CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-078

MEDICAL REVIEW

MEDICAL OFFICER'S REVIEW OF NDA

NDA # 21-078
MALARONE

Applicant
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Submission/Review Dates

Date of submission:	December 29, 1998
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Drug Identification
Generic name: atovaquone and proguanil hydrochloride
Proposed trade name: Malarone
Pharmacologic category: fixed combination antimalarial
Dosage formulation: Malarone tablets: atovaquone 250 mg/proguanil 100 mg
Malarone pediatric tablets: atovaquone 62.5 mg/proguanil 25 mg

Route of administration: oral

Proposed INDICATION AND USAGE and DOSAGE AND ADMINISTRATION
The following are quoted verbatim from the label proposed by GlaxoWellcome at the time of the submission of the NDA:

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

Treatment of Malaria: MALARONE is indicated for the treatment of acute, uncomplicated *P. falciparum* malaria.

DOSAGE AND ADMINISTRATION

Prophylactic treatment with MALARONE should be started 1 or 2 days before entering a malaria-endemic area and continued for 7 days after return.

Adults: One MALARONE tablet (adult strength = 250 mg atovaquone/100 mg proguanil hydrochloride) per day

Pediatric patients: The dosage for prevention of malaria in pediatric patients is based upon body weight:

Dosage for prevention of malaria in pediatric patients

Weight (kg)	ATQ/PRG total daily dose	Dosage regimen
11-20	62.5/25 mg	One MALARONE Pediatric Tablet daily
21-30	125/50 mg	Two MALARONE Pediatric Tablets as a single dose daily
31-40	187.5/75 mg	Three MALARONE Pediatric Tablets as a single dose daily
>40	250/100 mg	One MALARONE Tablet (adult strength) daily

DOSE: *Adults:* Four MALARONE Tablets (adult strength; total daily dose 1 gram atovaquone/400 mg proguanil hydrochloride) as a single dose daily for 3 consecutive days.

Pediatric patients: The dosage for treatment of acute malaria in pediatric patients is based upon body weight according to the following table.

Dosage for treatment of acute malaria in pediatric patients

Weight (kg)	ATQ/PRG total daily dose	Dosage regimen
11-20	250/100 mg	One MALARONE Tablet (adult strength) daily for 3 consecutive days
21-30	500/200 mg	Two MALARONE Tablets (adult strength) as a single dose daily for 3 consecutive days
31-40	750/300 mg	Three MALARONE Tablets (adult strength) as a single dose daily for 3 consecutive days
>40	1 gram/400 mg	Four MALARONE Tablets (adult strength) as a single dose daily for 3 consecutive days

Materials reviewed
NDA 21-078, Volumes 1.1, 1.1.35-1.69, submitted 12/29/98
NDA 21-078, SU 120-day safety update, submitted 4/27/99
IND — (Malarone) Divisional File
NDA 20-500, MO review and SE1-005 (Mepron, atovaquone suspension)
NDA 20-259, MO review (Mepron, atovaquone tablets)
NDA 19-591, MO review (Lariam, mefloquine)
NDA 20-250, MO review (Halfan, halofantrine)

Regulatory background
Pre NDA Meeting: September 10, 1997

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CLINICAL STUDIES

INTRODUCTION

This application included clinical studies to support two indications, prophylaxis and treatment of *P. falciparum* malaria. The review of the prophylaxis indication is found in the MO review of Dr Leonard Sacks. The treatment indication is reviewed below. The following table includes a summary of all treatment studies submitted in the NDA. It should be noted that the sequence in which the controlled studies are presented in Table 1 is not the sequence in which they were reviewed or in which they are presented below.

Table 1: Controlled and uncontrolled clinical trials of atovaquone and proguanil hydrochloride for treatment of malaria

Controlled Clinical Trials of Atovaquone and Proguanil Hydrochloride for Treatment of Malaria

Study Number	Document Number	Study Design	Treatments	Number of Subjects	Mean Age in Years (Range)	Duration of Therapy
115-120	BQRT/95/0002	Randomized, open-label, controlled study in Zambian adults with uncomplicated *P. falciparum* malaria	Atovaquone 1000 mg and proguanil HCl 400 mg daily Pyrimethamine 75 mg and sulfadoxine 1500 mg	163	25 (14-54)	3 days 1 day
115-122	BQRT/95/0003	Randomized, open-label, controlled study in Thai adults with uncomplicated *P. falciparum* malaria	Atovaquone 1000 mg and proguanil HCl 400 mg daily Mefloquine 1250 mg during 6 h	182	26 (15-63)	3 days 1 day
115-127	BQRT/96/0017	Randomized, open-label, controlled study in Brazilian adults with uncomplicated *P. falciparum* malaria	Atovaquone 1000 mg and proguanil HCl 400 mg daily Quinine 600 mg 3x/d and tetracycline 250 mg 4x/d	175	28 (18-60)	3 days 7 days
115-130	BQRT/96/0005	Randomized, open-label, controlled study in adults in France with uncomplicated *P. falciparum* malaria	Atovaquone 1000 mg and proguanil HCl 400 mg daily Halofantrine 500 mg q6h x 3; repeated after 7 days	48	36 (15-62)	3 days 1 day each
115-131	BQRT/95/0006	Randomized, open-label, controlled study in Kenyan children with uncomplicated *P. falciparum* malaria	Atovaquone ~20 mg/ kg and proguanil HCl ~8 mg/kg daily Halofantrine ~8 mg/kg q6h x 3 doses	168	6 (3-12)	3 days 1 day
115-134	BQRT/95/0004	Randomized, open-label, controlled study in adults in Gabon with uncomplicated *P. falciparum* malaria	Atovaquone 1000 mg and proguanil HCl 400 mg daily Amodiaquine 1500 mg (base) during 48 h	141	32 (15-80)	3 days 3 days
115-135	BQRT/95/0017	Randomized, open-label, controlled study in Filipino adults and adolescents with uncomplicated *P. falciparum* malaria	Atovaquone 1000 mg and proguanil HCl 400 mg daily Chloroquine 1500 mg (base) during 48 h Pyrimethamine 75 mg and sulfadoxine 1500 mg	110	30 (12-64)	3 days 3 days 1 day
115-136	BQRT/96/0006	Randomized, open-label, controlled study in Peruvian adults and adolescents with uncomplicated *P. falciparum* malaria	Atovaquone 1000 mg and proguanil HCl 400 mg daily Chloroquine 1500 mg (base) during 48 h Pyrimethamine 75 mg and	43	33 (15-65)	3 days 3 days 1 day

Uncontrolled Studies of Atovaquone and Proguanil Hydrochloride for Treatment of Malaria

Study Number	Document Number	Study Design	Treatments	Number of Subjects	Mean Age in Years (Range)	Duration of Therapy
115-005	BQRT/95/0001	Uncontrolled, open-label study in Thai adults with uncomplicated *P. falciparum* or *P. vivax* malaria	Atovaquone 750 mg qh8 Proguanil HCl 200 mg or 500 mg q12h	314	25 (15-60)	2-7 days 3 days
			Atovaquone (various doses) and proguanil HCl (various doses)			3-7 days
			Atovaquone 750 mg q8h and tetracycline 250 mg q6h			2 days 7 days
			Atovaquone 500 mg and doxycycline 100 mg q12h			3 days
			Atovaquone 500-1000 mg/d and pyrimethamine 25 mg/d			3 days
115-012	BQRT/95/0008	Uncontrolled, open-label study in adults in Zambian adults with uncomplicated *P. falciparum* malaria	Atovaquone 750 mg q8h	31	25 (16-45)	7 days
115-134	BQRT/95/0004	Uncontrolled, open-label study in adults in Gabon with non-falciparum malaria	Atovaquone 1000 mg and proguanil HCl 400 mg, daily	7	32 (10-73)	3 days

BACKGROUND

Malarone™ is a fixed combination product containing atovaquone and proguanil. It has been developed by GlaxoWellcome for treatment and prophylaxis of malaria. Atovaquone, a naphthoquinone, is an antiparasitic originally developed by Burroughs-Wellcome. It is an inhibitor of mitochondrial electron transport that has been shown to have activity against *Plasmodium* spp, *Pneumocystis carinii*, and *Toxoplasma gondii*. Atovaquone (BW566C80 or Mepron™) tablet 750 mg tid x 21 days was approved for treatment of PCP in November 1992. In February 1995, the suspension formulation, which provides a twofold increase in bioavailability, was approved for treatment of PCP at a dose of 750 mg bid x 21 days. Mepron™ suspension was approved for prophylaxis of PCP at a dose of 1500 mg per day in January 1999.

In the course of its development, atovaquone was found to be a potent antimalarial. *In vitro* studies demonstrated IC_{50} values against various strains of *Plasmodium falciparum* that ranged from 0.7 to 4.3 nM . Studies of these falciparum strains with chloroquine, the mainstay of antimalarial therapy for the last 50 years and rapidly being rendered ineffective by spreading resistance, yielded IC_{50} values ranging from 74 to 633nM. In early clinical trials, atovaquone treatment was associated with rapid parasite clearance but also an unacceptable 30-40% rate of recrudescence following the completion of treatment. *In vitro* susceptibility testing of clinical isolates from patients who recrudesced demonstrated increases in IC_{50} values that suggested the rapid development of resistance to atovaquone in the course of treatment.

It was thought that the antimalarial activity of atovaquone could be preserved by combination with a second agent. *In vitro* studies of atovaquone in combination suggested an antagonism between atovaquone and either the artemisinins or the quinolines. Combinations of atovaquone with tetracyclines or with dihydrofolate reductase (DHFR) inhibitors suggested a synergy. Proguanil, a DHFR inhibitor, was considered to most closely meet the requirements of safety and efficacy needed for a partner drug for atovaquone.

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 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. Mefloquine, a newer and extremely effective antimalarial, has been the prophylactic of choice in the US. Recent antimalarial prophylaxis guidelines in the UK have relied more heavily on chloroquine-proguanil as patient compliance with mefloquine has diminished due to neuropsychiatric adverse events that were experienced or anticipated. 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 previously an approved drug in the US. 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, Glaxo 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 — is held by . —————

As *P. falciparum* resistance to chloroquine, mefloquine, sulfadoxine-pyrimethamine, and quinine has developed, and as safety issues have attenuated the usefulness of the most recently approved antimalarials in the US, mefloquine (Lariam, NDA 19-591 approved 1989) and halofantrine (Halfan, NDA 20-250 approved 1992, never marketed in US), the supply of effective antimalarials has grown thin. When considering resistance patterns noted worldwide, the agents potentially available to treat multidrug resistant falciparum malaria are quinine-tetracycline, atovaquone-proguanil, and derivatives of the artemisinin class. It should be noted that quinine resistance has also been documented in at least two separate foci, Brazil and Thailand, and that there are no artemisinin derivatives approved for use in the US.

> MO COMMENT: Of the 12 treatment studies reviewed here, 11 studied atovaquone/proguanil administered as two separate preparations. Study #115-136 studied atovaquone/proguanil as a fixed combination product.

INDICATION: Treatment of uncomplicated *P. falciparum* malaria

Controlled Clinical Trials

There are eight controlled clinical trials of treatment of falciparum malaria in NDA 21-078. They are discussed separately below.

Study # 115-127
Comparative clinical trial of a combination of atovaquone and proguanil versus a combination of quinine and tetracycline in the treatment of acute *P. falciparum* malaria in adults in Brazil

STUDY OBJECTIVES AND DESIGN

This was an open-label, randomized, controlled trial of two multi-dose treatment regimens designed to compare the efficacy and safety of atovaquone and proguanil with that of quinine and tetracycline in adults with uncomplicated falciparum malaria. Components of the study were at the US Army Medical Research Unit- Brazil and the Hospital dos Garimpeiro, Peixoto, Brazil. All patient care took place at the Hospital dos Garimpeiro. The protocol was conducted in accordance with the provisions of the Declaration of Helsinki; it received approval from the Human Use Review and Regulatory Affairs Division, US Army and the Brazilian Ministry of Health.

PROTOCOL OVERVIEW

Study population
This study was conducted from April 1995 to February 1996. It enrolled 175 male patients aged 18 to 65 years in a gold mining region of Mato Grosso state in Brazil. This region of the southern Amazon has one of the highest malaria transmission rates in Brazil, ~ 300 cases per week. Most of the malaria is caused by *P. falciparum*, but almost an equal number of cases are caused by *P. vivax*. During the past few decades, falciparum resistance to chloroquine, pyrimethamine- sulfadoxine, and even quinine has developed. Currently, standard treatment of falciparum malaria in this area is quinine and tetracycline for seven days. Usually, patients are given enough drug for the first four days of therapy and told to return for the additional three days of medication. Many do not return and recrudescences are thought to be common. Recrudescences are treated with mefloquine or artesunate, both of which are available locally. Oral quinine is available in the US for the treatment of malaria. Tetracycline, which has marked activity against tissue (pre-erythrocytic) schizonts and slow activity against blood schizonts, is not an adequate antimalarial on its own. Its use in combination with quinine has been advocated since the early 1970s in SE Asia when decreasing efficacy rates were noted with quinine alone.

