CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-078

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA:	**21-078**
Generic (Brand®)	**Atovaquone and Proguanil Hydrochloride Malarone**
Submission Dates:	**12/29/98, 03/31/99, 04/16/99, 05/03/99, 05/21/99, 05/27/99, 06/03/99**
Type of Submission:	**4P**
Reviewer:	**Houda Mahayni**

Synopsis

Atovaquone is an antiprotozoal drug that inhibits mitochondrial electron transport. It is currently licensed in many countries for the treatment of *Pneumocystis carinii pneumonia* (PCP). Proguanil is a weak inhibitor of plasmodial dihydrofolate reductase and is metabolized to cycloguanil, which is a potent inhibitor of that enzyme. Atovaquone in combination with proguanil hydrochloride (Malarone®) is currently licensed in many European countries for the treatment of malaria.

Malarone tablets (250 mg atovaquone: 100 mg proguanil hydrochloride) are proposed for registration for the treatment of *P. falciparum* malaria in adults and children and for the prophylaxis of *P. falciparum* malaria in adults. These tablets are manufactured using proguanil hydrochloride supplied by [redacted] For the prophylaxis of *P. falciparum* in children it will be necessary to register a lower strength tablet (62.5 mg atovaquone: 25 mg proguanil hydrochloride) due to the lower dosage requirements in children who weigh <=40 kg. However, the pivotal prophylaxis study in children (MALB3003) was conducted using Malarone pediatric tablets (62.5 mg atovaquone: 25 mg proguanil hydrochloride) manufactured using proguanil hydrochloride supplied by [redacted]

An overview of the absorption and disposition of atovaquone was presented in NDA No. 20-259 (Mepron tablets application) and NDA No. 20-500 (Mepron suspension application). Both submissions were in support of the use of atovaquone in the treatment of *Pneumocystis carinii* pneumonia. Background information on the pharmacokinetics of proguanil was provided from literature articles.

Atovaquone is a highly lipophilic compound with low aqueous solubility and limited oral bioavailability that varies with dose and diet. In the fed state, extent of atovaquone absorption is dose proportional for doses up to 750 mg but less than dose proportional for doses greater than 750 mg. Atovaquone is highly protein bound (>99%). The mean apparent oral volume of distribution for 750 mg is 5.8L/kg. The plasma:whole blood ratio in healthy subject was 1.9:1. In a study where ^{14}C-labelled atovaquone was administered to healthy volunteers, greater than 94% of the dose was recovered as unchanged atovaquone in the feces over 21 days. There was little or no excretion of atovaquone in the urine (less than 0.6%). There is indirect evidence that atovaquone may undergo limited metabolism; however, a specific metabolite has not been identified. Oral clearance for 750 mg fasted single dose is 67 mL/min. The range of mean elimination half-lives of atovaquone in fasted healthy male caucasian subjects receiving single oral doses of 225-750 mg was 70-84 hour.

Proguanil hydrochloride has been approved for malaria prophylaxis at a daily dose of 200 mg, which is lower than the 400 mg daily dose proposed in the present application for the treatment of malaria. Proguanil is rapidly absorbed. Its absolute bioavailability is unknown. Proguanil is concentrated in erythrocytes and it is about 75% protein bound. It is metabolized to cycloguanil and 4-chlorophenyl biguanide. Metabolism to cycloguanil is mediated in the liver by both cytochromes P450 3A4 and 2C19. Less than 40% of proguanil is eliminated via the urine and the rest is by hepatic transformation. The half-life of proguanil in adults and children is 12-15 hours and that of cycloguanil is similar.

Recommendations

The clinical pharmacology/biopharmaceutics portion of NDA 21-078 has been reviewed.

1) From a biopharmaceutics prespective, the sponsor did not demonstrate that:

- The quarter strength tablets (QS-W & QS-J) are bioequivalent.
- The clinical trial formulations manufactured in UK are linked to formulations manufactured in Canada. Usually, dissolution data can be used to address site change issues. However, in the case of malarone, the sponsor did not provide a dissolution method that is acceptable. Therefore, it is recommended that a bioequivalence study be conducted to link the to-be-marketed formulations (FS-J & QS-J tablets) manufactured in Canada to the UK formulations (FS and QS tablets).

2) The in-vitro dissolution method for atovaquone is not acceptable. The sponsor should continue to work on developing an acceptable dissolution method for malarone with respect to the atovaquone component.
The in-vitro dissolution method for proguanil [redacted]) is found acceptable. The Q for proguanil should be changed to NLT [redacted] label strength dissolved in [redacted] mins.

3) The clinical implications of using malarone in patients with renal and hepatic dysfunction is unknown. It is recommended that the sponsor evaluate the pharmacokinetics of malarone in patients with renal and hepatic dysfunction as a phase IV commitment.

Based on the information provided in NDA 21-078, it is recommended that the sponsor submit the following as Phase IV commitments:

- **A dissolution method** for atovaquone that avoids using [redacted] as the dissolution medium should be developed and submitted.
- **A renal impairment study** that will provide dosing information in patients with severe renal impairment should be conducted and submitted within [redacted]
- **A liver impairment study** that will provide dosing information in patients with hepatic dysfunction should be conducted and submitted within [redacted]

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Appendix of Study Summaries (available from DPE-3 upon request)

I. Background

Glaxo Wellcome has submitted NDA 21-078 for atovaquone and proguanil hydrochloride (Malarone®) tablet. Malarone is to be indicated for the treatment and prophylaxis of malaria. It will be marketed in two strengths, an adult strength of 250 mg atovaquone:100 mg proguanil hydrochloride and a pediatric strength of 62.5 mg atovaquone: 25 mg proguanil hydrochloride. The dose for the treatment of malaria in adults is four malarone tablet (adult strength; total daily dose 1 gram atovaquone/400 mg proguanil hydrochloride) as a single dose daily for 3 consecutive days. The dose for the treatment of malaria in the pediatric population is based on body weight according to the following table:

Table 1: Dosage for Treatment of Acute Malaria in Pediatric Patients

Weight (Kg)	Atovaquone/Proguanil HCl Total Daily Dose	Dosage Regimen
11-20	250 mg/100 mg	One malarone tablet (adult strength) daily for 3 consective days
21-30	500 mg/200 mg	Two malarone tablets (adult strength) as a single dose daily for 3 consecutive days
31-40	750 mg/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

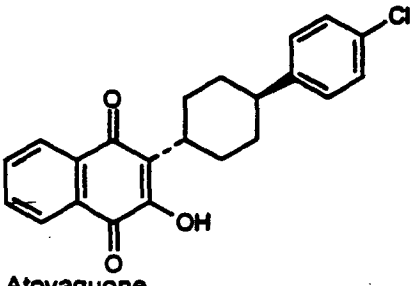
Prophylactic treatment with malarone should be started 1 or 2 days before entering a malaria-endemic area and continued for 7 days after return. The dose for prophylaxis indication in adult is one malarone tablet (adult strength =250 mg atovaquone/100 mg proguanil hydrochloride) per day. The dosage for prevention of malaria in pediatric patients is based upon body weight according to the following table.

Table 2: Dosage for Prevention of Malaria in Pediatric Patients

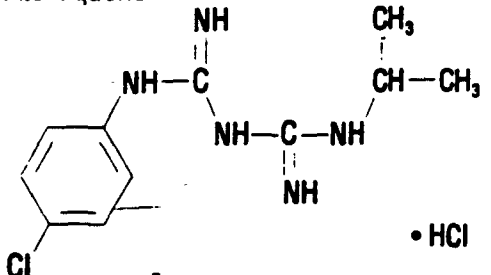
Weight (Kg)	Atovaquone/Proguanil HCl Total Daily Dose	Dosage Regimen
11-20	62.5 mg/25 mg	One malarone pediatric tablet daily
21-30	125 mg/50 mg	Two malarone pediatric tablets as a single dose daily
31-40	187.5 mg/75 mg	Three malarone pediatric tablets as a single dose daily
>40	250 mg/100 mg	One malarone tablet (adult strength) daily

The mechanism of action of atovaquone is due to its inhibition of mitochondrial electron transport. Whereas, proguanil hydrochloride exerts its antimalarial effects primarily by means of the metabolite cycloguanil, an inhibitor of dihydrofolate reductase.

Atovaquone ($C_{22}H_{19}ClO_3$) has a molecular weight of 366.84. It is practically insoluble in water. Proguanil hydrochloride ($C_{11}H_{16}ClN_5.HCl$) has a molecular weight of 290.20. It is soluble in water



Atovaquone



Proguanil Hydrochloride

II. Assay Method and Validation:

Parameter	Atovaquone	Proguanil	Cycloquanil
Limit of Quantification			
Linearity			
Specificity	Plasma tested for interferences. No peaks were Present at the retention times of any of the Compounds.		
Inter-assay precision			
Intra-assay precision			
Inter-assay accuracy			
Intra-assay accuracy			
Stability	Stable for when Protected From light at +4°C	Stable for at +4°C and when in processed extracts at ambient temperature for 22 hrs.	
Recovery			

III. Bioavailability and Bioequivalence

An Overview of the Absorption, Disposition and Elimination of Malarone

The absorption and disposition of atovaquone was presented in NDA No. 20-259 (Mepron tablet application) and NDA No. 20-500 (Mepron suspension application). The pharmacokinetic of proguanil was presented from literature articles.

Atovaquone is a highly lipophilic compound with low aqueous solubility and limited oral bioavailability that varies with dose and diet. In healthy fasted subjects, the absorption of atovaquone increased in proportion to dose following single doses of tablets between 25 and 450 mg but less than proportionally following 750 mg. The lack of dose proportionality at higher doses is likely to be due to the absorption of atovaquone being limited by the rate and extent of dissolution in the gut. Atovaquone is highly protein bound (>99%). Its mean apparent oral volume of distribution values for fasted single doses of 75-450 mg are 272-303 L (3.4-3.8L/kg) and 462 L(5.8L/kg) for 750 mg. The plasma:whole blood ratio in healthy subjects was 1.9:1 indicating that little atovaquone distributes into uninfected erythrocytes.

The main route of elimination of atovaquone in man is via the liver. The measured oral clearance depends on the reduction in absorption at higher doses and the effects of food on absorption. Its mean oral clearance for fasted single doses of 75-450 mg are 49-53 mL/min and for 750 mg are 67 mL/min. The range of mean elimination half-lives of atovaquone in fasted healthy male Caucasian subjects receiving single oral doses of 225-750 mg was 70-84 h; at the recommended dose of atovaquone alone and in combination with proguanil hydrochloride, in fed subjects, the half-life was about 60 h.

Proguanil hydrochloride has been approved for malaria prophylaxis at a daily dose of 200 mg, lower than the 400 mg daily dose proposed in the present application. Single-dose proportionality for the phamacokinetics of proguanil HCl has been demonstrated over the range of 50 to 500 mg.

Proguanil is rapidly absorbed with peak plasma concentrations occuring between 2-4 hours after 200 mg single doses and between 1-6 hours after 400 mg in the presence of 1000 mg atovaquone. The absolute bioavailability is not known.

Proguanil is concentrated in erythrocytes with whole blood concentrations approximately 5 times those of plasma; in contrast; plasma and whole blood concentrations of cycloguanil are similar. Proguanil is 75% protein bound and the binding in vitro is unaffected by therapeutic concentrations of atovaquone. Information is not available on the protein binding of cycloguanil.

Less than 40% of proguanil is eliminated via the urine and the rest is by hepatic transformation, with excretion of up to 20% of the metabolites in the urine. The half-life of proguanil and cycloguanil is similar about 12-15 hours. Renal clearance of both proguanil and cycloguanil are greater than glomerular filtration rate.

Effect of Food

Atovaquone: Dietary fat taken concomitantly with atovaquone tablets increases the rate and extent of absorption of atovaquone, increasing AUC 2-3 times and C_{max} 5 times over fasting. Food probably increases atovaquone absorption by increasing its solubility in the gut lumen. In the fed state, atovaquone shows linear pharmacokinetic behavior at doses up to 750 mg but less than dose proportional for doses greater than 750 mg.

Proguanil: The effect of food has not been studied. However, a cross-study comparison of proguanil hydrochloride pharmacokinetics in the fasting and fed state did not show any evidence of effect of food on the rate or extent of absorption of proguanil hydrochloride.

Mean (%CV) Atovaquone Pharmacokinetic Parameters from Bioequivalence/Bioavailability/Interaction Studies of Malarone (atovaquone and proguanil hydrochloride) Tablets

Study	Atovaquone Dose	Treatment	Food	N	C_{max} (µg/mL)	T_{max} (hr)	$AUC_{0-\infty}$ (hr.µg/m	$T_{1/2}$ (hr)
115-133	1000 mg	Alone	Fed	18	10.9 (25)	3.1 (22)	581 (34)	60 (33)
	1000 mg	+Proguanil	Fed	18	11.8 (20)	3.3 (23)	541 (35)	60 (23)
115-132	1000 mg	Separate	Fasted	26	4.22 (52)	33 (119)	633 (72)	94.2 (25)
	1000 mg	Combined	Fasted	26	4.33 (54)	23 (87)	605 (55)	98.9 (35)
MALB 1002	500 mg	FS-W	Fed	41	3.6 (35)	4.1 (114)	312 (39.5)	79.7 (31)
	500 mg	FS-J	Fed	41	3.5 (37)	4.7 (151.5)	265 (40)	73 (31.5)
	500 mg	QS-W	Fed	41	4.5 (39.5)	5.1 (106)	400 (36.5)	74 (28)
MALB 1004	500 mg	QS-W	Fed	30	1.96 (26)	16.4 (106)	237 (49)[a]	73 (37)[a]
	500 mg	QS-J	Fed	30	1.88 (32)	10.8 (178)	175 (39)[b]	71 (33)[b]

[a]n=29
[b]n=28

In comparing MALB1002 and MALB1004, it is observed from the result shown in the above table that atovaquone C_{max} in study MALB1004 is almost half the atovaquone C_{max} observed in study MALB1002 under very similar condition (i.e. dose, diet, sample size). Similar observation is seen in the atovquone AUC $_{0-\infty}$ between the two study. Atovaquone t_{max} was more than double in study MALB1004 than in study MALB1002 indicating slow release of the content from the formulation. Therefore, using a formulation utilizing one source for proguanil still resulted in inconsistency in the results obtained for atovaquone from the quarter strength formulation of both studies. The sponsor did not provide explanation to these observations. The reviewer believe that these results may be due to the time the samples were taken for the analysis of atovaquone. This is because atovaquone profiles has two peaks, the second is larger than the first. The results of proguanil component form MALB1002 and MALB1004 did not show big differences in the C_{max}, $AUC_{0-\infty}$, or T_{max} observed.

