CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

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STATISTICAL REVIEW AND EVALUATION

SPONSOR: Glaxo Wellcome Research and Development
INDICATIONS: 1. Treatment of malaria (eight controlled studies and five uncontrolled studies)
2. Prophylaxis of malaria (four controlled studies and one uncontrolled study)
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TABLE OF CONTENTS

I. TREATMENT OF MALARIA

I.A. INTRODUCTION

The Applicant submitted eight controlled studies as evidence to support that the combination of atovaquone and proguanil hydrochloride is safe and efficacious for the treatment of acute, uncomplicated malaria caused by *P.falciparum*. Statistical review focuses on the eight comparative clinical trials which formed the basis of this application. The general design of the studies is as follows (also see Table 1):

Study 154-120 was an open-label, randomized, controlled, comparative trial which compared the safety and efficacy of atovaquone/proguanil for a treatment duration of 3 days versus fansidar for a treatment duration of 1 days for the treatment of adults with acute falciparum malaria in Zambia. All eligible subjects had acute, uncomplicated falciparum malaria with parasite counts between 1,000 and 200,000/µl, were 12~65 years of age, weighed at least 40 kg, and had no underlying disease.

Study 154-122 was an open-label, randomized, controlled, comparative trial which compared the safety and efficacy of atovaquone/proguanil for a treatment duration of 3 days versus mefloquine for a treatment duration of 1 days for the treatment of adults with acute falciparum malaria in Thailand. All eligible subjects had acute, uncomplicated falciparum malaria with parasite counts between 1,000 and 200,000/µl were 16~65 years of age, weighed at least 40 kg, and had no underlying disease.

Study 154-127 was an open-label, randomized, controlled, comparative trial which compared the safety and efficacy of atovaquone/proguanil for a treatment duration of 3 days versus quinine/tetracycline for a treatment duration of 7 days for the treatment of adults with acute falciparum malaria in Brazil. All eligible subjects had acute, uncomplicated falciparum malaria with parasite counts between 1,000 and 200,000/µl, were 18~65 years of age, weighed at least 40 kg, and had no significant concomitant disease.

Study 154-130 was an open-label, randomized, controlled, comparative trial which compared the safety and efficacy of atovaquone/proguanil for a treatment duration of 3 days versus halofantrine for a treatment duration of 1 days for the treatment of adults with acute falciparum malaria in Europe. Subjects were selected from European travelers to malarious areas, or natives of malarious areas who had resided in non-malarious areas for at least one year, but who had acquired malaria on short trips or vacations to their country. All eligible subjects had acute, uncomplicated falciparum malaria with parasite counts between 1,000 and 100,000/µl, were 16~65 years of age, weighed more than 40 kg, and had no significant concomitant disease.

Study 154-131 was an open-label, randomized, controlled, comparative trial which compared the safety and efficacy of atovaquone/proguanil for a treatment duration of 3 days versus halofantrine for a treatment duration of 1 days for the treatment of children with acute falciparum malaria in Kenya. All eligible subjects were those who had acute, uncomplicated falciparum malaria with parasite counts between 1,000 and 200,000/µl, were 3~12 years of age, weighed more than 10 kg, and had no underlying disease.

Study 154-134 was an open-label, randomized, controlled, comparative trial which compared the safety and efficacy of atovaquone/proguanil for a treatment duration of 3 days versus amodiaquine for a treatment duration of 3 days for the treatment of adults with acute falciparum malaria in Gabon. All eligible subjects had acute, uncomplicated falciparum malaria with parasite counts between 200 and 100,000/µl, were 15~65 years of age, weighed more than 40 kg, and had no underlying diseases.

Study 154-135 was an open-label, randomized, controlled, comparative trial which compared the safety and efficacy of atovaquone/proguanil for a treatment duration of 3 days versus chloroquine for a treatment duration of 3 days, or the chloroquine/fansidar for a treatment duration of 1 days for the treatment of

subjects with acute falciparum malaria in the Philippines (three treatment regimens). All eligible subjects had acut , uncomplicated falciparum malaria with parasite counts between 1,000 and 200,000/µl, were 12–65 years of age, weighed more than 30 kg, and had no underlying disease.

Study 154-136 was an open-label, randomized, controlled, comparative trial which compared the safety and efficacy of atovaquone/proguanil for a treatment duration of 3 days versus chloroquine for a treatment duration of 3 days, or fansidar for a treatment duration of 1 days for the treatment of subjects with acute falciparum malaria in Peru (two phase trial and two treatment regimens per phase). All eligible subjects had acute, uncomplicated falciparum malaria with parasite counts between 1,000 and 200,000/µl, were 12–65 years of age, weighed more than 30 kg, and had no underlying disease.

These studies are outlined in Table 1.

TABLE 1: CONTROLLED CLINICAL TRIALS OF ATOVAQUONE AND PROGUANIL HYDROCHLORIDE FOR TREATMENT OF MALARIA

Study Number	Study Design	Treatments	Number of Subjects	Mean Age in Years (Range)	Duration of Therapy
115-120	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	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	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	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	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	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	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	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 sulfadoxine 1500 mg	43	33 (15-65)	3 days 3 days 1 day

I.B. METHODS

Subjects meeting the inclusion/exclusion criteria were randomized to treatment with either atovaquone/proguanil or control(s). Eligible subjects were sequentially admitted to the study. Following treatment, the subjects were monitored closely by sequential clinical and laboratory assessments until recrudescence, or 28 days. Blood specimens were also obtained when initially treated and at the time of any subsequent recrudescence for measurement of drug concentrations and for *in vitro* culture and sensitivity studies.

Efficacy analyses were performed on evaluable subjects and all enrolled subjects as well. The primary criterion for effectiveness of an anti-malarial drug was the 28-day cure rate, which was defined as the percentage of subjects in whom parasitemia was eliminated and did not recur during 28 days of follow-up. Only subjects whose outcome at 28 days was known could be evaluated for 28-day cure rates in the evaluable subject analysis. The secondary endpoints were parasite clearance times (PCT) and fever clearance times (FCT). The primary efficacy parameter in the studies was 28-day cure rate of evaluable subjects.

Reviewer's Note: *The Medical Officer agreed with evaluability criteria chosen by the Sponsor, and outcomes assessment defined by the Sponsor.*

Please refer to the Medical Officer's review for detailed descriptions of the Sponsor's efficacy outcome definitions and Medical Officer's comments.

All subjects who received at least one dose of study medication were evaluable for safety. Adverse experiences were defined as any clinical finding that first occurred, or increased in severity within 10 days of initiation of treatment. Symptom rates (percentage of subjects with symptom) were calculated for each adverse experience.

The comparisons of interest in these studies were conducted between the combination of atovaquone and proguanil hydrochloride and the control(s).

Reviewer's Note: *The following statistical analyses were performed by the reviewer to evaluate the efficacy and safety of atovaquone/proguanil versus its comparators.*

All efficacy analyses of the primary endpoint were conducted for evaluable subjects, who were assessed for their responses at 28 days, and for all enrolled subjects. In the analysis of all enrolled subjects, missing values were imputed as failures. Equivalence between the treatments with respect to the primary efficacy parameter was assessed by computing the two-tailed 95% confidence interval of the difference in 28-day cure rates. The confidence intervals were computed using a normal approximation to the binomial, and included a continuity correction. Bonferroni's adjustment in the Type I error probability was applied when there was more than one comparison in a study. The evaluation of whether the treatment groups were considered equally effective was judged by the draft DAIDP "Points to Consider" document pertaining to results of confidence intervals.

For comparisons between the treatments in secondary efficacy parameters, parasite and fever clearance times, Shapiro-Wilk's test was applied to test the normality of underlying data. If the assumption of normality was not established, medians of PCT and FCT were used to compare the treatments by Mann Whitney's U test, otherwise, means of PCT and FCT were compared by two-sample t test. The corresponding 95% confidence intervals for the difference in median or mean were also calculated. Analyses were conducted for both evaluable subjects and for all enrolled subjects, where missing values were not imputed.

DerSimonian-Laird's random effect approach was applied to conduct meta-analysis. This approach incorporates any observed heterogeneity of treatment effect across the studies to produce an integrated weighed estimate of treatment difference in cure rates. The associated 95% confidence intervals for the integrated weighed difference in cure rates were also calculated.

This reviewer conducted safety analyses with the rate of at least one adverse event and the rate of at

least one treatment related adverse event. Statistical comparisons between the two treatment groups were performed using Fisher's exact test.

All tests were two-sided and used a 5% level of significance. The test for homogeneity of treatment effect was deemed significant at the 0.15 level.

I.C. RESULTS

I.C.1. STUDY 115-120

A total of 163 Zambian Black African subjects were enrolled and were sequentially admitted to the study between December 1993 and May 1994. Of these enrolled subjects, 1 was lost to follow-up, and 2 were withdrawn from the study. The 160 subjects who were evaluable for 28-day cure rates remained in the hospital for the full duration of follow-up; 80 subjects received atovaquone/proguanil treatment and 80 subjects received fansidar treatment.

Reviewer's Note: *The number and percentage of subjects included in each analysis group, evaluated by the Applicant, are presented in Table 2. There were no statistically significant treatment differences with respect to the percentage of subjects included in each analysis group.*

TABLE 2: STUDY 115-120: NUMBER OF SUBJECTS INCLUDED IN EACH TREATMENT GROUP

Analysis Group	Subjects Included	
	Atovaquone/ Proguanil	Fansidar
All Enrolled Subjects	82	81
Evaluable Subjects	80 (97.6%)	80 (98.8%)
Subjects Lost to Follow-up	0 (0%)	1 (1.2%)
Withdrawn Subjects	2 (2.4%)	0 (0%)

Reviewer's Note: *The cure rates are shown for evaluable subjects and all enrolled subjects in Table 3. Confidence interval results from analyses showed that atovaquone/proguanil was therapeutically equivalent to fansidar with respect to the cure rates.*

The parasite or fever clearance times of evaluable subjects and all enrolled subjects are presented in Tables 4 and 5, respectively. In both analysis groups, atovaquone/proguanil subjects had significantly longer PCTs, but had a significantly shorter FCTs.