> MO COMMENT: The study was originally planned to enroll men and women. Because the hospital had only one dedicated, single-sex ward for the study, and because the majority of malaria patients in this area were men, the protocol was amended October 15, 1993 to enroll men only.

Inclusion criteria of note included uncomplicated *P. falciparum* malaria with acute manifestations and parasitemia between 1000 and 100,000 parasites/µl. Exclusion criteria of note included severe or cerebral malaria, mixed *Plasmodium* infections, or a history of antimalarial use for the present illness.

MO COMMENT: Fever is one of the possible acute manifestations of falciparum malaria. However, fever was not required for entry into the study.

MO COMMENT: Parasite counts of 100,000/µl represent approximately 2% parasitemia in patients with a normal hematocrit. Depending on the immune status of the host, there are sources that define severe malaria as including parasitemia > 5%, 2%, or even 1%. Thus the parasite counts defined in the inclusion criteria might have resulted in a study population with malaria of varying degrees of severity. Review of the clinical presentation of those patients with higher parasite counts at enrollment did not suggest a subpopulation in this study with more severe disease.

MO COMMENT: The protocol did not suggest that these patients were migrant workers. If they have lived for any extended period in an area with such a high malaria transmission rate, it is likely that they have some degree of immunity to *Plasmodium* infection. Such patients are less likely to experience severe complications or death from falciparum malaria than the non-immune host.

Study procedures

Patients with acute falciparum malaria presenting to the Hospital dos Garimpeiro were screened for study participation. Once enrollment criteria were met and informed consent obtained, a patient was assigned the next sequential study number and entered into the study to receive the investigational agent, atovaquone/proguanil, or the control treatment, quinine and tetracycline. All drug treatment was administered under supervision. Atovaquone and proguanil were co-administered in separate tablets, each containing 250 mg and 100 mg prospectively. Four tablets of each were given in a single dose on day 0 and this dose was repeated 24 and then 48 hours later. Whenever possible, food or milk was given within 45 minutes prior to dosing patients in this arm of the study. Quinine was administered in doses of 650 mg every 8 hours for seven days, tetracycline administered in doses of 250 mg every 6 hours for seven days. These two drugs were administered during the same seven-day period. Patients in the control arm did not necessarily have food or milk prior to dosing.

MO COMMENT: There were no details provided in the protocol or study report regarding the screening of patients. It is not clear where patients were diagnosed with malaria (at the Hospital dos Garimpeiro or at an outlying clinic), what clinical presentation(s) precipitated the preparation of a peripheral blood smear to look for malarial parasites, and whether or not all patients presenting with malaria were randomized or if there were some selection prior to evaluation for enrollment.

MO COMMENT: This trial did not use Malarone or another fixed combination of atovaquone/proguanil.

Patients were required to remain in the hospital until asymptomatic and aparasitemic, and for a minimum of seven days. Continued hospitalization for 28 days from the beginning

of therapy was strongly encouraged, though not always possible. Temperature was taken every four hours during the acute stage of illness, and then on days 7, 14, 21, and 28. Thick blood films were prepared every six hours for the determination of parasite counts until three consecutive films were negative. Thereafter, blood films were prepared weekly. A blood film was not considered negative until an examination of 200 oil-immersion fields showed no parasites. The films were stained with Giemsa stain and parasite counts determined by counting the number of asexual parasites per 200 white blood cells on a thick film, or 1000 red blood cells on a thin film, and expressing the results in parasites per µl.

MO COMMENT: This is an acceptable method of determining whether or not a blood film is negative for malarial parasites. Both thin and thick smears are acceptable for quantifying parasites by the methods described above (Manson 1996, Bruce-Chwatt 1993).

MO COMMENT: The protocol stated that a patient was to be considered aparasitemic when the first of three negative peripheral smears was noted. The study report stated that patients were considered to have cleared their parasites when the first of two consecutive slides were negative. Subsequent review of Case Report Tabulations showed that patients had three negative smears documented before six-hourly smears stopped being made.

Periodic physical examinations and laboratory determinations of hematology, clinical chemistry, and drug levels were performed. Blood was also obtained prior to treatment for *in vitro* parasite culture and assessment of drug sensitivity. If a patient developed symptoms of malaria during the follow-up period, blood films were to be made and examined for malaria parasites. If such a film revealed *P. vivax* rather than *P. falciparum*, the patient was to be treated with chloroquine 450 mg base to 'suppress this parasite without affecting any residual *P. falciparum* parasites' (NDA 21-078, vol 49, page 59).

MO COMMENT: The study report stated that analyses of drug concentrations were not available. No explanation was provided.

MO COMMENT: It is not possible to assume that the administration of chloroquine would not have any effect on *P. falciparum* parasitemia. While *P. falciparum* in Brazil is more likely to be resistant than sensitive to chloroquine, such resistance is not an absolute phenomenon. Chloroquine can still suppress the growth of 'resistant' strains, as evidenced by the spectrum of resistance described in the WHO scheme presented below (see Efficacy endpoints). Concomitant medications were carefully reviewed. Patients who received an antimalarial during the follow-up period were made unevaluable in the MO analysis.

Evaluability criteria

The protocol did not specifically state what made patients unevaluable for analysis, however it did describe the instances in which patients could be withdrawn. Patients could choose to withdraw from the study at any time. The protocol stated that patients

were to be withdrawn and treated with appropriate antimalarial therapy under any of the following conditions:

- The clinical condition deteriorated or impaired consciousness due to malaria developed
- There was no reduction of parasitemia within 48 hours of treatment
- The parasitemia was not cleared within seven days of treatment
- The patient's infection recrudesced
- The study drug was discontinued due to an adverse experience

The protocol also stated that patients who failed to complete follow-up were to be replaced by the addition of patients to the study.

MO COMMENT: In an unblinded study, the reasons for withdrawal were carefully reviewed for balance between treatment arms. Patients withdrawn for clinical or parasitologic failure were regarded as failures by the MO.

Efficacy endpoints

The primary efficacy parameter was the 28-day cure rate; the sponsor stated that only patients whose outcome at 28 days was known could be evaluated for the 28-day cure rate. The response to treatment was adapted from the World Health Organization (WHO) classification system and is presented below:

- Sensitive (S) or Cured: parasite clearance within 7 days without recrudescence during the 28-day follow-up period

- Resistant (R) or Not Cured:
  - RI parasite clearance within 7 days followed by recrudescence within 28 days
  - RII marked reduction but no clearance within 7 days
  - RIII no significant reduction in parasites within 48 hours

The **protocol** stated that patients who were withdrawn because of deterioration of clinical condition or because of an adverse experience were to be classified as withdrawn (W). Patients who initially responded to treatment but who did not complete follow-up were to be classified as undetermined (U). A (U) designation would also be assigned to those patients who received antimalarial medication in the absence of asexual parasitemia during the follow-up period. Cure rates were to be calculated for each treatment arm as the ratio of # S responses / # total (S + RI + RII + RIII+W) responses.
The **study report** stated that patients who were withdrawn (W) from the study were classified as unevaluable and were not included in the calculation of cure rates.

MO COMMENT: The WHO convention (S, RI, RII, RIII) for describing the response to antimalarial chemotherapy is established and widely accepted. Review of the protocol and the final study report, however, shows a discrepancy. According to the **study report**, patients who were withdrawn (W) were classified

as unevaluable or, according to the convention described in the **protocol**, undetermined (U) and not factored into the calculation of cure rates according to the equation above. All patients who were withdrawn were reviewed by the MO (see below). Patients who were withdrawn because of poor clinical or parasitologic response, even before the end of the 28-day period, were to be regarded as failures (not cured) in the MO analysis, and were to be included in the calculation of cure rates (scored 'W').

MO COMMENT: While the WHO criteria describe the spectrum of clinical responses to malaria and are widely accepted, it is important to recognize that not all malaria patients who fail therapy were infected with resistant parasites. Parasite resistance has traditionally been assumed when clinical response to a known therapy in a particular geographic area begins to diminish. However, patient compliance, symptoms affecting drug absorption, variations in metabolism and excretion, and intrinsic schizonticidal activity 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. The designations RI, RII, RIII are useful to describe the spectrum of clinical failures and will be used here. Parasite resistance, however, is not the assumed reason for clinical failure.

MO COMMENT: The statement, 'A (U) designation would also be assigned to those patients who received antimalarial medication in the absence of asexual parasitemia during the follow-up period' was somewhat ambiguous. The MO interpreted it to mean that if a patient were to present during the follow-up period with symptoms suggestive of malaria and were to be started on antimalarial therapy, but then were to be found to have a negative peripheral smear (ie no malaria parasites), that patients would be scored as a U. The MO concurred with this scoring.

The primary efficacy parameter required that clinical and parasitologic response be determined out to 28 days after the beginning of therapy. Patients who left the hospital before 28 days and who developed *P. falciparum* parasitemia may have been experiencing a recrudescence of their original falciparum infection, or they may have been reinfected. The protocol stated that efficacy analysis of such patients would assume an equal likelihood of reinfection in both the treatment and control groups.

Secondary efficacy endpoints were parasite clearance time (PCT) and fever clearance time (FCT). PCT was defined as the time from treatment initiation to the time of the first of three negative films. FCT was defined as the time from treatment initiation to the time of the first decrease in fever below 37.2°C that remains below this target for at least 24 hours.

MO COMMENT: The sponsor stated that the definitive nature of the major endpoints would not be affected by lack of blinding, and that the great disparity in dosing regimens between different groups and the difficulty in obtaining placebos 'would complicate a double-dummy study' (NDA 21-078, vol 49, page 55). While there would be considerable difficulty in performing a double-dummy study of these two treatment regimens and there is no absolute requirement for a blinded study, it is important to note that the examination of peripheral smears can be subject to bias much as any other human activity can. In general, a blinded study, where possible, is preferred in the evaluation of any antimicrobial.

Safety

Safety data were analyzed on all 175 patients. Adverse event rates were calculated based on signs and symptoms which developed or worsened within 7 days after initiation of treatment. Laboratory results were compared to laboratory reference ranges and the number of patients with abnormal results were calculated for each test at each time. Treatment groups were compared by determining the difference between median results for each laboratory test at each time period and the 95% confidence interval around that difference.

MO COMMENT: Adverse event reporting was limited to those that started or increased during the first seven days of the study. If an adverse event that started during the first seven days extended into the period from days 8-28, that too would be recorded. The protocol was not designed to capture events that started from days 8-28, when any study drug administration had ceased.

RESULTS

DEMOGRAPHICS

There were 175 patients enrolled in this study; 87 were treated with atovaquone/proguanil (ATQ/PRG) and 88 with quinine and tetracycline (Q+T). Demographic characteristics of patients in both treatment arms are presented in Table 1.

Table 1. Demography

Group	Race (B/W/M)	Sex (M/F)	Mean Age (yrs)	Mean Weight (kg)	G6PD Def	Mean IPC (Range)	Fever at presentn	Splenomegaly at presentn
ATQ /PRG	10/34/43	87/0	29.2	59.9	3/69	6973/µl 1008-96,220)	55/87 (63%)	86/87 (99%)
Q+T	9/34/45	88/0	27.8	61.9	1/70	6376/µl (879-89,030)	52/88 (59%)	85/88 (97%)

B/W/M= Black/White/Mixed; G6PD Def= G6PD deficient; IPC=Initial Parasite Count

Table 1 demonstrates that the two treatment arms were well matched for race, age, weight, mean initial parasite count, number of patients with fever at presentation, and

number of patients with splenomegaly. Almost all patients in both treatment groups had enlarged spleens at enrollment, suggesting that they had had repeated exposure to malaria, and thus were most likely semi-immune hosts. Indeed, as is noted above, this region of Brazilian Amazonia has a high malaria transmission rate, and individuals residing here for any length of time are likely to develop some degree of immunity to malaria. As can be seen from the ranges of the initial parasite counts, all of these patients had *Plasmodium* parasites in their blood at presentation. That only about 60% in each treatment arm were febrile also suggests some degree of malaria immunity.

Examination of the range of IPCs in Table 1 also shows that there were patients in each treatment group with parasite counts in the high end of the range specified for the entry criteria in this study (1000-100,000/µl). Because these were semi-immune hosts, it is less likely that even those patients with parasite counts at the high end of this range were likely to have severe malaria.

EVALUABILITY

Applicant assessment

One hundred seventy-five patients participated in the study; the applicant's analysis of patient evaluability is presented in Table 2.

Table 2. Patient evaluability per applicant

Investigator/Center	Atovaquone/proguanil			Quinine and tetracycline		
	Enrolled	Evaluable	%	Enrolled	Evaluable	%
	87	74	85.1	88	76	86.4

The applicant determined that 13 patients who received atovaquone/proguanil were unevaluable, and that 12 patients who received quinine and tetracycline were unevaluable. All of these patients were withdrawn from the study after treatment. The reasons for these withdrawals are presented in Table 3 below.

