CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-268

CROSS DISCIPLINE TEAM LEADER REVIEW

Addendum
Cross-Discipline Team Leader Review

Date	
From	Joette M. Meyer, Pharm.D. Acting, Clinical Team Leader Division of Special Pathogen and Transplant Products
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 22-268
Applicant	Novartis Pharmaceuticals Corporation
Date of Submission	June 27, 2008
PDUFA Goal Date	December 27, 2008
Date Review Completed	March 30, 2008
Proprietary Name / Established (USAN) names	Coartem® Tablets Artemether/Lumefantrine
Dosage forms / Strength	20 mg/120 mg tablets
Proposed Indication(s)	Treatment of malaria in patients of 5 kg bodyweight and above with acute, uncomplicated infections due to *Plasmodium falciparum* or mixed infections including *P. falciparum*. Coartem is effective against both drug-sensitive and drug-resistant *P. falciparum* and is recommended for malaria infections acquired in areas where the parasites may be resistant to other antimalarials.
Recommended:	**Approval, pending resolution of issues identified by the Office of Compliance during facilities inspections.**

Addendum Regarding Potential Pharmacodynamic Drug-Drug Interaction Between Primaquine and Coartem® Tablets Resulting in QT Interval Prolongation

On February 6, 2008, during a teleconference, the Division requested that the applicant conduct a literature search for any current or ongoing studies to examine whether primaquine had the potential to prolong the QT interval and whether concurrent or sequential use of primaquine and Coartem had the potential to cause additive effects on the QT interval.

The applicant performed a literature search and submitted their results on February 19, 2009. They concluded that the available data in the literature do not support a QT effect of primaquine. The following is a summary of their findings.

Primaquine was evaluated *in vitro* for its effects on sodium and potassium currents in isolated rat ventricular muscle and myocytes. (Orta-Salazar G et al. Br J Pharmacol

2002). The results suggest that primaquine blocks cardiac sodium channels, but not potassium channels. An effect on the sodium channel may result in the potential for decreased contractility but not QT prolongation, like seen with the potassium channel. There was no effect on action potential duration.

The C_{max} for a 45 mg dose of primaquine is 153 ± 24 ng/mL. (Hill DR et al. Am J Trop Med Hyg 2006). However, the usual clinical dose is 15 to 30 mg. At these doses, the primaquine exposure at C_{max} is approximately 220 nM. This concentration is about 45 fold below the IC_{50} for the effects on the sodium channel. It is also more than 100 fold less than the highest concentration tested without effect.

In two studies where primaquine was administered for 14 days following treatment by chloroquine, which is known to effect the potassium channel *in vitro*, no cardiac related adverse events were reported (Krudsood S et al. Korean J Parasitol 2007; Fryauff DJ et al. Ann Trop Med Parasitol 1997).which affects K channel *in vitro*, no cardiac related adverse events were reported (Krudsood S et al. Korean J Parasitol 2007; Fryauff DJ et al. Ann Trop Med Parasitol 1997). However, it should be noted that ECGs were not mentioned in this study and it is unlikely that they were performed. The applicant did not participate in this study and has no additional information beyond what is printed in the publication.

Finally, the applicant cites a clinical trial where 123 patients with *P. vivax* malaria in Indonesia were randomized to halofantrine or chloroquine. Primaquine was given to all subjects concurrent with the other antimalarials and continuing for 14 days, followed by alternate day therapy until day 28. Both halofantrine and chloroquine are known to cause QT prolongation by themselves. No cardiac related adverse events were reported during the trial (Fryauff DJ et al. Ann Trop Med Parasitol 1997). However, again, ECGs were not mentioned in this study and it is unlikely that they were performed.

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/s/

Joette Meyer
3/30/2009 12:40:05 PM
MEDICAL OFFICER

Cross-Discipline Team Leader Review

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From	Joette M. Meyer, Pharm.D. Acting, Clinical Team Leader Division of Special Pathogen and Transplant Products
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1 Introduction

Coartem® is an oral, fixed-dose combination, antimalarial product containing two drug substances, artemether 20mg (an artemisinin derivative) and 120mg of lumefantrine. Coartem is the first artemisinin-based combination treatment for malaria to be submitted as an NDA. The applicant is requesting approval of a 6-dose regimen of Coartem for the 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*. Coartem should be administered over 3-days for a total of 6 doses: an initial dose, second dose after 8 hours and then twice daily (morning and evening) for the following two days. The number of tablets per dose is dependent upon the patient's bodyweight and ranges from 1 to 4 tablets.

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. All studies in the proposed NDA were conducted outside the United States between 1993 and 2007 and were not conducted not under IND.

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 for the NDA. The safety database would include data from 4-dose (4 doses administered over 2 days) as well as 6-dose studies (4 doses administered over 3 days). The applicant also agreed to include interim data from a pregnancy registry and the results of a through QT study in the NDA.

The applicant began rolling in the submission in November 2007 with submission of the Pharmacology/Toxicology studies. The final module, clinical safety and efficacy, was filed on June 27, 2008, at which time the review was considered to be complete and the PDUFA time clock was started.

In the NDA, the efficacy and safety of Coartem was evaluated in male and female adult and pediatric patients with uncomplicated *P. falciparum* malaria infection in China, Europe, Columbia, Asia, and sub-Saharan Africa. The NDA contained data from twenty studies sponsored by Novartis; 4911 patients with malaria and 3599 of these patients were treated with Coartem. Of these twenty studies, eight were identified as primary studies to support the NDA. These eight studies included complete safety and efficacy information, including raw data and electronic data sets. In the eight primary studies, a total of 2462 patients were enrolled, 1026 adult patients (> 16 years old) and 1436 pediatric patients ≤ 16 years old. The eight primary studies are composed of two 4-dose studies assessing the efficacy of the components of the regimen (ABMO2 and A023), a study comparing 4-dose versus two 6-dose regimens (6 doses administered over 60 hours or 96 hours in Study A025), and five additional 6-dose regimen studies (A026, A028, A2401, A2403, and B2303).

Less complete information was submitted on an additional 16 supportive studies. In most cases, only the study report without raw data was submitted. These supportive studies include two non-comparative 4-dose studies, one dose response study (3 doses compared to 4 doses), and 13 active controlled studies, of which ten studied the 4-dose regimen and three studied the 6-dose regimen. FDA-approved comparators (e.g., chloroquine, sulfadoxine-pyrimethamine (Fansidar®), quinine, and mefloquine (Lariam®)) were used in the 4-dose supportive studies, some of which were blinded. Although the NDA did not contain complete information on all these supportive studies, from the brief reviews provided, there did not appear to be any selection bias on the part of the applicant in determining the primary studies and those that were supportive.

For the safety review, patients exposed to either the 4- or 6-dose regimens of Coartem were included in the safety population, but attention was primarily focused on the 6-dose regimen for which the applicant was seeking approval. The population that received the 6-dose regimen was composed of 1979 patients, 647 adults (older than 16 years) and 1332 children (16 years and younger) exposed to Coartem in mostly non-controlled, open label trials (81%). The pediatric data included patients who received the intact and crushed tablets, as well as an investigational dispersible tablet (for which the applicant is not seeking approval, at this time). Patients with malaria between ages 3 months to 78 years were included in these studies: 67% (1332) were 16 years and younger and 33% (647) were older than 16 years. Males represented 73% and 53% of the adult and pediatric populations, respectively. The majority of adult patients were enrolled in studies in Thailand, while the pediatric studies were conducted in Africa. Supportive data was obtained from patients exposed to the unapproved 4-dose regimen in 787 adults and 659 children.

The applicant conducted a Thorough QT study in healthy volunteers: Study A2101 was conducted with Coartem administered orally as a 6-dose regimen 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 applicant conducted a prospective pregnancy registry in Zambia in collaboration with the World Health Organization (WHO) from October 2004 to August 2007. The NDA contained the preliminary report (Study A2407) which compared pregnancy outcomes of women exposed to Coartem with those of women exposed to sulfadoxine-pyrimethamine (SP), the standard of care for treatment of malaria in pregnant women in Zambia.

2 Background

The antimalarial properties of artemisinin drugs were first discovered in China; the active constituent of an extract from the wormwood plant Artemisia annua (qinghao) identified and purified in the 1970s, and named qinghaosu, or artemisinin. A number of semi-synthetic derivatives such as artemether have since been developed to improve the drug's pharmacological properties and antimalarial potency. Many different artemisinin-containing regimens combined with various partner drugs have been studied in an effort to find effective, safe, and less expensive combination artemisinin therapies. The WHO (WHO Malaria Treatment Guidelines, 2006) recommends artemisinin-based combination therapy everywhere in the world irrespective of the immune status of the patient and/or of the multi-drug resistance status in the country.[1]

Both artemether and lumefantrine are blood schizonticidal in the life-cycle of *Plasmodium* species. Artemether has a short half-life (~ 2 hours) and a rapid onset of action and lumefantrine has a half-life of 3 to 6 days and a slow onset of action. The combination of drugs was developed to rapidly reduce parasites in the blood (artemether) and reduce the potential for late recrudescence (lumefantrine). There is, however, a concern that resistance could occur due to lingering sub-therapeutic levels of lumefantrine after the disappearance of artemether in the blood post-treatment.

2.1 Efficacy Endpoints

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. 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 (≥ 37.5°C axillary or ≥38°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 patients had clinical symptoms of malaria present at baseline and improved with treatment. Secondary endpoints include time to parasite clearance, and time to fever clearance.

[1] Guidelines for the Treatment of Malaria. World Health Organization, 2006

The inclusion/exclusion criteria, endpoints, definitions of the analysis populations used by the applicant in theses studies were similar to those in the draft Guidance to Industry, "Malaria: Developing Drug and Nonvaccine Biological Products for Treatment and Prophylaxis."[2] The FDA's ITT and Evaluable populations are essentially the same as the applicant's MITT and Evaluable populations. The ITT population was used as the FDA's primary analysis population since the evaluable population excludes subjects after randomization for reasons that may be treatment related and may result in a biased analysis. In the ITT population, patients with missing data for 28-day cure rate are included in the analysis as failures; therefore the reviewer's outcome rates are lower than rates for the evaluable population, where patients missing the 28-day visit were excluded from analysis.

2.2 Fixed-Dose Combination Drug

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). The two, 4-dose studies are considered essential studies in the NDA because the efficacy of the fixed-combination drug, Coartem, is compared to each of its individual components.

Using both early and late time points, as discussed in the clinical efficacy section, 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.

The applicant was asked to justify the clinical importance of each drug in the combination. They stated that the "The combination of an artemisinin derivative with another effective antimalarial drug that has a complementary mechanism of action and pharmacological profile can overcome the emergence of drug resistance. It allows faster malaria symptoms improvement/recovery and therefore ensures rapid and reliable cure avoiding progression to severe malaria."[3]

They further state that combinations of antimalarial drugs are now recommended by the WHO, because combination therapy is usually more effective than monotherapy and minimizes the risk of treatment failure due to the development of drug resistance during treatment. If a

[2] http://www.fda.gov/cder/guidance/7631dft.pdf
[3] Guidelines for the Treatment of Malaria. [World Health Organization 2006] http://www.who.int/malaria/docs/TreatmentGuidelines2006.pdf.

parasite resistant to one component of a combination emerges during treatment, it should be killed by the other component

In a trial by Van Vugt, et al. the addition of artesunate to atovaquone-proguanil reduced fever duration and shortened parasite clearance time compared to atovaquone-proguanil alone. In addition, adding artesunate reduced the risk of failure by 3-fold.[4]

Adjuik et al. performed a meta-analysis of data from 16 randomized trials (n=5948) that studied the effects of adding artesunate to standard treatment of P. falciparum malaria and concluded that the addition of artesunate substantially reduced recrudescence and treatment failure.[5]

The applicant was not able to identify efficacy data comparing lumefantrine administered with or without artemisinin derivatives in the literature, other than in the clinical trials described in the NDA. The state that because lumefantrine has never been used as monotherapy, resistance has not developed and therefore lumefantrine contributes to the efficacy of Coartem even in regions of resistance to other antimalarials.

2.3 Four versus Six Dose Regimen

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

[4] van Vugt M, Leonardi E, Phaipun L et al (2002). Treatment of Uncomplicated Multidrug-Resistant Falciparum Malaria with Artesunate-Atovaquone-Proguanil. Clinical Infectious Diseases; 35:1498–504.

[5] Adjuik M, Agnamey P, Babiker A,et al 2004. Artesunate combinations for treatment of malaria: meta-analysis. Lancet; 363: 9–17.

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 the US population because cases of malaria in the US are reported in persons who have traveled to endemic countries.

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 ABMO2), and (b) A025 which compared the 4-dose regimen to the 6-dose regimen. 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-pyrimethamine (Fansidar®), quinine, and mefloquine) were used as comparators in the 4-dose supportive studies, some of which were blinded.

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 *P. falciparum* 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 Priority Review

The applicant requested a priority review based upon the fact that "Coartem demonstrates evidence of safety and effectiveness in the pediatric subpopulation." The applicant stated in their request that children ≤ 12 years of age treated with a Coartem achieve an earlier reduction in parasite burden and a more rapid fever clearance time than other approved comparators, including quinine and sulfadoxine-pyrimethamine.

A Priority review was grated using the following criteria as specified in MaPP 6020.3:

- Evidence of increased effectiveness in treatment of acute, uncomplicated malaria
- Evidence of safety and effectiveness in a new subpopulation - pediatrics

At the time the Priority designation was being considered, the FDA statistical reviewers created a table of the 4-dose pediatric studies in the NDA. Note, that the definition of pediatric used by the applicant in the submission was ≤ 12 years, which is different from the FDA definition of ≤ 16 years.

The studies included in FDA Table 1 (A003, 008, 009, 010, and 011) are considered to be supportive of the 6-dose regimen. The applicant did not provide raw data in the NDA for these studies. Four of these studies are comparative (Studies 003, 008, 010, and 011).

The results suggest that 4 doses of Coartem result in a greater reduction in parasite burden at 24 hours (95% to 99%) compared to quinine in Study 003 (67%), SP in Study 010 (62%), and chloroquine in Study 011 (59%). Parasite reduction at 24 hours was not reported in Study 008 which used MAS as the comparator. The only comparative study to evaluate parasite clearance time (PCT) was Study 003 and Coartem achieved a greater PCT (40 hours) compared to quinine (77 hours).

Median fever clearance time (FCT) was 52 hours for Coartem compared to 88 hours for quinine in Study 003. FCT was reported as "normal by day 2" in 88% of the Coartem patients in Study 010 compared to 48% of the SP-treated patients. FCT was not reported in Studies

008 or 011. Parasitological cure at 28 days with Coartem was better with Coartem than with chloroquine (64% vs. 5%, respectively in Study 011), slightly lower than quinine (43% vs. 47% in Study 003), and substantially lower than with SP (77% vs. 87% in Study 010) or MAS (80% vs. 95% Study 008).

FDA Table 1
Efficacy Results for Subjects ≤ 12 years in Supportive 4-dose Studies

Study	Treatment arm n	28 day cure	Median PCT hours	Median FCT hours	Parasite reduction at 24 hours
003	Coartem 4 dose n=111 Quinine n = 108	48/111 (43.2) 51/108 (47.2)	40 77	52 88	98.6% 67.3%
008	Coartem 4 dose (n = 64) MAS (n = 64)	79.6% (n=48?) 94.6% (n=52?)			
010	Coartem 4 dose N=144 SP N=143	14-day Cure rate 111/144 (77.1%) 125/143 (87.4%)		Normal by day 2: 88.2% 48.2%	94.9% 62.4%
011	Coartem 4 dose N=130 Chloroquine N=130	Evaluable 75/118 (63.6%) 6/119 (5%)			97.5% 59%
009	Coartem 4 dose N = 60	71.7%	36	36 (n=58)	94.7

Source: Table created by Statistical Team Leader, Karen Higgins, Sc.D.

Four studies in the NDA evaluated the efficacy of the 6-dose regimen in children of body weight of 5 kg and above (Studies A025, A026, A2403 and B2303). These are 4 of the 8 studies considered to be primary efficacy studies (with raw data included).

As shown in FDA Table 2, only Studies A026 and A028 were comparative study (9 patients treated with MAS). In these studies, Coartem achieved a median PCT of 24 to 44 hours and a median FCT of 8 to 44 hours. MAS resulted in a median PCT of 24 hours, similar to Coartem, but the median FCT was longer at 21 to 41 hours. The shorter FCT for Coartem is being driven by the two large pediatric studies (A2403 and B2303) which both had a FCT of approximately 8 hours. Note, however, that the majority of patients in these studies were receiving antipyretics (75% and 95%, respectively).

Note this table was initially created at the time of the Priority review was being considered and has now been updated with the final results from the Medical Officer's review including all patients ≤ 16 years:

28-day Cure Rate, PCT, and FCT in Pediatric Patients (≤ 16 years of age) Across 6-dose Studies

Endpoint	**Study A025**			**Study A026**		**Study A028**		**Study A2403**	**Study B2303**	
	Coartem 4-dose (48 hours)	Coartem 6-dose (60 hours)	Coartem 6-dose (96 hours)	Coartem	***MAS***	Coartem	***MAS***		Coartem Dispersible Tablet	Coartem Crushed
28 day cure rate	18/21 (85.7%)	25/30 (83.3%)	26/29 (89.7%)	36/41 (87.8%)	***16/16 (100%)***	14/15 (93.3%)	***12/12 (100%)***	267/300 (86.5)	374/441 (84.8)	374/444
PCT (hrs) Median * [95%CI†] 25-75 percentile* Range**	44 [22,45] 22-45 19-72	43 [22,45] 22-45 18-68	44 [42,44] 42-45 19-67	ND	***ND***	24 [24,40] 22-40 16-48	***24 [16-32] 16-32 8-42***	24 [24.0,35.4] 23.8 – 36.0 (5.3 to 71.1)	34.3[24.6, 35.5] 23.9-36.1 6.5-169.0	34.9[25. 23.9-36. 6.6-165.
FCT (hrs) Median* [95%CI†] 25-75 percentile* Range**	22 [19,43] 19-43 12-70	27 [20,45] 20-46 18-70	22 [20,44] 20-44 18-164	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***	7.8 [7.8,7.9] 7.8 – 23.7 (4.1 to 332.4)	7.8 [7.8,7.9] 7.6-23.6 3.8-695.4	7.8 [7.8, 7.5-23.2 4.7-355.