TABLE 3: STUDY 115-120: CURE RATES		
Clinical Response	Atovaquone/ Proguanil	Fansidar
Evaluable Subjects		
Cured	80/80 (100%)	79/80 (98.8%)
Not Cured	0/80 (0%)	1/80 (1.2%)
A/P vs Fansidar: Cure	1.3%, 95% C.I.: -2.4%, 4.9%	
All Enrolled Subjects		
Cured	80/82 (97.6%)	79/81 (97.5%)
Not Cured and the Others*	2/82 (2.4%)	2/81 (2.5%)
A/P vs Fansidar: Cure	0.1%, 95% C.I.: -5.9%, 6.0%	
* "Other" refers to subjects who were either lost to follow-up or withdrawn		

TABLE 4: STUDY 115-120: PARASITE CLEARANCE TIMES		
Clinical Response	Atovaquone/ Proguanil	Fansidar
Evaluable Subjects		
Subjects (N)	80	80
Test of Normality	< 0.001	0.012
Median (hrs)	72.0	48.0
A/P vs Fansidar: Median	18.0, 95% C.I.: 12.0, 24.0 P-value (Mann-Whitney U test): <0.001	
Mean (hrs)	63.8	51.5
A/P vs Fansidar: Mean	12.3, 95% C.I.: 5.6, 19.0 P-value (2-sample t test): <0.001	
All Enrolled Subjects		
Subjects (N)	81	81
Test of Normality	< 0.001	0.009
Median (hrs)	72.0	48.0
A/P vs Fansidar: Median	18.0, 95% C.I.: 12.0, 24.0 P-value (Mann-Whitney's U test): <0.001	
Mean (hrs)	64.0	51.4
A/P vs Fansidar: Mean	12.6, 95% C.I.: 5.9, 19.3 P-value (2-sample t test): <0.001	

TABLE 5: STUDY 115-120: FEVER CLEARANCE TIMES		
Clinical Response	Atovaquone/ Proguanil	Fansidar
Evaluable Subjects		
Subjects (N)	67	76
Test of Normality	< 0.001	0.301
Median (hrs)	23.0	48.0
A/P vs Fansidar: Median	-19.0, 95% C.I.: -27.0, -9.0 P-value (Mann-Whitney's U test): <0.001	
Mean (hrs)	30.6	45.5
A/P vs Fansidar: Mean	-14.9, 95% C.I.: -23.3, -6.5 P-value (2-sample t test): <0.001	
All Enrolled Subjects		
Subjects (N)	67	77
Test of Normality	< 0.001	0.202
Median (hrs)	23.0	48.0
A/P vs Fansidar: Median	-19.0, 95% C.I.: -27.0, -8.0 P-value (Mann-Whitney's U test): <0.001	
Mean (hrs)	30.6	45.0
A/P vs Fansidar: Mean	-14.4, 95% C.I.: -22.8, -6.0 P-value (2-sample t test): <0.001	

Reviewer's Note: *For all enrolled subjects, the rate of at least one adverse event and the rate of at least one treatment related adverse event are presented in Table 6. There were no significant differences with respect to these parameters. No subjects died during the study.*

TABLE 6: STUDY 115-120: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Atovaquone/ Proguanil (N=82)	Fansidar (N=81)	Fisher's P-value
At Least One AE	75 (91.5%)	76 (93.8%)	0.766
At Least One Treatment Related AE	64 (78.1%)	65 (80.3%)	0.847

I.C.2. STUDY 115-122

A total of 182 Thai subjects were enrolled and were sequentially admitted to the study between August 1993 and July 1994. Of these enrolled subjects, 22 were lost to follow-up, and 2 were withdrawn from the study. The 158 subjects who were evaluable for 28-day cure rates remained in the hospital or in Bangkok for the full duration of follow-up; 79 subjects received atovaquone/proguanil treatment and 79 subjects received mefloquine treatment.

Reviewer's Note: *The number and percentage of subjects included in each analysis group, evaluated by the Applicant, are presented in Table 7. The two treatments were exactly the same with respect to the percentage of subjects included in each analysis group.*

TABLE 7: STUDY 115-122: NUMBER OF SUBJECTS INCLUDED IN EACH TREATMENT GROUP		
Analysis Group	Subjects Included	
	Atovaquone/ Proguanil	Mefloquine
All Enrolled Subjects	91	91
Evaluable Subjects	79 (86.8%)	79 (86.8%)
Subjects Lost to Follow-up	11 (12.1%)	11 (12.1%)
Withdrawn Subjects	1 (1.1%)	1 (1.1%)

Reviewer's Note: *The cure rates are shown for evaluable subjects and all enrolled subjects in Table 8. Confidence interval results from analyses showed that atovaquone/proguanil was therapeutically superior to mefloquine with respect to the cure rates of evaluable subjects, and marginally therapeutically superior to mefloquine with respect to the cure rates of all enrolled subjects. Recall that a fair amount of subjects were lost to follow-up in this study (approximately 12% in each arm).*

The parasite or fever clearance times of evaluable subjects and all enrolled subjects are presented in Tables 9 and 10, respectively. There were no significant differences in median of PCT and FCT, respectively.

TABLE 8: STUDY 115-122: CURE RATES		
Clinical Response	Atovaquone/ Proguanil	Mefloquine
Evaluable Subjects		
Cured Not Cured	79/79 (100%) 0/79 (0%)	68/79 (86.1%) 11/79 (13.9%)
A/P vs Mefloquine: Cure	13.9%, 95% C.I.: 5.0%, 22.8%	
All Enrolled Subjects		
Cured Not Cure and the Others*	79/91 (86.8%) 12/91 (13.2%)	68/91 (74.7%) 23/91 (25.3%)
A/P vs Mefloquine: Cure	12.1%, 95% C.I.: -0.3%, 24.5%	
* "Other" refers to subjects who were either lost to follow-up or withdrawn		

TABLE 9: STUDY 115-122: PARASITE CLEARANCE TIMES		
Clinical Response	Atovaquone/ Proguanil	Mefloquine
Evaluable Subjects		
Subjects (N)	79	79
Test of Normality	0.320	0.001
Median (hrs)	67.0	66.0
A/P vs Mefloquine: Median	-4.0, 95% C.I.: -12.0, 2.0 P-value (Mann-Whitney U test): 0.220	
Mean (hrs)	65.1	73.5
A/P vs Mefloquine: Mean	-8.4, 95% C.I.: -15.6, -1.1 P-value (2-sample t test): 0.025	
All Enrolled Subjects		
Subjects (N)	90	90
Test of Normality	0.675	<0.001
Median (hrs)	66.5	65.0
A/P vs Mefloquine: Median	-4.0, 95% C.I.: -11.0, 2.0 P-value (Mann-Whitney's U test): 0.218	
Mean (hrs)	65.3	73.9
A/P vs Mefloquine: Mean	-8.6, 95% C.I.: -15.7, -1.5 P-value (2-sample t test): 0.018	

TABLE 10: STUDY 115-122: FEVER CLEARANCE TIMES		
Clinical Response	Atovaquone/ Proguanil	Mefloquine
Evaluable Subjects		
Subjects (N)	73	77
Test of Normality	0.001	0.027
Median (hrs)	54.0	52.0
A/P vs Mefloquine: Median	5.0, 95% C.I.: -5.0, 16.0 P-value (Mann-Whitney's U test): 0.347	
Mean (hrs)	58.6	52.6
A/P vs Mefloquine: Mean	6.0, 95% C.I.: -4.7, 16.6 P-value (2-sample t test): 0.270	
All Enrolled Subjects		
Subjects (N)	84	88
Test of Normality	< 0.001	0.007
Median (hrs)	53.5	50.0
A/P vs Mefloquine: Median	6.0, 95% C.I.: -3.0, 18.0 P-value (Mann-Whitney's U test): 0.190	
Mean (hrs)	59.0	50.9
A/P vs Mefloquine: Mean	8.1, 95% C.I.: -2.2, 18.3 P-value (2-sample t test): 0.120	

Reviewer's Note: *For all enrolled subjects, the rate of at least one adverse event and the rate of at least one treatment related adverse event are presented in Table 11. There were no significant differences with respect to these parameters. No subjects died during the study.*

TABLE 11: STUDY 115-122: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Atovaquone/ Proguanil (N=91)	Mefloquine (N=91)	Fisher's P-value
At Least One AE	27 (29.7%)	23 (25.3%)	0.619
At Least One Treatment Related AE	1 (1.1%)	3 (3.3%)	0.621

I.C.3. STUDY 115-127

A total of 175 Brazilian subjects were enrolled and were sequentially admitted to the study between April 1995 and February 1996. Of these enrolled subjects, 25 were withdrawn from the study. There were 150 subjects who were evaluable for 28-day cure rates; 74 subjects received atovaquone/proguanil treatment and 76 subjects received quinine/tetracycline treatment.

Reviewer's Note: *The number and percentage of subjects included in each analysis group, evaluated by the Applicant, are presented in Table 12. There were no statistically significant treatment differences with respect to the percentage of subjects included in each analysis group.*

TABLE 12: STUDY 115-127: NUMBER OF SUBJECTS INCLUDED IN EACH TREATMENT GROUP		
Analysis Group	Subjects Included	
	Atovaquone/ Proguanil	Quinine/ Tetracycline
All Enrolled Subjects	87	88
Evaluable Subjects	74 (85.1%)	76 (86.4%)
Subjects Lost to Follow-up	0 (0%)	0 (0%)
Withdrawn Subjects	13 (14.9%)	12 (13.6%)

Reviewer's Note: *The cure rates are shown for evaluable subjects and all enrolled subjects in Table 13. Confidence interval results from analyses showed that atovaquone/proguanil was therapeutically equivalent to mefloquine with respect to the cure rates. Note that results were not very robust in this study due to the large amount of subjects who were withdrawn (approximately 14% in each arm).*

The parasite or fever clearance times of evaluable subjects and all enrolled subjects are presented in Tables 14 and 15, respectively. Two treatment groups were significantly different in median of PCT and FCT. Atovaquone/proguanil had shorter PCT and FCT respectively.

