

Briefing Package

Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research, FDA

NDA 22-268

**Coartem
(Artemether 20 mg/Lumefantrine 120 mg Tablets)**

Applicant: Novartis Pharmaceuticals Corporation

Anti-Infectives Advisory Committee Meeting

December 3, 2008

Proposed Indication: Treatment of malaria in patients of 5 kg body weight and above with acute, uncomplicated infections due to *Plasmodium falciparum* or mixed infections including *P. falciparum*

Proposed Dosing Regimen: A 3-day treatment schedule with a total of 6 doses is recommended and dosed based on body weight:
5 kg to < 15 kg: One tablet as an initial dose, 1 tablet again after 8 hours and then 1 tablet twice daily (morning and evening) for the following two days
15 kg to < 25 kg bodyweight: Two tablets as an initial dose, 2 tablets again after 8 hours and then 2 tablets twice daily (morning and evening) for the following two days
25 kg to < 35 kg bodyweight: Three tablets as an initial dose, 3 tablets again after 8 hours and then 3 tablets twice daily (morning and evening) for the following two days
35 kg bodyweight and above: Four tablets as a single initial dose, 4 tablets again after 8 hours and then 4 tablets twice daily (morning and evening) for the following two days

1	<i>Introduction</i>	6
1.1	Mechanism of Action.....	6
1.2	Activity In Vitro.....	6
1.3	Activity In Vivo	7
1.4	Drug Resistance	7
2	<i>General Review Issues</i>	8
2.1	Clinical Data Submitted.....	8
2.2	Combination Regimen	10
2.3	Four versus Six Dose Regimens	10
2.4	Populations Studied	11
2.5	Nature of the Studies.....	11
2.6	Comparison of Study Design to Draft Malaria Guidance Document.....	12
2.6.1	Entry Criteria	12
2.6.2	Endpoints	13
2.6.3	Analysis Populations.....	14
2.7	Mixed Infections	15
2.8	Parasitological Measurements	15
3	<i>Clinical Efficacy</i>	18
3.1	Factorial Design Studies to Evaluate the Components of the Fixed-Combination Drug (ABMO2 and A023)	18
3.1.1	Study Design.....	18
3.1.2	Demographics and Baseline Characteristics	19
3.1.3	Comparison of Results.....	20
3.1.4	Summary and Conclusions	24
3.2	Additional 4-dose Supportive Studies	24
3.3	Four-Dose Regimen Compared to 6-Dose Regimen, Study A025	26
3.3.1	Study Design.....	26
3.3.2	Demographic and Baseline Characteristics	27
3.3.3	Overall Efficacy Results	27
3.3.4	Timing of Parasite Clearance.....	30
3.3.5	Efficacy at 24 and 48 hours of Treatment.....	30
3.3.6	Late Treatment Failure (Recrudescence).....	30
3.3.7	Summary and Conclusions, Study A025	31
3.4	Studies with Comparator Arm, A026 and A028.....	31
3.4.1	Overall Efficacy Results	31
3.4.2	Efficacy Results in Adults and Children.....	32
3.4.3	Recrudescence.....	33
3.4.4	Summary and Conclusion, Studies A026 and A028.....	33
3.5	Study in Non-immune Adults, A2401	33
3.6	Studies in Pediatrics, Studies A2403 and B2303	35
3.6.1	Study A2403	35
3.6.2	Study B2303.....	37
3.6.3	Efficacy Summary	39

3.7	Additional Issues.....	39
3.7.1	Mixed Infections.....	39
3.7.2	Gametocyte Clearance.....	40
3.7.3	Pharmacokinetics.....	41
4	<i>Non-Clinical Safety</i>	45
4.1	Reproductive Toxicity.....	45
4.1.1	Fetal Exposure.....	45
4.2	Neurotoxicity.....	46
4.2.1	Beagle Dog Neurotoxicity Study Evaluations.....	47
4.2.2	Neurotoxicity Studies in Dogs: Conclusions.....	48
5	<i>Clinical Safety</i>	49
5.1	Safety Database.....	49
5.2	Disposition of Patients.....	50
5.3	Overall Safety Profile.....	52
5.3.1	Adult Subjects (> 16 years of age).....	52
5.3.2	Pediatric Subjects (≤ 16 years of age).....	55
5.4	Safety of 4-dose Compared to 6-dose Regimen in Study A025.....	58
5.5	Safety from Comparative Studies A026 and A028.....	61
5.5.1	Discontinuations due to Study Drug.....	61
5.5.2	Adult Subjects (> 16 years of age).....	61
5.5.3	Pediatric Subjects (≤ 16 years of age).....	64
5.6	Nervous System Disorders.....	67
5.6.1	Adult Subjects (> 16 years of age).....	67
5.6.2	Pediatric Subjects (≤ 16 years of age).....	69
5.6.3	Neurologic Examinations.....	72
5.7	Ear and Labyrinth Disorders.....	72
5.7.1	Adult Subjects (> 16 years of age).....	73
5.7.2	Pediatric Subjects (≤ 16 years of age).....	74
5.8	QT Interval Prolongation.....	75
5.9	Human Reproduction and Pregnancy.....	77
5.10	Summary of Clinical Safety.....	77
6	<i>Draft Questions for the Advisory Committee</i>	79
7	<i>References</i>	79
8	<i>Appendix 1</i>	81
9	<i>Appendix 2</i>	82

Tables

Table 1: <i>In vitro</i> activity of artemether, DHA, and lumefantrine against erythrocytic stages of <i>Plasmodium falciparum</i>	6
Table 2: Size range “bins” used to classify product sizes after PCR genotyping	16
Table 3: Summary of Design of Studies ABMO2 and A023	19
Table 4: Fever and Parasite Count at Baseline in Study ABMO2 and A023	20
Table 5: Efficacy Results in 4-dose Studies (ABMO2 and A023)	21
Table 6: Efficacy Results in 4-dose Studies (ABMO2 and A023) in Adults and Children.....	23
Table 7: Summary of Supportive Active-Controlled Studies with 4-Dose Coartem Regimen	25
Table 8: Efficacy of Supportive Active-Controlled Studies with 4-Dose Coartem Regimen	26
Table 9: Dosage of trial medications and time of administration in Study A025.....	27
Table 10: 28-day cure rate [95% CI] in ITT and Evaluable Populations in Study A025	28
Table 11: 28-day cure rate by study center in the ITT population in Study A025	28
Table 12: Time to Parasite Clearance (in hours) in Study A025	28
Table 13: Fever Clearance Time (in hours) in Study 025.....	29
Table 14: Comparison of 28-day cure rate, PCT, and FCT in Adults and Children (Study A025)	30
Table 15: 28-day cure rate [95% CI*] in ITT and evaluable populations (Studies A026 and A028)	31
Table 16: Comparison of 28-day cure rate, PCT, and FCT in Adults and Children	33
Table 17: Coartem 28-Day Cure Rate, PCT, and FCT in Study A2401.....	34
Table 18: Age and Body Weight in Study A2403	35
Table 19: Coartem 28-day cure rate, PCT, FCT by body weight in Study A2403.....	36
Table 20: Age and Body Weight in Study B2303	37
Table 21: Coartem 28-day cure rate, PCT, FCT in Study B2303.....	38
Table 22: Mixed Infections with <i>P. falciparum</i> and other <i>Plasmodium</i> species	40
Table 23: Summary of PK parameters of lumefantrine and desbutyl-lumefantrine in adult and pediatric malaria patients (mean plus minus SD, median for tmax).....	43
Table 24: Summary of PK parameters of artemether and dihydroartemisinin (DHA) in adult and pediatric malaria patients (mean plus minus SD, median for tmax).....	44
Table 25: Brain Histopathology.....	47
Table 26: Brain Regions with Histopathological Effects	48
Table 27: Clinical Neurological Evaluations.....	48
Table 28: Subjects included the FDA adult and pediatric pooled safety populations	50
Table 29: Reasons for discontinuation, FDA adult pooled population.....	51
Table 30: Reasons for discontinuation, FDA pediatric pooled population.....	51
Table 31: Most frequently reported AEs, FDA adult pooled safety population.....	52
Table 32: Number of patients who died, had other serious adverse events or discontinued prematurely due to AEs, FDA adult pooled safety population.....	53
Table 33: SAEs in the FDA adult pooled safety population*	53
Table 34: Most frequently reported AEs, FDA pediatric pooled safety population.....	55
Table 35: Number of patients who died, had other serious adverse events or discontinued prematurely due to AEs, FDA pediatric pooled safety population.....	56
Table 36: Patients who died, FDA pediatric pooled safety population	57
Table 37: SAEs in the FDA pediatric pooled safety population*	57

Table 38: Most frequently reported AEs occurring in $\geq 2\%$ of adult subjects in Study A025 by treatment group.....	59
Table 39: Most frequently reported AEs occurring in $\geq 2\%$ of pediatric subjects in Study A025 by treatment group.....	60
Table 40: Patient disposition for pooled Studies A026 and A028.....	61
Table 41: AEs by Preferred Term ($>2\%$) for pooled Studies A026 and A028.....	62
Table 42: Life-threatening and severe AEs in Studies A026 and A028, pooled adult population*.....	63
Table 43: SAEs in Studies A026 and A028, Adult pooled population.....	64
Table 44: Most frequently reported AEs by Preferred Term ($>2\%$), pediatric pooled safety population.....	66
Table 45: Adverse events affecting the SOC “Nervous system disorders”, FDA adult pooled safety population.....	68
Table 46: Nervous system disorder AEs of severe intensity, FDA adult pooled safety population.....	69
Table 47: Adverse events affecting the SOC “Nervous system disorders”, FDA pediatric pooled safety population.....	70
Table 48: Nervous system disorders in the 6-dose FDA pediatric pooled safety population by age group.....	71
Table 49: Adverse events affecting the auditory system, FDA adult pooled safety population...	74
Table 50: Adverse events affecting the auditory system, FDA pediatric pooled safety population.....	74
Table 51: Ear and labyrinth disorders in the 6-dose FDA pediatric pooled safety population by age group.....	75
Table 52: Largest Time-Matched Increase in QTcF by Treatment Group.....	75

1 Introduction

1.1 Mechanism of Action

Coartem is an oral fixed-dose tablet containing artemether (20 mg) and lumefantrine (120 mg) in a 1:6 ratio. Artemether is rapidly metabolized into an active metabolite dihydroartemisinin (DHA). Both artemether and DHA are sesquiterpenes with an endoperoxide moiety. The anti-malarial activity of artemether and DHA has been attributed to the endoperoxide moiety through the generation of free carbon-radicals. The exact mechanism by which lumefantrine exerts its anti-malarial effect is not well defined. Available data suggest lumefantrine inhibits the formation of β -hematin by forming a complex with hemin. Both artemether and lumefantrine have been shown to inhibit nucleic acid and protein synthesis.

1.2 Activity In Vitro

The activity of artemether, DHA, and lumefantrine was measured against several laboratory strains and clinical isolates from Thailand, Africa, China, Philippines, and French Guiana as measured by incorporation of ^3H -hypoxanthine or by microscopic method. The results, expressed as 50% and 90% inhibitory concentration (IC_{50} and IC_{90} , respectively) values, show that artemether, DHA, and lumefantrine are active against the erythrocytic stages of *P. falciparum* (Table 1). Artemether IC_{50} values were similar to DHA.

Table 1: *In vitro* activity of artemether, DHA, and lumefantrine against erythrocytic stages of *Plasmodium falciparum*

	Lumefantrine	Artemether	Dihydroartemisinin
Against laboratory strains			
IC_{50} ng/mL [range, (n)]			
<i>Microscopic method</i>	1.01 - 361.93 (n = 8)	0.05- 1.82 (n = 8)	0.1 - 6.54 (n = 7)
<i>Hypoxanthine incorporation</i>	ND	0.40 - 6.77 (n = 6)	0.25 - 1.48 (n = 3)
IC_{90} ng/mL [range, (n)]			
<i>Microscopic method</i>	50.57 - 240.8 (n = 3)	0.35 -10.6 (n = 4)	ND
Against clinical isolates			
IC_{50} ng/mL [range, (n)]			
<i>Microscopic method</i>	3.30 – 12.69 (n = 384)	0.06 - 18.91 (n = 31)	ND
<i>Hypoxanthine incorporation</i>	ND	0.07 - 22.69 (n = 1052)	0.15 - 6.6 (n = 128)
IC_{90} ng/mL [range, (n)]			
<i>Microscopic method</i>	2.0 – 126.9 (n = 137)	8.74 (n = 31)	ND

Note: IC_{50} = 50% Inhibitory Concentration; IC_{90} = 90% Inhibitory Concentration; n = number of laboratory or clinical strains tested; ND = not determined;

Combination of artemether with lumefantrine in ratios of 10:1 and 1:100 were tested against 3 strains of *P. falciparum* (K1, T-996, and LS-21). Results, expressed as IC₅₀ and IC₉₀ values, show that the combination of artemether with lumefantrine is 3 – 100 fold more active than either drug alone.

1.3 Activity In Vivo

The activity of artemether and lumefantrine *in vivo* was measured against the erythrocytic stages of *P. berghei*, *P. knowlesi*, and *P. falciparum* strains in either mice or monkeys.

Mice infected with the N strain of *P. berghei* and treated at time of infection with either lumefantrine or artemether (n=5 per group) showed a 50% reduction in parasitemia at doses of 1.27 mg/kg and 2.7 mg/kg, respectively. The time required for reducing the parasitemia by 50% was 2 times faster in mice treated with artemether (mean, 23 hours) compared to that of lumefantrine (mean, 54 hours). Treatment with lumefantrine resulted in clearance of parasitemia, whereas treatment with artemether often resulted in recrudescence of infection.

A combination of artemether to lumefantrine in a ratio of 1:0.375 resulted in a rapid reduction in parasitemia similar to that of artemether alone, and clearance of parasitemia similar to that of lumefantrine alone.

Monkeys (n=3 per group) infected with *P. knowlesi* and treated with artemether alone showed a faster reduction in parasitemia but did not clear the parasites. Treatment with lumefantrine alone showed a slower reduction in parasitemia; however, most animals were aparasitemic on day 105. A combination of artemether and lumefantrine (either 1:4 or 1:6) was more effective with a faster reduction of parasitemia and clearance of parasites from blood in all animals than either drug alone. Similar results were observed in monkeys infected with *P. falciparum*. There appears to be no antagonism between artemether and lumefantrine.

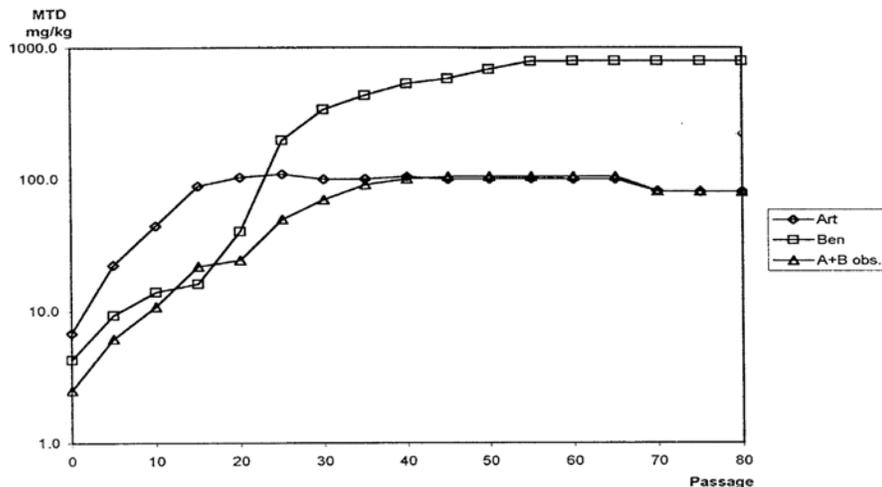
1.4 Drug Resistance

In vitro studies in which the erythrocytic forms of *P. falciparum* K1 strain were serially passed (number of passages not specified) showed no decrease in sensitivity to lumefantrine, artemether or the combination of artemether and lumefantrine.

The *in vitro* activity of artemether against *P. falciparum* clinical isolates from French Guiana, measured between 1997 and 2005, showed a trend towards a decrease in the *in vitro* sensitivity to artemether in 2002 and 2005. Nine of the isolates in 2002 and 1 isolate in 2005 had an IC₅₀ greater than 8.9 ng/mL and all these isolates had a *PfATPase6* –S769N mutant allele. Re-culture of the stored isolates with the mutant allele *PFATPase6*-S769N in the absence of artemether for 3-weeks showed a decrease in IC₅₀ value (1.42 ng/mL), suggesting a poor fitness of the mutant allele.

In vivo studies from mice infected with *P. berghei* strains showed that the potential to develop resistance to artemether, lumefantrine and a combination of artemether plus lumefantrine exists (Figure 1). A study also showed resistance to artemether may be unstable often resulting with the reversal to a more sensitive strain. The clinical relevance of such an effect is not known.

Figure 1: ED₉₀ to artemether, lumefantrine and a 2:0.075 combination of artemether and lumefantrine in male Swiss mice infected *P. berghei* Keyberg 173 N strain



2 General Review Issues

2.1 Clinical Data Submitted

The fixed-combination drug, artemether/lumefantrine, is marketed in multiple countries in the world; in Europe it is marketed under the name Riamet and in other parts of the world such as Africa and Asia it is marketed as Coartem. It was initially licensed in Europe in 1998, and 100 million courses have been dispensed, according to the manufacturer, Novartis.

The new drug application (NDA) for Coartem in the United States was the subject of a pre-NDA meeting between Novartis and the Division of Special Pathogen and Transplant Products (DSPTP) at the Food and Drug Administration (FDA). This meeting took place on October 30, 2006 to discuss the adequacy of the available data to support an NDA. During a teleconference dated June 27, 2007, Novartis and DSPTP discussed various regulatory issues and noted that some of the Modules in the Coartem/Riamet NDA would contain large amounts of data. Therefore, DSPTP asked Novartis if they had considered requesting fast track designation and submitting a step-wise NDA. This would provide the Agency with the opportunity to begin review of the large amount of data in the submission. Fast Track designation was requested by Novartis and granted by the Division on January 14, 2008.

Novartis requested orphan designation for Coartem and the request was granted for “*treatment of infections due to Plasmodium falciparum or mixed infections including P. falciparum*” by the Office of Orphan Products Development on August 31, 2007.

A second pre-NDA meeting was held November 9, 2007, during which there was further discussion on the format and content of the NDA application, including information and analyses that would be submitted. At the 2nd Pre-NDA meeting the Division and applicant agreed that complete information, including electronic datasets, from eight clinical studies would constitute substantial evidence of effectiveness as per the 1962 FD&C amendment. *Substantial evidence*

was defined in section 505(d) of the Act as “evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.”

The clinical section of the NDA submission (safety and efficacy) includes complete information on these eight primary studies, including raw data and electronic data sets. The eight primary studies are composed of two 4-dose studies assessing the efficacy of the components of the regimen (1994-1996) using a factorial study design, a study comparing a 4-dose versus a 6-dose regimen (1996), and 5 additional 6-dose regimen studies (1997-2007). Limited information, in some cases only the study reports, was submitted for an additional 16 studies that tested primarily the 4-dose regimen. These studies include two non-comparative 4-dose studies (1993-1996), a dose response study (1995), and 13 active controlled studies of which 10 included the 4-dose regimen (1993 – 2000) and three studied the 6-dose regimen (2000 – 2003). More details of the eight primary studies and 13 active controlled supportive studies are given below.

Eight Primary Studies:

- Two factorial designed 4-dose studies
 - ABM02: A double-blind, comparative trial of Coartem versus Artemether and Lumefantrine tablets conducted in China
 - A023: A partially blinded, comparative trial of Coartem versus Lumefantrine tablets and capsules conducted in China
- One comparative study of the 4-dose vs. 6-dose regimen
 - A025: A double-blind, comparative trial of Coartem 4-dose versus Coartem 6-dose over 60-hours and Coartem 6-dose over 96-hours conducted in Thailand
- Two descriptively comparative 6-dose studies, using a non FDA-approved comparator of mefloquine and artesunate (MAS)
 - A026: An open-label, comparative trial of Coartem versus MAS (2:1) conducted in Thailand
 - A028: An open-label, comparative trial of Coartem versus MAS (2:1) conducted in Thailand
- One non-comparative 6-dose study in non-immune travelers
 - A2401: An open-label, non-comparative trial of Coartem conducted in non-immune patients living in Europe who contracted malaria while traveling in endemic regions
- Two non-comparative 6-dose studies in children
 - A2403: An open-label, non-comparative trial of Coartem in African infants and children weighing 5 to 25 kg conducted in Kenya, Nigeria and Tanzania
 - B2303: A partially blinded trial of Coartem crushed tablets versus dispersible tablets in children weighing 5 to <35 kg conducted sub-Saharan Africa

Thirteen Supportive Active Controlled Studies:

- Ten supportive 4-dose active controlled studies
 - A003, A004, A005, A007, A008, A010, A011, A014, AIC04 (Senegal) and AIC04 (Cameroon) (See Tables 7 and 8 for details of these studies)
- Three supportive 6-dose studies
 - ABD01: Randomized, double-blind comparison of efficacy of Coartem and quinine-sulfadoxine/pyramethamine in the treatment of uncomplicated malaria in a multidrug resistant falciparum area in Bangladesh, in adult male patients >12 years.
 - A030: Randomized, open label trial comparing Coartem with artesunate-mefloquine (MAS) in adults in Vietnam
 - ABR01: Randomized, open label, comparative study of Coartem and quinine/doxycycline in adults in Brazil

2.2 Combination Regimen

Coartem is a combination product of two drugs: artemether and lumefantrine. Under 21 CFR 300.50, data are required to demonstrate that each component of a fixed-combination drug makes a measurable contribution to the claimed effects of the product and the combination is safe and effective.

Studies A023 and ABM02 compared the efficacy of 4-doses of Coartem compared to lumefantrine alone (A023) or lumefantrine or artemether alone (ABM02).

Using both early and late time points, as discussed further below, the applicant was able to demonstrate the superiority of Coartem compared to artemether alone on 28-day cure rate; and a shorter time to parasite clearance, fever clearance, and a greater parasite reduction at 24 hours compared to lumefantrine.

The individual pharmacokinetics of artemether and lumefantrine act in a complementary manner. There is a reduction in fever and parasite clearance within 24 hours due artemether (shorter half-life), and prevention of recrudescence of the parasites due to lumefantrine (longer half-life) after initial clearance by artemether.

2.3 Four versus Six Dose Regimens

No formal dose finding studies were performed with Coartem as part of the development plan. However, early studies were performed which determined the optimal ratio of artemether to lumefantrine in Study AMMS1, number of doses and days of treatment (4 doses for 3 days compared to 3 doses for 3 days compared to 4 doses over 2 days) in adults in Study AMMS3, and the efficacy of the 4 dose, 3 day regimen was confirmed in children aged 5 to 14 years in Study AMMS4. Based on these studies, the 4-dose regimen, each adult dose consisting of four tablets for a total of 80 mg artemether/480 mg lumefantrine per dose given at 0, 8, 24, and 48 hours was selected for further study.

While Studies A023 and ABMO2 demonstrated the efficacy of 4-doses of Coartem in China, a low transmission area, the 4-dose regimen achieved lower parasite clearance rates (<90%) in

Thailand in studies conducted between 1995 and 1996 (i.e., A004, A008, and A012), therefore the applicant decided to pursue a 6-dose regimen. The rationale for the proposed 6-dose regimen in adults and children has been addressed with the comparison for efficacy and safety between the 4-dose and 6-dose regimens in Study A025.

Note that the Division's review does not pool efficacy data across studies to compare the 4-dose regimen with the 6-dose regimen, since the studies of 4 doses versus 6 doses were performed at different times, in different countries, using different entry criteria and definitions of outcome. Therefore, comparing a pooled 6-dose regimen with a pooled 4-dose regimen is essentially making cross-study comparisons which may not be valid. Instead, comparison on the 4-dose regimen with the 6-dose regimen is made only with study A025, because this is the only study that directly compared a 4-dose and a 6-dose regimen.

2.4 Populations Studied

All studies conducted by the applicant were conducted outside the US and not under an IND. These studies included adult and pediatric patients studied in endemic areas, and European travelers to endemic areas. The patient data obtained by the applicant are considered to be applicable to the US population because cases of malaria in the US are reported in persons who have traveled to endemic countries.

The draft Guidance to Industry, "Malaria: Developing Drug and Nonvaccine Biological Products for Treatment and Prophylaxis"¹ from June 2007 (*see Appendix I*), recommends that ethnically diverse male and female subjects of all ages (including pediatric and geriatric patients) should be included in drug development programs for malaria in order to represent the diverse racial groups likely to be exposed to the drug if it is approved. In addition, studies should be conducted in different geographical regions to address differences in population host factors (e.g., immune status, blood type, etc). In conducting their studies, the applicant has provided information on Black, Caucasian, Asian and Hispanic (a few of the supportive studies were conducted in South America) patients, all of which are represented in the US population. The populations studied included adult travelers from non-endemic regions (Study A2401 conducted in Switzerland, Germany, France, Italy and the Netherlands) and those residing in South East Asia (6-dose studies A025, A026, and A028). The ages of these patients ranged from 18 to 70 years, but very few patients over 65 years of age were included (N=8). Studies in infants and children were primarily conducted in sub-Saharan Africa (6-dose studies A2403 and B2303), including Kenya and Tanzania. Some children (down to 12 years of age) were also enrolled in the Thailand studies. Malaria endemicity varies between Asia and Africa, but patients in these countries are considered to be semi-immune, while the very young children can be considered non-immune. Although patient populations differed in their degree of immunity, similar efficacy was observed across all these 6-dose studies.

2.5 Nature of the Studies

Eight studies were reviewed in detail to evaluate efficacy. The three most informative studies in assessing efficacy were (a) the two studies which compared Coartem to its components (Studies A023 and ABM02), and (b) A025 which compared the 4-dose regimen to the 6-dose regimen.

¹ <http://www.fda.gov/cder/guidance/7631dft.pdf>

ABMO2 and A025 were double blind studies. A023 contained three arms, Coartem, lumefantrine tablets and lumefantrine capsules. In A023, the Coartem and the lumefantrine tablets arms were blinded.

The remaining five studies were unblinded (i.e., open label) and essentially uncontrolled. The reason the studies were essentially uncontrolled, the applicant states, is either because no suitable comparator was available at the time the studies were initiated or because inclusion of a control arm would have increased the time to complete the study due to the need to recruit additional patients.

The open-label design was employed in the comparative studies (A026 and A028) because the applicant stated that using a double-blind, double-dummy methods would have been difficult in ensuring acutely-ill patients take a large number of tablets with adequate amounts of food. Studies A026 and A028 were randomized, open-label 6-dose studies using the non-approved comparator of mefloquine plus artesunate (MAS). Although these studies included a comparator arm, randomization was 2:1 (Coartem:MAS), and no formal statistical comparisons with the control was planned. Mefloquine was given as 25 mg/kg total dose, split 15 mg/kg on the 2nd day of treatment and 10 mg/kg on the 3rd day of treatment. Artesunate was dosed 4 mg/kg/day on days 1 to 3. Although not approved in the US, MAS is considered to be a standard-of-care in many parts of the world. In the US, mefloquine is approved as a single agent for the treatment of malaria, the recommended regimen in adults is five tablets (1250 mg total) given as a single oral dose; it should be taken with food and 8 ounces of water.

FDA-approved antimalarial drugs (e.g., chloroquine, sulfadoxine/pyramethamine (Fansidar®), quinine, and mefloquine) were used as comparators in the 4-dose supportive studies, some of which were blinded.

2.6 Comparison of Study Design to Draft Malaria Guidance Document²

2.6.1 Entry Criteria

According to the draft Guidance to Industry on Malaria, the following are recommended entry inclusion and exclusion criteria for studies of acute, uncomplicated malaria. The applicant's studies fulfilled these criteria, unless otherwise noted:

- Adult and pediatric males and females
- Fever present at entry, or documented within 24 hours of entry
- Entry parasitemia should be limited to values between 1000 and 200,000 μ L (0.25 to 4 percent)
- Patients with severe or complicated disease should be excluded
- Patients treated with prior antimalarials for the current episode should be excluded.
- In general, patient symptoms should include shivering, chills, malaise, headache, and loss of appetite in adults, and also include irritability, lethargy, and anorexia in children.

² *ibid*

Fever was not an inclusion criterion for the primary studies conducted in adults and adolescents. However, in the two studies that enrolled infants and small children (A2403 and B2303) patients had to have a fever ($\geq 37.5^{\circ}\text{C}$ axillary or $\geq 38^{\circ}\text{C}$ rectal) present at baseline or a history of fever in the preceding 24 hours (B2303 only). In addition, the applicant's trials did not specify that patients should have other clinical symptoms at baseline, but it is apparent from the manner in which adverse event data were collected, that many of the symptoms listed in the Guidance were present at baseline and improved with treatment.

2.6.2 Endpoints

The draft Guidance to Industry on Malaria recommends the primary endpoint in treatment studies be 28-day cure defined as follows:

The complete resolution of clinical signs and symptoms, malaria-related laboratory abnormalities, and elimination of asexual parasites by day 7, with no recurrence up to day 28 ± 2 . This definition also includes that a study assessment 48 hours after initiation of therapy demonstrate a decrease in the level of parasitemia to less than 25% of baseline with no clinical deterioration.

Recommended secondary endpoints include time to parasite clearance, and time to fever clearance.

Treatment failures are classified as early treatment failure, late treatment failure, or late parasitological failure, and defined as follows:

• Early treatment failure

- Development of severe malaria on day 1, 2, or 3 of treatment in the presence of parasitemia
- Parasitemia on day 2 greater than day 0 irrespective of axillary temperature
- Parasitemia on day 3 with axillary temperature greater than or equal to 37.5 degrees Celsius
- Parasitemia on day 3 greater than or equal to 25 percent of count on day 0

• Late treatment failure

- Development of severe malaria after day 3 in the presence of parasitemia without previously meeting any of the factors of early treatment failure
- Parasitemia any day from day 4 to 14 (intense transmission areas) or day 4 to 28 (low to moderate transmission areas) with axillary temperature greater than or equal to 37.5 degrees Celsius without previously meeting any of the factors of early treatment failure
- Any patients receiving additional antimalarial therapy not specified in the study protocol

- **Late parasitological failure**

- Parasitemia on day 14 (intense transmission areas) or any day from day 7 to 28 (low to moderate transmission areas) and axillary temperature less than 37.5 degrees Celsius.

The applicant’s primary endpoint in their studies was the 28-day cure, including clearance of asexual parasites within 7 days without recrudescence by day 28. As noted above, clinical signs and symptoms were not required for study entry, other than fever in small children.

The following efficacy endpoints were examined during the review of the application:

28-day microbiological cure rate (%) [95% CI] (ITT population)
Parasite Clearance Time (median) [95% CI] (ITT population)
Fever Clearance Time (median) (population of patients with fever at baseline)
Percent parasite reduction @ 24 hrs (populations of patients with repeat parasite counts)
Proportion of patients with parasite reduction of < 75% at 48 hours (i.e., patients not achieving a reduction to < 25% of baseline) in the ITT population
Early Treatment Failure (no. of patients with parasitemia @ 48 hours > baseline) in the ITT population
Proportion of patients with recrudescence of <i>P. falciparum</i> during the study in the ITT population
Proportion of patients with negative malaria slides at day 2, 3, and 4 in the ITT population

2.6.3 Analysis Populations

The draft Guidance to Industry on Malaria recommends two analysis populations for evaluating efficacy: the Modified intent-to-treat (MITT) and the Per Protocol (or Evaluable) populations.

- **Modified intent-to-treat (MITT)** — All randomized patients with parasitologically confirmed malaria who receive at least one dose of study drug. Depending on the specific study design, the intent-to-treat (ITT) population of all subjects enrolled can include subjects enrolled before complete parasitological confirmation but for whom malaria is not subsequently confirmed. These subjects should not be included in the MITT and per-protocol efficacy analyses.
- **Per protocol** — All patients included in the MITT population who have received at least 80 percent of the protocol-defined therapy and are clinically and microbiologically evaluable after 28 days.

The definitions of these analysis populations used by the applicant were similar to those in the guidance.

Our ITT and Evaluable populations are essentially the same as the applicant’s MITT and Evaluable populations, unless otherwise noted. The ITT population was used as the primary analysis population, unless otherwise noted. In the ITT population, patients with missing data

for 28-day cure rate are included in the analysis as failures, therefore outcome rates will be lower than rates for the evaluable population, where patients missing the 28-day visit are excluded from analysis. Since the Evaluable population excludes subjects after randomization for reasons that may be treatment related, the resulting analysis population may be a biased subset of subjects.

