	26.0	51.4	2344	4/5 (80%)	1/5 (20%)
P/S-II	7/2	32.8	61.0	4523	9/9 (100%)	3/9 (33%)

IPC=Initial Parasite Count

Table 1 demonstrates that the treatment arms were well matched for age, weight, initial parasite count, and fever or splenomegaly at presentation.

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

study in Peru. Many of these patients had received antimalarials prior to enrollment. The Kenyan children enrolled in study #115-131, a population generally considered 'less immune' than adults in malaria-endemic regions, presented with mean IPCs ~30,000/µl; the proportion who were febrile was ~75%. The European adults in study #115-130 presented with a mean IPC ~20,000 and ~90% were febrile. It should be noted that all of the IPC values under discussion here are relatively low; 25,000/µl is approximately a 0.5% parasitemia in patients with a normal hematocrit, and that peripheral parasite counts do not reflect the total body parasite mass, much of which can be sequestered in the microvasculature of various organ systems. Perhaps distinctions between IPCs ≤1% are not clinically meaningful. It is also noteworthy that the intensity of malaria transmission can vary widely in a number of areas in which the disease is 'endemic,' and there is little information in these studies regarding the use of antipyretics prior to presentation. However, the divergent rates of fever at presentation for a given value of IPC observed in these study populations does suggest different host responses among a group generally regarded as 'semi-immune.' A comparison of the highly diverse study populations in this NDA suggests a 'spectrum of immunity' to malaria, even among those individuals who are life-long residents of an endemic region. For further discussion of this issue, the reader is referred to the MO review of the Integrated Summary of Efficacy.

EVALUABILITY AND EFFICACY

Evaluability

The applicant's analysis of patient evaluability is presented in Table 3.

Table 3. Patient evaluability per applicant

	A/P - I	C-I	A/P-II	P/S-II
Total patients enrolled	15	14	5	9
Evaluable patients for cure rate	14 (93.3%)	13 (92.9%)	5 (100%)	7 (77.8%)
Withdrawn patients	1 (6.7%)	1 (7.1%)	0	2 (22.2%)

Patient #002 was randomized to A/P and withdrawn after treatment due to a serious adverse event (SAE), a partial seizure which generalized. Patient # 006 was withdrawn after treatment with chloroquine because he received TMP-SMX for a urinary tract infection during the follow-up period. Two patients randomized to Fansidar were withdrawn after treatment. Patient # 036 withdrew his consent seven days after treatment because he wanted to go home. Patient # 043 also withdrew seven days after treatment when he became asymptomatic. No patients died.

MO COMMENT: The MO reviewed the CRF for patient #002. She was a 48 year old woman with a prior history of a seizure disorder four years before enrollment. She had a focal seizure which generalized on day 2. The last parasite count taken before the seizure was 1/µl. The patient was withdrawn from the study and transferred to a hospital for further evaluation. She was found to have had a serum

Na of 115 mEq/L, serum glucose 80 mg/dl, a negative head CT, and a history of serious bleeding at the delivery of her last child several years earlier. The patient underwent an evaluation for hypopituitarism associated with Sheehan's syndrome. The results were not reported in the NDA. Review of these clinical events does not rule out malaria as a cause of the patient's seizure, but her history of a seizure disorder and the finding of hyponatremia strongly suggest alternative explanations. The MO assessment of her evaluability concurs with that of the applicant.

Efficacy

Overall cure

As noted above, cure was defined as elimination of parasite within 7 days with no recrudescence by day 28. The applicant's assessment of cure rates is presented in Table 4.

Table 4. Cure rates per applicant

	A/P - I	C - I	A/P - II	P/S-II
Total patients randomized	15	14	5	9
Evaluable patients	14	13	5	7
Cured ('sensitive' or S)	14(100%)	1(7.6%)	5 (100%)	7 (100%)
Not cured ('resistant' or RI, RII, RIII,)	0 (0%)	12 (92.4%)	0 (0%)	0 (0%)
Unevaluable patients	1	1	0	0

MO COMMENT: Of the 12 chloroquine failures, 7 had a RI response and 5 had a RII response. This study provides an opportunity to assess the clinical efficacy of atovaquone/proguanil in direct comparison to that of chloroquine. It establishes that atovaquone/proguanil is effective treatment for falciparum malaria in an area of a high rate of chloroquine failures, assumed to be due to resistance to chloroquine.

MO COMMENT: The MO reviewed pertinent line listings and agrees with the applicant's assessment of efficacy. In this small study population, atovaquone/proguanil in a fixed combination and pyrimethamine/sulfadoxine in a fixed combination (Fansidar) demonstrate high and comparable rates of efficacy.

PCT and FCT

The applicant noted no significant difference between treatment arms for the median values of either PCT or FCT. These results are presented in Table 5.

Table 5. PCT and FCT per applicant

	PCT (hrs)			FCT (hrs)		
Treatment group	No.	Median	Mean	No.	Median	Mean
A/P-I	14	57	55.7	14	46	42.9
C-I	9	48	58.7	11	48	48
A/P-II	5	42	44.4	5	40	38.4
P/S-II	9	42	38.0	9	44	48

MO COMMENT: The PCT and FCT observed for ATQ/PRG in this study was comparable to what has been observed in larger studies.