TABLE 13: STUDY 115-127: CURE RATES		
Clinical Response	Atovaquone/ Proguanil	Quinine/ Tetracycline
Evaluable Subjects		
Cured Not Cured	73/74 (98.6%) 1/74 (1.4%)	76/76 (100%) 0/76 (0%)
A/P vs Mefloquine: Cure	-1.4%, 95% C.I.: -5.3%, 2.6%	
All Enrolled Subjects		
Cure Not Cure and the Others*	73/87 (83.9%) 14/87 (16.1%)	76/88 (86.4%) 1/88 (13.6%)
A/P vs Mefloquine: Cure	-2.5%, 95% C.I.: -14.1%, 9.2%	
* "Other" refers to subjects who were either lost to follow-up or withdrawn		

TABLE 14: STUDY 115-127: PARASITE CLEARANCE TIMES		
Clinical Response	Atovaquone/ Proguanil	Quinine/ Tetracycline
Evaluable Subjects		
Subjects (N)	74	76
Test of Normality	0.655	0.058
Median (hrs)	58.0	66.0
A/P vs Mefloquine: Median	-8.0, 95% C.I.: -14.0, -2.0 P-value (Mann-Whitney U test): 0.021	
Mean (hrs)	55.5	63.6
A/P vs Mefloquine: Mean	-8.1, 95% C.I.: -14.3, -1.9 P-value (2-sample t test): 0.011	
All Enrolled Subjects		
Subjects (N)	84	83
Test of Normality	< 0.001	< 0.001
Median (hrs)	58.0	68.0
A/P vs Mefloquine: Median	-9.0, 95% C.I.: -15.0, -3.0 P-value (Mann-Whitney's U test): 0.007	
Mean (hrs)	55.4	64.6
A/P vs Mefloquine: Mean	-9.2, 95% C.I.: -15.1, -3.4 P-value (2-sample t test): 0.002	

TABLE 15: STUDY 115-127: FEVER CLEARANCE TIMES		
Clinical Response	Atovaquone/ Proguanil	Quinine/ Tetracycline
Evaluable Subjects		
Subjects (N)	54	52
Test of Normality	< 0.001	< 0.001
Median (hrs)	22.0	26.0
A/P vs Mefloquine: Median	-10.0, 95% C.I.: -17.0, -2.0 P-value (Mann-Whitney's U test): 0.017	
Mean (hrs)	22.5	32.3
A/P vs Mefloquine: Mean	-9.8, 95% C.I.: -18.1, -1.5 P-value (2-sample t test): 0.021	
All Enrolled Subjects		
Subjects (N)	62	58
Test of Normality	< 0.001	0.202
Median (hrs)	22.5	26.0
A/P vs Mefloquine: Median	-8.0, 95% C.I.: -16.0, -1.0 P-value (Mann-Whitney's U test): 0.024	
Mean (hrs)	23.8	32.5
A/P vs Mefloquine: Mean	-8.7, 95% C.I.: -16.3, -1.0 P-value (2-sample t test): 0.027	

Reviewer's Note: *For all enrolled subjects, the rate of at least one adverse event and the rate of at least one treatment related adverse event are presented in Table 16. There were no significant differences with respect to at least one adverse event, however, the atovaquone/proguanil group experienced a significantly lower rate than quinine/tetracycline group with respect to treatment related adverse events. No subjects died during the study.*

TABLE 16: STUDY 115-127: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Atovaquone/ Proguanil (N=87)	Quinine/ Tetracycline (N=88)	Fisher's P-value
At Least One AE	77 (88.5%)	84 (95.5%)	0.103
At Least One Treatment Related AE	48 (55.2%)	79 (89.8%)	< 0.001

I.C.4. STUDY 115-130

A total of 48 Europe subjects were enrolled and were sequentially admitted to the study between October 1994 and September 1995. Of these enrolled subjects, 4 were lost to follow-up, and 5 were withdrawn from the study. There were 39 subjects who were evaluable for 28-day cure rates; 21 subjects received atovaquone/proguanil treatment and 18 subjects received halofantrine treatment.

Reviewer's Note: *The number and percentage of subjects included in each analysis group, evaluated by the Applicant, are presented in Table 17. There were no statistically significant treatment differences with respect to the percentage of subjects included in each analysis group.*

TABLE 17: STUDY 115-130: NUMBER OF SUBJECTS INCLUDED IN EACH TREATMENT GROUP		
Analysis Group	Subjects Included	
	Atovaquone/ Proguanil	Halofantrine
All Enrolled Subjects	25	23
Evaluable Subjects	21 (84.0%)	18 (78.3%)
Subjects Lost to Follow-up	1 (4.0%)	3 (13.0%)
Withdrawn Subjects	3 (12.0%)	2 (8.7%)

Reviewer's Note: *The cure rates are shown for evaluable subjects and all enrolled subjects in Table 18. The parasite or fever clearance times of evaluable subjects and all enrolled subjects are presented in Tables 19 and 20, respectively. Since the sample sizes of the two treatment groups were considerably small, no formal statistical analyses were conducted.*

TABLE 18: STUDY 115-130: CURE RATES		
Clinical Response	Atovaquone/ Proguanil	Halofantrine
Evaluable Subjects		
Cured	21/21 (100%)	18/18 (100%)
Not Cured	0/21 (0%)	0/18 (0%)
All Enrolled Subjects		
Cure	21/25 (84.0%)	18/23 (78.3%)
Not Cure and the Others*	4/25 (16.0%)	5/23 (21.7%)
* "Other" refers to subjects who were either lost to follow-up or withdrawn		

TABLE 19: STUDY 115-130: PARASITE CLEARANCE TIMES		
Clinical Response	Atovaquone/ Proguanil	Halofantrine
Evaluable Subjects		
Subjects (N)	21	18
Median (hrs)	60.0	48.0
Mean (hrs)	62.7	50.0
All Enrolled Subjects		
Subjects (N)	24	22
Median (hrs)	60.0	48.0
Mean (hrs)	63.4	48.6

TABLE 20: STUDY 115-130: FEVER CLEARANCE TIMES		
Clinical Response	Atovaquone/ Proguanil	Halofantrine
Evaluable Subjects		
Subjects (N)	17	16
Median (hrs)	65.0	60.5
Mean (hrs)	61.1	62.9
All Enrolled Subjects		
Subjects (N)	18	19
Median (hrs)	62.5	57.0
Mean (hrs)	60.9	58.1

Reviewer's Note: *For all enrolled subjects, the rate of at least one adverse event and the rate of at least one treatment related adverse event are presented in Table 21. There were no significant differences with respect to these parameters. No subjects died during the study.*

TABLE 21: STUDY 115-130: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Atovaquone/ Proguanil (N=25)	Halofantrine (N=23)	Fisher's P-value
At Least One AE	20 (80.0%)	15 (65.2%)	0.335
At Least One Treatment Related AE	15 (60.0%)	8 (34.8%)	0.094

I.C.5. STUDY 115-131

A total of 168 pediatric Kenya subjects were enrolled and were sequentially admitted to the study between June 1994 and December 1994. Of these enrolled subjects, none was lost to follow-up, and 4 were withdrawn from the study. There were 164 subjects who were evaluable for 28-day cure rates, and children's parents/guardians agreed to return their child to the hospital during a 28 day follow-up period; 81 subjects received atovaquone/proguanil treatment and 83 subjects received halofantrine treatment.

Reviewer's Note: *The number and percentage of subjects included in each analysis group, evaluated by the Applicant, are presented in Table 22. There were no statistically significant treatment differences with respect to the percentage of subjects included in each analysis group.*

TABLE 22: STUDY 115-131: NUMBER OF SUBJECTS INCLUDED IN EACH TREATMENT GROUP		
Analysis Group	Subjects Included	
	Atovaquone/ Proguanil	Halofantrine
All Enrolled Subjects	84	84
Evaluable Subjects	81 (96.4%)	83 (98.8%)
Subjects Lost to Follow-up	0 (0%)	0 (0%)
Withdrawn Subjects	3 (3.6%)	1 (1.2%)

Reviewer's Note: *The cure rates are shown for evaluable subjects and all enrolled subjects in Table 23. Confidence interval results from analyses showed that atovaquone/proguanil was therapeutically equivalent to halofantrine with respect to the cure rates.*

The parasite or fever clearance times of evaluable subjects and all enrolled subjects are presented in Tables 24 and 25, respectively. In both analysis groups, there were no significant differences in median of FCT between the two treatment groups, however, atovaquone/proguanil subjects had a significant longer PCT.