Mean (%CV) Proguanil Pharmacokinetic Parameters from Bioequivalence/Bioavailability/Interaction Studies of MALARONE (atovaquone and proguanil hydrochloride) Tablets

Study	Proguanil Dose	Treatment	Food	n	C_{max} (ng/mL)	T_{max} (hr)	AUC_0 (hr·ng/mL)	$t_{½}$ (hr)
115-133	400 mg	Alone	Fed	18	562 (25)	3.1 (27)	6699 (29)	13.9 (18)
	400 mg	+ Atovaquone	Fed	18	521 (22)	3.4 (27)	6164 (23)	14.7 (17)
115-132	400 mg	Separate	Fasted	26	443 (29)	3.2 (31)	6278 (38)	16.5 (18)
	400 mg	Combined	Fasted	26	440 (30)	3.5 (32)	6117 (35)	16.8 (16)
MALB 1002	200 mg	FS-W	Fed	41	177 (22)	3.3 (31)	2162 (30.5)	15.3 (41)
	200 mg	FS-J	Fed	41	179 (22)	3.3(26.5)	2253 (31)	14.8 (38)
	200 mg	QS-W	Fed	41	172 (24)	3.2 (20)	2252 (31)	14.8 (27)
MALB 1004	200 mg	QS-W	Fed	31	161 (28)	3.3(28.5)	2460 (31)[a]	17.2 (43)[a]
	200 mg	QS-J	Fed	31	170 (25)	3.1 (33)	2349 (32)[b]	16.5 (38)[b]

[a] n=28

[b] n=29

Mean (%CV) Cycloguanil Pharmacokinetic Parameters from Bioequivalence/Bioavailability/Interaction Studies of MALARONE (atovaquone and proguanil hydrochloride) Tablets

Study[a]	Proguanil Dose	Treatment	Food	n	C_{max} (ng/mL)	T_{max} (hr)	AUC_0 (hr·ng/mL)	$t_{1/2}$ (hr)
115-133	400 mg	Alone	Fed	17	103 (55)	6.4 (20)	1558 (54)	12.0 (38)
	400 mg	+ Atovaquone	Fed	17	99 (53)	5.9 (25)	1337 (44)	12.6 (43)
MALB	200 mg	QS-W	Fed	31	75.3 (44)	5.8 (16)	1066 (40)[b]	11.1 (47)
1004	200 mg	QS-J	Fed	31	77.4 (44)	5.6 (18)	1066 (38)[c]	10.1 (38)

[a] Cycloguanil plasma levels were not measured in Studies 115-132 and MALB1002

[b] n=28

[c] n=29

Bioequivalence

Three bioequivalence studies were performed. The first study (115-132-V) was carried out to demonstrate bioequivalence between the separate tablet entities and the combination product intended for marketing. The data indicate that the two formulations are bioequivalent.

The second study (MALB 1002) was performed to investigate if malarone tablets (250 mg atovaquone and 100 mg proguanil hydrochloride) containing proguanil hydrochloride from were bioequivalent to malarone tablets containing proguanil hydrochloride from . The data indicate that the full strength FS-J) is bioequivalent to full strength (FS-W) in terms of atovaquone C_{max}, and Proguanil C_{max}, and AUC but missed bioequivalence in terms of atovaquone AUC (90% CI (0.79-0.91)). This study was also performed to determine if eight malarone pediatric tablets[2] (62.5 mg atovaquone and 25 mg proguanil hydrochloride) were bioequivalent to two malarone tablet (all tablets contained proguanil hydrochloride from

The data indicate that the quarter strength formulation (QS-W) is not bioequivalent to the full strength formulation (FS-W) in terms of atovaquone C_{max} (90% CI (1.14-1.36)) and AUC (90% CI (1.21-1.40)). (Table 1). Therefore, QS-W vs FS-W were bioequivalent for proguanil but were 30% greater in AUC and 25% greater in C_{max} for atovaquone.

The third study (MALB 1004) was conducted to investigate whether malarone pediatric tablets containing proguanil hydrochloride from were bioequivalent to malarone pediatric tablets containing proguanil hydrochloride from the bulk supplier for the proposed market image. The data indicate that the QS-J is bioequivalent to QS-W in terms of Atovaquone C_{max} and Proguanil C_{max} and AUC but failed bioequivalence in terms of atovaquone AUC (90% CI (0.71-0.88)) (Table 2). Therefore, QS-J was 21% less than QS-W in atovaquone AUC.

Site Change

The two formulations, the pilot formulation manufactured in UK and the clinical trial formulations (FS or QS), do not differ in terms of excipients but they differ in the supplier of the proguanil hydrochloride component. The clinical formulations used proguanil supplied by Whereas, the pilot formulation manufactured in UK used proguanil supplied by The sponsor is proposing Canada to be the site of the to-be-marketed formulation. There is no study that was submitted in this NDA that included any data from the proposed site of manufacture. The following are factors that highlight the importance of conducting a bioequivalence study to link the clinical formulations manufactured in UK to the Canadian formulations. **1)** Atovaquone is a drug that has low solubility and low permeability. **2)** The results obtained from the above studies failed to show bioequivalence between the clinical and the pilot formulations. **3)** The sponsor have closed down the manufacturing site in the UK. **4)** There is lack of a meaningful dissolution method for atovaquone to compare the dissolution profiles of the clinical and the to-be-marketed formulations. Therefore, based on the above factors, the clinical division will be advised to request another bioequivalence study to link the formulations manufactured in UK (FS and QS) to the to-be-marketed formulations manufactured in Canada.

Table 1. Summary Statistics of Pharmacokinetic Parameters of Malarone Formulations in Study MALB 1002

Drug	Parameter	Comparison[a]	Ratio	90% CI
Atovaquone	AUC	FS-J vs. FS-W	0.85	(0.79-0.91)
Atovaquone	C_{max}	FS-J vs. FS-W	0.96	(0.88-1.04)
Proguanil	AUC	FS-J vs. FS-W	1.04	(0.98-1.08)
Proguanil	C_{max}	FS-J vs. FS-W	0.97	(0.92-1.02)
Atovaquone	AUC	QS-W vs. FS-W	**1.30**	(1.21-**1.40**)
Atovaquone	C_{max}	QS-W vs. FS-W	**1.25**	(1.14-**1.36**)
Proguanil	AUC	QS-W vs. FS-W	1.04	(0.98-1.10)
Proguanil	C_{max}	QS-W vs. FS-W	0.94	(0.89-1.00)

[a]FS-W: 2 tablets each containing 250 mg atovaquone and 100 mg proguanil HCl; FS-J: 2 tablets each containing 250 mg atovaquone and 100 mg proguanil HCl; QS-W: 8 tablets each containing 62.5 mg atovaquone and 25 mg proguanil HCl. Bold Signifies Outside bioequivalence range of 0.80 to 1.25. AUC refers to $AUC_{0-\infty}$

Table 2. Summary Statistics of Pharmacokinetic Parameters of Malarone Formulations in Study MALB 1004.

Drug	Parameter	Comparison[a]	Ratio	90% CI
Atovaquone	AUC	QS-J vs. QS-W	**0.79**	(**0.71**-0.88)
Atovaquone	C_{max}	QS-J vs. QS-W	0.94	(0.85-1.04)
Proguanil	AUC	QS-J vs. QS-W	0.97	(0.92-1.03)
Proguanil	C_{max}	QS-J vs. QS-W	1.06	(1.00-1.13)

[a]QS-W: 8 tablets each containing 62.5 mg atovaquone and 25 mg proguanil HCl; QS-J: 8 tablets each containing 62.5 mg atovaquone and 25 mg proguanil HCl. Bold signifies outside bioequivalence range of 0.80 to 1.25. AUC refers to $AUC_{0-\infty}$.

IV. Metabolism

In vitro

Atovaquone: In vitro studies with human liver failed to demonstrate significant metabolism of atovaquone.

Proguanil HCl: Proguanil is metabolized to cycloguanil and 4-chlorophenyl biguanide. Metabolism to cycloguanil is mediated in the liver by both cytochrome P450 3A4 and 2C19. The latter enzyme exhibits genetic polymorphism.

In vivo

Atovaquone: ^{14}C-atovaquone was administered to healthy volunteers and there was no evidence of circulating metabolites in the plasma. Radioactivity was recovered in the feces as parent compound with negligible radioactivity (<1%) eliminated in the urine.

V. Special Populations

Hepatic

Sponsor did not perform a study to assess the potential influence of liver impairment on Malarone pharmacokinetics. Sponsor recommended no dosage adjustments for patients with mild or moderate impairement of hepatic function.

[1] Also referred to as Full Strength Tablets

[2] Also referred to as Quarter Strength Tablets

Note: Proguanil hydrochloride 100 mg tablets used in study 115-132-V were purchased from a commercial supplier

Renal

The sponsor did not conduct a study to assess the influence of renal impairment on the pharmacokinetics of malarone. Sponsor recommended no dosage adjustment for patients with mild or moderate impairment of renal function. In the label it was recommended that malarone should be administered with caution to patients with severe renal failure because of the renal route of elimination of proguanil and cycloguanil.

Race

The population pharmacokinetics studies performed showed racial effects on pharmacokinetics but they do not appear to warrant dosing adjustments for both atovaquone and proguanil.

Gender

To assess potential pharmacokinetic differences between gender, the sponsor performed population pharmacokinetic analysis. Results showed that there were no important gender effects on the pharmacokinetics of atovaquone or proguanil.

Pediatric

Dose adjustments based on body weight categories (1/4 dose for 11-20 kg, 1/2 dose for >20-30 kg, 3/4 dose for >30-40 kg and full dose for >40 kg) were used in clinical trials.

VI. Drug Interactions

In vitro

Studies using human livers showed the K_i values for inhibition of cycloguanil formation by atovaquone were similar to total plasma concentrations of atovaquone expected in therapeutic use (10µg/mL). However, the extensive protein binding of atovaquone to plasma proteins (>99.9%) means that actual free concentrations would be more than 100-fold lower compared to the k_i value predicted. Hence, inhibition of proguanil metabolism by atovaquone would not be anticipated in the clinical situation.

In vivo

There are no pharmacokinetic interactions between atovaquone and proguanil at the recommended dose.

Rifampin

In previously reported studies, concomitant treatment with rifampin have been associated with significant decreases in plasma concentrations of atovaquone.

Tetracycline

Population pharmacokinetic analysis of data obtained during malaria treatment studies showed that concomitant treatment with tetracycline is associated with a significant decrease in plasma concentrations of atovaquone.

VII. Pharmacokinetic/Pharmacodynamic Relationships

PK/PD was attempted, however, due to the high efficacy rate (~100%) such concentration/effect relationship was not found.

VIII. Formulation

The drug substance atovaquone will be manufactured by Glaxo Wellcome in Dartford, UK. Whereas, the drug substance proguanil hydrochloride will be manufactured by [redacted] Malarone tablet contains 250 mg atovaquone and 100 mg proguanil hydrochloride. Malarone pediatric tablet contains 62.5 mg atovaquone and 25 mg proguanil hydrochloride. Malarone and malarone pediatric tablet will be manufactured, packaged and labelled by Glaxo Wellcome in Ontario, Canada.

The compositions (weight in mg) of the formulation are given below:

Ingredient	*Amount per Tablet (mg)* Malarone	Malarone Pediatric
Tablet Core		
Atovaquone*	250.0	62.5
Proguanil hydrochloride	100.0	25.0
Low-substituted Hydroxypropyl Cellulose, NF	[redacted]	
Microcrystalline Cellulose, NF	[redacted]	
Povidone K30, USP	[redacted]	
Sodium starch Glycolate, NF	[redacted]	
Magnesium Stearate, NF	[redacted]	
Poloxamer 188, NF	[redacted]	
[redacted]	[redacted]	
Film Coat and Polish Coat	[redacted]	
[redacted]	[redacted]	
Polyethylene Glycol 400, NF	[redacted]	
Polyethylene Glycol 8000, NF	[redacted]	

Notes:

*The actual quantity of atovaquone is calculated from a potency factor so as to provide 250 mg or 62.5 mg atovaquone per tablet.

[redacted]

The proposed dissolution method for atovaquone is using [redacted] at a [redacted] of [redacted] per minute with a [redacted] prior to switching to [redacted] The proposed dissolution specification for atovaquone is Q = [redacted] label strength dissolved after 105 minutes (1 hour in [redacted] followed by 45 minutes in [redacted]

The proposed dissolution method for proguanil hydrochloride is using [redacted] operated at [redacted] in [redacted] The proposed dissolution specification for proguanil is Q= [redacted] label strength dissolved at 45 minutes.

In vitro dissolution of Malarone and Malarone Pediatric tablets using the proposed method

Tablet Lots	Percent Label Claim Dissolved
MALARONE[1]	
PDL/BMR/5276	@1HR&45MINS
PDL/BMR/5578	@1HR&45MINS
PDL/BMR/5297[3]	@1HR&45MINS
PDL/BMR/5878[3]	@1HR&45MINS
PROGUANIL HYDROCHLORIDE[2]	
PDL/BMR/5276	@45MINS
PDL/BMR/5578	@45MINS
PDL/BMR/5297[3]	@45MINS
PDL/BMR/5878[3]	@45MINS

[redacted] minute. [redacted] for the first hour. After 1 hour change

[redacted], with [redacted] as the dissolution medium

[3]Malarone Pediatric tablet.

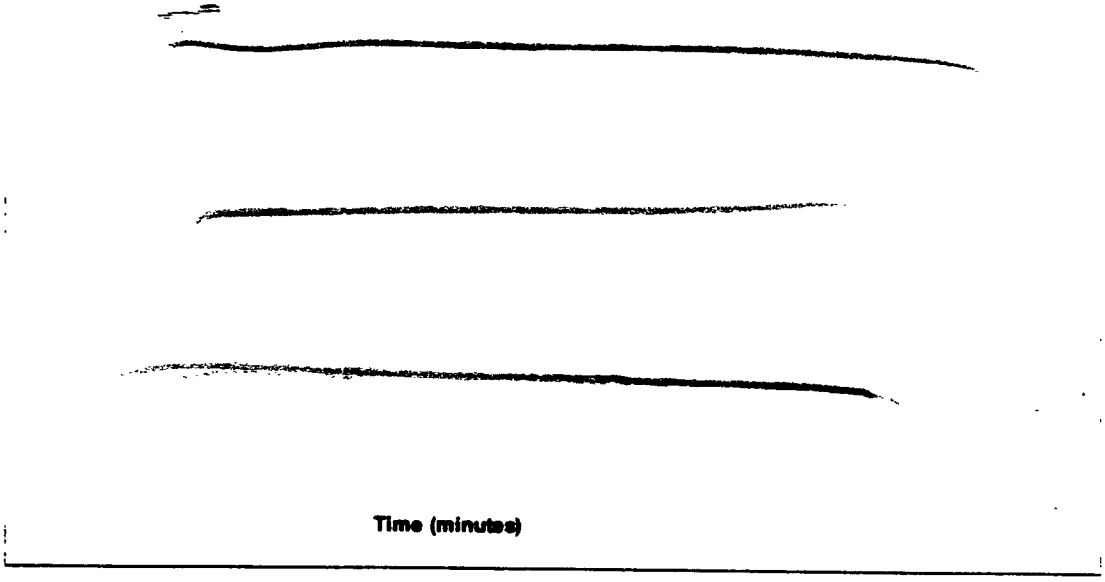
Comparison of Atovaquone Adut and Pediatric Clinical to Adult TBM Tablets

[redacted]

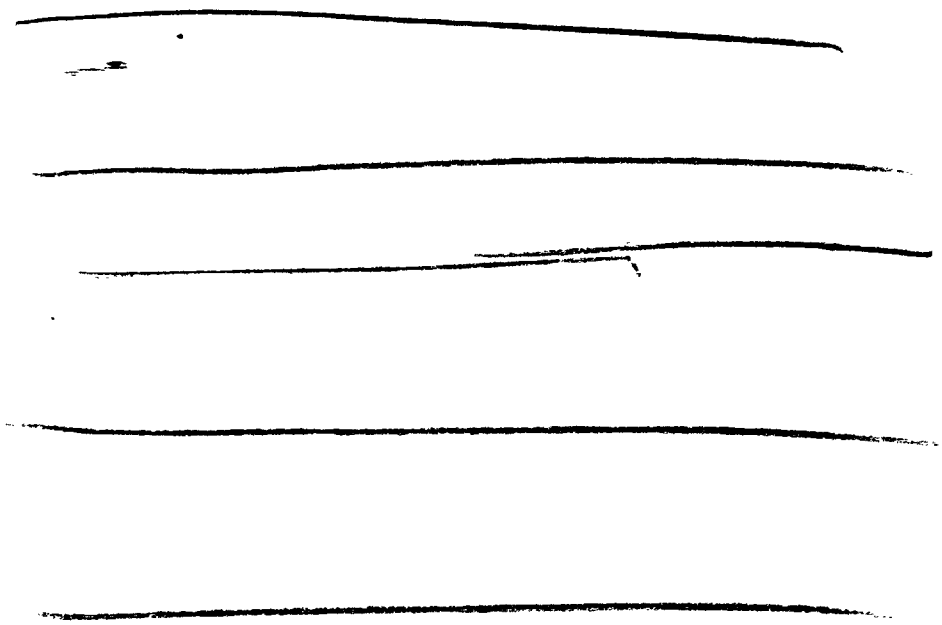
Time (minutes)

WITHHOLD 1 PAGE (S)

Comparison of Clinical and TBM Pediatric Tablets



IX. General Comments (Do not send to sponsor)



X. Labeling Comments (To be sent to Sponsor)

Pharmacokinetics:

Absorption: Atovaquone is a highly lipophilic compound with low aqueous solubility. The bioavailability of atovaquone shows considerable inter-individual variability.