Table 3. Reasons for withdrawal (W) per applicant

Reason	ATQ/PRG (pt no.)	Q and T (pt no.)
Other meds with antimalarial effect received	N=6 (001, 019, 031, 038, 091, 124*)	N=7 (004, 020, 024, 030, 034, 056,067**)
Consent withdrawn	N=3 (014, 135, 168)	N=1 (022)
Left hospital overnight during follow-up	N=1 (121)	
Infection mixed or *P. vivax*	N=2 (016, 082)	N=1 (048)
Incorrect dose of study drug	N=1 (088)	N=0
Concurrent illness thought to interfere with assessment	N=0	N=2 (107, 109)†
Serious adverse event	N=0	N=1 (036)‡
TOTAL	N= 13	N= 12

*Patients 001, 019, and 031 received chloroquine during the follow-up period for delayed primary attacks of *P. vivax*. Patients 038, 091, and 124 received trimethoprim-sulfamethoxazole (TMP-SMX) during the follow-up period for intercurrent otitis.
**Patients 004, 020, 024, 030, 034, 056 received chloroquine during the follow-up period for delayed primary attacks of *P. vivax*. Patient 067 received TMP-SMX during the follow-up period for treatment of a urinary tract infection.
† Patient 107 was withdrawn during treatment because he was found to have cutaneous leishmaniasis; patient 109 because he had diabetes mellitus.
‡Patient 036 developed hemolysis manifested by hematuria and decreased hematocrit. Quinine treatment was discontinued after four doses and the patient recovered.

MO COMMENT: While the final study report refers to these patients as 'withdrawn,' it is more consistent with the scoring system described prospectively in the protocol to refer to them as 'undetermined (U).' (see Table 4 below).

MO assessment

Evaluability was assessed by first reviewing the database of all 175 patients to determine that all had malaria due to *P. falciparum* only. The MO assessment agreed with that of the applicant in that patients 016, 048, and 082 were unevaluable for this reason.

Patients considered evaluable by applicant
Of the 172 patients who remained evaluable, all had either mild or moderate disease. None had severe malaria, and none had received any other antimalarial for his present illness at the time of enrollment. All except one (see below) had parasitemia in the range of 1000-100,000/ mm^3. Patient #128 had an initial parasite count of 879/µl. This was outside the range of 1000-100,000 parasites/µl specified in the protocol. This patient was considered evaluable by the applicant. He was a 33 year old man who presented with backache, chills or rigors, and weakness. He was found to be afebrile with hepatosplenomegaly. Admission CBC was noteworthy for a hematocrit of 28, and WBC 2.1K with 22% eosinophils. Platelet count and liver function tests were normal; stool exam for ova and parasites was negative. A patient with such a clinical presentation and

Plasmodium parasites seen on peripheral smear has malaria. The MO concurred with the decision to regard this patient as evaluable for overall cure.

There were nine individuals enrolled who were considered by the applicant to have disease of moderate severity. These were patients numbered 022, 027, 029, 032, 035, 046, 059, 122, and 125. Patients #027, 029, 046, 122, and 125 received ATQ/PRG. Thus 5/87 (5.7%) of patients treated with ATQ/PRG had moderate disease and 4/88 (4.5%) of patients of patients treated with QT had moderate disease. These rates are comparable and small. The MO reviewed all cases described as having moderate disease and concurred with the applicant's assessment of severity and evaluability. The MO reviewed the CRTs of those patients described as having had mild disease and one of the following findings at presentation: systolic blood pressure <100 mm Hg or no blood pressure recorded at enrollment, temperature ≥39°C, blood glucose ≤60 mg/dl or no glucose measurement recorded at enrollment, hematocrit <30%, or serum creatinine ≥ 2.0 mg/dl. The MO assessment of evaluability and severity generally agreed with that of the applicant.

> MO COMMENT: There were no data provided that documented the duration of the patient's malaria prior to enrollment in the study. In general, the longer a patient is parasitemic prior to treatment, the greater the likelihood of severe disease. The majority of patients enrolled in this study had mild illness. Data regarding the duration of illness would have helped to better characterize these cases of mild and moderate malaria, and would have permitted an additional comparison between treatment arms.

Patients considered unevaluable by applicant

The MO assessment of evaluability also included review of all patients considered unevaluable by the applicant. Case report tabulations and additional data on all patients noted in Table 3 were reviewed. It was possible to verify that all of the patients who had received chloroquine for *P. vivax* infection diagnosed during the follow-up period had cleared their *P. falciparum* parasitemia long before the administration of chloroquine. There was no database that provided independent verification of the reasons for administration of drugs with antimalarial activity to patients #001, 019, 031, 038, 091, 124, 004, 020, 024, 030, 034, 056, and 067. As it was noted above, data on adverse events that began after the end first seven days of the study were not submitted in the NDA. *P. vivax* was diagnosed in these patients some time between days 14 and 25. There were no additional data on the three patients found to have otitis, an unusual diagnosis in an adult. The dates for TMP-SMX administration were not provided.

> MO COMMENT: The administration of drugs with antimalarial activity described above was not recorded in the database that listed concurrent medications (Appendix B13, Concomitant Medications or ACCESS table (MEDS). That a patient received another drug with antimalarial activity was only noted in the COMMENTS field of Appendix B7 (Individual Patient Parasite Counts) and the ACCESS table (PARA) that was the electronic version of that appendix. This table was reviewed for any other patients who may have received

other drugs with antimalarial activity; none was found. There was no other record that captured this data, therefore it was not possible to independently query the database for other such patients.

MO COMMENT: It was noted that there were 22 other patients who were found to have *P. vivax* parasitemia during the follow-up period. There is no documentation that any of these patients received antimalarial therapy during the follow-up period. There is also no documentation explaining why some patients diagnosed with vivax malaria during the follow-up period received antimalarial therapy and why some did not. Of these 22 patients, 10 were listed as having had *P. vivax* parasitemia noted on day 28. The remaining 12 had *P. vivax* parasitemia diagnosed sometime during the period between days 21 and 27 of the follow-up period. There is no information regarding these patients' clinical condition at the time of diagnosis of *P. vivax* parasitemia. One may speculate that those who were not treated were not acutely ill. From the available data, there is no way to determine whether or not these patients received therapy for vivax malaria after conclusion of the study. Of the 22 patients diagnosed with *P. vivax* parasitemia during the follow-up period, 9 (9/87= 10.3%) were in the atovaquone/proguanil treatment group, and 13 (13/88= 14.8%) were in the quinine and tetracycline group. One may also speculate that some of those patients who were found to have *P. vivax* (a relapsing infection) during the follow-up period had presented with a mixed infection initially. An additional analysis of efficacy that excludes all patients who had *P. vivax* diagnosed during follow-up is a way to address this possibility (see below).

Four patients withdrew consent. For patients #014, 035, and 168, this occurred after treatment was completed and fever and parasitemia had resolved. There were no reasons provided for the withdrawal of consent. The adverse event profiles for all of these patients were reviewed. There were no adverse events temporally related to their withdrawals. Patient #022 withdrew consent 16 hours after enrollment. The study report states that this was because the patient did not want to remain on the malaria ward. The CRT and supporting tables showed that this patient was among the sicker of those enrolled. He presented with a fever of 39°C, HR 136, and hematocrit 15; his initial parasite count was 9261/µl, glucose was 125 mg/dl.

Two patients were withdrawn for concomitant illnesses. Patient #107 had cutaneous leishmaniasis.

MO COMMENT: It is not clear how a chronic skin ulcer would interfere with the assessment of this patient's response to antimalarial therapy. Since he was withdrawn during treatment, he is unevaluable.

Patient #109 had diabetes mellitus and was admitted with a blood glucose of 454.

MO COMMENT: The metabolic derangements of acute hyperglycemia can be similar to those of falciparum malaria (eg metabolic acidosis). It may have been

difficult to evaluate this patient's response to antimalarial therapy. The MO analysis concurs with this patient's withdrawal and unevaluability.

Patient 036 was withdrawn because of a serious adverse event. He was admitted with mild malaria and within 24 hours found to have red urine and jaundice. There were no hematocrits recorded after a pretreatment value of 37. His G6PD level at enrollment was normal. The study report states that quinine treatment was withdrawn after four doses and the patient recovered.

MO COMMENT: It is not possible to verify that this patient experienced hemolysis and that it was possibly due to quinine. While the incidence of severe hemolysis (blackwater fever) is known to be increased in patients with falciparum malaria who are treated with quinine, this phenomenon is also possible in untreated falciparum malaria. If this patient did appear to experience hemolysis to the degree that he developed dark urine and jaundice, he might have been considered to have severe malaria and would therefore have been unevaluable for the purposes of this study.

The MO assessment of evaluability concluded with the review of 7-day, 14-day, 21-day and 28-day blood smears of the 150 remaining patients. All had peripheral smears recorded for all four points during the follow-up period.

EFFICACY

Applicant assessment

Overall cure

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

Table 4. Cure rates per applicant

	ATQ/PRG	Q/T
Total patients randomized	87	88
Evaluable patients Cures ('sensitive' or S) Failures ('resistant' or RI, RII, RIII, or W)	74 73 1	76 76 0
Unevaluable patients ('undetermined' or U)*	13	12
Percent cured or S/(RI + RII + RIII + W) [90%CI]	98.6 [93.8-99.9]	100.0 [96.1-100]

*All patients scored as unevaluable (undetermined or U) by the applicant were withdrawn after treatment

MO COMMENT: As noted above, the applicant found that 13 patients in the ATQ/PRG group were withdrawn (W), and 12 patients in the Q/T group were

withdrawn (W). In the calculation of efficacy rates presented in Table 4, these patients were scored as unevaluable, or in the scoring system described in the protocol, undetermined (U). Their outcomes were not taken into account when overall efficacy rates were calculated.

MO COMMENT: The applicant appears to have calculated 90% confidence intervals around the point estimates of efficacy for each treatment regimen. The protocol stated a different planned statistical analysis that would compare the cure rates of the two treatment regimens by calculating the 95% confidence interval around the difference in the cure rates. The latter is a method of demonstrating equivalence with an active control that has been commonly used to establish efficacy of other antimicrobial agents under regulatory review. The 95% CI around the difference in the above efficacy rates is [-5.32, 2.61]. The lower bound of this confidence interval is >-10; it meets the statistical criterion for equivalence.

MO COMMENT: According to the applicant's analysis, there was one patient who received atovaquone/proguanil who was not cured, and recrudesced on day 23. Though parasitized red blood cells from this patient were preserved, the study report stated that there were no data currently available on parasite susceptibility to atovaquone. Such information would be especially useful, given the high rates of recrudescence and rising IC_{50} values that were observed in early trials of malaria patients treated with atovaquone alone.

PCT and FCT

The applicant also provided analyses of parasite clearance times (PCT) and fever clearance times (FCT). Patients were included in the calculation of FCT if they had fever charts in their CRFs, if they had fever when treatment was initiated or 24 hours thereafter, no concurrent illness causing fever, and were not withdrawn prior to parasite or fever clearance. These results are presented in Table 5.

Table 5. PCT and FCT per applicant

Treatment Group	Parasite Clearance Time (hrs)				Fever Clearance Time (hrs)			
	No. pts	Median	Mean	Range	No. pts	Median	Mean	Range
ATQ/PRG	84	57.5	55.3	[redacted]	62	22.5	23.8	[redacted]
Q/T	83	68.0	64.6	[redacted]	58	26.0	32.5	[redacted]

The applicant reported that atovaquone/proguanil eliminated parasites and fever more rapidly than did quinine/tetracycline. The differences were significant (p=0.006 and 0.02, respectively). The 95% CI of the differences in medians of the PCT was 2.8 to 14.3 hours. The 95% CI of the difference in medians of the FCT was 1 to 16 hours.

MO COMMENT: The population in which PCT was measured was larger than the population evaluable for cure. The population in which FCT was measured was smaller than the population evaluable for cure. The PCT can provide additional information about the parasite killing of a given treatment regimen. It analyzes the population of all patients who participated in the study long enough to have cleared parasites from their blood.

MO COMMENT: The FCT is more problematic. In a study such as the one under review, where only about 60% of patients were febrile at presentation, the population evaluable for FCT is quite small. A second factor that limits the usefulness of the FCT is the administration of antipyretics. Review of concomitant medications shows that 113/175 (64.6%) patients received an antipyretic at some point during the period of treatment with study drug. Twenty-six of those patients received an antipyretic more than once.

MO COMMENT: The applicant reported p values attesting to the significance in the differences between treatment arms for both PCT and FCT. However, the applicant did not make explicit what parameters were being compared. A review of vol 49, appendix C, Statistical Details, suggests that the applicant's analyses of PCT and FCT compare the median values of these parameters between treatment arms. Comparison of the medians is appropriate for use with skewed numerical data or numerical data with many outliers. See section entitled MO assessment for further discussion of this analysis.

MO COMMENT: The confidence intervals calculated around the differences in median PCT and FCT are indeed wide. Patients receiving ATQ/PRG could clear parasites anywhere from 2.8 to 14.3 hours sooner than patients receiving Q and T. For further discussion of the points raised in these MO COMMENTS, the reader is referred to the section Efficacy/MO Assessment.

