Division of Special Pathogen and Immunologic Drug Products

Summary of Clinical Review of Studies Submitted in Response to a Pediatric Written Request

Application:	NDA 21-078/SE5-006
Applicant	GlaxoSmithKline One Franklin Plaza P.O. Box 7929 Philadelphia, Pennsylvania 19101
Drug names	
Chemical:	(atovaquone) trans-2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-napthoquinone (proguanil) 1-(4-chlorophenyl)-5-isopropyl biguanide hydrochloride
Established:	Atovaquone and Proguanil Hydrochloride tablets
Proprietary:	Malarone®
Route	Oral
Formulations	Malarone® pediatric tablets: atovaquone 62.5mg/proguanil 25mg Malarone® (adult) tablets: atovaquone 250mg/proguanil 100mg

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Background

Malarone® is a fixed combination antimalarial product containing atovaquone and proguanil which was approved in 2000 for the prophylaxis and treatment of malaria in adults and in pediatric patients weighing over 11 kilograms (kg). Atovaquone is a naphthoquinone and proguanil is a chloroguanide.

It is administered orally as either pediatric or adult strength tablets:

Malarone® pediatric tablets: atovaquone 62.5mg/proguanil 25mg
Malarone® (adult) tablets: atovaquone 250mg/proguanil 100mg

This submission was a response to the Pediatric Exclusivity Written Request issued in January, 2003. It consists of 3 trials in pediatric subjects and provides pharmacokinetic and clinical data. The additional indication being sought is the treatment of malaria in pediatric patients weighing between 5 and 11 kg.

Study **MAL 30013** was an open label randomized trial in Gabon comparing the safety and efficacy of Malarone® to amodiaquine in the treatment of acute uncomplicated *P. falciparum* malaria in pediatric patients weighing between 5 and 11 kg. One hundred patients were enrolled in each arm of the study. The dose of Malarone® to treat patients 5 to 8 kg was 2 pediatric strength tablets a day for three days, and for patients 9 to 11 kg was 3 pediatric tablets a day for three days. Patients were seen and had parasite smears performed on Day 1, 2, 3, 4, 8, and 28 - 29. The primary endpoint was the presence or absence of parasitemia at the last follow-up visit (Day 28 or 29).

Study **MAL 30015** was a double-blind placebo-controlled study in Gabon, evaluating the safety and efficacy of Malarone® in the prevention of *P. falciparum* malaria in pediatric patients weighing between 11 and 40 kg. Pediatric patients with acute *P. falciparum* malaria were initially treated an effective regimen and were then randomized to receive either Malarone® or placebo in the appropriate daily prophylactic dose based on weight. (see table). One hundred and sixty-five subjects were enrolled in each arm into 3 weight strata (55 in each stratum): 11-20 kg, 21-30 kg, and 31-40 kg. The chemoprophylaxis phase lasted for 12 weeks. There was a 4 week follow-up phase. The primary endpoint was the presence or absence parasitemia during prophylaxis. A secondary endpoint was to determine if Malarone® chemoprophylaxis had any effect on the immunologic response to oral typhoid and cholera vaccines.

Study **MAL 30012** was an international open label randomized trial to compare Malarone® to chloroquine/proguanil in the prevention of malaria in non-immune pediatric travelers weighing between 11 and 50 kg. Two hundred and thirty two subjects were enrolled at sites in Canada and Europe. All were traveling to malaria endemic areas for a maximum of 28 days. Appropriate chemoprophylactic regimens were used in both arms. Malarone® was begun 1 to 2 days prior to travel and continued for 7 days after travel in the doses listed in the table below. Follow-up occurred at 7 and 28 days after travel was completed. The primary endpoint was the assessment of any adverse events

during the travel plus 7 day period. Laboratory safety data was obtained at baseline and 4 week follow-up in less than 20% of enrollees.

Prophylaxis Doses of Malarone® based on Weight (in kg) used in MAL 30015 and MAL 30012

	Weight of Subject			
	11-20kg	21-30kg	31-40kg	>40kg
Malarone® dose (atovaquone mg/proguanil mg)	1 pediatric tablet daily (62.5/25)	2 pediatric tablets daily (125/50)	3 pediatric tablets daily (187.5/75)	1 full-strength tablet daily (250/100)

Efficacy

In study **MAL 30013,** Malarone® was superior to amodiaquine in the treatment of acute uncomplicated malaria due to *P. falciparum* in pediatric patients weighing from 5 to 11 kg. There were 5 Malarone® and 37 amodiaquine failures (see table below). The table below depicts the results by Sensitive/Resistant categories, as defined by the World Health Organization:

Sensitive:	Clearance of asexual parasitemia within 7 days of initiation of treatment, without subsequent recrudescence during the 28-day follow-up period.
RI:	Clearance of asexual parasitemia as in sensitive cases, followed by recrudescence within 28 days.
RII:	Marked reduction of asexual parasitemia, but no clearance during 7 days.
RIII:	No marked reduction of asexual parasitemia during the first 48 hours.