Dietary fat taken with atovaquone increases the rate and extent of absorption, increasing AUC two to three times and C_{max} five times over fasting. The absolute bioavailability of the tablet formulation of atovaquone when taken with food is 23%. MALARONE tablets should be taken with food or a milky drink.

Proguanil hydrochloride is extensively absorbed regardless of food intake.

Distribution: Atovaquone is highly protein bound (>99%) over the concentration range of 1 to 90 µg/mL. The apparent volume of distribution of atovaquone after oral administration is approximately 3.5 L/kg.

Proguanil is 75% protein bound. The apparent volume of distribution is approximately 42 L/kg.

In human plasma, the binding of atovaquone and proguanil was unaffected by the presence of the other.

3 pages redacted from this section of the approval package consisted of draft labeling

XI. Signatures

Houda Mahayni, Ph.D., Pharmacokinetic Reviewer /S/ 6/14/99

Division of Pharmaceutical Evaluation III
Office of Clinical Pharmacology and Biopharmaceutics

RD/FT initialed by Funmi Ajayi, Ph.D., Team Leader /S/ 6/14/99

CPB briefing 6/1/99: L. Lesko, J. Lazor, A. Selen, M. Chen, M. Mehta, R. Hopkins, M. Dempsey, J. Smith, N. Schmuff, J. Meyer, D. Bashaw, K. Reynolds, F. Ajayi, H. Sun, H. Mahayni

CC: NDA 21-078 (orig., 1 copy), HFD-590(Meyerhoff and Sacks (MO), Mary Dempsey (CSO)), HFD-850(Lesko), HFD-880(DPEIII, Mahayni, Ajayi), Central Document Room (Barbara Murphy)

4/29/99
6/14/99

mw: a:c:NDA\21078review4, 04-29-99,05-25-99,06-04-99,06-09-99,06-10-99,06-11-99, 06-14-99

NDA 21-078 Atovaquone and Proguanil Hydrochloride (Malarone®)

Appendix

Study Summaries

Proposed Package Insert

VOL. 1.26-1.27

TITLE: A study to compare the bioavailability of atovaquone and proguanil from combination tablets and from atovaquone tablets and proguanil tablets given comcomitantly (Protocol No. 115-132-V)

INVESTIGATOR: Dr. R. Dixon

STUDY CENTER: Wellcome Clinical Investigation Unit
King's College Hospital

OBJECTIVES: To determine whether atovaquone and proguanil in the combination tablet are bioequivalent to those in the tablets containing the constituents separately, given at the same time in the same dose.

STUDY DESIGN: This was an open, 3-period, crossover study in 26 healthy volunteers. Twenty five subjects completed the study. One subject (No. 26) withdrew after 2 occasions because of prolonged headache after both occasions. The first two periods were according to a randomised, balanced, 2-period, crossover design in which all volunteers received combination tablets containing atovaquone and proguanil or separate tablets of atovaquone and proguanil given concomitantly. On the third occasion, 12 subjects repeated the combination tablet treatment and 13 subjects repeated the separate tablet treatment to assess the carry-over effect. If assigned to the combination treatment, the subject took 4 combination tablets orally, and, if assigned to the separate tablet treatment, each subject took 4 tablets of atovaquone and 4 tablets of proguanil concomitantly by mouth. All study medications were taken with 200 mL of water after an overnight fast. Between occasions, there was a washout of at least 3 weeks.
For atovaquone assay, blood was sampled for 14 days and for proguanil assay blood was sampled for 7 days. A non-compartmental model was used to determine $AUC_{0-\infty}$, $t_{1/2}$, CL/f and V_z/f for atovaquone and proguanil. C_{max} and T_{max} values were derived from the plasma concentration-time profiles.

NAME, BATCH NUMBER, DOSE and MODE of ADMINISTRATION of TEST PRODUCT(S):

1. Atovaquone 250 mg tablets. Analytical Lot No. 93A5017. This was supplied by Pharmaceutical Development Laboratories (PDL), [redacted]ion Ltd., Dartford, Kent.

2. Combination tablets containing 250 mg atovaquone and 100 mg proguanil. Analytical Lot No. 94C5276. This was supplied by Pharmaceutical Development Laboratories (PDL), Wellcome Foundation Ltd., Dartford, Kent.
3. Proguanil tablets with a strength of 100 mg (supplied as Paludrine). It was manufactured by [redacted]

Treatment 1 is defined as treatment with the separate tablets and treatment 2 is defined as treatment with the combination tablet.

PHARMACOKINETIC ANALYSIS:

- The pharmacokinetic parameters AUC $_{0-\infty}$, $t_{1/2}$, CL/f, V_z/f, C_{max} and T_{max} were determined for atovaquone and proguanil after treatment with the combination tablet and with the separate tablets given concomitantly.
- Non-compartmental model was used to determine AUC $_{0-\infty}$, $t_{1/2}$, CL/f and V_z/f for atovaquone and proguanil. C_{max} and T_{max} were derived from the plasma concentration-time profiles.
- The AUC $_{0-\infty}$ and C_{max} ratios for the comparison of the combination tablet and the separate tablets were estimated, along with their 90% confidence intervals.
- The pharmacokinetic parameters AUC $_{0-\infty}$ and C_{max} were subjected to analysis of variance taking into account sources of variation due to subject, period, treatment and treatment carry-over.
- The point estimate for the ratio of each of the pharmacokinetic parameters after the combination tablet compared to that of the separate tablets was calculated along with its 90% confidence interval.
- For atovaquone and proguanil, the median, minimum and maximum values of T_{max} were determined. For proguanil, the median difference in T_{max} between combination and separate tablets and the 90% confidence interval for this difference was calculated using the Wilcoxon Signed Rank method. T_{max} for atovaquone often occurred after 12 h, during which period sampling was infrequent. Hence it was considered inappropriate to calculate confidence intervals for the median difference in atovaquone T_{max} between the combination tablet and the separate tablets.

ANALYTICAL METHODS:

- For atovaquone, a [redacted] was utilized with a [redacted] The limit of quantification for the determination of atovaquone in human plasma is [redacted] The precision data shows that the %CV is less than [redacted] The bias values were dependent on the concentration with values of [redacted] for low, medium and high controls respectively. Testing was performed by the Division of Bioanalytical Sciences, Wellcome Research Laboratories, Beckenham, Kent. BR3 3BS.
- For proguanil, an [redacted] was utilized. The limit of quantification was [redacted] proguanil (as free base) per mL of human plasma. The range of proguanil concentrations was from [redacted] The % bias was [redacted] and the precision was [redacted] The testing was performed by [redacted]

RESULTS:

Summary of results:

Parameter[a]	Separate Tablet		Combination Tablet	
	Atovaquone	Proguanil	Atovaquone	Proguanil
C_{max}	4.32 µg/mL	433 ng/mL	4.25 µg/mL	429 ng/mL
$AUC_{0-\infty}$	630 µg.h/mL	6130ng.h/mL	585µg.h/mL	5809ng.h/mL

[a]Arithmetic Means

Arithmetic Mean Values (±SD) of Pharmacokinetic Parameters for Atovaquone and Proguanil after Treatment with the Separate Tablets (Treatment 1) and Combination Tablet (Treatment 2)

Parameters	Treatment 1 Mean ±SD	Treatment 2 Mean ±SD
	Atovaquone	
C_{max}(µg/mL)	4.32±2.22	4.25±2.15
AUC $_{0-\infty}$ (µg.h/mL)	630±406	585±349
$T_{½}$ (h)	95.3±24.4	94.5±31.0
CL/f (L/h)	2.36±1.45	2.51±1.98
CL/f/kg (mL/h/kg)	34.3±18.4	36.3±23.0
V_z/f (L)	303±164	304±174
V_z/f (L/kg)	4.37±2.10	4.36±1.95
	Proguanil	
C_{max} (ng/mL)	433±133	429±126
AUC $_{0-\infty}$ (ng.h/mL)	6130±2392	5809±1990
$T_{½}$ (h)	16.4±2.6	16.7±2.6
CL/f (L/h)	72.2±21.1	76.6±23.6
CL/f/kg (mL/h/kg)	1072±320	1130±327
V_z/f (L)	1677±432	1827±544
V_z/f (L/kg)	24.8±6.2	26.9±7.2

Treatment 1: 4x250 mg Atovaquone tablets + 4x100 mg Proguanil tablets
Treatment 2: 4x(250 mg Atovaquone + 100 mg Proguanil) tablets
Each value represents the mean of 26 values. Values of occasions 2 and 3 were averaged and then combined with values of occasion 1 to calculate summary statistics

Geometric Mean Values of Pharmacokinetic Parameters for Atovaquone and their Ratios (x100%) after Treatment with the Separate Tablets (Treatment 1, 39 occasions) and Combination Tablet (Treatment 2, 38 occasions) and 90% Confidence Intervals of these Ratios

Treatment2/Treatment 1				
Parameter	Geometric Means		Ratio x 100 (%)	90% CI
	Treatment 1	Treatment 2		
$AUC_{0-\infty}$ (µg.h/mL)	526.2	515.2	98	(86,111)
C_{max} (µg/mL)	3.80	3.83	101	(88,116)
$T_{½}$ (h)	94.1	91.3	97	(92,102)
CL/f (mL/h/kg)	28.3	28.9	102	(90,116)
V_z/f(L/kg)	3.84	3.81	99	(86,114)

Summary of T_{max} (h) Values for Atovaquone and Proguanil after the Separate Tablets (Treatment 1, 39 occasions) and the Combination Tablet (Treatment 2, 38 occasions)

Compound	Treatment	Median	Minimum	Maximum
Atovaquone	Treatment 1	12	2	144
	Treatment 2	28	1	72
Proguanil	Treatment 1	3	1	6
	Treatment 2	3	2	6

Geometric Mean Values of Pharmacokinetic Parameters for Proguanil and their Ratios (x100%) after Treatment with the Separate Tablets (Treatment 1, 39 occasions) and Combination Tablet (Treatment 2, 38 occasions) and 90% Confidence Intervals of these Ratios

Treatment 2/Treatment 1				
Parameter	Geometric Means		Ratio x100 (%)	90% CI
	Treatment 1	Treatment 2		
$AUC_{0-\infty}$(ng.h/mL)	5953	5680	95	(92,99)
C_{max}(ng/mL)	423	422	100	(95,105)
$t_{½}$ (h)	16.4	16.5	101	(97,105)
CL/f(mL/h/kg)	1000	1048	105	(101,109)
V_z/f(L/kg)	23.61	24.94	106	(100,112)

Median Difference and 90% Confidence Interval of the Difference in Proguanil T_{max} between the Separate Tablets (Treatment 1 and Combination Tablet (Treatment 2)

Median Difference (Treatment 2-Treatment 1)	90% Confidence Interval
0.25	(-.25, 0.5)

Values of occasions 2 and 3 were averaged prior to analysis

- 90% confidence intervals of $AUC_{0-\infty}$ and C_{max} ratios (x100%) between the combination tablet and separate tablet were within the range of 80-125% for atovaquone and proguanil.
- Values of $t_{1/2}$, CL/f and V_z/f were similar for the two formulations.
- Proguanil t_{max} was not significantly different for the combination tablet compared to the separate tablets.
- The atovaquone/proguanil combination tablet showed only minor adverse effects, and there were no abnormal trends in haematology and biochemistry tests.

CONCLUSIONS:

- The atovaquone/proguanil combination tablet is bioequivalent to the separate tablets for both atovaquone and proguanil.
- The atovaquone/proguanil combination tablet was well tolerated.

REVIEWER CONCLUSIONS:

Cycloguanil was not measured in this study. It is not clear why the clinicians specifically requested that cycloguanil concentration not be measured. It would have been clearer if the sponsor provided a rationale for this decision.

VOL. 1.31

TITLE: Pharmacokinetics of Atovaquone, Proguanil, and Cycloguanil After Combination Treatment of Acute *P. falciparum* Malaria in Thai Children (Study 115-123)

INVESTIGATORS: [redacted]

STUDY CENTER: [redacted]

OBJECTIVES:

- To assess the efficacy of a combination of atovaquone/proguanil in children with acute falciparum malaria in Thailand.
- To assess the safety and tolerance of a combination of atovaquone/proguanil in children with acute falciparum malaria in Thailand
- To characterize the pharmacokinetics of atovaquone in Thai Children with malaria who were receiving a combination of atovaquone/proguanil.

The safety and efficacy aspects of the study are addressed in the medical report. This report concerns the pharmacokinetic aspect of the study which was to characterize the pharmacokinetics of atovaquone and proguanil and its metabolite cycloguanil following combined therapy.

STUDY DESIGN: This was an open label uncontrolled clinical trial. Male and female patients aged 5 to 12 years, with uncomplicated falciparum malaria with acute manifestations (e.g. fever) and parasitemia between 1,000 and 200,000 parasites/μL were enrolled in the study. Atovaquone and proguanil were coadministered as separate tablets, each containing 250 mg and 100 mg, respectively, after food, Ovaltine or soy milk. Blood was sampled pre-dose and at 1, 2, 4, 8, 16, 24, 48, 54, 60, 72, 120, and 144 h after beginning treatment in 10 selected children from the thirty children who entered the study for pharmacokinetic characterization. One of these ten withdrew from the study. Thus, full plasma concentration-time profiles were available from nine patients. For the remaining twenty patients, blood was collected at 8 and 96 h after commencement of treatment.

Summary demographics for Thai children in whom full pharmacokinetic parameters were obtained

NUMBER OF SUBJECTS	AGE (years)	GENDER
2	6	F
1	8	M
1	9	M
2	10	F, M
3	12	1F, 2M

Summary of dosage regimen administered

NUMBER OF SUBJECTS	Atovaquone Dose (mg)	Proguanil Dose (mg)
3	250	100
5	500	200
1	750	300

NAME, BATCH NUMBER, DOSE AND MODE OF AMINISTRATION:

1. Atovaquone tablets strength 250 mg (Lot No. 93B5186) were supplied by Pharmaceutical Development Laboratories, Glaxo Wellcome, Dartford, Kent, UK.
2. Proguanil tablets strength 100 mg (Lot No. 94C5302) were supplied as [redacted] tablets manufactured by [redacted]

Daily doses of atovaquone and proguanil were administered on a mg/kg body weight basis once daily for a total of three days.

Body Weight (kg)	Atovaquone Dose (mg)	Proguanil Dose (mg)	Number of Patients with Full Profiles Total	Males	Females
11 to 20	250	100	3	1	2
21 to 30	500	200	5	3	2
31 to 40	750	300	1	1	0

PHARMACOKINETIC ANALYIS:

The following non-compartmental pharmacokinetic parameters were derived for atovaquone and proguanil and its metabolite, cycloguanil, from plasma concentration-time profiles following the final dose on Day 3: C_{max}, T_{max}, AUC, and $t_{1/2}$. Since this was neither a single nor a multiple (*i.e.*, steady-state) dose study the noncompartmental pharmacokinetics of atovaquone, proguanil and cycloguanil could not be directly calculated. Therefore, C_{max} and $AUC_{0-\infty}$ after the last dose on Day 3 were corrected for carry-over and

the data was treated as single dose data. Additionally, CL/F and V_z/F were calculated for atovaquone and proguanil and AUC ratio of cycloguanil to proguanil. Descriptive statistics were used to summarize the results.