MO assessment

Overall Cure

As noted in the protocol, patients whose outcome was designated S (sensitive) were the only ones considered cured. For a patient outcome to be scored as S, the patient's peripheral blood had to be clear of parasites within 7 days of the onset of treatment and there could have been no recrudescence of parasites in the peripheral blood during the follow-up period that lasted for 28 days following the onset of treatment. The MO assessment of efficacy concurs with that of the applicant; Table 6 presents the support for that concurrence.

MO COMMENT: To more fully assess the disease burden in each treatment arm, the clinical findings and laboratory results at enrollment of all patients with IPC > 50,000/µl and all those patients graded as having moderate disease (there were none with severe disease) were reviewed. There were 10 such patients; 6 received atovaquone proguanil. Their clinical status at presentation was comparable between treatment arms

Table 6. Cure rates per MO

Treatment Group	No. of patients evaluable	No. with 0 parasites at 7 d/ No. evaluable (%)	No. with 0 parasites from d 7 to d 28/ No. evaluable (%)*	Failures (RI, RII, RIII, or W)
ATQ/PRG	74	74 / 74(100)	73 / 74 (98.6)	RI: n=1
Q/T	76	76 / 76 (100)	76 / 76 (100.0)	

*95% CI around difference = [-5.32, 2.61]

In the above discussion of evaluability, it was noted that there were 9 patients excluded from evaluability by the applicant because they received chloroquine for vivax malaria that occurred during the follow-up period. Review of parasitologic responses for all patients revealed that there were an additional 22 patients who had *P. vivax* diagnosed in their peripheral smear during the follow-up period who did not receive antimalarial therapy. It is not clear why some of these patients were treated and not others. The possibility was raised that some proportion of these patients had been enrolled with a mixed falciparum and vivax infection and were therefore unevaluable. Table 7 presents an additional analysis that excludes all patients who were found to have *P. vivax* on peripheral smear during follow-up.

Table 7. Cure rates excluding patients with *P. vivax* on follow-up smear

Treatment Group	No. of patients evaluable	No. with 0 parasites at 7 d/ No. evaluable (%)	No. with 0 parasites from d 7 to d 28/ No. evaluable (%)*	Failures (RI, RII, RIII, or W)
ATQ/PRG	65	65 / 65 (100)	64 / 65 (98.5)	R1: n=1
Q/T	63	63 / 63 (100)	63 / 63 (100.0)	

*95% CI around difference = [-6.09, 3.02]

The 95% CI around the difference in point estimates of cure rates is slightly wider in this smaller population that excludes any patients who had *P. vivax* during the follow-up period. However the value of the lower bound of the CI does meet the criterion for equivalence. A stricter analysis that excludes patients who may have possibly presented with a mixed infection supports the demonstration of equivalence in the applicant's analysis.

Vomiting is a symptom of malaria that can affect the efficacy of any oral antimalarial regimen. This should be distinguished from treatment-related vomiting, which can affect both drug efficacy and safety. Review of the pretreatment symptoms of this study population revealed that vomiting was a presenting symptom for 53 patients. Table 8 presents data on patients who were vomiting by treatment group and by severity.

Table 8–Vomiting pretreatment and during treatment by treatment group and severity

Severity grade*	ATQ/PRG (no.of pts)			Q/T (no.of pts)		
	Pre-treatment	During Treat-ment	Total	Pre-treatment	During Treat-ment	Total
1	16	3	19	19	8	27
2	5	3	8	11	2	13
3	1	1	2	1	0	1
Total vomiting/ total enrolled (%)	22/87 (25.3)	7/87 (8.0)	29/87 (33.3)	31/88 (35.2)	10/88 (11.4)	41/88 (46.6)

*1=mild, 2=moderate, 3=severe

The following observations can be made regarding vomiting in this study:

1. About one-fourth of the patients who were randomized to atovaquone/proguanil were vomiting at presentation; over one-third of those randomized to quinine/tetracycline were vomiting at presentation.
2. Malaria alone was about three times as likely to be associated with vomiting as was malaria undergoing treatment with either atovaquone/proguanil or quinine/tetracycline.
3. About one-third of patients treated with ATQ/PRG experienced vomiting at some point during their participation in the study; about one-half of those treated with Q/T experienced the same.
4. There were comparable numbers of patients who had moderate or severe vomiting in the two treatment groups.
5. The only patient who failed, #066, did not experience vomiting.
6. There was no information provided on drug levels in any study patients. In the absence drug levels, one may speculate that there was little relationship between the high incidence of vomiting among study patients and the high efficacy rates observed for both treatment groups.

For further discussion of vomiting during treatment, the reader is referred to the SAFETY section of the review.

PCT and FCT

Parasite clearance time (PCT) is a measure of how quickly the drug clears the erythrocytic stage of *Plasmodium* parasites from the peripheral blood. While it has been shown that peripheral parasitemia does not necessarily reflect total parasite load or pathology in deep capillary beds of the malaria patient, the PCT can provide an assessment of efficacy that is complementary to the cure rate. As noted above, the combination of atovaquone and proguanil was shown to have an equivalent cure rate to quinine and tetracycline in this population of Brazilian malaria patients. A comparison of the PCTs for patients in each treatment group might further refine this evaluation of drug efficacy by comparing how rapidly each of these regimens acts as a blood schizonticide.

The applicant assessment of PCT compared the median values for each treatment group. The 95% CI around the difference between medians was quite wide, and did not permit a meaningful comparison of PCTs for the two treatment groups.

The MO concurred with the applicant's determination of the evaluable population for calculation of PCT. A review of a random sample of 10% of serial peripheral smears showed that PCT was accurately recorded as the time from treatment to the first of three negative peripheral smears.

The applicant did not provide any tabulation of serial temperature recordings for patients. It is not possible to verify the results recorded in Table 5. Given that the subpopulation that presented with fever was quite small, and that a majority of patients received an antipyretic, information provided by additional analysis is limited. Inspection of Table 5 shows that the Q/T treatment arm had a wider range of FCT values and that this extended to a value almost twice as long as the FCT range reported for A/Q. It is also noteworthy that the FCT was shorter than the PCT. It is possible that patients were afebrile while parasitemic. This has implications for monitoring during the follow-up period, demonstrating the importance of routine examination of peripheral smears and a low threshold for taking additional samples in the afebrile patient with other clinical findings suggestive of malaria recrudescence.

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 were recorded. There was a total of 345 adverse experiences in the patients receiving A/P and 371 adverse experiences in the patients receiving Q/T. Tinnitus and dizziness were significantly more frequent in patients receiving Q/T than in patients receiving A/P (69% v. 7% and 47% v. 25%, respectively). Headache was more frequent in patients who received A/P than in patients who received Q/T (47% v. 24%). The applicant's assessment of adverse experiences considered by investigators to be attributable to study medication is presented in Table 9.

> MO COMMENT: Cinchonism associated with quinine has been well described in the medical literature.

Table 9. Adverse experiences considered by investigators to be attributable to study medication

Adverse Experience	Number of Subjects Reporting an Adverse Experience			
	Atovaquone/Proguanil n=87		Quinine/Tetracycline n=88	
	N	%	N	%
Cutaneous System				
Pruritus	5	6	4	5
Sweating increased	2	2	0	
Musculoskeletal System				
Myalgia	3	3	1	1
Nervous/Psychiatric System				
Dizziness	12	14	39	44
Headache	19	22	8	9
Insomnia	1	1	5	6
Tremor	0		1	1
Special Senses				
Tinnitus	4	5	58	66
Gastrointestinal System				
Abdominal Pain	26	30	23	26
Anorexia	5	6	17	19
Diarrhea	7	8	11	13
Nausea	14	16	25	28
Vomiting	5	6	8	9
Cardiovascular System				
Palpitations	3	3	0	
Respiratory System				
Coughing	1	1	0	
Body as a Whole				
Asthenia	12	14	16	18
Back Pain	0		1	1
Chills/Rigors	1	1		
Fever	1	1	0	
Number and % of Subjects Reporting at Least One Adverse Experience	57	66	79	90

Two patients experienced serious adverse events during the course of the study, both were in the Q/T arm. Patient #036 developed hemolysis 17 hours after beginning treatment. Quinine was stopped and the event resolved within 4 days. Patient #077 developed symptoms of congestive heart failure four days after completing drug treatment. He was treated with digitalis and the event resolved within 12 hours.

Laboratory abnormalities

Examination of means or medians of chemistry, hematology, or urinalysis values for each treatment group showed that there was a significant difference between groups for one test, blood glucose level on day 3. The median value for patients who received A/P was 95.5 mg/dl, and for patients who received Q/T it was 88.0 mg/dl.

> MO COMMENT: While a statistically significant difference, this is not clinically significant.

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 10.

Table 10. Clinically significant laboratory abnormalities

Test	Criteria	Atovaquone/Proguanil			Quinine/Tetracycline		
		Number (%) Developing Abnormality		Number Abnormal at 28 Days	Number (%) Developing Abnormality		Number Abnormal at 28 Days
Hematocrit	<25%	1	(1.1%)	0	0		0
White Cell Count	<3000/µl	27	(31.0%)	1	20	(22.7%)	2
Neutrophil Count	<1000/µl	32	(36.8%)	7	15	(17.0%)	0
Lymphocyte Count	<500/µl	2	(2.3%)	0	1	(1.1%)	0
Eosinophil Count	>1000/µl	27	(31.0%)	19	17	(19.3%)	12
Platelet Count	<50/nl	0		0	0		0
Glucose	<50 mg/dl	0		0	0		0
Urea	>53.5 mg/dl	0		0	3	(3.4%)	1
Creatinine	>2.0 mg/dl	0		0	3	(3.4%)	0
Bilirubin	>2.0 mg/dl	0		0	3	(3.4%)	1
ALT	>100 U/l	1	(1.1%)	1	1	(1.1%)	0
AST	>100 U/l	1	(1.1%)	1	1	(1.1%)	0
Proteinuria	2+ or greater	0			0		
Hematuria	2+ or greater	0			0		

Most of these abnormalities are commonly seen in evolving malaria. The one patient treated with A/P who had a significant decrease in his hematocrit (#015) was not tested for red blood cell G6PD. His hematocrit returned to baseline within a few days without additional treatment.

> MO COMMENT: There were 139 patients tested for G6PD deficiency and 4 were deficient in this enzyme. Three of these patients received atovaquone/proguanil. A review of these patients serial hematocrit values showed that none of them experienced a drop in hematocrit with the initiation of treatment.

Many patients developed neutropenia or eosinophilia in both treatment groups. Neutropenia is common in acute malaria, and eosinophilia seen in convalescence, and in patients with helminthic infections.

> MO COMMENT: A review of the results of stool examinations showed that 139 were tested and there were 37 (26.7%) in which intestinal helminths were visualized.

The development of clinically significant increases in ALT or AST occurred in one patient in each treatment group. The patient in the Q/T group (#061) had elevated transaminases when admitted which increased and then returned to normal. The patient treated with A/P (#085) developed elevated transaminases on day #14. When discharged on day #28, they were still elevated. The study report states that no explanation was provided.

> MO COMMENT: A review of the CRT for patient #085 showed that he was 20 years old. His ALT value was first elevated at 70 IU on day 14 and increased to 185 IU on day 28. His AST value was 34 IU on day 14 and 112 IU on day 28. Also of note was that his platelet count, which is often depressed with acute malaria, was normal on enrollment (359K). By day 28, it had risen to 491K, suggesting an acute phase reaction. There were no adverse events reported for this patient. The possibility that there was a second process ongoing in this patient is raised by these laboratory results. Whether or not it was related to drug administration cannot be determined. Ongoing review of the safety of this combination drug should include careful attention to liver transaminase levels.

REVIEWER'S COMMENTS

This comparative trial of atovaquone/proguanil and quinine/tetracycline in a high-transmission malarious area of Brazil demonstrated that cure rates achieved with atovaquone/proguanil were equivalent to those achieved with the local standard of care, quinine and tetracycline. No serious safety problems were identified. A request to the applicant regarding the availability of *in vitro* susceptibility data on the clinical isolate from the one patient who failed on atovaquone/proguanil revealed that the information was unavailable because the parasites failed to grow in culture.

Study # 115-130
Comparative clinical trial of a combination of atovaquone and proguanil versus halofantrine in the treatment of acute *P. falciparum* malaria in non-immune adults in Europe

STUDY OBJECTIVES AND DESIGN

This was an open-label, randomized, controlled trial of two multi-dose treatment regimens designed to compare the efficacy and safety of atovaquone and proguanil with that of halofantrine in non-immune adults with uncomplicated falciparum malaria. The study was conducted at three treatment centers in France, two in Paris and one in Bordeaux, and in accordance with the provisions of the Declaration of Helsinki.