ND = not done * 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.

Source: Table created by CDTL using data from FDA clinical/statistical reviews

In order to address the impact of the use of antipyretics on FCT, the applicant was asked to provide an analysis. On November 20, 2008, the applicant provided the following table, which shows that FCT was similar in Study A2403 between those patients taking antipyretics and those not taking them. However, in Study B2303 the median FCT was higher in the antipyretic group, indicating the analysis may be confounded. Also antipyretics may have been prescribed to patients with a higher severity of disease at baseline.

Median time to fever clearance (95% CI), hours	**Study A2403**	**Study B2303**
Antipyretics in the 1st 4 days	N = 224 7.9 (7.9-8.2)	N = 140 22.0 (8.4-23.5)
No Antipyretics in the 1st 4 days	N = 85 7.8 (7.7-7.8)	N = 183 7.7 (7.6-7.7)

[1] Crushed tablet arm
N is the number of patients included in the analysis. Patients with a baseline body temperature <37.5 °C were not taken into account.
Modified ITT population: All (randomized) patients with parasitologically confirmed *P. falciparum* malaria who received at least one dose of study drug.
Source: Applicant's submission November 20, 2008

The applicant also summarize the literature and concluded that published studies on antimalarials other than artemisinin-combination therapies showed no consistent effect of antipyretics on the FCT and that the data from pediatric patients receiving the Coartem 6-dose regimen did not indicate an association between administration of antipyretics and fever clearance time.

In summary, the results suggest that in pediatric patients 4 doses of Coartem results in a greater reduction in parasite burden at 24 hours than quinine, SP and chloroquine; a shorter PCT than quinine; and a shorter FCT than quinine and SP. In 6-dose studies of pediatric patients, the FCT was more variable and in the two largest studies of the smallest children (A2403 and B2303) the FCT was shorter than seen in other 4-dose studies and the 6-dose studies using MAS as the comparator. It remains unclear whether the relatively short FCT in these two studies is due to concomitant use of antipyretics.

3 CMC/Device

From the chemistry, manufacturing and controls standpoint, the NDA is not currently recommended for approval. There are several outstanding issues currently pending for this NDA including the status of the manufacturing facilities.

The CMC review of this NDA was conducted by Dorota Matecka, Ph.D. (Drug Substance) and Shrikant Pagay, Ph.D. (Drug Product). The following summary is excerpted from their reviews.

3.1 General Product Quality Considerations

The artemether drug substance is a semi-synthetic moiety that is synthesized from the (b) (4) starting material. (b) (4) is an antimalarial agent extracted from the leaves of *Artemisia annua L*. Artemether is a methyl ether derivative of dihydroartemisinin. The latter is derived from (b) (4) through the reduction of the lactone functionality. The acidic methylation of hemi-acetal dihydroartemisinin in the synthesis of artemether drug substance favors the β-anomeric form of artemether. Artemether is a white to slightly yellow, crystalline powder with a melting point of 86º-90ºC and specific rotation of +166º to +173º. Artemether is freely soluble in acetone, soluble in methanol and ethanol, and practically insoluble in water. Artemether is an optically active molecule and contains eight asymmetric centers, seven of them are set from the naturally occurring starting material, (b) (4). There are two known polymorphs of artemether (Polymorphs A and B). Polymorph A, the stable species at room temperature, was chosen for pharmaceutical application. The quality of the artemether drug substance is controlled through a set of appropriate tests and acceptance criteria, including identity, assay, impurities, particle size, microbial limits, and residual solvents. Artemether has been shown stable through 12 months when stored at 5º ± 3ºC.

The lumefantrine drug substance is a synthetic moiety that is obtained in a (b) (4)-step synthesis starting from (b) (4) procedures to obtain final drug substance. Lumefantrine is a yellow, crystalline powder with a melting point of 128° - 132°C. Lumefantrine is freely soluble in DMF, chloroform and ethyl acetate, soluble in dichloromethane, slightly soluble in ethanol and methanol, and insoluble in water. Lumefantrine has one chiral center; the lumefantrine drug substance is isolated as a racemic mixture. Only one polymorphic form has been identified for lumefantrine. The quality of the lumefantrine drug substance is controlled through a set of appropriate tests and acceptance criteria, including identity, assay, impurities, particle size, microbial limits, and residual solvents. Lumefantrine drug substance has been shown stable at room temperature.

The proposed drug product, Coartem Tablets, is a fixed combination of two antimalarial drugs, artemether and lumefantrine. Each tablet contains 20 mg of artemether and 120 mg of lumefantrine for oral drug delivery. The tablets are yellow, round flat with beveled edges and score on one side. The light yellow color of the tablet is due to lumefantrine. For identification, the tablets are printed on the scored side of the tablet with N/C and on the other

side of the tablet with CG. The total tablet weight is 240 mg. The tablet components besides the active drugs are microcrystalline cellulose, croscarmellose cellulose, hypromellose (b) (4) silicon dioxide, polysorbate 80, magnesium stearate (b) (4) All inactive components meet USP/NF/Ph Eur quality standards. The tablets are packaged in (b) (4) bottles with child resistant closures and induction seals, and in (b) (4) blisters with push thru aluminum lidding foil backing.

(b) (4)

Artemether is slightly soluble in water and lumefantrine is insoluble. However, both drugs are highly lipophilic favoring better absorption if promptly dissolved in the GI tract. The proposed dissolution specifications, especially that of artemether with Q values (% dissolved specification = (b) (4) dissolved in (b) (4) and (b) (4) in (b) (4)) are not satisfactory; the method needs to be revised to achieve dissolution specification at Q= (b) (4) to insure consistent quality attribute. The dissolution test is primarily a quality control test since no information is available in the submission for relative or absolute bioavailability of the two drugs or that of the proposed formulation. All clinical/PK data supports that both drugs artemether and lumefantrine are available systemically. However, no data were provided to demonstrate if the proposed tablet formulation is optimally bioavailable. This issue of an unsatisfactory dissolution specification will be discussed further with the applicant, but is not considered an approvability issue, by the CMC reviewers.

The submission has included stability data on approximately (b) (4) production scale batches with data through the proposed shelf life. Multiple analytical testing procedures are proposed for the identification, dissolution, assay, impurities, and content uniformity to demonstrate that the tablet quality is robust, however, some test methods, specifically the (b) (4) for artemether degradation products (impurities) could be considered semi-quantitative. The sponsor will be encouraged to develop a more quantitative method. The proposed shelf life of 24 months was found to be acceptable by the reviewers.

3.2 Facilities Review/Inspection

Artemether drug substance is produced by (b) (4) Lumefantrine drug substance is produced by (b) (4) In addition, there are several other establishments involved in the (b) (4) of both drug substances and the drug product. Upon approval, the drug product will be manufactured and marketed by Novartis.

The following summary of the facility inspection issues was written by Anthony Charity, Acting TL, International Compliance Team, DMPQ, on December 22, 2008:

There are a total of eleven (11) firms named in this application. One firm [inspection] was cancelled by ONDQA on 12/12/08. Inspections were performed on four firms in which two firms were classified OAI. One firm is Novartis in Basel, Switzerland; the other is **(b) (4)** Another firm, **(b) (4)** was inspected and classified as VAI. There are two firms, both located in China that has planned inspections. **(b) (4)** has an inspection assigned for February 2009. We have asked for additional information on the address of the facility to determine if we have inspected them previously. The other facility, **(b) (4)** has never been inspected and is planned for February/March 2009.

OAI issues cited are (a) stability indicating methods, (b) laboratory controls and (c) other GMP deviations. While the **(b) (4)** is listed as VAI, there is some concerns internally that the VAI is borderline and may be indicative of broader issues within this facility. This VAI is undergoing evaluation. On 12/18/08 we received the written response from **(b) (4)** and the firm has adequately address corrective actions taken. We also reviewed written response from Novartis in Basel and they also adequately address corrective action taken. **(b) (4)** and Novartis in Basel have been upgraded to VAI and are considered acceptable.

Action Items:
Novartis in a teleconference with the agency on 12/18 agreed to contact their liaison in Switzerland that interfaces with the **(b) (4)** facility. They indicated that they believe a response letter will be sent to the agency this week but Novartis could possibly send a copy by this weekend. On 12/22/08 Novartis provided **(b) (4)** response and is been reviewed. A decision on **(b) (4)** should be finalized by today (12/22). Novartis will provide the address and a map of the Chinese sites that have not yet been inspected. One of the facilities listed **(b) (4)** has as its address the administration building. During the teleconference it was brought to Novartis attention that even after we made a decision to approve the three outstanding sites, the two sites in China will still need to be inspected and this will cause the application to miss the PDUFA date. Novartis said that they did understand this and would make a decision on whether to withdraw the two sites in China and re-submit a supplement to the application for **(b) (4)**

A second teleconference was held between DMPQ and Novartis later in the day on December 22, 2008. At that time it was decided that the facilities inspection issues could not be sorted out during the remaining time on the PDUFA review clock (December 27, 2008). DMPQ stated that the action would be delayed until all outstanding compliance issues were reviewed and resolved.

3.3 Other Notable Issues

The original application contains mostly adequate chemistry manufacturing and controls information regarding the quality of both drug substances and the drug product. During the review, a number of comments requesting additional information were forwarded to the applicant and several issues relating to the manufacturing process, testing and specifications were resolved satisfactorily.

An additional issue related to the qualification of the proposed acceptance criteria for impurities listed in both drug substances and the drug product specifications was discussed between ONDQA and the Pharmacology/Toxicology review team (see Section 4.4.3 below).

4 Nonclinical Pharmacology/Toxicology

The nonclinical toxicology program for artemether/lumefantrine 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. There are no nonclinical pharmacology or toxicology data that

preclude the approval of Coartem. The Pharmacology/Toxicology review of this NDA was conducted by Owen McMaster, Ph.D., Stephen Hundley, Ph.D., Terry Miller, Ph.D. and Rama Dwivedi, Ph.D. The following summary is excerpted from their reviews and from their proposed additions to the drug label.

4.1 General Nonclinical Pharmacology/Toxicology Considerations

Toxic effects observed in rats or dogs dosed with Coartem for one or three months were seen in the thyroids, liver, erythrocytes, lymph nodes, kidneys, spleen and brain. A NOAEL was not determined for any of the repeat-dose studies and this was most often due to effects on thyroid function, including increased TSH, decreased T4 or T3, increased thyroid weight and increased thyroid hyperplasia. Other effects seen at the lowest doses tested included hemosiderosis, vacuolation of the pituitary, hyaline droplets in the kidneys and lymph node histiocytosis. Higher doses resulted in enlarged lymph nodes, hypercellularity of the bone marrow, increased spleen weights, increased liver weights, increased kidney weights, increased urea, increased cholesterol, decreased triglycerides, increased α-1-globulin, ß-2-globulin, increased alkaline phosphatase (dogs) decreased alkaline phosphatase (rats) and increases or decreases in glucose levels.

It is not clear if these findings can be extrapolated into potential risks for patients treated with the proposed clinical regimen since the animals in these studies were dosed with artemether/lumefantrine for ten to thirty times as long as the proposed clinical regimen.

The adverse effects of special interest are reproductive and neurological toxicity (including auditory), which are attributed primarily to artemether (see additional discussion below).

4.2 Reproductive Toxicology

4.2.1 Impairment of Fertility

Pregnancy rates were reduced by about one half in female rats dosed for 2-4 weeks with the artemether-lumefantrine combination at 1000 mg/kg (about 9 times the clinical dose based on body surface area comparisons). Male rats dosed for 70 days showed increases in abnormal sperm (87 % abnormal) and increased testes weights at 30 mg/kg doses (about one third the clinical dose). Higher doses (about 9 times the clinical dose) resulted in decreased sperm motility and 100 % abnormal sperm cells.

4.2.2 Reproductive Toxicity

Pregnant rats dosed during the period of organogenesis, at or higher than 60 mg/kg/day with the artemether-lumefantrine combination (a dose about half the highest clinical dose based on body surface area comparisons), showed increases in the number of dead fetuses, early resorptions and post implantation losses. No adverse effects were observed in animals dosed at 40 mg/kg (about one third the clinical dose). Similarly, dosing in pregnant rabbits at 175 mg/kg/day (about three times the highest clinical dose based on body surface area comparisons) resulted in abortions, preimplantation losses, post implantation losses and decreases in the number of live fetuses. No adverse reproductive effects were detected in rabbits at 105 mg/kg/day, about two times the clinical dose based on body surface area comparisons.

Embryo-fetal loss is a significant reproductive toxicity. However, because metabolic profiles in animals and humans are dissimilar, artemether exposures in animals may not be predictive of human exposures.

Reviewer's Comment: As discussed below, data from a pregnancy registry of approximately 500 pregnant women who were exposed to Coartem Tablets, and published data of over 1,000 pregnant patients who were exposed to artemisinin derivatives, did not show an increase in teratogenic effects over background rate (see clinical safety discussion). In addition, data from the pregnancy registry, including a third of patients who were exposed in the first trimester, did not show an increase in adverse pregnancy outcomes. These human data can not rule out an increased risk for early pregnancy loss. However, pregnant women malaria often have a poor outcome, so Coartem will be labeled as Pregnancy category C (b) (4) *But the label will also state that Coartem should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.*

4.3 Carcinogenicity Studies

Due to the short duration of malaria treatment with Coartem, carcinogenicity studies were not required.

4.4 Other Notable Issues

4.4.1 Neurotoxicity

Artemether is known to be rapidly taken up into the brain. *In vitro* binding studies of neurotransmitter receptors have shown that artemether showed affinity for the kainate receptor, while benflumetol (lumefantrine) showed strongest interaction was with the NMDA receptor. Both kainate and NMDA receptors are thought to play a central role in pathological processes such as excitotoxic neurodegeneration.

The lowest IM dose of artemether resulting in histopathologic effects in multiple regions of the brains from beagle dogs was 20 mg/kg, administered over eight consecutive days. Brain lesions were prominent in the pontine nuclei, cerebellar nuclei, nucleus vestibularis, nucleus hypoglossus, and nucleus cuneatus and included chromatolysis, microgliosis, neuronal necrosis, axonal swelling, neurofilament clumping, eosinophilic cytoplasmic granulation, and spheroids. The severity of these lesions increased as dose levels increased to 40 and 80 mg/kg. Although histopathological effects were observed with IM dosing of artemether, no compound-related effects were observed in the clinical neurophysiological examinations performed prior to the terminal dose. The NOEL for brain histopathology following IM administration for 8 consecutive days was 10 mg/kg/day.

Dosing over thirty days with IM artemether in dogs (AUC values about 14-times clinical exposures) resulted in brain lesions, seizures and death.

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. Similarly, no

clinical neurophysiological effects were observed following oral artemether doses as high as 600 mg/kg/day. Repeat oral dosing with artemether resulted in a reduction of both Cmax and AUC values between day 1 and 8. This reduction in systemic exposure to artemether over time, was not seen in the repeat dose IM studies. Therefore, artemether when given orally, unlike IM administration which does not have a hepatic first pass effect, appears to induce its own metabolism.

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.

Reviewer's Comment: The Pharmacology/Toxicology reviewer stated that the toxicity observed following the first 600 mg/kg dose to dogs in this study appeared to be general excessive toxicity with the neurological signs being secondary. The dose level was reduced to 300 mg/kg for subsequent doses (Days 2 through 8) and no additional clinical effects were observed and no compound-related effects were observed in the neurophysiological examinations conducted prior to the Day 8 terminal dose.

In addition, the applicant conducted another study in dogs with 600 mg/kg orally prior to the study above. In this first study, no severe clinical effects were observed when 600 mg/kg of artemether was administered for eight consecutive days. The Day 1 plasma AUC for artemether from the second study in which the 600 mg/kg dose was subsequently reduced, was approximately 20-fold higher than the corresponding Day 1 AUC from the study in which the animals tolerated 600 mg/kg for eight days. The Pharmacology/Toxicology reviewer has no clear explanation regarding the differences in exposure between the two studies.

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.

Reviewer's Comment: In discussion with the Clinical Pharmacology reviewer and the Pharmacology/Toxicology reviewer, it was determined that the AUC_{0-24} achieved with 10 mg/kg IM artemether in animals corresponds to approximately 2.3 times the clinical dose on Day 1 and 12.7 times the clinical dose on Day 3. The AUC_{0-24} achieved with 600 mg/kg oral artemether in animals corresponds to approximately 4.2 times the clinical dose on Day 1 and 2.0 times the clinical dose on Day 3 (using Day 8 data in animals, since Day 3 data are not available).

In the clinical safety database, nervous system disorders, particularly headache and dizziness, were commonly reported in both adult and pediatric subjects, but were likely attributed to the symptoms of malaria. In adults, nervous system serious adverse events (SAEs) represented 0.5% of all adverse events (AEs), and were unlikely to be related to study drug. In pediatric subjects, analysis was further done according to pre-defined age strata, with no safety pattern observed to suggest cumulative neurotoxicity, or increased AEs in the younger subjects. SAEs were thought due to cerebral malaria or other infection.