SAFETY

The applicant's discussion of safety was divided into two parts: adverse experiences and laboratory abnormalities.

Adverse Experiences

Signs and symptoms first appearing or increasing in severity within 7 days of initiation of treatment and considered by investigators to be attributable to study medication are presented in Table 7.

Table 7. Adverse experiences considered by the investigators to be attributable to study medication

Adverse Experience	A + P n = 20		PYR + S n=9		C n=14	
	N	%	N	%	N	%
Cutaneous System						
Pruritus	0	0	1	11	2	14
Gastrointestinal System						
Abdominal Pain	2	10	0	0	0	0
Diarrhea	1	5	0	0	0	0
Nausea	4	20	0	0	0	0
Vomiting	3	15	1	11	0	0
Number and % of Subjects Reporting at Least One Adverse Experience	9	45	2	10	2	14

MO COMMENT: As noted in other studies, attributable nausea and vomiting occurred more frequently in patients who received ATQ/PRG than in those who received control drugs.

Laboratory results

Examination of clinically significant laboratory abnormalities in each treatment group revealed one abnormality in the patients treated with ATQ/PRG. This was hypoglycemia (glc < 50 mg/dL), and this was reported in two patients, #005 and #010. The applicant reported that these findings were recorded 7-28 days following the start of treatment and was not considered drug related.

MO COMMENT: Hypoglycemia can be a manifestation of severe malaria. The MO reviewed the serial blood glucose values and concurrent parasite counts for both of these patients. Patient #005 had a blood glucose value of 42 mg/dL on study day 28, at which time his peripheral smear was negative and had been negative for ~25 days. Patient #010 was enrolled with a blood glucose value of 42 mg/dL. All values obtained for this patient's blood glucose were <50 mg/dL until the last one on day 28. This patient cleared his parasitemia on day 3 and it did not recur. He had low blood glucose values with and without parasitemia; it is unlikely his low blood sugars were due to his infection.

REVIEWER'S COMMENTS

This trial of atovaquone/proguanil, chloroquine, and pyrimethamine/sulfadoxine in a population of Peruvian adults demonstrated that cure rates achieved with a fixed combination of atovaquone/proguanil were high and similar to those achieved with these drugs in a non-fixed combination in other study centers in Asia, Africa, and South America. It also demonstrated the efficacy of atovaquone/proguanil in an area of high failure rates for chloroquine. Initial parasite counts and rates of fever at presentation suggest speculation regarding different degrees of 'semi-immunity' among adults resident in malaria-endemic areas.

Uncontrolled clinical trials

There are [redacted] clinical trials of treatment of falciparum malaria in NDA 21-078. They are discussed separately below.

[redacted]

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Study #115-005
An open study to determine whether 566C80 (atovaquone) exhibits antimalarial activity in Thai patients with *P. falciparum* malaria

STUDY OBJECTIVES AND DESIGN

This was a phase II open-label study initially designed as a comparison of different doses of atovaquone as monotherapy for the treatment of adults with acute uncomplicated falciparum malaria. As the study progressed, and as information from study #115-003 became available, amendments were made to the protocol that changed the treatment regimens such that atovaquone would be studied in combination with other antimalarial agents. These agents were tetracycline, doxycycline, pyrimethamine, and proguanil. The objective was to determine cure rates at 28 days for these different regimens. The study was also planned to assess PCT and FCT for these regimens, and to determine whether recrudescent parasites had an altered susceptibility to atovaquone. A final amendment to the protocol was made to evaluate the response of a fixed dose combination of atovaquone and proguanil in the treatment of acute vivax malaria. The principal investigator was Professor Somchai Looareesuwan MD, Hospital for Tropical Diseases (HTD), Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand. All patient care took place at the HTD, Bangkok. The study was conducted in accordance with the provisions of the Declaration of Helsinki; the original protocol and all amendments were approved by the Ethics Committee of Mahidol University.

PROTOCOL OVERVIEW

The study was conducted from October 1990 to July 1993. It enrolled a total of 317 Asian men between 16 and 65 years old with acute uncomplicated malaria. Patients with falciparum malaria were enrolled sequentially into one of thirteen cohorts. A fourteenth cohort was included in this protocol; it enrolled patients with acute vivax malaria. All patients had initial parasite counts $\leq$ 100,000/µl; patients with schizonts on the peripheral smear were excluded. All patients agreed to remain in the hospital for the 28-day study period that included treatment and follow-up observation. Patients were monitored with regular assessments of temperature and of serial blood samples to assess clearance and recrudescence of parasitemia. Physical exams and serial blood sampling for drug levels, hematology, and routine biochemistry testing were also performed. Prior to treatment 92% of the 317 patients had plasma specimens analyzed for mefloquine or quinine concentrations, and 96% had urine analyzed for the presence of chloroquine or sulfonamides. The primary efficacy parameter was the 28-day cure rate, defined as the percentage of patients in whom parasitemia was eliminated and did not recur during the 28-day follow-up period. Responses were graded according to the WHO criteria described for study #115-127. The reader is referred to the MO review for #115-127 for a more detailed description of the WHO criteria and calculation of cure rates. Other efficacy endpoints included measurements of parasite clearance time (PCT) and fever clearance time (FCT), drug susceptibility of recrudescent parasites, and, for patients with vivax malaria, 14-day cure rates.