PROTOCOL OVERVIEW

Study population
This study was conducted from October 1994 to September 1995. It enrolled 48 men and women aged 16 to 65 years who had traveled to malarious areas and presented with acute, uncomplicated *P. falciparum* malaria following return to France. All patients were either Europeans who had never lived in an area endemic for malaria or natives of malarious areas who had resided in a non-malarious area for at least one year. According to figures provided by the French government and cited by the applicant, there have been 3500-4000 cases of malaria per year in France during the mid-1990s. About 85% of these cases are caused by *P. falciparum*. Infections occur in French travelers and expatriate Africans in about equal numbers. Because of widespread chloroquine resistance, the drugs used in France to treat falciparum malaria are halofantrine, quinine, and mefloquine. Halofantrine was approved by US FDA in 1992; it has not been marketed in this country.

Inclusion criteria of note included uncomplicated *P. falciparum* malaria with acute manifestations and parasitemia between 1000 and 100,000 parasites/µl. Patients also had to have a history of a recent, short-term exposure in a malarious area. Exclusion criteria of note included severe or cerebral malaria, significant concomitant disease that could mask the therapeutic response, pregnancy, mixed *Plasmodium* infections, primary residence in a malarious area in the preceding year, or prolonged QT interval.

MO COMMENT: Fever is one of the possible acute manifestations of falciparum malaria. However, fever was not required for entry into the study.

MO COMMENT: There is potentially some difference in the degree of (non) immunity to malaria in a population of Europeans who have never lived in a malarious area, and a population of expatriates who were exposed to malaria in childhood. Though the latter population can become acutely ill from malaria, there is probably some persistent degree of immunity to life-threatening *Plasmodium* infection (Bruce-Chwatt, 1993). The stability of the specific, acquired immunity conferred on those who survive childhood in malarious areas is dependent upon many factors including the length of time spent in an endemic area and the length of time spent away from that area.

MO COMMENT: Parasite counts of 100,000/µl represent approximately 2% parasitemia. Depending on the immune status of the host, there are sources that define severe malaria as including parasitemia > 5%, 2%, or even 1%. Thus the parasite counts defined in the inclusion criteria might have resulted in a study population with malaria of varying degrees of severity. Review of the clinical presentation of those patients with higher parasite counts at enrollment did not suggest a subpopulation with more severe disease.

MO COMMENT: Halofantrine has been shown to prolong the QT interval of the EKG at therapeutic doses.

Study procedures

Patients with acute falciparum malaria presenting to one of the three study centers were screened for study participation. Once enrollment criteria were met and informed consent obtained, a patient was assigned a sequential study number and entered into the study to receive the investigational agent, atovaquone/proguanil, or the control treatment, halofantrine (day 0). All patients were hospitalized at least until day 3 (4 days) or until asymptomatic, afebrile, and aparasitemic. If not still in the hospital, patients were to return for out-patient follow-up on days 7, 14, 21, 28, and 35. Atovaquone and proguanil were co-administered in separate tablets, each containing 250 mg and 100 mg prospectively. Four tablets of each were given in a single dose on day 0 and this dose was repeated 24 and then 48 hours later. Whenever possible, food or milk was given within 45 minutes prior to dosing patients in this arm of the study. Halofantrine was administered without food in doses of 500 mg (250 mg tab x 2) every 6 hours for three doses, followed seven days later by a repeat dose of 500 mg every 6 hours x 3 doses. The second course of halofantrine did not require readmission to the hospital, but the drug needed to be given under observation.

MO COMMENT: This trial did not use Malarone or another fixed combination of atovaquone/proguanil.

MO COMMENT: The dose of halofantrine used in this protocol is the same as the dose in the FDA-approved label.

Temperature was taken every 4-8 hours during the acute stage of illness. Parasite counts were performed on peripheral blood smears every 12 hours until the blood films were negative on two consecutive examinations of Giemsa-stained thick smears. Weekly smears were then performed on days 7, 14, 21, 28, and 35. A blood film was not considered negative until an examination of 200 oil-immersion fields showed no parasites. The films were stained with Giemsa stain and parasite counts determined by counting the number of asexual parasites per 200 white blood cells on a thick film, or 1000 red blood cells on a thin film, and expressing the results in parasites per µl.

MO COMMENT: This is an acceptable method of determining whether or not a blood film is negative for malarial parasites. Both thin and thick smears are acceptable for quantifying parasites by the methods described above (Manson 1996, Bruce-Chwatt 1993).

Periodic physical examinations and laboratory determinations of hematology, clinical chemistry, and drug levels were performed. Blood was also obtained prior to treatment for possible *in vitro* parasite culture and assessment of drug sensitivity in the event of a recrudescence. Blood was also to be obtained for drug levels at 8 and 96 hours after starting therapy. Such assays were also to be performed only in the event of recrudescence. EKGs were obtained prior to each dose of drugs and 6 and 168 hours after the last dose of drug.

Evaluability criteria
The original protocol did not specifically state what made patients unevaluable for analysis. In an amendment dated September 29, 1994, prior to enrollment of first patient, the following statement was added to the section of the protocol that discussed withdrawals:

Definition of an evaluable patient

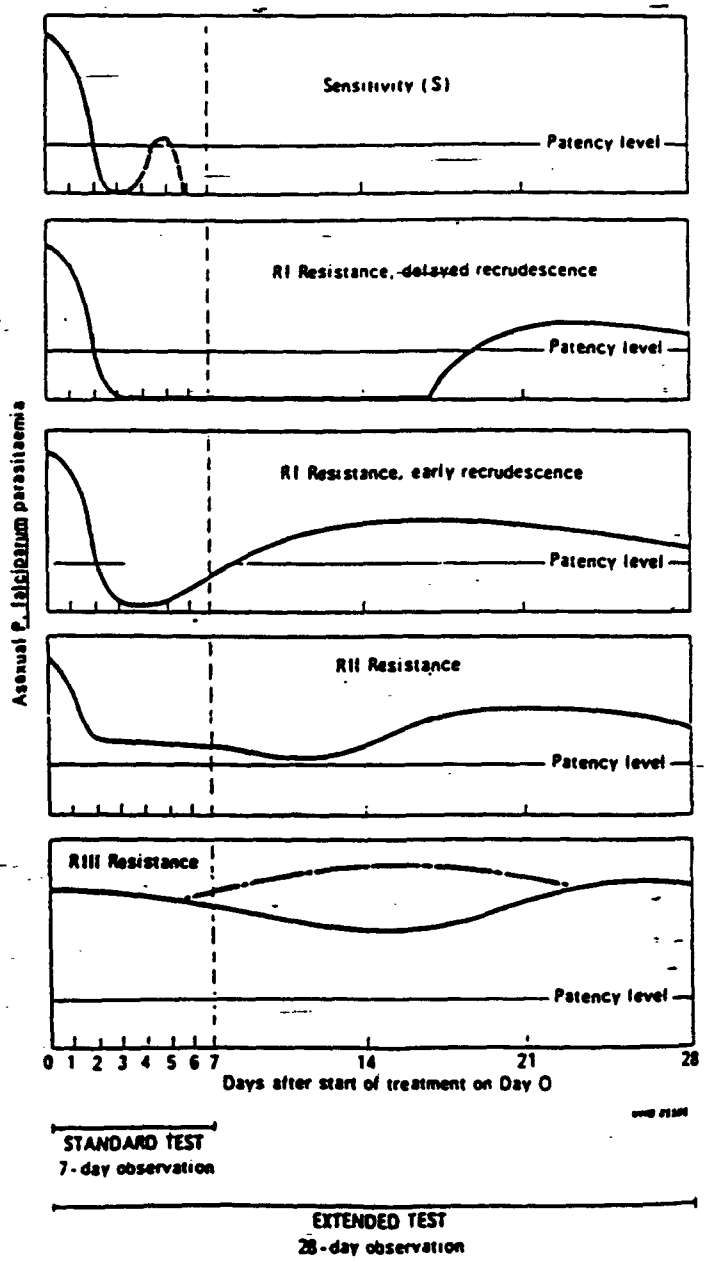
- *All patients randomized into the study will be considered for the safety and tolerance analysis.*
- *Any patients who will have received the full course of study medication and underwent at least Day 14 and Day 28 or 35 evaluations will be considered for the efficacy analysis.*

MO COMMENT: The MO concurred with both of these statements regarding patient evaluability. The MO also regarded as potentially evaluable any patients who did not complete a full course of therapy because of a treatment-limiting AE. These patients were reviewed individually by the MO and evaluability determined on a case by case basis.

MO COMMENT: It should be noted that following patients to 35 days is a longer follow-up period than specified by the WHO criteria for evaluating clinical

response to antimalarial therapy (see Efficacy endpoints below). Figure 1 below, taken from Bruce-Chwatt's Essential Malariology, 3rd edition, illustrates the classic WHO field test for response of *Plasmodium* to an antimalarial drug. Note that the Extended Test of 28 days includes a 7-day treatment period and a 21-day follow-up period.

Figure 1. WHO field test for response of malaria parasites to antimalarial drugs



The protocol also described the instances in which patients could be withdrawn. Patients could choose to withdraw from the study at any time. The protocol stated that patients were to be withdrawn and treated with appropriate antimalarial therapy under any of the following conditions:

- The clinical condition deteriorated or impaired consciousness due to malaria developed
- There was no reduction of parasitemia within 48 hours of treatment
- The parasitemia was not cleared within seven days of treatment
- The patient's infection recrudesced
- The study drug was discontinued due to an adverse experience

The protocol stated that patients who failed to complete follow-up were to be replaced by the addition of patients to the study.

> MO COMMENT: In an unblinded study such as this one, the reasons for withdrawal were carefully reviewed for balance between treatment arms. Patients withdrawn for clinical or parasitologic deterioration were regarded as failures.

Efficacy endpoints

The primary efficacy parameter was the 28-day cure rate; the sponsor stated that only patients whose outcome at 28 days was known could be evaluated for the 28-day cure rate. The response to treatment was adapted from the World Health Organization (WHO) classification system and is presented below:

- Sensitive (S) or Cured: parasite clearance within 7 days without recrudescence during the 28-day follow-up period

- Resistant (R) or Not Cured:
  - RI parasite clearance within 7 days followed by recrudescence within 28 days*
  - RII marked reduction but no clearance within 7 days
  - RIII no significant reduction in parasites within 48 hours

*The applicant noted that since the last three doses of halofantrine were given on day 7, the 28 day follow-up would be extended to day 35. See MO COMMENT above.

The **protocol** stated that patients who were withdrawn because of deterioration of clinical condition or because of an adverse experience were to be classified as withdrawn (W). Patients who initially responded to treatment but who did not complete follow-up were to be classified as undetermined (U). A (U) designation would also be assigned to those patients who received antimalarial medication in the absence of asexual parasitemia during the follow-up period. Cure rates were to be calculated for each treatment arm as the ratio of # S responses / # total (S + RI + RII + RIII+W) responses.

In the **study report**, patients who were withdrawn (W) from the study or lost to follow-up were classified as unevaluable and were not included in the calculation of cure rates.

MO COMMENT: The WHO convention (S, RI, RII, RIII) for describing the response to antimalarial chemotherapy is established and widely accepted. Review of the protocol and the final study report, however, shows a discrepancy. According to the **study report**, patients who were withdrawn (W) or lost to follow-up were classified as unevaluable or, according to the convention described in the **protocol**, undetermined (U) and not factored into the calculation of cure rates according to the equation above. All patients who were withdrawn or lost to follow-up were reviewed by the MO (see below). Patients who were withdrawn because of poor clinical or parasitologic response, even before the end of the 28-day period, were to be regarded as failures (not cured) in the MO analysis, and were to be included in the calculation of cure rates (scored 'W').

MO COMMENT: While the WHO criteria describe the spectrum of clinical responses to malaria and are widely accepted, it is important to recognize that not all malaria patients who fail therapy are infected with resistant parasites. Parasite resistance has traditionally been assumed when clinical response to a known therapy in a particular geographic area begins to diminish. However, patient compliance, symptoms affecting drug absorption, variations in metabolism and excretion, and intrinsic schizonticidal activity 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. The designations RI, RII, RIII are useful to describe the spectrum of clinical failures and will be used here. Parasite resistance, however, is not the assumed reason for clinical failure.

MO COMMENT: The statement, 'A (U) designation would also be assigned to those patients who received antimalarial medication in the absence of asexual parasitemia during the follow-up period' was somewhat ambiguous. The MO interpreted it to mean that if a patient were to present during the follow-up period with symptoms suggestive of malaria and were to be started on antimalarial therapy, but then were to be found to have a negative peripheral smear (ie no malaria parasites), that patients would be scored as a U. The MO concurred with this scoring.

Secondary efficacy endpoints were parasite clearance time (PCT) and fever clearance time (FCT). PCT was defined as the time from treatment initiation to the time of the first of two negative films. FCT was defined as the time from treatment initiation to the time of the first decrease in fever below 99°F that remains below this target for at least 24 hours.