2.7 Mixed Infections

The applicant is also requesting an indication for treatment of mixed infections including *P. falciparum*. According to the 2006 WHO Guidelines for the Treatment of Malaria³, mixed malaria infections are common and are underestimated by routine microscopy. In five of the applicant's 6-dose studies, patients were enrolled with mixed infections at baseline, primarily *P. falciparum* and *P. vivax*. Coartem was shown to clear circulating *P. vivax* along with *P. falciparum* from the blood. However, recurrences occurred in about a third of patients, which is not unexpected since Coartem does not have activity against the liver hypnozoites and therefore does not provide a radical cure. The WHO Guidelines also state that primaquine is needed along with artemisinin combination therapy for radical cure of *P. vivax* and *P. ovale*, except in high transmission settings where the risk of reinfection is high.

2.8 Parasitological Measurements

Cure rate in the clinical trials of Coartem was defined as the percentage of patients who cleared infection with no evidence of reappearance of the parasite within 28 days. Cure in this context was the absence of parasites based on microscopic examination of two consecutive negative peripheral blood smears. Some patients, although initially confirmed to have cleared parasites by microscopy, had reappearance of parasites within the 28-day trial window. These patients were regarded as treatment failures although the possibility remained that the reappearance of parasites following clearance was not due to recrudescence but a new infection. Methods exist for identification of distinct strains/clones and have been used in epidemiological studies. However, the ability of these assays to distinguish a true recrudescence from a new infection has not been standardized and validated.

Two different techniques in two different laboratories were used to distinguish the genotype of the parasite(s) detected prior to treatment from those seen at reappearance. Samples from Studies A025, A026, and A028 were analyzed at the Shoklo Malaria Research Unit (SMRU) by a polymerase chain reaction (PCR) assay. Differences between genotypes were identified by allelic polymorphisms in 3 genes using 3 primer sets: merozoite surface protein-1 (MSP-1), MSP-2 and glutamate rich protein (GLURP).

Each assay for each gene utilized a primary PCR with a second "nested" PCR on the product of the primary amplification. The differences between alleles were elucidated by comparing different PCR product lengths upon electrophoresis. The size of the PCR fragment was extrapolated by linear regression from a DNA ladder of known fragment sizes. The product was then sorted to a "bin" to classify the allele (See Table 2).

³ www.who.int/malaria/docs/TreatmentGuidelines2006.pdf

Table 2: Size range “bins” used to classify product sizes after PCR genotyping

Allele code (bin)	PCR product size		
	MSP-1	MSP-2	GLURP
1	400 - 439	400 - 439	
2	440 - 479	440 - 479	
3	480 - 519	480 - 519	
4	520 - 559	520 - 559	580 - 639
5	560 - 599	560 - 599	640 - 699
6	600 - 639	600 - 639	700 - 759
7	640 - 679	640 - 679	760 - 819
8	680 - 719	680 - 719	820 - 879
9		720 - 759	880 - 939
10			940 - 999
11			1000 - 1059
12			1060 - 1119

For example, an isolate which had a PCR product of 450 bp for MSP-1, 552 bp for MSP-2 and 833 bp for GLURP would be categorized as a MSP-1 (bin 2), MSP-2 (bin 4), GLURP (bin 8) genotype.

Samples from Studies 2401, 2403 and 2303 were tested at the Swiss Tropical Institute (STI) using a PCR and restriction fragment length polymorphism analysis (RFLP) assay. For PCR, 2 primer sets were used (MSP-1 and MSP-2). Like at the SMRU laboratory, assay for each gene utilized a primary PCR with a second “nested” PCR on the product of the primary amplification. Differences in MSP-2 were discerned using RFLP on the PCR products; if the baseline sample and that obtained at reappearance did not differ in genotype, then this was followed by analysis of MSP-1 which was clarified by differences in the length of the intact PCR products.

A single difference in the genotype post-treatment compared to baseline resulted in the parasite being classified as a “new infection” and the patient was considered cured by the applicant.

The PCR and RFLP assays are considered experimental assays and have not been standardized and validated for the purpose of differentiating new infection from recrudescence. The performance of these assays can vary from laboratory to laboratory. The performance characteristics of the assay were not submitted by the applicant for our review. Due to several limitations of the assay results must be interpreted with caution. Some of these limitations were discussed by the applicant in the NDA submission in one of the study reports (Study 1003; for details *see Appendix 2*). Additionally, other potential confounders of this method have been identified.

1. **a) Sensitivity i.e. lower limit of detection of the assay.** Different lower limits of detection were used at different sites: SMRU used 1 parasite/μL, while STI used 25 parasites/μL and was demonstrated with gel results provided by the applicant. Variation in the limits of detection (LOD) decreases the resolution of the genotyping procedure. Differences in the LOD between the 2 laboratories suggest that comparison across studies should not be conducted as the assays have not been standardized and validated.

b) Sensitivity of the assays in infections with multiple strains of *P. falciparum*. Many of the baseline infections in the studies submitted by the applicant were due to co-infection with more than one strain or clone of *P. falciparum*. No assays were performed which allowed determination of the lower limit of detection in infections with mixed strains. The PCR assays have the capacity to identify and genotype mixed infections, though interpretation is often subjective. Factors which may contribute to lowering the ability of the assay to consistently detect multiple strains/clones include primer bias, a disproportioned multiplicity of infection (MOI), and sequestration of one or more strains or clones of the parasites from the peripheral blood. These aspects of the assay are of critical importance since a strain missed at baseline would be improperly classified as a new infection if it is resistant to drug treatment.

2. **Specificity of the assay (human DNA or mixed infection with other species of *Plasmodium*).** The citation from which the primer sequences were taken stated that the assay is specific for *P. falciparum*. The applicant has stated that human DNA was run as a negative control on gels and results were discarded if the reaction yielded a product. However, the percentage of results which were discarded was not specified.
3. **Operator error and day to day variation in results (reproducibility and quality control).** No evidence was provided which showed reproducibility of the test results at each of the sites. Similar interpretation by at least two independent, experienced readers can provide assurance in the analysis of gel results. Gel results seem to have only been interpreted by a single reader. Additionally, the applicant has not submitted results of quality control testing.

There is inherent variability in determining fragment length by linear regression which could result in misclassification of a genotype because of the “bin” procedure used at SMRU. For example, the estimated lengths of the GLURP fragment amplified from the baseline blood sample and the blood sample taken at parasite reappearance for patient 145 in Study 028 were 971 and 988 base pairs (bps), respectively. Therefore, the difference in estimated fragment lengths was 17 bp. Both of these fragments were allocated to bin 10. These results, along with the same bin classification of fragments produced for MSP-1 and MSP-2, resulted in this reappearance being classified as recrudescence. In another case however, for patient 296, a 17 bp difference was seen between the estimated fragment lengths for MSP-2. In this case, however, due to the cutoff between adjacent bins, the baseline product was categorized as bin 8 (710 bp) and the fragment amplified from the sample obtained at reappearance was categorized as bin 9 (727 bp). This difference led to the classification of this patient’s reappearance as a new infection. Additionally, there may be bias in the assay for a high “false negative” rate due to operator and inherent day to day error (primarily misinterpretation of results, contamination or mislabeling). At SMRU, in order for paired isolates to be declared the same and thus the patient given the classification of recrudescence, 12 PCR reactions must yield identical products with no contamination or misinterpretation of results [2 samples (baseline & reappearance) x 3 genes (MSP-1, MSP-2, GLURP) x 2 PCRs (primary and nested)=12]. At STI, there are 8 PCRs which must perform without error. A single episode of contamination, mislabeling or misinterpretation will yield incongruent results and the reappearing isolate would be identified as a new infection.

4. **Product confirmation (i.e., sequencing of PCR product).** Not reported by the applicant.
5. **Mislabeled and missing information from gel results.** Some of the actual gel results were provided and many were impossible to interpret due to unlabeled gel images and subject IDs which were not the same as in the trials. Additionally, some gel images were of very low quality.

Some of the issues discussed above are also included in the World Health Organization consensus document.⁴

In, in the absence of performance characteristics, quality control, standardization and validation of the assays, results of either PCR or RFLP assays should not be used for determining the efficacy of Coartem. Efficacy should be based on presence or absence of parasites on blood smears (i.e. uncorrected cure rates).

Therefore, all efficacy results reported in this document reflect the uncorrected parasitological cure rates.

3 Clinical Efficacy

3.1 Factorial Design Studies to Evaluate the Components of the Fixed-Combination Drug (ABMO2 and A023)

3.1.1 Study Design

Studies ABMO2 and A023 are considered essential studies in the NDA because the efficacy of the fixed-combination drug, Coartem, is compared to each of its individual components, artemether and lumefantrine. These were randomized, comparative, single center, four dose trials conducted over 4 weeks. Both studies were conducted in the same single center in China (Navy Military Hospital in Sanya, Hainan Province). Study ABMO2 was double blinded and in Study A023 the Coartem arm and the lumefantrine tablet arm were blinded. A summary of the study design for both studies is shown in Table 3.

⁴<http://www.who.int/malaria/docs/drugresistance/MalariaGenotyping.pdf>: Methods and techniques for clinical trials on antimalarial drug efficacy: genotyping to identify parasite populations.

Table 3: Summary of Design of Studies ABMO2 and A023

	Study ABMO2	Study A023
DOSING Coartem Regimen (80 mg Artemether + 480 mg Lumefantrine/dose)	hours 0, 8, 24, 48	hours 0, 8, 24, 48
DOSING Comparators Regimen		
Artemether 80 mg per dose	hours 0, 8, 24, 48	-
Lumefantrine tablet 480 mg per dose	hours 0, 8, 24, 48	hours 0, 8, 24, 48
Lumefantrine capsule*	-	800 mg at hour 0 400 mg at hours 24, 48, 72
Dosage Adjusted by Weight for patients <35 kg	Yes	No
Study Timeline	6/2/1994 to 10/6/1994	6/21/1996 to 11/5/1996
Number of Patients Recruited	157	153
Number of Study Centers	1 (Navy Military Hospital in Sanya, Hainan Province)	1 (Navy Military Hospital in Sanya, Hainan Province)
Countries Where Studies Were Conducted	China	China

* In Study A023, lumefantrine capsules were dosed according to the dosing regimen in use at the time in China.

3.1.2 Demographics and Baseline Characteristics

The majority of patients in both studies were young adult males. Body weight was comparable among the treatment arms in each study.

As shown in Table 4, in Study A023 the Coartem arm had less fever and a lower parasite density at baseline than the lumefantrine arms. This difference was statistically significant for temperature ($P < 0.05$) but not for parasite density ($P = 0.0697$ for Coartem vs. lumefantrine tablets, $P = 0.1763$ for Coartem vs. lumefantrine capsules).

Table 4: Fever and Parasite Count at Baseline in Study ABMO2 and A023

	Study ABMO2 N=157			Study A023 N=153		
	Coartem N=53	Artemether N=52	Lumefantrine Tablet N=52	Coartem N=52	Lumefantrine Tablet N=51	Lumefantrine Capsule N=50
Temperature (°C)						
Median	38.2	38	38.3	37.45	37.9	38
≤ 37.5	15(28%)	22(42%)	14(27%)	28(54%)	20(39%)	15(30%)
37.5 - 39	25(47%)	19(37%)	22(42%)	18(35%)	17(33%)	22(44%)
≥ 39	13(25%)	11(21%)	16(31%)	6(12%)	14(27%)	13(26%)
Parasite Density (µL)						
Median	23,479	19,602	26,697	11,778	25,508	23,781
missing	2(4%)	-	-	-	-	-
<5,000	6(11%)	8(15%)	8(15%)	13(25%)	10(20%)	9(18%)
≥ 5,000 but < 15,000	13(25%)	12(23%)	10(19%)	15(29%)	6(12%)	9(18%)
≥15,000 but < 50,000	21(39%)	19(37%)	18(35%)	19(37%)	24(47%)	26(52%)
≥ 50,000	11(21%)	13(25%)	16(31%)	5(10%)	11(22%)	6(12%)

3.1.3 Comparison of Results

3.1.3.1 Overall Efficacy Results

The primary efficacy endpoint was the 28-day cure rate in the ITT population. The results of the 28-day cure rate and other important efficacy endpoints in study ABMO2 and A023 are presented in Table 5. The time to fever clearance was only analyzed for patients who were evaluable for this analysis, i.e. those who had a temperature >37.5°C at baseline.

Table 5: Efficacy Results in 4-dose Studies (ABMO2 and A023)
(Non-shaded columns represent primary comparisons planned in study protocols;
Gray shaded columns represent non-primary comparisons)

	Study ABMO2 N=157			A023 N=153		
	Coartem	Artemether	Lumefantrine Tablets	Coartem	Lumefantrine Tablets	Lumefantrine Capsules
28-day parasite. Cure						
ITT Population, N	53	52	52	52	51	50
Cure	50 (94.3%)	24 (46.2%)	47 (90.4%)	50 (96.2%)	45 (88.2%)	47 (94.0%)
P-value*	-	<0.001	n.s.	-	n.s.	n.s.
Evaluable, N	50	44	51	51	49	49
Cure	50 (100%)	24 (54.5%)	47 (92.2%)	50 (98%)	45 (91.8%)	47 (95.9%)
P-value*	-	<0.001	n.s.	-	n.s.	n.s.
Parasite Reduction (PR) at 24 hours						
Evaluable, N	51	52	52	52	51	49
Median	99.3%	99.9%	78.2%	99.9%	78.7%	86.7%
P-value*	-	0.0291	<0.001	-	<0.001	<0.001
Time to parasite clearance (PCT)						
ITT Population, N	53	52	52	52	51	50
Median	30 hours	30 hours	54 hours	30 hours	48 hours	54 hours
P-value *	-	0.0275	<0.001	-	<0.001	<0.001
Time to fever clearance (FCT)						
Evaluable, N	38	30	38	24	31	35
Median	24 hours	21 hours	60 hours	21 hours	36 hours	36 hours
P-value*	-	n.s.	<0.001	-	0.0297	0.0992

*P-value compares either artemether or lumefantrine with Coartem in Study ABMO2 and either lumefantrine tablet or capsule with Coartem in Study A023; n.s. = no statistical significance

P-values to test treatment effect on the 28-day cure rates were calculated using Fisher's Exact test. The treatment effect on parasite reduction at 24 hours was tested using a non-parametric Wilcoxon rank-sum test. Time to parasite clearance (PCT) and time to fever clearance (FCT) were analyzed by the Kaplan-Meier method and the treatment effect was tested using the Wilcoxon test.

In Study ABMO2, the 28-day cure rate in the ITT population was significantly higher for Coartem (94.3%) compared to artemether (46.2%), while the median PCT was significantly shorter for Coartem (30 hours) compared to lumefantrine tablets (54 hours). A total of 106 patients who had a baseline temperature >37.5°C were evaluable for the analysis of time to fever clearance. Coartem had an advantage over lumefantrine with a median FCT of 24 hours versus 60-hours, respectively. Note that the artemether evaluable population contained only 44 subjects; 6 of the 8 subjects excluded from the evaluable population discontinued the study due to unsatisfactory therapeutic effect but were excluded from the evaluable population due to receipt of rescue medication because of appearance of *P. vivax*.

In Study A023, there was no statistically significant difference between the 28-day cure rates for the three treatment arms in the ITT and evaluable populations, as would be expected given the fact that all arms contained lumefantrine. The median PCT was significantly longer for both

lumefantrine formulations than for Coartem, i.e. 54 and 48 hours compared to 30 hours. The median FCT was numerically shorter in the Coartem arm compared to the two lumefantrine arms; however, the administration of steroids confounds this result. Dexamethasone was administered to the patients who presented with high fever (73% of the study population).

3.1.3.2 Difference in Baseline Parasite Densities

In study A023, there was an imbalance in the baseline parasite densities for the Coartem and lumefantrine (tablets and capsules) arms. The lower baseline count for Coartem compared to the other two treatment arms (median values of 11,778/ μL versus 25,508 and 23,781/ μL) may have introduced a bias which led to improved results in this treatment arm. In order to assess the affect of this imbalance, an analysis by baseline parasite count was conducted.

The overall 28-day cure rates, PCT, and FCT were compared between treatments by baseline parasite density. Overall, the results with respect to different baseline parasite density showed similar pattern among treatment arms. Compared to either lumefantrine formulation, Coartem treatment was associated with greater parasite reduction, as well as quicker parasite and fever clearance. Overall 28-day cure rate remained similar across the three arms.

3.1.3.3 Outlier Analysis

In an attempt to evaluate efficacy in patients with more severe disease, an outlier analysis was performed using patients whose baseline parasite density was $\geq 100,000/\mu\text{L}$. There were 13 patients in Study ABMO2 and 3 patients in Study A023 who met this criterion. Though the sample size was small, results for these patients was similar to the overall efficacy results, for 28-day cure rate, parasite reduction at 24 hours, PCT, and FCT.

3.1.3.4 Analysis of Efficacy in Adults and Children

Pediatric patients, age 12 to 16 years were enrolled in these two studies. The efficacy rates were analyzed for adults (> 16 years of age) and children (≤ 16 years old). The 28-day cure for Coartem was $\geq 93\%$ for adults and children in both studies, as shown in Table 6. Results were similar to the overall 28 day-cure rates for the entire study population.

Table 6: Efficacy Results in 4-dose Studies (ABMO2 and A023) in Adults and Children

	Study ABMO2 N=157			Study A023 N=153		
	Coartem	Artemether	Lumefantrine	Coartem	Lumefantrine Tablet	Lumefantrine Capsule
28-day parasitological cure rate, n/N (%)						
ITT population						
Children (12-16)	12/12 (100%)	4/8 (50.0%)	11/12 (91.7%)	10/10 (100%)	8/9 (88.9%)	11/12 (91.7%)
Adults (>16)	38/41 (92.7%)	20/44 (45.5%)	36/40 (90.0%)	40/42 (95.2%)	37/42 (88.1%)	36/38 (94.7%)
Evaluable patients						
Children	12/12 (100%)	4/7 (57.1%)	11/12 (91.7%)	10/10 (100%)	8/9 (88.9%)	11/12 (91.7%)
Adults	38/38 (100%)	20/37 (54.1%)	36/39 (92.3%)	40/41 (97.6%)	37/40 (92.5%)	36/37 (97.3%)
Median PR (%) at 24 hours (Evaluable patients)						
Children	94.2 (n=12)	98.8 (n=8)	80.0 (n=12)	99.9 (n=10)	75.0 (n=9)	90.7 (n=12)
Adults	99.4 (n=39)	100 (n=44)	71.1 (n=40)	99.8 (n=42)	80.8 (n=42)	84.7 (n=37)
Median PCT (hours) (ITT population)						
Children	36.0 (n=12)	30.0 (n=8)	54.0 (n=12)	29.9 (n=10)	48.0 (n=9)	48.0 (n=12)
Adults	30.0 (n=41)	24.0 (n=44)	60.0 (n=40)	30.0 (n=42)	53.9 (n=42)	54.0 (n=38)
Median FCT (hours) (Evaluable patients)						
Children	12.0 (n=9)	12.0 (n=6)	66.0 (n=9)	24.0 (n=9)	30.1 (n=8)	42.0 (n=12)
Adults	24.0 (n=29)	24.0 (n=24)	54.0 (n=29)	17.9 (n=15)	42.0 (n=23)	30.0 (n=23)

3.1.3.5 Efficacy at 24 and 48 hours of Treatment

The early treatment efficacy of Coartem in reducing parasite density was analyzed by assessing parasite reduction in the first 48 hours of treatment compared to baseline parasite density. In both studies, more than 96% of patients with parasites at baseline treated with Coartem or artemether achieved a $\geq 75\%$ reduction in parasite density at 24 hours and 100% of patients achieved a $\geq 75\%$ reduction in parasite density at 48 hours. Note that two subjects treated with Coartem in Study ABMO2 did not have any parasite counts recorded at baseline or during the study.

In Study ABMO2, 6/52 patients treated with lumefantrine had an increase in parasite count compared to baseline within the first 48 hours, but all reached clearance within 7 days. One patient had reappearance of *P. falciparum* by Day 29. Three patients on lumefantrine had a

reduction of <75% of baseline at 48 hours and 2 patients on lumefantrine had an increase from baseline at 48 hours.

In Study A023, at 24 hours after the initial dose, 3/51 patients treated with lumefantrine tablets and 6/49 patients treated with lumefantrine capsules had a higher parasite count compared to baseline. One patient also had parasitemia at 48 hours greater than the baseline count, but all nine were cleared of parasites within 4 days. In these analyses, parasite count at 48 hours was assumed to be zero for patients whose records were missing at 48 hours and who were cleared within 30 hours without recrudescence (15 patients on Coartem, 2 patients on lumefantrine tablets, and 2 patients on lumefantrine capsules). Note that the analyses did not include two patients, one lumefantrine capsule subject who had no parasite record past 18 hours at which point subject had only a 1% reduction from baseline and one lumefantrine tablet subject who had no parasite record past 24 hours at which time subject had an 84% reduction from baseline.

3.1.3.6 Late Treatment Failure (Recrudescence)

In the study ABMO2, among 145 patients who completed the 28-day trial period, 24 had a recrudescence of parasitemia, mostly in the artemether arm. There were no recrudescences of *P. falciparum* in the Coartem arm. Twenty of 44 (45.5%) patients in the artemether arm had recrudescences of parasitemia between study days 12 to 28. Four of 51 patients (7.8%) had recrudescences in the lumefantrine arm between study days 25 to 28.

In Study A023, among 149 evaluable patients, there were seven recrudescences between days 15 and 29: one patient in the Coartem arm on day 26, four in the lumefantrine tablet arm (days 15, 25, 28, and 29), and two in the lumefantrine capsule arm (days 22 and 25).

All recrudescences were considered to be R-I treatment failures, i.e., initial clearance of parasitemia within 7 days, followed by recrudescence.

3.1.4 Summary and Conclusions

The efficacy results from Studies ABMO2 and A023 support that the combination of Coartem was superior to artemether in terms of 28-day cure rate. Coartem also demonstrated a shorter time to parasite and fever clearance and a greater parasite reduction at 24 hours compared to lumefantrine. Additional analyses performed for Study A023 to account for the lower baseline parasite counts in the Coartem arm, resulted in similar conclusions to the applicant's. The interpretation of results of these studies is limited by the fact that they were single center studies, both performed at the same site in China, and only Study ABMO2 included an arm of artemether alone.

3.2 Additional 4-dose Supportive Studies

Additional studies of Coartem, administered as a 4-dose regimen administered over 48 hours (hours 0, 8, 24, 48), were performed between 1993 and 2000, including two (Study ABMO1 and A009) open-label, non-comparative studies to confirm efficacy and tolerability, one (Study A012) was a double-blind, parallel-group, dose optimization study to compare 4-dose with two lower doses, and ten active-controlled studies which compared the 4-dose regimen of Coartem with other antimalarials. These studies were submitted as study reports only without efficacy data sets. Table 7 summarizes the study design and Table 8 summarizes the efficacy results of

the 10 active-controlled studies. The first section of Table 8 reports the 4 studies where Coartem lead to higher 28 day cure rates compared to the comparator. Parasite reduction at 24 hours was also higher. The next section shows the studies where Coartem had similar results as the comparator. In the last section Coartem had lower 28 day cure rates compared to the comparator. Note that parasite reduction at 24 hours was high in these studies. While the safety of 4-doses of Coartem was further supported by these studies, its superiority to various comparators in 28-day cure rate could not be established. These studies were conducted in areas of high transmission, as compared to Studies ABMO2 and A023, which were conducted in China.

Table 7: Summary of Supportive Active-Controlled Studies with 4-Dose Coartem Regimen

Study No.	Study Design / Objective	No. of patients		Population	Year/ Study Location
		Coartem	Comparator		
A003	Open, randomized, parallel group efficacy/safety Coartem vs quinine	111	Quinine: 108	Children (2-12 yr)	1995-96 Thailand
A004	Double-blind, randomized, parallel group efficacy/safety Coartem vs mefloquine	126	Mefloquine: 126	Adults Children (≥ 13 yr)	1995-96 Thailand
A005	Open, randomized, parallel group efficacy/safety Coartem vs quinine/Fansidar	12	Quinine/ Fansidar: 11	Adults	1996-97 UK
A007	Double-blind, randomized, parallel group efficacy/safety Coartem vs chloroquine	89	Chloroquine: 90	Adults	1995-96 India
A008	Open, randomized, parallel group efficacy/safety Coartem vs MAS	309	MAS: 308	Adults Children (≥ 5 yr)	1995-96 Thailand
A010	Double-blind, randomized, parallel group efficacy/safety Coartem vs Fansidar	144	Fansidar: 143	Children (≤ 5 yr)	1996-97 Gambia
A011	Open, randomized, parallel group efficacy/safety Coartem vs chloroquine	130	Chloroquine: 130	Children (≤ 5 yr)	1996 Tanzania
A014	Double-blind, randomized, parallel group efficacy/safety Coartem vs halofantrine	51	Halofantrine: 52	Adults (≥ 17 yr)	1996-97 Europe
AIC04	Open, randomized, parallel group efficacy/safety Coartem vs chloroquine	36	Chloroquine: 36	Adults	2000 Senegal
AIC04	Open, randomized, parallel group efficacy/safety Coartem vs Fansidar	30	Fansidar: 30	Adults	2000 Cameron

Fansidar = sulfadoxine/pyramethamine

Table 8: Efficacy of Supportive Active-Controlled Studies with 4-Dose Coartem Regimen

Study No.	Group	N	Cure Rate			Time to Parasite Clearance (Median)	Parasite Reduction at 24 hours (Median)	Time to Fever Clearance (Median)
			7-day	14-day	28-day			
A007	Coartem Chloroquine	89	-	-	95.4%	36 hr	98.8%	18 hr
		90	-	-	19.7%	60 hr	70.7%	27 hr
A011	Coartem Chloroquine	130	92.4%	84.1%	-	-	97.8%	-
		130	29.6%	8.6%	-	-	59%	-
AIC04 Senegal	Coartem Chloroquine	36	-	100%	-	1 day	94.3%	-
		36	-	63.9%	-	2 days	54.7%	-
AIC04 Cameroon	Coartem Fansidar	30	-	93.3%	-	2 days	76.8%	-
		30	-	53.3%	-	7 days	49.2%	-
A005	Coartem Quinine/ Fansidar	12	-	-	100%	36 hr	99.2%	-
		11	-	-	100%	69 hr	87.6%	-
A010	Coartem Fansidar	144	-	93.3%	-	-	99.2%	-
		143	-	97.7%	-	-	92.5%	-
A003	Coartem Quinine	111	-	-	60.8%	40 hr	98.6%	52 hr
		108	-	-	71.8%	77 hr	67.3%	88 hr
A004	Coartem Mefloquine	126	-	-	69.3%	43 hr	98.6%	32 hr
		126	-	-	82.4%	66 hr	76.1%	54 hr
A008	Coartem MAS	309	-	-	82.1%	-	100%	-
		308	-	-	97.3%	-	100%	-
A014	Coartem Halofantrine	51	-	-	82.2%	32 hr	99.7%	24 hr
		52	-	-	100%	48 hr	89.6%	32 hr

Fansidar = sulfadoxine/pyramethamine

3.3 Four-Dose Regimen Compared to 6-Dose Regimen, Study A025

Results of 4-dose studies conducted by the applicant in areas of high transmission and high resistance in Thailand during 1995-96 (A003, A004, A008) showed lower efficacy results than in the studies in China. Therefore, Study A025 was designed to compare the 4-dose regimen to a longer 6-dose treatment regimen.

3.3.1 Study Design

Study A025 was a randomized, double-blind, two-center study conducted in Thailand comparing the 4-dose, 48-hour regimen of Coartem to a 6-dose, 60-hour regimen, and a 6-dose, 96-hour regimen. In Bangkok (Center 1) patients were ≥ 12 years of age and treated as inpatients during the 28-day trial period. Patients in MaeLa (Center 2) were ≥ 2 years of age and treated as outpatients, seen daily for the first week and weekly thereafter until Day 28 with a long-term follow-up visit on Day 63.

Table 9 shows the dosing schedule for the three treatment arms.

Table 9: Dosage of trial medications and time of administration in Study A025

Dose Number	1	2	3	4	5	6	7	8
Time (hr.)	0	8	24	36	48	60	72	96
Timing of Dosing								
4 doses over 48 hours	X	X	X	P	X	P	P	P
6 doses over 60 hours	X	X	X	X	X	X	P	P
6 doses over 96 hours	X	X	X	P	X	P	X	X

X= Coartem tablets

P=placebo tablets

Dosage was adjusted for weight.

As this table shows, the three treatment arms were identical for the first three doses (up to 36 hours), starting with the fourth dose the regimens started to differ in the dosing and timing of administration.

3.3.2 Demographic and Baseline Characteristics

There were 359 patients enrolled in the study. Over 65% of the patients were male. Of the 259 patients recruited in MaeLa, 43 (17%) were children \leq 12 years old. The baseline median parasite density was slightly higher in patients in the 4-dose arm than in the two 6-dose arms.

A total of 76 patients discontinued prematurely from the trial, of whom 26 had a poor therapeutic response (20 in the 4-dose arm, 4 in the 6-dose, 60-hour arm, and 2 in the 6-dose, 96-hour arm). Of the remaining 50 (14%) patients, 45 patients were lost to follow-up (9% of patients in Bangkok and 14% in MaeLa). Therefore, 309/359 or 86% of patients completed the 28 day trial period (90% in Bangkok, 84.6% in MaeLa). Two patients died in the 4-dose arm – one was shot by a military group and one died after stepping on a landmine.

3.3.3 Overall Efficacy Results

3.3.3.1 28-day Cure Rate

The primary efficacy endpoint is 28-day cure rate, as shown in Table 10. The 6-dose, 60-hour regimen (the applicant's proposed regimen) had numerically higher cure rates than the 4-dose regimen, significantly so in the evaluable population. The 6-dose, 96-hour regimen was significantly superior to the 4-dose regimen for both the ITT and the evaluable populations.

Table 10: 28-day cure rate [95% CI] in ITT and Evaluable Populations in Study A025

	Coartem 4-doses (48 hours)	Coartem 6-dose (60 hours)	Coartem 6-dose (96 hours)
ITT	85/120 (70.8%)	96/118 (81.4%)	104/121 (86.0%)
<i>Diff [CI]</i>		10.5% [-1.9%, 22.8%]	15.1% [2.8%, 27.3%]
<i>p-value</i>		0.069	0.0048
Evaluable	84/104 (80.8%)	93/96 (96.9%)	104/106 (98.1%)
<i>Diff [CI]</i>		16.1% [6.0%, 26.7%]	17.3% [7.6%, 27.7%]
<i>p-value</i>		< 0.001	< 0.001

Fisher's exact test p-values and 97.5% exact CI for differences in cure rates between six dose (60-hour or 96-hours) and four- dose regimens

There was a center effect in cure rates in that the Bangkok site had higher parasite count at baseline and lower 28-day cure rate than the MaeLa site, as shown in Table 11. Additionally, in a logistic regression model after controlling for baseline parasite count, center remained a significant predictor of 28-day cure rate. Given the differences in patient populations between the two sites (based on age and inpatients vs. outpatients), this effect is not surprising. Note that the interaction terms between center and treatment were not significant, i.e., treatment effects did not vary significantly between centers.

Table 11: 28-day cure rate by study center in the ITT population in Study A025

	Coartem 4-dose (48 hours)	Coartem 6-dose (60 hours)	Coartem 6-dose (96 hours)
Center 1 (Bangkok)	20/34 (58.8%)	27/32 (84.4%)	30/34(88.2%)
Center 3 (Maela)	65/86 (75.6%)	69/86 (80.2%)	74/87(85.1%)

3.3.3.2 Parasite Clearance Time (PCT)

PCT is reported in Table 12. There were no statistically significant differences in PCT among the treatment arms, as would be expected given that the treatment arms did not differ until 36 hours.

Table 12: Time to Parasite Clearance (in hours) in Study A025

	Coartem 4-dose (48 hours)	Coartem 6-dose (60 hrs)	Coartem 6-dose (96 hrs)
	N=120	N=118	N=121
Median* [95%CI]	44 [43,44]	44 [43, 45]	44 [43,44]
25-75 percentile	34 – 51	22 - 47	40 - 47
Range**	18 - 72	17 - 166	17 - 90

* Kaplan-Meier method

** Not including censored times

3.3.3.3 Fever Clearance Time

There were no statistically significant differences in fever clearance time among the three treatment arms overall (Table 13) as would be expected given that the treatment arms did not differ prior to 36 hours.