RESULTS

EVALUABILITY

There were 292 patients enrolled with falciparum malaria and 25 patients with vivax malaria. Eighteen patients were well when allowed to go home, but did not return for follow-up examinations. Three patients were withdrawn after retreatment with atovaquone for persistent parasitemia. Thus there were 21 patients excluded from efficacy analysis; they are listed in Table 1. The remainder of the 296 patients remained in the hospital or in metropolitan Bangkok, an area without malaria transmission, for the full duration of the follow-up. No patients died during the study and no patients were withdrawn due to an adverse event.

Table 1. Excluded patients

Cohort	No. of patients	Pt # and reasons for exclusion from analysis
2	2	#49 and #50 withdrawn 59 and 60 hours after treatment for persistent parasitemia
4	4	#85, #89, #94 lost to f/u on days 24, 8, 21 #102 withdrawn day 10 for persistent parasitemia
5	4	#114, #133, #152, #158 lost to f/u on days 11, 4, 18, 20
8	1	#190 lost to f/u day 8
10	1	#214 lost to f/u day 7
11	1	#248 lost to f/u day 10
12	1	#259 lost to f/u day 7
13	1	#291 lost to f/u day 3
14	6	#305, #308, #310, #315, #316, #317 lost to f/u days 12, 4, 11, 13, 6, 11

MO COMMENT: The MO reviewed the line listings for all patients in Table 1 who were withdrawn for persistent parasitemia. All such patients were considered evaluable and not cured by the applicant (ie RI, RII, or RIII). The MO concurred with this analysis.

Of the remaining 296 patients evaluable for cure, 194 (65.5%) had evidence of exposure to one or more antimalarials; 102 (34.5%) had no evidence of exposure. By analyzing efficacy by exposure to prior treatment, the applicant contended that there was no relationship between prior antimalarial exposure and cure rates (see EFFICACY below), and thus regarded these patients as evaluable.

MO COMMENT: The MO reviewed the applicant's analysis of efficacy according to prior antimalarial exposure, and agreed that there was no relationship demonstrated between prior antimalarial exposure and cure rate. The MO performed an additional analysis on the subpopulation of patients with falciparum malaria who were not cured by the regimen assigned to their cohort. Of the 46 patients who were not cured and who had data available for both plasma and urine assays for antimalarials, 31 had evidence of having received prior antimalarial therapy, and 15 had no evidence of prior therapy by both serum and urine assays

for all four agents listed above. Patients who failed therapy were more likely to have evidence of prior antimalarial exposure than not. It should be noted that among those 46 patients were 11 who were not treated with an atovaquone-containing regimen; they received proguanil alone. The MO concurred that there was no correlation between prior antimalarial exposure and observed efficacy for a given study regimen. In addition, the evaluation of patients with prior exposure to antimalarials provided an opportunity to evaluate drug efficacy in a setting more relevant to clinical use.

EFFICACY

Cure rates, PCT and FCT are presented by cohort in Table 2.

Table 2. Efficacy by cohort

Cohort	No. of Pts	Atovaquone Dose	Other Drug	Dose Regimen	Evaluable Pts	Cure Rate (%)	PCT (hrs)	FCT (hrs)
1	25	750 mg q8h x 4 doses	none		25	72	64	59
2	25	750 mg q8h x 21 doses	none		23	61	60	48
3	25	750 mg q8h x 4 doses	Tetracycline	250 mg qid x 7 days	25	100	68	31
4	30	750 mg q8h x 4 doses	Proguanil	200 mg qd x 7 days	26	96	61	43
5	34	500 mg bid x 3 days	Proguanil	200 mg bid x 3 days	30	93	60	46
6	22	500 mg bid x 3 days	Doxycycline	100 mg bid x 3 days	22	91	65	52
7	24	500 mg bid x 3 doses	Proguanil	200 mg bid x 3 doses	24	83	64	64
8	5	none	Proguanil	200 mg bid x 3 days	4	0	nc	nc
9	13	none	Proguanil	500 mg bid x 3 days	13	8	124	69
10	25	1000 mg qd x 3 days	Pyrimethamine	25 mg qd x 3 days	24	75	64	43
11	25	1000 mg qd x 3 days	Proguanil	400 mg qd x 3 days	24	100	65	61
12	25	500 mg bid x 5 days	Proguanil	200 mg bid x 5 days	24	100	71	85
13	14	500 mg qd x 3 days	Pyrimethamine	25 mg qd x 3 days	13	77	63	59
14	25	1000 mg qd x 3 days	Proguanil	400 mg qd x 3 days	19	100	106	47

MO COMMENT: Atovaquone tablet 750 mg po q 8 hours is the regimen approved by FDA for treatment of *P. carinii* pneumonia. For this indication, the drug is administered for 21 days. Atovaquone suspension, which provides a twofold increase in bioavailability over the tablet, was approved by FDA for prophylaxis of *P. carinii* pneumonia at a dose of 1500 mg per day. Drug exposure for atovaquone-containing regimens in the study under review does not exceed previously approved regimens.