TABLE 23: STUDY 115-131: CURE RATES		
Clinical Response	Atovaquone/ Proguanil	Halofantrine
Evaluable Subjects		
Cured Not Cured	76/81 (93.8%) 5/82 (6.2%)	75/83 (90.4%) 8/83 (9.6%)
A/P vs Halofantrine: Cure	3.5%, 95% C.I.: -6.0%, 12.9%	
All Enrolled Subjects		
Cure Not Cure and the Others*	76/84 (90.5%) 8/84 (9.5%)	75/84 (89.3%) 9/84 (10.7%)
A/P vs Halofantrine: Cure	1.2%, 95% C.I.: -9.1%, 11.5%	
* "Other" refers to subjects who were either lost to follow-up or withdrawn		

TABLE 24: STUDY 115-131: PARASITE CLEARANCE TIMES		
Clinical Response	Atovaquone/ Proguanil	Halofantrine
Evaluable Subjects		
Subjects (N)	81	83
Test of Normality	0.003	0.203
Median (hrs)	65.0	50.0
A/P vs Halofantrine: Median	16.0, 95% C.I.: 12.0, 21.0 P-value (Mann-Whitney U test): <0.001	
Mean (hrs)	65.0	50.2
A/P vs Halofantrine: Mean	14.8, 95% C.I.: 10.0, 19.6 P-value (2-sample t test): <0.001	
All Enrolled Subjects		
Subjects (N)	83	84
Test of Normality	0.003	0.217
Median (hrs)	65.0	50.5
A/P vs Halofantrine: Median	15.0, 95% C.I.: 12.0, 21.0 P-value (Mann-Whitney's U test): <0.001	
Mean (hrs)	64.9	50.2
A/P vs Halofantrine: Mean	4.7, 95% C.I.: 10.0, 19.4 P-value (2-sample t test): <0.001	

TABLE 25: STUDY 115-131: FEVER CLEARANCE TIMES		
Clinical Response	Atovaquone/ Proguanil	Halofantrine
Evaluable Subjects		
Subjects (N)	66	72
Test of Normality	< 0.001	< 0.001
Median (hrs)	26.5	35.0
A/P vs Halofantrine: Median	-3.0, 95% C.I.: -11.9, 6.0 P-value (Mann-Whitney's U test): 0.495	
Mean (hrs)	34.4	38.2
A/P vs Halofantrine: Mean	-5.5, 95% C.I.: -13.3, 5.8 P-value (2-sample t test): 0.440	
All Enrolled Subjects		
Subjects (N)	68	73
Test of Normality	< 0.001	< 0.001
Median (hrs)	29.5	35.0
A/P vs Halofantrine: Median	-2.0, 95% C.I.: -12.0, 6.0 P-value (Mann-Whitney's U test): 0.583	
Mean (hrs)	35.9	39.3
A/P vs Halofantrine: Mean	-3.4, 95% C.I.: -13.2, 6.5 P-value (2-sample t test): 0.510	

Reviewer's Note: *For all enrolled subjects, the rate of at least one adverse event and the rate of at least one treatment related adverse event are presented in Table 26. There were no significant differences with respect to these parameters. No subjects died during the study.*

TABLE 26: STUDY 115-131: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Atovaquone/ -Proguanil (N=84)	Halofantrine (N=84)	Fisher's P-value
At Least One AE	43 (51.2%)	53 (63.0%)	0.160
At Least One Treatment Related AE	22 (26.2%)	26 (31.0%)	0.609

I.C.6. STUDY 115-134

A total of 141 Gabon subjects were enrolled and were sequentially admitted to the study between July 1994 and March 1995. Of these enrolled subjects, 12 were lost to follow-up, and 3 were withdrawn from the study. The 126 subjects who were evaluable for 28-day cure rates returned to the hospital during a 28 day follow-up period; 70 subjects received atovaquone/proguanil treatment and 71 subjects received amodiaquine treatment.

Reviewer's Note: *The number and percentage of subjects included in each analysis group, evaluated by the Applicant, are presented in Table 27. There were no statistically significant treatment differences with respect to the percentage of subjects included in each analysis group.*

TABLE 27: STUDY 115-134: NUMBER OF SUBJECTS INCLUDED IN EACH TREATMENT GROUP		
Analysis Group	Subjects Included	
	Atovaquone/ Proguanil	Amodiaquine
All Enrolled Subjects	70	71
Evaluable Subjects	63 (90.0%)	63 (88.7%)
Subjects Lost to Follow-up	5 (7.1%)	7 (9.9%)
Withdrawn Subjects	2 (2.9%)	1 (1.4%)

Reviewer's Note: *The cure rates are shown for evaluable subjects and all enrolled subjects in Table 28. Confidence interval results from analyses showed that atovaquone/proguanil was therapeutically superior to amodiaquine with respect to the cure rates. Note, however, that there were approximately 10% subjects with missing data.*

The parasite or fever clearance times of evaluable subjects and all enrolled subjects are presented in Tables 29 and 30, respectively. In both analysis groups, there were no significant differences in median of FCT between the two treatment groups, however, atovaquone/proguanil subjects had a significant longer PCT.

TABLE 28: STUDY 115-134: CURE RATES		
Clinical Response	Atovaquone/ Proguanil	Amodiaquine
Evaluable Subjects		
Cured Not Cured	62/63 (98.4%) 1/63 (1.6%)	51/63 (81.0%) 12/63 (19.0%)
A/P vs Amodiaquine: Cure	17.5%, 95% C.I.: 5.7%, 29.2%	
All Enrolled Subjects		
Cure Not Cure and the Others*	62/70 (88.6%) 8/70 (11.4%)	51/71 (71.8%) 20/71 (28.2%)
A/P vs Amodiaquine: Cure	16.7%, 95% C.I.: 2.5%, 31.0%	
* "Other" refers to subjects who were either lost to follow-up or withdrawn		

TABLE 29: STUDY 115-134: PARASITE CLEARANCE TIMES		
Clinical Response	Atovaquone/ Proguanil	Amodiaquine
Evaluable Subjects		
Subjects (N)	63	63
Test of Normality	0.001	< 0.001
Median (hrs)	83.0	60.0
A/P vs Amodiaquine: Median	12.0, 95% C.I.: 0, 12.0 P-value (Mann-Whitney U test): 0.027	
Mean (hrs)	72.9	65.8
A/P vs Amodiaquine: Mean	7.1, 95% C.I.: 0.3, 13.8 P-value (2-sample t test): 0.040	
All Enrolled Subjects		
Subjects (N)	67	71
Test of Normality	< 0.001	< 0.001
Median (hrs)	83.0	60.0
A/P vs Amodiaquine: Median	12.0, 95% C.I.: 0, 12.0 P-value (Mann-Whitney's U test): 0.049	
Mean (hrs)	72.1	65.8
A/P vs Amodiaquine: Mean	6.3, 95% C.I.: -0.6, 13.2 P-value (2-sample t test): 0.075	

TABLE 30: STUDY 115-134: FEVER CLEARANCE TIMES		
Clinical Response	Atovaquone/ Proguanil	Amodiaquine
Evaluable Subjects		
Subjects (N)	37	46
Test of Normality	< 0.001	< 0.001
Median (hrs)	12.0	12.0
A/P vs Amodiaquine: Median	0, 95% C.I.: 0, 12.0 P-value (Mann-Whitney's U test): 0.299	
Mean (hrs)	27.2	19.6
A/P vs Amodiaquine: Mean	7.6, 95% C.I.: 0.3, 15.0 P-value (2-sample t test): 0.041	
All Enrolled Subjects		
Subjects (N)	39	52
Test of Normality	< 0.001	< 0.001
Median (hrs)	12.0	12.0
A/P vs Amodiaquine: Median	0, 95% C.I.: 0, 12.0 P-value (Mann-Whitney's U test): 0.258	
Mean (hrs)	27.4	19.8
A/P vs Amodiaquine: Mean	7.6, 95% C.I.: 0.4, 14.7 P-value (2-sample t test): 0.039	

Reviewer's Note: *For all enrolled subjects, the rate of at least one adverse event and the rate of at least one treatment related adverse event are presented in Table 31. There were no significant differences with respect to these parameters. No subjects died during the study.*

TABLE 31: STUDY 115-134: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Atovaquone/ Proguanil (N=70)	Amodiaquine (N=71)	Fisher's P-value
At Least One AE	55 (78.6%)	61 (85.9%)	0.278
At Least One Treatment Related AE	42 (60.0%)	50 (70.4%)	0.219

I.C.7. STUDY 115-135

A total of 110 adult and pediatric Philippines subjects were enrolled and were sequentially admitted to the study between October 1994 and March 1995. Of these enrolled subjects, none was lost to follow-up, and 1 was withdrawn from the study. The 109 subjects who were evaluable for 28-day cure rates remained in hospital during a 28-day follow-up period; 54 subjects received atovaquone/proguanil treatment, 23 subjects received chloroquine treatment, and 32 subjects received chloroquine/fansidar treatment.

Reviewer's Note: *The number and percentage of subjects included in each analysis group, evaluated by the Applicant, are presented in Table 32. This study was a comparative trial with three treatment regimens; the allocation of subjects was not balanced amongst the treatment groups as subjects were randomized in a 2:1:1 ratio.*

TABLE 32: STUDY 115-135: NUMBER OF SUBJECTS INCLUDED IN EACH TREATMENT GROUP			
Analysis Group	Subjects Included		
	Atovaquone/ Proguanil	Chloroquine	Chloroquine/ Fansidar
All Enrolled Subjects	55	23	32
Evaluable Subjects	54 (98.2%)	23 (100%)	32 (100%)
Subjects Lost to Follow-up	0 (0%)	0 (0%)	0 (0%)
Withdrawn Subjects	1 (1.8%)	0 (0%)	0 (0%)

Reviewer's Note: *The cure rates are shown for evaluable subjects and all enrolled subjects in Table 33. The parasite and fever clearance times of evaluable subjects and all enrolled subjects are presented in Tables 34 and 35, respectively. Since the sample sizes of the treatment groups were considerably small, no formal statistical analyses were conducted.*

TABLE 33: STUDY 115-135: CURE RATES			
Subject Bacteriological Response	Atovaquone/ Proguanil	Chloroquine	Chloroquine/ Fansidar
Evaluable Subjects			
Cure	54/54 (100%)	7/23 (30.4%)	28/32 (87.5%)
Not Cure	0/54 (0%)	16/23 (69.6%)	4/32 (12.5%)
All Enrolled Subjects			
Cure	54/55 (98.2%)	7/23 (30.4%)	28/32 (87.5%)
Not Cure and the Others*	1/55 (1.8%)	16/23 (69.6%)	4/32 (12.5%)
* "Other" refers to subjects who were either lost to follow-up or withdrawn			