Table 13: Fever Clearance Time (in hours) in Study 025

	Coartem 4-dose (48 hours)	Coartem 6-dose (60 hrs)	Coartem 6-dose (96 hrs)
	N=61	N=59	N=77
Median* [95%CI†]	23 [21, 36]	35 [22, 43]	22 [21, 34]
25-75 percentile*	20 - 44	20 - 46	20 - 44
Range **	19 - 95	9 - 160	9 - 164

* Kaplan-Meier method.

** Not including censored times.

†Based on the sign test (Brookmeyer and Crowley, 1982).

3.3.3.4 Efficacy Results in Adults and Children

Efficacy was evaluated in adult and pediatric patients separately as shown in Table 14. Results were similar between adults and children treated with 6-doses Coartem.

Table 14: Comparison of 28-day cure rate, PCT, and FCT in Adults and Children (Study A025)

	Coartem 4-dose (48 hours)	Coartem 6-dose (60 hours)	Coartem 6-dose (96 hours)
Adults			
28 day cure rate	67/99 (67.7%)	71/88 (80.7%)	78/92 (84.8%)
PCT (hrs)			
Median * [95%CI†]	44 [43,44.4]	44 [43,45]	44 [43,44.1]
25-75 percentile*	40-52	40-53	37-50
Range**	18-72	17-166§	18-90
FCT (hrs)			
Median* [95%CI†]	34 [21-41]	36 [22-44]	21 [20.9, 34]
25-75 percentile*	20-44	21-45	20-43
Range**	18-95	9-160	9-142
Children			
28 day cure rate	18/21 (85.7%)	25/30 (83.3%)	26/29 (89.7%)
PCT (hrs)			
Median * [95%CI†]	44 [22,45]	43 [22,45]	44 [42,44]
25-75 percentile*	22-45	22-45	42-45
Range**	19-72	18-68	19-67
FCT (hrs)			
Median* [95%CI†]	22 [19,43]	27 [20,45]	22 [20,44]
25-75 percentile*	19-43	20-46	20-44
Range**	12-70	18-70	18-164

* Kaplan-Meier method ** Not including censored times. †Based on the sign test (Brookmeyer and Crowley, 1982). § in one subject no slide was available between Days 2 and 8, thus PCT was calculated as 166 hours.

3.3.4 Timing of Parasite Clearance

To assess timing of clearance of parasites from the bloodstream, the number of patients who had negative slides for malaria on day 2, 3, 4, and 7 were analyzed for each of the treatment arms. Approximately 23%, 77%, and 94% of subjects had a negative slide after one, two, and three days of treatment, respectively, across all three treatment arms. There were no obvious differences between the arms.

3.3.5 Efficacy at 24 and 48 hours of Treatment

The early treatment efficacy of Coartem in reducing parasite density was analyzed by assessing parasite reduction in the first 48 hours of treatment compared to baseline parasite density. Subjects who achieved a $\geq 75\%$ reduction in their baseline parasite counts at 24 hours and 48 hours were evaluated. More than 90% of patients in all treatment arms achieved a $\geq 75\%$ reduction by 24 hours.

3.3.6 Late Treatment Failure (Recrudescence)

During the specified study period (day 1 to 29), 20/120 patients experienced recrudescence of *P. falciparum* in the 4-dose arm between days 15 to 29, in the 6-dose, 60-hour arm 3/118 patients

recrudesced (days 14, 15, and 21), and in the 6-dose, 96-hour arm 2/121 patients recrudesced (days 15 and 29).

3.3.7 Summary and Conclusions, Study A025

The 28-day cure rates of the 6-dose, 60-hour and 96-hour regimens were numerically higher than the 4-dose regimen, significantly so in the evaluable population. There was little difference in terms of parasite clearance between the study arms, which was expected given that the treatment arms did not differ from one another until after 36 hours. As discussed in the review of clinical safety (Section 5.5), the safety profile of the two 6-dose regimens was similar to the 4-dose regimen. The 6-dose, 60-hour regimen was chosen by the applicant for use in future trials for ease of administration.

The limitation of this study is that there were only two centers, so generalizing this result to a wider population may be a concern.

3.4 Studies with Comparator Arm, A026 and A028

Studies A026 and A028 were randomized, open-label studies designed to evaluate the six-dose Coartem regimen compared to a combination of mefloquine plus artesunate (MAS).

Randomization was 2:1 (Coartem:MAS) in these studies and no formal statistical comparisons with MAS were planned by the applicant. MAS was the standard of care for treatment of uncomplicated *P. falciparum* malaria in Thailand at the time the studies were conducted.

Study A026 was conducted in the same two sites in Thailand as Study A025. Study A028 was conducted only at the Bangkok site. Study A026 enrolled subjects aged ≥ 2 years and A028 enrolled subjects >12 years. Pediatric subjects represented 20% (84/419) of subjects from these two studies.

In Study A026 there were 200 patients enrolled (150 Coartem: 50 MAS) and 219 in Study A028 (164 Coartem:55 MAS).

3.4.1 Overall Efficacy Results

The primary efficacy endpoint of 28-day cure rate is shown in Table 15. The cure rates were 87% and 90% for Studies A026 and A028, respectively, and similar to MAS.

Table 15: 28-day cure rate [95% CI*] in ITT and evaluable populations (Studies A026 and A028)

	Study 026		Study 028	
	Coartem	MAS	Coartem	MAS
ITT	130/150 (86.7%) [80.2%, 91.7%]	47/50 (94.0%) [83.5%, 98.7%]	148/164 (90.2%) [84.6%, 94.3%]	53/55 (96.4%) [87.5%, 99.6%]
<i>Diff in %</i>		-7.3[-15.6, 3.6]		-6.1[-12.8, 3.0]
Evaluable	130/134 (97.0%) [92.5%, 99.2%]	47/47 (100%) [92.5%, 100%]	148/155 (95.5%) [90.9%, 98.2%]	53/53 (100%) [93.3%, 100%]
<i>Diff in %</i>		-3.0[-7.9, 4.4]		-4.5[-9.3, 2.1]

*Exact method.

The median FCT times were high and similar in both treatment arms in both studies (22 hours and 29 hours, respectively). PCT was not defined in the protocol for Study A026, but in Study A028 the median PCT was about 30 hours in both treatment arms.

All evaluable patients in both studies achieved a >75% reduction in their baseline parasite count at 48 hours. Four patients in Study A026 and one patient in Study A028 in the Coartem arm had an increase in parasite counts from baseline at 24 hours but subsequently cleared.

In Study A026, on Day 2, about 24 hours after start of treatment, parasitemia was cleared in more than 21% of the patients in both treatment arms. By Day 3, about 48 hours after start of treatment approximately 88% of patients were negative for malaria parasites; 100% of patients in both treatment arms were negative at 72 hours after the start of treatment.

In Study A028, on Day 2, about 24 hours after start of treatment, parasitemia was cleared in more than 43% of the patients in both treatment arms. By Day 3, about 48 hours after start of treatment approximately 94% of patients were negative for malaria parasites; 100% of patients in both treatment arms were negative on day 4

3.4.2 Efficacy Results in Adults and Children

Efficacy was evaluated in adult and pediatric patients separately as shown in Table 16. Results were similar between adults and children treated with Coartem, with the exception of a longer FCT in children.

Table 16: Comparison of 28-day cure rate, PCT, and FCT in Adults and Children (Studies A026 and A028)

Endpoint	Population	Study A026		Study A028	
		Coartem	MAS	Coartem	MAS
28-day cure rate	Adults	94/109 (86.2%)	31/34 (91.2%)	134/149 (89.9%)	41/43 (95.4%)
	Children	36/41 (87.8%)	16/16 (100%)	14/15 (93.3%)	12/12 (100%)
PCT (hrs)	Adults Median*[95%CI†] 25-75 percentile* Range**	ND	ND	30[26,32] 18-40 7-64	32[26-32] 25-40 7-57
	Children Median*[95%CI†] 25-75 percentile* Range**	ND	ND	24[24,40] 22-40 16-48	24[16-32] 16-32 8-42
FCT (hrs)	Adults Median*[95%CI†] 25-75 percentile* Range**	21[20,24] 19-44 1-68	22[20,26] 20-42 18-142	29[22,32] 8-48 3-163	28[15,31] 15-35 6-155
	Children Median*[95%CI†] 25-75 percentile* Range**	44[22,45] 21-45 18-163	41[21,66] 21-66 18-164	38[25,54] 25-54 7-55	21[6,28] 15-23 6-28

ND = not done. * Kaplan-Meier method. ** Not including censored times. †Based on the sign test (Brookmeyer and Crowley, 1982).

3.4.3 Recrudescence

In Study A026, four patients in the Coartem arm and no patients in the MAS arm had recrudescence of malaria parasites during the study period through day 29. Three of the patients with recrudescence were found to have low lumefantrine levels.

In Study A028, seven patients in the Coartem arm and no patients in the MAS arm had recrudescence of malaria parasites during the study period. Three of the patients with recrudescence were found to have low lumefantrine levels.

3.4.4 Summary and Conclusion, Studies A026 and A028

Efficacy results in Studies A026 and A028 were similar to the 6-dose Coartem arms in Study A025. All three studies were conducted at the same sites in Thailand.

3.5 Study in Non-immune Adults, A2401

Study 2401 is an open-label, multi-center, non-comparative, single-arm, study of Coartem in non-immune adult patients conducted in Europe (Switzerland, Germany, France, Netherlands, Italy) and Columbia. The definition of a non-immune patient was: individuals who have not spent the first 5 years of life nor the most recent 5 years in endemic areas and who have not had a diagnosis of acute uncomplicated *P. falciparum* malaria in the past 5 years.

The study was designed as a non comparative study because of difficulty with recruitment due to the low numbers of travelers with malaria returning to Europe. Subsequently an additional study (n=15 patients) was done to get more PK data (“rich” PK study) and results for are also included for the primary endpoints.

Adults age 16 to 66 years were enrolled. The majority had parasite counts < 5,000/μL. The patient population was generally of higher body weight (mean 73 kg, with a range of 41 to 119 kg) than the populations of previous studies with the 6-dose regimen of Coartem in adults, which were conducted in South-East Asia.

A majority of the patients (n=139, 92.7%) completed the full 6-dose course of study drug. Two patients discontinued due to an unsatisfactory therapeutic response. Seventeen patients were lost to follow up mainly due to the fact that they did not attend the final Day 28 clinic visit. A significant proportion of patients failed to return to the centers once their malaria symptoms had resolved. It is perhaps notable that such discontinuations and protocol violations were uncommon in the Colombian patients as compared with their European counterparts.

3.5.1.1 Overall Efficacy Results

Results for the 28-day cure rate (primary efficacy endpoint), PCT, and FCT in the ITT and evaluable populations are summarized in Table 17.

Table 17: Coartem 28-Day Cure Rate, PCT, and FCT in Study A2401

	Core Study	Core plus PK study
28 day cure rate (ITT) [95% CI§]	109/147 (74.1%) [66.3, 81.0]	120/162 (74.1%) [66.6, 80.6]
28 day cure rate (evaluable) [95% CI§]	108/113 (95.6%) [90.0, 98.5]	119/124 (96%) [90.8, 98.7]
PCT (hrs, ITT) Median * [95% CI†]	41.8 [40.5, 44]	41.8[40.3, 43.8]
FCT (hrs, evaluable) Median* [95% CI †]	36.8[24.0, 40.0]	36.8[24.5, 40.0]

§ Exact method. * Kaplan-Meier Method. †Based on the sign test (Brookmeyer and Crowley, 1982).

In the evaluable population, the 28-day cure rate was > 95% in the core study and including the rich PK population. The low cure rates (74%) observed in the ITT population are most likely due to the large number of patients (n=29, 19%) in the core study who were lost to follow-up. Two of these patients had an unsatisfactory response to treatment but all were counted as treatment failures in the efficacy analysis.

The parasite clearance time and the fever clearance time were similar to those observed in other studies.

Five patients were considered treatment failures: one was withdrawn due to unsatisfactory therapeutic effect before receiving the full treatment course of Coartem; one patient did not achieve parasite clearance within 7 days, but cleared by day 10 and no other treatment was

given; and three patients had recrudescence of parasites on days 22, 24 and 28 after initial clearance.

3.5.1.2 Conclusion, Study A2401

Study A2401 was conducted in a nonimmune, primarily Caucasian, population. The 28-day parasitological cure rate in the ITT population was lower than seen in other 6-dose studies and was due to the relatively high number of patients who were lost to follow-up and counted as failures.

3.6 Studies in Pediatrics, Studies A2403 and B2303

Two studies were conducted in African children. Study A2403 was an open-label, single arm, multicenter study conducted in Kenya, Nigeria, and Tanzania to obtain information on the use of Coartem in young children with body weights as low as 5 kg. Study B2303 was a partially blinded, randomized multicenter trial of Coartem tablets (crushed for administration) compared to Coartem dispersible tablets in children weighing 5 to < 35 kg in sub-Saharan Africa. The applicant is not requesting approval of the dispersible tablet in this NDA application.

Patients were dosed with Coartem based on body weight in both studies as shown:

≥5 kg to <15 kg = 1 tablet per dose

≥15 kg to <25 kg = 2 tablets per dose

≥25 kg to <35 kg = 3 tablets (only used in Study B2403) per dose

In both studies, study medication should have been followed whenever possible by food/drink (e.g. broth, milk [preferably condensed milk]) as appropriate. In Study A2403 if the infant/child was unable to swallow tablets, the tablets were dissolved and then given to the child.

3.6.1 Study A2403

There were 310 patients enrolled in the study. Subjects are categorized by body weight, as shown in Table 18. Approximately 50% of the patients were in the 5 - < 10 kg body weight group (age range approximately 2 months to 3 years), representing a non-immune population at high risk of malaria and of death due to malaria.

Table 18: Age and Body Weight in Study A2403

	5 - <10kg	10 - < 15kg	15 - 25kg	Total
No. of patients	154	110	46	310
Age in years (median)	1.1	2.8	6.1	2.0
Range	0.2 - 3.1	0.8 - 6.8	2.9 - 9.9	0.2-9.9
Age Distribution – number (%)				
0 to 6 months	26 (17)	0	0	26 (8)
> 6 to 12 months	49 (32)	2 (2)	0	51 (17)
> 12 to 24 months	65 (42)	14 (13)	0	79 (26)
> 2 to 4 years	14 (9)	77 (70)	6 (13)	97 (31)
> 4 to 6 years	0	15 (13)	17 (37)	32 (10)
> 6 years	0	2 (2)	23 (50)	25 (8)

A total of four patients discontinued treatment prematurely, one due to an adverse event, two withdrew consent, and one was withdrawn due to a protocol violation. Three of these patients completed the 28-day follow-up. Three further patients discontinued during the follow-up period although they had completed the treatment period: two were lost to follow-up and one died.

The primary objective of this study was to evaluate the safety of Coartem 6-dose treatment in the target population of young African children. Assessment of efficacy was a secondary objective of the study.

The overall 28-day cure rate was 86% (268/310) in the ITT population, as shown in Table 19. Cure rates were similar across all age groups. Among the 42 patients classified as failures, there were 32 patients with recrudescence of *P. falciparum*, three patients without a parasite count on Day 28, one patient who received rescue medication, and four patients who were censored prior to Day 28. In 26 of the cases of recrudescence, parasitemia was detected at the Day 28 visit (day 29 of study).

The median PCT was 24 hours in all body weight groups. Although the median PCT was longer in the 10 to < 15 kg group (35 hours), the range was similar to the other groups. Fever clearance time was approximately 8 hours in all groups. It should be noted that a large proportion of patients (over 75%) took paracetamol (acetaminophen) as a concomitant medication during the study, which may have accounted for the more rapid FCT compared to other studies.

Table 19: Coartem 28-day cure rate, PCT, FCT by body weight in Study A2403

	5 - < 10kg	10 - < 15kg	15 - 25kg	Total
28 day cure rate (ITT) n/N (%) [95% CI§]	133/154 (86.4) [79.9, 91.4]	94/110 (85.5) [77.5, 91.5]	41/46 (89.1) [76.4, 96.4]	268/310 (86.5) [82.1, 90.1]
28 day cure rate (evaluatable) n/N (%) [95% CI§]	133/149 (86.4) [83.1, 93.7]	94/107 (85.5%) [80.1, 93.4]	40/44 (89.1) [78.3, 97.5]	267/300 (86.5) [84.9, 92.3]
PCT Median* [95%CI†] 25-75 percentile* Range**	24[24, 35.4] 23.8 – 36.0 (5.3 to 68.0)	35.5[24, 35.8] 23.8 – 36.0 (7.7 to 59.9)	24[23.8-24.2] 23.7 – 35.9 (7.2 to 71.1)	24[24.0,35.4] 23.8 – 36.0 (5.3 to 71.1)
FCT Median* [95%CI†] 25-75 percentile* Range**	7.8[7.8,7.9] 7.8 – 23.8 (5.9 to 170.8)	7.9 [7.8,8.0] 7.8 - 23.6 (4.1 to 332.4)	7.8 [7.8,8.0] 7.8 – 8.4 (7.2 to 308.7)	7.8[7.8,7.9] 7.8 – 23.7 (4.1 to 332.4)

§ Exact method. * Kaplan-Meier Method. ** Not including censored times. †Based on the sign test (Brookmeyer and Crowley, 1982).

On Day 2, about 24 hours after start of treatment, parasitemia was cleared in more than 50% of the patients. By Day 3, about 48 hours after start of treatment, approximately 95% of patients were negative for malaria parasites; 100% of patients were negative for malaria at 72 hours post first dose.

In this study the 6-dose regimen of Coartem demonstrated good efficacy in infants and children, with a cure rate similar to earlier studies in adults and older children. Cure rates were similar across all body weight groups, even in young infants. Response to treatment was rapid, with a median time to PCT of 24 hours and a FCT of 8 hours.

3.6.2 Study B2303

The study population consisted of male and female infants and children ≤12 years of age, with body weight of ≥ 5 kg and <35 kg. Patients were admitted to hospital for the first 3 days and all treatments were given under hospital supervision. All randomized patients remained under medical surveillance (if possible within hospital grounds) for the following 4 days (until Day 7) and were then followed until Day 42.

As shown in Table 20, a total of 899 patients were enrolled. Over 50% of patients were aged 2 to < 6 years of age. A total of 60.8% of patients were in the 5 to <15 kg body weight group, compared to 32.1% in the 15 to <25 kg group and 7.0% in the 25 to <35 kg group.

Table 20: Age and Body Weight in Study B2303

	Coartem Dispersible N=447	Coartem Crushed N=452	Total N= 899
Age in years – median (range)	3.0 (0-12)	3.0 (0-12)	3.0 (0-12)
Weight in kg – median (range)	13 (5-34)	13 (6-34)	13 (5-34)
Age Distribution – number (%)			
0 to 3 months	1 (<1%)	1 (<1%)	2 (<1%)
3 to < 6 months	6 (1)	7 (1)	13 (1)
6 to < 12 months	23 (5)	28 (6)	51 (6)
12 to < 24 months	81 (18)	73 (16)	154 (17)
2 to < 4 years	145 (32)	149 (33)	294 (33)
4 to < 6 years	92 (21)	89 (20)	181 (20)
6 to 12 years	99 (22)	105 (23)	204 (23)

The median parasite density was slightly lower in the dispersible tablet group compared to the crushed tablet group although they were comparable for densities below 100,000/μL (87.1% dispersible tablet group vs. 84.1% crushed tablet group). A total of 14% of patients had a high parasite density of 100,000 to 200,000/μL.

All patients who were randomized were treated with at least one dose of study medication. Over 85% of patients in each treatment group completed the study. The main reason for patients discontinuing treatment early in both groups was adverse events, (see clinical safety in Section 5)

The overall 28-day cure rate, PCT, and FCT in the ITT population, are shown in Table 21. Cure rates were similar between the two treatment arms and similar to Study A2403. The median PCT was 35 hours for both treatment groups. Median FCT was less than 8 hours and was comparable between body weight groups within and between treatment groups. Of those patients with fever (body temperature $\geq 37.5^{\circ}\text{C}$) at baseline, the majority achieved fever clearance by 24 hours, with the proportion being lower in the dispersible tablet group (55%) compared to the crushed tablet group (59%). It should be noted that almost all patients (over 95%) took an antipyretic, primarily panadol/paracetamol (acetaminophen), as a concomitant medication during the study, which may have accounted for the more rapid FCT compared to other studies.

Table 21: Coartem 28-day cure rate, PCT, FCT in Study B2303

	Dispersible Tablet	Crushed Tablet
28 day cure rate (ITT)		
n/N (%)	374/441 (84.8)	374/444 (84.2)
[95% CI§]	[81.1,88.0]	[80.5,87.5]
28 day cure rate (evaluable)		
n/N (%)	368/398 (92.5)	367/406 (90.4)
[95% CI§]	[89.4,94.9]	[87.1,93.1]
PCT (hrs, ITT)		
Median* [95%CI†]	34.3[24.6, 35.5]	34.9[25.2,35.6]
25 th -75 th percentile*	23.9-36.1	23.9-36.0
Range**	6.5-169.0	6.6-165.6
FCT (hrs, evaluable)		
Median* [95%CI†]	7.8[7.8,7.9]	7.8[7.8,7.9]
25 th -75 th percentile*	7.6-23.6	7.5-23.2
Range**	3.8-695.4	4.7-355.4

§ Exact method. * Kaplan-Meier Method. ** Not including censored times. †Based on the sign test (Brookmeyer and Crowley, 1982).

On study Day 2, about 24 hours after start of treatment, parasitemia was cleared in more than 39% of the patients. By Day 3, about 48 hours after start of treatment, approximately 94% of patients in both treatment groups were negative for malaria parasites. Three patients (0.7%) in each treatment group had parasite present at > 72 hours.

There were two patients (0.5%) in the dispersible tablet group and no patients in the crushed tablet group with early treatment failure. Both patients developed severe malaria during the first 3 days of the study.

During the study period (day 1 to 29) a further five patients (crushed group, n=4; dispersible group, n=1) developed severe malaria. Late parasitological failure occurred in 47 (10.4%) in the crushed tablet group and 39 (8.7%) patients in the dispersible tablet group. After day 29, a further 55 (12.2%) in the crushed tablet and 48 (10.7%) of patients in the dispersible tablet group had recrudescence of parasites in the ITT population.

In this study the 6-dose crushed tablet of Coartem demonstrated good efficacy in children, with cure rates similar to earlier studies in children and adults. Cure rates were similar across all body weight groups. The median PCT was slightly longer than in Study A2403, while FCT was similar between the two studies, but most patients received antipyretics.

3.6.3 Efficacy Summary

A 4-dose regimen of Coartem in the ITT population has been shown to be superior to each of the individual components: to artemether in terms of 28-day cure rate and to lumefantrine in PCT and FCT in Studies ABMO2 and A023. The 28-day cure rate was approximately 95% in these two studies conducted in China. In Study A025 conducted in Thailand the 28-day cure rate of 4 doses of Coartem was only 71% and 6-doses of Coartem given over 60 hours resulted in a numerically higher cure rate (81%). In the comparative studies A026 and A028, also conducted in Thailand, 6 doses of Coartem consistently demonstrated similar 28-day cure rates (87% and 90%, respectively). While some children were enrolled in these studies, additional studies conducted in young African children (A2403 and B2303) demonstrated similar cure rates to the Thailand studies (86% and 85%, respectively). In European travelers, the cure rate was somewhat lower (74%) than that seen in other studies, but may have been due to a relatively large number of patients who were lost to follow-up and counted as failures.

The results for PCT and FCT across the 6-dose studies were also similar with a median PCT ranging between 24 to 44 hours and a median FCT between 22 to 37 hours, with the exception of the African pediatric studies. In Studies A2403 and B2303 the median FCT was only 8 hours, but the majority of these children also received anti-pyretic medications.

3.7 Additional Issues

3.7.1 Mixed Infections

Patients with mixed infection with *P. falciparum* and another *Plasmodium* species were observed in five studies as shown in Table 22. The outcomes for these patients are summarized in the following table. There were 55 patients who had mixed malaria infections. The second *Plasmodium* species, *P. vivax* (43), *P. ovale* (3), *P. malariae* (8) was identified in all but one patient. All patients cleared their parasitemia within 48 hours. The patients with *P. vivax* were not treated with primaquine and therefore a high percentage 14/43 (33%) had recurrence during the study or during follow up.

Table 22: Mixed Infections with *P. falciparum* and other *Plasmodium* species

Study #	Design	Type of Infection Mixed with <i>P. falciparum</i> in Coartem arm / No.	Outcome of patients (pts.)
A025	Coartem 6-dose vs. 4-dose regimen	<i>P. vivax</i> (n=20) (8 patients ≤ 12 years of age)	All cleared within 48 hours; 9/20 patients had reappearance of vivax (6 pts. on or before Day 28 and 3 pts. between Days 28 and Day 42)
A026	Coartem 6 dose vs. mefloquine/artesunate	<i>P. vivax</i> (n=5) (all > 12 years of age)	All cleared by 24 hrs; 2/5 had reappearance of vivax (Day 29 and Day 49)
A028	Coartem 6 dose vs. mefloquine/artesunate	<i>P. vivax</i> (n=16)	All cleared within 48 hours; 3/16 had reappearance of vivax
B2303	Coartem Tablet vs. dispersible tablet in infants and children	Mixed (n=6) (age: 5-9 yrs): <i>P. ovale</i> (3), <i>P. malariae</i> (2), Unidentified (1)	All cleared by Day 2; 0/6 had reappearance
A2401	Coartem 6 dose non-comparative in non-immune	Mixed (n=8) <i>P. malariae</i> (6); <i>P. vivax</i> (2)	All cleared by 48h; 1/6 with <i>P. malariae</i> had had reappearance on Day 28; 0/2 with <i>P. vivax</i> had recurrence
		Total: <i>P. vivax</i> (43) <i>P. ovale</i> (3) <i>P. malariae</i> (8) Unidentified (1)	Recurrence: <i>P. vivax</i> : 14/43 (33%) <i>P. ovale</i> : 0/3 (100%) <i>P. malariae</i> : 1/8 (13%)

3.7.2 Gametocyte Clearance

The applicant states that Coartem has anti-gametocyte activity. Clearance of gametocytes is important because it breaks the cycle of transmission between the human host and the mosquito vector. The sponsor defines gametocyte clearance time as time from first dose until the first total and continued disappearance of gametocytes which remains at least a further 48 hours. Gametocyte clearance times were calculated for patients with presence of gametocytes at any time during the first 72 hours.

The following methodology was generally used by the applicant to detect the presence of gametocytes.

Blood Examination during Screening

At screening, 20 thick film high power fields for malaria parasites were examined. If there were no parasites seen the patient was not eligible for enrollment. If asexual forms of the parasite were seen then 200 thick film fields were screened for *Plasmodium* species.

If *P. falciparum* was confirmed, a count was made of the asexual forms against leucocytes, using a tally counter. Counting was based on 200 leucocytes which is in accordance with WHO standards. If insufficient parasites were detected, counting was extended to 500 leucocytes. The parasite density was calculated according to the equation:

Parasite density per μl = No. of parasites x actual WBC / Number of leucocytes counted (200)

If gametocytes of *P. falciparum* were present, a gametocyte count was made by counting gametocytes per 1000 leucocytes. If less than five gametocytes were counted this was repeated against 2000 leucocytes.

Blood Examination for Malaria during the 28 day Trial Period

Blood was examined four times per day for the first three days of the study, daily until day 8 and then day 15, 22, 29.

- A total of 200 thick film fields were examined (tally counter) before a slide was confirmed negative.
- If asexual forms of *P. falciparum* were present, a parasite count was required
- If *Plasmodium* species other than *P. falciparum* were found, species and count were recorded.
- If *P. falciparum* gametocytes were found, a gametocyte count was performed.

Therefore, we believe that the evaluation of gametocyte clearance is problematic as the sensitivity of the tests for gametocytes are not well defined.

3.7.3 Pharmacokinetics

The pharmacokinetics of lumefantrine and artemether following administration of Coartem was determined in several studies involving malaria patients. The studies are given below:

- **Study A025:** this study was conducted in 1996/97 in Thailand at the Faculty of Tropical Medicine, Mahidol University, Bangkok, and at Shoklo Malaria Research Unit (SMRU), Mae Sot, Thailand. It aimed to compare the 4-dose regimen (given over 2 days, total dose 320 mg artemether/1920 mg lumefantrine) with the 6-dose regimen given over 3 or 5 days (total dose of 480 mg artemether/2880 mg lumefantrine). In total, 359 adult male and female patients and few children were enrolled in this study and were randomized to one of the three treatments. Detailed PK data for lumefantrine was obtained in 51 adult patients (18 patients treated with the 6-dose regimen over 3 days).
- **Study A028:** this study was conducted in 1998/99 in Thailand at the Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand. It aimed to confirm the safety and efficacy of the 6-dose regimen of co-artemether (final marketed formulation) in acute *Plasmodium falciparum* malaria patients. This was an open-label, randomized, parallel group and multicenter 4-week trial including a control arm with MAS (mefloquine and

artesunate) to bridge results with previous experience. In total, 219 adult male and female patients were enrolled, of whom 164 received Coartem. Detailed PK for artemether, dihydroartemisinin (DHA) and lumefantrine was obtained from 25 patients.

- **Study A2401:** this study was conducted from 2001 to 2005 in non-immune travelers in four countries in Europe: Switzerland (5 centers), Germany (4 centers), France (4 centers), Italy (1 center), and the Netherlands (1 center), and in one non endemic country in South America: Colombia (1 center). This was an open label, multi-center, non-comparative efficacy, safety and tolerability study of the 6-dose regimen of Coartem in the treatment of acute uncomplicated *Plasmodium falciparum* malaria in non-immune patients. A total of 165 male (69%) and female patients entered the study, 118 from Europe and 47 from Colombia. Detailed PK for lumefantrine and desbutyl-lumefantrine was obtained from 15 patients in Colombia.
- **Study A2403:** this study was conducted in 2002-2003 in three countries in Africa, Kenya, Nigeria and Tanzania (one center per country). This was an open label, multicenter study for the evaluation of the safety and efficacy of Coartem (6-dose regimen, dose was based on body weight) in 300 African infants and children weighing between 5 and 25 kg (age range 0.2-9.9 years) with acute uncomplicated falciparum malaria. Considering the target population (very small infants and children), the study comprised a single plasma PK sample per patient at six different time-points across patients for the determination of lumefantrine concentrations. Two hundred patients (from Kenya and Nigeria centers) participated in the pharmacokinetic (lumefantrine) part of the study.
- **Study B2303:** this study was conducted in 2006-2007 in five countries, Benin, Kenya, Mali, Mozambique, and Tanzania, and included 899 (447 in the Coartem dispersible tablet group and 452 in the Coartem crushed tablet group) male and female children. It was a randomized, investigator-blinded, multicenter, parallel-group study to compare efficacy, safety and tolerability of co-artemether (6-dose regimen, dose was based on body weight) as an investigational dispersible tablet formulation versus crushed tablet in the treatment of acute uncomplicated *P. falciparum* malaria in infants and children less than 12 years with body weight of ≥ 5 kg and < 35 kg. Two blood samples for the measurement of artemether and DHA in plasma were collected at 1 and 2 hours post first dose of Coartem (anticipated t_{max}) in those patients recruited until the interim (safety/efficacy) analysis. After the interim analysis, the remaining patients had one blood sample taken per patient for lumefantrine determination. Sample was taken at 6 different time-points across the patient population.

The PK parameters in adult and pediatric patients of lumefantrine and its metabolite desbutyl-lumefantrine and artemether and its metabolite dihydroartemisinin, are summarized in Table 23 and Table 24, respectively.