MO COMMENT: Proguanil, also known as chloroguanide, was developed by the British during World War II. Though a potent blood schizonticide, it is one of the slowest-acting antimalarials for clearing parasites and reducing fever. Its main value is as a causal prophylactic or radically curative agent against sensitive strains of *P falciparum*; it kills pre-erythrocytic schizonts. Of note is that it also has activity against gametocytes, and therefore some potential activity as a transmission-blocking agent. Proguanil 300 mg bid for 10 days was originally used for treatment of malaria. Because of high failure rates, it ceased to be recommended for this purpose. However this drug has been used as a prophylactic, alone or in combination, since the 1940s. The development of resistance to proguanil noted in the 1960s and 70s was overcome in part by increasing the daily dose of the prophylactic regimen from 100 to 200 mg per day. In recent years, perhaps as a result of this higher dose, there has been an increased recognition of side effects such as hair loss, mouth ulcers, scaling of the palms and soles, and abdominal symptoms. Patients with renal failure have developed megaloblastic anemia and thrombocytopenia while taking proguanil. Nonetheless, chloroquine - proguanil is an important antimalarial prophylactic regimen prescribed in Canada, the UK, and many other countries outside the US. Standard texts (Manson, Bruce-Chwatt, Goodman and Gilman) refer to proguanil as one of the safest antimalarials because of its many decades of widespread use. Proguanil (Paludrine, NDA 0-6453, held by Burroughs Wellcome & Co,) was approved by the FDA in April 1948. Editions of the PDR from 1968-1970 (the earliest available to date) list Paludrine, manufactured by Ayerst, but there is no label for the drug in any of these editions. In 1971, in an attempt to close a large number of NDAs that were for drugs that had been discontinued or never marketed, the FDA withdrew approval for Paludrine. When asked, GlaxoWellcome was unable to provide any additional information regarding the marketing history of Paludrine in the US. To date, no information has been found that suggests it was withdrawn for safety reasons. There remains an active IND for proguanil on file with FDA; IND [redacted] is held by [redacted]

Atovaquone alone (cohorts 1, 2) cured only about two-thirds of patients, even when relatively large doses were administered for seven days. When either tetracycline or proguanil were given concurrently for seven days (cohorts 3, 4), cure rates were >95%. Efficacy remained high when these regimens were shortened to five days or three days (cohorts 5, 6, 12). Proguanil alone (cohorts 8, 9), even at high doses, was markedly less effective than other regimens studied in this trial. Pyrimethamine was less effective with atovaquone than was proguanil (cohorts 10, 13). The applicant noted that the most

effective and most convenient regimen given for the shortest interval for the treatment of falciparum malaria was the combination of atovaquone and proguanil given in single large daily doses for three days (cohort 11). Efficacy was also demonstrated in the treatment of the erythrocytic (acute) phase of *P. vivax* infection (cohort 14).

MO COMMENT: The present study demonstrated that the combination of atovaquone and proguanil resulted in a better cure rate compared to either atovaquone or proguanil alone.

MO COMMENT: The cure rate observed for vivax malaria is limited to the erythrocytic phase of the parasite with follow-up to 14 days following the initiation of therapy.

MO COMMENT: This study is the basis for the selection of the atovaquone 1000 mg /proguanil 400 mg daily dose taken for three days evaluated for treatment in the phase III clinical trials and the dose recommended in the applicant's draft label for the treatment of acute falciparum malaria. This dose provides 20 mg/kg atovaquone and 8 mg/kg proguanil per day to a 50 kg adult. The cohort in whom this dose of atq/prg was tested (cohort 11) included 25 Thai adult males whose mean weight was 50.2 kg (range 44-60 kg). There were 8 patients who weighed more than 50 kg. The average US adult can weigh considerably more than 50 kg; the standard weight used for US adult males for the purposes of calculation is often 70 kg. Such a patient would receive 14.2 mg/kg atq / 5.7 mg/kg prg in the treatment regimen above. For additional analysis of drug efficacy according to patient weight, the reader is referred to the MO review of the Integrated Summary of Efficacy.

SAFETY

Adverse events and laboratory abnormalities

Observations regarding adverse events or laboratory abnormalities are difficult to interpret in this study of multiple drug combinations and dosage regimens. The MO reviewed the applicant's tabulations of adverse events and laboratory abnormalities and agreed that the most noteworthy observation was that 11.7% of all patients enrolled had an elevated ALT during the course of the study. There was no analysis of this finding by treatment group. It is a noteworthy finding because, though transaminase abnormalities are commonly seen in acute malaria, another study of Thai patients, # 115-122, also found transaminase elevations associated with those patients receiving atovaquone/proguanil. There was some speculation by the sponsor that underlying viral hepatidites, common in SE Asia, may have been a factor in this observed abnormality of liver function.

Parasite susceptibility studies

A total of 53 patients from cohorts 1-13 had persistent falciparum parasitemia after treatment or later recrudesced. The applicant provided data on IC50 values for paired isolates from patients treated for 3 days or more with atovaquone alone or with

atovaquone and proguanil. Table 3 presents the mean results of susceptibility studies performed on these isolates.