TABLE 34: STUDY 115-135: PARASITE CLEARANCE TIMES			
Subject Bacteriological Response	Atovaquone/ Proguanil	Chloroquine	Chloroquine/ Fansidar
Evaluable Subjects			
Subjects (N)	54	19	32
Median (hrs)	49.0	52.0	42.0
Mean (hrs)	47.3	60.1	42.9
All Enrolled Subjects			
Subjects (N)	55	19	32
Median (hrs)	49.0	52.0	42.0
Mean (hrs)	46.8	60.1	42.9

TABLE 35: STUDY 115-135: FEVER CLEARANCE TIMES			
Subject Bacteriological Response	Atovaquone/ Proguanil	Chloroquine	Chloroquine/ Fansidar
Evaluable Subjects			
Subjects (N)	50	16	27
Median (hrs)	35.0	47.8	25.0
Mean (hrs)	38.7	46.8	34.7
All Enrolled Subjects			
Subjects (N)	51	16	27
Median (hrs)	36.0	47.5	25.0
Mean (hrs)	38.9	46.9	34.7

Reviewer's Note: *For all enrolled subjects, the rate of at least one adverse event and the rate of at least one treatment related adverse event are presented in Table 36. Atovaquone/proguanil subjects had significantly higher rates than chloroquine/fansidar subjects as per adverse events and treatment related adverse events, respectively. There were no significant differences between the treatments of atovaquone/proguanil and chloroquine with respect to these parameters. No subjects died during the study.*

TABLE 36: STUDY 115-135: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Atovaquone/ Proguanil (N=55)	Chloroquine (N=23)	Chloroquine/ Fansidar (N=32)
At Least One AE	24 (43.6%)	13 (56.5%)	5 (15.6%)
Fisher's P-value:	A/P vs. C.: 0.330		A/P vs. C/F: 0.009
At Least One Treatment Related AE	13 (23.6%)	2 (8.7%)	0 (0%)
Fisher's P-value	A/P vs. C.: 0.207		A/P vs. C/F: 0.002

I.C.8. STUDY 115-136

A total of 43 Peruvian adult or pediatric subjects were enrolled and were sequentially admitted to the study between June 1995 and May 1996. There were two phases of this trial, 15 subjects received atovaquone/proguanil and were compared with 14 subjects receiving chloroquine; an additional 5 subjects received atovaquone/proguanil for comparison with 9 subjects who received fansidar. Of these enrolled subjects, none was lost to follow-up, and 4 were withdrawn from the study. There were 39 subjects who were evaluable for 28-day cure rates; of whom 14 subjects received atovaquone/proguanil treatment and 13 subjects received chloroquine treatment in the 1st phase; 5 subjects received atovaquone/proguanil treatment and 7 subjects received fansidar treatment in the 2nd phase.

Reviewer's Note: *The number and percentage of subjects included in each analysis group, evaluated by the Applicant, are presented in Table 37.*

TABLE 37: STUDY 115-136: NUMBER OF SUBJECTS INCLUDED IN EACH TREATMENT GROUP				
Analysis Group	Subjects Included			
	1st Phase		2nd Phase	
	Atovaquone/ Proguanil	Chloroquine	Atovaquone/ Proguanil	Fansidar
All Enrolled Subjects	15	14	5	9
Evaluable Subjects	14 (93.3%)	13 (92.9%)	5 (100%)	7 (77.8%)
Subjects Lost to Follow-up	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Withdrawn Subjects	1 (6.7%)	1 (7.1%)	0 (0%)	2 (22.2%)

Reviewer's Note: *The cure rates are shown for evaluable subjects and all enrolled subjects in Table 38. The parasite or fever clearance times of evaluable subjects and all enrolled subjects are presented in Tables 39 and 40, respectively. Since the sample sizes of the four treatment groups were considerably small, no formal statistical analyses are conducted.*

TABLE 38: STUDY 115-136: CURE RATES				
Clinical Response	Atovaquone/ Proguanil	Chloroquine	Atovaquone/ Proguanil	Fansidar
Evaluable Subjects				
	1st Phase		2nd Phase	
Cured	14/14 (100%)	1/13 (7.7%)	5/5 (100%)	7/7 (100%)
Not Cured	0/14 (0%)	12/13 (92.3%)	0/5 (0%)	0/7 (0%)
All Enrolled Subjects				
	1st Phase		2nd Phase	
Cured	14/15 (93.3%)	1/14 (7.1%)	5/5 (100%)	7/9 (77.8%)
Not Cure and the Others*	1/15 (6.7%)	13/14 (92.9%)	0/5 (0%)	2/9 (22.2%)
* "Other" refers to subjects who were either lost to follow-up or withdrawn				

TABLE 39: STUDY 115-136: PARASITE CLEARANCE TIMES				
Clinical Response	Atovaquone/ Proguanil	Chloroquine	Atovaquone/ Proguanil	Fansidar
Evaluable Subjects				
	1st Phase		2nd Phase	
Subjects (N)	14	8	5	7
Median (hrs)	57.0	48.0	42.0	42.0
Mean (hrs)	55.7	54.1	44.4	38.6
All Enrolled Subjects				
	1st Phase		2nd Phase	
Subjects (N)	14	9	5	9
Median (hrs)	57.0	48.0	42.0	42.0
Mean (hrs)	55.7	58.7	44.4	38.0

TABLE 40: STUDY 115-136: FEVER CLEARANCE TIMES				
Clinical Response	Atovaquone/ Proguanil	Chloroquine	Atovaquone/ Proguanil	Fansidar
Evaluable Subjects				
	1st Phase		2nd Phase	
Subjects (N)	14	7	5	7
Median (hrs)	46.0	40.0	40.0	44.0
Mean (hrs)	42.9	40.6	38.4	44.6
All Enrolled Subjects				
	1st Phase		2nd Phase	
Subjects (N)	14	11	5	9
Median (hrs)	46.0	48.0	40.0	44.0
Mean (hrs)	42.9	48.0	38.4	48.0

Reviewer's Note: *For all enrolled subjects, the rate of at least one adverse event and the rate of at least one treatment related adverse event are presented in Table 41. Significantly more atovaquone/proguanil subjects experienced treatment related adverse events in the 2nd phase of the study. No subjects died during the study.*

TABLE 41: STUDY 115-136: CLINICAL ADVERSE EVENT RATES				
Safety Outcome	1st Phase		2nd Phase	
	Atovaquone/ Proguanil (N=15)	Chloroquine (N=14)	Atovaquone/ Proguanil (N=5)	Fansidar (N=9)
At Least One AE	11 (73.3%)	11 (78.6%)	5 (100%)	7 (77.8%)
Fisher's P-value	1.000		0.505	
At Least One Treatment Related AE	4 (26.7%)	2 (14.3%)	5 (100%)	2 (22.2%)
Fisher's P-value	0.651		0.021	

I.C.9. COMBINED EFFICACY ANALYSIS

Reviewer's Note: *In the indication of treatment of malaria for adult subjects, there were four adequate and well-controlled studies. The efficacy outcomes in these studies were assessed in terms of difference in 28-day cure rates and their results are presented in Tables 42 and 43. The results from four studies did not always reach identical conclusions; atovaquone/proguanil was shown equivalent in some studies, but superior in the others.*

In order to draw a comprehensive conclusion about the efficacy of atovaquone/proguanil, the reviewer performed a meta-analysis with respect to the differences in 28-day cure rates of evaluable subjects and all enrolled subjects between atovaquone/proguanil and its comparators. Results are shown in Tables 42 and 43. Significant heterogeneity was detected across the studies regarding the primary efficacy endpoint, and was incorporated into the estimate of the difference in cure rates and the associated 95% confidence intervals presented below. Atovaquone/proguanil was considered marginally superior in evaluable subjects, and was equivalent in all enrolled subjects. In evaluable subjects, note that

atovaquone/proguanil rates were pretty consistent across the four studies, but that the rates among the controls varied somewhat.

TABLE 42: CURE RATES OF EVALUABLE SUBJECTS IN ADEDUATE AND WELL CONTROL STUDIES FOR ADULT SUBJECTS			
Study	Cure Rate		95% Confidence Interval of A/P vs. Control by Cure Rate
	Atovaquone/ Proguanil	Control	
115-120	80/80 (100%)	79/80 (98.8%)	1.3%, 95% C.I.: -2.4%, 4.9%
115-122	79/79 (100%)	68/79 (86.1%)	13.9%, 95% C.I.: 5.0%, 22.8%
115-127	73/74 (98.6%)	76/76 (100%)	-1.4%, 95% C.I.: -5.3%, 2.6%
115-134	62/63 (98.4%)	51/63 (81.0%)	17.5%, 95% C.I.: 5.7%, 29.2%
Meta-Analysis			
Test of Homogeneity, P-value: < 0.001		95% C.I.: -0.1%, 11.8%	

TABLE 43: CURE RATES OF ALL ENROLLED SUBJECTS IN ADEDUATE AND WELL CONTROL STUDIES FOR ADULT SUBJECTS			
Study	Cure Rate		95% Confidence Interval of A/P vs. Control by Cure Rate
	Atovaquone/ Proguanil	Control	
115-120	80/82 (97.6%)	79/81 (97.5%)	0.1%, 95% C.I.: -5.9%, 6.0%
115-122	79/91 (87.8%)	68/91 (74.7%)	12.1%, 95% C.I.: -0.3%, 24.5%
115-127	73/87 (83.9%)	76/88 (86.4%)	-2.5%, 95% C.I.: -14.1%, 9.2%
115-134	62/70 (88.6%)	51/71 (71.8%)	16.7%, 95% C.I.: 2.5%, 31.0%
Meta-Analysis			
Test of Homogeneity, P-value: 0.025		95% C.I.: -2.8%, 13.8%	

II. PROPHYLAXIS OF MALARIA

II.A. INTRODUCTION

The Applicant submitted four controlled studies as evidence to support that atovaquone or the combination of atovaquone and proguanil hydrochloride is safe and efficacious for prophylaxis of *P.falciparum* malaria in subjects who did not have malaria parasitemia when prophylactic therapy was initiated. Statistical review focuses on the three comparative clinical trials which had adequate subject sample sizes and formed the basis of this application. It is noteworthy that there was no adequate and well-controlled study to support atovaquone alone for this indication. The general design of the studies is as follows (also see Table 44):

Study MALB-2001 was a randomized, double-blind, placebo controlled, parallel group trial which compared the efficacy, safety and tolerance of atovaquone/proguanil for a treatment duration of at least ten weeks versus placebo for the chemoprophylaxis in volunteers at risk of developing *P.falciparum* malaria. The trial was conducted at a single research site in western Kenya during the peak malaria transmission season. All eligible subjects included healthy volunteers 18~65 years of age residing in a highly malarious area of Kenya.