In summary, while IM dosing of artemether was shown to cause neurotoxic effects in multiple regions of the brain in dogs, systemic plasma concentrations of artemether following oral administration to beagle dogs were lower and did not achieve concentrations sufficient to cause brain histopathology. Therefore, the neurotoxicity with IM artemether in dogs may not be relevant to the oral use of Coartem in patients. Malaria adult and pediatric patients treated with Coartem for 6-doses did not appear to exhibit nervous system adverse events, other than those related to their infection.

4.4.2 Auditory Toxicity

Compound-related auditory effects were not observed in dogs receiving IM doses of artemether for 8 consecutive days. However, dogs dosed orally with 143 mg/kg artemether showed a statistically measureable effect on the hearing threshold at 20 dB. This dose is equivalent to about 29 times the highest artemether clinical dose (160 mg/day) based on body surface area comparisons.

Reviewer's Comment: As discussed below in the clinical safety review by Dr. Sue Lim, there were no safety signals of ear/labyrinth disorders in the clinical safety database, and no adverse events related to audiologic changes in the pooled analyses of adult and pediatric patients (see clinical safety discussion). However, it was 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.

The applicant also performed a study to evaluate possible auditory system effects of Coartem treatment. Study A2412 was an open-label, single-center study, using audiological measurements to evaluate the effects of Coartem, 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 (Coartem: 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 Coartem group is ≥ 15% (p-value 0.042). Four patients in the Coartem 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: An open label, single center study of the effects of Coartem, Malarone and artesunate-mefloquine on auditory function following the treatment of acute uncomplicated P. falciparum malaria in patients 12 years of age or older in Columbia.

4.4.3 Potential Genotoxicity of Process Impurities or Degradants

Although artemether and lumefantrine are not mutagenic, several in silico evaluations have revealed evidence of genotoxic potential for some of the process impurities or degrandants of Coartem Tablets. The applicant is proposing impurity limits that exceed the levels in drug

batches used in toxicology studies. Therefore, the Pharmacology/Toxicology reviewers are recommending that the applicant conduct genotoxicity studies with these compounds.

From the Pharmacology/Toxicology Review Addendum:

DSPTP Pharmacology/Toxicology has reviewed the applicant's proposed final product release limits and shelf life limits for impurities. At this time, we accept each of the applicant's proposed specifications (limits) for each impurity.

Measurements of specific impurities in nonclinical or in clinical batches qualify some of the proposed final product release limits, but none of the proposed shelf limits. Please note that regulatory specifications are shelf life limits.

Because malaria is a serious and life-threatening disease, and because the clinical experience with this product to date has been extensive, and because the clinical reviewers have deemed the product reasonably safe, we are not concerned that these impurities may be direct-acting (i.e., local and systemic) toxicants.

However, some of the impurities have structural alerts for genetic toxicity and, therefore, we are requiring the applicant to provide further information about four of them, in accordance with CDER Pharmacology/Toxicology Guidance (December 2008). Should any of those four specific impurities (b) (4) test positive in bacterial reverse-mutation in vitro assays, we will reconsider the specifications for them further. The *in vitro* assays will be Post-Marketing Requirements.

4.5 Recommendations for Nonclinical Studies (Postmarketing Requirements)

1. Conduct bacterial reverse mutation studies (Ames assays) for lumefantrine impurities (b) (4) and artemether impurities (b) (4)

2. Conduct an oral neurotoxicity study of artemether with juvenile rats that includes neurologic functional batteries, toxicokinetics, and extensive brain histopathology. This study should consist of a main study group, a toxicokinetic group and a recovery group. Information from this study will help to assess how exposure and toxicity in young animals compares with older animals and humans, and whether neurologic deterioration occurs following the terminal dose. A complete draft protocol should be submitted to the Review Division for comments.

Reviewer's Comment: The Pharmacology/Toxicology reviewers provided the following rationale for requesting this study:
Brain hemorrhages arising peripherally from the meninges These animals were not properly evaluated postmortem and so a repeat study is being requested.

In Study 0570013, brain hemorrhages were observed in 60-70% of 7-day-old rats dosed orally with artemether at 100 mg/kg/day on postpartum days 7-21. The dose was

equivalent to a human dose of 16.2 mg/kg/day or 6 times the clinical artemether dose based on body surface area comparisons. However, problems with the study include excessive clotting of hematologic samples collected for CBC and TK analyses, limited histopathologic review of the high dose treatment group, high mortality preventing proper blood collection/analysis, and poor tissue fixation resulting in severe post-mortem tissue damage. This study should have provided data to compare exposure and toxicity between young and older animals and with humans dosed orally, but the study results are significantly confounded and mostly uninterpretable. Because serious pathologies were observed in Study 0570013 and many results are uninterpretable, this important study should be modified and repeated.

5 Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology/Biopharmaceutics information submitted for Coartem is acceptable from the perspective of the Office of Clinical Pharmacology (OCP). The Clinical Pharmacology/Biopharmaceutics review of this NDA was conducted by Dakshina Chilukuri, Ph.D and Gerlie Geiser, Ph.D. The following summary is excerpted from their reviews and from their proposed wording for the drug label.

5.1 General Clinical /Pharmacology/Biopharmaceutics Considerations

The pharmacokinetics (PK) of the two components of co-artemether, i.e. artemether and lumefantrine, as well as their respective active metabolites, i.e. dihydroartemisinin (DHA) and desbutyl-lumefantrine, were characterized on the basis of single- and multiple-dose data from several studies in healthy volunteers and in patients with malaria.
Artemether is characterized by a rapid absorption with peak plasma concentrations (C_{max}) being reached about 2 h after dosing, followed by an equally rapid clearance from plasma with an estimated apparent elimination half-life of about 2 hours. Its active metabolite, DHA, is formed rapidly (t_{max} about 2 h), and its disposition is similar to that of the parent drug. The PK of artemether is time-dependent (induction of its metabolism), with exposure to artemether decreasing with repeated administration, while the exposure of its active metabolite DHA increases.

The absorption of lumefantrine, a highly lipophilic compound, is slow and starts after a lag-time of around 2 hours. C_{max} is reached in about 6-8 h. Its clearance from plasma is also slow with a terminal elimination half-life of 4 to 6 days. Its active metabolite, desbutyl-lumefantrine, represents less than 1% (AUC) of the parent compound exposure in plasma. The systemic exposure of lumefantrine increases with repeated administration of co-artemether, essentially attributed to accumulation consistent with dosing regimen and elimination half-life. Consistent with the long elimination half-life, steady state of lumefantrine is not reached over the short treatment duration of 3 days.

5.1.1 Food Effect

Food intake significantly increases the bioavailability of co-artemether. In healthy volunteers, the relative bioavailability of artemether was increased more than 2-fold, and that of lumefantrine 16-fold after a standard FDA breakfast compared to fasting conditions. Given the pronounced increase in systemic concentrations when administered with food, malaria patients

studied in all subsequent Phase I/II studies and the Phase III clinical efficacy and safety trials were encouraged to take co-artemether with food, in particular fat-containing meals, as soon as food was tolerated. Food has also been shown to increase the absorption of lumefantrine in patients with malaria, although to a lesser extent (approximately 2-fold), probably due to the lower fat content of the food ingested by acutely ill patients. Patients should therefore be encouraged to take the medication with a normal diet as soon as food can be tolerated

5.1.2 Drug-Drug Interactions

In human liver microsomes and recombinant CYP450 enzymes, the metabolism of artemether was catalyzed predominantly by CYP3A4/5. Dihydroartemisinin (DHA) is one of the active metabolites of artemether. The metabolism of artemether was also catalyzed to a lesser extent by CYP2B6, CYP2C9 and CYP2C19. *In vitro* studies with artemether at therapeutic concentrations revealed no significant inhibition of the metabolic activities of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, CYP4A9/11.
During repeated administration of Coartem Tablets, systemic exposure of artemether decreased significantly, while concentrations of DHA increased, although not to a statistically significant degree. The artemether/DHA AUC ratio is 1.2 after a single dose and 0.3 after 6 doses given over 3 days. This suggests that there was induction of the enzyme responsible for the metabolism of artemether.

In human liver microsomes and in recombinant CYP450 enzymes, lumefantrine was metabolized mainly by CYP3A4 to desbutyl-lumefantrine. The systemic exposure to the metabolite desbutyl-lumefantrine was less than 1% of the exposure to the parent compound. *In vitro* lumefantrine significantly inhibits the activity of CYP2D6 at therapeutic plasma concentrations.

Caution is recommended when combining Coartem with substrates, inhibitors, or inducers of CYP3A4, especially anti-retroviral drugs and those that prolong the QT interval (e.g., macrolides, pimozide, terfenadine, astemizole, cisapride).

Coadministration of Coartem with CYP2D6 substrates may result in increased plasma concentrations of the CYP2D6 substrate and increase the risk of adverse reactions. In addition, many of the drugs metabolized by CYP2D6 can prolong the QT interval and should not be administered with Coartem Tablets due to the potential additive effect on the QT interval (e.g., flecainide, imipramine, amitriptyline, clomipramine).

5.1.3 Pathway of Elimination

Artemether and dihydroartemisinin are rapidly cleared from plasma with an elimination half-life of about 2 hours. Lumefantrine is eliminated slowly with a terminal half-life of 2-3 days in healthy volunteers and 4-6 days in patients with *P. falciparum* malaria. Demographic characteristics such as gender and weight appear to have no clinically relevant effects on the pharmacokinetics of co-artemether.

No urinary excretion data are available for humans. In rats and dogs, unchanged artemether has not been detected in feces and urine due to its rapid and high first-pass metabolism, but several metabolites (unidentified) have been detected in both feces and urine. Lumefantrine is

eliminated via the bile in rats and dogs, with excretion primarily in the feces. After oral dosing in rats and dogs qualitative and quantitative recovery of metabolites in bile and feces was relatively low, most of the dose being recovered as parent drug.

5.2 Critical Intrinsic Factors Potentially Affecting Elimination

5.2.1 Age

No specific pharmacokinetic studies have been performed in elderly subjects. There were only 8 patients in the clinical database who were ≥ 65 years of age, so no comment can be made on the safety or efficacy of the product in this population.

Two studies were conducted in infants and children with malaria, i.e. Study A2403 and Study B2303. Crushed standard tablets of Coartem were used in both studies. Artemether and DHA concentrations observed in Study B2303 were in line with those observed previously in adult malaria patients in Thailand (Study A028) treated with the 6-dose regimen of Coartem. The PK estimates for lumefantrine were consistent between Studies B2303 and A2403.

According to the following table, the estimated C_{max} and AUC values of lumefantrine for the three body weight groups seemed to suggest an increase in exposure with rising doses (i.e. the number of tablets), despite the fact that the total dose of lumefantrine in mg/kg body weight did not vary substantially between body weight groups (66.7 to 82.9 mg/kg in Study B2303). Lumefantrine exposure for the 25 to <35 kg group was most likely overestimated due to the limited number of samples and some extreme values in this group. Therefore, the data for this group was only a rough estimate and was difficult to compare with other groups or other studies. A food effect may have contributed to the trend to increasing lumefantrine exposure with rising body weight despite similar body weight normalized lumefantrine doses. Younger children, as opposed to older ones, were likely to eat less, and might not have taken enough food with all doses of Coartem. Since food was shown to increase bioavailability of lumefantrine by 16-fold on average in healthy adult subjects, small differences in dietary conditions (i.e. ability to eat, quantity and type of food) between weight groups may have been responsible for the findings.

Clinical efficacy in Studies A2403 and B2303 was high and similar in both studies (28-day cure rate of 86% and 85%, respectively).

Table 9b. Lumefantrine PK parameters following co-artemether crushed or dispersible tablet in pediatric patients

	Study CCOA566A2403		Study CCOA566B2303		
	5-<15 kg BW (6 x 1 tablet)	15-25 kg BW (6 x 2 tablets)	5-<15 kg BW (6 x 1 tablet)	15-<25 kg BW (6 x 2 tablets)	25-<35 kg BW (6 x 3 tablets)
Crushed tablet	(n = 156)	(n = 25)	(n = 194)	(n = 102)	(n = 19)
C_{max} (µg/mL)	4.71	12.6	6.13	9.37	21.9[1]
AUC_{last} (µg·h/mL)	372	655	577	699	1150
Dispersible tablet			(n = 191)	(n = 102)	(n = 17)
C_{max} (µg/mL)	na	na	5.16	8.03	12.3
AUC_{last} (µg·h/mL)	na	na	441	704	1260

na = not available (not tested); BW = body weight; [1]n = 1.

Source: Applicant's study report, Study B2303

If lumefantrine concentrations of all children in Study B2303 were pooled per treatment, C_{max} was 7.69 and 6.27 µg/mL and AUC_{last} was 636 and 574 µg·h/mL for the crushed and the dispersible tablet, respectively. Overall, lumefantrine exposure in pediatric patients was comparable to that reported recently in literature in adult malaria patients given the 6-dose regimen of co-artemether. In one study conducted in adult patients in Thailand, median C_{max} was 6.98 µg/mL and AUC_{last} was 410 µg·h/mL. Another study conducted in malaria pediatric and adult patients in Africa showed C_{max} of around 7.0 µg/mL in children up to 15 years (up to 25.0 kg body weight on average), and of 5.60 µg/mL in patients ≥15 years (i.e. up to 56.3 kg on average). A previous Novartis sponsored study in adult malaria patients Study A025 showed median (model derived) C_{max} of 9.0 µg/mL and AUC of 561 µg·h/mL. Taken together, with the dose regimens and body weight groups used in the pediatric studies, the systemic exposure to lumefantrine in children is in the same order of magnitude as that in adults.

5.2.2 Sex

The influence of age, sex and bodyweight on the PK of lumefantrine was evaluated in malaria patients using a model-based population approach combining full (rich) profiles and sparse data. This prospective population evaluation was conducted using data from Study A025 conducted in malaria patients in Thailand. The evaluation showed that age, body weight and gender had no effect on any of the main PK parameters of lumefantrine.

5.2.3 Race

There was no formal investigation of the effect of race on the PK of co-artemether. Coartem studies have been conducted in ethnically diverse areas of the world, e.g. Africa, Southeast Asia.

5.2.4 Hepatic and Renal Impairment

No specific pharmacokinetic studies have been carried out in patients with hepatic or renal impairment.

Upon review of the clinical efficacy data, it was noted by Dr. O'Shaughnessy that in adult patients with mild to moderate renal impairment, the 28-day cure rate and Parasite Clearance Times (PCT) and Fever Clearance Time (FCT) were similar compared to patients with normal renal function. In pediatric patients, there were no clear effects on the 28-day cure rate and

FCT between patients with mild, moderate or severe renal impairment. It is unclear why PCT was shorter in pediatric patients with severe renal impairment nonetheless, all patients with renal impairment cleared blood parasites within 48 hours.

In adults, the 28-day cure rate decreased, and PCT and FCT were slower as baseline hepatic impairment declined from mild, moderate, and severe compared to patients with normal hepatic function. An assessment of efficacy in patients with severe hepatic function impairment base is limited due to the low numbers of patients (n = 17) in the severe hepatic impairment group.

In pediatric patients, no clear effects of baseline hepatic function on efficacy were apparent in patients with mild to moderate hepatic impairment compared to those with normal hepatic function. PCT and FCT were slower in patients with moderate to severe hepatic impairment. There were too few patients with severe impairment (n = 2) to make a definitive conclusion on efficacy in patients with severe hepatic impairment.
In summary, patients with hepatic impairment had decreased cure rates and longer time to parasite clearance. However, hepatic function improved in the majority of patients who were treated with Coartem suggesting that hepatic impairment at baseline was due to *P. falciparum* infection.

There were no adult patients with severe renal impairment and only a few patients with severe hepatic impairment (17 adults and 2 children) in the clinical trials. There were 92 pediatric patients classified by the applicant as severe renal impairment. *P. falciparum* infection combined with evidence of severe organ dysfunction (renal impairment, jaundice) would indicate severe malaria and patients with severe malaria would ordinarily have been excluded from these studies of uncomplicated malaria.

According to Dr. Lim's clinical safety review, most patients with acute malaria present with some degree of related hepatic and/or renal impairment. In clinical studies, the adverse event profile did not differ in patients with mild or moderate hepatic impairment compared to patients with normal hepatic function. In addition, the adverse event profile did not differ in patients with mild or moderate renal impairment compared to patients with normal renal function.

Therefore, the labeling will reflect the above clinical findings and no specific dose adjustments will be recommended for patients with mild to moderate renal or hepatic impairment. The labeling will also reflect that caution should be exercised when administering Coartem Tablets in patients with severe hepatic or renal impairment, since there were too few patients included in the clinical trials to make any definitive conclusions.

5.3 Other Notable Issues

5.3.1 Exposure-Response

The exposure-response (E-R) response relationship of Coartem was evaluated in malaria patients based on two studies conducted in Thailand (Studies A012 and A025). Study A012 (260 patients) tested three different dose regimens over 2 days, i.e. either 3x4 tablets, 4x2

tablets or 4x4 tablets. Study A025 (359 patients) compared the 4-dose regimen (2 days) with the 6-dose regimen given over 3 or 5 days.

Lumefantrine AUC was identified as the key pharmacokinetic parameter influencing the 28-day cure rate, i.e. higher lumefantrine AUC significantly increases the chance of cure. The extent of systemic exposure to lumefantrine is thus clearly associated with cure, and its long lasting exposure/effect when co-administered with artemether is to prevent recrudescence. The effect of dosage regimen was found to be significant, with lower dose regimen being associated with a lower cure rate compared to higher dose regimens. As described above, cure rates in study 025 were 97% and 99% with the 6-dose regimen (over 2 or 3 days, respectively) versus 83% with the 4-dose regimen.