ANALYTICAL METHODS: Assay of plasma atovaquone was performed by [redacted] detection. The limits of quantification were between [redacted] µg/mL. During the validation the intra-day precision in the calibration range [redacted] ranged from [redacted] with corresponding biases ranging from [redacted] The inter-day precision in the calibration range [redacted], ranged from [redacted] with corresponding biases ranging from 3.3-15.4%. The extraction recoveries of atovaquone and the internal standard (58C80) from human plasma were [redacted] respectively. Proguanil and cycloguanil were assayed simultaneously using a validated [redacted] method. The limit of quantification were [redacted] ng/mL for both proguanil and cycloguanil. During the validation for proguanil and cycloguanil the accuracy, expressed as overall % bias ranged from [redacted] and [redacted] respectively. For proguanil the within assay precision ranged from [redacted], and the between assay ranged from negligible [redacted] For cycloguanil the within assay precision ranged from [redacted] and the between assay ranged from negligible - [redacted]. Extraction recoveries of proguanil and cycloguanil from plasma were found to be [redacted] at low, medium and high concentrations (20, 200, and 400 ng/mL). Both methods were performed by the Wellcome Foundation, Ltd., Department of Bioanalysis and Drug Metabolism, Beckenham, Kent, UK.

RESULTS:

The pharmacokinetics of atovaquone, proguanil, and cycloguanil were evaluated in nine (5 male and 4 female) patients with acute *P. falciparum* malaria receiving three once-daily doses of atovaquone and proguanil. They were (mean±SD) 9±2 years of age with an average body weight of 25±5 kg. Doses of atovaquone and proguanil were adjusted according to body weight and averaged 444±167 mg for atovaquone (17.3±3.9 mg/kg) and 178±67 mg for proguanil (6.9±1.6 mg/kg). Mean (±SD) values for the major noncompartmental pharmacokinetic parameters were:

Parameter (units)	Atovaquone	Proguanil	Cycloguanil
T_{max} (hr)	11.4±7.6	8.0±3.0	7.5±2.8
C_{max}	5.07±2.06	306±108	44.3±27.3
$C_{max}^{corrected\ (a)}$	2.81±1.44	244±92	35.6±23.3
$AUC_{0-\infty}$	299.7±169.1	6571±1932	1048±532
$AUC_{0-\infty}^{corrected\ (a)}$	161.8±126.9	4646±1226	787±397
$t_{1/2}$ (hr)	31.8±8.9	14.9±3.3	14.6±2.6
CL/F (mL/hr/kg)	162±89	1600±706	-
V_z/F(L/kg)	8.10±6.41	32.7±8.9	-

[a] C_{max} and AUC units are µg/mL and µ.hr/mL, respectively, for atovaquone and ng/mL and ng.hr/mL, respectively, for proguanil and cycloguanil. Values were corrected for carry-over from previous doses.

SPONSOR CONCLUSIONS:

- For atovaquone the corrected peak concentration, time to peak concentration, AUC and half-life in Thai children with acute falciparum malaria given weight adjusted doses of atovaquone (≈17 mg/kg) and proguanil (≈ 7 mg/kg) in combination were 2.81 µ/mL , 11.4 hr, 161.8 µg.h/mL, and 31.8 hr, respectively.
- For proguanil the corrected peak concentration, time to peak concentration, AUC and half-life in Thai children with acute falciparum malaria given weight adjusted doses of atovaquone (≈17 mg/kg) and proguanil (≈ 7 mg/kg) in combination were 244 ng/mL, 8.0 hr, 4646 ng.hr/mL, and 14.9 hr, respectively.
- For cycloguanil the corrected peak concentration, time to peak concentration, AUC and half-life in Thai children with acute falciparum malaria given weight adjusted doses of atovaquone (≈17 mg/kg) and proguanil (≈ 7 mg/kg) in combination were 35.6 ng/mL, 7.5 hr, 787 ng.hr/mL, and 14.6 hr, respectively.
- Despite some differences in the pharmacokinetics of atovaquone and proguanil in children when compared with adults, the 100 % cure rate and low incidence of adverse experiences observed in the present study suggest that the following body weight adjusted dosing regimen is appropriate:

Body Weight (kg)	Atovaquone Dose (mg)	Proguanil Dose (mg)
11 to 20	250	100
21 to 30	500	200
31 to 40	750	300

REVIEWER CONCLUSIONS:

The average dose given in the present study (17.3 mg/kg) was higher than the 9.2 mg/kg administered to adults (750 mg/81.1kg). Also, the corrected peak concentrations on Day 3 (2.81±1.44 µg/mL) were higher than the 1.58 µg/mL C_{max} observed in healthy adults taking 750 mg of atovaquone in the fasted state. The corrected AUC for atovaquone in the children (162µg.h/mL) was within the range of average AUC values for healthy adults receiving single 750 mg atovaquone while fasting. Three factors can be of concern considering the differences in the pharmacokinetics of atovaquone and proguanil in children when compared with adults. Firstly, at doses ≥ 750 mg the pharmacokinetic of atovaquone are not dose proportional. Secondly, in the label it is recommended that the dose be given with food. Thirdly, only one patient out of nine received the higher dose in atovaquone (750 mg) and proguanil (300 mg). In a previous study, following food intake with high fat content, the peak plasma concentration (C_{max}) and AUC increased by factors of 5.4 and 3.1, respectively, compared to the fasted state. The present study was performed in the fasted state. Therefore, one would anticipate that C_{max} and AUC will be higher in the pediatric patient population when given as recommended in the label. But because clearance was higher in children since the corrected AUC for atovaquone in children was comparable to adult receiving 750 mg while fasting, the recommended dosing regimen is appropriate, especially, when the duration of dosing is limited to only 3 days. Comparing the present study to a study done in adult given 200 mg dose of proguanil, The corrected AUC values for proguanil, cycloguanil and the C_{max} for proguanil were higher. Whereas, C_{max} for cycloguanil was lower than values achieved in the adult study. This could be explained by the greater "per kilogram" dose received by the children and the smaller sample size used to conduct this study. There were 9 children and two of the nine were poor metabolizers of proguanil. It would have been more informative to have larger sample size including patients with equal proportion of poor metabolizers to non-poor metabolizers and with more patients less than 6 years old in order to further evaluate the reason for the smaller C_{max} for cycloguanil obtained in this study.

VOL. 1.31

TITLE: Population Pharmacokinetics of Atovaquone in *Acute P. Falciparum* Malaria Patients. (Report BLVS/96/0003)

OBJECTIVES:

- To describe the pharmacokinetics of atovaquone in patients with *acute P. falciparum* malaria
- To assess the effect of patient covariates (*e.g.*, weight, age and gender) and concomitant therapy with other anti malarial agents on the pharmacokinetics of atovaquone
- To describe the magnitudes of interpatient variability and residual variability in the pharmacokinetics of atovaquone

METHODOLOGY:

Data from 467 pediatric and adult patients enrolled in 6 Phase II/III efficacy and safety trials (005, 120, 123, 131, 134, and 135) for the treatment of acute *P. falciparum* malaria were pooled and subjected to non-linear mixed effect modeling analysis using the software program NONMEM.

NUMBER OF PATIENTS:

Four hundred and sixty-seven (467) pediatric and adult patients. The population consisted of 204 Blacks, 208 Orientals and 55 Malays of whom 371 were males and 96 females. Most patients received combined therapy with atovaquone and proguanil (n=391) and in study 005 some patients received atovaquone alone (n=27) or concomitantly with pyrimethamine (n=25) or tetracycline (n=24). Age ranged from 3 to 65 years (mean = 22.7 years) and weight from 11 to 110 kg (mean = 46.7 kg).

DURATION OF TREATMENT:

Data included in the analyses from study 005 were from Thai males who received one of the following dosing regimens:

- 750 mg atovaquone q8h x 4 doses;
- 750 mg atovaquone q8h x 21 doses;
- 750 mg atovaquone q8h x 4 doses and 250 mg tetracycline qid x 7 days;
- 750 mg atovaquone q8h x 4 doses and 200 mg proguanil qd x 7 days;
- 500 mg atovaquone bid x 3 days and 200 mg proguanil bid x 3 days;
- 500 mg atovaquone bid x 3 doses and 200 mg proguanil bid x 3 days;
- 1000 mg atovaquone qd x 3 days and 25 mg pyrimethamine qd x 3 days;

- 1000 mg atovaquone qd x 3 days and 400 mg proguanil qd x 3 days;
- 500 mg atovaquone bid x 5 days and 200 mg proguanil bid x 5 days;

In all other studies, patients weighing more than 40 kg received 1000 mg atovaquone and 400 mg proguanil once daily for 3 days. The respective doses for patients weighing 11-20 kg, 21-30 kg, and 31-40 kg were 250+100 mg , 500+200 mg, and 750+300 mg. In all studies, the drugs were given approximately 45 minutes after ingestion of liquid nourishment, usually consisting of Ovaltine, soy milk, or fruit drink.

DIAGNOSIS AND KEY INCLUSION CRITERIA:
Male or female patients with uncomplicated falciparum malaria with acute manifestation (e.g. fever) and parasitemia between 1,000 and 200,000 parasites/μL.

PHARMACOKINETIC AND STATISTICAL ANALYSES:
Atovaquone plasma concentration-time profiles were fitted to a one compartment open model with first-order absorption and elimination. The combined bioavailability of the 750 and 1000 mg doses, relative to 250 and 500 mg doses, was estimated. The effects of the covariates body weight, age, race, gender, and concomitant therapy with proguanil, pyrimethamine or tetracycline on apparent oral clearance and apparent volume of distribution, as the primary pharmacokinetic parameters, were evaluated.

SUMMARY OF RESULTS:
After the incorporation of bioavailability into the pharmacokinetic model, the only statistically significant effects were those of weight, race (Orientals and Malays) and tetracycline on oral clearance and of weight, race (Malays only) and pyrimethamine on volume of distribution. There were no effects of age, gender, proguanil, and pyrimethamine on clearance and of Oriental race, age, gender, proguanil and tetracycline on volume.

The final population estimate of relative bioavailability for the 750 and 1000 mg doses, compared with 250 and 500 mg doses, was 75%. Hence, atovaquone plasma concentrations for the 750 and 1000 mg doses are 13 and 50%, respectively, higher than for a 500 mg doses which may be important clinically. Atovaquone oral clearance showed a 0.394 power relationship with weight, predicting a 31% increase in apparent oral clearance of an 80 kg patient relative to a 40 kg patient. For a typical 70 kg patient, population oral clearance is 2.74 L/h in Blacks and is 165% (7.26 L/h) and 80% (4.93 L/h) higher in Orientals and Malays, respectively. In Orientals, atovaquone

CL/F in patients receiving atovaquone and tetracycline concomitantly was 68% higher than that in patients receiving atovaquone alone or concurrently with either proguanil or pyrimethamine.
Volume of distribution showed a 0.931 power relationship with weight, predicting a 91% increase in V_z/F for an 80 kg patient relative to a 40 kg patient. The population estimate of V_z/F for a typical 70 kg patient is similar for Blacks and Orientals (497 L) but is 32% larger in Malays (657 L). Also, V_z/F is 33% smaller due to the effect of pyrimethamine co-administration. Because CL/F and V_z/F showed a 0.394 and 0.931 power relationship, respectively, with weight, elimination half-life showed a 0.537 power relationship with weight (predicting a 45% increase in half-life of an 80 kg patient relative to a 40 kg patient). A typical 70 kg Black, Oriental and Malay patient would have a half-life of 125, 47 and 92 h, respectively.
The final magnitudes of interpatient variability in absorption rate constant, CL/F and V_z/F were 90%, 65% and 55%, respectively.

SPONSOR CONCLUSIONS:

- The final population pharmacokinetic parameter estimates for oral clearance (2.47 L/h), apparent volume of distribution (497 L) and relative bioavailability for the 750 and 1000 mg doses of atovaquone (75%), in Black patients were generally in good agreement with findings from studies in healthy Caucasian subjects.
- Atovaquone plasma concentrations for the 750 and 1000 mg doses are 13 and 50%, respectively, higher than for a 500 mg dose.
- Oral clearance and volume of distribution were related to weight to the power 0.394 and 0.931, respectively. Consequently, elimination half-life showed a 0.537 power relationship with body weight.
- Atovaquone oral clearance in Orientals and Malays was 165% and 80%, respectively, higher than in Blacks and 68% higher in patients co-administered with tetracycline. Thus, plasma concentrations are predicted to be 40% lower in patients co-administered with tetracycline.
- Volume of distribution was similar in Blacks and Orientals but 32% larger in Malays and 33% smaller in Patients co-administered with pyrimethamine.
- There were no additional significant effects of age, gender, proguanil, and pyrimethamine on CL/F.
- There were no additional significant effects of Oriental race, age, gender, proguanil, and tetracycline on V_z/F.

- Plasma concentrations of atovaquone in cured and recrudesced patients receiving the same dosing regimen are predicted to be similar.
- The final magnitude of interpatient variability in oral clearance and volume of distribution were moderate at 65 and 55%, respectively.

REVIEWER CONCLUSIONS:
The reviewer is in agreement with the sponsor conclusions.

VOL. 1.32

TITLE: Population Pharmacokinetics of Proguanil in Acute *P. falciparum* Malaria Patients. (Report BLVS/96/0004/01)

OBJECTIVES:

The objectives of these analyses were:

- To describe the pharmacokinetics of proguanil in patients with acute *P. falciparum* malaria
- To assess the effect of patient covariates (*e.g.*, weight, race, age and gender) on the pharmacokinetics of proguanil
- To describe the magnitudes of interpatient and residual variability in the pharmacokinetics of proguanil

METHODOLOGY:

Data from 370 pediatric and adult patients enrolled in 6 Phase II/III efficacy and safety trials (005, 120, 123, 131, 134 and 135) for the treatment of acute *P. falciparum* malaria were pooled and subjected to non-linear mixed effect modeling analysis using the software program NONMEM.

NUMBER OF PATIENTS:

Three hundred and seventy (370) child and adult patients. The population consisted of 203 Blacks, 112 Orientals and 55 Malays of whom 274 were males and 96 females. All patients included in the population pharmacokinetic analysis received combination therapy with proguanil and atovaquone. Age ranged from 3 to 65 years (mean = 22.0 years) and weight from 11 to 110 kg (mean 44.7 kg).

DURATION OF TREATMENT:

Data included in the analyses from study 005 were from male Thai patients who received one of the following dosing regimens:

- 750 mg atovaquone q8h x 4 doses and 200 mg proguanil qd x 7 days.
- 500 mg atovaquone bid x 3 days and 200 mg proguanil bid x 3 days.
- 500 mg atovaquone bid x 3 doses and 200 mg proguanil bid x 3 days.
- 1000 mg atovaquone qd x 3 days and 400 mg proguanil qd x 3 days.
- 500 mg atovaquone bid x 5 days and 200 mg proguanil bid x 5 days.

In all three studies, patients were co-administered atovaquone and proguanil once daily for 3 days according to body weight as outlined below:

Body Weigh (kg)	Atovaquone Dose (mg)	Proguanil Dose (mg)
11-20	250	100
21-30	500	200
31-40	750	300
>40	1000	400

In all studies, the drugs were given approximately 45 minutes after ingestion of liquid nourishment, usually consisting of Ovaltine, soy milk, or fruit drink.

DIAGNOSIS AND KEY INCLUSION CRITERIA:
Male and female patients with uncomplicated *P. falciparum* malaria with acute manifestation (*e.g.* fever) and parasitemia between 1,000 and 200,000 parasites/μL.

PHARMACOKINETIC AND STATISTICAL ANALYSES:
Proguanil plasma concentration-time profiles were fitted to a one compartment open model with first-order absorption and elimination. The effects of the covariates body weight, age, race, gender, dose, and of proguanil to cycloguanil metabolism classification (i.e., 'poor' vs 'extensive' metabolizers) on oral clearance and weight and age on apparent volume of distribution were evaluated.