Table 23: Summary of PK parameters of lumefantrine and desbutyl-lumefantrine in adult and pediatric malaria patients (mean plus minus SD, median for tmax)

Study	Location/Year/Dose/Objective	Analyte	Cmax (µg/mL)	AUClast (µg·h/mL)	Tmax (h)	t½ (h)
Adult patients						
A025	Thailand/1996-97/ 4- & 6-dose regimens Double-blind, randomized (1/1), parallel group, comparative efficacy/safety trial of 3 dose regimens of co-artemether (4-dose over 2 days, and 6-dose over 3 or 5 days)	Lumefantrine (results for 6-dose regimen over 3 days)	10.5 ± 8.39 (n=18)	758 ± 651 (n=18)	60.02 (n=18)	NA
A028	Thailand/1998-99/6-dose regimen Open-label, randomized (3/1), parallel group, confirmatory efficacy/safety trial of the 6-dose regimen and comparison with mefloquine/artesunate	Lumefantrine	25.7 ± 16.3 (n=25) ³	NA	NA	NA
A2401 ⁴	Europe + Columbia/2001-05/6-dose regimen Open-label, non-comparative, efficacy/safety trial in non-immune patients	Lumefantrine	5.72 ± 2.91 (n=15)	272 ± 1595 (n=15)	62.422 (n=15)	NA
Pediatric patients						
A2403	Africa/2002-03/6-dose regimen Open-label, non-comparative, efficacy/safety trial in children (5-25 kg bodyweight)	Lumefantrine 5 to <15 kg (n=156) ⁶ 15 to <25 kg (n=25) ⁶	4.71 12.6	372 655	6.0 6.0	58.0 82.0
B2303 ¹⁰	Africa/2006-07/6-dose regimen Investigator blind, randomized, parallel group, efficacy/safety trial in infants and children (5- 35 kg bodyweight)	Lumefantrine 5 to <15 kg (n=194) ⁶ 15 to <25 kg (n=102) ⁶ 25 to <35 kg (n=19) ⁶	6.13 9.37 21.9 ¹¹	577 ⁷ 699 ⁷ 1150 ⁷	6.0 6.0 6.0	NA NA NA

AUClast = AUC0-240h ("0" is time of first dose of Coartem)

2 post first dose of Coartem

3 value observed after last (sixth) dose of Coartem on Day 3

4 shown is rich PK (i.e. patients in Colombia)

5 AUClast = AUC0-168h ("0" is time of first dose of Coartem)

6 n represents the number of values (one sample was taken per patient) used in the re-constitution of the population mean plasma concentration-time profile; AUClast

was calculated from mean concentration-time profile by non-compartmental method; Cmax and tmax were taken from the mean concentration-time profile

7 AUClast = AUC0-14 days ("0" is time of first dose of Coartem)

8 post dose 6

9 post dose 3

10 shown are values for crushed commercial tablet

11 n = 1

12 post dose 5

na = not available

Table 24: Summary of PK parameters of artemether and dihydroartemisinin (DHA) in adult and pediatric malaria patients (mean plus minus SD, median for t_{max})

Study	Location/Year/Dose/Objective	Analyte	C _{max} (µg/mL)	AUC _{last} (µg·h/mL)	T _{max} (h)	t _{1/2} (h)
Adult patients						
A028	Thailand/1998-99/6-dose Regimen Open-label, randomized (3/1), parallel group, confirmatory efficacy/safety trial of the 6-dose regimen and comparison with mefloquine artesunate	Artemether ¹				
		Day 1	186 ± 125 (n=25)	535 ± 272 (n=25) ²	2.0 (N=25)	1.6 ± 0.3 (n=12)
		Day 3	66.2 ± 54.3 (n=25)	211 ± 109 (n=22) ²	2.0 (N=25)	2.2 ± 1.0 (n=7)
		DHA				
Day 1	101 ± 58.0 (n=25)	320 ± 159 (n=25) ²	2.0 (N=25)	1.5 ± 0.5 (n=7)		
Day 3	205 ± 102 (n=25)	604 ± 259 (n=25) ²	2.0 (N=25)	1.6 ± 0.4 (n=12)		
Pediatric patients						
B2303 ³	Africa/2006-07/6-dose regimen Investigator-blind, randomized, parallel group, efficacy/safety trial in infants and children (5- 35 kg bodyweight)	Artemether				
		5 to <15 kg (n=156) ⁶	223 ± 309 (n=55) ⁴	NA	NA	NA
		15 to <25 kg (n=25) ⁶	198 ± 179 (n=29) ⁴	NA	NA	NA
		15 to <25 kg (n=25) ⁶	174 ± 145 (n=8) ⁴	NA	NA	NA
		DHA				
		5 to <15 kg (n=156) ⁶	54.7 ± 58.9 (n=56) ⁴	NA	NA	NA
15 to <25 kg (n=25) ⁶	79.8 ± 80.5 (n=29) ⁴	NA	NA	NA		
15 to <25 kg (n=25) ⁶	65.3 ± 23.6 (n=8) ⁴	NA	NA	NA		

1 shown are values post first dose (i.e. Day 1) and post last (sixth) dose (i.e. Day 3) of Coartem

2 AUC_{last} = AUC_{0-8h}

3 shown are values for crushed commercial tablet

4 two samples were taken at 1 and 2 hr post first dose (Day 1) in each patient. The highest of the two concentrations was considered as C_{max} estimate

na = not available

4 Non-Clinical Safety

The nonclinical toxicology program for artemether/lumefantrine (in a ratio of approximately 1:6) was comprehensive and included safety pharmacology studies, genetic toxicology studies, reproductive toxicology studies, phototoxicity studies as well as single dose, one-month and three-month toxicity studies in rats and dogs. Several studies were conducted to characterize effects of artemether in juvenile animals, including neurotoxicity. The adverse effects of special interest are reproductive and neurological toxicity, which are both attributed primarily to artemether.

4.1 Reproductive Toxicity

Several reproductive toxicology studies of artemether/lumefantrine were conducted in rats and rabbits during the period of organogenesis (Gestation Days 6 through 17 for rats and Gestation Days 7 through 19 for rabbits), and they suggest that patients who take Coartem while pregnant are at risk for fetal loss.

Pregnant rats dosed with artemether/lumefantrine at 100 mg/kg/day or higher (approximately equal to the clinical dose when adjusted for body surface area) experienced 100% postimplantation loss. At doses of 60 and 80 mg/kg/day, 3 of 8 dams experienced 100% fetal resorptions, and additional dams in these groups experienced partial fetal loss. A nonembryotoxic dose in rats was determined to be 3 mg/kg/day, which is more than 100 times lower than the clinical dose.

In rabbits, similar reproductive toxicity was observed, although rabbits were not as sensitive to embryotoxicity from artemether/lumefantrine as rats. Rabbits dosed at 175 mg/kg/day (approximately 3 times the daily clinical dose adjusted for body surface area), experienced abortions and postimplantation losses at four times the control values. Higher doses resulted in 100 % resorptions; however, at the next lower dose (105 mg/kg/day, or twice the clinical dose) and below, postimplantation losses were similar to controls and there were no abortions.

Pharmacokinetic analyses in animal studies demonstrate that plasma artemether levels are sporadic and not consistently dose-related. Artemether has a complex metabolic profile which appears similar among animal models and humans, but the profiles are not identical. Nonclinical studies have not identified which artemether-related compounds are embryotoxic. Therefore, we are unable to compare directly a safe level of artemether from animal studies with human exposure. Although body surface area comparisons between administered doses in animals and humans are generally considered conservative, they may not be conservative in this case. The absence of more specific embryotoxic mechanistic information limits the quantitative predictivity of the animal study findings.

4.1.1 Fetal Exposure

The levels of artemether-related radioactivity in rat and rabbit fetuses were between 0.5 to 1.0 times the levels in maternal blood. Exposure of rats and rabbits to radio-labeled lumefantrine resulted in fetal exposures representing only 2-3% of maternal blood levels, and these plasma levels largely represented unchanged lumefantrine.

Immature rat studies

Juvenile Wistar Hannover, Crl:WI(Glx/BRL/Han)IGS BR rats were dosed orally with artemether at 10, 30 or 100 mg/kg between Day 7 and 21 postpartum. Notable adverse effects seen at 30 and 100 mg/kg included tremors (1/28 and 12/28 respectively), decreased activity (1/28 and 7/28 respectively), brain congestion (1/22 and 8/28 respectively) and brain hemorrhage (21/28 at 100 mg/kg). Artemether AUC_(0-24h) values were about 250 ng.h/mL on Day 21, an exposure in the range of AUC's calculated on Day 1 for patients receiving the recommended dose.

In contrast, a 13-week study of artemether/lumefantrine, weanling Tif:RAIf (SPF) rats (3-5 weeks old) were dosed at 100, 300 and 1000 mg/kg, containing 14.3, 43 and 143 mg/kg artemether, respectively. No serious adverse clinical signs were recorded. Postmortem examination revealed pituitary cellular vacuolation in 8/10, 10/10 and 10/10 males compared to 2/10 control males. These results show that comparable doses of artemether (administered as coartemether) in older rats did not result in the brain congestion and hemorrhage observed with younger Wistar Hannover, Crl:WI(Glx/BRL /Han)IGS BR rats.

The reason for the apparent discrepancy between these two studies is unclear. The two studies produced different results following administration of different compounds for different durations to different strains of rats of different ages. The multiple variables preclude definitive conclusions regarding the neurologic risk to very young patients.

4.2 Neurotoxicity

The potential for artemether-induced neurotoxicity was evaluated in several studies with beagle dogs dosed orally or intramuscularly with artemether. The study designs included extensive brain histopathology and comprehensive clinical neurological evaluations. The following list summarizes the results of these studies.

- Histopathological effects were observed in multiple regions of the brain following intramuscular (IM) doses of 20 mg/kg/day for 30 days and 20, 40, and 80 mg/kg/day for 8 days. Histopathological effects were not observed in the brain at oral doses of 300 and 600 mg/kg/day for 8 consecutive days.
- Compound-related neurophysiologic effects (see Table 27) were not observed in five separate repeat-dose (IM and oral) toxicity studies with beagle dogs. Clinical evaluations were made prior to the terminal dose (Day 3, 7, or 25) in the respective studies.
- The NOEL for brain histopathology following IM administration for 8 consecutive days was 10 mg/kg/day.
- In one study, dogs dosed orally with a single 600 mg/kg dose of artemether showed vomiting, tremors of the head, staggered gait and recumbency. Artemether AUC values were about 100-fold the clinical exposure. A second dog study at this oral dose for eight days (artemether AUC values 1-9 times the clinical exposures) resulted in vomiting.

- In a 30-day study, dogs dosed by the intramuscular route showed tremors, swaying gait, restlessness, aggressive behavior and tonic-clonic convulsions on Days 27 through 30 with artemether AUC values about 14-times clinical exposures.
- Artemether plasma AUC at the 10 mg/kg IM dose (NOEL) on Day 8 was equivalent to the AUC values from the Day 1, 600 mg/kg oral dose. [Comparative artemether AUCs: 10 mg/kg IM and 600 mg/kg oral \cong 1.8 $\mu\text{g}\cdot\text{hr}/\text{ml}$; 20 mg/kg IM \cong 5.4 $\mu\text{g}\cdot\text{hr}/\text{ml}$.]
- Artemether was detected/quantitated in CSF following IM dosing at average concentrations of 0.025, 0.060, and 0.071 $\mu\text{g}/\text{ml}$ two hours following the 20, 40, and 80 mg/kg doses, respectively. Artemether was not detected in CSF following 600 mg/kg oral dose. Dihydroartemisinin was not detected in the CSF following IM or oral administration.
- Metabolism studies with orally administered ^{14}C -artemether to beagle dogs indicated intestinal absorption of at least 60 percent (based on urinary excretion) with extensive and rapid first pass metabolism to multiple metabolites in plasma.
- Repeat oral dosing with artemether appears to induce hepatic first pass metabolism based upon the reduction of both Cmax and AUC values between Day 1 and Day 8 of oral dosing.

4.2.1 Beagle Dog Neurotoxicity Study Evaluations

The neurotoxicity studies with beagle dogs extensively examined multiple parts of the brain (Table 25) for compound-related histopathological effects (Table 26). In addition, these studies included extensive clinical neurophysiological evaluations which were administered prior to the terminal artemether dose (Table 27). The following tables list the regions of the brain which were examined by histopathological techniques, brain regions which exhibited histopathology, and the clinical neurophysiological assessments.

Table 25: Brain Histopathology

Ganglion spirale (left & right)	Corpus geniculatum mediale	Nucleus ruber
Vestibular-Cochlear nerves	Cortex temporalis	Nucleus ambiguus
Corti's Organ	Hypothalamic nuclei	Nucleus hypoglossus
Nucleus cochlearis dorsalis	Thalamic nuclei	Nucleus cuneatus
Nucleus cochlearis ventralis	Pontine nuclei	Nucleus gracilis
Formatio reticularis	Pons (central gray)	Nucleus vagus
Nucleus olivaris superior	Nucleus nervi trigemini	Nucleus olivaris
Corpus trapezoideum	Cerebellar nuclei	Cerebellum
Leminiscus lateralis	Nucleus vestibularis lateralis	Remaining white matter
Colliculus caudalis	Nucleus vestibularis medialis	Remaining gray matter

**Table 26: Brain Regions with Histopathological Effects
(IM dosing)**

Pontine nuclei	Nucleus cuneatus	Nucleus nervi trigemini
Cerebellar nuclei	Nucleus cochlearis	Nucleus olivaris
Nucleus Vestibularis	Formatio reticularis	Nucleus ambiguus
Nucleus hypoglossus	Colliculus caudalis	Cerebral cortex

The effects were prominent in the pontine nuclei, cerebellar nuclei, nucleus vestibularis, nucleus hypoglossus, and nucleus cuneatus. Histopathological observations included: chromatolysis, microgliosis, neuronal necrosis, axonal swelling, neurofilament clumping, eosinophilic cytoplasmic granulation, and spheroids

Table 27: Clinical Neurological Evaluations

Acoustic response	Hopping response	Patellar reflex
Activity	Landing response	Pupil reflex
Bicipital reflex	Menace response	Placing reactions (visual and tactile)
Extensor strength (muscular)	Muscle tone	Posture
Flexor reflex	Muscle wasting	Proprioceptive placing
Gait	Nystagmus	Wheel barrowing
Muscle coordination	Sensor motor functions	Neck reflex

4.2.2 Neurotoxicity Studies in Dogs: Conclusions

The lowest IM dose resulting in histopathologic effects in different regions of the brains from beagle dogs was 20 mg/kg, administered over eight consecutive days. Artemether plasma $AUC_{0-24 \text{ hr}}$ values from this dose level were approximately 5.4 $\mu\text{g}\cdot\text{hr}/\text{ml}$. This level of systemic artemether exposure for a relatively short duration of dose administration (seven days) was sufficient to generate brain histopathologic effects such as chromatolysis, neuronal necrosis, and microgliosis. The severity of these lesions increased as dose levels increased to 40 and 80 mg/kg. The CSF artemether concentrations at these respective dose levels were 0.025, 0.060, and 0.071 $\mu\text{g}/\text{ml}$ and were sufficient to cause brain histopathology. The apparent artemether NOEL for brain histopathology was 10 mg/kg administered IM for eight consecutive days. Plasma artemether AUC values averaged 1.8 $\mu\text{g}\cdot\text{hr}/\text{ml}$. Orally administered artemether at dose levels as high as 600 mg/kg for eight consecutive days did not result in histopathological effects in different regions of the brain. The artemether plasma $AUC_{0-24 \text{ hr}}$ following the initial 600 mg/kg dose was approximately 1.73 $\mu\text{g}\cdot\text{hr}/\text{ml}$. However, by the seventh dose the plasma $AUC_{0-24 \text{ hr}}$ dropped to 0.25 $\mu\text{g}\cdot\text{hr}/\text{ml}$. Artemether was not detected in CSF following the terminal 600 mg/kg oral dose.

Although histopathological effects were observed in multiple regions of the brain from beagle dogs receiving IM doses of artemether, no compound-related effects were observed in the clinical neurophysiological examinations performed prior to the terminal dose. Similarly, no clinical neurophysiological effects were observed following oral artemether doses as high as 600 mg/kg/day. Radiolabeled ADME studies indicated that approximately 60 percent of an orally

administered dose of ^{14}C -artemether was intestinally absorbed and the relatively low systemic level of artemether was due to extensive first pass metabolism. In addition, the pharmacokinetic data from repeat dose studies suggest that repeat oral administration of artemether induces its metabolism. Therefore, systemic plasma concentrations of artemether following oral administration to beagle dogs do not achieve concentrations sufficient to cause brain histopathology.

5 Clinical Safety

5.1 Safety Database

The database used for the FDA's analysis of clinical safety included all subjects who had received either the 4-dose (4 tablets over 2 days) or 6-dose (4 tablets over 3 days) Coartem regimens. This included eight primary studies selected for efficacy in addition to eight additional supportive studies which used these dosing regimens. Pediatric subjects who received either crushed or dispersible tablet formulations were also included. Alternate dosing regimens, including 3-dose, and a 4-dose regimen where only half the dose (2 tablets) were administered at each dosing interval instead of 4 tablets, were not included as these represented lower exposures to Coartem.

Many studies were not designed as comparative trials and the rigor of collection of safety data varied from study to study, and thus tables which show 4- and 6-dose Coartem AEs are presented for descriptive purposes and should not be used to compare the 4-dose with the 6-dose regimen. The most informative information on safety for comparing the 4-dose regimen with the 6-dose regimen comes from study A025 which is discussed in Section 5.4. Tables which contain comparator data with either mefloquine artesunate (MAS) in adults, or MAS and sulfadoxine-pyremethamine (SP) in children should be interpreted as comparative with caution, since most studies were not designed as comparative trials. The exception is with the pooling of A026 and A028 in section 5.4, since these studies were both comparative studies versus MAS.

Two safety populations were defined: Adults (>16 years of age) and pediatrics (≤ 16 years of age). A total of 1427 adult subjects and 1992 pediatric subjects were exposed to Coartem as shown in Table 28 along with the demographic characteristics of gender and race. With the exception of 8 subjects, all adults were ≤ 65 years of age.

Table 28: Subjects included the FDA adult and pediatric pooled safety populations

	Adults N=1427		Pediatrics N=1992	
	4-dose N=782 (%)	6-dose N=645 (%)	4-dose N=659 (%)	6-dose N=1333 (%)
Male gender	581 (74.3)	471 (73.0)	402 (61.0)	711 (53.3)
Race				
Black	40 (5.1)	40 (6.2)	-	1209 (90.7)
Caucasian	21 (2.7)	79 (12.2)	-	-
Not collected	721 (92.2)	437 (67.8)	-	115 (8.6)
Oriental	0	44 (6.8)	-	9 (0.7)
Other	0	45 (7.0)	-	-

The following is a further subdivision of the pediatric safety population, which was used for the nervous system disorder analysis (in Section 5.5): age ≤ 2 years (587 subjects), age > 2 to ≤ 6 years (473 subjects), age > 6 to ≤ 12 years (207 subjects), and age > 12 to ≤ 16 years (66 subjects).

5.2 Disposition of Patients

It should also be noted that in some early studies it was not possible to determine whether patients discontinued due to specific adverse events (AEs), as the Case Report Form (CRFs) did not collect details of action taken in response to AEs, although the study completion pages did collect AEs as a reason for discontinuation. As discussed in the Applicant’s briefing package, “discontinuation” refers to discontinuation at any point during the studies, and not just discontinuation of treatment. Reasons for discontinuations for the FDA adult and pediatric pooled populations are shown in Tables 29 and 30.

Most subjects completed the studies, as treatment periods were typically 2-3 days. In both adult and pediatric populations, the discontinuation rate was lower for the Coartem 6-dose regimen than the 4-dose regimen, and this difference appeared to be almost entirely due to a difference in the proportions of patients discontinuing due to unsatisfactory therapeutic effect. Unsatisfactory therapeutic effect most commonly referred to reappearance of parasites after clearance. In the pediatric population, loss to follow up also accounted for the difference between the 6-dose regimen than the 4-dose regimens.

Table 29: Reasons for discontinuation, FDA adult pooled population

Reason for Discontinuation	Coartem 4 dose N=782 (%)	Coartem 6 dose N=645 (%)
Abnormal test procedure result(s)	0	2 (0.3)
Administrative problems	1 (0.1)	1 (0.2)
Adverse Event(s)	0	1 (0.2)
Death	3 (0.4)	0
Lost to follow-up	83 (10.6)	69 (10.7)
Non-compliance	8 (1.0)	1 (0.2)
P. vivax rescue medication	1 (0.1)	0
Protocol violation	3 (0.4)	7 (1.1)
Subject withdrew consent	2 (0.3)	2 (0.3)
Subject's condition no longer requires study drug	0	1 (0.2)
Unsatisfactory therapeutic effect	114 (14.6)	24 (3.7)
Discontinued study – total number of subjects	215 (27.5)	108 (16.7)

Table 30: Reasons for discontinuation, FDA pediatric pooled population

Reason for Discontinuation	Coartem 4 dose N=659 (%)	Coartem 6 dose N=1333 (%)
Abnormal test procedure result(s)	0	1 (0.8)
Administrative problems	5 (0.8)	0
Adverse Event(s)	4 (0.6)	71 (5.3)
Death	0	4 (0.3)
Lost to follow-up	54 (8.2)	40 (3.0)
Non-compliance	2 (0.3)	0
Protocol violation	12 (1.8)	1 (0.8)
Subject withdrew consent	4 (0.6)	19 (1.4)
Unsatisfactory therapeutic effect	85 (12.9)	6 (0.5)
Discontinued study – total number of subjects	166 (25.2)	142 (10.7)

5.3 Overall Safety Profile

5.3.1 Adult Subjects (> 16 years of age)

5.3.1.1 Most Frequently Reported Adverse Events

The FDA's analysis was very similar to the applicant with respect to the most frequently reported AEs, which included (for the 6-dose regimen) headache, asthenia, dizziness, anorexia, arthralgia, myalgia, nausea and fatigue. Table 31 below shows an abbreviated table of the most frequently reported AEs in the adult pooled safety population in bold. The most frequent AEs reported in the 4-dose regimen were similar to those in the 6-dose arm. AEs were reported more frequently with the 4-dose than 6-dose regimen, which likely was due to differences in study methodology and collecting AEs. Most AEs occurred on days 1-3 and were likely malaria symptoms. The majority were of mild or moderate intensity.

Table 31: Most frequently reported AEs, FDA adult pooled safety population

MedDRA system organ class (V 10.1)	MedDRA preferred term (V 10.1)	Coartem 4 dose N=782 (%)	Coartem 6 dose N=645 (%)	Mefloquine Artesunate N=280 (%)
Gastrointestinal disorders	Nausea	327 (42)	263 (41)	161 (58)
	Vomiting	224 (29)	177 (27)	94 (34)
	Abdominal pain	189 (24)	156 (24)	88 (31)
General disorders and administration site conditions	Asthenia	369 (47)	364 (56)	229 (82)
	Chills	355 (45)	212 (33)	110 (39)
	Fatigue	270 (34)	218 (34)	133 (48)
	Pyrexia	1 (0.1)	208 (32)	64 (23)
Metabolism and nutrition disorders	Anorexia	478 (61)	354 (55)	219 (78)
Musculoskeletal and connective tissue disorders	Arthralgia	253 (32)	294 (46)	209 (75)
	Myalgia			
Nervous system disorders	Dizziness	424 (54)	354 (55)	234 (84)
	Headache	591 (76)	476 (74)	255 (91)
Psychiatric disorders	Sleep disorder	265 (34)	175 (27)	138 (49)

Severe AEs were reported in 5.4% of 6-dose Coartem subjects. In the Coartem 6-dose group, the most frequently reported severe AE was pyrexia (2.2%). Most severe AEs were reported in at most one patient with the exception of pyrexia, splenomegaly, *P. falciparum* infection, and headache in the 6-dose group.

5.3.1.2 Deaths, Serious Adverse Events (SAEs), and Adverse Events Leading to Study Discontinuation

Deaths, serious adverse events (SAEs) and AEs leading to premature discontinuation are summarized for the FDA adult pooled safety population in Table 32.

Table 32: Number of patients who died, had other serious adverse events or discontinued prematurely due to AEs, FDA adult pooled safety population

Serious or significant AEs	Coartem 4-dose N=782 (%)	Coartem 6-dose N=645 (%)	Total Coartem N=1427 (%)
Death	3 (0.4)	0	3 (0.2)
Serious AE	6 (0.8)	9 (1.4)	15 (1.1)
AE leading to study drug Discontinuation	0	1 (0.2)	1 (0.1)

Three deaths (0.2%) occurred in the adult pooled safety population (3/1427 subjects treated with Coartem). All Coartem-treated patients in the adult pooled safety population who died had received the 4-dose regimen (Studies A008 and A025 in Thailand) and in all 3 cases, death was due to violence or accidental trauma.

Serious adverse events in the FDA's adult pooled safety population are summarized in Table 33.

Table 33: SAEs in the FDA adult pooled safety population*

MedDRA system organ class (V 10.1)	MedDRA preferred term (V 10.1)	Coartem 4 dose N=782 (%)	Coartem 6 dose N=645 (%)
Blood and lymphatic system disorders	Anemia	1 (0.1)	0
	Thrombocytopenia	0	1 (0.2)
Gastrointestinal disorders	Abdominal pain	0	1 (0.2)
	Vomiting	0	1 (0.2)
General disorders and administration site conditions	Chills	0	1 (0.2)
	Disease progression	0	1 (0.2)
	Malaise	0	1 (0.2)
	Pyrexia	0	1 (0.2)
Hepatobiliary disorders	Chronic hepatitis	1 (0.1)	0
	Hepatocellular damage	0	1 (0.2)
Infections and infestations	Endocarditis	0	1 (0.2)
	Hepatitis viral	1 (0.1)	0
	<i>Plasmodium falciparum</i> infection	3 (0.4)	2 (0.3)
	Typhoid fever	0	1 (0.2)
Investigations	Blood bilirubin increased	0	1 (0.2)

MedDRA system organ class (V 10.1)	MedDRA preferred term (V 10.1)	Coartem 4 dose N=782 (%)	Coartem 6 dose N=645 (%)
	Electrocardiogram T wave abnormal	0	1 (0.2)
	Laboratory test abnormal	1 (0.1)	0
	Liver function test abnormal	0	1 (0.2)
	Transaminases increased	0	1 (0.2)
Metabolism and nutrition disorders	Fluid overload	0	1 (0.2)
Nervous system disorders	Coma	0	1 (0.2)
	Headache	0	1 (0.2)
	Mental impairment	0	1 (0.2)
Renal and urinary disorders	Hematuria	0	1 (0.2)
Respiratory, thoracic and mediastinal disorders	Dyspnea	0	1 (0.2)
Skin and subcutaneous tissue disorders	Urticaria	0	0
	Total number of subjects reporting SAEs	6 (0.8)	9 (1.4)

* patients may have reported more than one SAE

Overall, there were few SAEs reported. In the 6-dose Coartem group, 9 subjects (1.4%) experienced 22 SAEs whereas 6 subjects (0.8%) had 7 SAEs in the 4-dose group and 1 subject (10.4%) reported 1 SAE in the MAS group (urticaria, data not shown). Most AEs were reported only once. The most frequently reported SAE by MedDRA Preferred Term (PT) was *P. falciparum* infection (3 subjects in 4-dose, 2 subjects in 6-dose).

Of the 9 subjects with SAEs in the Coartem 6-dose group, 6 (and 18 of the 22 SAEs) were from Study A2401. The SAEs from this study were categorized as such because they led to hospitalization or prolongation of hospitalization. The majority of SAEs reported were likely related to malaria (2 cases) or malaria recrudescence/efficacy failure (2 cases). Two SAEs (both elevated transaminases) were possibly related to Coartem exposure in 2 subjects. In both cases, a relationship to drug could not be ruled out.

In patients treated with the 4-dose regimen, seven SAEs were reported by 6 patients. Four of the patients were from Study A014: two of these patients had recurrence of malaria (in one case suspected by the investigator to be related to study drug). One of the other two patients from this study had severe viral hepatitis, and the other had severe anemia, the latter being suspected to be study drug-related. The remaining patients with SAEs were from Study A025: one patient had mild chronic hepatitis, another severe malaria accompanied by elevated bilirubin, creatinine and blood urea levels (preferred term 'Laboratory test abnormal'). None of these SAEs were considered to be related to study medication.

5.3.2 Pediatric Subjects (≤ 16 years of age)

5.3.2.1 Most Frequently Reported Adverse Events

Table 34 shows an abbreviated table of the most frequently reported AEs in the FDA’s pediatric pooled safety population. The FDA’s analysis was similar to the Applicant with respect to the most frequently reported AEs (for the 6-dose regimen), which included pyrexia, vomiting, *P. falciparum* infection, anorexia, headache, splenomegaly, anemia and hepatomegaly, as shown in bold. Many of these were likely signs and symptoms of malaria, particularly as AEs were reported most frequently on Days 1-3. Cough was reported in 21% and 23% of pediatric subjects compared to 5% and 6% of adult subjects who received the 4- and 6-dose regimens of Coartem, respectively. This may be related to the higher incidence of upper respiratory tract infection, respiratory tract infection, lower respiratory tract infection, bronchitis and pneumonia in the pediatric subjects compared to adults.

Table 34: Most frequently reported AEs, FDA pediatric pooled safety population

MedDRA system organ class (V 10.1)	MedDRA preferred term (V 10.1)	Coartem 4 dose N=659 (%)	Coartem 6 dose N=1333 (%)	Mefloquine Artesunate N=150 (%)	SP N=143 (%)
General disorders and administration site conditions	Pyrexia	37 (5.6)	388 (29.1)	20 (13.3)	6 (4.2)
	Chills	262 (39.8)	79 (5.9)	66 (44.0)	38 (26.6)
	Asthenia	199 (30.2)	74 (5.6)	97 (64.7)	94 (65.7)
	Fatigue	235 (35.7)	57 (4.3)	59 (39.3)	0
Respiratory, thoracic and mediastinal disorders	Cough	137 (20.8)	302 (22.7)	1 (0.7)	37 (25.9)
Gastrointestinal disorders	Vomiting	279 (42.3)	247 (18.5)	64 (42.7)	89 (62.2)
	Abdominal pain	236 (35.8)	114 (8.6)	45 (30.0)	54 (37.8)
	Diarrhea	88 (13.4)	101 (7.6)	7 (4.7)	25 (17.5)
	Nausea	153 (23.2)	71 (5.3)	65 (43.3)	1 (0.7)
Infections and infestations	<i>Plasmodium falciparum</i> infection	0	224 (16.8)	0	0
	Rhinitis	0	51 (3.8)	0	0
	Upper respiratory tract infection	28 (4.3)	32 (2.4)	0	15 (10.5)
	Respiratory tract infection	2 (0.3)	28 (2.1)	0	1 (0.7)
	Bronchitis	1 (0.2)	26 (2)	1 (0.7)	0
Metabolism and	Anorexia	283 (42.9)	188 (14.1)	111 (74.0)	0

MedDRA system organ class (V 10.1)	MedDRA preferred term (V 10.1)	Coartem 4 dose N=659 (%)	Coartem 6 dose N=1333 (%)	Mefloquine Artesunate N=150 (%)	SP N=143 (%)
nutrition disorders					
Nervous system disorders	Headache	369 (56.0)	181 (13.6)	137 (91.3)	56 (39.2)
	Dizziness	153 (23.2)	67 (5.0)	104 (69.3)	6 (4.2)
	Clonus	7 (1.1)	11 (0.8)	1 (0.7)	0
Blood and lymphatic system disorders	Splenomegaly	183 (27.8)	133 (10)	56 (37.3)	33 (23.1)
	Anemia	146 (22.2)	116 (8.7)	15 (10.0)	77 (53.9)
Hepatobiliary disorders	Hepatomegaly	147 (22.3)	85 (6.4)	38 (25.3)	21 (14.7)

SP= sulfadoxine/pyramethamine

Severe AEs were reported in 7.3% of subjects. In the Coartem 6-dose regimen group, the most frequently reported severe AEs were pyrexia (4%), splenomegaly (0.9%), *P. falciparum* infection (0.7%) and anemia (0.5%).

5.3.2.2 Deaths, SAEs, and Adverse Events Leading to Study Discontinuation

Deaths, serious adverse events and adverse events leading to premature discontinuation are summarized for the FDA pediatric pooled safety population in Table 35.

Table 35: Number of patients who died, had other serious adverse events or discontinued prematurely due to AEs, FDA pediatric pooled safety population

Serious or significant AEs	Coartem 4 dose N=659	Coartem 6 dose N=1333	Total Coartem N=1992	MAS N=150	SP N=143
Death	0	4 (0.3)	4 (0.2)	0	0
Serious AE	7 (1.1)	17 (1.3)	24 (1.2)	0	3 (2.1)
AE leading to study drug discontinuation	4 (0.6)	71* (5.3)	75 (3.8)	0	0

* 70/71 subjects were enrolled in Study B2303, which specified in the protocol that subjects were to be discontinued if they vomited after a dose of study drug

SP= sulfadoxine/pyramethamine

Table 36 shows deaths in the pediatric pooled safety population. Four patients died (0.2%), all of whom were treated with the 6-dose regimen of Coartem and in all but one case the cause of death was infection. None of the deaths were suspected by the investigators to be related to study treatment.

Table 36: Patients who died, FDA pediatric pooled safety population

Study	Age/Sex/Race	Day of Last Dose	Day of Death	Cause of Death
A2403	4 yrs/Female/Black	4	9	Gastroenteritis
B2303	5 mo/Male/Black	4	31	<i>Plasmodium falciparum</i> infection
B2303	2 yrs/Male/Black*	4	7	Hemorrhage
B2303	4 mo/Male/Black*	2	3	Infection

*received Coartem 6-dose regimen with the dispersible tablet

Serious adverse events in the FDA pediatric pooled safety population are presented in Table 37.