MO COMMENT: The sponsor stated that the definitive nature of the major endpoints would not be affected by lack of blinding, and that the great disparity in dosing regimens between different groups and the difficulty in obtaining placebos 'would complicate a double-dummy study' (NDA 21-078, vol 50, page 68). While there would be considerable difficulty in performing a double-dummy study of these two treatment regimens and there is no absolute requirement for a blinded study, it is important to note that the examination of peripheral smears can be subject to bias much as any other human activity can. In general, a blinded study, where possible, is preferred in the evaluation of any antimicrobial.

Safety

Safety data were analyzed on all 48 patients. Adverse event rates were calculated based on signs and symptoms which developed or worsened within 14 days after initiation of treatment. Laboratory results were compared to laboratory reference ranges and the number of patients with abnormal results were calculated for each test at each time. Treatment groups were compared by determining the difference between median results for each laboratory test at each time period and the 95% confidence interval around that difference.

MO COMMENT: Adverse event reporting was limited to those that started or increased during the first 14 days of the study. If an adverse event that started during the first seven days extended into the period from days 14-35, that too would be recorded. The protocol was not designed to capture events that started from days 14-35, when any study drug administration had ceased.

RESULTS

DEMOGRAPHICS

There were 48 patients enrolled in this study; 25 were treated with atovaquone/proguanil (ATQ/PRG) and 23 with halofantrine (HFN). Demographic characteristics of patients in both treatment arms are presented in Table 1.

Table 1. Demography

Group	Race (B/W)	Sex (M/F)	Mean Age (yrs)	Mean Weight (kg)	G6PD Deficient	Mean IPC /µl (Range)	Fever at presentation	Splenomegaly at presentation
ATQ/ PRG	15 /.10	16/9	35.4	66.3	6/15	21, 204 (393-180,500)	22/25 (88%)	6/25 (24%)
HFN	15 / 8	15/8	37.7	73.4	3/16	19,2071 (826-151,457)	20/23 (87%)	5/23 (22%)

B/W= Black/White; IPC=Initial Parasite Count

Table 1 demonstrates that the two treatment arms were well matched for race, age, weight, mean initial parasite count, number of patients with fever at presentation, and

number of patients with splenomegaly. Almost 90% of patients in both treatment groups had fever at presentation. This is contrasted with the semi-immune Brazilian (this sentence may eventually discuss all other phase III patients) patients enrolled in study 115-127, of whom only about 60% had fever at presentation. It is also noteworthy that only 20-25% of patients in the present study had splenomegaly on enrollment. This is a much smaller proportion than the >95% of Brazilian patients in study 115-127 who presented with splenomegaly. Some proportion of cases of acute falciparum malaria does present with splenomegaly. The patients enrolled in the present study were more likely to have enlarged spleens for this reason. They had either had no prior experience of malaria or remote experience (at least > 1 year before enrollment) that would not have been the repeated and constant exposure that can lead to a chronically enlarged spleen.

> MO COMMENT: The NDA submission did not include listings on individual patients that distinguished between those who had never lived in malarious area and those with a remote history of same. However, the profile of the population enrolled in the present study demonstrates that almost all patients were febrile at presentation, and that there was not a high rate of splenomegaly. This characterization suggests that the immune status of the population enrolled in study 115-130 more closely approximated that of malaria patients seen in Europe and the US.

Examination of the range of IPCs in Table 1 also shows that there were patients in each treatment group with parasite counts greater than the upper end of the range specified for the entry criteria (1000-100,000/µl). Review of the IPC for all patients showed that there were 9 patients enrolled with IPC >100,000/µl. Seven of these patients were treated with ATQ/PRG and 2 were treated with HFN (see EVALUABILITY section for further discussion of these patients).

EVALUABILITY

Applicant assessment

Forty-eight patients participated in the study; the applicant's analysis of patient evaluability is presented in Table 2.

Table 2. Patient evaluability per applicant

Investigator/Center	Atovaquone/proguanil			Halofantrine		
	Enrolled	Evaluable	%	Enrolled	Evaluable	%
, France	4	3	75	2	2	100
, France	11	10	90.9	12	11	91.7
, France	10	8	80.0	9	5	55.5
TOTAL	25	21	84.0	23	18	78.3

The proportion of enrolled patients who were evaluable was comparable between treatment groups. The applicant determined that 4 patients who received atovaquone/proguanil were unevaluable, and that 5 patients who received halofantrine were unevaluable. Of these 9 patients, 4 were lost to follow-up and 5 were withdrawn. Table 3 presents the unevaluable patients by reason and by treatment arm according to the applicant's analysis.

Table 3. Reasons for unevaluability per applicant

Reason	ATQ/PRG (pt no.)	HFN (pt no.)
Lost to follow-up	N=1 (054)	N=3 (051, 093, 099)
Withdrawn from study		
Underage	N=0	N=1 (094)
Withdrew consent	N=0	N=1 (089)
Persistent vomiting	N=3 (044, 086, 095)	N=0
TOTAL	N= 4	N= 5

MO COMMENT: The protocol stated that patients who were withdrawn from the study would be scored as 'W.' Patients with a score of W entered into the calculation of efficacy according to the equation described in the above discussion of the primary efficacy endpoint. According to Table 3, such patients were considered unevaluable or undetermined (U) according to the applicant's original scoring system described in the protocol. For further discussion of this issue, see below, EVALUABILITY-MO assessment.

MO assessment

Evaluability was assessed by first reviewing the parasitology database of all 48 patients to determine that all had malaria due to *P. falciparum* only. The MO assessment agreed with that of the applicant; all patients had falciparum malaria.

Patients considered evaluable by applicant
Of the 48 patients with falciparum malaria, all were scored by the applicant as having had either mild or moderate disease. There were nine patients whose initial parasite count was outside the upper limit of the range specified in the entry criteria (1000-100,000/ µl). These were patients #046, 054, 082, 086, 090, 092, 095, and 098. All of these patients had IPC values greater than 100,000/ µl but less than 200,000/ µl. Seven of these patients received atovaquone/proguanil (#046, 054, 086, 092, 095, and 098) and two received halofantrine (# 082 and 090). The MO reviewed the presenting signs and symptoms of all nine of these patients and concurred that all had a clinical presentation that could be graded as mild or moderate.

There were two patients who had IPC values of less than 1000/µl (#053 and #114). Review of the presentation of patient #053 demonstrated symptoms and signs consistent with malaria. This patient was evaluable in the MO assessment. Patient #114 was more complex. He had an IPC of 393/µl and was started on ofloxacin on day #2 of the study for typhoid fever. This drug was continued for the next 10 days. Because this patient had a parasite count below the limit set for the inclusion criteria, because he had a concurrent illness that could confound the therapeutic response, and because he received therapy with a fluoroquinolone, a drug from a class that may have some degree of antimalarial activity, he was considered unevaluable by the MO.

Concomitant medications were reviewed for all patients. It was noted by the MO that patient #052 started therapy with roxithromycin for bronchitis two days prior to enrollment. This antimicrobial was continued for ten days. Because macrolide antibiotics are known to have some antimalarial activity, this patient was considered unevaluable by the MO.

Patients considered unevaluable by applicant
The MO assessment of evaluability also included review of all patients considered unevaluable by the applicant. Case report tabulations and additional data on all patients noted in Table 3 were reviewed. The following discussion will first focus on patients who were withdrawn from the study for the reasons stated in table 3, then will review the patients who were lost to follow-up.

Five patients were withdrawn from the study. The reasons for these withdrawals were persistent vomiting (n=3), withdrawal of consent (n=1), and inappropriate age (n=1). The three patients withdrawn for vomiting all received atovaquone/proguanil. These patients

warranted careful review. Vomiting may be a presenting symptom of acute falciparum malaria or it may be a treatment-related adverse event. Patients with treatment-related vomiting that was severe enough to withdraw them from the study could be viewed as treatment failures. The MO reviewed the CRTs of the three patients withdrawn for vomiting (#044, 086, 095) to determine if they were vomiting prior to treatment, if the time of onset of the vomiting were near the time of presentation, or if it were near the time of drug administration. Patient #086 presented with vomiting. After 10 hours, he was withdrawn for persistent vomiting. Patient #086 did not clearly have treatment-related vomiting. The MO agreed that he was unevaluable. Patient #044 did not present with vomiting. She tolerated her first dose of atovaquone/proguanil. Her first episode of vomiting was 22.5 hours after the first dose of study drug administration. She was withdrawn when she vomited the second dose of study drug. There was no worsening of her parasitemia at this time. The MO considered this patient unevaluable. Patient #095 started vomiting 16 hours after the second dose of study drug and was withdrawn. This patient's parasitemia was observed to increase from 137K to 208K during this interval. He was considered by the MO to be evaluable and a failure. Further discussion of this patient is presented below (EFFICACY-MO assessment).

> MO COMMENT: Patients who are appropriately treated for malaria and who are cured (S or sensitive response) can manifest a rise in parasitemia during the first 24-48 hours of treatment. While this may have been what was observed for patient #095, it is also possible that treatment-related vomiting did not permit adequate drug levels in the blood and led to the observed increase in parasite count. Because vomiting has been a prominent treatment-related AE in patients receiving atovaquone/proguanil in the clinical trials submitted in NDA 21-078, a more conservative analysis that considered the effect of treatment-related vomiting on efficacy was undertaken by the MO (see below).

Patient #089 was enrolled with mild malaria and withdrew consent after receiving the first three doses of halofantrine. There were no adverse events recorded for this patient; the MO agreed that she was unevaluable. Patient #094 was enrolled in the study for two weeks before it was determined that she was underage because she was 15 years old. Because this patient was not followed-up to 28 days, the MO agreed that she was unevaluable.

The MO reviewed the CRTs for all four patients withdrawn because they were lost to follow-up. None of these patients failed to respond to initial therapy and none were available for evaluation at day 28. The MO concurred that they were unevaluable.

In summary, the MO analysis regarded patient #095 as evaluable and a failure and regarded patients #052 and #114 as unevaluable. The MO assessment of patient evaluability is presented in Table 4.

Table 4. Unevaluability per MO

Reason	ATQ/PRG (pt no.)	HFN (pt no.)
Lost to follow-up	N=1 (054)	N=3 (051, 093, 099)
Withdrawn from study		
Underage	N=0	N=1 (094)
Withdrew consent	N=0	N=1 (089)
Persistent vomiting	N=2 (044, 086)	N=0
Received antimicrobial agent with antimalarial activity	N=1 (114)	N=1 (052)
TOTAL	N=4	N= 6

EFFICACY

Applicant assessment

Overall cure

As noted above, cure was defined as elimination of parasite within 7 days with no recrudescence by day 28 or day 35. The applicant's assessment of cure rates is presented in Table 5.

Table 5. Cure rates per applicant

	ATQ/PRG	HFN
Total patients randomized	25	23
Evaluable patients	21	18
Cures ('sensitive' or S)	21	18
Failures ('resistant' or RI, RII, RIII, or W)	0	0
Unevaluable patients ('undetermined' or U)*	4	5
Percent cured or S/(RI + RII + RIII + W)	100.0 (21/21)**	100.0 (18/18)**

*All patients scored as unevaluable (undetermined or U) by the applicant were withdrawn after treatment

** The 95% CI around the difference in cure rates above is [-5.16, 5.16].

MO COMMENT: As noted above, the applicant found that 4 patients in the ATQ/PRG group were withdrawn (W), and 5 patients in the HFN group were withdrawn (W). In the calculation of efficacy rates presented in Table 5, these patients were scored as unevaluable, or in the scoring system described in the protocol, undetermined (U). Their outcomes were not taken into account when overall efficacy rates were calculated.

MO COMMENT: The protocol stated a planned statistical analysis that would compare the cure rates of the two treatment regimens by calculating the 95% confidence interval around the difference in the cure rates. The latter is a method of demonstrating equivalence with an active control that has been commonly used to establish efficacy of other antimicrobial agents under regulatory review. The 95% CI around the difference in the above efficacy rates is shown above. The lower bound of this confidence interval is >-10; it meets the statistical criterion for equivalence.

PCT and FCT

The applicant also provided analyses of parasite clearance times (PCT) and fever clearance times (FCT). Patients were included in the calculation of FCT if they had fever charts in their CRFs, if they had fever when treatment was initiated or 24 hours thereafter, no concurrent illness causing fever, and were not withdrawn prior to parasite or fever clearance. These results are presented in Table 7.

Table 6. PCT and FCT per applicant

Treatment Group	Parasite Clearance Time (hrs)				Fever Clearance Time (hrs)			
	No. pts	Median	Mean	Range	No. pts	Median	Mean	Range
ATQ/PRG	24	60.0	63.3		18	62	60.8	
HFN	22	48.0	49.4		19	57	58.2	

The applicant reported that halofantrine eliminated parasites and significantly more rapidly than did atovaquone/proguanil (p=0.02 for median values). Nevertheless these data are perhaps best viewed in context of the overall summary of drug efficacy.

MO COMMENT: The FCT as an indicator of drug efficacy is also problematic in that 31/48 (65%) patients received an antipyretic at some point during the period of treatment with study drug.

MO assessment

Overall Cure

Table 7 presents the MO analysis of overall cure rates by treatment group.