Table 3. In vitro susceptibility results on recrudescent paired isolates

Treatment	Number of pairs	Pretreatment IC50 (ng/ml)	Recrudescent IC50 (ng/ml)
Atovaquone alone	12	3.3	4947
Atovaquone with proguanil	3	1.2	3.8

Isolates cultured from patients who recrudesced following treatment with atovaquone alone demonstrated a marked rise in IC50 values suggesting the development of parasite resistance following exposure to atovaquone. This increase in IC50 was not demonstrated in paired isolates from patients who recrudesced on following treatment with the combination of atovaquone and proguanil.

MO COMMENT: It should be noted that the very small number of paired isolates available for testing from those patients who received combination therapy (n=3) makes it premature to conclude that the addition of proguanil reliably attenuates the development of resistance of *P. falciparum* to atovaquone. It should also be noted that data on drug levels from the patients who recrudesced were not available at the time of the NDA submission.

REVIEWER'S COMMENTS

The combination of atovaquone and proguanil provides considerable advantage over either atovaquone or proguanil alone in the treatment of uncomplicated falciparum malaria. The choice of the treatment regimen studied in the phase III trials and recommended in the applicant's draft label is well supported by the results observed in the present study. Susceptibility testing performed on a small number of paired isolates from patients who recrudesced suggests that resistance to atovaquone alone can develop in parasites exposed to this drug when used as a single treatment agent. The improved clinical efficacy achieved by the addition of proguanil may be due to attenuation of parasite resistance, however this hypothesis remains to be tested with a larger number of paired isolates and data regarding drug levels in recrudescent patients.

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Study #115-012
An open study to determine whether 566C80 (atovaquone) exhibits antimalarial activity in Zambian patients with *P. falciparum* malaria

STUDY OBJECTIVES AND DESIGN
This was an early phase II open-label study initially designed as a comparison of different doses of atovaquone as monotherapy for the treatment of adults with acute uncomplicated falciparum malaria in Zambia. The present study, along with #115-005 conducted in Thai adults, was undertaken to determine if atovaquone monotherapy were appropriate for testing in phase III clinical trials. The study report stated that Zambia was chosen as a site for this aspect of the evaluation of atovaquone because *P. falciparum* in this part of Africa is known to be only 'mildly resistant' to chloroquine and susceptible to other drugs. Drug evaluation in this setting would provide data complementary to data developed in Thailand where *P. falciparum* strains are resistant to several antimalarial agents. This characterization of *P. falciparum* susceptibility in Zambia is largely consistent with what was described for Zambian malaria in the study report for #115-120 in that the parasite was susceptible to agents other than chloroquine including mefloquine, pyrimethamine-sulfadoxine, and halofantrine. However, the study report for #115-120 also cited data from a WHO/CHEMAL malaria study in 1989-90 which demonstrated a cure rate of 37% for chloroquine at Ndola. While it is possible that for the country of Zambia as whole, chloroquine resistance may be described as mild, this does not appear to be the observation in recent clinical studies at Ndola.

Because the first dosing cohort, which received the maximum practical dose of 750 mg q 8 hours x 7 days, had an unacceptable rate of recrudescence, the study was stopped after the enrollment of the first cohort, and the use of atovaquone as monotherapy in falciparum malaria was abandoned. The primary objective was to determine cure rates at 42 days. The study was also planned to assess PCT and FCT, and to determine *in vitro* drug susceptibility of pretreatment clinical isolates of *P. falciparum* using the WHO microtest. The principal investigators were Dr M Mukuyandela and Dr JMK Ekue, Tropical Diseases Research Centre (TDRC), Ndola Central Hospital, Ndola, Zambia. All patient care took place at the TDRC. The study was conducted in accordance with the provisions of the Declaration of Helsinki, the protocol and was approved by the Ethical Committee of the TDRC.

PROTOCOL OVERVIEW
The study was conducted from January 1991 to March 1991. It enrolled a total of 31 African men between 16 and 45 years old with acute uncomplicated falciparum malaria. All patients were to have initial parasite counts between 1000 and 100,000/µl. Patients were excluded if schizonts were visible on peripheral smear, if they had received antimalarial therapy in the 7 days prior to enrollment, or if they had a urine assay that was positive for chloroquine or amodiaquine. All patients agreed to remain in the hospital for the 42-day study period that included the 7-day course of treatment with atovaquone 750 mg q 8 hours and the 35-day follow-up. Patients were monitored with regular assessments of temperature and of serial blood samples to assess clearance and recrudescence of parasitemia. Physical exams and serial blood sampling for drug levels,

hematology, and routine biochemistry testing were also performed. The primary efficacy parameter was the 42-day cure rate, defined as the percentage of patients in whom parasitemia was eliminated and did not recur during the 42-day follow- up period. The standard WHO 28-day cure rate was a secondary endpoint. Responses were graded according to the WHO criteria described for study #115-127. The reader is referred to the MO review for #115-127 for a more detailed description of the WHO criteria and calculation of cure rates. In the present study, patients who recrudesced after 28 days were to be scored as an RI response. Other efficacy endpoints included measurements of parasite clearance time (PCT) and fever clearance time (FCT), and drug susceptibility of pretreatment parasites.