Table 37: SAEs in the FDA pediatric pooled safety population*

MedDRA system organ class (V 10.1)	MedDRA preferred term (V 10.1)	Coartem 4 dose N=659 (%)	Coartem 6 dose N=1333 (%)
Blood and lymphatic system disorders	Anemia	3 (0.5)	2 (0.2)
	Iron deficiency anemia	0	1 (0.1)
Eye disorders	Conjunctivitis	1 (0.2)	0
Gastrointestinal disorders	Diarrhea	0	1 (0.1)
	Vomiting	1 (0.2)	1 (0.1)
General disorders and administration site conditions	Face edema	0	1 (0.1)
	Pyrexia	0	3 (0.2)
Infections and infestations	Bronchitis	0	1 (0.1)
	Bronchopneumonia	1 (0.2)	0
	Gastroenteritis	0	1 (0.1)
	Hepatitis viral	0	1 (0.1)
	Infection	0	1 (0.1)
	Lower respiratory tract infection	0	1 (0.1)
	<i>Plasmodium falciparum</i> infection	0	7 (0.5)
	Pneumonia	1 (0.2)	1 (0.1)
	Pneumonia primary atypical	0	1 (0.1)
	Hemoglobin decreased	0	1 (0.1)
Metabolism and nutrition disorders	Dehydration	0	1 (0.1)
	Oral intake reduced	0	1 (0.1)
Nervous system disorders	Convulsion	0	3 (0.2)
	Hypotonia	0	1 (0.1)

MedDRA system organ class (V 10.1)	MedDRA preferred term (V 10.1)	Coartem 4 dose N=659 (%)	Coartem 6 dose N=1333 (%)
	Lethargy	0	1 (0.1)
Renal and urinary disorders	Glomerulonephritis acute	0	1 (0.1)
Skin and subcutaneous tissue disorders	Urticaria	0	1 (0.1)
Vascular disorders	Hemorrhage	0	1 (0.1)
	Total number of subjects reporting SAE	7 (1.1)	17 (1.3)

* patients may have reported more than one SAE

Similar to the adult pooled population, there were few SAEs reported in the pediatric population, 1.1% and 1.3% in the 4- and 6-dose groups respectively. The most frequently reported SAEs were anemia (4-dose) and *P. falciparum* infection (6-dose).

In the total Coartem 6-dose regimen group, 30 SAEs (26 non-fatal) were reported in 17 patients. Of the SAEs reported with the 6-dose tablet formulation, there were only 2 which were or possibly were related to study drug. Subject 145 had efficacy failure which was definitely related to study drug. Subject 222 had urticaria with onset after 2 doses of study drug and resolved after discontinuing study drug. While she was concurrently receiving paracetamol (acetaminophen) with study drug, she received paracetamol several days later with no recurrence of the urticaria.

5.4 Safety of 4-dose Compared to 6-dose Regimen in Study A025

Study A025 was the only study amongst the 8 primary studies which directly compared the 4-dose and 6-dose Coartem regimens in the same study. Study A025 was a randomized, double-blind study of 359 subjects administered 4-doses over 48 hours, 6 doses over 60 hours or 6 doses over 96 hours. Adverse Events reported at $\geq 2\%$ for adults is shown in Table 38, and data for pediatric subjects is shown in Table 39. The results for both 6-dose arms are combined in these tables. Overall, the profile and rate of AEs in the Coartem 6-dose regimens appeared comparable to the 4-dose regimen.

Table 38: Most frequently reported AEs occurring in $\geq 2\%$ of adult subjects in Study A025 by treatment group.

MedDRA system organ class (V 10.1)	MedDRA preferred term (V 10.1)	Coartem 4 dose N=98 (%)	Coartem 6 dose (60 and 96 hours) N=180 (%)
Blood and lymphatic system disorders	Anemia	5 (5.1)	10 (.6)
	Splenomegaly	22 (22.5)	31 (17.2)
Cardiac disorders	Palpitations	42 (42.9)	71 (39.4)
Gastrointestinal disorders	Abdominal pain	36 (36.7)	57 (31.7)
	Diarrhea	6 (6.1)	10 (5.6)
	Nausea	48 (49.0)	91 (50.6)
	Peptic ulcer	1 (1.0)	3 (1.7)
	Vomiting	31 (31.6)	68 (37.8)
General disorders and administration site conditions	Asthenia	82 (83.7)	147 (81.7)
	Chills	40 (40.8)	86 (47.8)
	Fatigue	29 (29.6)	73 (40.8)
Hepatobiliary disorders	Hepatomegaly	19 (19.4)	28 (15.6)
Infections and infestations	Abscess	5 (5.1)	3 (1.7)
	Helminthic infection	3 (3.1)	10 (5.6)
	Nasopharyngitis	2 (2.0)	8 (4.4)
	Pneumonia	3 (3.1)	0
	Urinary tract infection	0	3 (1.7)
Investigations	Blood potassium decreased	2 (2.0)	0
Metabolism and nutrition disorders	Anorexia	83 (84.7)	156 (86.7)
Musculoskeletal and connective tissue disorders	Arthralgia	70 (71.4)	135 (75)
	Myalgia	75 (76.5)	134 (74.4)
Nervous system disorders	Ataxia	2 (2.0)	2 (1.1)
	Clonus	5 (5.1)	17 (9.4)
	Dizziness	72 (73.5)	141 (78.3)
	Headache	92 (93.9)	173 (96.1)
	Nystagmus	1 (1.0)	4 (2.2)
	Tremor	8 (8.2)	15 (8.3)
Psychiatric disorders	Sleep disorder	43 (43.9)	84 (46.7)
Renal and urinary disorders	Hematuria	2 (2.0)	3 (1.7)
	Proteinuria	2 (2.0)	5 (2.8)
Respiratory, thoracic and mediastinal disorders	Asthma	2 (2.0)	1 (0.6)
	Cough	3 (3.1)	5 (2.8)
	Pharyngolaryngeal pain	4 (4.1)	5 (2.8)

MedDRA system organ class (V 10.1)	MedDRA preferred term (V 10.1)	Coartem 4 dose N=98 (%)	Coartem 6 dose (60 and 96 hours) N=180 (%)
Skin and subcutaneous tissue disorders	Pruritus	13 (13.3)	12 (6.7)
	Rash	13 (13.3)	13 (7.2)
Vascular disorders	Pallor	2 (2.0)	0

Table 39: Most frequently reported AEs occurring in $\geq 2\%$ of pediatric subjects in Study A025 by treatment group

MedDRA system organ class (V 10.1)	MedDRA preferred term (V 10.1)	Coartem 4 dose N=21 (%)	Coartem 6 dose (60 and 96 hours) N=59 (%)
Blood and lymphatic system disorders	Anemia	4 (19.1)	8 (13.6)
	Splenomegaly	7 (33.3)	18 (30.5)
Cardiac disorders	Palpitations	4 (19.1)	14 (23.7)
Gastrointestinal disorders	Abdominal pain	3 (14.3)	18 (30.5)
	Diarrhea	1 (4.8)	3 (5.1)
	Nausea	7 (33.3)	27 (45.8)
	Vomiting	9 (42.9)	22 (37.3)
General disorders and administration site conditions	Asthenia	10 (47.6)	37 (62.7)
	Chills	7 (33.3)	25 (42.4)
	Fatigue	4 (19.1)	12 (20.3)
Hepatobiliary disorders	Hepatomegaly	3 (14.3)	18 (30.5)
Infections and infestations	Ascariasis	1 (4.8)	2 (3.4)
	Helminthic infection	1 (4.8)	3 (5.1)
	Parasitic gastroenteritis	3 (14.3)	12 (20.3)
	Pneumonia	1 (4.8)	5 (8.5)
Metabolism and nutrition disorders	Anorexia	18 (85.7)	48 (81.4)
Musculoskeletal and connective tissue disorders	Arthralgia	6 (28.6)	22 (37.3)
	Myalgia	11 (52.4)	30 (50.9)
Nervous system disorders	Dizziness	8 (38.1)	31 (52.5)
	Headache	20 (95.2)	56 (94.9)
Psychiatric disorders	Sleep disorder	5 (23.8)	15 (25.4)
Skin and subcutaneous tissue disorders	Pruritus	0	2 (3.4)

5.5 Safety from Comparative Studies A026 and A028

Studies A026 and A028 were the only studies among the 8 primary studies selected which contained a comparator treatment arm. Both studies were randomized, open label parallel group studies comparing Coartem with mefloquine artesunate (MAS). While the open label aspect of the studies may have affected the safety data collected, it was still relevant to know the safety profile of Coartem relative to MAS, and to determine if the profile, distribution, severity and seriousness of AEs differed from the FDA's pooled safety populations. Note that these latter populations consisted of studies which were either non-comparative or compared Coartem with its components.

The inclusion criteria for both studies allowed the enrollment of pediatric subjects. Study A026 enrolled subjects aged 2 years or greater, and A028 enrolled subjects >12 years. There were a total of 84 pediatric subjects 16 years or younger, with 57 and 27 subjects enrolled in studies A026 and A028 respectively. Pediatric subjects represented 20% (84/419) of subjects from these combined studies. There was only 1 subject from A028 who met the geriatric age criteria of greater than 65 years of age.

5.5.1 Discontinuations due to Study Drug

Table 40 summarizes patient disposition in the A026 and A028 pooled adult and pediatric populations. Most subjects completed the studies. Unsatisfactory therapeutic response (re-appearance of parasites after clearance) was the most common reason for discontinuation among pediatric subjects who received Coartem, whereas adults who received Coartem were lost to follow-up.

Table 40: Patient disposition for pooled Studies A026 and A028

	Adult population		Pediatric population	
	Coartem n=257 (%)	MAS N=77 (%)	Coartem N=56 (%)	MAS N=28 (%)
Enrolled	257	77	56	28
Incomplete	2 (0.8)	1 (1.3)	0	0
Discontinuation due to:				
Unsatisfactory therapeutic response	7 (2.7)	0	4 (7.1)	-
Lost to follow up	23 (9)	7 (9.1)	3 (5.4)	-
Protocol violation	1 (0.4)	0	0	-
Non compliance	1 (0.4)	0	0	-

5.5.2 Adult Subjects (> 16 years of age)

5.5.2.1 Most Frequently Reported Adverse Events

AEs according to PTs greater than 2% for Coartem and MAS groups are shown in Table 41. The most frequently reported in both groups were headache (Coartem 94.9%, MAS 96.1%), asthenia (Coartem 79%, MAS 84.4%), dizziness (Coartem 77.8%, MAS 76.6%), and pyrexia (Coartem 77%, MAS 83.1%). These AE rates were comparable between groups and were likely symptoms and signs of malaria. Rates for the other PTs were also comparable between groups, with overall slightly lower rates reported for Coartem than MAS. The only exception was cough (Coartem

5.1%, MAS 1.3%). This was similarly observed in the FDA adult pooled safety population, where the rate of cough was 5.9% in the 6-dose group, 4.7% in the 4-dose group and 1.1% in the MAS group. This may be due to the higher incidence of upper respiratory tract infection (0.8% vs. 0), lung infection (0.4% vs. 0) and nasopharyngitis (3.1% vs. 2.6%) in the Coartem group compared to MAS.

Table 41: AEs by Preferred Term (>2%) for pooled Studies A026 and A028

MedDRA system organ class (V 10.1)	MedDRA preferred term (V 10.1)	Coartem N=257 (%)	Mefloquine Artesunate N=77 (%)
Blood and lymphatic system disorders	Anemia	9 (3.5)	3 (3.9)
	Splenomegaly	68 (26.5)	20 (26.0)
Cardiac disorders	Palpitations	54 (21.0)	19 (24.7)
Gastrointestinal disorders	Abdominal pain	88 (34.2)	27 (35.1)
	Diarrhea	23 (9.0)	6 (7.8)
	Dyspepsia	11 (4.3)	4 (5.2)
	Nausea	157 (61.1)	53 (68.8)
	Vomiting	90 (35.0)	32 (41.6)
General disorders and administration site conditions	Asthenia	203 (79.0)	65 (84.4)
	Chills	112 (43.6)	36 (46.8)
	Fatigue	135 (52.5)	41 (53.3)
	Pyrexia	198 (77.0)	64 (83.1)
Hepatobiliary disorders	Hepatomegaly	78 (30.4)	21 (27.3)
Infections and infestations	Nasopharyngitis	8 (3.1)	2 (2.6)
Injury, poisoning and procedural complications	Overdose	0	3 (3.9)
Metabolism and nutrition disorders	Anorexia	171 (66.5)	53 (68.8)
	Hypokalemia	5 (2.0)	2 (2.6)
Musculoskeletal and connective tissue disorders	Arthralgia	156 (60.7)	49 (63.6)
	Myalgia	162 (63.0)	48 (62.3)
Nervous system disorders	Dizziness	200 (77.8)	59 (76.6)
	Headache	244 (94.9)	74 (96.1)
	Tremor	2 (0.8)	2 (2.6)
Psychiatric disorders	Sleep disorder	89 (34.6)	33 (42.9)
Respiratory, thoracic and mediastinal disorders	Asthma	0	2 (2.6)
	Cough	13 (5.1)	1 (1.3)
	Pharyngolaryngeal pain	8 (3.1)	4 (5.2)
Skin and subcutaneous tissue disorders	Pruritus	9 (3.5)	4 (5.2)
	Rash	7 (2.7)	5 (6.5)

The incidence of most frequently reported AEs was significantly lower in the FDA adult pooled population compared with the pooled A026/A028 population: headache 73.8% vs. 94.9%; asthenia 56.4% vs. 79%; dizziness 54.9% vs. 77.8%; pyrexia 32.3% vs. 77%. It is important to note that all PTs are consistently higher in the pooled A026/A028 population, but the most commonly reported AEs are the same in both pooled populations. This may be due to the fact that the other 6-dose studies were non-comparative. Investigators in A026 and A028 may have been more vigilant in collecting AEs from all subjects, as they knew a proportion of their randomized subjects were receiving MAS and the AE profile of mefloquine is well established. There may also have been other differences in data collection and study design differences to account for this observation.

Studies A026 and A028 both included “life-threatening” as a severity grade along with the standard gradings of mild, moderate and severe, although in the end there was only one AE coded as life-threatening (coma). Table 42 shows the life-threatening and severe AEs in the two studies. The incidence of severe AEs was 8.9% (23/257) in Coartem subjects compared to 9.1% of MAS subjects, and 5.4% of 6-dose regimen subjects in the FDA adult pooled population. Again, the higher incidence of severe AEs goes along with the overall higher rate of AEs and was likely due to study design differences.

Table 42: Life-threatening and severe AEs in Studies A026 and A028, pooled adult population*

MedDRA system organ class (V 10.1)	MedDRA preferred term (V 10.1)	Coartem N=257 (%)	MAS N=77 (%)
Blood and lymphatic system disorders	Anemia	1 (0.4)	1 (1.3)
	Splenomegaly	5 (2.0)	2 (2.6)
General disorders and administration site conditions	Pyrexia	14 (5.5)	4 (5.2)
Hepatobiliary disorders	Hepatomegaly	1 (0.4)	0
Infections and infestations	Urinary tract infection	0	1 (1.3)
Metabolism and nutrition disorders	Fluid overload	1 (0.4)	0
Nervous system disorders	Coma**	1 (0.4)	0
Respiratory, thoracic and mediastinal disorders	Dyspnea	1 (0.4)	0
	Total number of subjects reporting AEs	23 (8.9)	7 (9.1)

* patients may have reported more than one AE

** coded as life-threatening

MAS= mefloquine artesunate

There were 24 severe AEs in 23 subjects treated with Coartem. The majority of these were signs and symptoms of malaria, with pyrexia (5.5%) and splenomegaly (2%) as the most frequently reported. Severe AEs which occurred with greater frequency in the Coartem group compared to the MAS group were pyrexia, hepatomegaly, fluid overload and dyspnea. The latter two severe

AEs were iatrogenic, while the differences in pyrexia and hepatomegaly between groups were small.

The one case of life-threatening SAE – coma – was not likely to be related to study drug. Further details are included on this case:

Subject 259 was a 17 year old male enrolled in Study A026. He presented at baseline with anorexia, dizziness, fever, chills, headache, nausea, vomiting, arthralgia, myalgia, asthenia and sleep disorder. All of these AEs resolved by study day 8. Coma was recorded on study day 14. His baseline *P. falciparum* asexual form count was 10 826 and was cleared in 3 days although gametocytes did not clear until day 15. Two days prior to the onset of coma, the subject had experienced fever, chills and feeling unwell (according to subject’s sister). He then “became unconscious with fever and vomiting”. His temperature on day 15 was 40.5°C. He received phenobarbital, quinine, paracetamol and glucose, and later received chloramphenicol for possible meningitis and diazepam for convulsions. A lumbar puncture was attempted but was not successful. No parasites were found in his blood smear. The subject received ampicillin and metronidazole for aspiration pneumonia for the duration of the SAE. The case report form coded the SAE as “febrile coma, reason unknown”. The subject made a complete recovery on day 24. Information regarding follow up was not available

There were few SAEs in these studies (Table 43). SAEs occurred in 0.8% of subjects in the Coartem group compared to 1.3% in the MAS group and 1.4% in the FDA adult pooled population (6-dose regimen). There were no deaths in these studies and none of the SAEs were likely to be related to study drug.

Table 43: SAEs in Studies A026 and A028, Adult pooled population

MedDRA system organ class (V 10.1)	MedDRA preferred term (V 10.1)	Coartem N=257 (%)	MAS N=77 (%)
Metabolism and nutrition disorders	Fluid overload	1 (0.4)	0
Nervous system disorders	Coma	1 (0.4)	0
Respiratory, thoracic and mediastinal disorders	Dyspnea	1 (0.4)	0
Skin and subcutaneous tissue disorders	Urticaria	0	1 (1.3)
	Total number of subjects reporting SAEs	2 (0.8)	1 (1.3)

MAS= mefloquine artesunate

5.5.3 Pediatric Subjects (≤ 16 years of age)

5.5.3.1 Most Frequently Reported Adverse Events

AEs according to PTs (>2%) are shown in Table 44. The most frequently reported in both groups was headache (Coartem and MAS both 89.3%). For Coartem, other frequently reported

AEs were anorexia, pyrexia, asthenia and dizziness. For MAS, dizziness, asthenia, pyrexia and nausea were the most commonly reported. The rates for the most commonly reported AEs as well as other AEs were similar between groups. However, AE rates were significantly lower in the FDA pooled pediatric population compared to the pooled A026/A028 analysis (pyrexia 52.5% vs. 73.2%; anorexia 54.9% vs. 76.8%; headache 73.8% vs. 89.3%). As previously discussed, this is likely due to between study differences.

Table 44: Most frequently reported AEs by Preferred Term (>2%), pediatric pooled safety population

MedDRA system organ class (V 10.1)	MedDRA preferred term (V 10.1)	Coartem N=56 (%)	Mefloquine Artesunate N=28 (%)
Blood and lymphatic system disorders	Anemia	5 (8.9)	2 (7.1)
	Splenomegaly	27 (48.2)	14 (50.0)
Cardiac disorders	Palpitations	11 (19.6)	4 (14.3)
Gastrointestinal disorders	Abdominal pain	19 (33.9)	14 (50.0)
	Dyspepsia	0	1 (3.6)
	Nausea	28 (50.0)	17 (60.7)
	Vomiting	28 (50.0)	14 (50.0)
General disorders and administration site conditions	Asthenia	36 (64.3)	21 (75.0)
	Chills	26 (46.4)	9 (32.1)
	Fatigue	16 (28.6)	8 (28.6)
	Pyrexia	41 (73.2)	20 (71.4)
Hepatobiliary disorders	Hepatomegaly	27 (48.2)	9 (32.1)
Infections and infestations	Bronchitis	0	1 (3.6)
	Nasopharyngitis	1 (1.8)	3 (10.7)
	Parasitic gastroenteritis	0	1 (3.6)
	Respiratory tract infection	2 (3.6)	0
	Subcutaneous abscess	0	1 (3.6)
Metabolism and nutrition disorders	Anorexia	43 (76.8)	15 (53.6)
Musculoskeletal and connective tissue disorders	Arthralgia	21 (37.5)	10 (35.7)
	Myalgia	13 (23.2)	10 (35.7)
Nervous system disorders	Clonus	0	1 (3.6)
	Dizziness	34 (60.7)	21 (75.0)
	Headache	50 (89.3)	25 (89.3)
Psychiatric disorders	Sleep disorder	15 (26.8)	10 (35.7)
Respiratory, thoracic and mediastinal disorders	Cough	0	1 (3.6)
	Epistaxis	0	3 (10.7)
	Pharyngolaryngeal pain	2 (3.6)	0
Skin and subcutaneous tissue disorders	Urticaria	0	1 (3.6)
Vascular disorders	Pallor	0	1 (3.6)

There were no severe AEs, or SAEs in the pooled A026/A028 pediatric population.

In conclusion, comparator studies A026 and A028 did not show any safety findings which were significantly different than the FDA adult and pediatric pooled populations. AE rates for the most common AEs and severe AEs were generally uniformly higher in the pooled A026/A028 population, but the types of AEs reported were similar. The difference in AE incidence can be attributed to study design differences.

5.6 Nervous System Disorders

In animal models, artemisinin derivatives such as artemether have been associated with neurotoxicity affecting pathways involved in hearing and balance. In dogs, microscopic lesions mainly in the brainstem and cerebellar roof nuclei were observed in dogs administered 20 mg/kg/day IM doses of artemether following 30 days of treatment, and clinical data showed tremors in one animal and convulsions in another animal after > 27 days of treatment. Additional studies at artemether doses ranging from 10 to 80 mg/kg/day for 5 to 8 days of treatment have confirmed that brain lesions are observed following IM doses in the dog when animals are treated for 8 or more days at high doses. Daily 10 mg/kg/day IM dosing for 8 days did not cause brain lesions.

Oral doses in the general toxicity program showed no brain lesions and no clinical evidence of neurotoxicity (eg. no seizures or tremors) in the dog at up to 300 mg/kg/day of artemether for 13 weeks. A further study was conducted and showed that dogs administered an oral 600 mg/kg artemether dose exhibited tremors and vomiting and sporadic vomiting was noted at the 300 mg/kg/day dose thereafter. Hearing tests revealed minimal hearing loss at 20 dB and this change was not accompanied by any histopathologic changes in the brain.

Toxicokinetic studies have shown that in dogs, artemether exposure is considerably higher following IM doses compared to oral exposures. This is likely due to the fact that artemether is rapidly and extensively metabolized by the liver, reducing exposure to artemether and its biologically active main metabolite dihydroartemisinin. Thus the route of administration of artemether and subsequent exposure to this compound may account for the development of neurologic lesions.

5.6.1 Adult Subjects (> 16 years of age)

Nervous system AEs affecting the MedDRA System Organ Class (SOC) 'Nervous system disorders' in the FDA adult pooled safety population are shown in Table 45.

Table 45: Adverse events affecting the SOC “Nervous system disorders”, FDA adult pooled safety population

MedDRA preferred term (V 10.1)	Coartem 4 dose N=782 (%)	Coartem 6 dose N=645 (%)	Mefloquine Artesunate N=280 (%)
Ataxia	10 (1.3)	5 (0.8)	14 (5.0)
Clonus	5 (0.6)	20 (3.1)	0
Coma	0	1 (0.2)	0
Convulsion	1 (0.1)	0	0
Coordination abnormal	0	0	1 (0.4)
Dizziness	424 (54.2)	354 (54.9)	234 (83.6)
Dysgeusia	1 (0.1)	0	0
Fine motor delay	0	3 (0.5)	2 (0.7)
Headache	591 (75.6)	476 (73.8)	255 (91.1)
Hypersomnia	1 (0.1)	0	0
Hypoaesthesia	3 (0.4)	4 (0.6)	7 (2.5)
Lethargy	1 (0.1)	0	0
Mental impairment	0	1 (0.2)	0
Nystagmus	8 (1.0)	5 (0.8)	16 (5.7)
Paraesthesia	32 (4.1)	0	27 (9.6)
Somnolence	1 (0.1)	3 (0.5)	0
Syncope vasovagal	1 (0.1)	0	0
Tremor	22 (2.8)	17 (2.6)	14 (5.0)

By far, the most frequently reported AEs in all treatment groups was headache followed by dizziness. These were likely symptoms of malaria. The only AE which stood out in the 6-dose regimen was clonus (3.1% compared to 0.6% for Coartem 4-dose, none for MAS). The cases of clonus occurred in subjects enrolled in Studies A025 and A026 and were originally reported as “involuntary muscle contraction” in the clinical study reports, and were recoded in MedDRA as clonus. All but one case of clonus were reported on days 1-3 and all but one case were of mild intensity. All were not thought to be related to study medication. AEs representing balance (PTs ataxia, coordination abnormal, dizziness, nystagmus and tremor) were generally higher in the 4-dose regimen, and may have been a result of differences in reporting methods between studies. While comparisons between groups must be performed with caution, nervous system AEs in the MAS group were reported more frequently than the either Coartem groups, including the balance AEs mentioned previously.

Nervous system AEs of severe intensity represented 0.5% and 0.8% of AEs reported in the 4- and 6-dose Coartem groups respectively, as shown in Table 46. There were no severe AEs in adult subjects who received MAS.

Table 46: Nervous system disorder AEs of severe intensity, FDA adult pooled safety population

MedDRA preferred term (V 10.1)	Coartem		Relationship to Study Drug
	4-dose N=782 (%)	6-dose N=645 (%)	
Coma*	0	1 (0.2)	Unlikely
Headache	3 (0.4)	3 (0.5)	3 possible 3 unlikely
Somnolence	0	1 (0.2)	Possible
Syncope vasovagal	1 (0.1)	0	Unlikely
Total number of subjects	4 (0.5)	5 (0.8)	

* coded as life-threatening

There was only one AE which could have been related to study drug. Somnolence was reported in a 37 year old Caucasian female enrolled in A2401. On study day 2, dizziness, hyperglycemia, influenza-like illness, myalgia, vaginal hemorrhage and vomiting were reported, all of mild severity. On study day 3, the subject received her last dose of study drug and her blood smear was negative for parasites. Somnolence was reported on study day 3, the same day that existing vomiting was coded as severe. No action was taken for somnolence, and the AE resolved on study day 4. The subject received domperidone (1 dose) and paracetamol (acetaminophen) for vomiting and fever/headache respectively on study day 1. It is noted that domperidone overdose/toxicity includes CNS symptoms of drowsiness, disorientation and extrapyramidal reactions, and that the subject had mild renal impairment at baseline (creatinine 90 umol/L). However, onset of somnolence was on study day 3 and the subject only received 1 dose of domperidone.

All SAEs within the Nervous system disorders SOC were reported in the 6-dose group. There were 3 cases in total, 1 case each of coma, headache and mental impairment, representing 0.5% of all AEs in the 6-dose group. The cases of headache and mental impairment were related to malaria recrudescence in 2 subjects. The AE coma was unlikely to be related to study drug.

5.6.2 Pediatric Subjects (≤ 16 years of age)

Table 47 shows the most common nervous system AEs observed in the FDA pediatric pooled safety population, and Table 48 shows nervous system AEs for the 6-dose regimen by age group.

Table 47: Adverse events affecting the SOC “Nervous system disorders”, FDA pediatric pooled safety population

MedDRA preferred term (V 10.1)	Coartem 4-dose N=659	Coartem 6-dose N=1333	Mefloquine Artesunate N=150	SP N=143
Aphasia	1 (0.2)	0	0	0
Ataxia	3 (0.5)	1 (0.1)	5 (3.3)	0
Clonus	7 (1.1)	11 (0.8)	1 (0.7)	0
Convulsion	6 (0.9)	4 (0.3)	0	1 (0.7)
Coordination abnormal	2 (0.3)	0	0	0
Dizziness	153 (23.2)	67 (5.0)	104 (69.3)	6 (4.2)
Dyskinesia	0	1 (0.1)	2 (1.3)	0
Epilepsy	0	1 (0.1)	0	0
Facial palsy	1 (0.2)	0	0	0
Febrile convulsion	1 (0.2)	0	0	2 (1.4)
Fine motor delay	8 (1.2)	0	0	0
Headache	369 (56.0)	181 (13.6)	137 (91.3)	56 (39.2)
Hyperreflexia	2 (0.3)	6 (0.5)	0	0
Hypersomnia	1 (0.2)	0	0	0
Hypokinesia	44 (6.7)	0	0	0
Hypotonia	0	0	0	1 (0.7)
Lethargy	34 (5.2)	0	0	1 (0.7)
Myoclonus	0	3 (0.2)	0	0
Nystagmus	4 (0.6)	1 (0.1)	4 (2.7)	0
Paraesthesia	4 (0.6)	0	4 (2.7)	0
Somnolence	2 (0.3)	4 (0.3)	0	1 (0.7)
Speech disorder	33 (5.0)	0	0	1 (0.7)
Tremor	3 (0.5)	2 (0.2)	1 (0.7)	0

Table 48: Nervous system disorders in the 6-dose FDA pediatric pooled safety population by age group

MedDRA preferred term (V 10.1)	Age group (years)			
	≤ 2 N=587 (%)	>2 to ≤ 6 N=473 (%)	>6 to ≤ 12 n=207 (%)	>12 to ≤16 N=66 (%)
Ataxia	0	0	0	1 (1.5)
Clonus	9 (1.5)	1 (0.2)	0	1 (1.5)
Convulsion	2 (0.3)	2 (0.4)	0	0
Dizziness	1 (0.2)	2 (0.4)	20 (9.7)	44 (66.7)
Dyskinesia	0	1 (0.2)	0	0
Epilepsy	0	1 (0.2)	0	0
Headache	4 (0.7)	46 (9.7)	74 (35.8)	57 (86.4)
Hyperreflexia	5 (0.9)	1 (0.2)	0	0
Myoclonus	1 (0.2)	2 (0.4)	0	0
Nystagmus	0	0	0	1 (1.5)
Somnolence	0	3 (0.6)	1 (0.5)	0
Tremor	0	1 (0.2)	0	1 (1.5)

Nearly all nervous system AE rates were lower with the pediatric population compared to adults, and may be due to the fact that infants and small children cannot report symptoms. Table 50 confirms that subjective symptoms that smaller children may have been less able to report, such as dizziness and headache, occurred at lower rates in children ≤ 2 years of age, and increased in frequency with age. Objective neurologic findings were generally similar between age categories.

Most AEs were reported on study days 1-3. The most frequently reported nervous system AEs for all treatment groups were headache and dizziness, which were the same AEs reported with the adult population. Although between group comparisons should be interpreted with caution, headache was most frequently reported with MAS (91.3%) followed by Coartem 4-dose (56%) and 6-dose (26.3%). The frequency of headache was similar between adults and pediatrics for the MAS groups (91.1% and 91.3% respectively), but the rate of headache was significantly higher in adults compared to pediatrics for the 6-dose Coartem group (73.8% vs. 13.6%).

AEs were generally higher for the 4-dose compared to 6-dose Coartem regimens, the exceptions being clonus (6-dose 2.5% vs. 4-dose 1.1%), hyperreflexia (1.4% vs. 0.3%) and myoclonus (0.7% vs. 0%). This similar pattern has been noted with all AEs and was attributed to differences in collecting AEs and study design.

AEs representing balance (PTs ataxia, coordination abnormal, dizziness, nystagmus and tremor) were higher with the 4-dose than 6-dose regimen. They were also higher with the MAS group than either Coartem group.

There were 4 nervous system disorder AEs coded as severe in the FDA pediatric population: 1 convulsion and 3 headaches. All occurred in Coartem treatment groups, with none in the MAS

or SP groups. The case of convulsion was due to meningitis, and the 3 cases of headache were likely due to malaria.

All SAEs from the nervous system disorder SOC were reported in the 6-dose group. There were 3 cases of convulsion, 1 case each with the crushed tablet, dispersible tablet and standard tablet forms. In none of the cases was the study drug suspected to be the cause - two of the convulsions were related to cerebral malaria, and the remaining case was due to meningitis. There was 1 case of hypotonia and 1 case of lethargy reported in subjects receiving SP.

5.6.3 Neurologic Examinations

Neurological examinations were performed in Studies A2403, B2303 and at one site only in both studies A025 and A026. In studies AB/MO2, A023, A028, A2401, neurological findings were recorded as AEs only.