Table 7. Cure rates per MO

Treatment Group	No. of patients evaluable	No. with 0 parasites at 7 d/ No. evaluable (%)	No. with 0 parasites from d 7 to d 28-35/ No. evaluable (%)	Failures (RI, RII, RIII, or W)
ATQ/PRG	21	20/21 (95.2)	20/21 (95.2)	W: n=1 (vomiting, increasing parasitemia
HFN	17	17/17 (100)	17/17 (100.0)	No failures

PCT and FCT

The populations in which these parameters were assessed were quite small. The MO assessment of these measures of drug efficacy generally agreed with that of the applicant. It is noteworthy that the PCT for halofantrine was significantly shorter than that for atovaquone/proguanil. The reader is referred to the review of study #115-131 for a comparison of these two treatment regimens in a larger population.

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 14 days of initiation of treatment were recorded. There was a total of 57 adverse experiences in the patients receiving A/P and 26 adverse experiences in the patients receiving HFN. When all treatment-emergent AEs were considered, vomiting was significantly more frequent in patients receiving atovaquone/proguanil (44%) than in those receiving halofantrine (4%) with $p<0.005$. The applicant's assessment of adverse experiences considered by investigators to be attributable to study medication is presented in Table 8.

Table 8. Attributable Adverse Experiences

Adverse Experience	Number of Subjects Reporting an Adverse Experience			
	A + P n=25		HLF n=23	
	N	%	N	%
Cutaneous System				
Pruritus	1	4	1	4
Nervous/Psychiatric System				
Dizziness	1	4	2	9
Insomnia	2	8	1	4
Gastrointestinal System				
Abdominal Pain	1	4	0	0
Anorexia	1	4	0	0
Diarrhea	3	12	2	9
Nausea	4	16	2	9
Vomiting	11	44	1	4
Respiratory System				
Coughing	0	0	1	4
Body as a Whole				
Asthenia	1	4	0	0
Chest Pain	0	0	1	4
Number and % of Subjects Reporting at Least One Adverse Experience	15	60	8	35

MO COMMENT: It is noteworthy that all episodes of vomiting reported were considered by the investigators to be attributable to study drug. Again, this is a very small population from which to draw conclusions about drug safety. Rather, it should be viewed as a possible signal to be evaluated in an integrated summary of safety.

Laboratory abnormalities

Examination of means or medians of chemistry, hematology, or urinalysis values for each treatment group showed that there were no laboratory tests which met the criterion for a statistical difference in medians ($p < 0.005$)

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 9.

Table 9. 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%	1 (4%)	0	0	0
Hemoglobin	<7.5 g/dl	1 (4%)	0	0	0
Red Cell Count	<3.0/pl	1 (4%)	0	0	0
White Cell Count	<3000/µl	1 (4%)	0	2 (9%)	0
Neutrophil Count	<1000/µl	0	0	1 (7%)	0
Eosinophil Count	>1000/µl	0	0	1 (7%)	0
Platelet Count	<50/nl	1 (4%)	0	2 (9%)	0
Glucose	<50 mg/dl	0	0	0	0
BUN	>25 mg/dl	0	0	0	0
Creatinine	>2.0 mg/dl	0	0	0	0
Albumin	<3.0 g/dl	3 (15%)	0	3 (17%)	0
Bilirubin	>2.0 mg/dl	1 (4%)	0	0	0
ALT	>100 U/l	2 (8%)	0	3 (14%)	0
AST	>100 U/l	1 (4%)	0	2 (9%)	0
Proteinuria	2+ or greater	0		0	
Hematuria	2+ or greater	0		0	

Most of these abnormalities are commonly seen in evolving malaria. The one patient treated with A/P who had a significant decrease in his hematocrit (#046) was not deficient in red blood cell G6PD. It is noteworthy that this patient was found to have a dental abscess and cytomegalovirus infection (diagnostic method not specified) on day 4 of the study.

Hypoalbuminemia was seen in both treatment groups. It was not considered to be drug related by the applicant.

> MO COMMENT: Three patients in each treatment group had serum albumin <3.0g/dl at some point in the course of the study. In all six patients this had resolved by day 28. This could be attributed to a catabolic process such as the systemic infection ongoing at the time of enrollment.

The development of clinically significant increases in ALT or AST occurred in two patients treated with ATQ/PRG and three patients treated with HFN. All but one of these patients had elevated enzymes prior to treatment and all returned to normal during follow-up. None were attributed to drug treatment.

> MO COMMENT: Transaminase elevations are commonly seen in acute malaria.

REVIEWER'S COMMENTS

This comparative trial of atovaquone/proguanil and halofantrine in a small population of non-immune travelers returning to France 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 Kenyan children can be found in the review of study #115-131. The population under review in the present study was small; it suggested that the issue of treatment-related vomiting should be explored further in an integrated summary of efficacy.

Study # 115-131
Comparative clinical trial of a combination of atovaquone and proguanil versus halofantrine in the treatment of acute *P. falciparum* malaria in children in Kenya

STUDY OBJECTIVES AND DESIGN

This was an open-label, randomized, controlled trial of two multi-dose treatment regimens designed to compare the efficacy and safety of atovaquone and proguanil with that of halofantrine in children with acute falciparum malaria in Kenya. The principle investigator was Dr Gabriel Anabwani, Professor and Head, Department of Child Health, Paediatrics, and Adolescent Medicine, Moi University Faculty of Health Sciences, Eldoret, Kenya. The study was conducted at one treatment center, Eldoret District Hospital, Eldoret, Kenya, a highland location that has been the site of recent epidemics of 'highland malaria' since the early 1990s. The study was conducted in accordance with

the provisions of the Declaration of Helsinki and received the approval of the Moi University Research and Ethics Committee.

PROTOCOL OVERVIEW

Study population
This study was conducted from June 1994 to December 1994. It enrolled 168 boys and girls aged 3-12 years in a highland region of Kenya. It is noteworthy that in recent years, falciparum malaria has again spread from the endemic lowland regions in Kenya to the high-altitude areas (5000-10,000 feet) where the population was relatively non-immune. Malaria did not exist in the Kenyan highlands until the second decade of the 20th century. Malaria outbreaks accompanied the building of railroads and development of agriculture in the highlands, when the area began to be exposed to infective mosquitoes and parasitized humans. Such development was associated with sporadic epidemics from the 1920s until the 1950s, when an extensive control program essentially eliminated malaria from the highlands. During the 1960s and 70s, the Kenyan highlands were considered free of malaria, but in the last 10-15 years malaria has been increasing again in this area (Malakooti, Biomondo, Shanks, EID, 1998). In the prior experience of the principal investigator of the study under review, patients presenting in the Central and Western highlands of Kenya had acquired their malaria in lowland areas around Lake Victoria or in the savannah of the Great Rift Valley. In 1991, a severe epidemic of 'highland malaria' occurred around Eldoret, Kenya, with more than 11,000 cases in a three month period. Subsequently, this area has been considered endemic for malaria. Prior experience treating children with chloroquine around Eldoret has shown 40-60% resistance; treatment with halofantrine showed a cure rate >90%.

Inclusion criteria of note included uncomplicated *P. falciparum* malaria with acute manifestations and parasitemia between 1000 and 200,000 parasites/µl. Exclusion criteria of note included severe or cerebral malaria, significant concomitant disease that could mask the therapeutic response, pregnancy, mixed *Plasmodium* infections, inability to tolerate oral therapy, weight ≤ 10 kg, or QT interval > 0.44 sec.

MO COMMENT: Fever is one of the possible acute manifestations of falciparum malaria. However, fever was not required for entry into the study.

MO COMMENT: This protocol differs from many of the others included in NDA 21-078 in that patients with higher parasite counts were eligible for enrollment. Most other trials' inclusion criteria specified an initial parasite count of 1000-100,000/µl.

MO COMMENT: Parasite counts of 200,000/µl represent approximately 4% parasitemia. Depending on the immune status of the host, there are sources that define severe malaria as including parasitemia > 5%, 2%, or even 1%. A pediatric highland population with parasite counts as high as 200,000/µl may include patients with more severe disease and greater risk for complications than the populations enrolled in other studies.

MO COMMENT: Halofantrine has been shown to prolong the QT interval of the EKG at therapeutic doses.

Study procedures

Patients with acute falciparum malaria presenting to the study center were screened for study participation. Once enrollment criteria were met and informed consent obtained, a patient was assigned a sequential study number and entered into the study to receive the investigational agent, atovaquone/proguanil, or the control treatment, halofantrine (day 0). All patients were hospitalized until clinically well, then were transferred to a residential in-patient facility such that all patients were in-patients for seven days. Patients were to return for out-patient follow-up on days 14, 21, and 28. Atovaquone and proguanil (A/P) were co-administered in separate tablets, each containing 250 mg and 100 mg on a weight-adjusted basis (atovaquone 20 mg/kg). These doses were the same as those proposed in the draft label submitted by the applicant in the NDA under review. A/P was administered with hot chocolate. Patients were dosed with A/P every 24 hours for three doses. Halofantrine 8 mg/kg was administered every 6 hours for three doses.

MO COMMENT: This trial did not use Malarone or another fixed combination of atovaquone/proguanil.

MO COMMENT: Halofantrine was approved by the US FDA in 1992; it has not been marketed in the US. The dose of halofantrine used in this protocol is the dose in the FDA-approved label, adjusted for weight.

Temperature was taken every 4-8 hours during the acute stage of illness. Parasite counts were performed on peripheral blood smears every 12 hours until the blood films were negative on three consecutive examinations of Giemsa-stained thick smears. Weekly smears were then performed on days 7, 14, 21, 28. A blood film was not considered negative until an examination of 200 oil-immersion fields showed no parasites. The films were stained with Giemsa stain and parasite counts determined by counting the number of asexual parasites per 200 white blood cells on a thick film, and expressing the results in parasites per µl.

MO COMMENT: This is an acceptable method of determining whether or not a blood film is negative for malarial parasites. Both thin and thick smears are acceptable for quantifying parasites by the methods described above (Manson 1996, Bruce-Chwatt 1993).

Periodic physical examinations and laboratory determinations of hematology, clinical chemistry, and drug levels were performed. Blood was also obtained prior to treatment for possible *in vitro* parasite culture and assessment of drug sensitivity in the event of a recrudescence. Blood was also to be obtained for drug levels at 8 and 96 hours after starting therapy. Such assays were also to be performed only in the event of recrudescence. The study report stated that isolates from all patients who had a recrudescence were contaminated and susceptibility studies could not be done.

The protocol was amended in September 1994, three months after the start of the study. This amendment permitted the retreatment of patients who were found to have recurrent parasitemia during the follow-up period. The rationale behind this amendment was the recognition that patients with recurrent parasitemia could have been reinfected or could have recrudesced. If patients responded to retreatment, it was thought that this would more likely suggest reinfection. The study report stated that efficacy data were only collected following the second treatment of these patients.

MO COMMENT: The assumption underlying this retreatment strategy was that the reason patients could develop parasitemia during the follow-up period was because of the development of parasite resistance. This does not take into account other reasons for treatment failure such as impaired drug absorption or poor drug tolerance. Without susceptibility data and/or parasite PCR from parasites isolated from patients with recurrent parasitemia, it is not possible to distinguish between reinfection and recrudescence. One would expect the rate of reinfection to be the same for patients whether they received A/P or HFN.

Evaluability criteria

The original protocol did not specifically state what made patients unevaluable for analysis. The protocol did describe the instances in which patients could be withdrawn. Patients/parents could choose to withdraw from the study at any time. The protocol stated that patients were to be withdrawn and treated with appropriate antimalarial therapy under any of the following conditions:

- The clinical condition deteriorated or impaired consciousness due to malaria developed
- There was no reduction of parasitemia within 48 hours of treatment
- The parasitemia was not cleared within seven days of treatment
- The patient's infection recrudesced
- The study drug was discontinued due to an adverse experience

The protocol also stated that patients who failed to complete follow-up were to be replaced by the addition of patients to the study.

MO COMMENT: In an unblinded study, the reason for withdrawal should be carefully reviewed for balance between treatment arms. Patients withdrawn for clinical or parasitologic failure should be regarded as failures.

Efficacy endpoints

The primary efficacy parameter was the 28-day cure rate; patients who were cured were those in whom parasitemia was eliminated and did not recur during the 28-day follow-up. The response to treatment was adapted from the World Health Organization (WHO) classification system and is presented below:

- Sensitive (S) or Cured: parasite clearance within 7 days without recrudescence during the 28-day follow-up period
- Resistant (R) or Not Cured:
  - RI parasite clearance within 7 days followed by recrudescence within 28 days
  - RII marked reduction but no clearance within 7 days
  - RIII no significant reduction in parasites within 48 hours

The **protocol** stated that patients who were withdrawn because of deterioration of clinical condition or because of an adverse experience were to be classified as withdrawn (W). Patients who initially responded to treatment but who did not complete follow-up were to be classified as undetermined (U). A (U) designation would also be assigned to those patients who received antimalarial medication in the absence of asexual parasitemia during the follow-up period. Cure rates were to be calculated for each treatment arm as the ratio of # S responses / # total (S + RI + RII + RIII+W) responses.
In the **study report,** patients who were withdrawn (W) from the study were classified as unevaluable and were not included in the calculation of cure rates.