RESULTS:
Proguanil oral clearance showed a 0.786 power relationship with body weight and it was 13% higher in Orientals than in Blacks and Malays. Also, oral clearance was 17.2% lower in 'poor' than 'extensive' metabolizers. Apparent volume of distribution showed 0.879 power relationship with body weight and was 33% higher for patients > 15 years of age than younger children. The final magnitudes of interpatient variability in CL/F and V/F were 22.5% and 17.0%, respectively. There were no effects of age, dose and gender on oral clearance. Following is a summary table of the final parameter estimates:

Parameter	Units	Estimated Value	95% CI	
			Lower	Upper
Oral Clearance	L/h	3.22	2.35	4.09
Power of weight of CL/F	-	0.786	0.713	0.859
Apparent volume of distribution	L	41.6	22.58	60.62
Power of weight on V/F	-	0.879	0.735	1.023
First-order absorption rate constant	1/h	0.513	0.406	0.620
Factor of Age>15 y on V/F	-	1.330	1.134	1.526
Factor for Race = Orientals on CL/F	-	1.130	1.059	1.201
Factor for 'poor' metabolizers on CL/F	-	0.828	0.774	0.882
CV for interpatient variability of CL/F	%	22.54	19.47	25.24
CV for interpatient variability of V/F	%	17.03	12.79	20.41
CV for residual variability when obs conc =0	%	92.57	88.20	96.75
CV for residual variability when time < 48 h	%	48.37	44.92	51.59
CV for residual variability in all other cases	%	29.70	26.00	32.98

SPONSOR CONCLUSIONS:

- The final population pharmacokinetic parameter estimates for oral clearance (62-74 L/h), apparent volume of distribution (1868 L) and elimination half-life (15.3-17.3 h) of proguanil in Black and Malay patients classified as 'extensive' metabolizers were generally in good agreement with findings from studies in healthy Caucasian subjects.
- Oral clearance and volume of distribution were related to weight to the power 0.786 and 0.879, respectively. Consequently, elimination half-life showed 0.093 power relationship with body weight.
- Proguanil oral clearance was similar in Blacks and Malays but 13% higher in Orientals and 17.2% lower in 'poor' than in 'extensive' metabolizers. Oral clearance was unaffected by gender and dose.
- In view of the 30-50% residual variability in plasma concentration of proguanil, the effects of Orientals and 'poor' metabolizers on oral clearance are unlikely to have clinical significance. Thus, dose recommendation of proguanil will be based on body weight only.
- Proguanil apparent volume of distribution in patients > 15 years of age was 33% larger than in younger children.
- The final magnitude of interpatient variability in oral clearance and apparent volume of distribution were relatively low at 22.5 and 17.0%, respectively.

REVIEWER CONCLUSIONS:

The reviewer concur with the conclusions made by the sponsor.

VOL. 1:25

TITLE: Report of a Randomized Study to Evaluate a Potential
Pharmacokinetic Interaction between Proguanil and Atovaquon
Adult Volunteers (Protocol No. 115-133)

INVESTIGATORS:

75015 PARIS

OBJECTIVES:
To assess the magnitude of a putative effect of atovaquone on t
pharmacokinetics of proguanil and to determine whether the
pharmacokinetics of atovaquone were affected by concomitant
administration of proguanil with both drugs administered for t
healthy adult volunteers.

STUDY DESIGN:
This was an open-label, randomized, 3-way cross-over study
healthy volunteers (9M, 9F) aged 18-55 years were enrolled.
received 400 mg proguanil, 1000 mg atovaquone and 1000 mg
400 proguanil. Each treatment was given once daily for 3 days
weeks wash-out period between each occasion. For assay of pr
cycloguanil and atovaquone, blood was sampled before dosing
intervals over 8 days when proguanil was given, and over 17 d
atovaquone was given. Drugs were administered after a standa
(breakfast).

NAME, BATCH NUMBER, DOSE AND MODE OF ADMIN

- Proguanil, batch number UP 346, 100 mg tablets, dose=40
daily for 3 days;
- Atovaquone, batch number 3A5017, 250 mg tablets, dose=
daily for 3 days;
- Combined treatment =100 mg proguanil + 250 mg atovaquo
batch number 4C5275, dose = 4 tablets once daily for 3 da

SAMPLING:
After proguanil dosing, blood samples for proguanil and cyclo
were collected before the first dosing on day 1 and pre-dose and
6,

8, 12, 16, 24, 32, 48, 72, 96, and 120 hours after the last dose on day 3. After atovaquone alone or atovaquone + proguanil in combination, blood samples were taken at the above sampling times and additional samples were collected at 144, 168, 240 and 336 hours for atovaquone, proguanil and cycloguanil assays.

PHARMACOKINETIC ANALYSIS:

All plasma data generated by the study were submitted for pharmacokinetic analysis in the Department of Clinical Pharmacology, Glaxo Wellcome France. Model independent plasma pharmacokinetic parameters for atovaquone and proguanil after oral dosing were determined using a PC pharmacokinetic package Siphar-dos version 4.0 b. For atovaquone and proguanil, AUC_{0-24}, $AUC_{0-\infty}$, C_{max}, V_z/f (proguanil only) and $t_{1/2}$ were $\log_e$-transformed prior to analysis using analysis of variance, allowing for effects due to sex, subjects within sex, period and treatment. For cycloguanil, the same analyses were performed for $AUC_{0-\infty}$, AUC_{0-24}, C_{max}, $t_{1/2}$ and the ratio $AUC_{CG\ 0-\infty}/AUC_{PG\ 0-\infty}$. The presence of a treatment by period interaction or crossover effect and error diagnostics were examined for each analysis. Estimates of the treatment effects (ratios) between combination and mono therapy were based on least square means and presented on the untransformed scale along with the associated 90% confidence interval. Tmax was analyzed on a pairwise basis using the Wilcoxon Signed Rank test, ignoring periods. Estimates of the treatment effects (differences) between combination and mono therapy were based on medians and presented with the associated 90% nonparametric confidence interval.

STATISTICAL METHODS:

Pharmacokinetic parameters for atovaquone, proguanil and cycloguanil were $\log_e$-transformed prior to analysis using analysis of variance, allowing for effects due to sex, subjects within sex, period and treatment. Estimates of the treatment effects (ratios) between combination and mono therapy were based on least square means and presented on the untransformed scale along with the associated 90% confidence intervals.

T_{max} was analyzed on a pairwise basis using the Wilcoxon Signed Rank test, ignoring periods. Estimates of the treatment effects (differences) between combination and mono therapy were based on medians and presented with the associated 90% nonparametric confidence intervals.

ANALYTICAL METHOD:

[redacted]

RESULTS:

Adverse Events

Atovaquone and proguanil were well tolerated during the study. Drug-related adverse events were reported by 7 (33%) subjects in the proguanil group, by 6 (33%) subjects in the atovaquone group, and by 11 (44%) subjects in the proguanil and atovaquone combined regimen group. The most frequently reported drug-related adverse events, reported by more than 10% of subjects, were:

- Proguanil group: abdominalgias (14%), epigastralgias (10%), cephalalgias (14%);
- Atovaquone and proguanil combined regiment group: nausea and vomiting (20%), diarrhea (12%).

No events were serious and all but one severe headache were of mild or moderate intensity.

No new or unexpected adverse events were identified with either treatment.

Pharmacokinetics

For the comparison of the two regimes, atovaquone alone versus atovaquone in combination with proguanil, the 90% confidence intervals for all atovaquone pharmacokinetic parameters fell with the range 79-125%.

For the comparison of the two regimens, proguanil in combination with atovaquone versus proguanil alone, the 90% confidence intervals for all proguanil pharmacokinetic parameters fell within the range 80-125%, except V_z/f.

For the comparison of the two regimes, proguanil alone versus proguanil in combination with atovaquone, the 90% confidence intervals for all cycloguanil pharmacokinetic parameters fell within the range 79-125%.

Exploratory statistical analysis showed no important gender effects on the pharmacokinetics of atovaquone, proguanil or cycloguanil.

Summary Results (Lsmeans) for Atovaquone Parameters

Parameters	Atovaquone alone	Atovaquone + Proguanil	Ratio (%)	90% C.I.
$AUC_{0-\infty}$(µg/mL.h)	549	510	92.9	78.8-109.5
AUC_{0-24}(µg/mL.h)	180	193	107.5	99.6-116.1
C_{max} (µg/mL)	10.52	11.54	109.7	102.2-117.7
$t_{1/2}$ (h)	57.1	59.0	103.4	96.1-111.2
T_{max} (h)[a]	3	3	0[b]	-0.5-0.5

[a]Median values
[b]T_{max} median difference (h)

Summary Results (Lsmeans) for Proguanil Parameters

Parameters	Proguanil alone	Proguanil + Atovaquone	Ratio (%)	90% C.I.
$AUC_{0-\infty}$(ng/mL.h)	6437	5998	93.2	84.1-103.2
AUC_{0-24}(ng/mL.h)	6296	5819	92.4	86.2-99.1
C_{max} (ng/mL)	547.6	509.4	93.0	87.1-99.3
V_z/f (L)	1226	1399	114.1	101.8-127.8
$t_{1/2}$ (h)	13.7	14.5	106.3	99.7-113.3
T_{max} (h)[a]	3	3	0[b]	0-1

[a]Median values
[b]T_{max} median difference (h)

Summary Results (Lsmeans) for Cycloguanil Parameters

Parameters	Proguanil alone	Proguanil + Atovaquone	Ratio (%)	90% C.I.
$AUC_{0-\infty}$(ng/mL.h)	1355	1203	88.8	79.3-99.4
AUC_{0-24}(ng/mL.h)	1297	1187	91.5	85.5-98.0
C_{max} (ng/mL)	82.1	79.2	96.5	92.1-101.0
$t_{1/2}$ (h)	11.1	11.8	105.6	93.0-119.9
AUC_{CG}/AUC_{PG}	0.22	0.21	94.1	85.9-103.1
T_{max} (h)[a]	6	6	-1[b]	-1-0

[a]Median values
[b]T_{max} median difference (h)

CONCLUSIONS:

- Atovaquone and proguanil, alone or in combination, were well tolerated in this study.
- The pharmacokinetics of atovaquone and proguanil and its metabolite, cycloguanil, were not modified when atovaquone and proguanil were given alone or in combination.
- Gender differences for the pharmacokinetics of atovaquone and proguanil are small.

REVIEWER CONCLUSIONS:

Gender differences conclusion is general and the reviewer feels that the differences seen may be related to the differences in weight between male and female patients. For example, female patients receive more drug on a mg/kg basis than male patients do. So that, if one normalize clearance to weight that difference may become negligible.

VOL. 1.33

TITLE

A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP STUDY TO EVALUATE THE SUPPRESSIVE PROPHYLACTIC ACTIVITY OF MALARONE® (ATOVAQUONE/PROGUANIL) IN VOLUNTEERS AT RISK OF DEVELOPING *P. FALCIPARUM* MALARIA IN ZAMBIA. (PHARMACOKINETICS ASPECTS) (PROTOCOL NO. MALB 3001)

OBJECTIVES

The specific objectives of this analysis were:

- to describe the pharmacokinetics of atovaquone and proguanil in the chemoprophylaxis of *P. falciparum* malaria and their relationship to efficacy and safety;
- to assess the effect of patient covariates (demographic, co-medication) on the pharmacokinetics of atovaquone and proguanil;
- to examine the steady state exposure to the major active metabolite, cycloguanil.

METHODOLOGY

Descriptive statistical analyses of steady state plasma concentrations (C_{min-ss}) at trough of atovaquone, proguanil and its active metabolite, cycloguanil were performed. A Non-Linear Mixed Effect parametric analysis (utilizing NONMEM) was also conducted using a previously validated population PK model developed for atovaquone and proguanil during treatment of patients with malaria.

SUBJECTS

Trough plasma samples were obtained from 100 subjects for atovaquone assessment and 95 subjects for proguanil and cycloguanil assessment. Age ranged from 18 to 64 years (mean = 32.5 years) and weight from 37 to 79 kg (mean = 58.5 kg).

TREATMENTS

This study was a double-blind, placebo-controlled, parallel group randomised trial conducted in a highly endemic area in Zambia. The study

consisted of three phases: radical curative treatment for 3 days (3 daily doses), followed immediately by chemosuppression for at least 10 weeks (see table below) and follow-up for-up to 4 weeks. The total duration of study was approximately 14 weeks. Study medication was taken within approximately 45 minutes after food.

Study Phase	Treatment Group	Daily Dosage	Dosing Period
Radical Cure	MALARONE[a]	4 tablets	3 days
Chemosuppression	MALARONE[a]	1 tablet	10 weeks
	Or	or	
	Placebo	1 tablet	

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

MEASUREMENTS

Pharmacokinetics and Statistical Analyses

Standard descriptive statistical analysis was performed on all three analytes and is graphically presented.

For the parametric analysis of the plasma data in the present study using NONMEM, the basic population PK models developed and published for atovaquone and proguanil were utilized. Due to lack of adequate sampling design, the absorption and volume of distribution rate constants and corresponding variances were fixed and only the oral clearance parameter and its variability were estimated.

RESULTS

Descriptive Statistics

The summary statistics of the average steady-state plasma concentrations of atovaquone, proguanil and cycloguanil as well as the ratio of proguanil to cycloguanil using pooled trough sampling times are shown in the table below:

Summary statistics of trough levels[a] of atovaquone, proguanil and cycloguanil

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

[a] Median trough sampling time 23 hours [b]SD Standard Deviation

The observed average $C_{(min-ss)}$ of atovaquone at trough (2.07 µg/mL) is consistent with the predicted plasma levels following parametric modeling of the trough data with the previously developed population PK model for atovaquone. Thus, the final estimate for CL/F of atovaquone was on average 4.71 L/h corresponding to a predicted average steady state concentrations of 2.07 µg/mL. Inter-subject variability in the Css of atovaquone was relatively low at 34.4% in this fairly homogenous group of adult Zambians. However, residual variability which represents a composite of model mis-specification, variability in sampling time and analytical method as well as intra-subject variability was high at 36.5% at the Css value of 2.07 µg/mL. No covariates (age, gender, body weight, lean body mass, body surface area or visit period) appeared to influence the steady state CL/F of atovaquone.

Final Estimates of Atovaquone Population Pharmacokinetic Parameters from the Final Optimal Model

				95% CI[a]	
Parameter	*Symbol*	*Units*	*Estimate*	*Lower*	*Upper*
Oral clearance (CL/F)	θ_1	L/h	4.71	4.26	5.16
Apparent volume of distribution (V/F)	θ_2	L/kg	7.98	Fixed	
First-order absorption rate constant (K_a)	θ_3	1/h	0.263	Fixed	
CV[b] for inter-subject variability in CL/F	CV	%	34.4	20.0	44.7
CV[b] for inter-subject variability in V/F	CV	%	48.6	Fixed	
CV[b] for inter-subject variability in K_a	CV	%	106.8	Fixed	
Residual variability	σ	(µg/mL)	0.737	0.579	1.14

[a] Confidence Interval
[b] Coefficient of Variation
Note that the basic model is also the final model since there were no influential covariates

At steady-state, plasma concentrations of proguanil were approximately 2.9-fold higher than cycloguanil plasma concentrations. The observed average Css plasma concentrations of proguanil are comparable to those obtained from fitting these plasma data in the previously validated population PK model which included age and weight as significant covariates in clearance and in which weight influenced the volume parameters. Thus, the proguanil CL/F showed a 0.718 power relationship with weight and was inversely related to age showing a -0.496 power relationship with age. No other covariates studied showed any influence in the CL/F of proguanil.

Final Estimates of Proguanil Population Pharmacokinetic Parameters from the Final Optimal Model

Parameter	*Symbol*	*Units*	*Estimate*	*95% CI[a]*	
				Lower	*Upper*
Oral clearance (CL/F)	θ_1	L/h	26.2	(-)1.8	54.2
Apparent volume of distribution (V/F)	θ_2	L/kg	36.2	Fixed	
First-order absorption rate constant (K_a)	θ_3	1/h	0.513	Fixed	
Power of body weight on V/F	θ_4	—	0.880	Fixed	
Power of body weight on CL/F	θ_5	—	0.718	0.453	0.983
Power of age on CL/F	θ_6	—	(-)0.496	(-)0.558	(-)0.367
CV[b] for inter-subject variability in CL/F	CV	%	11.0	(-)7.0	17.0
CV[b] for inter-subject variability in V/F	CV	%	17.3	Fixed	
Residual variability	σ	ng/mL	10.2	8.4	11.8

a Confidence Interval.
b Coefficient of Variation

The treatment failure in one of the two subjects with available plasma data cannot be explained on the basis of exposure to atovaquone, proguanil and cycloguanil and is unlikely to be related to the dosing regimen.