The effects of artemether and DHA AUCs on cure rate were not found to be significant. However, these two compounds were found to influence the parasite clearance time (PCT) in a similar way, i.e. a higher AUC of these compounds was found to decrease PCT. In contrast, lumefantrine had no effect on PCT. This confirmed that most of the parasite clearance in the first 48 h of treatment is due to artemether and DHA.

Based on the high cure-rates (90-95%) observed in the pivotal clinical trials in adults and pediatric patients, further extensive evaluation of the E-R relationships was considered unnecessary. Moreover, there are no labeling changes based on the E-R analysis conducted by the applicant and thus extensive review was considered unlikely to be useful from a labeling perspective. The E-R analysis indicates that the 6-dose regimen is better than the 4-dose regimen and that no association of exposure and safety was discovered.

5.3.2 Thorough QT study

Since lumefantrine is chemically related to halofantrine, an antimalarial known to be associated with significant prolongation of the QT interval, a Through QT study (Study A2101) was conducted by the applicant. Coartem was administered orally as a 6-dose regimen 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.

In addition to conducting the through QT study (TQT), the applicant obtained ECGs in the clinical trials. DSPTP requested a consult from the QT-IRT and asked them to comment on whether or not the TQT study was conducted appropriately and on the clinical significance of the QT prolongation in adults and children seen in the healthy volunteer studies and in the malaria clinical trials. The following is a summary of QT-IRT findings:

The QT interval in Study A2101 was measured using Fridericia's correction formula (QTcF). Table 5 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 ($\Delta\Delta$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.

Reviewer's Comment: Fridericia's correction for QT is more accurate than Bazett's correction in subjects with altered heart rates. Patients with malaria in the clinical trials often had elevated heart rates until parasitemia began to resolve. QT correction by Fridericia's formula was used for analysis of ECGs in the clinical trials, as well as in this healthy volunteer study.

The largest lower bound of the two-sided 90% CI for the ΔΔQTcF 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 1: Largest Time-Matched Increase in QTcF by Treatment Group

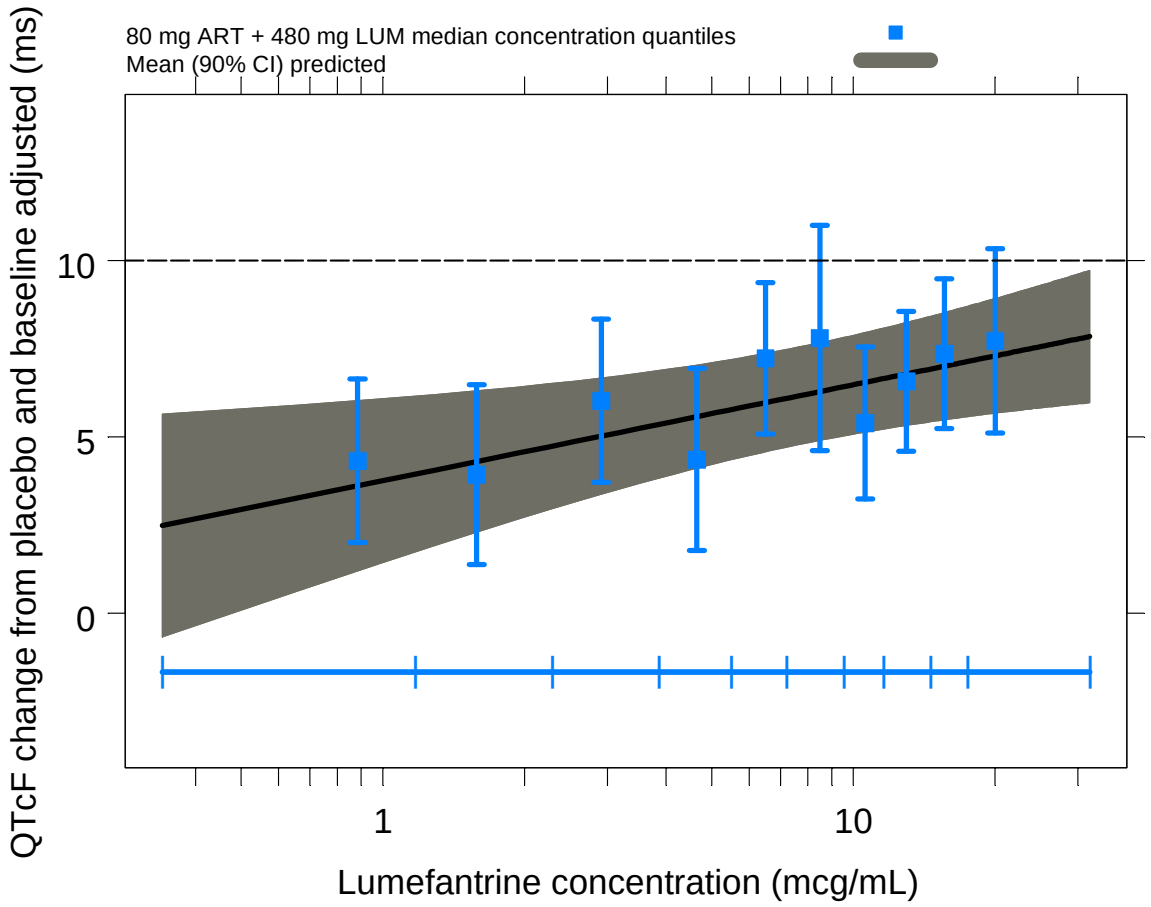
Treatment	Time, hr	ΔΔQTcF, ms	90% CI, ms
Coartem	72	7.29	(3.6, 11.0)
Moxifloxacin	61*	14.1	(8.9, 19.4)

* Moxifloxacin was administered at time 60-hours
Source: Reproduced from the QT-IRT review, NDA 22-268

Significant positive lumefantrine concentration-ΔΔQTcF relationship was identified (

Figure 1). Based on a linear relationship, the predicted mean (90% confidence interval) ΔΔQTcF 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 1: Mean (90% CI) predicted ΔΔQTcF vs. Lumefantrine Concentration (black line and shaded grey area) and observed median-quartile concentrations and associated mean ΔΔQTcF (90% CI)



Source: Reproduced from the QT-IRT review, NDA 22-268

Only the therapeutic dosing regimen of Coartem was tested in this TQT 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 µg.h/ml) did not exceed the exposure level in healthy subjects (mean AUC∞ was 1320 µg.h/ml). The lumefantrine C_{max} ranged between 5.72 ± 2.91 µg/mL to 10.5 ± 6.39 µg/mL in malaria patients and between 5.09 ± 1.9 µg/mL to 28.3± 13.6 µg/mL in other studies of healthy volunteers. The highest C_{max} observed in other healthy volunteer studies exceeds that seen in this study (~16 µg/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 ~30 µg/mL would be <10 msec. Also, the inter-subject variability was high (~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.

5.3.3 Bioavailability of Various Tablet Formulations

Formulation F81 was the original Chinese formulation manufactured at the Academy of Military Medical Sciences (AMMS) in People's Republic of China and was used in Study ABMO2, one of the eight primary clinical safety and efficacy studies. The Final Market Image (FMI) formulation (F4) and the formulation intended for use in the US, was used in five PK studies in healthy volunteers and in seven of the eight primary clinical safety and efficacy studies: A023, A025, A026, A028, A2401, A2403, and B2303.

No relative BA study was conducted to compare the clinical trial formulation (F81) and the to-be-marketed formulation (F4). Given that there are 7 clinical trials which demonstrated effectiveness and safety of Coartem F4 formulation, a pivotal BE study to compare the F4 and F81 formulations was not conducted. The two formulations are markedly different in terms of inactive ingredients as shown below:

1.3 Composition of clinical formulations

Table 1-2 Composition of tablets formulations (mg/tablet)

Component	20 + 120 mg Tablet F.81[1]	20 + 120 mg Tablet F.4	20 + 120 mg (b) (4)
Artemether	20.0	20.0	20.0
Lumefantrine	120.0	120.0	120.0
(b) (4)	b) (4)		
Cellulose microcrystalline			
Croscarmellose sodium			
(b) (4)			
Hypromellose			
Silica, colloidal anhydrous			
Polysorbate 80			
(b) (4)			
Magnesium stearate			
(b) (4)			
Tablet weight	(b) (4)	240.0	(b) (4)

Source: Chemistry, Manufacturing, and Control (CMC), Drug Product, p.39

According to the applicant there were no direct PK comparisons of formulations F81 and F4 in the NDA studies, and across-study comparisons are complex and difficult because of the high inter-subject (and across-study) variability in drug exposure parameters and the different conditions of administration, in particular food intake. Across-study comparisons of clinical outcomes showed comparable clinical efficacy outcomes between formulations F4 (Study A023) and F81 (Study ABMO2) as shown below:

Table 3-15 Comparison of efficacy results obtained with formulations F4 and F81 used in Chinese studies

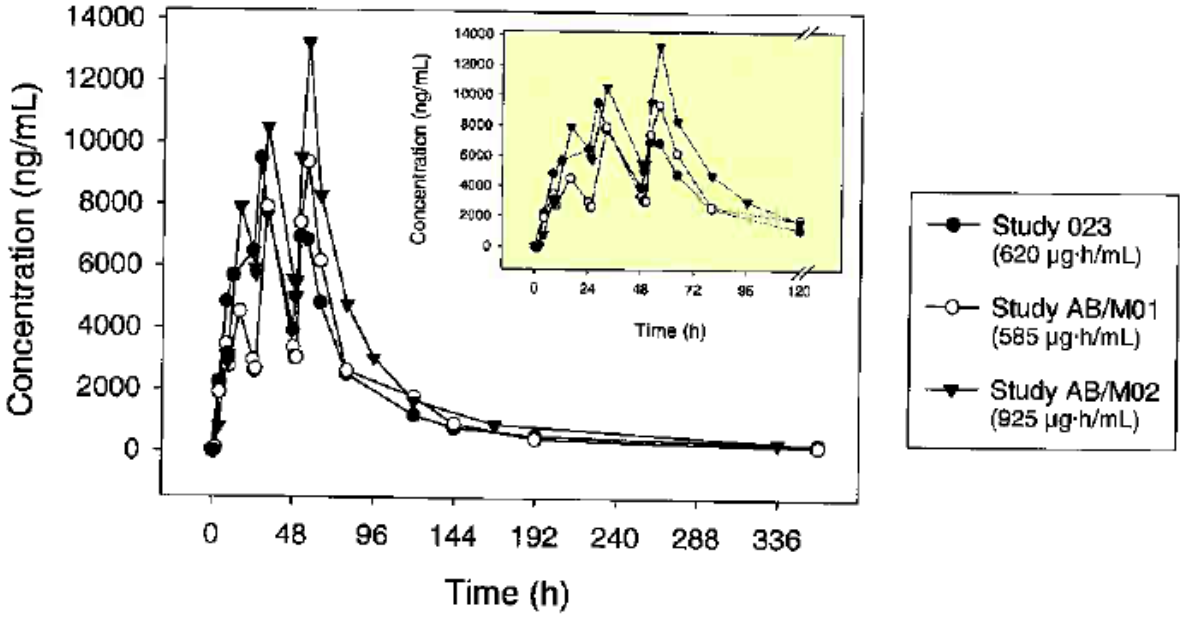
Efficacy endpoints	F4 (study 023)	F81 (study AB/M01)	F81 (study AB/M02)
28-day cure rate [95% CI]	98% [89.6%,100%]	96.1% [91.8%,98.7%]	100% [92.9%,100%]
Time to parasite clearance [95% CI]	30 h [24h,30h]	30 h [30h,36h]	30 h [30h,36h]
Parasite reduction at 24 h 25th-75th percentiles	99.9% 99%-100%	99.4% 97.9%-100%	99.3% 93.5%-100%
Time to fever clearance [95% CI]	21 h [12h,24h]	18 h [12h,24h]	24 h [12h,36h]

Source: Table 3-15 in applicant's Summary of Biopharmaceutics and Clinical Pharmacology Studies

Therefore, the applicant concluded that these results assessed the clinical bioequivalence between the Chinese formulation F81 and formulation F4 intended for the market.

The mean full plasma profiles of lumefantrine observed in Studies A023 and ABM02 are shown below. The AUC was highest in study ABM02 (925 µg·h/mL) and about 35% lower in Study A023 (620 µg·h/mL).

Figure 3-11 Mean plasma profiles of lumefantrine observed in studies 023, AB/M01 and AB/M02. AUC(0-t) are given in brackets



Source: Figure 3-11 in applicant's Summary of Biopharmaceutics and Clinical Pharmacology Studies

Based on across study comparisons performed by the Clinical Pharmacology reviewer, the PK estimates for artemether, DHA and lumefantrine following administration of the two formulations across various studies is given below. The Coartem doses used in the studies are the 6-dose regimen i.e., 4 tablets of 20mg artemether/120 mg lumefantrine gives as 6 doses. The $AUC_{0\text{-}8,\ FD}$ and $AUC_{0\text{-}8,\ LD}$ for F81 in Study ABMO2 and F4 in Study A028 are similar, although the C_{max} for F81 appears slightly higher than for F4 (84 vs. 66 ng/mL).

Study #	**Formulation used**	**Artemether**	
		C_{max} (ng/mL)	(ng-h/mL)
A023	F.4	58.5±30.8	$AUC_{0\text{-}360}$ 767±671
ABM02	F.81	83.9±62	$AUC_{0\text{-}672}$ 1711±770 $AUC_{0\text{-}8,\ FD}$ 503 $AUC_{0\text{-}8,\ LD}$ 260
A028	F.4	66.2±54.3	$AUC_{0\text{-}8,\ FD}$ 535±272 $AUC_{0\text{-}8,\ LD}$ 211±109

Notes: FD – first dose, LD – last dose

Study #	Formulation used	DHA	
		C_{max} (ng/mL)	(ng-h/mL)
A023	F.4	96.7± 49.9	AUC_{0-360} 1160 ±553
ABM02	F.81	217.7±65.5	AUC_{0-672} 3032±1390
A028	F.4	205±102	AUC_{0-8} 604±259

Study #	Formulation used	Lumefantrine	
		C_{max} (µg/mL)	(µg-h/mL)
A023	F.4	10.9±4.4	AUC_{0-360} 620 ±356
ABM02	F.81	13.3±5.7	AUC_{0-672} 924.9±403
A025	F.4	11.0±6.8	AUC_{0-inf} 1132±771

Source: Clinical Pharmacology review, by Dakshina Chilukuri, Ph.D.

Reviewer's Comment: The applicant conducted an exposure-response analysis using five 4-dose regimen studies and one 6-dose regimen study. The Clinical Pharmacology reviewer states that no relationship was established by the applicant between the systemic exposure of artemether and dihydroartemisinin (DHA) and clinical efficacy. The only caveat is that the applicant used data from only one 4-dose clinical study in their exposure-response analysis for artemether and DHA. High concentrations of lumefantrine were associated with a reduced probability of recrudescence in the applicant's analysis. The exposure-response analysis for lumefantrine included data from only one 6-dose study (A025) and data from the other 6-dose clinical trials was not used to confirm the results; therefore, the results should be interpreted with caution. Across the clinical studies in patients, the estimates of exposure are highly variable. Also, as stated previously, food increases the exposure to artemether and lumefantrine and is necessary to ensure adequate exposure. The magnitude of the effect of food on exposure to artemether and lumefantrine is much greater than the magnitude of the differences between the formulations of F81 and F4.

Therefore, given that seven of the eight primary safety and efficacy trials were conducted using F4 and the efficacy results are similar between Studies A023 (F4) and ABMO2 (F81), both studies were conducted at the same site in China, the Clinical Pharmacology reviewer felt comfortable that a pivotal BE study between the two formulations was not necessary for approval.

6 Clinical Microbiology

This NDA should be approved with respect to Microbiology pending an accepted version of the labeling. The Microbiology Reviewers were Aaron Ruhland, Ph.D. and Simone Shurland, Ph.D. The following summary is excerpted from their reviews.

6.1 Mechanism of Action

Coartem is a fixed dose combination of artemether and lumefantrine in the ratio of 1:6. 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 endoperoxide moiety 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 were shown to inhibit nucleic acid and protein synthesis.

6.2 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 ^{3}H–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.* Artemether IC_{50} values were similar to DHA.

Combination of artemether with lumefantrine in the ratio of 10:1 and 1:100 was tested against 3 strains of *P. falciparum* (K1, T-996, and LS-21). Results, expressed as IC_{50} and IC_{90} values, show that a combination of artemether with lumefantrine to be 3 – 100 fold more active than either drug alone.

6.3 Activity In Vivo

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

Mice infected with the N strain of *P. berghei* and treated at time of infection with 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.

Monprimarys (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 in a faster reduction of parasitemia and clearance of parasites from blood in all animals than either drug alone. Similar results were observed in monprimarys infected with *P. falciparum.* There appears to be no antagonism between artemether and lumefantrine.

6.4 Drug Resistance

In vitro studies in which the erythrocytic forms of *P. falciparum* K1 strain were serially passaged (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 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 IC_{50} greater than 8.9 ng/mL. Molecular typing indicated that these isolates had a *PfATPase*6 –S769N mutant allele. Re-culture of the stored isolates with the mutant allele *PFATPase* 6-S769N in the absence of artemether for 3-weeks showed a decrease in IC_{50} 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+ lumefantrine exists. A study also showed resistance to artemether may be unstable often resulting with the reversal to a more sensitive strain. Clinical relevance of such an effect is not known.