In studies A025, A026 and 2403, neurological abnormalities, commonly tandem walk and gait abnormal, clonus, nystagmus, tremor, Romberg test positive, were reported in a limited number of patients at baseline; these symptoms were generally attributed to malaria. Most abnormalities still observed postbaseline were mild and resolved by Day 8. In two patients in Study A2403, neurological abnormalities were still present at Day 28; these were hyperreflexia and/or clonus, and are included in the cases described previously. Results of neurological clinical examinations performed in study B2303 at each visit including baseline reported the following: seven of the 899 patients (0.8%) had abnormalities, most commonly tandem walk and gait abnormal, at baseline; only one patient had any postbaseline abnormalities and this was a patient treated with the dispersible tablet who had gait abnormal and tandem walk at 8 and 24 hours. Both abnormalities were already present at baseline. All reported abnormalities were mild.

5.7 Ear and Labyrinth Disorders

The neurotoxicity observed in animals when given large parenteral doses of some artemisinin derivatives is focused on lesions in specific brain nuclei involving the auditory and vestibular pathways. Clinical and pathological studies (Price, 2000; Ribeiro and Olliaro 1998; Kissinger, et al 2000; Hien, et al 2003) have found no evidence to date of similar lesions in human malaria patients.

In 2004 the results of an audiometry study of workers at a construction site in Mozambique was published (Toovey and Jameson 2004). This retrospective case-control study found that workers who developed malaria and were treated with Coartem had significantly greater increases in pure-tone thresholds (although the changes were subclinical) than matched control patients who had not had malaria and were not treated with Coartem. The methodology of this study has been criticized, (Winstanley and Molyneux 2004; Mehta, et al 2005) and the results were not supported by other case control studies in which evaluation of auditory brainstem responses (ABR) and other audiological measurements were performed in patients exposed to several courses of artemisinin derivatives (Kissinger, et al 2000; Van Vugt, et al 2000) or in patients treated with Coartem (Hutagalung, et al 2006). A study in volunteers with experimental malaria treated with Coartem also found no evidence of drug-related damage to hearing (McCall, et al 2006).

The sponsor also performed a study to evaluate possible auditory system effects of coartemether treatment. Study A2412 was an open-label, single-center study, using audiological measurements to evaluate the effects of co-artemether, atovaquone-proguanil and MAS on auditory function following the treatment of acute uncomplicated *Plasmodium falciparum* malaria. The audiology technician was blinded to the treatment the patients were receiving. Adult and adolescent patients were randomized in a 3:1:1 ratio (co-artemether: atovaquone-proguanil: MAS), but the study was terminated prematurely for administrative reasons, with only 87 of the planned 265 patients randomized. In addition, a large proportion of subjects did not receive valid auditory brainstem response (ABR) assessments. Despite these limitations, the study analysis rejected the null hypothesis, namely that the proportion of patients with ABR Wave III latency changes at Day 7 in the co-artemether group is $\geq 15\%$ (p-value 0.042). Four patients in the coartemether group and one patient in the MAS group had post-baseline increases in ABR Wave III and/or V latencies of > 0.3 msec, but these changes were not thought to be drug-related as they tended to be transient and unilateral. No relationship between drug levels and ABR wave latency increases could be seen with artemether, dihydroartemisinin or lumefantrine. Due to the limitations of study size and ABR assessments, the Applicant is currently performing a similar study to A2412 (Study A2417).

5.7.1 Adult Subjects (> 16 years of age)

Table 49 shows AEs affecting the auditory system, including relevant preferred terms from the SOC “Infections and infestations”, i.e. infections affecting the ear, as well the SOC ‘Ear and labyrinth disorders’ in the FDA adult pooled safety population. Overall, few AEs affecting the auditory system occurred in this population. For the Coartem 6-dose regimen group, the most frequent AE affecting the ear was vertigo. In the 6 dose regimen group, 20/21 cases of vertigo were reported as mild and only one case was considered related to study drug. Fifteen cases of vertigo were reported between Days 1 and 3, 5 between Days 4 and 8 and 2 between Days 16 and 29.

Hypoacusis was the most frequently reported AE in the Coartem 4-dose group, but no cases were reported with the 6-dose regimen. The Applicant found 12 cases whereas FDA review identified 10. In the Applicant’s review, the 12 cases were all mild except for one case reported as moderate, and only two cases were reported as suspected to be drug related. Ten of these 12 cases occurred between Days 1 and 3, two cases between Days 4 and 8 and one between Days 9 and 15.

Tinnitus was the second most frequently reported AE in both Coartem groups. Of four cases in the Coartem 6-dose group, 2 cases were reported between Days 1 and 3, one between Days 4 and 8 and one between Days 16 and 29. Three cases were mild and one was of moderate severity. Only one case was reported as suspected to be drug related by the investigator. In the Coartem 4-dose group, all three cases of tinnitus were mild and all were considered by the investigator to be unrelated to study drug. One case was reported between Days 9 and 15, the other two between Days 16 and 29.

One patient in the Coartem 6-dose regimen group had the AE deafness. This was a patient from Study A2401 who reported mild worsening of hearing loss that was present at baseline,

following the first dose of Coartem; this was reported to have resolved by Day 3. There were no AEs of severe intensity, and no SAEs reported in the SOC Ear and labyrinth disorders.

Table 49: Adverse events affecting the auditory system, FDA adult pooled safety population

MedDRA preferred term (V 10.1)	Coartem 4 dose N=782 (%)	Coartem 6 dose N=645 (%)	Mefloquine Artesunate N=280 (%)
Deafness	0	1 (0.2)	0
Ear pain	1 (0.1)	0	0
Ear pruritus	0	0	1 (0.4)
Hypoacusis	10 (1.3)	0	20 (7.1)
Middle ear inflammation	0	1 (0.2)	0
Motion sickness	0	2 (0.3)	0
Tinnitus	3 (0.4)	4 (0.6)	1 (0.4)
Vertigo	0	21 (3.3)	0
Otitis media	0	1 (0.2)	0

5.7.2 Pediatric Subjects (≤ 16 years of age)

Table 50 shows AEs affecting the auditory system in the FDA pediatric pooled safety population. Table 51 shows the same AEs for the Coartem 6-dose regimen by age group.

Unlike adults, there were no cases of vertigo, but this may be related to the age of the subjects. There were no cases of hypoacusis reported with the Coartem 6-dose regimen, and 5 cases in the Coartem 4-dose regimen group (four in the Applicant's count, all reported between Days 1 and 3, all mild, and all reported as not drug related). The other AEs affecting the ear in this population were unlikely to be due to neurological effects.

Table 50: Adverse events affecting the auditory system, FDA pediatric pooled safety population

MedDRA system organ class (V 10.1)	MedDRA preferred term (V 10.1)	Coartem 4-dose N=659	Coartem 6-dose N=1333	Mefloquine Artesunate N=150	SP N=143
Ear and labyrinth disorders	Cerumen impaction	0	1 (0.1)	0	0
	Ear disorder	0	0	0	2 (1.4)
	Ear pain	0	3 (0.2)	0	0
	Ear pruritus	0	1 (0.1)	0	0
	Hypoacusis	5 (0.8)	0	3 (2.0)	0
	Otorrhea	0	1 (0.1)	0	1 (0.7)
Infections & infestations	Otitis media	5 (0.8)	10 (0.8)	0	8 (5.6)
	Otitis externa	6 (0.9)	3 (0.2)	0	0

MAS= mefloquine artesunate ;SP = sulfadoxine/pyramethamine

Table 51: Ear and labyrinth disorders in the 6-dose FDA pediatric pooled safety population by age group

MedDRA preferred term (V 10.1)	Age group	
	≤ 2 years N=587 (%)	>2 to ≤ 6 years N=473 (%)
Cerumen impaction	1 (0.2)	0
Ear pain	2 (0.3)	1 (0.2)
Ear pruritus	1 (0.2)	0
Otorrhoea	1 (0.2)	0

There were no AEs of severe intensity, and no SAEs in the SOC “Ear and labyrinth disorders”.

In conclusion, there were no safety signals in the SOC Ear and labyrinth disorders, and no AEs related to audiologic changes in the pooled analysis. It is noted that systematic testing of hearing at baseline and after treatment was not done, and it is possible that subclinical hearing loss could have occurred and not been detected. While Study A2412 did not find a significant difference in auditory brainstem response wave III and or V latencies of >0.3 msec between subjects randomized to Coartem compared to MAS and atovaquone-proguanil, the results need to be confirmed in a larger study.

5.8 QT Interval Prolongation

Lumefantrine is chemically related to halofantrine, an antimalarial known to be associated with significant prolongation of the QT interval. Therefore, a definitive QT study, Study A2101, was conducted with Coartem administered orally as a 6-dose regimen of 80/480 mg Coartem over 3 days in a randomized, placebo-controlled parallel study in 126 healthy subjects. Moxifloxacin was used as the positive control in the study to establish assay sensitivity.

The QT interval was measured using Fridericia’s correction formula (QTcF). Table 52 summarizes the study results for QTcF. With the therapeutic dosing regimen for Coartem, the upper 90% CI for the maximum mean change in baseline- and placebo-adjusted QTcF ($\Delta\Delta\text{QTcF}$) exceeded 10 msec, the threshold for regulatory concern as described in the Guidance for Industry, E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.

The largest lower bound of the two-sided 90% CI for the $\Delta\Delta\text{QTcF}$ for moxifloxacin was greater than 5 msec indicating that the study was adequately designed and conducted to detect a small effect on the QT interval. There were no clinically significant effects on the PR and QRS intervals (maximum upper bound of 90% CI 3.6 and 2.8 msec respectively).

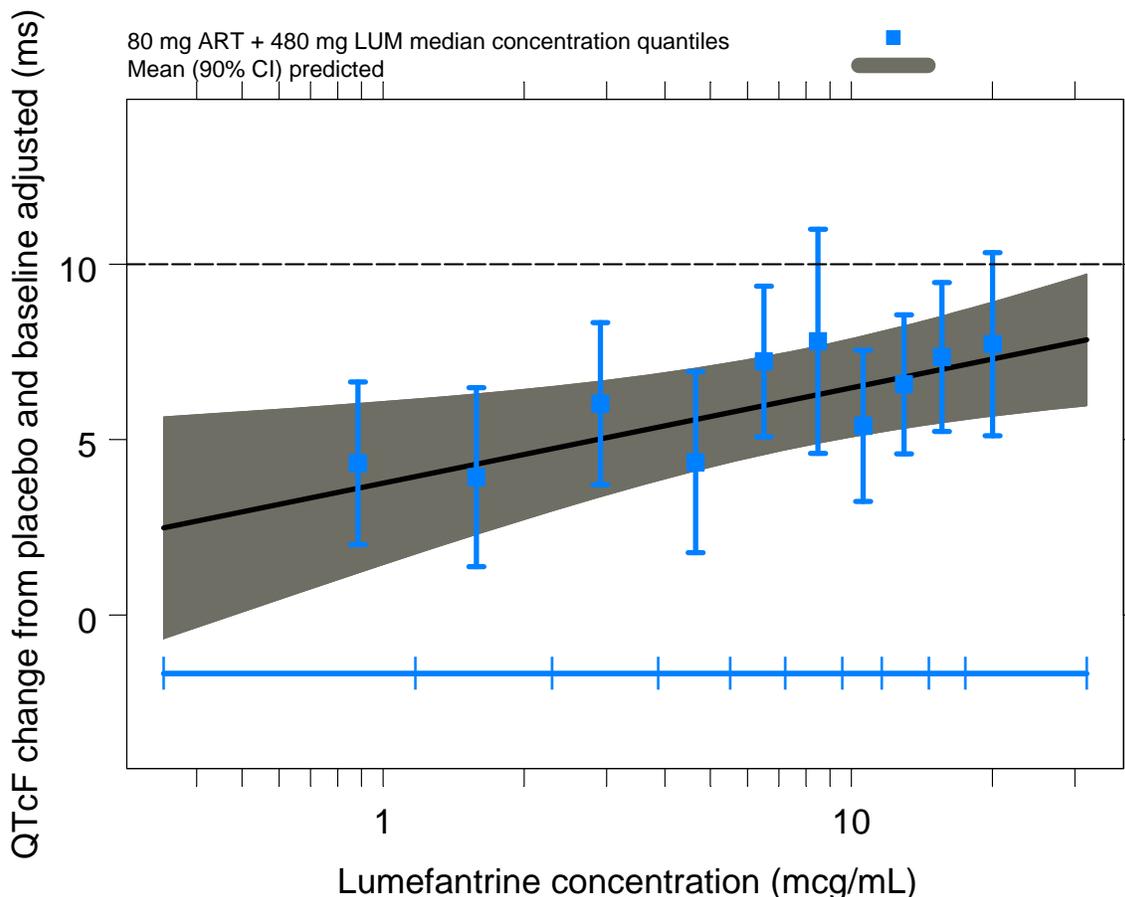
Table 52: Largest Time-Matched Increase in QTcF by Treatment Group

Treatment	Time, hr	$\Delta\Delta\text{QTcF}$, ms	90% CI, ms
Coartem	72	7.29	(3.6, 11.0)
Moxifloxacin	61*	14.1	(8.9, 19.4)

* Moxifloxacin was administered at time 60-hours

Significant positive lumefantrine concentration- $\Delta\Delta\text{QTcF}$ relationship was identified (Figure 2). Based on a linear relationship, the predicted mean (90% confidence interval) $\Delta\Delta\text{QTcF}$ for the mean C_{max} of 480 mg lumefantrine dose was 7.0 (5.5, 8.5) msec. These findings are consistent with the primary statistical analysis.

Figure 2: Mean (90% CI) predicted $\Delta\Delta\text{QTcF}$ vs. Lumefantrine Concentration (black line and shaded grey area) and observed median-quantile concentrations and associated mean $\Delta\Delta\text{QTcF}$ (90% CI)



Only the therapeutic dosing regimen of Coartem was tested in this QT study. No specific pharmacokinetic studies have been performed in subjects with hepatic and renal impairment or in elderly patients to determine the highest expected clinical exposure. In four studies in adult or child malaria patients using the 6-dose regimen of Coartem (A025, A2401, A2403, and B2303), the lumefantrine exposure (mean AUC_{∞} ranged from 335 to 1260 $\mu\text{g}\cdot\text{h}/\text{ml}$) did not exceed the exposure level in healthy subjects (mean AUC_{∞} was 1320 $\mu\text{g}\cdot\text{h}/\text{ml}$). The lumefantrine C_{max} ranged between $5.72 \pm 2.91 \mu\text{g}/\text{mL}$ to $10.5 \pm 6.39 \mu\text{g}/\text{mL}$ in malaria patients and between $5.09 \pm 1.9 \mu\text{g}/\text{mL}$ to $28.3 \pm 13.6 \mu\text{g}/\text{mL}$ in other studies of healthy volunteers. The highest C_{max} observed in other healthy volunteer studies exceeds that seen in this study ($\sim 16 \text{ mg}/\text{mL}$), but it is unlikely to result in clinically significant QT prolongation, given that the concentration-QT relationship predicts that the mean QT prolongation at an exposure of $\sim 30 \text{ mg}/\text{mL}$ would be $< 10 \text{ msec}$. Also, the inter-subject variability was high ($\sim 50\%$) in both healthy volunteers and patients.

For drugs that are found to prolong the QT interval greater than the 10 msec threshold at clinically relevant exposures, ICH E14 specifies that an expanded ECG safety evaluation during later stages of drug development might be appropriate to describe the QT effect of the drug in the target population. In the Coartem development program, ECG evaluations were performed in most studies (20 total) and were included in the pooled safety population. Approximately 7% (55/830) of adults and adolescents, defined as those > 12 years of age, had a QTcF increase of > 60 msec from baseline in the clinical trials. An absolute increase in QTcF >500 msec was reported in 3 (0.3%) patients. In children, defined as those ≤ 12 years of age, approximately 5% (65/1226) of children had an increase in QTcF of over 60 msec and no child had an absolute QTcF measurement >500 msec. The main cardiac adverse event reported in the clinical trials was palpitation, which is consistent with fever and anemia associated with the disease state. There were no reports of adverse events related to QT prolongation, such as syncope, sudden cardiac death, seizure, or significant ventricular arrhythmias in the clinical trials.

5.9 Human Reproduction and Pregnancy

Study A2407 was a multicenter, prospective observational study which enrolled women who had used Coartem or SP to treat symptomatic malaria during pregnancy. Over 1000 pregnant subjects were assigned to exposure groups (1:1 enrollment ratio) based on the antimalarial treatment they had received for the treatment of the most recent malaria episode prior to registry entry (index episode). Approximately 85% of the enrolled pregnant women completed the registry to 6 weeks after delivery. Over 90% of the pregnant women had live births, with approximately 2% having stillbirth and around 1% having spontaneous abortion.

The primary analysis showed no difference between exposure groups in rates of perinatal or neonatal mortality, rates of abortion, stillbirth, preterm delivery, or low birth weight. Rates of birth defects were low in both exposure groups, and no major malformations, apart from in one patient with a chromosomal abnormality were reported. There was no difference between groups with respect to other birth defects, with single reports in most cases. Other infant outcomes (length, gestational age, birth weight, head circumference) were also similar in the two exposure groups, as was maternal mortality.

In this study, 33% of patients were inadvertently exposed to co-artemether and 26% received SP during the first trimester. Exploratory analyses suggested that exposure to co-artemether in the first trimester was not associated with an increased risk of neonatal death or stillbirth.

Malaria carries a higher risk of morbidity and mortality in pregnant women than in the general population, and is associated with poor obstetrical outcomes. Based on the data in the pregnancy registry, use of Coartem during pregnancy does not seem to show an increased risk for major malformations or increased rates of spontaneous abortion, and therefore should not be withheld in life-threatening situations where no other effective anti-malarials are available. During the second and the third trimester, treatment should only be considered if the expected benefit to the mother outweighs the risk to the fetus.

5.10 Summary of Clinical Safety

Based on pooled analyses of over 3400 subjects (1427 adult subjects, 1992 pediatric subjects) exposed to either a 4- or 6-dose regimen of Coartem, the following conclusions can be made:

Adults:

- The most frequently reported AEs for the Coartem 6-dose regimen were headache, asthenia, dizziness and anorexia, which were likely malaria symptoms as they occurred on days 1-3.
- The majority of AEs were of mild or moderate intensity. Severe AEs were reported in 5.4% of 6-dose Coartem subjects, with pyrexia the most frequently reported severe AE.
- Deaths (0.2%) and SAEs (6-dose group 1.4%) were reported infrequently. The majority of SAEs were likely related to malaria (2 cases) or malaria recrudescence/efficacy

Children:

- The most frequently reported AEs for the Coartem 6-dose regimen were pyrexia, vomiting, *P. falciparum* infection and anorexia. Like adults, these were likely symptoms of malaria as they occurred on days 1-3.
- Severe AEs were reported in 7.3% of Coartem 6-dose regimen subjects. The most frequently reported severe AEs were pyrexia (4%).
- High incidence of cough may be related to the higher incidence of respiratory tract infection in children compared to adults.
- Deaths (0.2%) were primarily due to infection.
- SAEs in the 6-dose group (1.3%) were composed mostly of *P. falciparum* infection.

Other safety:

- The pooled comparator studies A026 and A028 did not show any safety findings which were significantly different than the FDA adult and pediatric pooled populations.
- The most frequently reported nervous system disorder AEs were identical in adults and pediatrics, namely headache followed by dizziness. These were likely symptoms of malaria.
- Adults:
 - Nervous system AEs of severe intensity represented 0.8% of AEs reported in the 6-dose Coartem group. There was only one AE which could have been related to study drug (somnia).
 - SAEs within the Nervous system disorders SOC were all reported in the 6-dose group. There were 3 cases in total, 1 case each of coma, headache and mental impairment representing 0.5% of all AEs in the 6-dose group.
- Peds:
 - Rates of nervous system disorder AEs were lower in the pediatric population, and may be related to the inability to report symptoms in very young children
 - 4 nervous system disorder AEs coded as severe: 1 convulsion (due to meningitis) and 3 headaches (due to malaria)
 - 3 nervous system SAEs were reported in the Coartem 6-dose group: 3 cases of convulsion, 2 related to cerebral malaria and the remaining case due to meningitis.
- Ear and labyrinth disorders were infrequent. For adults (Coartem 6-dose group), the most frequent AE affecting the ear was vertigo. Most cases were mild and unrelated to study drug. In pediatrics, AEs were unlikely to be neurologic effects.
- A definitive QTc study, Study A2101, showed that Coartem was associated with a mean maximum increase in QTcF relative to placebo of 7.29 msec (3.6, 11.0). ECG safety evaluations showed approximately 5% of adults and children had a QTcF increase of 60

ms from baseline. There were no reports of AEs related to QT prolongation, such as syncope, sudden cardiac death seizure and significant ventricular arrhythmias.

- A pregnancy registry with 495 females exposed to Coartem (1/3 in the first trimester) did not show an increase in teratogenic effects or spontaneous abortions.

6 Draft Questions for the Advisory Committee

1. Based on the information presented from the clinical studies of Coartem, has the proposed 6-dose regimen been shown to be effective for the treatment of malaria? (vote)
2. Based on the information presented from the clinical studies of Coartem, has the proposed 6-dose regimen been shown to be safe for the treatment of malaria? (vote)
3.
 - a) If the answer to number 2 is no, are there any additional studies (e.g., in vitro, preclinical, clinical, surveillance) that you would recommend Novartis conduct before the application is approved? After the application is approved? For example, should additional investigation into the potential neurotoxicity be conducted?
 - b) If the answer to numbers 1 and 2 is yes, should specific post-marketing surveillance studies be conducted? Should studies to evaluate or follow development of resistance be conducted?
4. Do you consider the data presented for non-falciparum malaria sufficient to demonstrate efficacy of Coartem in treating patients with coinfections due to *P. vivax*?
5. Is there specific efficacy, safety or other information that you would recommend be reflected in the Coartem product labeling?

7 References

Brookmeyer, R. and Crowley, J. (1982), A Confidence Interval for the Median Survival Time, *Biometrics*, 38, 29 - 41.

Hien TT, Turner GDH, Mai NTH, et al (2003). Neuropathological assessment of artemether treated severe malaria. *Lancet*; 362 : 295-6.

Kissinger E, Hien TT, Hung NT, et al (2000) Clinical and neurophysiological study of the effects of multiple doses of artemisinin on brain-stem function in Vietnamese patients. *Am J Trop Med Hyg*; 63: 48-55.

Price RN (2000). Artemisinin drugs: novel antimalarial agents. *Exp Opin Invest Drugs*; 9:1815–27.

Ribeiro IR and, Olliaro P (1998). Safety of artemisinin and its derivatives. A review of published and unpublished clinical trials. *Med Trop* ; 58: 50–3.

Toovey S (2006). Are currently deployed artemisinin neurotoxic? *Toxicol Lett*; 166: 95-104.

Winstanley P and Molyneux M (2004). Comment on: Audiometric changes associated with the treatment of uncomplicated falciparum malaria with co-artemether. *Trans R Soc Trop Med Hyg* ; 98:268-9.

Mehta U, Barnes KI, Kathard H, et al (2005). Comment on: Audiometric changes associated with the treatment of uncomplicated falciparum malaria with co-artemether. *Trans R Soc Trop Med Hyg* ; 99: 313-4.

Van Vugt M, Angus BJ, Price RN, et al (2001). A case-control auditory evaluation of patients treated with artemisinin derivatives for multidrug-resistant *Plasmodium falciparum* malaria. *Am J Trop Med Hyg* ; 62: 65-9.

Hutagalung R, Paiphun L, Ashley EA, et al (2006). A case control auditory evaluation of patients treated with artemether-lumefantrine. *Am J Trop Med Hyg* ; 74: 211-4.

McCall MBB, Beynon AJ, Mylanus EAM, et al (2006). No hearing loss associated with the use of artemether-lumefantrine to treat experimental human malaria. *Trans R Soc Trop Med Hyg*; 100: 1098-104.

8 Appendix 1

Draft Guidance to Industry, “*Malaria: Developing Drug and Nonvaccine Biological Products for Treatment and Prophylaxis*”

www.fda.gov/cder/guidance/7631dft.pdf

9 Appendix 2

Rationale and limitation of the PCR analysis

The renewal of clinical activity (called recrudescence or re-infection in the analysis) when observed subsequent to treatment of a malaria case, and within an arbitrary 28 days period, is termed a clinical recrudescence. The success of the treatment as defined by the occurrence and timing of this clinical recrudescence (in association with regular microscopic examination of the blood during this 28 days period), serves to classify the parasites as sensitive (S) or increasingly resistant (RI-II) to the drug used. The clinical recrudescence is generally associated with both a rise in parasite numbers and with a concomitant return of malaria symptoms. In highly resistant cases (RIII) clinical symptoms and parasitaemia do not abate appreciably throughout the observation period.

Amongst the parameters used to assess the efficacy of a new treatment, the rate of clinical recrudescences is of some importance, as it reflects the effectiveness with which the drug removes and/or suppresses parasite growth. Clinical recrudescences are interpreted as resulting from parasite populations that survive the treatment in sufficient numbers to re-initiate a further symptomatic wave of parasitaemia. A problem in the interpretation of clinical trial results is encountered when the patient is still subject to bites by infective mosquitoes before, during and after treatment, as is the case in many endemic settings. Since the incubation period of *P. falciparum* can be as little as 8-10 days, the possibility exists that the renewed clinical activity following initiation of treatment results from a re-infection by a mosquito, rather than by survival of any of the parasites present at the time of admission. Another overlooked possibility is the release into the blood, of parasites from the liver, which could have been inoculated by a mosquito before or during the first few days after initiation of treatment. A number of the drugs used to treat the blood stage parasites are not effective against the liver stages, and by the time the liver stage parasites mature and are released in the blood stream, drug concentrations might have reached sub-optimal doses.

P. falciparum parasites are known to be highly diverse. This diversity is reflected in the occurrence of many highly polymorphic proteins and the genes which encode them. In endemic regions extensive polymorphism of the parasite populations are frequently observed even in small villages of a few hundred inhabitants. Three *P. falciparum* genes which contain such polymorphic regions are MSP 1, MSP 2 and GLURP. When these three genes are used as genetic markers a genotype pattern for the parasite population present in a the sample analysed is obtained. Provided the relative frequency of the different allelic variants for the genetic markers is not highly skewed, and a sufficient number of variants for each of the markers is observed in a given area, there is low probability that infections initiated by different mosquitoes will result in parasite populations in the blood that share the same genotype pattern.

Therefore, the genotype pattern of the *P. falciparum* parasites present in the blood at the time of admission and during a renewal of clinical activity was obtained by PCR amplification of the polymorphic regions of the MSP 1, MSP 2 and GLURP genes. The genotype patterns of the two samples were then compared. This analysis was undertaken in order to ascertain whether it is possible to differentiate between genuine parasite recrudescences (survival of the drug treatment and therefore classified as a failure), and a case of re-infection (classified as a success).

It must be pointed out that the PCR analysis carried out in this study, and for that matter any other PCR analysis, will not and can not provide any conclusive evidence in favour of either alternatives (re-infection versus recrudescence). There are a number of reasons why this is the case:

1 - Parasites present at very low levels in the blood when the admission sample is taken are unlikely to be present in the aliquot analysed by PCR, and will not be therefore detected. These low levels could either be due to genuinely low parasite numbers for a particular population, or could result from the sequestration of mature parasites away from the peripheral vasculature. *P. falciparum* parasites are sequestered for the last 20 - 30 hours of their 48 hour erythrocytic cycle. Thus if two or more broods of parasites are present on alternate days (as is sometimes observed), or in asynchronous waves, it is quite possible to miss one parasite population when a single sample is analysed. Additionally, competition during the PCR amplification reaction, between two allelic variants of the same marker, might result in the detection of one but not the other.

2 - Parasites present in the liver during the early phases of treatment will not be detected by PCR analysis of blood samples.

The consequence of these two points is that detection of "novel" alleles in the renewal of clinical activity sample, could only be interpreted as circumstantial evidence that re-infection might have taken place.

3 - In cases where the genetic profiles are the same in the paired samples (or the pattern from the second sample represents a subset of the first), an interpretation of probable recrudescence of the original parasite population is acceptable. There is however, the possibility that the person acquires a new infection with a parasite profile similar to the admission sample. This cannot be excluded by simple frequency analysis of the alleles present, since mosquitoes can remain associated with a particular house (sheltering and feeding without leaving the dwelling), and the sporozoites they carry could retain their infectivity for 2 or more weeks.

Given that it is clear that no PCR analysis (as performed at present) can provide data for an unequivocal proof of a re-infection or recrudescence, the results of this study must be interpreted and conclusions derived bearing in mind the limitations described above.

Guidance for Industry Malaria: Developing Drug and Nonvaccine Biological Products for Treatment and Prophylaxis

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Leonard Sacks at 301-796-1600.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**June 2007
Clinical/Medical**

Guidance for Industry Malaria: Developing Drug and Nonvaccine Biological Products for Treatment and Prophylaxis

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**June 2007
Clinical/Medical**

TABLE OF CONTENTS

I.	INTRODUCTION.....	1
II.	BACKGROUND	2
A.	Use of Foreign Studies.....	2
B.	Biology of Malaria Parasite	2
III.	SPECIFIC INDICATIONS.....	4
IV.	DEVELOPMENT PROGRAM.....	5
A.	General Considerations	5
1.	<i>Preclinical Microbiology</i>	<i>5</i>
a.	Mechanism of action	5
b.	Activity in vitro	5
c.	Activity in vivo.....	6
d.	Activity of metabolites.....	7
e.	Drug resistance and cross-resistance.....	7
f.	Drug combinations.....	7
2.	<i>Drug Development Population.....</i>	<i>8</i>
3.	<i>Efficacy Considerations</i>	<i>8</i>
4.	<i>Safety Considerations.....</i>	<i>9</i>
5.	<i>Labeling Considerations</i>	<i>9</i>
B.	Treatment Studies	9
1.	<i>Study Design.....</i>	<i>9</i>
a.	Combination regimens	9
b.	Sequential regimens	9
2.	<i>Study Population</i>	<i>10</i>
3.	<i>Entry Criteria</i>	<i>10</i>
4.	<i>Randomization, Stratification, and Blinding</i>	<i>11</i>
5.	<i>Special Populations.....</i>	<i>11</i>
6.	<i>Choice of Comparators</i>	<i>12</i>
7.	<i>Efficacy Endpoints.....</i>	<i>12</i>
8.	<i>Study Procedures and Timing of Assessments.....</i>	<i>14</i>
9.	<i>Parasite Evaluation.....</i>	<i>15</i>
10.	<i>Statistical Considerations.....</i>	<i>15</i>
11.	<i>Accelerated Approval (Subpart H) Considerations.....</i>	<i>17</i>
C.	Prophylaxis Studies	17
1.	<i>Study Design.....</i>	<i>17</i>
2.	<i>Study Population</i>	<i>19</i>
3.	<i>Entry Criteria</i>	<i>19</i>
4.	<i>Randomization and Blinding</i>	<i>20</i>
5.	<i>Special Populations.....</i>	<i>20</i>
6.	<i>Choice of Comparators</i>	<i>20</i>
7.	<i>Efficacy Endpoints.....</i>	<i>20</i>
8.	<i>Study Procedures and Timing of Assessments.....</i>	<i>21</i>
9.	<i>Statistical Considerations.....</i>	<i>23</i>
a.	Primary endpoint evaluation	23
b.	Secondary endpoint evaluation	24

10. <i>Risk-Benefit Considerations</i>	24
11. <i>Labeling Considerations</i>	24
GLOSSARY	25
APPENDIX A: MICROBIOLOGICAL EVALUATIONS	28

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Guidance for Industry¹
Malaria: Developing Drug and Nonvaccine Biological
Products for Treatment and Prophylaxis

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is one in a series of documents developed by the Office of Antimicrobial Products in the Center for Drug Evaluation and Research at the Food and Drug Administration (FDA) to assist pharmaceutical manufacturers and clinical sponsors in developing antimicrobial drug and nonvaccine biological products.² The purpose of this guidance is to assist sponsors in the clinical development of drugs for the treatment and/or prophylaxis of malaria. Specifically, this guidance addresses the FDA's current thinking regarding development programs for antimalarial drugs and the design of the clinical trials to be conducted in these programs. It is the intention of this guidance to serve as a focus for continued discussions among the Division of Special Pathogens and Transplant Products (DSPTP), pharmaceutical sponsors, the academic community, and the public.³

This guidance does not address vaccine development, which is regulated by the Center for Biologics Evaluation and Research. This guidance also does not discuss general issues of clinical trial design or statistical analysis. Those topics are addressed in the ICH guidances for industry *E8 General Considerations for Clinical Trials*, *E9 Statistical Principles for Clinical Trials*, and *E10 Choice of Control Group and Related Issues in Clinical Trials*.⁴ This guidance

¹ This guidance has been prepared by the Division of Special Pathogens and Transplant Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

² For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

³ In addition to consulting guidances, sponsors are encouraged to contact the DSPTP to discuss issues that arise during antimalarial drug development and to schedule meetings with the FDA as needed.