Study MALB-3001 was a randomized, double-blind, placebo controlled, parallel group trial which compared the suppressive prophylactic activity of atovaquone/proguanil for a treatment duration of at least ten weeks versus placebo for the chemoprophylaxis in volunteers at risk of developing *P.falciparum* malaria. The trial was conducted at a single research site in Zambia during the peak malaria transmission season. All eligible subjects included healthy volunteers 16~65 years of age residing in a highly malarious area of Zambia.

Study MALB-3002 was a randomized, double-blind, placebo controlled, parallel group trial which compared the suppressive prophylactic activity, safety and tolerance of atovaquone/proguanil for a treatment duration of at least twelve weeks versus placebo for the chemoprophylaxis in pediatric volunteers at risk of developing *P.falciparum* malaria. The trial was conducted at a single research site in Gabon during the peak malaria transmission season. All eligible subjects included healthy pediatric volunteers 4~16 years of age at risk of malaria infection.

These studies are outlined in Table 44.

TABLE 44. CONTROLLED STUDIES OF ATOVAQUONE AND PROGUANIL HYDROCHLORIDE FOR PROPHYLAXIS OF MALARIA

Study Number	Study Design	Treatments	Number of Subjects	Mean Age in Years (Range)	Duration of Therapy
MALB 2001	Randomized, double-blind, controlled trial in Kenyan adults	Atovaquone 250 mg and proguanil HCl 100 mg daily Atovaquone 500 mg and proguanil HCl 200 mg daily Placebo	205	30 (18-55)	10 weeks
MALB 3001	Randomized, double-blind, controlled trial in Zambian adults	Atovaquone 250 mg and proguanil HCl 100 mg daily Placebo	274	32 (16-64)	10 weeks
MALB 3003	Randomized, double-blind, controlled trial in children in Gabon	Atovaquone 5 mg/kg and proguanil HCl 2 mg/kg daily Placebo	265	10 (5-16)	12 weeks

II.B. METHODS

All studies evaluated the prophylactic activity of atovaquone/proguanil in subjects who did not have malaria parasitemia when prophylactic therapy was initiated. Volunteers meeting the inclusion/exclusion criteria were randomized to treatment with either atovaquone/proguanil or placebo for 10 to 12 weeks. Following the prophylaxis phase of the study, subjects entered a follow-up phase for up to 4 weeks. Eligible subjects were sequentially admitted to the study.

Efficacy analyses were performed on two populations, ITT as primary and Per Protocol as secondary. ITT population was defined as the subjects who were randomized to receive either atovaquone/proguanil or placebo during chemosuppression, who received at least one dose of treatment during chemosuppression, and who had a negative baseline smear. The Per Protocol population was the ITT population minus those who withdrew before week 10 for reasons other than a treatment-related adverse events. The Sponsor's primary efficacy parameter was the success rate of prophylaxis of ITT subjects during chemosuppression. The success of prophylaxis was defined as a subject who had a negative baseline malaria smear and was observed to have remained negative throughout chemosuppression (Weeks 0 to 10), regardless of missing smears before Week 10. The secondary endpoints were success of prophylaxis of Per Protocol subjects during chemosuppression.

Reviewer's Note: *The Medical Officer did not fully agree with the evaluation methods in efficacy chosen by the Sponsor. The definition of success and failure of prophylaxis and the assessments for outcomes according to the Sponsor criteria were agreed to (except Study MALB-3003), but the Medical Officer used a different primary efficacy endpoint.*

The Medical Officer believed that the primary efficacy parameter for the study should be the time to failure of prophylaxis in the ITT subjects. This reflected and was in line with the study objective of investigating the development of parasitemia during chemoprophylaxis. Subjects with a negative baseline malaria smear who still remained negative at the end of chemotherapy were classified as success of prophylaxis,

and their exact times of discontinuing from the study were treated as censored times. The time to event was the occurrence of a failure of prophylaxis, which was defined as a subject who had a positive smear, or withdrew due to a treatment-related adverse event, or withdrew for other reasons. The secondary efficacy parameters were the success rates for both ITT and Per Protocol subjects. The reviewer also examined the time to failure of prophylaxis, defined only as a subject who had a positive smear (subjects who withdrew from the study were censored at the time they withdrew). The results were not presented in this report as they were similar to the primary efficacy endpoints.

Please refer to the Medical Officer's review for detailed descriptions of the Sponsor's efficacy outcome definitions and the Medical Officer's comments.

All subjects who received at least one dose of study medication were evaluable for safety. Adverse experiences were defined as any untoward medical occurrence experienced by the volunteer. A causal relationship to study drug was not necessarily implied.

The comparisons of interest in these studies were conducted between the combination of atovaquone and proguanil hydrochloride and placebo.

Reviewer's Note: *The following statistical analyses were performed by the reviewer to evaluate the efficacy and safety of atovaquone/proguanil versus placebo.*

The primary efficacy analyses were conducted for ITT subjects, in whom prophylactic activity for subjects at risk of developing malaria were assessed during study period. The survival curves for subjects with the occurrence of a failure of prophylaxis receiving either atovaquone/proguanil or placebo were estimated by Kaplan-Meier's method. Survival curves were compared between the treatments by the logrank test.

Differences between the treatments with respect to the secondary efficacy parameters were assessed by computing the two-tailed 95% confidence interval of the difference in 28-day cure rates of ITT subjects and Per Protocol subjects as well. The confidence intervals were computed using a normal approximation to the binomial, and included a continuity correction. Bonferroni's adjustment in the Type I error probability was applied when there was more than one comparison in a study.

This reviewer conducted safety analyses with the rate of at least one adverse event and the rate of at least one treatment related adverse event. Statistical comparisons between the two treatment groups were performed using Fisher's exact test.

All tests were two-sided and used a 5% level of significance.

II.C. RESULTS

II.C.1. STUDY MALB-2001

A total of 216 volunteers were screened and enrolled into the 3-day curative treatment phase of the trial between April 1996 and August 1996. Of these enrolled subjects, 205 completed the 3-day curative phase and were randomized to one of three prophylaxis treatments; 70 received one atovaquone/proguanil tablet, 67 received two atovaquone/proguanil tablets, and 68 received placebo. There were 198 subjects included in the primary efficacy analysis (ITT population) and 162 included in the secondary efficacy analysis (Per Protocol population).

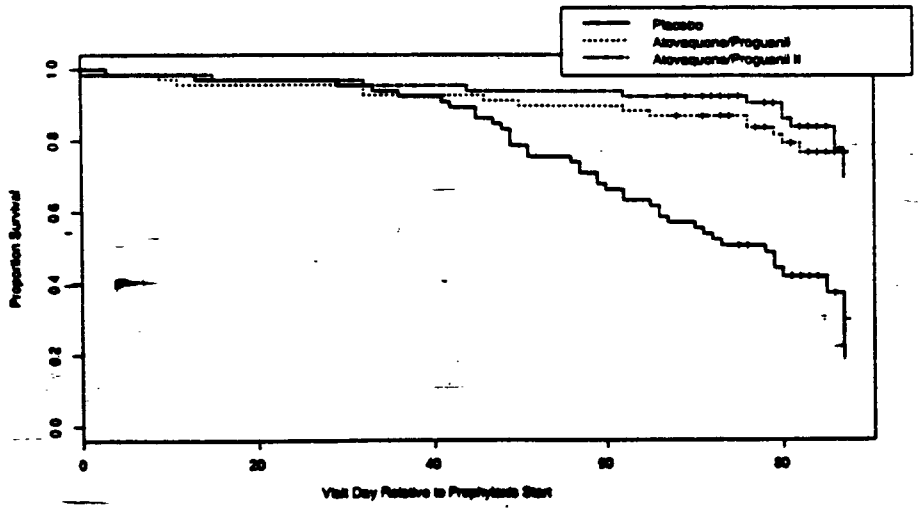
Reviewer's Note: *The number and percentage of subjects included in each analysis group, evaluated by the Applicant, are presented in Table 45. It is notable that a pretty high percentage of ITT subjects withdrew from treatment in each treatment arm.*

TABLE 45: STUDY MALB-2001: NUMBER OF SUBJECTS INCLUDED IN EACH TREATMENT GROUP

Analysis Group	Subjects Included		
	Atovaquone/ Proguanil	Atovaquone/ Proguanil II	Placebo
All Enrolled Subjects	70	67	68
ITT Subjects	68 (97.1%)	65 (97.0%)	65 (95.6%)
Subjects Developing Parasitemia	0 (0%)	0 (0%)	28 (41.2%)
Withdrawn Subjects (treatment-related)	0 (0%)	0 (0%)	0 (0%)
Withdraw Subjects (other reasons)	14 (20.0%)	11 (16.4%)	11 (16.2%)
Evaluable Subjects	54 (77.1%)	54 (80.6%)	54 (79.4%)
Subjects Developing Parasitemia	0 (0%)	0 (0%)	28 (41.2%)
Withdrawn Subjects (treatment-related)	0 (0%)	0 (0%)	0 (0%)

Reviewer's Note: *Kaplan-Meier estimates of the survival curves for ITT subjects with the occurrence of a failure of prophylaxis receiving treatment with either atovaquone/proguanil or placebo are illustrated in Figure 46. The result of the logrank test of significance for the comparison of survival curves between the treatments concluded the prophylaxis with both one and two atovaquone/proguanil tablets were significantly more effective than that with placebo (p-values=0.0001, 0.0001).*

FIGURE 46: STUDY MALB-2001: TIME TO PROPHYLAXIS FAILURE IN ITT SUBJECTS



The success rates are shown for ITT subjects and Per Protocol subjects in Table 47. Confidence interval results from analyses showed that the prophylaxis with both one and two atovaquone/proguanil tablets were superior in efficacy to that with placebo with respect to the success rates.