6.5 Clinical Microbiology

The applicant submitted 24 clinical studies supporting the efficacy of Coartem in the treatment of uncomplicated falciparum malaria in China, Thailand, Kenya, Nigeria, Tanzania, Mozambique, Mali, Republic of Benin as well as non-immune travelers from Germany, Switzerland and Colombia. Of the 24 studies, datasets were available for 8 clinical studies. The parasitological evaluations were performed using Giemsa stained thick and/or thin smears. Coartem was nearly 100% effective in accomplishing microscopically confirmed parasite clearance within 7 days of treatment with a median parasite clearance time (PCT) of 34 hours. Parasites subsequently reappeared in some patients by day 28. Irrespective of the dose and regimen of Coartem, the overall cure rates across all studies in the intent to treat (ITT) and per protocol (PP) populations were approximately 89% and 97%, respectively. Gametocyte counts were performed in each trial and results show that the time to clearance of gametocytes was longer than the asexual PCT though most patients who presented with gametocytemia at baseline were free of gametocytes by day 7. However, some patients who presented with gametocytes at baseline remained positive for gametocytes until their last examination.

6.6 Other Notable Issues

In six of the eight primary studies, the sponsor presented the 28-day cure rates as PCR-corrected cure rates, based on genotyping, in the proposed package insert. Genotyping was done to differentiate recrudescence from a new infection. The applicant utilized two different polymerase chain reaction (PCR) techniques, in 2 different laboratories. The PCR assay performed at the Shoklo Malaria Research Unit was used to analyze samples from Studies A025, A026, and A028. Samples from Studies A2401, A2403 and B2303 were tested by PCR and restriction fragment length polymorphism assays at the (b) (4) However, due to a lack of performance characteristics of the assay and quality control, the results of these analyses should be interpreted with caution and only uncorrected cure rates should be used in determining the efficacy of Coartem.

Reviewer's Comment: As shown below in the clinical efficacy section, 28-day cure rates are only reported as uncorrected parasitological cure rates.

7 Clinical/Statistical - Efficacy

In general, the clinical and statistical reviewers agreed with the applicant's efficacy endpoints and analyses. In general, there were no major issues of disagreement between the reviewers, the CDTL, or the applicant on the analyses of the data and interpretation of outcomes in the NDA.

The Clinical Efficacy review was performed by Elizabeth O'Shaughnessy, M.D. Statistical reviews were conducted by Xianbin Li, Ph.D. and Lan Zheng, Ph.D. A Statistical Team Leader review was also completed by Karen Higgins, Sc.D. The following summary is an excerpt from Dr. O'Shaughnessy review, which relies, in part, on information from the statistical reviews.

7.1 Clinical/Statistical Efficacy Conclusions

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. The results from these studies were robust (i.e., highly statistically significant and maintained when examined by gender, age, and baseline parasite counts).

Study A025 compared a 4-dose regimen with two 6-dose regimens (a 6-dose over 60 hours regimen and a 6-dose over 96 hours regimen) in Thailand. In the ITT population, the 28-day cure rate of 4 doses of Coartem was 71% and both 6-dose regimens of Coartem resulted in numerically higher cure rates (81% for 6-doses over 60 hours and 86% for 6-doses over 96 hours). The 6-dose regimen given over 60 hours was chosen by the applicant for further study due to a simpler dosing administration. The 6-dose over 60 hours regimen showed significantly higher cure rates compared to the 4-dose regimen in the evaluable population, but not the ITT population. Despite the lack of significantly higher results in the ITT population, the clinical and statistical reviewers felt the results were not cause for concern because the cure rates of the 6 dose regimens were higher than the 4-dose regimen in this study and higher than the 4-dose regimen in the previous studies (ABMO2 and A023). In addition, in the subsequent 6-dose studies the cure rates were consistent with the 6-dose, 60 hour regimen in Study A025 (i.e., greater than 80% in the ITT population, with the exception of Study A2401). Given the severity of the disease and the lack of concern of the safety of the 6-dose regimen compared to the 4-dose regimen (as concluded by Sue Lim, M.D., in safety review), a 6-dose regimen of Coartem appears appropriate.

Reviewer's Comment: As noted by Dr. Higgins, in her review, a limitation with the most important studies in the NDA, Studies ABMO2, A023, is that they were conducted in a very limited number of investigative sites. Both ABMO2 and A023 were conducted in one site in China, while A025 was conducted in two sites in Thailand. Additionally, Studies A026 and A028, discussed below, were also conducted in these same two sites in Thailand. This reliance

on a limited number of sites may limit our ability to generalize the results to a larger population or different geographic areas. However, other studies, both 4-dose and 6-dose, contained within this NDA were conducted in geographically diverse areas (various countries in Africa, Vietnam, Bangladesh, Brazil, Columbia, and Europe) and supported the efficacy of Coartem.

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. This was due to the fact that in the ITT population, 31 patients (19%) had missing data (most lost-to-follow up), but there were also 11 patients (7%) who were efficacy failures. In the evaluable population, the 28-day cure rate was over 90%.

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.

The applicant is requesting an indication for treatment of mixed infections including *P. falciparum*. According to the 2006 WHO Guidelines for the Treatment of Malaria[6], 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 (*P. vivax 14/43 or 33%*), 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.

7.2 Notable Efficacy Issues

7.2.1 Adults with Bodyweight ≥ 70 kg

As discussed earlier, all the studies in the NDA were conducted outside the US. Since adult patients in developing countries may be of smaller size than the typical US adult, the clinical and statistical reviewers evaluated the results of studies by body weight (i.e., < 70 kg and ≥ 70 kg). As can be seen in the table below, very few patients were enrolled with a weight of 70 kg or above, with the exception of Study A2401, which was performed in European travelers. The efficacy appears somewhat low in the larger patients (67%) in Study A2401, but was impacted by the amount of missing data in the ITT population (24% in the ≥ 70 kg patients compared to 8% for patients < 70 kg). The rates of efficacy failure were also slightly higher in the ≥ 70 kg group (8%) compared to the < 70 kg group (5%).

[6] www.who.int/malaria/docs/TreatmentGuidelines2006.pdf

	Study A025		Study A026	Study A028	Study A2401*	Total
	4-dose	6-dose 60 hr.	6-dose			
≥70kg	1/1 (100%) 95% CI [2.5%, 100%]	2/3 (67%) 95% CI [9%, 99%]	0/1 (0) 95% CI [0, 97%]	4/4 (100%) 95% CI [40%, 100%]	66/98 (67%) 95% CI [57%, 77%]	73/107 (68%) 95% CI [59, 77%]
< 70 kg	84/119 (71%) 95% CI [61%, 79%]	94/115 (82%) 95% CI [73%, 88%]	130/149 (87%) 95% CI [81%, 92%]	144/160 (90%) 95% CI [84%, 94%]	54/64 (84%) 95% CI [73%, 92%]	506/607 (83%) 95% CI [80%, 86%]

* 3 subjects did not have weight listed in study 2401
Source: Table created by Statistical Reviewer, Xianbin Li, Ph.D.

7.2.2 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 Malaria[7], 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, relapses occurred in about a third of patients (14/43; 33%), 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*, except in high transmission settings where the risk of reinfection is high.

A recommendation regarding approval or non-approval of Coartem for the treatment of acute uncomplicated malaria in patients with mixed infections including *P. falciparum* was discussed at the Anti-Infectives Advisory Committee Meeting on December 3, 2008. The review team discussed the committees recommendations after the meeting (see Section 9 for a summary of the discussion) and it was decided that efficacy information discussing the 43 patients with mixed infections of *P. falciparum* and *P. vivax* would be added to the Clinical Studies section of the labeling, but the applicant would not be granted an indication for mixed infection.

8 Safety

The clinical safety reviewers concluded that there was no safety signal that would preclude approval.

[7] www.who.int/malaria/docs/TreatmentGuidelines2006.pdf

The Clinical Safety Reviewers were Sue Lim, M.D. (integrated safety review) and Ozlem Belen, M.D., M.Sc., M.P.H. (pediatric safety). The following summary is excerpted from Dr. Lim's review.

8.1 Adequacy of the Safety Database and Foreign Marketing Experience

Safety data available for review included clinical trials and postmarketing data. In the clinical development program for Coartem, over 3500 patients with malaria were exposed to Coartem in 20 studies conducted between 1993 and 2007. In addition, a postmarketing database is available, since Coartem was first approved for clinical use in 1998. It is estimated that approximately (b) (4) patients have been treated with Coartem since this time, with 70% of treatment courses administered to children (under 35 kg body weight) and 30% in adults (above 35 kg body weight).

Data regarding exposure to Coartem during pregnancy was obtained from postmarketing data and an observational pregnancy study where over 500 subjects were exposed to Coartem.

8.2 Special Safety Concerns

In animal models, artemisinin derivatives such as artemether have been associated with neurotoxicity, particularly with pathways involved in hearing and balance. Therefore, AEs related to the nervous system and ear/labyrinth were selected out for further analysis. Nervous system disorders, particularly headache and dizziness, were commonly reported in both populations and, in most cases, were likely symptoms of malaria. In pediatric patients, analysis was further done according to pre-defined age strata, with no safety pattern observed to suggest cumulative neurotoxicity, or increased AEs in the younger patients. Similarly, no safety concerns could be found with respect to ear and labyrinth disorders in the pooled analyses.

As lumefantrine is chemically related to halofantrine, an antimalarial associated with prolongation of the QTc interval, particular attention was also paid to AEs affecting the cardiovascular system. A thorough QTc study showed that Coartem was associated with a mean maximum increase in QTcF relative to placebo of 7.29 msec (3.6, 11.0).

AEs related to the nervous system and ear/labyrinth were selected out for further analysis given previous known toxicities of the artemisinin derivatives. In animal models, artemisinin derivatives such as artemether have been associated with neurotoxicity, particularly with pathways involved in hearing and balance. Nervous system disorders, particularly headache and dizziness, were commonly reported in both populations and, in most cases, were likely symptoms of malaria. In pediatric patients, analysis was further done according to pre-defined age strata, with no safety pattern observed to suggest cumulative neurotoxicity, or increased AEs in the younger patients. Similarly, no safety concerns could be found with respect to ear and labyrinth disorders in the pooled analyses.

Postmarketing data provided additional reassurance on the absence of any specific nervous system, ear/labyrinth and QT safety signals.

8.3 Deaths, Serious Adverse Events, and Discontinuations due to AEs.

8.3.1 Deaths

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

Four pediatric patients died, all of whom were treated with the 6-dose regimen of Coartem in Africa. In all but one case the cause of death was infection (gastroenteritis, P. falciparum infection, unspecified infection, and hemorrhage).

None of the deaths were suspected by the investigators to be related to study treatment.

8.3.2 SAEs

Overall, there were few SAEs reported. In adults in the 6-dose Coartem group, 9 subjects (1.4%) experienced 22 SAEs. Six of the nine subjects were enrolled in Study A2401. The SAEs from this study were categorized as such because they led to hospitalization or prolongation of hospitalization. The table below summarizes the SAEs by patient.

Summary of 6-dose SAEs in the FDA adult pooled safety population

Subject number/ Study	SAE	Related to study medication?	Comments
11/A2401	1- liver function test abnormal 2 - hematuria 3 - malaise 4 - abdominal pain 5 -thrombocytopenia	SAEs 1, 2, 3 – no SAEs 4, 5 - unlikely	SAEs 1, 2, 3 were present at baseline Patient had hepatomegaly and splenomegaly on baseline physical exam which could account for SAEs 4,5
7/A2401	1 – blood bilirubin increased 2 – transaminases increased 3 – mental impairment 4 – disease progression 5 – vomiting	SAEs 1, 2 – possible SAEs 3, 4, 5 - unlikely	SAEs 1, 2 present at baseline but worsened on therapy
2/A2401	1 – chills 2 – pyrexia 3 – headache 4 – *Plasmodium falciparum* infection	Yes – efficacy failure	Efficacy failure
3/A2401	1 – hepatocellular damage	Possible	SGOT elevated at baseline but

Subject number/ Study	SAE	Related to study medication?	Comments
			worsened on therapy with co-artemether, paracetamol and metamizole
22/A2401	1 – endocarditis	No	
1/A2401	1 – electrocardiogram abnormal 2 – *Plasmodium falciparum* infection	SAE 1 – unlikely SAE 2 – efficacy failure	Efficacy failure
41/A025	1- typhoid fever	No	
28/A028	1 – dyspnea 2 – fluid overload	No	Iatrogenic
259/A026	1 – coma	Unlikely	Etiology of coma unknown but unlikely given temporal occurrence and confounders

Source: Table created by Clinical Safety reviewer, Sue Lim, M.D.

In summary, the majority of SAEs reported were likely related to malaria (subjects 11, 7) or malaria recrudescence/efficacy failure (subjects 2, 1). Two SAEs (both elevated transaminases) were possibly related to Coartem exposure in 2 subjects (subjects 7, 3). In both cases, a relationship to drug could not be ruled out.

Similar to the adult pooled population, there were few SAEs reported in the pediatric population, with 1.3% of subjects reporting SAEs in the 6-dose group (30 SAEs in 17 subjects). The table below summarizes the SAEs for the 6-dose standard tablet formulation. All subjects were enrolled in Study A2403.

SAE summary in the FDA pediatric pooled safety population receiving the 6-dose standard tablet regimen

Subject number	SAE	Related to study medication?	Comments
204	1- gastroenteritis 2 – death	SAEs 1, 2 - No	Temporal presentation of SAE 6 days after last dose makes it unlikely to be related to study drug
149	1 – hepatitis viral	No	Baseline liver enzymes elevated prior to initiating study drug
145	1 – convulsion 2 – *Plasmodium falciparum* infection	SAEs 1, 2 – Yes, efficacy failure	Efficacy failure
222	1 – pneumonia primary atypical 2 – urticaria	SAE 1 – No SAE 2 - possible	Urticaria following 2 doses of study drug which resolved 3 days after discontinuing study drug on antihistamine and chlorapheniramine

Source: Table created by Clinical Safety reviewer, Sue Lim, M.D.

In summary, of the SAEs reported with the 6-dose standard 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 with study drug, she received paracetamol several days later with no recurrence of the urticaria.

8.3.3 Discontinuation due to AEs

Discontinuation of Coartem due to adverse drug reactions occurred in 1.1% of patients treated with the 6-dose regimen overall: 0.2% (1/647) in adults and 1.6% (21/1332) in children. The most common adverse drug reaction leading to discontinuation in children was vomiting, which was specified in one study protocol (Study B2303) as criteria for discontinuation.

8.4 General AEs

The most frequently reported treatment emergent adverse events (AEs) in both the pooled adult and pediatric populations were likely related to malaria signs and symptoms. In adults, the most frequently reported AEs (> 30%) were headache, anorexia, dizziness, asthenia, arthralgia, and myalgia. In children, the most common AEs (> 15%) were pyrexia, cough, and vomiting, and *Plasmodium falciparum* infection. Most adverse reactions were mild, and did not lead to discontinuation of study medication.

8.5 Laboratory AEs

The range of clinical laboratory parameters evaluated in the Coartem development program was somewhat limited, reflecting the local laboratory facilities that were available at the study centers. In addition, there were differences between studies in the parameters evaluated, and the time points at which assessments were made. Central laboratories were not used in the analysis of routine clinical laboratory parameters. Laboratory data are presented separately for the adult and pediatric pooled safety populations.

For hematology, in adults anemia was reported more than any other preferred term, and occurred about 4% in both the 4-dose and 6-dose Coartem groups. There were only 2 cases of severe anemia (one 4-dose Coartem and one 6-dose Coartem treated subject). The other cases of anemia, and all other hematology AEs were of either mild or moderate severity.

As in the adult population, anemia was by far the most common AE in the pediatric population (22% for 4-dose Coartem and 9% for 6-dose Coartem). Anemia was commonly reported in the Day 1-3 time window for the Coartem 4-dose regimen, and in the Day 4-8 window for the 6-dose regimen. Increased reticulocyte count, which could represent hemolysis, was observed in three patients treated with the Coartem 6-dose regimen. These patients were all from Study B2303 (2 treated with the standard tablet, 1 with the dispersible tablet). The reticulocyte increases were reported as mild, and hemoglobin levels increased during the study in all patients, and all showed increases in leukocyte and platelet counts concomitantly with the reticulocyte count increases. None of the patients with reticulocyte increases had severe anemia.

Liver transaminases were also evaluated in depth. In adults, the Coartem treatment groups showed decreases from baseline at all time windows in aspartate aminotrasferase (AST), and decreases from baseline in alanine aminotransferase (ALT) at most time windows (4-dose group showed increases at the Day 5-12 and Day 27-40 time window; 6-dose regimen at the Day 5-12 window). Shift table analysis from baseline to each time window showed only very few patients shifted to grade 3 or 4. Most patients who were did not have normal values at baseline tended to show shifts to lower grades particularly in later time windows. No patient in the 6 dose regimen had a Grade 3 or 4 toxicity that had not shifted to lower than Grade 3 or 4 by their last visit.

The adult and adolescent pooled safety population was searched by the reviewer for patients with baseline transaminases values grade 0, 1 or 2 who experienced an increase by 2 Grades, and at least up to Grade 3 (corresponding to 5.1 to 10 x ULN). Six patients in this category had normal ALT and AST at baseline, three had an increase of AST between 5 and 10 x ULN, and three for ALT (two of them occurring at day 28 and day 42, respectively). For three of these patients, an increase in ALT or AST up to 6 x ULN was observed, two of which normalized.