MO COMMENT: The WHO convention (S, RI, RII, RIII) for describing the response to antimalarial chemotherapy is established and widely accepted. Review of the protocol and the final study report, however, shows a discrepancy. According to the **study report**, patients who were withdrawn (W) or lost to follow-up were classified as unevaluable or, according to the convention described in the **protocol**, undetermined (U) and not factored into the calculation of cure rates according to the equation above. All patients who were not cured were reviewed by the MO (see below).

MO COMMENT: While the WHO criteria describe the spectrum of clinical responses to malaria and are widely accepted, it is important to recognize that not all malaria patients who fail therapy are infected with resistant parasites. Parasite resistance has traditionally been assumed when clinical response to a known therapy in a particular geographic area begins to diminish. However, patient compliance, symptoms affecting drug absorption, variations in metabolism and excretion, and intrinsic schizonticidal activity 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. The designations RI, RII, RIII are useful to describe the spectrum of clinical failures and will be used here. Parasite resistance, however, is not the assumed reason for clinical failure.

MO COMMENT: The statement, 'A (U) designation would also be assigned to those patients who received antimalarial medication in the absence of asexual parasitemia during the follow-up period' was somewhat ambiguous. The MO

interpreted it to mean that if a patient were to present during the follow-up period with symptoms suggestive of malaria and were to be started on antimalarial therapy, but then were to be found to have a negative peripheral smear (ie no malaria parasites), that patients would be scored as a U. The MO concurred with this scoring.

Secondary efficacy endpoints were parasite clearance time (PCT) and fever clearance time (FCT). PCT was defined as the time from treatment initiation to the time of the first of two negative films. FCT was defined as the time from treatment initiation to the time of the first decrease in fever below 99°F that remained below this target for at least 24 hours.

Safety

Safety data were analyzed on all 168 patients. Adverse event rates were calculated based on signs and symptoms which developed or worsened within 10 days after initiation of treatment. Laboratory results were compared to laboratory reference ranges and the number of patients with abnormal results were calculated for each test at each time. Treatment groups were compared by determining the difference between median results for each laboratory test at each time period and the 95% confidence interval around that difference.

MO COMMENT: Adverse event reporting was limited to those that started or increased during the first 10 days of the study. The protocol was not designed to capture events that started from days 10-28, when any study drug administration had ceased.

RESULTS

DEMOGRAPHICS

There were 168 patients enrolled in this study; 84 were treated with atovaquone/proguanil (ATQ/PRG) and 84 with halofantrine (HFN). All patients were black Africans. Demographic characteristics of patients in both treatment arms 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	39/45	6.4	18.1	5.8	29,686	62/84 (73.8%)	43/84 (51.2%)
HFN	38/46	5.6	17.0	1.8	31,474	64/84 (76.2%)	45/84 (53.6%)

IPC=Initial Parasite Count

Table 1 demonstrates that the two treatment arms were well matched for age, weight, mean initial parasite count, number of patients with fever at presentation, and number of patients with splenomegaly. About 75% of patients had fever at presentation. This is

contrasted with the 90% of European travelers studied in protocol #130, and the 60% of semi-immune Brazilian patients enrolled in study #127. Whether or not a patient is febrile with parasitemia is a rough indicator of that patient's immunity to malaria. Non-immune patients are much more likely to be febrile with relatively low parasite counts, while adult patients with repeated malaria exposure are less likely to be febrile at a given parasite count, and usually develop fever only with higher grade parasitemia.

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	HFN
Total patients enrolled	84	84
Evaluable patients for cure rate	81 (96.4%)	83 (98.8%)
Patients lost to follow-up	0	0
Withdrawn patients	3 (3.6%)	1 (1.2%)

No patients were lost to follow-up. There were four patients who were withdrawn; three were treated with A/P, one was treated with HFN. The parents of patients #014 (HFN) and #111 (A/P) withdrew consent at 14 days after treatment. No reasons were provided for these parents' decision to withdraw. MO review of these two patients' CRTs showed that both patients had cleared their parasitemia, and did not have AEs recorded near the time of the withdrawals. The MO assessment of these patients' evaluability agreed with that of the applicant. Patient #011 (A/P) was vomiting prior to treatment and was unable to retain her initial dose of A/P during a four-hour period. She was withdrawn, allowed resting for eight hours, and then treated with Fansidar. Because this patient's vomiting was a pre-existing condition, the applicant did not consider it an adverse event. The MO agreed that this patient should be scored as unevaluable. The vomiting associated with her infection did not permit oral therapy at the time of presentation. In some settings, such a patient may not have been a candidate for oral therapy at all. Patient #141 was withdrawn from the A/P group because she was inadvertently treated with chloroquine for a cough at another facility. The MO reviewed this patient's CRT. Parasitemia was cleared at 64 hours, chloroquine was administered on day 12. There was no documentation of other symptoms suggestive of a *Plasmodium* parasitemia up to this point. While it is possible that a malaria recrudescence can present with cough and other unusual symptoms, it is also common practice in some malaria-endemic regions to treat empirically with antimalarials when a child presents with an acute illness. With no other information available, the MO agreed that this patient was unevaluable.

MO COMMENT: The protocol stated that patients who were withdrawn from the study would be scored as 'W.' Patients with a score of W entered into the calculation of efficacy according to the equation described in the above discussion of the primary

efficacy endpoint. According to Table 2, such patients were considered unevaluable or undetermined (U) according to the applicant's original scoring system described in the protocol. For further discussion of this issue, see below, EVALUABILITY-MO assessment.

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	HFN
Total patients randomized	84	84
Evaluable patients Cures ('sensitive' or S) Failures ('resistant' or RI, RII, RIII, or W)	81 76 (93.8%)** 5 (6.2%)	83 75 (90.4%)** 8 (9.6%)
Unevaluable patients ('undetermined' or U)*	3	1

*All patients scored as unevaluable (undetermined or U) by the applicant were withdrawn after treatment started.

** The 95% CI around the difference in cure rates is [-6.0, 12.9]. This meets the statistical criterion for equivalence.

There were 5 patients who were treated with A/P and not cured. All five of these patients had an RI response. There were eight patients who were treated with HFN who were not cured. All of these patients had an RI response as well. All of these patients became parasitemic between day 14 and day 28. The rates of RI failures in each treatment group were comparable. Of the total study population, 7.7% (13/168) manifested an RI response. A comparison of rates of recurrence of parasitemia for A/P and HFN may be made between study #130, returning European travelers, and the present study of Kenyan children. In study #130, in which patients were followed-up in a non-malarious European country, there were no recurrences of parasitemia in either treatment group. In the present study, where children were only in-patients for 7 of the 28 days of the study, approximately 8% manifested an RI response. Without more data on the clinical isolates, it is not possible to distinguish between recrudescence and reinfection in these RI patients. One may hypothesize, however, that some component of these RI responses is due to reinfection.

MO COMMENT: As noted above, the applicant found that 3 patients in the ATQ/PRG group were withdrawn (W), and 1 patient in the HFN group was withdrawn (W). In the calculation of efficacy rates presented in Table 3, these patients were scored as unevaluable, or in the scoring system described in the protocol, undetermined (U). Their outcomes were not taken into account when overall efficacy rates were calculated.

MO COMMENT: The MO reviewed the individual cases for each of the 13 cases scored as 'not cured,' and agrees with the applicant's assessment of these patients' outcomes. It is noteworthy, however, that only seven of these 13 patients were retreated. This was not related to the point at which parasitemia recurred, since those retreated spanned the entire period from day 14 to day 28. There was no explanation for this selective retreatment provided by the applicant.

Two of the three patients retreated with A/P and all four patients retreated with HFN were cured with their second course of treatment. The applicant concluded that these results suggested that the recurrent parasitemias were mostly reinfections, with the exception of the one patient who failed to respond to retreatment with A/P.

MO COMMENT: It is difficult to conclude that all treatment failures are due to parasite drug resistance and that all recurrent parasitemia that responds to retreatment is due to reinfection. Both of these conclusions assume that these treatment regimens work in all patients infected with susceptible parasites (this is what is being asked in the clinical trial under review), and that one strain of *P. falciparum* can be distinguished from another simply on the basis of response to therapy (a strain infecting a patient at enrollment and a second strain infecting a patient during follow-up may both respond to the same treatment regimen). Data on plasma drug concentrations in the individuals who failed and data on parasite PCR and *in vitro* drug susceptibility would provide additional evidence to support or refute these conclusions. Without them, the applicant's conclusions regarding retreatment are only speculative.

PCT and FCT

The applicant also provided analyses of parasite clearance times (PCT) and fever clearance times (FCT). Patients were included in the calculation of FCT if they had fever charts in their CRFs, if they had fever when treatment was initiated or 24 hours thereafter, no concurrent illness causing fever, and were not withdrawn prior to parasite or fever clearance. These results are presented in Table 4.

Table 4. PCT and FCT per applicant

Treatment Group	Parasite Clearance Time (hrs)			Fever Clearance Time (hrs)		
	No. pts	Median	Mean	No. pts	Median	Mean
ATQ/PRG	83	64.5	64.9	68	29.8	35.9
HFN	84	50.4	50.2	73	35.3	39.2

As was demonstrated in study #130, patients treated with halofantrine had a significantly shorter PCT than did patients treated with A/P. It should be noted that both treatment groups had a PCT well within the 168 hours required for an S response by the WHO criteria.

MO COMMENT: The FCT as an indicator of drug efficacy is problematic in that about 65% patients received an antipyretic at some point during the period of treatment with study drug.

Plasma Drug Concentrations

These data were reported by the applicant as incomplete at the time of the preparation of the final study report. The applicant did report that atovaquone concentrations, 8 and 96 hours after initiation of treatment, were measured in nine patients, two of whom had recrudescences. These two patients had concentrations of atovaquone that were reported as comparable to the concentrations of atovaquone in the seven patients who were cured with atovaquone/proguanil. The values for these drug levels were not provided.

EVALUABILITY AND EFFICACY

MO assessment

Evaluability

Evaluability was assessed by first reviewing the parasitology database of all 168 patients to determine that all had malaria due to *P. falciparum* only. The MO assessment agreed with that of the applicant; all patients had falciparum malaria.

Subsequent MO assessment of patient evaluability and treatment efficacy was accomplished with the use of a random sample that selected approximately one third (61/164) of the study population for review by the MO. Each of these patients' CRTs and other data listings were reviewed for agreement between the MO and the applicant regarding patient evaluability and outcome. The MO review of these patients did not suggest any changes from the applicant assessment of either evaluability or outcome. The MO assessment agrees with the applicant analyses presented in Tables 2, 3, and 4.

MO review of the line listings of clinical and laboratory findings at presentation provided some additional information about the population studied which may be helpful in understanding treatment efficacy. Five of the patients enrolled had IPC > 200,000/µl. Three of these patients were randomized to A/P. None of the five were among those who were not cured. Of the total study population, 18% were graded by the investigator as having severe disease at enrollment (15.5% A/P, 20.2% HFN). It should be noted that these patients did not meet the criteria for severe malaria established by the WHO (eg. hypoglycemia, cerebral malaria). Rather there was some feature(s) of their presentations (vital signs, hematocrit, overall clinical condition) that warranted a scoring of 'severe' clinical condition by the investigator.

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 were recorded. There was a total of 73 adverse experiences in the patients receiving A/P and 119 adverse experiences in the patients receiving HFN. Those AEs with a frequency greater than 2% are recorded in Table 5.

Table 5. Treatment Emergent AEs >2%

	Atovaquone/Proguanil		Halofantrine	
	Number	Percent	Number	Percent
Abdominal Pain	8	9.8%	19	23.2%
Coughing	10	12.2%	14	17.1%
Headache	8	9.8%	15	18.3%
Vomiting	13	15.9%	7	8.5%
Pruritus	9	11.0%	8	9.8%
Diarrhea	4	4.9%	8	9.8%
Anorexia	3	3.7%	8	9.8%
Insomnia	2	2.4%	7	8.5%
Rash	3	3.7%	5	6.1%
Chills/Rigors	2	2.4%	3	3.7%
Epistaxis	1	1.2%	5	6.1%
Weakness	1	1.2%	4	4.9%
Herpes Labialis	3	3.7%	0	
Myalgia	0		3	3.7%
Palpitations	1	1.2%	2	2.4%

When all treatment-emergent AEs were considered, vomiting was almost twice as frequent in patients who received A/P (15.9%) as in those who received HFN (8.5%). Thirteen patients who received A/P required readministration of their medications compared to only one who received HFN. Abdominal pain, diarrhea, and anorexia occurred at least twice as frequently in patients receiving HFN.

Laboratory abnormalities

Examination of means or medians of chemistry, hematology, or urinalysis values for each treatment group showed that there were no laboratory tests which met the criterion for a statistical difference in medians ($p < 0.005$)