SPONSOR CONCLUSIONS

- Average steady-state concentrations (Css) of atovaquone at trough in the prophylactic treatment dosing regimen with MALARONE were 2.07 µg/mL with a 34% inter-subject variability in oral clearance.
- At steady-state, plasma concentrations of proguanil were approximately 2.9-fold higher than cycloguanil plasma concentrations. Proguanil oral clearance showed a 0.718 power relationship with weight and a -0.496 power relationship with age. The magnitude of inter-subject variability for oral clearance was relatively low at 11%.

REVIEWER CONCLUSIONS

The reviewer is in agreement with the sponsor conclusions.

VOL. 1.27-1.28

TITLE

A study to evaluate the bioequivalence of Malarone tablets with proguanil hydrochloride supplied by Weiders (reference) or Jacobus and a quarter-strength paediatric tablet. (Protocol No. MALB1002)

INVESTIGATOR

OBJECTIVES

The aims of this study were to determine the bioequivalence of three different formulations of Malarone tablets, a reference tablet containing proguanil hydrochloride supplied by a tablet with proguanil hydrochloride supplied by and a quarter-strength tablet intended for pediatric patients with proguanil hydrochloride supplied by

DESIGN

This was an open, randomised, three-way, crossover study with 3 weeks washout periods.

SETTING/STUDY DATES

This study was carried out at between 09 November 1996 and 16 January 1997.

SUBJECTS

Forty-three healthy, young, volunteers took part in the study. Subjects 1681 and 1690 withdrew from the study after the first dosing occasion and one subject was replaced.

TREATMENTS

On separate occasions, subjects received a single oral dose of 2xMalarone tablets containing 250mg atovaquone/100mg proguanil hydrochloride by (2x), 2xMalarone tablets containing 250mg atovaquone/100mg proguanil hydrochloride by (2x), or 8xMalarone tablets containing 62.5mg atovaquone/25mg proguanil

hydrochloride by [redacted] (8x [redacted], swallowed with 200mL of water. There was a wash-out interval of at least three weeks between dosing occasions.

MEASUREMENTS

Pharmacokinetics

Blood samples (7.5mL) were taken at the following times to provide plasma samples for the determination of plasma concentrations of atovaquone, proguanil and cycloguanil :pre-dose, 1, 2, 3, 4, 6, 8, 12, 16, 24, 32, 48, 72, 96, 120, 144, 168, 240* and 336* hours post-dose.

* = sample assayed for atovaquone only. On those occasions when atovaquone alone was analyzed, 5mL blood samples were taken.

Analytical: HPLC-UV

Parameter		Atovaquone	Proguanil	Cycloguanil
Limit of Quantification				
Linearity				
Specificity				
Intra-assay precision	(n=85)			
	(n=88)			
	(n=89)			
Cross Validation precision	(n=6)			
	(n=2)			
	(n=2)			
	(n=2)			
	(n=2)			
Intra-assay accuracy	(n=85)			
	(n=88)			
	(n=89)			
Cross Validation accuracy	(n=6)			
	(n=2)			
	(n=2)			
	(n=2)			
	(n=2)			

RESULTS

Pharmacokinetics

The results of the pharmacokinetic analysis of the plasma atovaquone and proguanil concentration-time data obtained following the three treatments are summarized below:

Atovaquone Results

Least squares estimates of the geometric mean pharmacokinetic parameter values and associated 95% confidence intervals (CI) are shown overleaf:

Parameter	Treatment	Geometric LS mean	95% CI
AUC_{∞} (µg.h/mL)	2x	288	271 – 307
	2x'	244	229 – 260
	8x'	376	353 – 400
C_{max} (µg/mL)	2x'	3.4	3.2 - 3.7
	2x'	3.3	3.0 - 3.5
	8x'	4.2	3.9 - 4.6
$t_{1/2}$ (h)	2x	76.1	72.3 - 80.1
	2x'	69.7	66.2 - 73.3
	8x'	71.6	68.0 - 75.3
*t_{max} (h)	2x'	3	2 – 32
	2x'	4	2 – 48
	8x'	4	2 – 32

AUC_{∞} is the area under the curve from zero to infinity; C_{max} is the maximum plasma concentration; t_{max} is the time to C_{max}; $t_{1/2}$ is the apparent terminal half-life.

* = median and range given for t_{max}.

The estimated treatment mean ratios and associated 90% CI and p-values are given below:

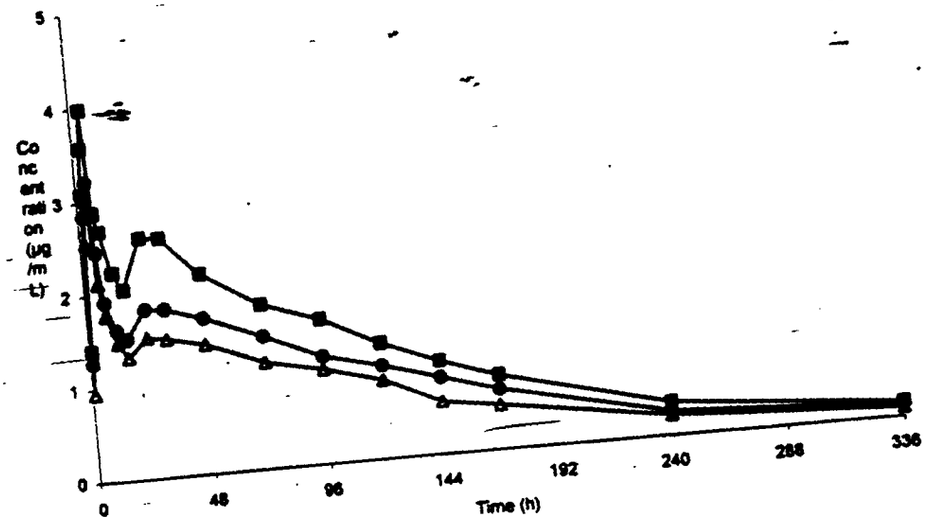
Parameter	Treatment comparison	Mean Ratio (%)	90% CI	p – value
AUC_{∞}	2x — 2x	85%	79% - 91%	0.0003
	8x' — 2x'	130%	121% - 140%	<0.0001
C_{max}	2x — 2x	96%	88% - 104%	0.4000
	8x' — 2x'	125%	114% - 136%	0.0001
*t_{max} (h)	2x — 2x	0.5	0.0 - 1.5	0.1972
	8x — 2x	1.0	0.5 - 1.5	0.0107

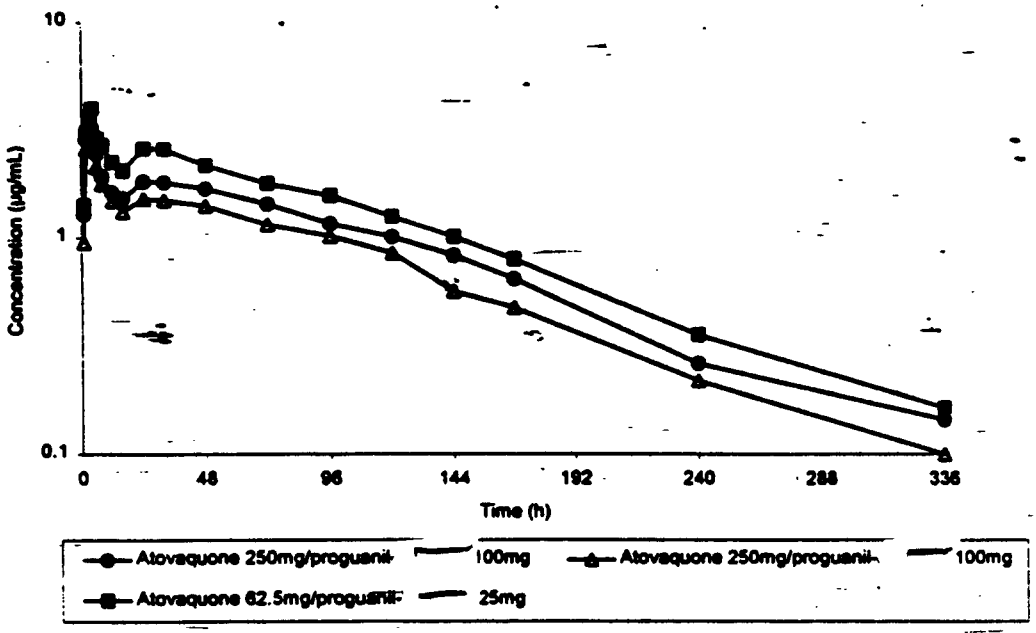
* = median difference and associated 90% CI for t_{max}.

The adult —— tablets were shown to be bioequivalent to the adult —— tablets with respect to the ratio and 90% CI for C_{max} values which were within the 0.80 to 1.25 bioequivalence criteria. Although the ratio for AUC_{∞} between the two formulations of 0.85 was within the acceptance criteria, the 90% CI of 0.79-0.91 very narrowly missed the lower limit of the accepted CI.

The pediatric strength tablet was not bioequivalent to the adult tablet since the point estimates and 90% CI for both C_{max} and AUC_{∞} were outside the bioequivalence acceptance range of 0.80 to 1.25. Increased surface area from the 8xPaediatric strength tablets versus the adult 2xAdult tablets may have promoted the absorption of atovaquone leading to the observed 25% increase in C_{max} and 30% increase in AUC_{∞}.

Comparative linear and semi-logarithmic plot of the median atovaquone plasma concentration-time profiles following administration of Malarone tablets with proguanil by —— and ·· —— and quarter-strength pediatric tablets




10
1
0.1
Concentration (µg/mL)
0
48
96
144
192
240
288
336
Time (h)
Atovaquone 250mg/proguanil 100mg
Atovaquone 250mg/proguanil 100mg
Atovaquone 62.5mg/proguanil 25mg

Proguanil Results

Least squares estimates of the geometric mean pharmacokinetic parameter values and associated 95% confidence intervals (CI) are given below:

Parameter	Treatment	Geometric LS mean	95% CI
AUC_{∞} (ng.h/mL)	2x	2065	1966 – 2168
	2x	2144	2042 – 2252
	8x	2147	2045 – 2255
C_{max} (ng/mL)	2x	177	169 – 186
	2x	171	164 – 179
	8x	167	160 – 175
$t_{1/2}$ (h)	2x	14.1	12.7 - 15.8
	2x	13.8	12.4 - 15.5
	8x	14.3	12.8 - 16.0
*t_{max} (h)	2x	3	1 – 6
	2x	3	1 – 6
	8x	3	2 – 4

* = median and range given for t_{max}.

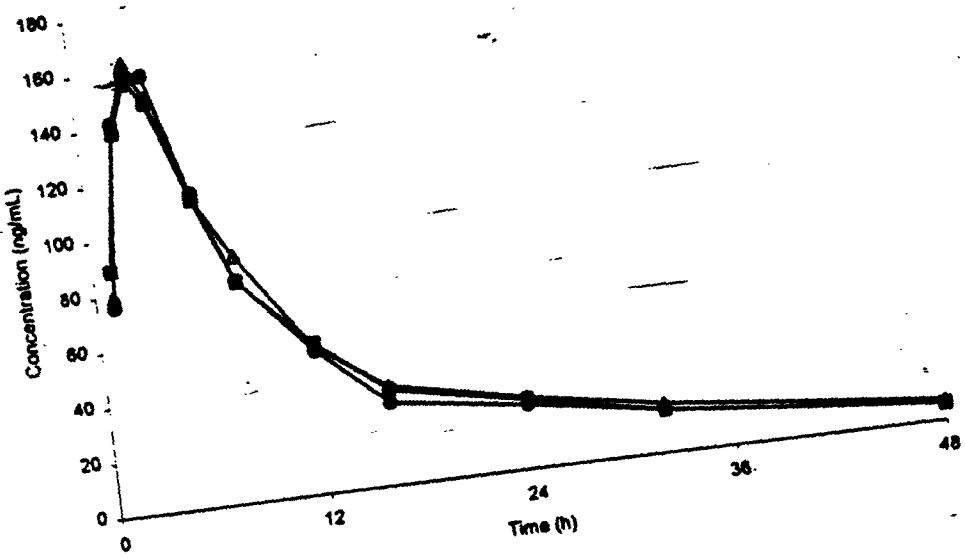
The estimated treatment mean ratios and associated 90% CI and p-values are given below:

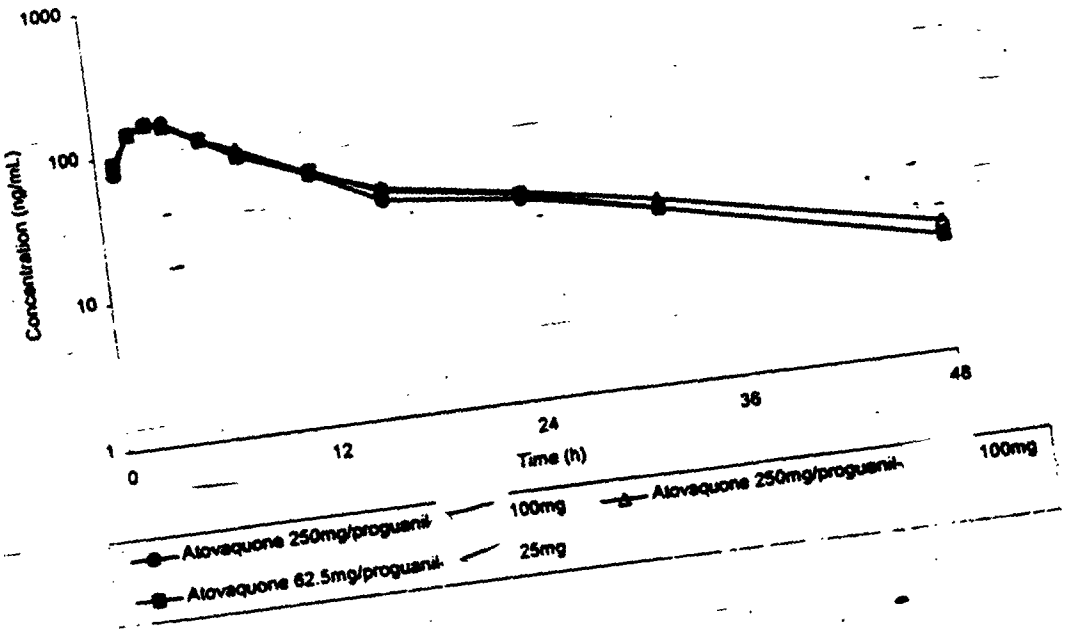
Parameter	Treatment comparison	Mean Ratio (%)	90% CI	p – value
AUC_{∞}	2x — 2x	104%	98% - 110%	0.2775
	8x — 2x	104%	98% - 110%	0.2604
C_{max}	2x — 2x	97%	92% - 102%	0.3201
	8x — 2x	94%	89% - 100%	0.0842
*t_{max} (h)	2x — 2x	0.0	-1.0 - 1.0	0.9261
	8x — 2x	0.0	-1.0 - 0.0	0.5808

* = median difference and associated 90% CI for t_{max}.

There were no statistically significant differences for either treatment comparison in any of the derived proguanil pharmacokinetic parameters.

Comparative linear and semi-logarithmic plot of the median proguanil plasma concentration-time profiles following administration of Malarone tablets with proguanil by ——— and ——— and quarter-strength pediatric tablets





SPONSOR CONCLUSIONS

Two Malarone tablets each containing 250mg atovaquone and 100mg proguanil by [redacted] were bioequivalent to two Malarone tablets each containing 250mg atovaquone and 100mg proguanil by [redacted] with respect to their proguanil bioavailability.