⁴ We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web page at <http://www.fda.gov/cder/guidance/index.htm>.

Contains Nonbinding Recommendations
Draft — Not for Implementation

36 focuses on drug development and clinical trial design issues that are unique to the study of
37 malaria. This guidance may be revised as new scientific information accumulates regarding
38 malaria and its treatment or prevention.

39
40 FDA’s guidance documents, including this guidance, do not establish legally enforceable
41 responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should
42 be viewed only as recommendations, unless specific regulatory or statutory requirements are
43 cited. The use of the word *should* in Agency guidances means that something is suggested or
44 recommended, but not required.

45
46

47 **II. BACKGROUND**

48

49 **A. Use of Foreign Studies**

50

51 Malaria is a global problem with the greatest burden of disease and mortality occurring in
52 developing countries. Although cases of malaria are uncommon in the United States,
53 antimalarial drugs have significant public health importance in the United States: antimalarial
54 prophylaxis is used extensively by U.S. travelers and by U.S. citizens residing in or deployed to
55 endemic areas (e.g., military personnel). Since malaria is uncommon in the United States, drugs
56 or nonvaccine biological products developed for the treatment of malaria can be eligible for
57 orphan drug designation.

58

59 Because malaria is not endemic in the United States, clinical data used to support an application
60 for a new antimalarial therapy (or regimen) probably will be obtained from studies conducted
61 abroad. FDA regulations permit studies performed in foreign countries to be used for drug
62 approval when these studies meet FDA standards for the conduct and design of clinical trials (21
63 CFR 314.106).

64

65 The FDA recognizes the challenges involved in performing studies abroad, and the need to
66 reconcile regulatory requirements with local laws and practices in countries where studies are
67 done. However, complete and comprehensive data for efficacy and safety evaluation are
68 important for drug approval: technical or financial constraints at foreign sites should be
69 addressed by the sponsor during drug development to ensure that FDA regulations regarding
70 clinical trials and good clinical practice are followed.⁵ Foreign sites also should be prepared to
71 allow FDA auditing of the site, if requested.

72

73 **B. Biology of Malaria Parasite**

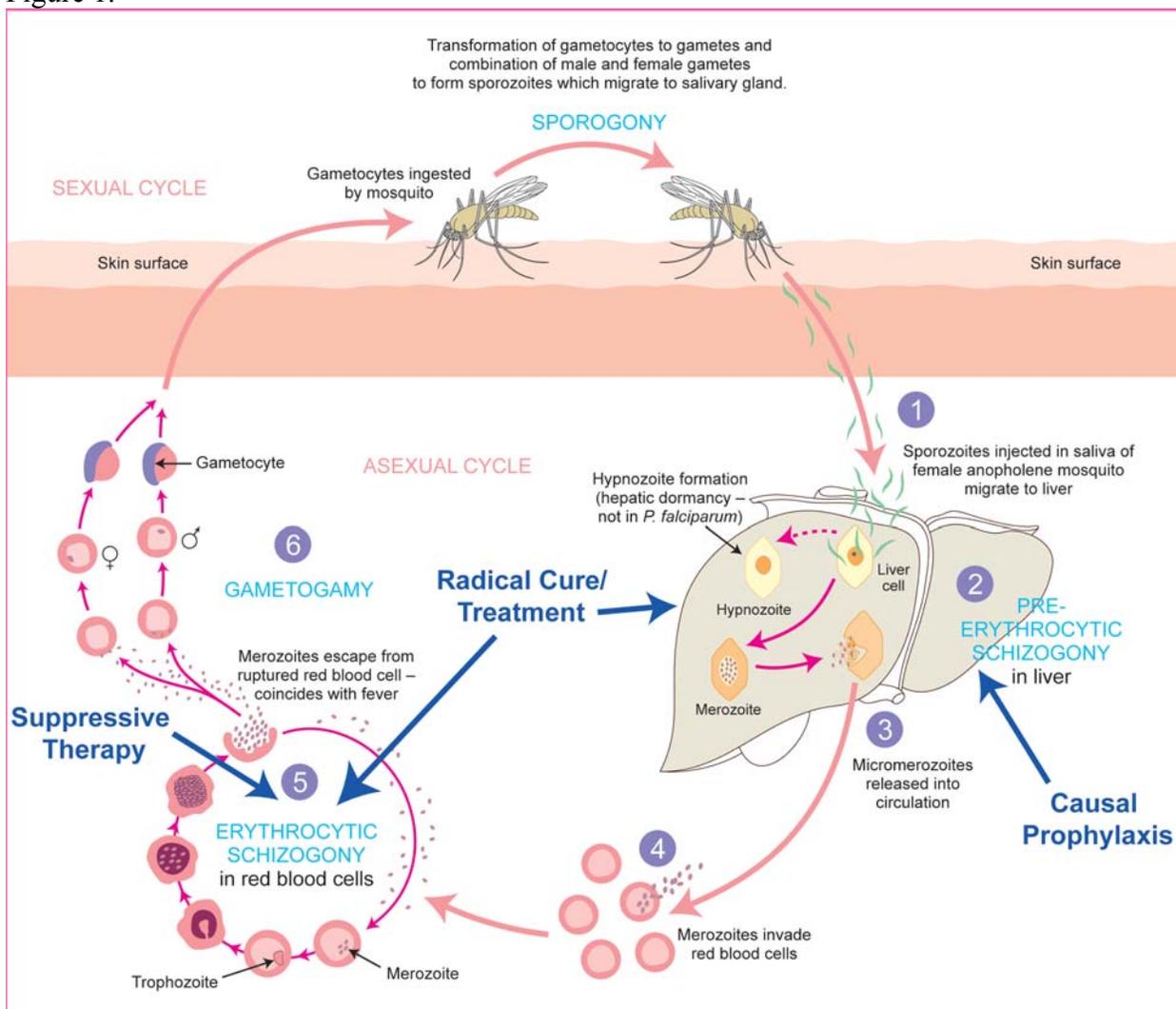
74

75 The unique life cycle of plasmodial species (malaria parasite) has specific implications for
76 antimalarial drug development. Following the inoculation of sporozoites by the mosquito,
77 plasmodia undergo initial replication in hepatocytes (hepatic or exoerythrocytic phase) followed
78 by cycles of replication in the peripheral blood (hematogenous or erythrocytic phase), as shown
79 in Figure 1.

80

⁵ See <http://www.fda.gov/oc/gcp/default.htm>.

81 Figure 1.¹



82

83 ¹ Reproduced with modification by permission of Health Protection Agency, United Kingdom
84 (<http://www.hpa.org.uk/infections/toolkit/mosquito.htm>).

85

86 The type of antimalarial activity that drugs demonstrate may depend on the stage of plasmodial
87 replication that they target (i.e., exoerythrocytic forms (including hypnozoites) or erythrocytic
88 forms (including gametocytes)). Depending on the target, antimalarials can be suitable for
89 radical treatment (elimination of erythrocytic and exoerythrocytic forms), suppressive therapy
90 (suppression of erythrocytic forms following exposure to prevent symptomatic malaria, with no
91 effect on exoerythrocytic forms), causal prophylaxis (eradication of exoerythrocytic forms
92 during prophylaxis), and radical cure (eradication of hypnozoites in relapsing malaria). These
93 terms should be used as appropriate in the development of clinical protocols.

94

95

96 **III. SPECIFIC INDICATIONS**
97

98 The treatment and prophylaxis of malaria include the following specific FDA-recognized
99 indications:

- 100
- 101 • **Treatment of malaria caused by:**
 - 102 – *Plasmodium falciparum* infection
 - 103 – *Plasmodium vivax, ovale, or malariae* infection
- 104

105 Qualifiers of a treatment indication include:⁶

- 106 – Uncomplicated malaria
 - 107 – Severe or complicated malaria
 - 108 – Radical cure of relapsing malaria
 - 109 – Chloroquine-resistant malaria
 - 110 – Multidrug-resistant malaria⁷
- 111

- 112 • **Prophylaxis of malaria caused by:**
 - 113 – *Plasmodium falciparum*
 - 114 – *Plasmodium vivax, ovale, or malariae*
- 115

116 Qualifiers of a prophylaxis indication include:

- 117 – Suppressive therapy
 - 118 – Causal prophylaxis
 - 119 – Prophylaxis of chloroquine-resistant malaria
- 120

121 The safety and efficacy of new drugs for the treatment of malaria can be most clearly established
122 in patients with uncomplicated malaria. Effective therapies should have high clinical and
123 parasitological cure rates. In uncomplicated malaria, rescue treatment can be provided promptly
124 to patients who do not respond to study drugs if clinical deterioration occurs, and observations of
125 drug adverse effects are not obscured by the signs and symptoms of severe or complicated
126 malaria. In contrast, study of new drugs for severe or complicated malaria may be difficult to
127 interpret in the face of high mortality rates from complications that are often independent of the
128 parasite load; accordingly, proposals for studies in severe or complicated malaria should be
129 discussed with the DSPTP.

130

131 To demonstrate radical cure of relapsing malaria, studies should include adequate numbers of
132 patients with *P. vivax* or *P. ovale* infection to evaluate the eradication of hypnozoites. Patients
133 should be followed for a sufficient duration of time to exclude relapse. The drug under study for
134 the radical cure of malaria should be compared to a drug recognized to be effective against
135 hypnozoites; or should demonstrate a statistically significant reduction in relapse rate when
136 compared to a drug without activity against hypnozoites.

⁶ These terms are defined in the following text and in the Glossary.

⁷ Clinical development of antimalarial therapy should address regional variation in malarial resistance. This is discussed in the following sections.

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137
138 The activity of antimalarial drugs against chloroquine-resistant malaria (for treatment or
139 prophylaxis) can be inferred when studies are performed in regions with known high rates of
140 chloroquine resistance. Activity against more broadly resistant malarial isolates (i.e., multidrug-
141 resistant strains), can be supported by a combination of clinical, epidemiological, and
142 microbiological data (see section IV.A.).

143
144

145 **IV. DEVELOPMENT PROGRAM**

146

147 **A. General Considerations**

148

149 *1. Preclinical Microbiology*

150

151 Drugs for the treatment and/or prophylaxis of malaria should be tested in vitro and in animal
152 models before submission of an initial investigational new drug application (IND). Pre-
153 investigational new drug application (pre-IND) guidance regarding the choice of appropriate
154 preclinical models is available from the FDA.⁸ The following sections describe preclinical
155 microbiology assessments that should be considered by sponsors as components of the drug
156 development program.

157

158 a. Mechanism of action

159

160 The mechanism by which the drug exhibits antiparasitic activity should be investigated, if
161 possible. These studies should include an evaluation of the biochemical and molecular effect of
162 the drug on the different stages of the parasite.

163

164 b. Activity in vitro

165

166 In vitro activity of an antimalarial drug can be measured against the erythrocytic and
167 exoerythrocytic stages of the *Plasmodium* species using an appropriate model. The results can
168 be expressed as an effect on growth and/or morphology by microscopic examination, or the
169 uptake of radio-labeled hypoxanthine. Other methods may be appropriate, but should be
170 discussed with the DSPTP.

171

172 Testing should include laboratory strains of *Plasmodium* species with known patterns of
173 resistance to currently approved antimalarials, and at least 100 clinical isolates from different
174 geographical areas such as Africa or Southeast Asia. Isolates from the regions where clinical
175 trials are planned also should be tested. Appropriate positive controls (e.g., currently approved
176 antimalarial drugs) and negative controls (e.g., drug vehicle) should be included in the study.
177 Different concentrations of the drug under development should be tested in vitro to determine
178 the:

179

- Optimal concentration effective for inhibiting growth and/or killing of the organism
- Effect of drug on different stages of the parasite in synchronous cultures

181

⁸ See <http://www.fda.gov/cder/ode4/preind/default.htm>.

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182
183 There should be an effort to optimize the in vitro testing conditions. This can involve assessing
184 the effects of:

- 185
186
- Using culture-adapted versus fresh isolates
 - 187 • Using synchronous versus asynchronous cultures
 - 188 • Having different inoculum sizes
 - 189 • Using different incubation periods
- 190

191 If optimal testing conditions have been previously established, then the references supporting the
192 testing conditions used should be included in the IND or pre-IND submission. Attempts also
193 should be made to identify and designate a quality control strain during testing.

194
195 c. Activity in vivo

196
197 Appropriate animal models should be identified to measure the activity of the drug when
198 administered for either prophylaxis or treatment. Considerations when choosing an appropriate
199 model and experimental design include selecting *Plasmodium* species relevant to human
200 infection, the similarity of the course of infection and disease in animals and humans, and the
201 ability to obtain reproducible parasitemia. Endpoints should include:

- 202
- Survival
 - 204 • Reduction in parasitemia
 - 205 • Effect on erythrocytic and exoerythrocytic stages
 - 206 • Time to parasite clearance and relapse or recrudescence
- 207

208 In animal studies, parasitological counts and other laboratory measurements should be done at
209 baseline, at regular intervals after the initiation of therapy, and post-treatment. Post-treatment
210 counts and assessments should include evaluations after animals are aparasitemic. Evaluation of
211 the effect of host splenectomy can be useful for determining if a curative effect is sustained.
212 Similar to in vitro studies, appropriate positive and negative controls should be included in each
213 animal study.

214
215 Sampling for drug concentrations and pharmacokinetic assessments is strongly encouraged in
216 animal studies, and should be included whenever possible.

217
218 The progression of disease in the animal model selected for the study should mimic the disease
219 in humans. Some of the parameters that should be measured include:

- 220
- Prepatent period
 - 222 • Peak parasitemia
 - 223 • Duration of parasitemia
 - 224 • Presence or absence of different developmental forms in the blood and liver (including
225 hypnozoites)
 - 226 • Infectivity of gametocytes
- 227

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228 If such parameters were previously established in an animal model (*Plasmodium* species/host
229 animal used), supporting references should be included in the IND or pre-IND submission. In
230 addition, efforts should be made to optimize the testing conditions such as inoculum size or the
231 time therapy is initiated if not already known.

232
233 d. Activity of metabolites

234
235 The activity of any drug metabolite, identified in humans, should be determined in appropriate in
236 vitro and/or animal models of infection.

237
238 e. Drug resistance and cross-resistance

239
240 The ability of *Plasmodium* strains to develop resistance when subjected to drug pressure should
241 be examined in appropriate in vitro and/or in vivo models; this examination should include
242 evaluating the potential for cross-resistance to drugs in the same class or in other classes. If
243 resistance is demonstrated, it is important to identify the mechanism of resistance. Attempts
244 should be made to evaluate the clinical significance of any changes in phenotype (e.g., in vitro
245 susceptibility to the drug) or genotype observed in preclinical studies by correlating such
246 changes with clinical outcome.

247
248 f. Drug combinations

249
250 Preclinical evaluations can be valuable for examining whether there is a potential advantage of
251 combination treatment relative to individual drugs. The following situations should be studied if
252 combination regimens are being considered for study in humans:

- 253
- 254 • In vitro activity of the combination versus individual drugs against laboratory strains and
255 clinical isolates
 - 256 • Activity in appropriate animal models of infection
 - 257 • Activity in vitro and in animal studies against resistant isolates or strains, including those
258 from the geographical areas where the drug is intended to be used
 - 259 • Characterization of the mechanism by which the drugs exhibit additive or synergistic
260 microbiological effects
 - 261 • The potential for development of resistance in vitro and in vivo
- 262

263 There are other possible reasons for using combination therapy that may not be reflected in
264 preclinical models (e.g., reducing drug toxicity or convenience of the regimen). However, for
265 combinations that are proposed on the basis of superior antimalarial activity, this effect should be
266 demonstrated in preclinical models before clinical studies are initiated. (For information
267 regarding preclinical safety evaluation of combination therapy, see the guidance for industry
268 *Nonclinical Safety Evaluation of Drug or Biologic Combinations*.)
269

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270 2. *Drug Development Population*

271
272 Ethnically diverse male and female subjects of all ages should be included in drug development
273 programs for malaria.⁹ Since children living in endemic areas are at particular risk for
274 complications from malaria because of the absence of immunity, appropriate pediatric
275 formulations and dose recommendations should be established early in the drug development
276 program so that children can be included in phase 3 studies.

277
278 3. *Efficacy Considerations*

279
280 Similar to drug development in other therapeutic areas, two or more adequate and well-
281 controlled studies generally are appropriate for approval of an indication for the treatment of
282 malaria. The Indications and Usage section of the labeling for antimalarial drugs should restrict
283 indications to the specific plasmodial species studied and found to be effectively eradicated in
284 clinical trials.

285
286 Although parasitemia is a direct measure of antimalarial drug activity, and an important endpoint
287 in clinical studies, the evaluation of parasitemia can be complicated by variability in the
288 sensitivity and specificity of malaria smears. This is of particular concern for prophylaxis
289 studies where laboratory methods should maximize sensitivity for the detection of breakthrough
290 parasitemia. In treatment studies, parasitological and clinical endpoints generally should be
291 combined into a composite study endpoint, recognizing that fatal complications of malaria may
292 occur after parasites have been effectively eliminated or that asymptomatic parasitemia may
293 exist.

294
295 The development of drugs to treat infections caused by resistant plasmodial species represents an
296 important public health need at the present time. The FDA will consider a combination of the
297 following types of data used to support a claim that an investigational antimalarial drug is active
298 against plasmodia species resistant to another approved antimalarial drug:

- 299
- 300 • Evidence of superior efficacy when the investigational antimalarial drug is compared
 - 301 with another approved antimalarial drug to which resistance is encountered.
 - 302 • Epidemiological evidence of clinical drug resistance to another approved antimalarial
 - 303 drug in the area where the study is to be performed. High clinical failure rates provide
 - 304 the strongest evidence for antimalarial drug resistance in a given region.
 - 305 • Evidence of clinical response in patients who have failed alternative treatments because
 - 306 of drug resistance.
 - 307 • In vitro evidence of activity against isolates with genetic markers of resistance to other
 - 308 antimalarial drugs.
 - 309 • In vitro evidence of activity against isolates resistant to other approved antimalarial drugs
 - 310 in drug sensitivity assays.
- 311

⁹ See the guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials* and the ICH guidance for industry *E5 Ethnic Factors in the Acceptability of Foreign Clinical Data* (<http://www.fda.gov/cder/guidance/index.htm>).

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312 4. *Safety Considerations*

313
314 A safety database of at least 1,000 subjects in phase 1, 2, and 3 studies exposed to the proposed
315 dose and for the proposed duration of treatment should be included in an application for an
316 antimalarial indication. Safety populations should include males and females spanning all ages
317 (i.e., including pediatric and geriatric subjects). The safety population also should sufficiently
318 represent the diverse racial groups likely to be exposed to the drug if it is approved. Drug
319 interaction studies for the drug under development also should be included, as appropriate.

320
321 5. *Labeling Considerations*

322
323 The Indications and Usage section should reflect the specific indications and plasmodial species
324 studied. Any important limitations to use also should be included.

325
326 **B. Treatment Studies**

327
328 1. *Study Design*

329
330 Clinical trials for a treatment indication should be randomized and double-blinded unless
331 blinding is precluded by technical aspects of the study. If a study cannot be fully blinded,
332 attempts should be made to blind as many study personnel as possible (e.g., study
333 microbiologists interpreting malarial smears). Studies should be conducted in different
334 geographical regions to address variations in the susceptibility of isolates to existing antimalarial
335 therapy, as well as to reflect differences in population host factors.

336
337 Antimalarial therapy can take the form of a single antimalarial drug, a combination of drugs, or
338 more than one drug used sequentially. The following sections include specific concerns
339 regarding the development of a combination or a sequential regimen.¹⁰

340
341 a. Combination regimens

342
343 Under 21 CFR 300.50, data are required to demonstrate that each component of a fixed-dose
344 combination contributes a measurable advantage over the individual components (e.g., increased
345 efficacy, reduced emergence of resistance, fewer (or less severe) adverse events, or a simplified
346 treatment regimen). Development of a combination regimen for the sole purpose of reducing the
347 emergence of resistance should be discussed with the DSPTP before initiating studies as this
348 endpoint may be difficult to demonstrate even in large clinical trials.

349
350 b. Sequential regimens

351
352 Several existing treatment regimens employ a short-acting antimalarial drug together with, or
353 followed by, a long-acting drug to prevent recrudescence. Ideally, the comparator and
354 investigational regimens would differ only by the drug used for the corresponding phase of
355 treatment so that differences in outcome can be clearly attributed to the investigational drug.

¹⁰ This is primarily when two active antimalarial drugs are used. Considerations may differ in other circumstances (e.g., when drugs can be combined to improve the pharmacokinetics of one part of a combination regimen).

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356 When this is not possible, additional strategies should be used to demonstrate the contribution of
357 each component of a sequential regimen.

358
359 2. *Study Population*

360
361 Although most clinical studies for treatment are carried out in symptomatic patients with
362 documented malaria, initial *proof of concept* studies can be performed in patients with
363 asymptomatic parasitemia to minimize the risk and consequences of treatment failure.

364
365 We prefer studies of malaria treatment to be conducted with subjects monitored in a hospital
366 setting so that adverse events can be assessed and treated, and possible treatment failure can be
367 expeditiously addressed. At a minimum, subjects should remain in a monitored setting until
368 resolution of clinical and parasitological abnormalities. In some situations it may be appropriate
369 for subjects to remain in a controlled, monitored setting for the duration of the study to prevent
370 re-infection, thereby permitting a more accurate assessment of cure and recrudescence rates.

371
372 Host responses to malaria vary depending on several factors, including immune status (e.g.,
373 those living in endemic areas for many years may experience low levels of parasitemia with no
374 ill effect), blood type (e.g., Duffy negative blood types are resistant to infection with *P. vivax*),
375 pregnancy, and age (e.g., pregnant patients and infants are particularly susceptible to complicated
376 malaria). Study designs should take these factors into account. Both immune and nonimmune
377 subjects should be studied, and unless contraindicated, pregnant women and children should be
378 included either in large studies or in specific studies of these subpopulations.

379
380 The pharmacokinetics of the drug under development should be characterized in the populations
381 where the drug will be used. This should include study across all age ranges (i.e., pediatric and
382 geriatric subjects), pregnant women, and members of different ethnic groups.

383
384 Pharmacogenomic differences between study populations may be a particular concern in malaria
385 studies, and may affect the tolerability or efficacy of antimalarial therapy (e.g., G6PD deficiency
386 resulting in hemolysis following the use of certain antimalarial drugs). Pharmacogenomic
387 concerns should be addressed in the clinical development plan.

388
389 3. *Entry Criteria*

390
391 The following general entry criteria are recommended for malaria treatment studies:

- 392
- 393 • Both adult men and women should be enrolled at all stages of drug development, barring
394 specific sex-related concerns.
 - 395 • Pregnant subjects should be included when preclinical and human safety data indicate
396 that benefit from use outweighs risk since pregnant women are a population at particular
397 risk for malarial morbidity.
 - 398 • Children can be included in efficacy trials if preliminary data on adult safety and efficacy
399 are available from earlier studies, and sufficient information is available for determining
400 appropriate pediatric dosing. Though not routinely expected, toxicology studies in
401 juvenile animals should be considered if concerns emerge indicating potential increased

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402 sensitivity in children.¹¹ Pharmacokinetic studies in children should be conducted early
403 in drug development so that information to guide pediatric dosing is available at the time
404 larger efficacy studies are initiated.

- 405 • Patients should have fever at entry, or patients afebrile at enrollment should have fever
406 documented within 24 hours of entry.
- 407 • In general, patient symptoms should include shivering, chills, malaise, headache, and loss
408 of appetite in adults, and also include irritability, lethargy, and anorexia in children.
- 409 • The infecting *Plasmodium* species should be identified, and entry parasitemia should be
410 limited to values between 1,000/μl and 200,000/μl (0.25 percent to 4 percent).¹²
411 Proposals to study parasitemia outside of this range should be discussed with the DSPTP
412 before protocol submission.
- 413 • Patients with mixed plasmodial infections can be included in *P. falciparum* treatment
414 studies with the protocol indicating how these patients will be evaluated.
- 415 • Patients with severe or complicated malaria usually should be excluded from studies to
416 evaluate an investigational drug's efficacy and safety. It may be difficult to demonstrate
417 the effect of the drug on these patients because in advanced disease, even active drug
418 therapy may not be able to reverse the progression to a fatal outcome. However, research
419 study of these patients may be appropriate in certain circumstances and/or after the drug
420 has been successfully studied in patients with uncomplicated malaria.
- 421 • Patients with prior antimalarial therapy for the current episode should be excluded unless
422 the new drug is under development for patients failing treatment with other drugs.
- 423 • Patients with concurrent febrile illnesses (e.g., typhoid fever) should be excluded.

424 4. *Randomization, Stratification, and Blinding*

425 All studies should be double-blinded and randomized. If subject and/or investigator blinding is
426 not possible, it is highly desirable to blind other study personnel (e.g., study microbiologists
427 during evaluation of parasitemia in blood samples).

428 In areas where the human immunodeficiency virus (HIV) is prevalent, subjects should be
429 stratified by the presence or absence of HIV at enrollment. HIV status should be confirmed after
430 enrollment, if possible, and CD4 cell counts measured as appropriate, although we recognize that
431 protocol-mandated HIV testing may be problematic in certain areas.

432 5. *Special Populations*

433 All age ranges should be studied in malaria treatment studies, including pediatric and geriatric
434 subjects. It is particularly important to study pregnant women and children during drug
435 development as these populations are at greatest risk of morbidity from malaria.

436 The need to study other special populations (e.g., patients with hepatic or renal failure) should be
437 based on the characteristics of the specific drug under development. For example, targeted study

¹¹ See the guidance for industry *Nonclinical Safety Evaluation of Pediatric Drug Products*
(<http://www.fda.gov/cder/guidance/index.htm>).

¹² Based on a normal red blood cell (RBC) count of 5×10^6 RBCs per μl blood.

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444 of subjects with renal insufficiency may not be necessary for a drug that has complete hepatic
445 metabolism and no renal excretion. These considerations usually should be addressed after
446 completion of the initial absorption, disposition, metabolism, and excretion studies of the new
447 drug and should be addressed during drug development. Studies in special populations should
448 include pharmacokinetic evaluation; in some circumstances, population pharmacokinetic
449 assessments may be nested within larger treatment studies.

450

451 6. *Choice of Comparators*

452

453 We strongly recommend that clinical studies compare treatment with the new drug to treatment
454 with a regimen containing FDA-approved antimalarial drugs. Although the use of unapproved
455 comparators generally is discouraged, unapproved comparators may be appropriate if they
456 represent the local standard of care. If a sponsor wants to use an unapproved comparator, we
457 strongly recommend that the sponsor discuss this with the DSPTP at the time of protocol
458 development. Unapproved drugs that are being considered for use as comparator drugs should
459 have satisfactory evidence of safety and efficacy (e.g., an efficacy rate greater than 95 percent in
460 a large randomized clinical trial) and this information should be provided to the FDA at the time
461 of protocol development. Such data may be less critical if the study goal is to demonstrate that
462 the new drug is superior to the control drug.

463

464 We anticipate that, within the application, at least some, if not all, of the controlled clinical
465 studies will include an FDA-approved drug as a control.

466

467 7. *Efficacy Endpoints*

468

469 The primary endpoints that should be used in malaria treatment trials are defined as follows:

470

- 471 • **Cure** — The complete resolution of clinical signs and symptoms, malaria-related
472 laboratory abnormalities, and elimination of asexual parasites by day 7, with no
473 recurrence up to day 28 (+/- 2 days). This definition also includes that a study
474 assessment 48 hours after initiation of therapy demonstrate a decrease in the level of
475 parasitemia to less than 25 percent of baseline with no clinical deterioration. For drugs
476 with long half-lives, a follow-up visit at 42 days or longer may be warranted.

477

478 Recurrent parasitemia may represent a new infection rather than a true recrudescence.
479 Attempts should be made to characterize and differentiate the isolate collected at the time
480 of recurrent parasitemia from baseline. This can involve samples being obtained at
481 baseline and at the time of recurrence, and storing these samples under conditions
482 appropriate to enable further characterization of the parasite, such as by genetic methods
483 (e.g., polymerase chain reaction (PCR)) and/or phenotypic methods (see Appendix A).
484 Both crude cure rates and rates adjusted by genotypic and phenotypic information should
485 be reported. Methods to be used for adjusting cure rates should be included in the
486 clinical protocol.

487

- 488 • **Radical cure (for *P. vivax* and *P. ovale*)** — The absence of parasitemia, clinical signs
489 and symptoms, and laboratory abnormalities by day 7 without relapse for at least 6

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490 months after completion of treatment. Relapses of *P. vivax* and *P. ovale* generally occur
491 within the first 6 months of infection, but temperate strains may take more than 1 year to
492 relapse. Whether 6 or 12 months of follow-up is necessary should be discussed with the
493 DSPTP before protocol submission. As the duration of follow-up is extended, genetic
494 and phenotypic comparison of baseline isolates to later isolates becomes increasingly
495 important as a possible means to distinguish relapse from re-infection (see Appendix A).
496

497 The secondary endpoints that should be used in malaria treatment trials are defined as follows:
498

- 499 • **Parasite clearance time** — Time in hours from the initiation of therapy until the first of
500 two successive parasite-negative smears are obtained.
501
- 502 • **Fever clearance time** — Time in hours from the initiation of therapy until disappearance
503 of fever for at least 24 hours.
504

505 For both *P. falciparum* and *P. vivax* /*P. ovale* infections, baseline blood samples should be
506 retained to allow comparison with the original strain should parasitemia recur. Appropriate
507 techniques may distinguish recrudescence, relapse, and re-infection (see the Glossary and
508 Appendix A).
509

510 Treatment failures can be classified as early treatment failure, late treatment failure, or late
511 parasitological failure, as follows:
512

- 513 • **Early treatment failure**
 - 514 – Development of severe malaria on day 1, 2, or 3 of treatment in the presence of
515 parasitemia
 - 516 – Parasitemia on day 2 greater than day 0 irrespective of axillary temperature
 - 517 – Parasitemia on day 3 with axillary temperature greater than or equal to 37.5 degrees
518 Celsius
 - 519 – Parasitemia on day 3 greater than or equal to 25 percent of count on day 0
520
- 521 • **Late treatment failure**
 - 522 – Development of severe malaria after day 3 in the presence of parasitemia without
523 previously meeting any of the factors of early treatment failure
 - 524 – Parasitemia any day from day 4 to 14 (intense transmission areas) or day 4 to 28 (low
525 to moderate transmission areas) with axillary temperature greater than or equal to
526 37.5 degrees Celsius without previously meeting any of the factors of early treatment
527 failure
 - 528 – Any patients receiving additional antimalarial therapy not specified in the study
529 protocol
530
- 531 • **Late parasitological failure**
 - 532 – Parasitemia on day 14 (intense transmission areas) or any day from day 7 to 28 (low
533 to moderate transmission areas) and axillary temperature less than 37.5 degrees
534 Celsius.
535

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536 8. *Study Procedures and Timing of Assessments*
537

538 The following assessments should be included in a malaria treatment study protocol:
539

540 • **At study entry**

- 541 – History and physical examination, including history of prior malaria episodes, prior
542 treatment history, and documentation of splenomegaly.
- 543 – Laboratory studies for parasite count, chemistry and glucose, complete blood count
544 (CBC), and liver function tests. A specimen should be archived for genetic and/or
545 phenotypic studies were recurrent parasitemia to occur.
546

547 • **During study**

- 548 – Laboratory testing as clinically relevant for the specific trial or drug under study (e.g.,
549 testing for hypoglycemia, anemia, thrombocytopenia, or renal dysfunction).
- 550 – Temperature and vital signs monitoring every 6 hours until resolution of fever,
551 defined as being afebrile for 24 hours.
- 552 – Repeat malaria smears every 6 to 12 hours until parasitemia has been eradicated,
553 defined as two successive parasite-negative smears.
- 554 – Daily recording of signs and symptoms until all have resolved.
- 555 – If parasitological eradication has occurred, subsequent malaria smears on days 7, 14,
556 21, and 28 of study to document that parasitemia is absent. When a late follow-up
557 visit is included (see below), additional smears should be obtained on days 35 and 42.
- 558 – Malaria smears for patients presenting at any time with fever or other signs or
559 symptoms suggestive of malaria.
- 560 – Specimens obtained to perform genetic and phenotypic comparisons with baseline
561 samples if recurrent parasitemia is detected in either symptomatic or asymptomatic
562 individuals.
- 563 – Samples for drug level assays at the time an early treatment failure is documented.
564

565 • **At test-of-cure visit¹³**

- 566 – History and physical examination to confirm resolution of malaria symptoms and
567 absence of fever.
- 568 – Laboratory tests for parasitemia and other tests as appropriate for the drug under
569 study. There also should be repeat assessment of any unresolved laboratory
570 abnormalities from previous tests, and laboratory abnormalities should, in general, be
571 followed to resolution.
572

573 We recognize that in rare cases recrudescence infection may occur more than 28 days after initial
574 therapy. Inclusion of a late follow-up visit 42 days after initiation of therapy should be
575 considered, particularly when antimalarial drugs with prolonged half-lives are being studied.
576

577 The following study evaluations should be included in malaria treatment studies:
578

¹³ Unless otherwise indicated, the test-of-cure visit should occur at 28 days (+/- 2 days) after starting treatment. Cure is defined as negative malarial smears from day 7 through day 28.