RESULTS

EVALUABILITY

There were 31 patients enrolled with falciparum malaria, two were excluded from the calculation of cure rate. There were 29 patients evaluable for cure. One patient (# 007) was withdrawn from the study because he had <1000 parasites/µl at enrollment, and no parasites seen on peripheral smear 30 minutes after treatment. One patient (#005) was considered unevaluable (U) because he died during the follow-up period. This patient was a 23 year old man with a history of psychiatric treatment at age 19 who was afebrile at enrollment and had an IPC of 5250/µl. He was documented to have cleared his parasitemia at 90 hours (day 4). On day 5, he had an episode of bizarre behavior during which he became restless, anxious, agitated, and experienced suicidal ideation. He continued to receive atovaquone for the two days remaining in his treatment regimen, and on study day 10 was transferred to the psychiatric ward of the hospital. He was treated with haloperidol, diazepam, and benzhexol. On study day 13, the patient became drowsy, was observed to be 'gasping' and died before resuscitative efforts were underway. Autopsy was sought but refused.

MO COMMENT: The MO reviewed the case report form (CRF) for this patient. Additional information obtained included that there were no clinical or laboratory findings suggestive of a recrudescence or deterioration of the patient's malaria, though only limited data were available to evaluate this possibility. The patient had been hospitalized in 1987 on the same psychiatric ward, from which he absconded in favor of a traditional healer. It is not recorded in the CRF whether the patient was taking any traditional remedies at the time of his enrollment in the study. In the CRF, benzhexol was also referred to as artane, an anticholinergic with the US generic name of trihexyphenidyl, used to alleviate extrapyramidal symptoms associated with neuroleptic use. There have been no other reports of psychiatric symptoms in the studies of atovaquone/proguanil reviewed to date. The possibility of a drug interaction between atovaquone, which has a long half-life, and one of the psychotropic drugs prescribed or an undisclosed traditional remedy cannot be excluded. There is no additional information in the CRF suggesting why this patient died. The MO concurred that he was unevaluable.

MO COMMENT: After reviewing pertinent line listings for the 29 patients considered evaluable by the applicant, the MO agreed that these patients were evaluable.

MO COMMENT: This protocol included HIV antibody testing as part of the enrollment evaluation. Patients who were HIV infected were not excluded. Of the 31 Zambian men enrolled, 12 (40%) were HIV positive. While there has been considerable speculation in the medical literature regarding a possible relationship between HIV and malaria, such a relationship has not been demonstrated. Nonetheless, this study provides an approximation of the HIV seropositivity rate of young Zambian men. The larger, controlled phase III trial of atovaquone/proguanil and Fansidar conducted at Ndola (#115-120) did not include HIV testing as part of the enrollment evaluation, but the study population probably had a comparable HIV seropositivity rate. It is noteworthy that the cure rate for ATQ/PRG in study #115-120 was high (100%) and comparable to cure rates demonstrated in other controlled trials. ATQ/PRG efficacy was unchanged in a study population with a significant number of HIV infected patients.

EFFICACY

Cure rates, PCT and FCT are presented in Table 1.

Table 1. Efficacy rates

Parasite Clearance Time			Fever Clearance Time			Cure Rate		
Number of patients	Med (hr)	Mn (hr)	Number of patients	Med (hr)	Mn (hr)	Number of patients	28-day	42-day
31	85.4	74.6	26	14.0	27.8	29	75.9%	75.9%

Seven patients recrudesced between days 12 and 28. There were no recrudescences reported after day 28.

MO COMMENT: The MO reviewed the line listings of all patients' serial parasite counts, and agreed with the applicant's assessment of cure rate and times of recrudescences. All patients who were not cured had an RI response.

MO COMMENT: The present study demonstrated similar findings to #115-005 in that the efficacy of atovaquone monotherapy, even at high doses, is not acceptable in the treatment of acute falciparum malaria.

SAFETY

Adverse events and laboratory abnormalities

This trial evaluated a dose of atovaquone (2250 mg/day) that was considerably higher than the dose studied in phase III and recommended for treatment in the draft label (1000 mg/day). The MO reviewed the applicant's tabulations of adverse events and laboratory abnormalities and found that the most noteworthy observation was that two patients manifested psychiatric symptoms. One patient was #005, described above. The other was

#027, who was noted to be crying and reporting headache, backache, numbness in the lower extremities, palpitations, insomnia, and 'a feeling of weight on my heart' on day 2 of the study. Treatment continued and the patient's symptoms resolved within 24 hours. It was noted that the patient was a habitual marijuana user.

MO COMMENT: As noted above, there have been no reports of psychiatric symptoms in other studies reviewed to date. The dose of atovaquone studied here is higher than that studied in most other trials in the NDA under review. Additional information about psychiatric AEs seen with the use of atovaquone 750 mg tid may be found in the databases of trials of PCP treatment and prophylaxis.

Parasite susceptibility studies

In vitro drug susceptibility was tested in clinical isolates from all 31 patients. A total of 186 tests were performed, all but 8 were successful. All tests showed the parasites were sensitive to chloroquine, amodiaquine, Fansidar, quinine, halofantrine, and mefloquine.