Two Malarone tablets containing 250mg atovaquone and 100mg proguanil by [redacted] were bioequivalent to two Malarone tablets each containing 250mg atovaquone and 100mg proguanil by [redacted] with respect to atovaquone Cmax and the 90% CI for AUC_∞ (0.79-0.91) of atovaquone only narrowly missed the lower limit of the bioequivalence accepted criteria of 0.80-1.25.

Eight Malarone tablets each containing 62.5mg atovaquone and 25mg proguanil (pediatric) by [redacted] were bioequivalent to two Malarone tablets each containing 250mg atovaquone and 100mg proguanil (adult) by [redacted] with respect to both Cmax and AUC_∞ of proguanil. However, the pediatric strength tablets were not bioequivalent to the adult tablets in terms of atovaquone bioavailability and showed, on average, a 25% and 30% increase in Cmax and AUC_∞, respectively.

REVIEWER CONCLUSIONS

- Fasted bioequivalency study
- The batch size of the FS-W is [redacted] and of FS-J is [redacted] tablets. Whereas, the batch size of QS-W is [redacted] and of QS-J is [redacted] tablets. The differences in the batch sizes of these formulation may have an impact on the result observed.
- The dissolution profile comparing these formulation are presented under section VIII. Formulation.

VOL. 1.29-1.30

TITLE

A study to evaluate the bioequivalence of low-strength pediatric Malarone tablets with proguanil hydrochloride supplied by [redacted] (reference) and [redacted] (Protocol No. MALB1004)

INVESTIGATOR

[redacted]

OBJECTIVES

The objective of this study was to demonstrate the bioequivalence between the low-strength Malarone tablet with proguanil hydrochloride supplied by [redacted] and the reference low-strength Malarone tablet with proguanil hydrochloride supplied by [redacted]

DESIGN

This was an open, randomised, two-way, cross-over study with 3 weeks washout period between dosing.

SETTING/STUDY DATES

This study was carried out at [redacted] between 23 July 1997 and 03 October 1997.

SUBJECTS

Thirty healthy, young, volunteers completed the study. Subjects 1814 and 1823 withdrew from the study (not drug related) after the first dosing occasion and were replaced.

TREATMENTS

On separate occasions, subjects received a single oral dose of 8xMalarone tablets containing 62.5mg atovaquone and 25mg proguanil hydrochloride supplied by [redacted] (8x [redacted], or 8xMalarone tablets containing 62.5mg atovaquone and 25mg proguanil hydrochloride supplied by [redacted] (8x [redacted]. The tablets were swallowed with 200mL of water. There was a wash-out interval of three weeks between dosing occasions.

A total of 30 subjects were required to demonstrate bioequivalence between low-strength MALARONE made with —— proguanil and low-strength MALARONE made with —— proguanil. Bioequivalence would be declared if the 90% confidence intervals for the treatment ratio fell between 0.8 and 1.25 for both C_{max} and AUC_{∞}. This was based on at least 80% power, a 5% level of significance, and an estimated standard deviation of 0.2344 µg/mL for the more variable parameter, log transformed C_{max} of atovaquone, from a previous study.

MEASUREMENTS

Pharmacokinetics

Blood samples (7.5mL) were taken at the following times to provide plasma samples for the determination of plasma concentrations of atovaquone, proguanil and cycloguanil :pre-dose, 1, 2, 3, 4, 6, 8, 12, 16, 24, 32, 48, 72, 96, 120, 144, 168, 240* and 336* hours post-dose.

* = sample assayed for atovaquone only. On those occasions when atovaquone alone was analyzed, 5mL blood samples were taken.

RESULTS

Pharmacokinetics

The results of the pharmacokinetic and statistical analysis of the plasma atovaquone and proguanil concentration-time data obtained following the two treatments are summarized below. Pharmacokinetic and statistical evaluation of cycloguanil, the main metabolite of proguanil, after administration of both Malarone formulations are also presented.

Atovaquone Results

Estimates of the geometric mean pharmacokinetic parameter values and associated 95% confidence intervals (CI) are shown overleaf:

Parameter	Treatment	N	Geometric mean	95% CI
AUC_∞ ... (µg.h/mL)	8x [redacted]	29	214	180 - 255
	8x [redacted]	28	165	145 - 188
AUC_L (µg.h/mL)	8x [redacted]	30	200	170 - 236
	8x [redacted]	30	154	134 - 178
C_{max} (µg/mL)	8x [redacted]	30	1.90	1.73 - 2.08
	8x [redacted]	30	1.78	1.58 - 2.02
$t_{1/2}$ (h)	8x [redacted]	29	67.6	58.1 - 78.6
	8x [redacted]	28	66.6	58.0 - 76.5
*t_{max} (h)	8x [redacted]	30	4.00	2.00- 48.1
	8x [redacted]	30	4.00	2.00 - 72.5

AUC_∞ is the area under the curve from zero to infinity; AUC_L is the area under the curve from zero to last quantifiable sampling time, C_{max} is the maximum observed plasma concentration; t_{max} is the first time to C_{max}; $t_{1/2}$ is the apparent terminal half-life.
* = median and range given for t_{max}.

The estimated treatment mean ratios and associated 90% CI and p-values are given below:

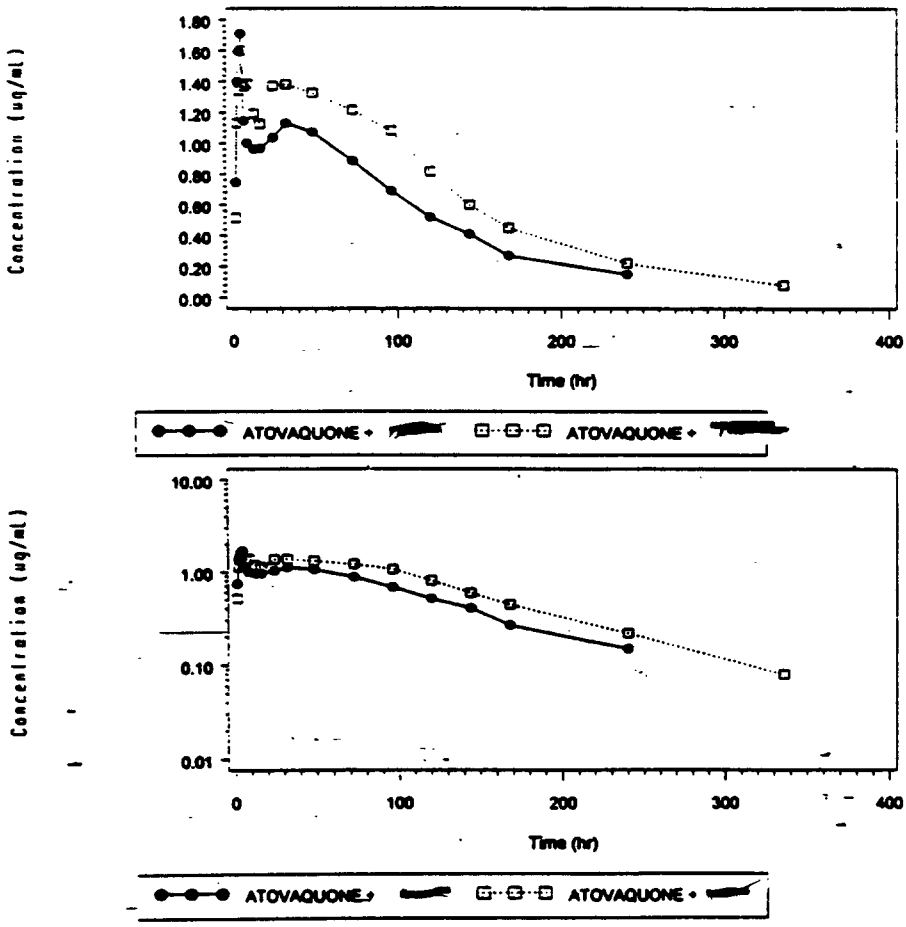
Parameter	Treatment comparison	Mean Ratio (%)	90% CI	p - value
AUC_∞ #	8x [redacted] 8x [redacted]	79%	71% - 88%	0.001
C_{max} #	8x [redacted] 8x [redacted]	94%	85% - 104%	0.292
*t_{max} (h)	8x [redacted] -8x [redacted]	-1.50	-13.0 - 0.00	0.080

* = median difference and associated 90% CI for t_{max}. # = Primary parameters

The ratio and 90% CI for C_{max} values were within the 80% to 125% bioequivalence criteria. However, the ratio for AUC_∞ between the two formulations of 79% missed the bioequivalence acceptance criteria of 80% to 125%. Hence, the [redacted] tablets are not bioequivalent to the [redacted] tablets with respect to the extent of absorption of atovaquone.

Comparative linear and semi-logarithmic plot of the median atovaquone plasma concentration-time profiles following administration of quarter-strength Malarone tablets with proguanil by [redacted] and [redacted]

MALB1004
Atovaquone Plasma Concentration Versus Time
- Median



ATOVAQUONE + JAC — 8 Malarone tables each containing 62.5 mg atovaquone and 25 mg proguanil HCL supplied by [redacted]

ATOVAQUONE + WEI — 8 Malarone tables each containing 62.5 mg atovaquone and 25 mg proguanil HCL supplied by [redacted]

Proguanil Results

Estimates of the geometric mean pharmacokinetic parameter values and associated 95% confidence intervals (CI) are given below:

Parameter	Treatment	N	Geometric mean	95% CI
AUC_{∞} (ng.h/mL)	8x [redacted]	28	2343	2070 - 2653
	8x [redacted]	29	2226	1956 - 2534
AUC_L (ng.h/mL)	8x [redacted]	31	1939	1679 - 2239
	8x [redacted]	31	1955	1710 - 2235
C_{max} (ng/mL)	8x [redacted]	31	155	141 - 171
	8x [redacted]	31	165	150 - 180
$t_{1/2}$ (h)	8x [redacted]	28	16.2	14.2 - 18.4
	8x [redacted]	29	15.6	13.7 - 17.7
*t_{max} (h)	8x [redacted]	31	3.00	2.00 - 6.00
	8x [redacted]	31	3.00	1.00 - 6.00

AUC_{∞} is the area under the curve from zero to infinity; AUC_L is the area under the curve from zero to last quantifiable sampling time, C_{max} is the maximum observed plasma concentration; t_{max} is the first time to C_{max}; $t_{1/2}$ is the apparent terminal half-life.

* = median and range given for t_{max}.

The estimated treatment mean ratios and associated 90% CI and p-values are given below:

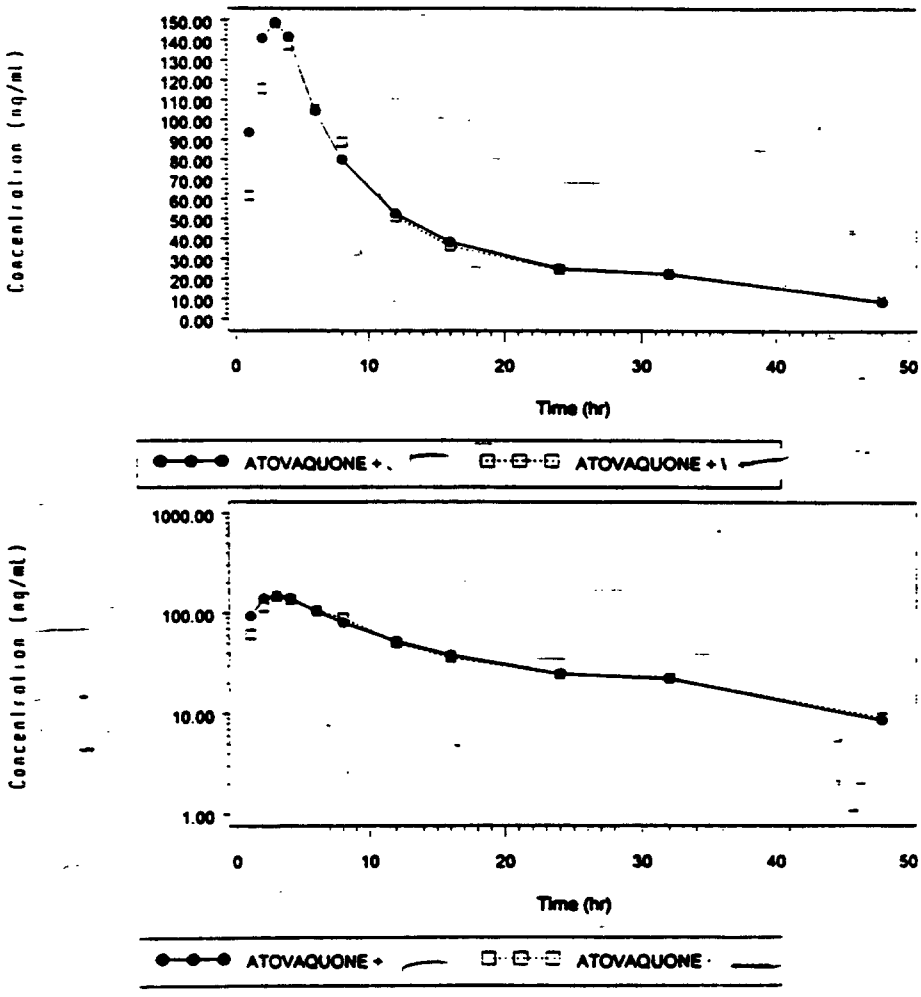
Parameter	Treatment comparison	Mean Ratio (%)	90% CI	p - value
AUC_{∞} #	8x [redacted] 8x [redacted]	97%	92% - 103%	0.452
C_{max} #	8x [redacted] 8x' [redacted]	106%	100% - 113%	0.100
*t_{max} (h)	8x' [redacted] 8x [redacted]	0.00	-0.50 - 0.00	0.285

* = median difference and associated 90% CI for t_{max}. # = Primary parameters

The 8x' [redacted] tablets were bioequivalent to 8x [redacted] with respect to the rate and extent of availability of proguanil since both C_{max} and AUC_{∞}, were within the acceptance bioequivalence criteria of 80 to 125%. In addition, there was no evidence for a difference in the observed t_{max} between the two malarone formulations since the point estimate was 0.00.

Comparative linear and semi-logarithmic plot of the median proguanil plasma concentration-time profiles following administration of quarter-strength Malarone tablets with proguanil by and

MALB1004
Proguanil Plasma Concentration versus Time
Median



ATOVAQUONE + 8 Malarone tables each containing 62.5 mg atovaquone and 25 mg proguanil HCL supplied by

ATOVAQUONE + 8 Malarone tables each containing 62.5 mg atovaquone and 25 mg proguanil HCL supplied by

Cycloguanil Results

Estimates of the geometric mean pharmacokinetic parameter values and associated 95% confidence intervals (CI) are given below:

Parameter	Treatment	N	Geometric mean	95% CI
AUC_∞ (ng.h/mL)	8x [redacted]	29	975	820 - 1160
	8x [redacted]	30	979	828 - 1157
AUC_L (ng.h/mL)	8x [redacted]	31	819	654 - 1025
	8x [redacted]	31	813	651 - 1016
C_{max} (ng/mL)	8x [redacted]	31	66.4	53.9 - 81.9
	8x [redacted]	31	68.2	55.2 - 84.2
$t_{1/2}$ (h)	8x [redacted]	29	10.2	8.70 - 11.9
	8x [redacted]	30	9.50	8.30 - 10.8
*t_{max} (h)	8x [redacted]	31	6.00	4.00 - 8.00
	8x [redacted]	31	6.00	3.00 - 8.00

AUC_∞ is the area under the curve from zero to infinity; AUC_L is the area under the curve from zero to last quantifiable sampling time, C_{max} is the maximum observed plasma concentration; t_{max} is the time to C_{max}; $t_{1/2}$ is the apparent terminal half-life.

* = median and range given for t_{max}.