The adult and adolescent pooled safety population was searched for cases potentially qualifying for Hy's Law cases, i.e. cases of elevated total bilirubin > 2 x ULN with ALT/AST elevations >3 x ULN, in a context of pure hepatocellular injury, without cholestasis (i.e. with normal alkaline phosphatase), and for which no other reason can be found to explain the combination of increased ALT/AST and total bilirubin. There were three such patients receiving the 6-dose regimen, all from Study A028, and ten patients treated with the 4-dose regimen who had post-baseline values of ALT or AST $\geq$ 3 x ULN in association with total bilirubin $\geq$ 2 x ULN. In twelve of these patients, alkaline phosphatase levels were also elevated. All patients but one had abnormal values at baseline. In nine cases, the values improved during the study.

Mean and median total bilirubin showed decreases from baseline at all time windows in all Coartem groups, with similar findings for comparator treatment groups.

As in the adult population for both AST sand ALT, most pediatric patients in the Coartem groups with baseline grades above 0 shifted to lower Grades. There were very few patients with shifts to Grade 3 or 4 at any time window for either of these transaminases. Shift table analysis based on baseline to worst post-baseline value showed that of 6 Coartem patients with Grade 4 AST, 4 still had Grade 3 or 4 abnormalities at their final visit: these included one patient who had had a Grade 4 abnormality at baseline.

The pediatric pooled safety population was also searched by the reviewer for patients with baseline transaminase values of Grade 0, 1 or 2 who experienced an increase by 2 Grades, and at least up to Grade 3 (corresponding to 5.1 to 10 x ULN). Four patients with normal transaminases levels at baseline, had an increase between 5 and 10 x ULN, which normalized at last visit (day 42/43) and two patients experienced delayed increases above 10 x ULN, one of which normalized while the other was detected at the last study visit.

The pediatric pooled safety population was also searched for cases potentially qualifying for Hy's Law and revealed two patients. One patient was treated with the 6-dose regimen of Coartem in Study A2403. He had abnormal values at baseline attributed to a viral hepatitis by the investigator but not documented by serology that improved during the study. One patient was treated with the 4- dose regimen in Study A003. He had only a slight elevation of AST at baseline, which increased up to 3.5 x ULN at day 4 and normalized at day 15.

8.6 Primary Reviewer's Comments and Conclusions

Based on pooled analyses of over 3400 subjects (1434 adult subjects,1991 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 5.3% 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, cough, 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 (somnolence).
    - 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. All were unlikely to be related to study drug.
- Children:
    - 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
    - 2 nervous system disorder AEs coded as severe in the 6-dose Coartem group: 1 convulsion (due to meningitis) and 1 headache (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.

9 Advisory Committee Meeting

A meeting of the Anti-Infectives Advisory Committee to discuss NDA 22-268 was held on December 3, 2008. The following is a Quick Minutes summary prepared by Janie Kim from the Advisors and Consultants Staff.

Quick Minutes
Meeting of the Anti-Infective Drugs Advisory Committee
December 3, 2008

The following is an internal report which has not been reviewed. A verbatim transcript will be available in approximately two-four weeks, sent to the Division and posted on the FDA website at http://www.fda.gov/ohrms/dockets/ac/cder08.html#AntiInfective.

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

The Anti-Infective Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on December 3, 2008, at the Hilton/Washington DC Ballroom, 8727 Colesville Road, Silver

Spring, Maryland. Prior to the meeting, members and invited consultants were provided copies of the background material from the FDA and the sponsor. The meeting was called to order by Thomas A. Moore, M.D. (Committee Chair); the conflict of interest statement was read into the record by Janie Kim, Pharm.D. (Designated Federal Official). There were approximately 100 persons in attendance. There was one (1) speaker for the Open Public Hearing session.

Issue: The committees will discuss NDA 22-268, artemether 20 mg/lumefantrine 120 mg, sponsored by Novartis Pharmaceuticals Corporation, for the proposed indication of treatment of acute, uncomplicated malaria infection due to *Plasmodium falciparum* or mixed infections including *P. falciparum*.

Attendance:
Anti-Infective Drug Advisory Committee Members Present (Voting):
W. Kemper Alston, M.D., Archana Chatterjee, M.D., Dean Follmann, Ph.D., Matthew Goetz, M.D., Sheldon Kaplan, M.D., Susan Rehm, M.D., Kent Sepkowitz, M.D., Margo Smith, M.D., Melvin Weinstein, M.D.

Anti-Infective Drug Advisory Committee Member Present (Non-Voting):
John Rex, M.D. (Industry Representative)

Special Government Employee Consultants Present (Voting):
Diane Aronson (Consumer Representative), Chandy John, M.D., Dennis Kyle, Ph.D., Thomas Ten Have, Ph.D., M.P.H., Martin Wolfe, M.D.

Regular Government Employee Consultants Present (Voting):
Alan Magill, M.D., Philip E. Coyne, Jr., M.D., MSPH, Laurence Slutsker, M.D., M.P.H.
Guest Speaker Present (Non-Voting): None.

Anti-Infective Drugs Advisory Committee Members Not Present:
Peter Katona, M.D., Annie Wong-Beringer, Pharm.D. (Consumer Representative)

FDA Participants (Non-Voting): Edward Cox, M.D., M.P.H., Renata Albrecht, M.D., Elizabeth O'Shaughnessy, M.D., Sue Lim, M.D., Joette Meyer, Pharm.D.

Designated Federal Official:
Janie Kim, Pharm.D.
Open Public Hearing Speaker:
Merrill Goozner, Integrity for the Public Interest, Center for Science in the Public Interest

The agenda was as follows:
Call to Order and Introductions **Thomas A. Moore, M.D. (**Committee Chair)

Conflict of Interest Statement **Janie Kim, Pharm.D.**
Designated Federal Official
==========

Welcome & Introductory Remarks	Renata Albrecht, M.D. Director, Division of Special Pathogen and Transplant Products (DSPTP) Office of Antimicrobial Products (OAP)
Sponsor Presentation Introduction	Novartis Pharmaceuticals Corporation Mathias Hukkelhoven, Ph.D. Senior Vice President, Global Head Drug Regulatory Affairs Novartis Pharmaceuticals, Inc.
Disease Background & Epidemiology	Philip Rosenthal, M.D. Professor of Medicine University of California

	San Francisco School of Medicine
Clinical Development Program and Efficacy/Safety	Anne Claire Marrast, M.D. Global Program Medical Director Novartis Pharma AG
Benefit/ Risk Assessment	Philip Rosenthal, M.D.
Questions to the Presenters	
FDA Presentations	
Clinical Efficacy Presentation	Elizabeth O'Shaughnessy, M.D., Medical Officer, DSPTP, OAP
Clinical Safety Presentation	Sue Lim, M.D., Medical Officer, DSPTP, OAP
Questions to the Presenters	
Open Public Hearing	
Questions to the AIDAC and AIDAC Discussion	
Adjourn	

Questions to the 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 uncomplicated *Plasmodium falciparum* malaria, including demonstrating the contribution of artemether and lumefantrine to the treatment effect? (vote yes or no)
Vote : Yes= 18 No = 0 Abstain = 0

Please discuss your rationale for your vote.

Committee members agreed that the clinical data demonstrated the efficacy of the proposed 6-dose regimen of Coartem for the treatment of uncomplicated Plasmodium falciparum malaria but some members expressed concerns about the limited number of non-immune traveler, the intended patient population in the U.S., who were enrolled in the clinical studies.

If the answer is no, what additional information is needed or what additional studies should be conducted (e.g., in vitro, preclinical, clinical)?

None of the Committee members voted "no."

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 uncomplicated P. falciparum malaria?
(vote yes or no)
Vote : Yes= 17 No = 1 Abstain = 0

a. Please discuss your rationale for your vote.

Committee members took into consideration the following factors in voting on the question:

- *Favorable risk benefit analysis for Coartem*
- *Record of safety with global use of the Coartem*
- *Confidence in FDA's ability to mitigate risks associated with the drug through labeling*

b. If the answer is no, what additional information is needed or what additional studies should be conducted (e.g., in vitro, preclinical, clinical)?

The Committee member who voted "no" to question 2 commented on the limited data on non- immune travelers (the anticipated patient population in the U.S.) and that there is potential for drug interactions between Coartem and other drugs.

3. Do you consider the data presented for patients co-infected with *P. falciparum* and *P. vivax* sufficient to demonstrate efficacy and safety of Coartem in treating these patients? (vote yes or no)

Vote : Yes= 9 No = 8 Abstain = 1

a. Please discuss your rationale for your vote.
Committee members took into consideration the following factors in voting on the question:

- *Narrow or broad interpretations of the question*
- *Limited data in patients with mixed P. falciparum and P. vivax infections*
- *Distinction between cure and radical cure for mixed P. falciparum and P. vivax infections*
- *The rarity of reported P. vivax infections in the U.S.*
- *The common practice of treating the more serious P. falciparum infections first and worrying about treating the P. vivax infections later.*

b. If the answer is no, what additional studies do you recommend?

Committee members discussed the following additional studies:

- *Studies of Coartem used in conjunction with Primaquine for the treatment of mixed infections with P. falciparum and P. vivax*
- *Additional studies with larger numbers of patients with mixed infections with P. falciparum and P. vivax*

4. If the answer to numbers 1 and 2 is yes, should any specific post-marketing studies be conducted?

Committee members considered the following post-marketing studies:

- *Pharmacokinetic/pharmacodynamic studies in special populations (e.g., pregnant, elderly, pediatric, obese or morbidly obese patients)*
- *Safety and efficacy studies following repeated use of Coartem*
- *Drug Interaction studies (Cytochrome P450 3A4 drugs, antiarrhythmics, other antimalarial drugs, drugs that prolong QT intervals [e.g., quinolones, antifungals])*

5. Is there specific efficacy, safety or other information that you would recommend be reflected in the Coartem product labeling?

Committee members discussed adding the following information to Coartem's product labeling:

- *Risks associated with use during pregnancy*
- *Limited information with regard to Geriatric/pediatric non-immune patients*
- *Possible QT prolongation associated with use of the drug*
- *Possible drug interactions with anti-arrhythmic, antidepressants, antifungals, other antimalarial drugs*
- *Information on dosage (e.g., pediatric, geriatric, obese patients) and administration (e.g., fatty foods, grapefruit)*
- *Limited information on efficacy in patients with mixed P. falciparum and P. vivax infections*

Please see the transcript for detailed discussion.

The session adjourned @ approximately 4:30 p.m.

10 Pediatrics

In the NDA submission, the safety and effectiveness of Coartem Tablets have been established for the treatment of acute, uncomplicated *P. falciparum* malaria in studies involving pediatric patients weighing 5 kg or more. The safety and effectiveness have not been established in pediatric patients who weigh less than 5 kg.

Coartem has Orphan Product designation and, as such, does not have to provide a pediatric plan for Coartem in patients less than 5 kg of body weight.

11 Other Relevant Regulatory Issues

11.1 DSI Consult

A DSI consult was requested by DSPTP because Coartem is a NME and the NDA studies were not conducted under IND. There were no efficacy or safety concerns that let to the request. Two of the primary studies that are considered pivotal to the approval are Studies A023 and ABMO2 which were factorial design studies and were conducted at the same site in China. The PI was Dr. Jiao Xiu-Qing, now retired, at the Institute of Microbiology and Epidemiology, Academy of Military Medical Sciences, Bejing China. The studies were conducted at the Navy Military Hospital in Sanya, Hainan Province. These are the only studies which evaluate the contribution of each component to the combination.

In addition, DSI inspected sites in Thailand because one of the sites (PI Dr. Sornchai Looareesuwan, deceased, from Faculty of Tropical Medicine, Mahidol University, records moved to (b) (4), near the original site) participated in Studies A025, A026, and A028 and was the sole investigator for Study A028. The other Thai site (Dr. Francois Nosten, Shoklo Marlaria Research Unit, MaeLa Camp, Mae Sot Tak) enrolled the majority of patients in Studies A025 and A026. Study A205 was of interest because in this study the 4-dose regimen was directly compared to the 6-dose regimen and Thailand is an endemic area for falciparum malaria.

Finally, DSPTP requested inspections of the African sites that contributed patients to the two large studies in infants and small children (A2403 and B2303) because they provide important safety and efficacy data in children ≥ 5 kg. The following sites were inspected for Study A2403: (b) (4)

In addition, DSI also inspected the applicant's headquarters (Novartis Pharma AG, Basel, Switzerland).

The following is a summary of DSI's clinical observations entered into DFS on November 3, 2008:

Dr. Srivicha Krudsood for Dr. Sornchai Looareesuwan, deceased. Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand
Generally found to have executed the study adequately, several deviations from FDA regulations noted pertaining to protocol and recordkeeping violations (subjects who should have been excluded for elevated liver enzymes were enrolled, some patients missing study visits, SAEs were reported > 24 hours after onset).

Addendum by DSI, December 10, 2008: A Form FDA 483 was issued due to several deviations from FDA regulations. In addition to what was noted initially, inspectors also noted that the total number of subjects screened at the site can not be determined since screening was performed as part of the hospital admission process and the study staff only confirmed that a subjects was appropriate for the study.

DSI concluded that the new information does not change the previous conclusion regarding data integrity at this site, since it is unlikely that these errors will impact the final outcome of the study and it does not appear that the rights, safety and welfare of the subjects was compromised due to these inaccuracies.

Dr. Francis Nosten, Shoklo Malaria Research Unit, Mae Sot Tak, Thailand
Generally, the investigator was found to have executed the study adequately, although several deviations from FDA regulations were noted: investigator did not adhere to the investigational plan (timing of dosing and blood microscopy did not always occur according to the protocol schedule) and did not prepare and maintain adequate and accurate case histories (documentation of inclusion/exclusion criteria was not complete in patient chart)

Addendum by DSI, December 10, 2008: A Form FDA 483 was issued due to several deviations from FDA regulations. In addition to what was noted initially, the inspectors reported that the investigators performed pre-screenings and then entered subjects if qualified. There was no record of anyone failing screening.

Also, during the inspection of the sponsor, Novarits, it was noted that Dr. Nosten did not have a valid license to practice medicine in Thailand at the time he participated in Study A2412 (conducted several years after Studies A025 and A026) and had not received IRB approval from the government of Thailand, although he did have IRB approval from Mihadol Hospital. The DSI Medical Officer commented that although there was no documentation of Dr. Nosten's valid medical license at the time of Studies A025 and A026, he was not in violation of the Thai GCP or IRB requirements, at the time. In addition, patient care does not appear to have been compromised since (b) (4) conducted the study procedures and treated patients at this site and she appears to have a valid medical license.

DSI concluded that the new information does not change the previous conclusion regarding data integrity at this site, since it is unlikely that these errors will impact the final outcome of the study and it does not appear that the rights, safety and welfare of the subjects was compromised due to these inaccuracies.

(b) (4)

Current contact information: (b) (4)
Generally, the investigator was found to have executed the study adequately, although several deviations from FDA regulations were noted: investigator did not prepare and maintain adequate and accurate case histories (e.g., inconsistencies noted in the dosage administration documents, documentation of IRB approval could not be located, some blood slides could not be located, some SAEs were reported > 24 hours after onset). The inspector considered that there was no evidence of fraud and that (b) (4) appeared to be a dedicated and knowledgeable researcher.

Addendum by DSI, December 10, 2008: A Form FDA 483 was issued due to several deviations from FDA regulations. (b) (4) submitted a written explanation for some of the inspector's observations; however, no information to contradict the deficiencies noted on the 483 were presented. DSI concluded that the previous conclusions regarding data integrity do not change: athough recordkeeping violations occurred, it is unlikely that these errors will impact the final outcome of the study.

(b) (4)
Generally, the investigator was found to have executed the study adequately, although several deviations from FDA regulations were noted: investigator did not adhere to the investigational plan (did not use the protocol-specified method for determining parasite density for blood slides, documentation of IRB approval could not be located) and did not prepare and maintain adequate and accurate case histories (source documentation of parasite counts, hemoglobin measurements were not performed on-site during screening).

(b) (4)
Issues:
1. The test article preparation and dispensing log is incomplete and suffered water damage. The inspector reports that a good portion of this source data has been manipulated and rewritten in the log, with an attempt made to pass it off as source data. In addition, the log is missing source data for the test article selection, preparation and dispensing to 12 of the 240 patients who completed the study.

2. A study nurse was in the room when the drug was prepared, where she could see how the drug was prepared, with a mortar & pestle being used for standard Coartem versus a vial of water for the dispersible Coartem. The same nurse subsequently administered the test article to a number of subjects and was responsible for some patient care (e.g., vital signs). The protocol requires that the drug be dispensed and administered by an independent study person.

There appeared to be protocol and record keeping violations at (b) (4) site, on the basis of the information audited thus far after the first week of the inspection. Some of these deficiencies are still undergoing investigation. In particular, the attempts to repair the damaged preparation and dispensing log are of concern.

Addendum by DSI, December 10, 2008: A Form FDA 483 was issued due to several deviations from FDA regulations. Regarding #1, the DSI Medical Officer commented that it appears the dispensing log was traced over, rather than being intentionally manipulated.

Regarding #2, DSI requested that copies of the Pharmacy Preparation and Dispensing log be faxed to them for further examination. On examination of photos of the blister packs, they felt it was apparent that there was a 2-part label containing the randomization number which was to be affixed to the source document. In addition, blister packs of dispersible and conventional tablets were visually distinctive. Finally, verification of the formulation a given subject received could be accomplished by comparison of the randomization number with the master records kept by Novartis in Basel, Switzerland. Therefore, the initial concern that the form of Coartem administered to a given subject could not be verified was not validated. Although a regulatory violation, there was no evidence that data integrity was impacted.

On November 15, 2008 (b) (4) responded to the 483 and claimed that the Pharmacy Preparation and Dispensing Log was in fact not a source document, and was not required in the protocol or in the specified standard operating procedures (SOPs) of the study at the site. The rest of the deficiencies were acknowledged.