MO COMMENT: It is difficult to interpret these *in vitro* tests of chloroquine susceptibility in light of what has been reported about the clinical efficacy of chloroquine at Ndola, which was most recently quantified at 37% (see above discussion of WHO/CHEMAL malaria study in **STUDY OBJECTIVES AND DESIGN**). There is concurrence between the results observed in clinical trials at Ndola reported in the MO review of study #115-120 (**PROTOCOL OVERVIEW** section) and *in vitro* susceptibility testing of clinical isolates from Ndola against Fansidar, mefloquine, and halofantrine reported here. However it is difficult to determine what proportions of *P. falciparum* strains infecting patients in Ndola are chloroquine susceptible and chloroquine-resistant. The combination of atovaquone/proguanil demonstrated comparable and high clinical efficacy rates in Zambia (#115-120) and Thailand (#115-122). These areas are compared because they are thought to represent opposite ends of the spectrum of resistance to other antimalarial agents, including Fansidar, mefloquine, and halofantrine. Zambia is regarded as an area with relatively low rates of *P. falciparum* resistance to these newer agents, while Thailand is regarded as an area with relatively high rates of same.

REVIEWER'S COMMENTS

Atovaquone monotherapy (750 mg q 8 hr x 7 days) is not acceptable in the treatment of acute falciparum malaria. The present study supports the findings of study 115-005, in which an unacceptable recrudescence rate was also demonstrated for several doses of atovaquone monotherapy. The present study provides some information suggesting that atovaquone/proguanil demonstrates comparable clinical efficacy in Zambia, a region of relatively low parasite resistance (high susceptibility) to Fansidar, mefloquine, and halofantrine, and Thailand, a region of relatively high parasite resistance to chloroquine, Fansidar, mefloquine, and halofantrine.

INTEGRATED SUMMARY OF EFFICACY

The applicant presented data from 12 clinical trials conducted in 1824 patients to support the efficacy of MALARONE in the treatment of acute uncomplicated malaria caused by *P. falciparum*. Eight of these trials were controlled trials that evaluated the efficacy of atovaquone/proguanil 1000 mg/400 mg daily for three days compared to that of standard of care in the region under study. All of these studies were unblinded, though technicians reading the peripheral blood smears were usually unaware of the patient's treatment. In these controlled trials, 471 patients were treated with atovaquone/proguanil at the doses recommended in the label, and 474 were treated with a comparator. Seven of the controlled studies took place in an area of malaria endemicity where the subjects were thought to have some degree of malaria immunity with the possible exception of the adults studied in Thailand (study #115-122). One study was conducted in travelers returning to France. Seven of these studies were conducted in adults; one (#115-131) was conducted in children. Three of these studies were designed to keep the patients in the hospital only for as long as they were treated or for the first seven days of the study. The patients in these trials were then followed as out-patients for the remainder of the 28-day follow-up period. The studies with such a design were #115-130, #115-131; and #115-134. In #131 and #134, patients were discharged to home in a malaria endemic area where they were at risk for reinfection with *P. falciparum*. The other studies kept patients in a malaria-free environment during follow-up. Table 1 presents a summary of clinical efficacy rates achieved in these controlled trials. It is noteworthy that the studies in which slightly lower efficacy rates were noted for atovaquone/proguanil were also studies in which patients were followed-up as out-patients.

Table 1. Parasitologic Cure Rates for Patients Treated with Atovaquone and Proguanil Hydrochloride or a Comparator Antimalarial Drug

Study Number	Location	Comparator	Cure Rate (%)	
			ATQ/PGN[a]	Comparator
115-120	Zambia	Pyrimethamine/sulfadoxine	100	99
115-122	Thailand	Mefloquine	100	86
115-127	Brazil	Quinine/tetracycline	99	100
115-130	France	Halofantrine	100	100
115-131	Kenya	Halofantrine	94	90
115-134	Gabon	Amodiaquine	98	81
115-135	Philippines	Chloroquine Chloroquine plus pyrimethamine/sulfadoxine	100	30 88
115-136	Peru	Chloroquine Pyrimethamine/sulfadoxine	100	8 100

a ATQ/PGN = atovaquone and proguanil hydrochloride

Four of the trials were uncontrolled, and provided data to support the use of this combination compared to either component alone. Recrudescence rates with either atovaquone or proguanil alone were unacceptably high. As demonstrated in study #115-005, combinations of these two agents resulted in 28-day cure rates >90% (see MO Review of Study #115-005). Three of these studies were conducted in adults, one (#115-123) was conducted in children. A small number of patients provided efficacy data on MALARONE for the treatment of acute non-falciparum malaria (ie malaria due to *P. vivax*, *P. ovale*, or *P. malariae*). When considering the data regarding MALARONE efficacy in the treatment of non-falciparum species, it is important to recognize that only activity against the erythrocytic stage of the parasite was demonstrated. No data were presented that suggest MALARONE has activity against hepatic hypnozoites of either *P. vivax* or *P. ovale*.