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- 579
- 580 • **Evaluation of early treatment failure.** Transient rises in parasitemia can be seen
581 following treatment with certain antimalarial drugs. Rises in parasitemia observed less
582 than 12 hours after the initiation of treatment and not accompanied by any clinical
583 deterioration may allow ongoing administration of the study drug at the investigator's
584 discretion. Sustained rises in parasitemia or clinical deterioration after 12 hours indicate
585 drug failure and salvage therapy should be instituted. Exceptions to this time frame in a
586 proposed study should be discussed with the DSPTP before protocol submission.
 - 587 • **Evaluation for relapsing malaria.** For the assessment of radical cure for *P. vivax* or *P.*
588 *ovale* infection, an additional follow-up period of 6 to 12 months after completion of
589 therapy should be included to document the occurrence of either recurrent fever or
590 relapse over this period. Subjects should be instructed to return to study centers for
591 malaria smears and a complete clinical evaluation if symptoms suggestive of malaria
592 occur. Blood samples should be obtained for genetic and phenotypic comparison with
593 the original strain if malaria is confirmed.

594

595 A final study visit should be included at the completion of the follow-up period. This visit can
596 be conducted as a telephone interview, during which a history should be obtained confirming
597 absence of malaria symptoms or antimalarial treatment after the completion of therapy.

598

599 The efficacy of a drug to prevent relapses may be difficult to determine in patients remaining in
600 endemic areas, particularly so if suitable genetic and phenotypic studies cannot be performed
601 when malaria-like symptoms recur.

602

603 9. *Parasite Evaluation*

604

605 Conventional microscopy using blood smears is considered to be the currently established
606 standard method for detection and morphological identification of the malarial parasite, and thus
607 a direct measurement of drug activity (see Appendix A for details). However, newer
608 experimental procedures are available for establishing parasitemia. If newer methods are used in
609 addition to blood smears in a clinical study, the details of those methods and the performance
610 characteristics of the assays used should be included in the clinical protocol. Study procedures
611 for quality control and interobserver reliability of parasite measurements should be described in
612 the clinical protocol.

613

614 Newer microbiological methods may allow detection of drug resistance by genotyping and
615 phenotyping, and possibly can differentiate between new infection and relapse or recrudescence.
616 If any of these methods are used in a clinical trial, the details of these methods also should be
617 included in the clinical protocol.

618

619 10. *Statistical Considerations*

620

621 The two primary analysis populations for evaluating efficacy and safety treatment studies are
622 defined as follows:

623

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- 624 • **Modified intent-to-treat (MITT)** — All randomized patients with parasitologically
625 confirmed malaria who receive at least one dose of study drug. Depending on the
626 specific study design, the intent-to-treat (ITT) population of all subjects enrolled can
627 include subjects enrolled before complete parasitological confirmation but for whom
628 malaria is not subsequently confirmed. These subjects should not be included in the
629 MITT and per-protocol efficacy analyses.
630
- 631 • **Per protocol** — All patients included in the MITT population who have received at least
632 80 percent of the protocol-defined therapy and are clinically and microbiologically
633 evaluable after 28 days.
634

635 All subjects who received at least one dose of study drug should be included in the safety
636 analysis of the study.
637

638 Studies should be appropriately powered (at least 80 percent) to achieve the primary study
639 objective. The estimated treatment success rates described in the study protocol should be
640 referenced and based on valid estimation methods. The exact number of subjects necessary for
641 each study will be dependent on the population and specific indication under study.
642

643 All statistical tests should be two-sided with a Type I error rate of 0.05. For noninferiority
644 studies, a 95 percent two-sided confidence interval (CI) should be constructed around the
645 difference in outcome rates (experimental regimen-control regimen) with any prespecified
646 adjustments. If the lower bound of the 95 percent CI is greater than a prespecified, scientifically
647 justified noninferiority margin for both MITT and per-protocol study populations, noninferiority
648 of the experimental regimen can be concluded. For a discussion of factors to consider in the
649 selection of an appropriate noninferiority margin, see ICH E10.
650

651 For parasite clearance, 95 percent CIs should be constructed around the 24- and 48-hour time
652 points. Parasite clearance time and fever should be analyzed by Kaplan Meier survival methods.
653

654 Patients who prematurely discontinue assigned study treatment and/or receive alternative therapy
655 should be treated as failures in all analyses. Patients who discontinue treatment but who are not
656 lost to follow-up and do not receive additional treatment should be evaluated according to their
657 study outcome in the ITT analysis. Patients lost to follow-up should be counted as treatment
658 failures in the ITT analysis. Sample size calculations should take into account subject dropout
659 and loss to follow-up rates.
660

661 Demographics and baseline characteristics should be summarized and compared between
662 treatment groups using descriptive statistics.
663

664 Clinical and laboratory adverse events information should be summarized and compared
665 between treatment groups using descriptive statistics.
666

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667 11. *Accelerated Approval (Subpart H) Considerations*
668

669 In general, treatment and prophylaxis indications for malaria have been based on adequate and
670 well-controlled trials using clinical and parasitological endpoints. Exceptional cases where a
671 sponsor is seeking approval for treatment based on 21 CFR 314.500, subpart H, regulations
672 should be discussed with the DSPTP as early as possible during the drug development process.
673

674 **C. Prophylaxis Studies**
675

676 1. *Study Design*
677

678 Clinical studies supporting an indication for the prophylaxis of malaria should demonstrate the
679 following:
680

- 681 • Efficacy for the prevention of infection following documented or presumed malaria
682 exposure.
- 683 • Safety in the target population for the proposed duration of prophylaxis at the proposed
684 dose. Physiological diversity in patients likely to use the proposed treatment should be
685 addressed.
- 686 • Efficacy in nonimmune subjects.
687

688 An application for a prophylaxis indication should include at least two adequate and well-
689 controlled clinical studies, with subjects enrolled from two or more distinct geographical regions.
690 Applications for prophylaxis indications also can be significantly strengthened by other studies
691 with the drug demonstrating efficacy for the treatment of established malaria infection.
692

693 The following study designs have been used to support a malaria prophylaxis indication:
694

- 695 • **Efficacy studies in malaria endemic communities.** Studies in communities with
696 endemic malaria and significant levels of malarial immunity offer the advantage of
697 studying new antimalarial therapy while limiting the potential risk to patients if efficacy
698 is found to be suboptimal. Placebo-controlled studies may be appropriate in this setting
699 (see below). If a study is performed in a malaria-endemic community as support for a
700 regulatory filing, then other studies in the new drug application (NDA) submission
701 should demonstrate drug efficacy in nonimmune subjects as well.
702
- 703 • **Active-controlled and historical-controlled studies in individuals deployed to**
704 **malaria-endemic areas.** The deployment of military personnel or civilian cohorts to
705 malaria-endemic regions provides an opportunity to study antimalarial prophylaxis in
706 malaria-naive subjects. Since such deployments may last for many months, it is possible
707 to standardize duration of malaria exposure. When placebo-controlled studies cannot be
708 performed, well-characterized epidemiological attack rates can be used to calculate
709 protective efficacy (see section IV.C.9.). See ICH E10 regarding considerations on use
710 of historical controls.
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712 • **Active-controlled studies in travelers.** Travelers may be a valuable population in which
713 to study the safety of antimalarial prophylaxis; however, outcome data in these trials may
714 be difficult to interpret if the overall incidence of malaria is below expected rates in all
715 treatment arms. In this situation, it may not be possible to distinguish drug efficacy from
716 low exposure to malaria (e.g., because of the locations visited, the duration of exposure,
717 or the use of ancillary protection such as bed nets or air-conditioning). The design of
718 these studies should be discussed with the DSPTP before submission to ensure that the
719 expected baseline exposure rate in the treatment groups is quantified and well supported.

720
721 • **Challenge studies.** Challenge studies ensure a high malaria attack rate in volunteers,
722 while intensive monitoring may ethically permit the use of a placebo arm (i.e., with
723 intervention occurring at the first clinical or laboratory sign of active malaria infection).
724 Generally, challenge studies should be performed with well-characterized strains of
725 chloroquine sensitive *P. falciparum* and should involve 6 weeks of follow-up.

726
727 Since challenge studies generally are limited to one or two laboratory strains, they may
728 not reflect the effect of different strains of malaria or the effect of repeated exposure.
729 Accordingly, challenge studies alone are considered insufficient and should be
730 accompanied by additional studies for a prophylaxis indication.

731
732 A specific study can be either placebo-controlled or have an active comparator based on the
733 population being studied.

734
735 • **Use of a placebo-control.** In certain circumstances studies enrolling subjects residing in
736 malaria-endemic regions may justify the use of a placebo arm if antimalarial
737 chemoprophylaxis is not the standard of care in the community and there is a high level
738 of preexisting immunity in the study population. It is expected that in this setting the
739 level of immunity present would be sufficient to protect individuals from severe malaria
740 in the absence of prophylaxis. Appropriate approval by local regulatory authorities and
741 individual informed consent are required (21 CFR 50.25). In general, the use of placebo
742 arms should be confined to studies enrolling only adults older than 18 years of age. Since
743 participants entering such trials commonly have asymptomatic or incubating parasitemia,
744 a course of radical treatment typically should be given at study enrollment regardless of
745 the presence of parasitemia.

746
747 Use of a placebo arm has the advantage of directly estimating the malaria attack rate in
748 the study population. Protective efficacy (PE) can then be calculated as $1 - (\text{the incidence of malaria in experimental arm} / \text{incidence of malaria in placebo arm})$.

749
750
751 • **Use of an active-control.** Active-controlled studies do not allow a direct determination
752 of the malaria attack rate in the study population; therefore, a background attack rate
753 should be determined. The risk of infection can be indirectly estimated from local
754 epidemiological data in endemic areas. Ideally, active-controlled studies should be
755 sufficiently large to demonstrate the anticipated breakthrough rate for the comparator,
756 confirming the expected background infection rate. Because breakthrough rates for
757 known prophylactic regimens seldom exceed 1 to 2 percent even in malaria-endemic

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758 regions, large study sample sizes should be used to unequivocally demonstrate efficacy
759 relative to an active-control. This problem is exacerbated in areas with lower background
760 malaria attack rates.

761
762 Investigational approaches to this problem by measurement of circumsporozoite
763 antibodies have not yet proven reliable for determining the exposure to malaria and are
764 not recommended at this time.

765 766 2. *Study Population*

767
768 Prophylaxis studies should enroll asymptomatic individuals for whom malaria exposure is
769 anticipated and where active or incubating malaria has been either excluded or eradicated.
770 Children can be included in prophylaxis studies after safety in adults, appropriate pharmacology
771 and toxicology data, and appropriate pediatric dosing have been explored. Pregnant women can
772 be included if animal toxicology studies do not indicate a risk to the fetus. When an antimalarial
773 drug is being developed for both treatment and prophylaxis indications, initial safety data in
774 pregnancy should be obtained during treatment rather than prophylaxis since the potential risk-
775 benefit ratio is relatively greater for treatment.

776 777 3. *Entry Criteria*

778
779 Entry criteria for field studies and challenge studies are as follows:

- 780
- 781 • **Field studies**
 - 782 – Male or nonpregnant female subjects older than 16 years of age; pregnant subjects
783 can be included after pharmacokinetics in pregnant women have been characterized
784 and reproductive animal toxicology studies have been completed, assessed, and
785 support inclusion of pregnant women. Studies that enroll pregnant women should
786 include targeted assessment of the mother and newborn at the time of delivery and 3
787 months post-delivery.
 - 788 – Subjects younger than 16 can be included if adult safety and pharmacokinetics, and
789 pharmacology and toxicology data, as appropriate, are characterized in prior studies.
 - 790 – Mosquito nets and repellants can be used, but subjects should be stratified at
791 enrollment based on anticipated use. This information should be recorded in the case
792 report form. If possible, the study should incorporate the use of subject diaries for the
793 purpose of tracking use of mosquito bed nets and repellants.
 - 794 • **Challenge studies**
 - 795 – Generally, challenge studies should be limited to healthy, nonpregnant adult
796 volunteers. Females of childbearing potential¹⁴ should use appropriate contraception
797 during the study.
 - 798
 - 799

¹⁴ Females are considered *females of childbearing potential* if they are older than 10 years of age and if they have not been previously documented to have either a hysterectomy or menopause.

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800 4. *Randomization and Blinding*

801
802 All prophylaxis studies should be double-blinded and randomized to minimize potential bias.

803
804 5. *Special Populations*

805
806 Pregnant women should be studied once the prerequisite animal toxicology and human
807 pharmacokinetic studies have been completed and do not show risk to fetus; for children, adult
808 safety also should be characterized before enrollment into studies. Though not routinely
809 expected, toxicology studies in juvenile animals should be considered if concerns emerge
810 indicating potential increased sensitivity in children.¹⁵ Other special populations (e.g., patients
811 with hepatic or renal failure) should be studied when appropriate. For example, a study of
812 subjects with renal insufficiency may be appropriate for a drug with renal excretion but would
813 likely not be appropriate if the drug were hepatically metabolized. Many of these considerations
814 arise after the initial absorption, disposition, metabolism, and excretion studies with the new
815 drug, but should be completed and included in the NDA or biologics license application
816 submission.

817
818 6. *Choice of Comparators*

819
820 When studies with an active comparator are performed, comparator drugs should be selected
821 from FDA-approved drugs that have well-characterized safety and prophylactic efficacy rates.
822 The choice of comparators may involve discussions with regional health authorities to address
823 local public health concerns. The use of unapproved comparators is discouraged as efficacy
824 rates and safety may not be well characterized; if an unapproved comparator is proposed for use
825 in a clinical trial for prophylaxis, this should be discussed with the DSPTP before protocol
826 submission.

827
828 7. *Efficacy Endpoints*

829
830 The following endpoints should be used in malaria prophylaxis trials:

- 831
- 832 • **Primary endpoint**
 - 833 – Prophylactic success, defined as the absence of detectable parasitemia during
 - 834 prophylactic drug administration. Negative smears should be demonstrated for 4
 - 835 weeks after completing study drug administration for studies where subjects leave the
 - 836 malaria-endemic area (see Appendix A for details of microbiological evaluation).
 - 837
 - 838 • **Secondary endpoints**
 - 839 – Mean/median time to first slide-proven parasitemia during prophylaxis.
 - 840 – Cumulative incidence of slide-proven parasitemia.
 - 841 – Incidence of slide-proven parasitemia during the follow-up phase for subjects who
 - 842 remain in the malaria-endemic area.

¹⁵ See the guidance for industry *Nonclinical Safety Evaluation of Pediatric Drug Products* (<http://www.fda.gov/cder/guidance/index.htm>).

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8. *Study Procedures and Timing of Assessments*

Radical treatment to eradicate all active or incubating infections at study onset typically should be included in studies that enroll subjects living in malaria-endemic areas. The following study assessments are recommended during prophylaxis studies:

- **Baseline evaluation/start of prophylaxis**
 - If radical treatment is used, smear confirmation of the absence of asexual forms in the blood within 7 days of starting therapy.
 - Initiation of prophylaxis following completion of radical treatment or on arrival to the malaria-endemic region.
 - Baseline clinical assessment, including documentation of any history of prior malaria and examination for splenomegaly.
 - Laboratory tests including CBC with platelets, chemistry, and liver function tests. Additional studies (e.g., electrocardiograms) may be appropriate based on specific safety concerns for the drugs under study.
- **On-therapy visits**
 - Field studies
 - Blood smears obtained weekly during the period of prophylaxis and for 4 weeks after completion of prophylaxis. Additional protocol-defined study visits should be specified for subjects developing symptoms suggestive of malaria (e.g., fever, rigors, malaise) to include a complete parasitological and clinical evaluation.
 - Recorded use of bed nets, mosquito repellent, and air-conditioning in the case report form. At the time any malarial breakthrough is documented, a blood sample should be obtained for measurement of drug levels.
 - Challenge studies
 - Daily smears from day 6 to 14, then every second day until day 21, then weekly for a total of 6 weeks. Other investigational assays such as PCR have been of supportive value in the early detection of parasitemia.
 - A blood sample obtained for measurement of drug levels at the time any malarial breakthrough is documented.
- **End of therapy**
 - Field studies: the primary endpoint evaluated at the end of therapy, generally after 10 to 12 weeks of prophylaxis, for studies of subjects who remain in malaria-endemic areas. This allows adequate exposure to malaria, and covers the usual anticipated therapeutic duration in travelers. Assessments should include:
 - History and physical examination for signs and symptoms of malaria
 - Blood smear for malaria
 - Other laboratory studies as appropriate for evaluation of safety

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888 For studies of subjects who do not remain in malaria-endemic areas (such as
889 travelers), and effective causal prophylaxis is not anticipated, suppressive therapy
890 typically should be continued for 4 to 6 weeks after leaving the endemic area. The
891 primary endpoint should be determined 4 weeks after completion of therapy.

- 892
- 893 – Challenge studies (performed 6 weeks after challenge):
 - 894 ▪ History and physical examination for signs and symptoms of malaria
 - 895 ▪ Blood smear for malaria
 - 896 ▪ Other laboratory studies as appropriate for evaluation of safety
 - 897
 - 898 • **Post-therapy visits.** Post-therapy assessments are similar for field and challenge study
899 designs; however, post-therapy assessments differ on whether *P. falciparum* or relapsing
900 malarias are the focus of study:
 - 901
 - 902 – *P. falciparum* studies. Among subjects who remain in malaria-endemic areas after
903 completing the study, a post-therapy visit 4 weeks after completion of therapy
904 captures infections incubating at the time prophylaxis is complete. We recognize that
905 it may be difficult to distinguish recrudescence from new infections with increasing
906 time off prophylaxis. Evaluations include:
 - 907
 - 908 ▪ A history and physical examination to confirm the absence of malaria symptoms
 - 909 ▪ A malaria smear to confirm the absence of parasitemia
 - 910
 - 911 – Relapsing malaria studies. To document the occurrence of malaria after completion
912 of prophylaxis, an additional follow-up period of 6 to 12 months should be included
913 for subjects who leave the endemic area.

914

915 During the follow-up period, subjects should be instructed to return to study centers
916 for malaria smears and a complete clinical evaluation if symptoms suggestive of
917 relapsing malaria occur.

918

919 A final visit should be included at the completion of the follow-up period. This visit
920 can be conducted as a telephone interview, during which a history should be obtained
921 confirming absence of malaria symptoms or antimalarial treatment after the
922 completion of therapy.

923

924 For drugs being tested for causal prophylactic activity against *P. falciparum*, causal prophylaxis
925 can be confirmed in challenge studies where the prophylactic drug is given for a week or less
926 following exposure to malaria.

927

928 Field trials in individuals leaving the malaria area after completing prophylaxis also can be
929 assessed for causal prophylactic efficacy. Therapy should be stopped within a week of leaving
930 the endemic area and the test-of-cure visit should occur 4 weeks after completion of therapy.

931 This visit should include:
932

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- 933 • A history and physical examination to confirm the absence of malaria symptoms
934 • A malaria smear to confirm the absence of parasitemia
935

936 Appropriate approved regimens for the treatment of breakthrough infections in prophylaxis
937 studies should be described in the study protocols.
938

939 9. *Statistical Considerations*
940

941 The two primary analysis populations for prophylaxis studies are defined as follows:
942

- 943 • **Intent-to-treat** — All randomized subjects receiving at least one dose of study drug.
944
945 • **Per protocol** — All randomized subjects taking between 80 percent and 120 percent of
946 the dosing regimen who are not lost to follow-up, and who do not prematurely
947 discontinue study drug because of intolerance. Subjects who receive concomitant
948 medication that could influence efficacy findings should be considered failures.
949

950 Subjects who prematurely discontinue assigned study treatment because of intolerance and
951 receive alternative therapy should be treated as failures in ITT analyses. Subjects who are lost to
952 follow-up should be counted as treatment failures in the ITT analysis. All subjects who receive
953 at least one dose of study drug should be included in the safety analysis of the study.
954

955 All statistical tests should be two-sided with a Type I error rate of 0.05 unless otherwise
956 specified.
957

958 a. Primary endpoint evaluation
959

960 The proportion of subjects free of detectable parasitemia during prophylaxis (primary endpoint)
961 should be calculated for both the ITT and per-protocol populations. Depending on study design,
962 primary endpoints can be evaluated as follows:
963

- 964 • **Placebo-controlled studies.** The percent PE should be calculated as:
965

966 PE = [1 - (cumulative incidence of parasitemia during prophylaxis in the
967 experimental group/cumulative incidence of parasitemia during prophylaxis in the
968 placebo group)] x 100
969

970 These studies should be designed to show an anticipated PE rate of greater than or equal
971 to 95 percent, with a minimum sample size of 200 subjects per arm.
972

- 973 • **Historical-controlled studies.** PE also should be calculated using the same calculation
974 as for placebo-controlled studies with the cumulative incidence in untreated
975 epidemiological control group substituted for the placebo group incidence. These studies
976 should be designed to demonstrate an anticipated PE rate of greater than or equal to 95
977 percent, with a minimum sample size of 200 subjects per arm.
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979 The calculation of PE in historical-controlled studies should employ epidemiological
980 attack rates in the study area from at least the past two malaria seasons. Epidemiological
981 attack rates should closely reflect anticipated attack rates in the study population and
982 should be derived from the same geographical area, during the same seasonal period,
983 with similar rainfall and similar subject exposure. Collection and calculation methods
984 should be prospectively defined in the study protocol and statistical analysis plan.
985 Results should be well documented in the final study report.

986
987 An active comparator arm should be included as reference to identify problems in the
988 conduct of the study (e.g., errors in laboratory procedures, adherence to therapy), as well
989 as to determine comparative safety.

990
991 Sample size calculations should take into account subject dropout and loss to follow-up rates.

992
993 b. Secondary endpoint evaluation

994
995 For secondary endpoints, the following should be evaluated:

- 996
997
- 998 • Incidence (density) rate can be calculated as the number of cases of slide-proven
999 parasitemia divided by the total person-time of follow-up
 - 1000 • Comparative efficacy of time to slide-proven parasitemia can be performed using
1001 Kaplan-Meier methods and log rank tests
 - 1002 • Cumulative incidence can be calculated as the proportion of subjects who develop
1003 parasitemia during the study

1004 Demographics and baseline characteristics should be summarized and compared between
1005 treatment groups using descriptive statistics.

1006 1007 *10. Risk-Benefit Considerations*

1008
1009 Drugs that are intended for use as prophylaxis should be sufficiently well tolerated to achieve a
1010 satisfactory risk-benefit ratio.

1011 1012 *11. Labeling Considerations*

1013
1014 For antimalarial prophylactic drugs, patient labeling (e.g., a Patient Package Insert or Medguide)
1015 should be considered depending on the risk-benefit analysis, with the intention of
1016 communicating safety concerns and educating patients about the use of prophylaxis, given that
1017 they may not have immediate access to a physician.

1018

GLOSSARY

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Causal prophylaxis — Prophylaxis that is effective against hepatic forms of the parasite. Effective causal prophylactics can be discontinued a few days after leaving the region with malaria.

Consolidation regimen — Therapy used together with or after a rapidly acting drug to prevent recrudescence.

Cure — Complete resolution of clinical signs and symptoms, complete resolution of laboratory abnormalities, and elimination of asexual parasites by day 7 with no recurrence up to day 28 (+/- 2 days). This definition also includes that a study assessment 48 hours after initiation of therapy demonstrate a decrease in the level of parasitemia to less than 25 percent of baseline with no clinical deterioration.

Early treatment failure — Any of the following should be considered early treatment failure:

- Development of danger signs or severe malaria on day 1, 2, or 3 in the presence of parasitemia
- Parasitemia on day 2 greater than day 0 irrespective of axillary temperature
- Parasitemia on day 3 with axillary temperature greater than or equal to 37.5 degrees Celsius
- Parasitemia on day 3 greater than or equal to 25 percent of count on day 0

Failure (of treatment) — Persistent or recrudescence parasitemia regardless of parasite density and/or failure of clinical abnormalities to resolve.

Late parasitological failure — Parasitemia on day 14 (intense transmission areas) or any day from day 7 to 28 (low to moderate transmission areas), with axillary temperature less than 37.5 degrees Celsius.

Late treatment failure — Any of the following should be considered late treatment failure:

- Development of danger signs or severe malaria after day 3 in the presence of parasitemia without previously meeting any of the factors of early treatment failure
- Parasitemia on any day from day 4 to 14 (intense transmission areas) or day 4 to 28 (low to moderate transmission areas) with axillary temperature greater than or equal to 37.5 degrees Celsius without previously meeting any of the factors of early treatment failure
- Patients receiving additional antimalarial therapy not specified in the study protocol

Prepatent period — Interval between inoculation of parasites and detection of erythrocytic forms.

Prophylactic success — The absence of detectable parasitemia during prophylaxis, defined by PE, which is determined by the incidence of breakthrough infections.

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1065 **Prophylaxis** — Prevention of clinical or parasitological malaria infection. Prophylaxis can take
1066 the form of suppressive therapy, when medication is administered for a period sufficient to
1067 encompass several hematogenous/erythrocytic cycles of replication following which parasitemia
1068 does not occur. In general, suppressive therapy is continued for 4 to 6 weeks after leaving areas
1069 with malaria. Prophylaxis also can be *causal* when the drug can be shown to eliminate parasites
1070 during the hepatic phase before their entry into the blood. Causal prophylactic drugs generally
1071 should be continued for a week or less after leaving areas with malaria.

1072
1073 **Protective efficacy** — PE is calculated as $1 - (\text{the incidence of malaria in experimental}$
1074 $\text{arm/incidence of malaria in placebo arm})$.

1075
1076 **Radical cure** — Eradication of hypnozoites in the liver of patients with relapsing malaria, and
1077 by doing so, elimination of relapses attributable to the original infection.

1078
1079 **Radical treatment** — Curative treatment employed at the beginning of prophylaxis studies in
1080 endemic areas with the goal of eradicating baseline asymptomatic parasitemia and hypnozoites
1081 before initiation of prophylaxis.

1082
1083 **Recrudescence** — Recurrence of the original parasitemia with *P. falciparum*.

1084
1085 **Re-infection** — Infection with a genetically distinct plasmodial strain after successful treatment
1086 of initial infection during enrollment in a clinical trial. When re-infection can be reliably
1087 distinguished from recrudescence, re-infection should not be regarded as a treatment failure.

1088
1089 **Relapse** — Recurrence of original parasitemia attributable to the original *P. vivax* or *P. ovale*.

1090
1091 **Severe or complicated malaria** — The baseline definition of severe or complicated malaria
1092 includes cerebral malaria, severe anemia, renal failure, pulmonary edema, hypoglycemia,
1093 circulatory collapse, spontaneous bleeding, repeated generalized seizures, acidemia, macroscopic
1094 hemoglobinuria, and in some geographical regions impaired consciousness, prostration
1095 hyperparasitemia, jaundice, and hyper pyrexia (Trans R Soc Trop Med Hyg, 1990, 84(2)1-65).
1096 This definition can be expanded for use in specific clinical trials. Patients with severe malaria
1097 generally have levels of parasitemia greater than 5 percent (greater than 250,000/μl blood).
1098 *Moderately severe* disease occasionally has been used in previous treatment studies but is not
1099 recommended without prior discussion with the DSPTP.

1100
1101 **Suppressive therapy** — Prophylaxis that is ineffective against the hepatic forms of the parasite,
1102 but if given for an extended period after leaving the region with malaria, will eliminate residual
1103 erythrocytic forms (thereby preventing subsequent recrudescence).

1104
1105 **Terminal prophylaxis** — The addition of a drug at the end of standard prophylaxis to eliminate
1106 hypnozoites and prevent relapse.

1107
1108 **Treatment** — Treatment of patients with a microbiologically confirmed diagnosis of malaria.
1109 *Presumptive treatment* has been used to refer to self-administered antimalarial therapy, which is
1110 taken before reaching medical care by individuals experiencing malaria symptoms.

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1112 **Uncomplicated malaria** — Symptomatic malaria (e.g., fevers, rigors, malaise, headache)
1113 without any of the complications previously listed, and a parasite count of less than 5 percent
1114 (less than 250,000/ μ l blood).
1115

APPENDIX A:
MICROBIOLOGICAL EVALUATIONS

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Microbiological evaluations within a clinical trial include:

- Detection or identification of the erythrocytic stages of *Plasmodium* species for:
 - Enrollment of patients in the clinical trial (as part of inclusion and exclusion criteria)
 - Measuring drug efficacy
- Measurement of drug resistance (genotyping and phenotyping)
- Differentiating new infection from relapse or recrudescence

Conventional microscopy using blood smears is considered to be the established method for morphological identification of the parasite and measuring drug efficacy. In addition, several experimental procedures are available. The details of the method used for parasitological evaluation should be included in the clinical protocol.

Blood smears

Thin and thick blood smears should be prepared for identification of the species and measuring parasite density. For preparation of blood smears and staining procedures, refer to the Clinical and Laboratory Standards Institute (formerly National Committee for Clinical and Laboratory Standards) guidelines (M15-A, volume 20, number 12) or the World Health Organization (http://mosquito.who.int/cmc_upload/0/000/011/403/malaria_diagnosis.htm). It should be specified whether thin or thick smears were used for measuring parasite count. The quantification of parasitized erythrocytes should be obtained by counting either 200 white blood cells (WBCs) or 1,000 red blood cells (with an oil immersion objective), but should remain consistent within a clinical trial. For example, if the parasite count is obtained by counting 200 WBCs, then the same procedure should be done for all smears collected from all subjects at different time points within a clinical trial. Effort should be made to determine both asexual parasite counts and gametocyte counts.

It should be ensured that:

- The method used is consistent within a given trial.
- Slides are read by two trained microscopists. Discordant readings should be adjudicated by a third microscopist.
- Microscopists are blinded to the treatment.
- Ten percent of the negative and positive slides are reviewed by a third microscopist for the purpose of quality control.
- Morphological speciation is performed on all smears at baseline, and on those obtained at the time of treatment failure.

Experimental procedures

Several experimental procedures such as microhematocrit centrifugation with acridine orange staining, immunochromatographic method, indirect fluorescent antibody tests, enzyme-linked immunosorbent assay, phenotyping (e.g., by determining in vitro susceptibility of clinical isolates to antimalarial drugs), and polymerase chain reaction have been used for:

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- Detection of parasites
- Identification of *Plasmodium* species
- Quantification of the parasite
- Measurement of exposure to the parasite in a prophylactic study
- Measurement of drug resistance (relapse or recrudescence)
- Differentiating new infection from relapse or recrudescence

It should be noted that the use of these procedures has not been fully validated in clinical trials for measuring drug efficacy. The use of experimental assays in a clinical trial should be accompanied by the standard blood smear technique. Although the use of experimental methods is encouraged, the performance characteristics of the assays should be carefully and critically evaluated in the laboratory where the actual testing of clinical samples will be done. The clinical study report should address performance characteristics of the assay such as reproducibility, quality controls, sample storage and stability, reagent storage and stability, accuracy of measurement, limit of detection, limit of quantification, cross-reactivity with other relevant pathogens, and positive and negative predictive value of the experimental procedure. Test results should be correlated with clinical outcome. Sponsors are encouraged to contact the DSPTP for more details. It also should be noted that these tests are not approved for in vitro diagnostic use. The sponsor of the test or device is encouraged to contact the Office of In Vitro Diagnostic Devices Evaluation and Safety, Center for Devices and Radiological Health, for approval of the device for marketing.

If there is the intention during a clinical trial to develop a combination of drug or nonvaccine biological product with a new test (i.e., information from a study will be used for approval of a new test that will be used with the drug), then the sponsor of the trials should contact the Office of Combination Products for additional information on developing drug-device combinations.