DSI concluded that the previous conclusions regarding data integrity do not change: although recordkeeping violations occurred, it is unlikely that these errors will impact the final outcome of the study. Also, it does not appear that the rights, safety and welfare of the subjects was compromised due to these inaccuracies.

Dr. Jiao Xiu-Qing, Institute of Microbiology and Epidemiology, The Academy of Military Medical Sciences, Beijing, China
No information was available as of November 3, 2008.

Addendum by DSI, December 10, 2008: A Form FDA 483 not was issued. Generally the investigator was found to have executed the study adequately.

Sponsor/Monitor/CRO: Novartis Pharma AG, Basel, Switzerland
The FDA investigators reviewed Novartis procedures and records for protocols A023, ABMO2, A025, A026, A028, A2401, A2403, and B2303.

The data collected and maintained at the sponsor's site, as it pertains to the eight clinical sites audited, appear consistent with that submitted to the agency.

DSI conclusions:
Although protocol and recordkeeping violations occurred at the sites inspected, it is unlikely that these errors will impact the final outcome of the study, nor does it appear that the rights, safety, and welfare of any of the randomized subjects were compromised due to these inaccuracies. The data appear acceptable for use in support of the indication of the treatment of acute malaria due to infections with *P. falciparum* or mixed infections including *P. falciparum.*

In general, the audited sites adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. The inspection of documents supports that audited subjects exist, met eligibility criteria, received assigned study

medication, adhered to protocol, and signed informed consent documents. The inspections documented minor regulatory violations at the sites of Drs. Looareesuwan, Nosten, (b) (4) regarding protocol and recordkeeping violations. In general, the studies at these sites appear to have been conducted adequately, and the data generated by these sites may be used in support of the indication.

Addendum by DSI, December 10, 2008: The inspector encountered technical difficulties at the conclusion of the inspection. Because of these difficulties, he chose not to issue a Form FDA 483, but instead communicated the deficiencies noted during the inspection to Novartis representatives. His intention was to issue the Form FDA 483 at a later time; however, his supervisor decided that no Form FDA 483 could be issued once the inspector had departed the site. Information was sent to the DSI Medical Officer, with the statement that these items would have been included on a Form FDA 483, including (b) (4) (i.e., see previous discussion regarding Dr. Nosten and his lack of a valid medical license).

DSI concluded that the data collected and maintained at the sponsor's site, as it pertains to the eight clinical sites, appear consistent with that submitted to the agency as part of and in support of NDA 22-268. It is unlikely that the deficiencies identified above will impact data integrity or the final outcomes of the studies.

DSI's overall assessment and recommendations, as of December 10, 20008:
In general, the audited sites adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. The inspection of documents supports that audited subjects exist, met eligibility criteria, received assigned study medication, adhered to protocol, and signed informed consent documents. There were no significant regulatory violations documented at Dr. Xiu-Qing's site for Protocols A023 and ABMO2. The inspections documented minor regulatory violations at the sites of Drs. Looareesuwan, Nosten, (b) (4) regarding protocol and recordkeeping violations. In general, the studies at these sites appear to have been conducted adequately, and the data generated by these sites may be used in support of the indication.

The data collected and maintained at the sponsor's site, as it pertains to the eight clinical sites audited in accordance with the sponsor-monitor oriented BIMO compliance program CP 7348.810, appear consistent with that submitted to the agency as part of and in support of NDA 22-268.

11.2 Maternal Health Team Consult

The MHT review conducted by Dr. Leyla Sahin evaluated the applicant's interim report from a pregnancy registry (Study A2407) and a summary of the MHT's findings is presented below:

The sponsor conducted a prospective pregnancy registry in Zambia in collaboration with the

World Health Organization (WHO) from October 2004 to August 2007. The registry compared pregnancy outcomes of 495 women exposed to Coartem with those of 501 women exposed to sulfadoxine and pyrimethamine (SP), which is the standard of care for treatment of malaria in pregnant women in Zambia. There were 144 exposures to Coartem in the first trimester of pregnancy. The results show no difference between exposure groups in rates of spontaneous abortion, preterm delivery, low birth weight, perinatal mortality, or neonatal mortality. The incidence of birth defects was low in both exposure groups. Although data from this cohort study have limitations due to study design, access to care, and cultural traditions, the data collected still provide important information regarding pregnancy exposure. Published findings on more than one thousand pregnancies exposed to artemisinin derivatives are consistent with outcomes from the registry.

MHT recommends that Coartem should not be contraindicated in the first trimester of pregnancy based on: cumulative human safety data, which do not show an increased risk for major malformations overall or increased rates of spontaneous abortion; potential clinical benefit and animal reproductive toxicology studies that show only increased embryo-fetal loss. Based on regulatory definitions of the pregnancy categories, Coartem should be assigned a Pregnancy Category C due to the increase in embryo-fetal loss in animal studies.

MHT Recommendations:

1. Do not contraindicate Coartem during the first trimester of pregnancy

Reviewer's Comment: (b) (4)

2. Assign a Pregnancy Category C

Reviewer's Comment: The labeling will be revised to reflect Pregnancy Category C.

3. The sponsor should continue pregnancy exposure surveillance and consider establishing an international pregnancy exposure registry

Reviewer's Comment: The applicant will be encouraged to consider establishing an international registry with other antimalarial drug developers and international agencies, like the WHO. This recommendation will not be considered a postmarketing requirement or commitment.

4. For the final pregnancy registry report, the sponsor should reclassify spontaneous abortion, stillbirth, neonatal deaths, perinatal mortality, and maternal mortality according to standard U.S. definitions, as discussed in this review, and in their final report should report their results according to these definitions

Reviewer's Comment: The applicant will be encouraged to submit the final study report for Study A2407, when complete, for inclusion into labeling.

5. The sponsor should do a pK study in pregnant women to determine appropriate dosing

that will optimize the chance for effective therapy. This may be important for preventing the development of drug resistance, as well.

Reviewer's Comment: The MHT review refers to a published study in Thailand as well as a 2008 personal communication with the lead author (McGready). In the published study 13 pregnant women (five in the second trimester and eight in the third trimester) with uncomplicated P falciparum malaria exposed to Coartem had reduced (approximately half) plasma concentrations of artemether, and lumefantrine compared to historical data in non-pregnant (1 female and 16 males) patients with malaria. [8] *All patients treated with Coartem in this study were cured despite lower exposure to artemether and lumefantrine. In the personal communication, Dr. McGready provided data from a recent trial conducted in 103 pregnant women with falciparum malaria in the second and third trimester of pregnancy and treated with Coartem. Plasma concentrations (mean [range] ng/mL) of lumefantrine (measured on day 7) were higher (483 [134-1454]) in pregnant women than those observed in non-pregnant adults (350 [204-869]) and previously reported (384 [62-835]) in the published study.*

The review team felt that a PK study in pregnant women was not necessary, for the following reasons:

- *Artemether, DHA, and lumefantrine have been shown to demonstrate high variability in the plasma concentrations in healthy volunteers and non-pregnant patients with malaria. Therefore, it may be difficult to determine whether differences in the PK data in pregnant women are clinically meaningful.*
- *While the pharmacokinetics are variable, the efficacy of Coartem is consistent across various populations and, as noted in the publication, all pregnant women were cured of malaria.*
- *No efficacy exposure-response relationship has been demonstrated for artemether and lumefantrine in the NDA. For lumefantrine, higher concentrations are associated with a reduced probability of recrudescence. However, administering Coartem with food, can maximize exposure to lumefantrine.*
- *The applicant has already provided data from a large pregnancy database, which does not suggest any safety issues with Coartem.*

6. The sponsor should do a lactation study. The sponsor should submit a draft protocol for review within six months of approval.

Reviewer's Comment: The review team felt that a lactation study was not necessary based on the fact that even if artemether and/or lumefantrine was excreted into breast milk, exposures would be lower than the exposures seen in small infants treated with a 6-dose regimen of Coartem in the clinical studies, which was found to be safe. In addition, the Pharmacology/Toxicology review team is recommending a postmarketing study in juvenile dogs which may be used to address concerns regarding the potential for neurotoxicity in newborn babies.

[8] McGready R, Stepniewska K, Lindegardh N, et al (2006). The pharmacokinetics of artemether and lumefantrine in pregnant women with uncomplicated falciparum malaria. Eur J Clin Pharmacol; 62:1021-31.

11.3 Division of Neurology Products Consult

DSTP consulted the non-clinical and clinical reviewers in the Division of Neurology Products (DNP) regarding the known neurotoxic effects of Coartem seen in the non-clinical studies and the potential for neurotoxicity in humans.

Dr. Dave Hawver and Dr. Kenneth Bergmann reviewed the nonclinical and the clinical material, respectively. In addition Dr. Eric Bastings, the Deputy Division Director for DNP, wrote a separate memo summarizing their findings and the division's position.

DNP noted that the clinical data provided by DSPTP from the NDA submission did not provide evidence suggesting that significant neurotoxicity occurs in humans. Dr. Bergmann noted that the most consistent pathology across species is found in the lateral vestibular nucleus (coordination and balance) and the trapezoid auditory brainstem nucleus (sound localization, not hearing per se). He also observed that there is limited published human data regarding neurotoxicity (the drug is marketed in foreign countries). In a Medline search, he found one single case-control study of patients receiving either artesunate or artemether, and which revealed no safety signal in either audiometry or brainstem auditory evoked potentials.

Dr. Bergmann and Dr. Bastings believe that serious human toxicity is likely rare due to the long marketing history outside of the United States and the lack of reported CNS serious adverse event in the literature. Dr. Bastings does point out, however, the limitations of postmarketing reporting, in particular in foreign countries which may not have a reliable postmarketing reporting system, and suspect that there is a high degree of under-reporting with Coartem.

Dr. Bergmann and Dr. Bastings both point out that systematic neurological examination of patients was not performed in the clinical trials and therefore asymptomatic or mild neurological toxicity can not be ruled out.

Dr. Hawver's summary of the non-clinical findings is as follows:

a. Intramuscular (i.m.) artemether induced degenerative brain lesions when administered to dogs for 8 days at 20, 40, or 80 mg/kg/day, or for 27-30 days at 20 mg/kg/day, but NOT after 8 days at 10 mg/kg/day (N=3M), after 5 days at 40 mg/kg/day (N=3M) or after 3 days at 40 mg/kg/day (± 6 day recovery period; N=3M/group).

b. The evidence suggests that the neurotoxicity observed in dogs and rats given artemether i.m. correlates better with the level of sustained plasma exposures to artemether and its active metabolite (DHA) over several days rather than with the maximal plasma exposures.

c. The lowest artemether exposure (AUC0-24 hr) associated with brain lesions was observed in dogs treated for 8 days at 20 mg/kg/day i.m., and ranged from 1340-5920 ng*hr/mL, increasing over the 8 days of treatment. The NOEL for brain lesions in dogs (10 mg/kg/day i.m. for 8 days) resulted in exposures ranging from 537-2560 ng*hr/mL. Estimated human plasma exposure to artemether at the maximum recommended dose of 80 mg BID p.o. is 1070 ng*hr/mL.

d. Repeated intramuscular administration of artemether to dogs has allowed evaluation of artemether plasma exposures several-fold above those expected in humans given the recommended dosage of Coartem, but the DHA plasma exposures in these studies have generally been lower than those expected in humans.

e. Repeated oral administration of artemether to dogs results in rapid dramatic reduction in plasma exposure to artemether and DHA due to induction of metabolic enzymes; by 7 days of dosing at 300 or 600 mg/kg/day, plasma exposures to artemether and DHA were much lower than those expected in humans given the recommended dosage of Coartem.

f. The mechanism of action of the neurotoxicity induced by artemether and DHA is not clear; therefore, it possible that other metabolites whose concentrations have not been measured may contribute to the toxicity.

g. The possibility that co-treatment with lumefantrine may alter the level or duration of plasma exposure of artemether/DHA needed to induce brain lesions in dogs has not been evaluated.

h. The possibility that artemether and DHA plasma exposures could be maintained near or above those expected in humans by increasing the oral dose given to dogs each day to compensate for the induction of metabolic enzymes has not been explored.

i. Artemether-induced brain lesions were NOT correlated with treatment-related changes in neurology evaluations (3 i m. studies in dog; 1 i.m. study in rat) or audiometric evaluations (including Brainstem Auditory Evoked Potentials; 1 i m. study in dog).

Dr. Hawver concluded that the Applicant's nonclinical evaluation of neurotoxicity was not adequate, and proposed a nonclinical study in dogs to evaluate AUC exposures to artemether, DHA and lumefantrine at 2- and 10-fold above those expected in humans.

DSPTP asked DNP for labeling recommendations and DNP requested that labeling include a description of the findings of degenerative brain lesions in rats and dogs, and a statement that these lesions were seen at exposure levels close to that of the human dosing regimen, but that no serious drug related neurotoxicity was observed in clinical trials. And that the interaction between Coartem and grapefruit juice leading to a two-fold increase in AUC of artemether and DHA should also be added to the label.

Reviewer's Comment: DSPTP has incorporated these suggestions into the proposed labeling.

Regarding the need for non-clinical or clinical studies postmarketing, Dr. Bastings replied:

Non-Clinical:
We believe that the available non clinical data are sufficient to raise a safety concern. The study suggested by Dr. Hawver would not be substantially decrease or strengthen this concern, unless an oral study could be conducted at doses producing high multiples of the anticipated human plasma exposure (to artemether and DHA).

We recommend a study comparing oral and i.m. administration using doses that result in similar plasma AUCs (for both artemether and DHA). The i.m. dose should be one that has been shown to reliably produce the characteristic neurotoxicity. If, in such a study, oral dosing was not associated with brain lesions and i.m. dosing was, then it would indicate that it is the shape of the curve (i.e., sustained exposure) that is associated with neurotoxicity, which would decrease the safety concern for possible human neurotoxicity.

Clinical:
The requirement for a post-marketing clinical trial must be balanced with the risk/benefit profile of the product and the availability of other less toxic drug products to treat malaria. If the product is believed to have a robust

efficacy, there is no safer alternative, and the potential for mild or asymptomatic neurotoxicity is acceptable considering the drug's efficacy, it may be reasonable not to require a clinical trial.

Otherwise, if DSPTP considers that in this clinical setting mild or asymptomatic neurotoxicity should be better characterized, we recommend a controlled clinical trial with detailed neurological examination prior to treatment, and at several timepoints after treatment, with a particular emphasis upon gait, balance, coordination, and auditory function. The clinical trial should include audiograms. Vestibular testing may also be considered. The use of auditory evoked potentials may also be entertained, although that testing in animal studies did not identify any abnormality, so that its use in human trials will likely be of limited yield. The trial should include pediatric patients, in which behavior and development should also be assessed. The control used in the trial should not have any known neurotoxicity; otherwise, the study would be uninterpretable (a noninferiority design does not seem reasonable or practicable to address that issue).

We also recommend post-marketing surveillance of adverse events of interest, i.e those related to balance and audition.

Reviewer's Comment; The Pharm/Tox reviewers in DSPTP do not agree with the proposed non-clinical study suggested by DNP, citing relevance to humans as the main reason, and instead suggested that the review team consider a clinical trial.

The following Addendum by Dr. Lim documents the Clinical (safety) review team's response to the benefit of a clinical trial, and the recommendations in the DNP review.

Dr. Bergmann (Medical Officer, DNP) noted that there were limitations of the safety data provided by the Applicant. In particular, the lack of systematic neurological examinations would "limit the detection of mild or asymptomatic neurological toxicity. In addition, some of the expected symptoms (e.g. dizziness, vertigo) can be a manifestation of the treated condition (malaria) and not represent neurotoxicity." However, he also noted that the clinical materials provided by our Division "do not provide evidence suggesting that significant neurotoxicity occurs in humans." Deaths were unrelated to study drug, and nervous system SAEs occurred at less than 0.1% and "cannot be distinguished from effects of cerebral malaria or severe general illness." In addition, Dr. Bergmann's review of the scientific literature and the Applicant's information "did not identify a single report documenting a neuropathological examination of a person dying after taking an artemisinin-class agent", suggesting that "serious human toxicity is likely rare".

The Clinical reviewer agrees that the safety database was limited by the absence of baseline and systematic neurological exams. Furthermore, physical exams were not conducted by neurologists attuned to the subtleties of neurologic changes. Similar criticisms can be made regarding the audiologic information in the clinical safety database. While subclinical nervous system adverse events may not have captured, the reviewer believes (despite the underreporting which is generally recognized with post-marketing data) that a serious or clearly apparent neurologic abnormality would have been detected with **(b) (4)** patients treated with Coartem. Therefore the reviewer completely agrees that a post-marketing requirement of a clinical trial should be conducted if the intent is to capture mild neurologic changes on physical examination.

However, there are several issues associated with requesting such a trial, and implications with what to do with the collected information. First, even if baseline neurologic exams are

performed prior to Coartem administration, we know from our analysis of the safety database that patients with malaria may already have abnormal neurologic exams due to malaria infection. Worsening of these neurologic symptoms or signs is difficult to distinguish from the natural history of resolving malaria itself in the absence of knowledge of the background rate of abnormal neurologic exams in the population of interest. To gather such information would require conducting neurologic exams on uninfected malaria subjects from the population of interest, which is an unfeasible request. Second, the clinical significance of subtle neurologic findings is unknown, and it is unclear how clinicians should act upon such information. Third, the pathologic locations of the lesions affect coordination and balance, and sound localization (and not hearing per se according to DNP Deputy Director's memo). In young children and infants unable to walk, it is impractical and difficult to assess coordination and balance. Furthermore, it is unclear to what degree audiograms would assess sound localization rather than hearing loss. Changes in behavior and development in children were suggested as additional neurologic signs of neurotoxicity, but these are both non-specific and long-term indicators of which a 3-day course of Coartem is unlikely to affect.