The following discussion will focus on 1) the efficacy of atovaquone/proguanil compared with drugs of established and enduring efficacy for the treatment of *P. falciparum*, 2) the efficacy of atovaquone/proguanil in areas where there may be *P. falciparum* resistance to other antimalarials, 3) the efficacy of atovaquone/proguanil as expressed by parasite clearance times, 4) the efficacy of atovaquone/proguanil analyzed by patient weights in adults and children, 5) the efficacy of atovaquone/proguanil in the context of the immune status of the study population, and 6) the efficacy of atovaquone/proguanil for the treatment of non-falciparum malaria.

Efficacy compared to antimalarial agents with enduring efficacy

Studies #115-120, #115-130, and #115-127 provided opportunities to compare the efficacy of atovaquone/proguanil with that of drugs with acceptable efficacy rates in the regions in which they were studied. In these studies, the comparators were pyrimethamine-sulfadoxine, halofantrine, and quinine and tetracycline. The US regulatory status of each of these comparators deserves comment. Pyrimethamine-sulfadoxine, a fixed combination product, (Fansidar, NDA 18-557) was approved by the FDA for the treatment of falciparum malaria in 1981. While this may still be an effective drug in some parts of the world, as demonstrated in Zambia, falling efficacy rates in other regions have made this drug less reliable as treatment for acute *P. falciparum* malaria in the returning traveler. Halofantrine, (Halfan, NDA 20-250) approved in 1992, was the last antimalarial approved for use in the US. It has never been marketed in this country and causes prolongation of the QT interval at the prescribed dose that has resulted in sudden death. Quinine, a blood schizonticide, has been the mainstay of therapy for falciparum malaria for centuries, since the antipyretic activity of the bark of the cinchona tree was noted by Jesuit missionaries in 17th century Peru. It has been marketed in the US for decades, and remains a grandfather drug (DESI regulations) labeled for prescription sale only. In the 1970s, resistance to quinine therapy developed in SE Asia to the point that 1973 recommendations issued by WHO advocated the oral combination of this drug with tetracycline, a tissue schizonticide. At this time, a 3-day regimen of this combination was effective for the treatment of falciparum malaria. Oral tetracycline (Achromycin, NDA 50-264) has been marketed in this country since 1963, though its US label does not

include an indication for malaria. Doxycycline (Vibramycin, NDA 50-006, approved 1967), a related drug, does include an indication for *P. falciparum* malaria in its US label. As efficacy has diminished in certain areas for this three-day regimen of quinine and tetracycline, standard treatment courses have been extended to seven days in areas of South America (Brazilian Amazonia, see MO Review, study #115-127) and SE Asia. This last combination remains the gold standard of therapy for falciparum malaria in most areas of the world, though diminishing efficacy rates have again been noted for this regimen in SE Asia. Nonetheless, in the areas studied in the listed clinical trials, these three regimens (pyrimethamine/sulfadoxine, halofantrine, and quinine/tetracycline) achieved high (99-100%) 28-day cure rates. Atovaquone/proguanil achieved comparable efficacy rates in each of these studies.

Efficacy in areas of *P. falciparum* resistance to established antimalarials

The controlled clinical trials of MALARONE were conducted in West, East, and Southern Africa, Southeast Asia, South America, and Europe. The European study, conducted in France, was not located in a malaria endemic region; most of the travelers studied in #115-130 had visited Africa. These studies provided information on MALARONE efficacy in a wide variety of geographic areas, each with different rates of clinical efficacy for established antimalarials. Parasite resistance has traditionally been assumed when clinical response to a known therapy in a particular geographic area begins to diminish. It should be recognized that other factors such as patient compliance, symptoms affecting drug absorption, and variations in metabolism and excretion are some of the reasons other than parasite resistance that can result in clinical failure. Only recently has the technology been available to assess parasite drug susceptibility *in vitro*. Moreover, the correlation between measurements of *in vitro* susceptibility and clinical outcome is not as well established for parasites as for other infectious agents such as bacteria. Nonetheless, for the purposes of assessing clinical efficacy, the term 'resistance' has been used to describe the lack of efficacy associated with various antimalarial agents in certain parts of the world. It should be noted that rates of resistance to a given antimalarial can vary with geographic region. Falciparum malaria in some regions is characterized by diminishing efficacy of one or two agents, while falciparum malaria in other areas is known to have poor response rates when treated with almost all antimalarials. Zambia is an example of the first type of area described above, and Thailand an example of the second type of area.

Atovaquone/proguanil was studied in several areas where chloroquine treatment for falciparum malaria is associated with unacceptable failure rates. Chloroquine has been a highly efficacious antimalarial in use in the US (Aralen, NDA 6002, approved 1949) and around the world for more than 50 years. Foci of chloroquine resistance were first noted in Thailand and Colombia in the 1960s. Subsequent decades have seen diminishing efficacy to chloroquine emerge in almost all areas of malaria endemicity. Indeed, the US Centers for Disease Control reports that chloroquine resistance is established and this drug is not recommended for malaria prophylaxis for US travelers visiting Brazil, Gabon, Kenya, Thailand, and Zambia. For the Philippines and Peru, the CDC lists certain areas where chloroquine resistance is established, and recommends chloroquine for prophylaxis