TABLE 47: STUDY MALB-2001: SUCCESS RATES			
Subject Bacteriological Response	Atovaquone/ Proguanil	Atovaquone/ Proguanil II	Placebo
ITT Subjects			
Success Failure	54/68 (79.4%) 14/68 (20.6%)	54/65 (83.1%) 11/65 (16.9%)	26/65 (40.0%) 39/65 (60.0%)
A/P vs Placebo: Success A/P II vs Placebo: Success	39.4%, 98.3% C.I.: 19.2%, 59.6% 43.1%, 98.3% C.I.: 23.2%, 62.9%		
Per Protocol Subjects			
Success Failure	54/54 (100%) 0/54 (0%)	54/54 (100%) 0/54 (0%)	26/54 (48.1%) 28/54 (51.9%)
A/P vs Placebo: Success A/P II vs Placebo: Success	51.9%, 98.3% C.I.: 33.7%, 70.0% 51.9%, 98.3% C.I.: 33.7%, 70.0%		

Reviewer's Note: *For ITT subjects, the rate of at least one adverse event and the rate of at least one treatment related adverse event are presented in Table 48. In the two comparisons, there were no significant differences between the treatments of atovaquone/proguanil and placebo with respect to these parameters. No subjects died during the study.*

TABLE 48: STUDY MALB-2001: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Atovaquone/ Proguanil (N=68)	Atovaquone/ Proguanil II (N=65)	Placebo (N=65)
At Least One AE	28 (41.2%)	26 (40.0%)	28 (43.1%)
Fisher's P-value:	A/P vs. Placebo.: 0.862		A/P II vs. Placebo: 0.859
At Least One Treatment Related AE	24 (35.3%)	21 (32.3%)	21 (32.3%)
Fisher's P-value	A/P vs. Placebo.: 0.855		A/P II vs. Placebo: 1.000

II.C.2. STUDY MALB-3001

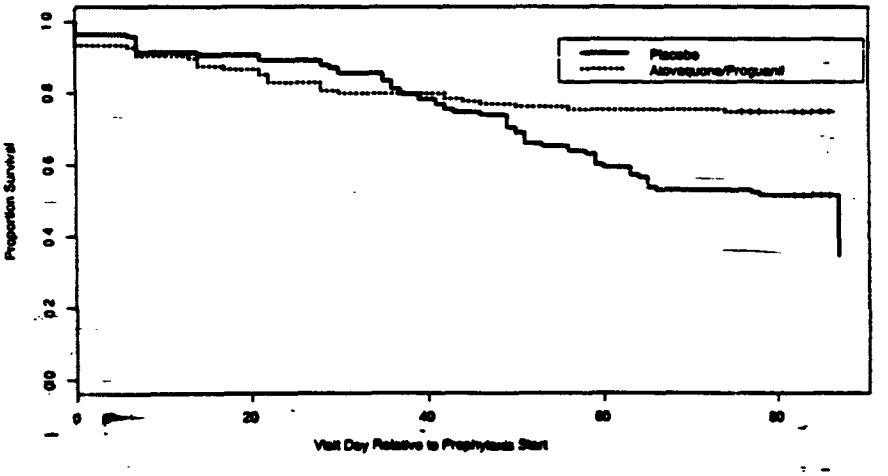
A total of 299 volunteers were screened and enrolled into the 3-day curative treatment phase of the trial between February 1997 and July 1997. Of these enrolled subjects, 274 completed the 3-day curative phase and were randomized to one of two prophylaxis treatments; 136 received atovaquone/proguanil and 138 received placebo. There were 272 subjects included in the primary efficacy analysis (ITT population) and 213 included in the secondary efficacy analysis (Per Protocol population).

Reviewer's Note: *The number and percentage of subjects included in each analysis group, evaluated by the Applicant, are presented in Table 49. It is notable that a pretty high percentage of ITT subjects withdrew from treatment in each treatment arm.*

TABLE 49: STUDY MALB-3001: NUMBER OF SUBJECTS INCLUDED IN EACH TREATMENT GROUP		
Analysis Group	Subjects Included	
	Atovaquone/ Proguanil	Placebo
All Enrolled Subjects	136	138
ITT Subjects	134 (98.5%)	138 (100%)
Subjects Developing Parasitemia	2 (1.5%)	41 (29.7%)
Withdrawn Subjects (treatment-related)	0 (0%)	0 (0%)
Withdraw Subjects (other reasons)	32 (23.5%)	27 (19.6%)
Evaluable Subjects	102 (75.0%)	111 (80.4%)
Subjects Developing Parasitemia	2 (1.5%)	41 (29.7%)
Withdrawn Subjects (treatment-related)	0 (0%)	0 (0%)

Reviewer's Note: *Kaplan-Meier estimates of the survival curves for ITT subjects with the occurrence of a failure of prophylaxis receiving treatment with either atovaquone/proguanil or placebo are illustrated in Figure 50. The result of the logrank test of significance for the comparison of survival curves between these two treatments concluded atovaquone/proguanil was significantly more effective than placebo (p-value=0.0007).*

FIGURE 50: STUDY MALB-3001: TIME TO PROPHYLAXIS FAILURE IN ITT SUBJECTS



The success rates are shown for ITT subjects and Per Protocol subjects in Table 51. Confidence interval results from analyses showed that atovaquone/proguanil was superior in efficacy to placebo with respect to the success rates.

TABLE 51: STUDY MALB-3001: SUCCESS RATES		
Clinical Response	Atovaquone/ Proguanil	Placebo
ITT Subjects		
Success Failure	100/134 (74.6%) 34/134 (25.4%)	70/138 (50.7%) 68/138 (49.3%)
A/P vs Placebo: Success	23.9%, 95% C.I.: 12.0%, 35.8%	
Per Protocol Subjects		
Success Failure	100/102 (98.0%) 2/102 (2.0%)	70/111 (63.1%) 41/111 (36.9%)
A/P vs Placebo: Success	35.0%, 95% C.I.: 24.7%, 45.3%	

Reviewer's Note: *For ITT subjects, the rate of at least one adverse event and the rate of at least one treatment related adverse event are presented in Table 52. There were no significant differences with respect to these parameters. No subjects died during the study.*

TABLE 52: STUDY MALB-3001: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Atovaquone/ Proguanil (N=134)	Placebo (N=138)	Fisher's P-value
At Least One AE	20 (14.9%)	25 (18.1%)	0.517
At Least One Treatment Related AE	16 (11.9%)	20 (14.5%)	0.594

II.C.3. STUDY MALB-3003

A total of 319 pediatric volunteers were screened and enrolled into the 3-day curative treatment phase of the trial between January 1997 and July 1997. Of these enrolled subjects, 265 completed the 3-day curative phase and were randomized to one of two prophylaxis treatments; 125 received atovaquone/proguanil and 140 received placebo. There were 262 subjects included in the primary efficacy analysis (ITT population) and 245 included in the secondary efficacy analysis (Per Protocol population).

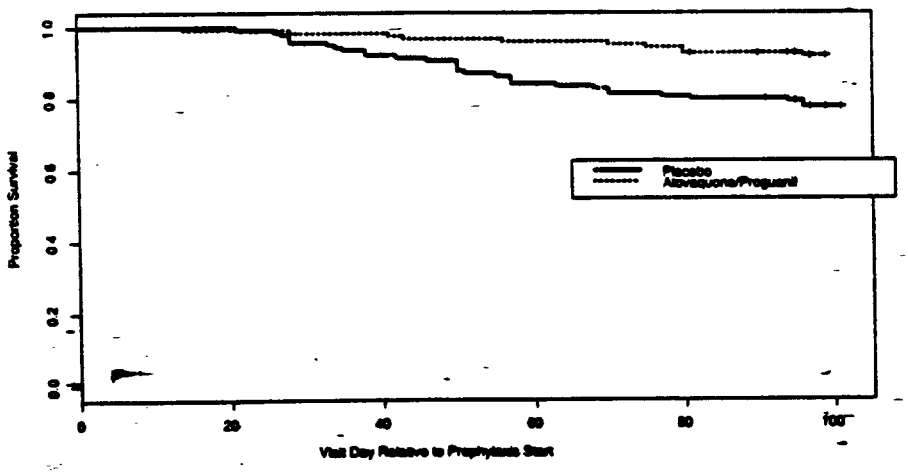
Reviewer's Note: *The Medical Officer commented that three cases should be reclassified; two subjects in the placebo group were excluded from ITT population due to non-falciparum malaria occurring; the outcome of one ITT subject in the atovaquone/proguanil group was rated failure due to protocol violation. The number and percentage of subjects included in each analysis group, re-evaluated by the Medical Officer, are presented in Table 53. It is notable that a pretty high percentage of ITT subjects withdrew from treatment in each treatment arm.*