In addition, despite limitations of the safety database analyzed, it is important to note that approximately 1980 patients were evaluated in this NDA submission (647 adults, 1332 children) of which serious nervous system AEs were infrequently reported, of mild intensity, and resolved within the study period. None of the SAEs were felt to be related to study drug by the reviewer. Lastly, as a postmarketing requirement, the Applicant will be required to complete and submit the final report of their ongoing audiologic study A2417, which assesses auditory function following treatment of acute, uncomplicated *P. falciparum* malaria in patients 12 year of age or older treated with Coartem, Malarone and artesunate-mefloquine.

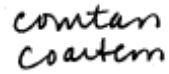
Therefore, this reviewer does not recommend conducting a clinical study, as collecting such data is difficult (need for a neurologist to conduct exams), and the specificity of such findings, such as behavioral and developmental changes, are questionable in children. Abnormal neurologic findings may be manifestations of malaria, and distinguishing this from drug effect may not be possible. Furthermore, it is unclear what recommendations should be made regarding the management of subclinical neurologic signs detected on physical exam.

12 Labeling

12.1 Proprietary name

DSPTP requested a consult for the review of the proprietary name, Coartem from the Division of Medication Error Prevention (DMEP). DMEP informed DSPTP that they noted the name refers only to one ingredient in the established name and that is in violation of 21 CFR 201.6(b). However, the DSPTP requested DMEP continue with the name review from a medication error perspective. In their April 15, 2008, review DMEP commented that, upon further evaluation, it was determined that because the individual ingredients in Coartem, artemether and lumefatrine, are not available in the U.S. nor commonly recognized in the U.S. healthcare community, the anticipated risk of confusion with this name would be minimal if only one component was communicated in the proprietary name.

In addition in their April 15, 2008 review, DMEP commented that the proprietary name Comtam (entacapone, adjust treatment for Parkinson's disease) was determined to be likely to lead to medication errors with Coartem. An excerpt form their review follows:

> Comtan is available as a 200 mg tablet and is given with each dose of levodopa/carbidopa up to a maximum of 8 tablets/day.
>
> Comtan and Coartem look similar when written because they share the first two letters ('Co') and end in letters that are not clearly distinguishable from each other ('an' vs. 'em'). Also, both of these names have an upstroke (lower case 't') in the same position of the names. This name pair also appears to be similar in length when written although Coartem is one letter longer.
>
> 
>
>
> Comtan and Coartem share some product characteristics. Both drugs share the same route of administration (oral) and dosage form (tablet). They are also available in a single strength (120 mg/20 mg vs. 200 mg) which means prescriptions for either of these products could be prescribed and/or dispensed without an indication of strength. Additionally both Comtan and Coartem have unique and complex dosing regimens depending upon the patient's body weight for Coartem or the amount of levodopa/carbidopa for Comtan. As noted in the Coartem product information…the total regimen is 6 doses. However, depending on the patient's weight the Coartem dose may be 4 tablets twice daily, 2 tablets twice daily or 1 tablet twice daily. Similarly, the dose of Comtan can also be variable and is dependent upon the frequency of levodopa/carbidopa. These similar dosing frequencies increase the similarity of these two products.
>
> Moreover, prescribers may write 'Take orally as directed' on the prescription and provide the detailed directions for the patient on a separate sheet of paper. This practice may circumvent the ability to initiate interventions by pharmacists and/or nurses when reviewing the prescription. If a patient were to receive Comtan instead of Coartem, there is the potential for ingestion of multiple tablets at once leading to an adverse event secondary to drug toxicity. Conversely if Coartem were received instead of Comtan, there is the potential for inadequate treatment of Parkinson's disease.
>
> Based upon their look-alike characteristics when written and overlapping product characteristics such as dosage form (tablet), route of administration (oral) and frequency of administration (twice daily), the Division of Medication Error Prevention believes this name pair cannot safely coexist in the marketplace. Furthermore, 21 CFR 201.10(c)(5) states 'the labeling of a drug may be misleading by reason (among other reasons) of designation of a drug or ingredient by a proprietary name that, because of similarity in spelling or pronunciation, may be confused with the proprietary name or the established name of a different drug or ingredient.'

The applicant was informed by DSPTP that the name Coartem was found to be unacceptable based upon look-alike similarities with Comtan. In response, the applicant sumitted a rebuttal in support of the name Coartem asserting that there is little risk of name confusion because Coartem will not likely stock the drug, only a limited patient population will use it, and it will be mainly used in a hospital care environment. The rebuttal also stated the applicant's willingness to commit to Phase 4 monitoring for medication errors related to the Proprietary name. On June 24, 2008, DSPTP asked DMEP, now known as the Division of Medication Error Prevention and Analysis (DMEPA), to reconsider the acceptability of the proposed name.

On November 7, 2008, the Division of Medication Error Prevention and Analysis (DMEPA) reversed their initial decision, and found the proprietary name of Coartem to be acceptable. The following is DMEPA rationale:

We also acknowledge that initiation of therapy for this product will likely occur in the hospital setting in the U.S. and that in this setting of care it is less likely an order will be transcribed with ambiguous directions for use such as 'UD' (as directed).

…The Applicant states that Coartem will be available only through 3 major wholesalers nationwide for distribution to a hospital or retail pharmacy within 24 hours, thus reducing the chance that Coartem could mistakenly be dispensed to a patient requiring Comtan. Additionally, Novartis plans to initially produce only 300 units of Coartem. With more than 70,000 locations in the U.S. capable of dispensing prescription drugs, the likelihood of a pharmacy stocking this drug product is low.

Moreoever, given that malaria treatment should begin as soon as possible, communication would have to occur between the pharmacist and the physician, nurse and/or patient regarding the expected time of arrival of the medication. During this dialogue pertinent patient information would be conveyed alerting the pharmacist to the possibility of a misinterpretation of the order.

12.2 DDMAC comments

The DDMAC review was completed on November 10, 2008 and entered into DFS. The reviewers, Kathleen Klemm, Pharm.D. and Carrie Newcomer, PharmD., had extensive comments regarding the proposed product labeling and proposed patient package insert (PPI). Their comments were incorporated into DSPTP's revised version of labeling.

12.3 Physician Labeling

The applicant's draft label was substantially revised by the review team. The following recommendations from the consultants were also incorporated. An initial revised version of the PLR label was sent to the applicant on November 21, 2008 and discussed in a teleconference on November 24, 2008. Subsequent versions of the label were discussed during teleconferences on December 16, 2008 and December 19, 2008.

The following are the QT-IRT's recommendations for labeling:

(b) (4)

The following are the MHT's recommendations for labeling:

(b) (4)

[redacted]

8.3 Nursing Mothers
It is not known whether Coartem is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Coartem is administered to a nursing woman. Animal data suggest excretion into breast milk. The benefits of breastfeeding to mother and infant should be weighed against potential risk from infant exposure to Coartem through breast milk.

12.4 Carton and Container Labels

The carton label (4 x 6 tablet blister card) and immediate container labels (24 count bottle and 6 tablet blister card) were reviewed by OSE/DMEPA and entered into DFS on November 7, 2008. The reviewer (Denise Baugh, Pharm.D.) had one general comment that was forwarded to the applicant:

> Increase the prominence of the established name commensurate with the prominence of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).

The applicant submitted a revised immediate carton and container packaging on December 18, 2008 and DMEPA stated their recommended revision to the carton labeling and container label had been incorporated by the Applicant and is acceptable on December 23, 2008.

12.5 Patient Labeling/Medication Guide

DRISK consult was completed November 26, 2008 by LaShawn Williams. A summary of their comments and recommendations regarding the Patient Package Insert (PPI) follows and was incorporated into the proposed labeling:

1. The sponsor uses the term [(b) (4)] in the proposed PPI. [(b) (4)] is vague and less commonly understood. We have changed this term throughout the PPI to "healthcare provider."
2. In the section, "How should I take Coartem?":
   - we removed the verbose and potentially confusing instruction that read: [(b) (4)] We added a day- by- day dosing regimen as this provides clarity and reduces patient confusion.
   - we recommend adding an instruction to use water [(b) (4)] The PPI must be consistent with the PI.
3. We added a "What are the ingredients in Coartem?" section and listed the active and the inactive ingredients to the end of the PPI. This is a standard section in patient labeling.
4. In the section, "How should I store Coartem?," we have deleted [(b) (4)] as it is more realistic to provide the acceptable temperature storage range.
5. In the section "What are the possible side effects of Coartem?" we bulleted the side effects as bullets are easier to read.
6. Contractions should not be used in patient information as they are generally not understood at lower reading levels. Sponsor uses the contraction [(b) (4)] This was replaced with "does not."
7. We have added the statement:

   > Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

   This verbatim statement is required for all Medication Guides effective January 2008 (see 21 CFR 208.20 (b)(7)(iii); also see Interim Final Rule, *Toll-Free Number for Reporting Adverse Events on Labeling for Human Drug Products* in Federal Register Vol. 73, No. 2, p.402-404, 1/3/2008). Although, not required for voluntary patient information, like Coartem, we recommend adding this statement to all FDA-approved patient labeling for consistency.

The following two additional comments were sent to DSPTP by DRISK on December 12, 2008:

- Anorexia and headache have been added to Clinical studies (6.2) of the PI we recommend adding them as [(b) (4)] and "headache" in the PPI under "the most common side effects in children" section.

- New information on the fact that Coartem tablets may reduce the effectiveness of hormonal contraceptives has been added to the PI. We recommend that "hormonal

methods of birth control (for example, birth control pills or patch)" be added to the PPI under "What should I tell my healthcare provider before taking Coartem?

13 Recommendations/Risk Benefit Assessment

Coartem administered as a 6-dose treatment regimen over 3 days has been shown to be safe and effective for the treatment of malaria in patients of 5 kg body weight and above with acute uncomplicated *P. falciparum* infection. Approval is recommended.

A recommendation regarding approval of Coartem for the treatment of acute uncomplicated malaria in patients with mixed infections including *P. falciparum* was discussed at the Anti-Infectives Advisory Committee Meeting on December 3, 2008. It was decided that efficacy information discussing the 43 patients with mixed infections of *P. falciparum* and *P. vivax* would be added to the Clinical Studies section of the labeling, (b) (4)

An oral fixed dose artemisinin combination drug would be a useful addition to the current armamentarium of antimalarial drugs available in the USA for the treatment uncomplicated *P. falciparum* infection. Untreated *P. falciparum* infection can lead to severe malaria and death. Most malaria-associated deaths are due to *Plasmodium falciparum*; children under the age of five years and non-immune travelers are especially vulnerable to severe infection.[9] When the risks of untreated malaria are compared to the benefit associated with Coartem therapy, the benefit of the therapy greatly outweighs the risks associated with the disease.

The following are the limitations of use for Coartem:

- Coartem is not indicated for patients with severe or complicated *P. falciparum* malaria.
- Coartem is not indicated for the prevention of malaria.

However, despite the clinical recommendation for approval, the unsatisfactory facilities inspections must be resolved by the Office of Compliance before an action can be taken.

13.1 Recommendation for Postmarketing Risk Management Activities

1. Conduct a descriptive study of the use of Coartem Tablets in non-immune travelers.

Collect baseline patient demographic information (including age, weight, height, sex, race, prior medications and concomitant medications, as well as immune status), adverse reactions, including potential nervous system and cardiac adverse reactions, and efficacy outcome. You should include representation of adults > 65 years, children ≤ 16 years, and overweight patients (BMI ≥ 25 kg/m^2). Submit yearly reports summarizing data on patients treated with Coartem within the previous year and the final report integrating information on all patients in the Final Report Submission.

[9] Filler St al., Malaria surveillance--United States, 2001. MMWR Surveill Summ 2003 Jul 18;52(5):1-14.

2. Conduct a systematic surveillance study to evaluate the potential development of resistance to Coartem Tablets.

Submit a yearly report describing the reported resistance to a combination of artemether and lumefantrine in malaria endemic countries as obtained from ongoing resistance monitoring programs on antimalarials collected by international consortia and organizations (e.g., World Health Organization).

3. Conduct a neurotoxicity study of oral artemether in juvenile rats including neurologic functional batteries, toxicokinetics, and extensive brain histopathology.

Conduct a neurotoxicity study of oral artemether in juvenile rats to assess how exposure and toxicity in young animals compares with older animals and humans, and whether neurologic deterioration occurs following the terminal dose. This study should consist of a main study group, a toxicokinetic group, and a recovery group. In this study, comprehensive histopathological examination of the central nervous system should be conducted.

4. Conduct bacterial reverse mutation studies (Ames assays) for lumefantrine impurities (b) (4) and artemether impurities (b) (4)

Lumefantrine impurities (b) (4) and artemether impurities (b) (4) have structural alerts for genotoxicity, and the proposed release limits for these compounds are higher than levels that are qualified by available toxicology studies.

5. Conduct an *in vitro* study to characterize the induction potential of artemether, dihydroartemisinin (DHA), and lumefantrine on the metabolism of substrates of CYP3A.

Conduct an *in vitro* study to evaluate the induction potential of artemether, DHA, and lumefantrine on the metabolism of co-administered drugs that are substrates of the Cytochrome P450 3A4 (CYP3A4) enzyme system (e.g., oral contraceptives). Refer to the guidance for industry titled *Drug Interaction Studies--Study Design, Data Analysis, and Implications for Dosing and Labelin*g (http://www.fda.gov/cder/guidance/6695dft.pdf) for details on the conduct of the *in vitro* study.

6. Conduct an *in vitro* study to characterize the potential interaction between artemether and lumefantrine and rifampin.

If, upon review, it is determined that the clinical trial discussed in Item 10 below is acceptable, then an *in vitro* study to characterize the potential interaction between artemether and lumefantrine and rifampin will not be needed. Otherwise, refer to the guidance for industry titled *Drug Interaction Studies--Study Design, Data Analysis,*

*and Implications for Dosing and Labelin*g for details on the conduct of the *in vitro* study.

7. Conduct an *in vitro* study to characterize the potential interaction between artemether and lumefantrine and protease inhibitors (PIs).

If, upon review, it is determined that the clinical trial discussed in Item 11 below is acceptable, then an *in vitro* study to characterize the potential interaction between artemether and lumefantrine and PIs will not be needed. Otherwise, refer to the guidance for industry titled *Drug Interaction Studies--Study Design, Data Analysis, and Implications for Dosing and Labelin*g for details on the conduct of the *in vitro* study.

8. Conduct an *in vitro* study to characterize the potential interaction between artemether and lumefantrine and non-nucleoside reverse transcriptase inhibitors (NNRTIs).

If, upon review, it is determined that the clinical trial discussed in Item 12 below is acceptable, then an *in vitro* study to characterize the potential interaction between artemether and lumefantrine and NNRTIs will not be needed. Otherwise, refer to the guidance for industry titled *Drug Interaction Studies--Study Design, Data Analysis, and Implications for Dosing and Labelin*g for details on the conduct of the *in vitro* study.

9. Complete and submit the final report for the currently ongoing trial "An open label, single center study of the effects of Coartem, Malarone and artesunate-mefloquine on auditory function following the treatment of acute uncomplicated *P. falciparum* malaria in patients 12 years of age or older in Columbia."

10. Conduct a clinical drug interaction trial to evaluate the effect of a co-administered inducer on the pharmacokinetics of Coartem Tablets (artemether and lumefantrine).

Conduct a clinical drug interaction trial using a potent CYP3A4 inducer, such as rifampin, to evaluate the effect of co-administering the inducer on the pharmacokinetics of Coartem Tablets (artemether and/or lumefantrine). If, upon review, it is determined that the trial is acceptable, then an *in vitro* study to characterize the potential interaction between artemether and lumefantrine and rifampin will not be needed (see Item 6 above).

11. Conduct a clinical drug interaction trial to evaluate the two-way interaction between a protease inhibitor and Coartem Tablets (artemether and lumefantrine).

Submit the final report for a clinical drug interaction trial using a representative protease inhibitor (PI), such as lopinavir/ritonavir or ritonavir, to evaluate the two-way

interaction between a PI and Coartem Tablets (artemether and lumefantrine). If, upon review, it is determined that the trial is acceptable, then an *in vitro* study to characterize the potential interaction between artemether and lumefantrine and a PI will not be needed (see Item 7 above).

12. Conduct a clinical trial to evaluate the two-way interaction between a non-nucleoside reverse transcriptase inhibitor and Coartem Tablets (artemether and lumefantrine).

Submit the final report for a clinical drug interaction trial using a representative non-nucleoside reverse transcriptase inhibitor (NNRTI), such as efavirenz or nevirapine, to evaluate the two-way interaction between a NNRTI and Coartem Tablets (artemether and lumefantrine). If, upon review, it is determined the trial is acceptable, then an *in vitro* study to characterize the potential interaction between artemether and lumefantrine and an NNRTI will not be needed (see Item 8 above).

13. Conduct a clinical interaction trial to evaluate the induction potential of Coartem Tablets (artemether and lumefantrine) on CYP3A4 substrates.

If the results of the *in vitro* study (see Item 5 above) are positive, an *in vivo* trial will be needed to further characterize the effect of Coartem Tablets (artemether and lumefantrine) on the pharmacokinetics of co-administered drugs that are metabolized by the CYP3A4 enzyme system, such as oral contraceptives.

13.2 Recommendation for other Postmarketing Study Commitments

None.

13.3 Recommended Comments to Applicant

None.

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/s/

Joette Meyer
12/23/2008 02:59:33 PM
MEDICAL OFFICER