The estimated treatment mean ratios and associated 90% CI and p-values are given below:

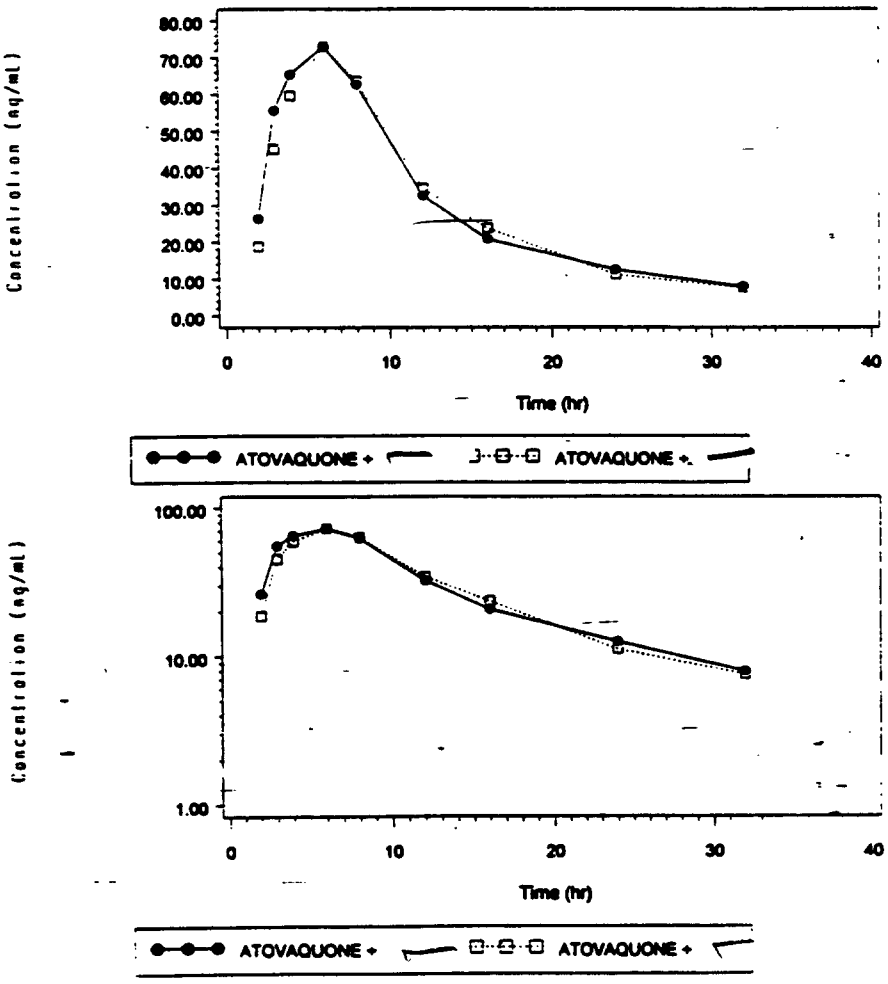
Parameter	Treatment comparison	Mean Ratio (%)	90% CI	p - value
AUC_∞	8x [redacted] 8x [redacted]	99%	93% - 105%	0.841
C_{max}	8x [redacted] 8x [redacted]	103%	98% - 107%	0.334
*t_{max} (h)	8x [redacted] -8x [redacted]	0.00	0.00 - 0.00	0.904

* = median difference and associated 90% CI for t_{max}. # = Primary parameters

The 8x [redacted] tablets were bioequivalent to 8x [redacted] with respect to the formation of the active metabolite, cycloguanil from proguanil, since both C_{max} and AUC_∞, were within the acceptance bioequivalence criteria of 80 to 125%. In addition, there was no difference in the observed t_{max} between the two malarone formulations since the point estimate was 0.00.

Comparative linear and semi-logarithmic plot of the median cycloguanil plasma concentration-time profiles following administration of quarter-strength Malarone tablets with proguanil by — and —

MALB1004
Cycloguanil Plasma Concentration Versus Time
- Median



ATOVAQUONE + — 8 Malarone tables each containing 62.5 mg atovaquone and 25 mg proguanil HCL supplied by —

ATOVAQUONE + — 8 Malarone tables each containing 62.5 mg atovaquone and 25 mg proguanil HCL supplied by —

SPONSOR CONCLUSIONS

Eight Malarone tablets each containing 62.5mg atovaquone and 25mg proguanil (pediatric) by [redacted] were bioequivalent to eight Malarone tablets each containing 62.5mg atovaquone and 25mg proguanil by [redacted] with respect to both C_{max} and AUC_{∞} of proguanil.

Eight Malarone tablets containing 62.5mg atovaquone and 25mg proguanil by [redacted] were bioequivalent to eight Malarone tablets each containing 62.5mg atovaquone and 25mg proguanil by [redacted] with respect to the rate of absorption of atovaquone. The point estimate and 90% CI for C_{max} were within the 80-125% range and there was no evidence for a difference in median t_{max} between the two formulations. However, the two formulations were not bioequivalent in terms of extent of availability of atovaquone based on AUC_{∞}. Compared to the [redacted] the [redacted] formulation was, on average, 21% less bioavailable (90% CI 71% to 88%).

REVIEWER CONCLUSIONS

- Fasted bioequivalency study
- The reviewer is in agreement with sponsor conclusions
- Although the geometric mean of T_{max} showed similar results between QS-W and QS-J formulation, the spread of data showed a wide range.
- The batch size of QS-W is [redacted] and of QS-J is [redacted] tablets. The differences in the batch sizes of these formulation is not large enough to impact the result obtained.
- The dissolution profile comparing these formulation are presented under section VIII. Formulation.
- The sponsor is proposing a manufacturing site different from the site that was used in these bioequivalency study. The proposed manufacturing site is in Canada and how formulations manufactured in Canada will compare to formulations used in clinical studies or to formulations used in England is not yet determined.

VOL 1.33

Title of Study:

A randomised, double-blind, placebo-controlled, parallel group study to evaluate the suppressive prophylactic activity of Malarone (Atovaquone/Proguanil) in children at risk of developing *Plasmodium falciparum* Malaria. (Protocol No. MALB3003)

(Population Pharmacokinetics Aspects)

Objectives:

The objectives of the analysis were:

- to describe the pharmacokinetics of atovaquone and proguanil from sparse sampling (trough concentrations) obtained during a phase III clinical trial in children at a risk of developing *P. falciparum* malaria
- To identify the influence of subject covariates on atovaquone and proguanil pharmacokinetics.

Methodology:

Data from up to 121 children at a risk of developing *P. falciparum* malaria enrolled in a Phase III efficacy and safety trials (Protocol No. MALB3003) were pooled and subjected to non-linear mixed effect modelling analysis using the software program NONMEM.

Number of Patients:

One hundred and twenty-one (121) Black children. The population consisted of 63 males and 58 females. All children included in the population pharmacokinetic analysis received Malarone®, a combined therapy with proguanil (PG) and atovaquone (ATV). Age, weight, height, lean body mass and body surface area ranged from 5 to 15 years (mean=9.48 years), 14 to 60 kg (mean=29.5 kg), 102 to 174 cm (mean = 133.9 cm), 17.5 to 53.3 kg (mean=31.3 kg) and 0.66 to 1.67 m^2 (mean=1.05 m^2), respectively.

Duration of Treatment:

Data included in the analyses were from children who initially received a radical curative dose of Malarone® given once daily for three days, after food as per the following table:

Stratum	*Weight (kg)*	*Daily Dosage- ATV/PG*	*Dosing Period*
Stratum 1	11 - 20	250 mg/100 mg once daily	3 days
Stratum 2	> 20 - 30	500 mg/200 mg once daily	3 days
Stratum 3	> 30 - 40	750 mg/300 mg once daily	3 days
Stratum 4	>40	1000 mg/400 mg once daily	3 days

Immediately, children were randomised to one of two treatment groups, within the four strata viz. Malarone® or placebo in the chemosuppression phase of the study. Children received their tablet(s) daily, within 45 minutes after food for at least 12 Weeks, under the supervision of the investigator or co-investigator as per the following table:

Stratum	*Weight (kg)*	*Treatment Group*	*Daily Dosage-ATV/PG*	*Dosing Period*
Stratum 1	11 - 20	Malarone®	62.5 mg/25 mg once daily (one ¼ strength Malarone® tablet)	at least 12 Weeks (84 days)
		OR	OR	
		placebo	1 tablet	
Stratum 2	>20 - 30	Malarone®	125 mg/50 mg once daily (two ¼ strength Malarone® tablet)	at least 12 Weeks (84 days)
		OR	OR	
		placebo	2 tablets	
Stratum 3	>30 - 40	Malarone®	187.5 mg/75 mg once daily (three ¼ strength Malarone® tablet)	at least 12 Weeks (84 days)
		OR	OR	
		placebo	3 tablets	
Stratum 4	>40	Malarone®	250 m/100 mg once daily (one full strength Malarone® tablet)	at least 12 Weeks (84 days)
		OR	OR	
		placebo	1 tablet	

Diagnosis and Key Inclusion Criteria:

The trial subjects were male and female children, aged ≥ 4 and ≤ 16 years, at risk of malaria infection but otherwise in good health.

Pharmacokinetic and Statistical Analyses:

A one compartment open model with first-order absorption and elimination was fitted to proguanil and atovaquone plasma concentration-time profiles at steady-state, using non-linear mixed effect modelling (using NONMEM software), with first-order (FO) estimation. Since only trough concentrations were collected in the study, the population parameter estimates of apparent volume of distribution (V/F), first-order absorption rate constant (K_a) and the respective inter-subject variances for both atovaquone and proguanil were fixed to those previously reported for the drug. For each drug, the effects of body weight, height, body surface area (BSA), lean body mass (LBM), age, and gender on steady-state oral clearance (CL/F) and any trend in steady-state CL/F between Weeks 6 and 12 were evaluated. In addition, the bioavailability of the 50, 75 and 100 mg doses of proguanil was examined relative to the 25 mg dose. For atovaquone, the bioavailability of the 125, 187.5 and 250 mg doses was examined relative to the 62.5 mg dose.

Summary of Demographic Characteristics for Children Included in the Population Analysis

	Age (years)	*Height (cm)*	*Lean Body Mass (kg)*	*Body Surface Area (m^2)*	*Weight (kg)*
Females					
Median	9.00	129.0	24.51	0.97	26.0
Mean	9.21	132.9	26.42	1.04	29.1
SD	3.13	17.8	6.49	0.27	11.8
%CV	34.0	13.4	24.6	26.0	40.5
Min	5.00	102.0	17.47	0.66	14.0
Max	15.00	162.0	39.62	1.6	56.0
N	58	58	58	58	58
Males					
Median	10.00	134.0	34.75	1.04	27.0
Mean	9.85	135.6	35.94	1.07	30.2
SD	2.84	17.4	7.08	0.25	10.9
%CV	28.8	12.8	19.7	23.4	36.1
Min	5.00	107.0	25.79	0.69	15.0
Max	15.00	174.0	53.29	1.67	60.0
N	63	63	63	63	63
All					
Median	9.00	133.0	31.44	0.99	26.0
Mean	9.48	133.9	31.25	1.05	29.5
SD	3.01	17.7	8.31	0.26	11.3
%CV	31.8	13.2	26.6	24.8	38.3
Min	5.00	102.0	17.47	0.66	14.0
Max	15.00	174.0	53.29	1.67	60.0
N	121[a]	121	121	121	121

[a]Of the 121 children, the database for proguanil included data from 111 subjects only

Summary of Results:

Summary Statistics for Observed Proguanil, Cycloguanil and Atovaquone Plasma Concentrations in Children from Study MALB3003 to evaluate the suppressive prophylactic activity of malarone

	Proguanil Hydrochloride Dose (mg)			
	25	*50*	*75*	*100*
Proguanil				
Mean (ng/mL)	13.1	16.2	23.3	21.7
Median (ng/mL)	9.3	13.5	20.4	18.9
SD	8.2	7.9	12	10.4
CV (%)	62.6	48.8	51.5	47.9
N	41	52	38	40
s.e.	1.3	1.1	1.9	1.6
Min				
Max				
Cycloguanil				
Mean (ng/mL)	7.9	8.1	10.3	9.4
Median (ng/mL)	6.3	7.5	8.4	8.8
SD	3.1	2.2	6.1	2.6
CV (%)	39	28	59	28
N	13	25	23	24
s.e.	0.9	0.4	1.3	0.5
Min				
Max				

	Atovaquone Dose (mg)			
	62.5	*125*	*187.5*	*250*
Mean (µg/mL)	2.52	3.28	3.98	2.84
Median (µg/mL)	2.34	2.95	3.91	2.52
SD	1.27	1.86	1.99	1.67
CV (%)	50	57	50	59
N	71	65	46	50
s.e.	0.15	0.23	0.29	0.24
Min				
Max				

PROGUANIL

Proguanil steady-state oral clearance showed a 0.772 power relationship with body weight. The final magnitude of inter-subject variability in CL/F was 6.9%. There were no significant effects of age, lean body mass, body surface area, height and gender on CL/F, and oral clearance on Weeks 6 and 12 was similar. The 25, 50, 75 and 100-mg doses were equally bioavailable. Following is a summary table of the final population parameter estimates:

Parameter	*Symbol*	*Units*	*Estimate*	*95% CI*	
				Lower	*Upper*
Oral clearance (CL/F)	θ_1	L/h	3.74	2.24	5.24
Apparent volume of distribution (V/F)	θ_2	L	36.2	Fixed	
First-order absorption rate constant (K_a)	θ_3	1/h	0.513	Fixed	
Power of weight on V/F	θ_4	—	0.880	Fixed	
Power of weight on CL/F	θ_5	—	0.772	0.655	0.889
CV for inter-subject variability in CL/F	ω_{CL}	%	6.9[a]	-11.9	15.4
CV for inter-subject variability in V/F	ω_V	%	17.3	Fixed	
Residual variability	σ	ng/mL	8.61	6.50	10.29

[a] Inter-subject variability in oral clearance was poorly estimated.

ATOVAQUONE

Atovaquone steady-state oral clearance was linearly related to body weight at 0.0559 L/h/kg. The final magnitude of inter-subject variability in CL/F was 23.7%. There were no significant effects of age, lean body mass, body surface area, height and gender on CL/F, and steady-state CL/F on Weeks 6 and 12 was similar. The 62.5, 125 and 187.5 mg doses were equally bioavailable whereas the relative bioavailability of the 250 mg tablet was 0.746. Following is a summary table of the final population parameter estimates:

Parameter	Symbol	Units	Estimate	95% CI	
				Lower	Upper
Oral clearance (CL/F)	θ_1	L/h/kg	0.0559	0.0511	0.0607
Apparent volume of distribution (V/F)	θ_2	L/kg	7.98	Fixed	
First-order absorption rate constant (K_a)	θ_3	1/h	0.263	Fixed	
Relative bioavailability for 250 mg dose	θ_4	—	0.746	0.603	0.889
CV for inter-subject variability in CL/F	ω_{CL}	%	23.7	13.5	30.6
CV for inter-subject variability in V/F	ω_V	%	48.6	Fixed	
CV for inter-subject variability in K_a	ω_{ka}	%	48.6	Fixed	
Residual variability	σ	µg/mL	1.49	1.26	1.69

Sponsor Conclusions

- The final population estimates for steady-state oral clearance of proguanil (51 L/h) and atovaquone (1.65 L/h) in black healthy children were generally in good agreement with findings from studies in black children with acute *P. falciparum* malaria.
- Oral clearance for proguanil was related to weight to the power 0.772 whereas CL/F for atovaquone was linearly related to weight.
- For both proguanil and atovaquone, steady-state oral clearance in black children was not significantly affected by age, gender, lean body mass, body surface area, height, and duration of treatment.
- The 25, 50, 75 and 100 mg doses of proguanil were equally bioavailable at steady-state. For atovaquone, the 250 mg dose (full-strength tablet) was less bioavailable than the 62.5, 125 and 187.5 mg dose (F=0.746).
- Median steady-state cycloguanil plasma concentrations ranged between 6.3 and 8.8 ng/mL across dosing strata.

Reviewer Conclusions

The reviewer is in agreement with sponsor conclusion.

13 pages redacted from this section of the approval package consisted of draft labeling

WITHHELD 6 PAGE(S)