TABLE 53: STUDY MALB-3003: NUMBER OF SUBJECTS INCLUDED IN EACH TREATMENT GROUP

Analysis Group	Subjects Included	
	Atovaquone/ Proguanil	Placebo
All Enrolled Subjects	125	140
ITT Subjects	124 (99.2%)	138 (98.6%)
Subjects Developing Parasitemia	0 (0%)	23 (16.4%)
Withdrawn Subjects (treatment-related)	0 (0%)	0 (0%)
Withdraw Subjects (other reasons)	10 (8.0%)	6 (4.3%)
Protocol Violation	1 (0.8%)	0 (0%)
Evaluable Subjects	113 (90.4%)	132 (94.3%)
Subjects Developing Parasitemia	0 (0%)	23 (16.4%)
Withdrawn Subjects (treatment-related)	0 (0%)	0 (0%)

Reviewer's Note: *Kaplan-Meier estimates of the survival curves for ITT subjects with the occurrence of a failure of prophylaxis receiving treatment with either atovaquone/proguanil or placebo are illustrated in Figure 54. The result of the logrank test of significance for the comparison of survival curves between these two treatments concluded that atovaquone/proguanil was significantly more effective than placebo (p-value=0.001).*

FIGURE 54: STUDY MALB-3003: TIME TO PROPHYLAXIS FAILURE IN ITT SUBJECTS



The success rates are shown for ITT subjects and Per Protocol subjects in Table 55. Confidence interval results from analyses showed that atovaquone/proguanil was superior in efficacy to placebo with respect to the success rates.

TABLE 55: STUDY MALB-3003: SUCCESS RATES		
Clinical Response	Atovaquone/ Proguanil	Placebo
ITT Subjects		
Success Failure	113/124 (91.1%) 11/124 (8.9%)	109/138 (79.0%) 29/138 (21.0%)
A/P vs Placebo: Success	12.1%, 95% C.I.: 2.9%, 21.3%	
Per Protocol Subjects		
Success Failure	113/113 (100%) 0/113 (0%)	109/132 (82.6%) 23/132 (17.4%)
A/P vs Placebo: Success	17.4%, 95% C.I.: 10.1%, 24.7%	

Reviewer's Note: *For ITT subjects, the rate of at least one adverse event and the rate of at least one treatment related adverse event are presented in Table 56. There were no significant differences with respect to these parameters. No subjects died during the study.*

TABLE 56: STUDY MALB-3003: CLINICAL ADVERSE EVENT RATES			
Safety Outcome	Atovaquone/ Proguanil (N=134)	Placebo (N=138)	Fisher's P-value
At Least One AE	17 (12.7%)	22 (15.9%)	0.491
At Least One Treatment Related AE	16 (11.9%)	21 (15.2%)	0.482

III. SUMMARY AND CONCLUSIONS
(Which May be Conveyed to the Sponsor)

TREATMENT OF MALARIA

Reviewer's Note: *In this section, confidence intervals for differences in cure rates (atovaquone/proguanil minus comparator) are reported as $_{n1,n2}(l, u)_{p1,p2}$, where n1 is the number of atovaquone/proguanil patients, n2 is the number of comparator patients, l and u are the lower and upper bounds of the 95% confidence interval, respectively, p1 is the response rate in atovaquone/proguanil patients, and p2 is the response rate in comparator patients.*

This indication was primarily supported by eight controlled studies to demonstrate the efficacy and safety of atovaquone/proguanil.

Statistical evaluation of efficacy was based upon the two-sided 95% confidence interval of the difference in cure rates between the atovaquone/proguanil groups and the control groups for evaluable subjects and all enrolled subjects.

Statistical evaluation of safety was based upon the comparison of adverse event rates between the treatment groups in all enrolled subjects receiving at least one dose of study medication by two-sided Fisher's exact test.

1. In two controlled studies (115-120 and 114-127), the 95% confidence intervals for the difference in cure rates of atovaquone/proguanil minus its comparator for evaluable subjects were $_{80, 80}$ (-2.4%, 4.9%) $_{100\%, 98.8\%}$ and $_{74, 76}$ (-5.3%, 2.6%) $_{98.6\%, 100\%}$, respectively. Both results demonstrated that atovaquone/proguanil was therapeutically equivalent in efficacy to fansidar or quinine/tetracycline in the treatment of acute falciparum malaria of adult subjects. For both studies, the same conclusion was drawn from all enrolled subjects as that from evaluable subjects, where the 95% confidence intervals for the difference in cure rates of atovaquone/proguanil minus its comparator were $_{82, 81}$ (-5.9%, 6.0%) $_{97.6\%, 97.5\%}$ and $_{87, 88}$ (-14.1%, 9.2%) $_{83.9\%, 86.4\%}$, respectively. Note that results from study 114-127 were not as robust due to the fair amount of missing data.

2. In two controlled studies (115-122 and 114-134), the 95% confidence intervals for the difference in cure rates of atovaquone/proguanil minus its comparator for evaluable subjects were $_{79, 79}$ (5.0%, 22.8%) $_{100\%, 86.1\%}$ and $_{63, 63}$ (5.7%, 29.2%) $_{98.4\%, 81.0\%}$, respectively. Both results demonstrated that atovaquone/proguanil was therapeutically superior in efficacy to mefloquine or amodiaquine in the treatment of acute falciparum malaria of adult subjects. For ITT subjects, the results from two studies showed that atovaquone/proguanil was therapeutically marginally superior and therapeutically superior in efficacy to its comparator, respectively, where the 95% confidence intervals for the difference in cure rates of atovaquone/proguanil minus its comparator were $_{91, 91}$ (-0.3%, 24.5%) $_{87.8\%, 74.7\%}$ and $_{70, 71}$ (2.5%, 31.0%) $_{88.6\%, 71.8\%}$, respectively. Note that in both studies there was a fair amount of missing data.

3. Study 115-131 was a pediatric trial, in which atovaquone/proguanil was therapeutically equivalent in efficacy to halofantrine in the treatment of acute falciparum malaria of pediatric subjects. The 95% confidence interval for the difference in cure rates of atovaquone/proguanil minus its comparator for evaluable subjects was $_{81, 83}$ (-6.0%, 12.9%) $_{93.8\%, 90.4\%}$. For ITT subjects, the same conclusion was drawn as that from evaluable subjects, where the 95% confidence interval for the difference in cure rates of atovaquone/proguanil minus its comparator was $_{84, 84}$ (-9.1%, 11.5%) $_{90.5\%, 89.3\%}$.

4. Since the sample sizes of the three controlled studies (115-130, 115-135 and 115-136) were too small

to have sufficient power, no formal statistical analyses for efficacy were conducted.

5. In the meta-analysis for four adequate and well-controlled studies with adult subjects (115-120, 115-122, 115-127, and 115-134), the associated 95% confidence interval demonstrated that compared to the "control", atovaquone/proguanil was marginally superior in evaluable subjects, and was equivalent in all enrolled subjects, whereas significant heterogeneity was detected across the studies regarding the efficacy endpoint.

6. In two studies (115-135 and 115-136), significantly higher rates of treatment related adverse event were detected in atovaquone/proguanil subjects. Significantly more atovaquone/proguanil subjects experienced adverse events in study 115-135.

REVIEWER CONCLUSIONS: *For the five adequate and well-controlled studies, the efficacy analyses of evaluable subjects demonstrated that atovaquone/proguanil was therapeutically equivalent or superior in efficacy to its comparators in the treatment of acute falciparum malaria of adult and pediatric subjects. Results from the safety analysis also suggested that atovaquone/proguanil and its comparator yield nearly comparable safety results.*

RECOMMENDED REGULATORY ACTION: *Based on the above analyses, from a statistical standpoint, the combination of atovaquone and proguanil hydrochloride is recommended for approval in the treatment of acute falciparum malaria.*

PROPHYLAXIS OF MALARIA

This indication was primarily supported by three controlled studies to demonstrate the efficacy and safety of atovaquone/proguanil.

Statistical evaluation of efficacy was mainly based upon the logrank test of significance for the comparison of time to prophylaxis curves between the treatment groups in ITT subjects.

Statistical evaluation of safety was based upon the comparison of adverse event rates between the treatment groups in ITT subjects by two-sided Fisher's exact test.

1. In two controlled studies in adults (MALB-2001 and MALB-3001), subjects receiving atovaquone/proguanil displayed differences in developing parasitemia during chemoprophylaxis compared to placebo, and atovaquone/proguanil was significantly more effective than placebo. There was, however, a substantial amount of missing data in both studies.

2. Study MALB-3003 was a pediatric trial, in which atovaquone/proguanil was showed to be significantly more effective than placebo.

3. In these three controlled studies, atovaquone/proguanil and placebo groups were not significantly different in safety with respect to the rates of at least one adverse event and the rates of at least one treatment related adverse event.

REVIEWER CONCLUSIONS: *For the three adequate and well-controlled studies, the efficacy analyses of ITT subjects demonstrated that atovaquone/proguanil was significantly more effective compared to placebo in the prophylaxis of acute falciparum malaria of adult and pediatric volunteers. Results from the safety analysis also suggested that atovaquone/proguanil and placebo appear to have comparable safety profiles.*

RECOMMENDED REGULATORY ACTION: *Based on the above analyses, from a statistical standpoint, the combination of atovaquone and proguanil hydrochloride is recommended for approval in the prophylaxis of acute falciparum malaria. Note that there was no data to suggest that atovaquone can be used alone in this indication.*

LST 6/11/99

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HFD-590
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HFD-725/Dr.Silliman
HFD-725/Dr.Jiang
HFD-725/Chron.
This review contains 38 pages and 56 tables/figures.
MicrosoftWord 7.0/NDAmala
6/11/99