MAL 30013: 28-Day Cure Rate in Intent-to-treat Population (using WHO Criteria)

Response Grade	**Malarone®**	**Amodiaquine**
	N=100	**N=100**
WHO Categories		
Sensitive	87	42
Resistant		
RI	3 (2 new infections-by PCR)	31 (15 new infections by PCR)
RII	0	2
RIII	2	4
Unevaluable	8	21 (11 lost to followup)

Study **MAL 30015** showed that Malarone® was superior to placebo in the prevention of acute *P. falciparum* malaria in an endemic population in pediatric patients weighing greater than 11kg. There were 4 cases of parasitemia in the Malarone® arm, one breakthrough parasitemia during the prophylaxis period and 3 occurring 2 to 4 weeks after Malarone® dosing. There was no effect detected on the response to oral typhoid and cholera vaccines by prophylaxis with Malarone®.

MAL 30015: Success or Failure of Chemoprophylaxis in the Per-Protocol Population

	Malarone®	**Placebo**
Failure	1(<1%)	31(22%)
Success	149(99%)	113(78%)
Total Subjects	150	144

In study **MAL 30012** Malarone® compared favorably with chloroquine/proguanil in the prevention of acute malaria in non-immune pediatric patients; however this trial was too small to detect any significant difference between the two treatments. No subject in either arm became parasitemic.

Safety

Study **MAL 30013** showed that the safety of Malarone® in the treatment of acute uncomplicated malaria is similar to amodiaquine. Gastrointestinal complaints were the most common (6-7%) adverse event reported in the Malarone® arm and only one (persistent vomiting) was considered serious. The only other serious adverse event in the Malarone® arm was a 1 year old with a rapidly rising parasite count and low glucose level who experienced seizures within a few hours after the receipt of her first and only dose of Malarone®. It is unlikely that this event was related to Malarone® (see table below).

MAL 30013: Summary of Drug-Related Adverse Events Experienced between the First Dose of Study Drug and Day 8 by Frequency

	Malarone® N=100	**amodiaquine N=100**
Number with any drug-related adverse event	11	13
Diarrhea	6	7
Vomiting	2	2
Cough	1	3
Pruritus	1	1
Constipation	1	0
Decreased Appetite	0	1
Nausea	0	1

Adapted from Table 17 MAL 30013 of the applicant's submission

In study **MAL 30015**, adverse events occurring during chemoprophylaxis were reported by a similar percentage of Malarone® and placebo recipients (44% and 42%, respectively). The most frequently reported adverse events were headache, cough, fever and abdominal pain. Headache and cough were reported by 13% and 10%, respectively, for both treatment groups. Abdominal pain and vomiting were more common in the Malarone® group at 13% and 5%, respectively, in comparison to 8% and 3%. Fever was reported more commonly in the placebo group (13%) but only 5% of the Malarone® group. Routine laboratory data was obtained in less than 20% of enrollees.

Study **MAL 30012** compared Malarone® to chloroquine/proguanil in the prevention of malaria in non-immune subjects. The drug-related adverse events are tabulated below. Rare cases of blurred vision were reported in the Malarone® subjects.

MAL 30012: Drug-Related Treatment Emergent Adverse Events (% of subjects)

Adverse Event	**Malarone®**	**chloroquine/ proguanil**	**Malarone®**	**chloroquine/ proguanil**
	Travel + 7 days (n=110)	**Travel + 7D (n=111)**	**Travel+28 days (n=110)**	**Travel +28 days (n=111)**
Any Adverse Event	7	8	8	14
Abdominal pain	<1	4	2	7
Nausea	0	3	<1	7
Vomiting	<1	3	2	5
Diarrhea	3	2	4	3
Oral ulceration	2	2	2	2
Dreams	2	<1	2	<1
Lethargy	0	0	2	0

Adapted from Data Table 15 and 16 MAL30012 from the applicant's submission

Conclusions and Recommendations

1. The applicant submitted all the data requested in the Pediatric Written Request. Pediatric exclusivity was granted in August 2003.
2. The data support updating of the Malarone® package insert to include treatment recommendations for pediatric patients weighing between 5 and 11 kg. for the treatment of acute malaria due to *P. falciparum*.

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/s/

Renata Albrecht

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